HORMONE
RESEARCH IN
PÆDIATRICS

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Abstracts

Plenary Lectures

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Genetic and environmental determinants of type 1 diabetes

Abstract unavailable.

PL2
New advances in monogenetic diabetes

Abstract unavailable.

PL3
New Advances on Human Evolution from the Analysis of Ancient Genomes

Carles Lalueza-Fox

Institute of Evolutionary Biology, Barcelona, Spain

New developments in massive sequencing techniques allow now the generation of an unprecedented amount of genomic data, including the generation of complete ancient genomes. Among those, the Neandertal and Denisovan genomes, dated between 40 000 and 50 000 years ago, are shedding new light on evolutionary processes such as the genetic basis of archaic hominins and modern humans specific adaptations -including morphological, metabolical and behavioural traits- as well as the extent and nature of the admixture events among different hominin lineages. In a more recent time scale, the arrival of farming in Europe beginning around 8500 years ago required adaptation to new environments, pathogens, diets, and likely social organizations. The analysis of prehistoric European genomes provides evidence of ongoing natural selection associated with diet and pigmentation.

PL4
Genomic Diversity in Present day Humans: Evolutionary Aspects

Alan Templeton[a,b]

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Background: The amount and distribution of genetic diversity in and among human populations are primarily determined by our recent evolutionary past. Since the Mid-Pleistocene, about 700 000 years ago, our evolution has been dominated by population expansions coupled with admixture, recurrent genetic interchange (gene flow), and local adaptation. **Objective and hypotheses:** To understand the evolutionary factors influencing present-day genetic variation in humans. **Method:** Phylogeographic analysis, ancient DNA, and analysis of fossil data. **Results:** An accurate and cross-validated reconstruction of recent human evolutionary history is estimated. **Conclusion:** Admixture and gene flow tend to increase genetic diversity within populations and reduce differences between. Although we make much of our population differences, humans are one of the most genetically homogeneous species on the planet despite our global distribution. Because much of the gene flow in our species has been constrained by geographic distance throughout much of our evolutionary history, the best predictor of the degree of genetic differentiation between any two populations is simply their geographic distance from each other. Skin color, "race", and other cultural classifications are not good predictors of molecular genetic differentiation. Local adaptation to physical factors (such as UV radiation) and biological factors (such as infectious diseases) tends to increase diversity between populations. This differentiation is not related directly to geographic distance, but rather relates to the geographic distribution of the environmental factor or factors leading to natural selection for local adaptation. Many of these local adaptations represent trade-offs between various traits and are responsible for most of genetic diversity that is of clinical importance.

PL5

Ontogeny of FGF21 in the Human: Implications for Metabolic Health

Francesc Villarroya[a,b]

[a]University of Barcelona, Barcelona, Spain; [b]CIBER Fisiopatologia de la Obesidad y Nutrición, Barcelona, Spain

Background: FGF21 is a hormonal factor with powerful anti-diabetic and anti-obesity properties in adults.. Studies in rodent models indicated that hepatic FGF21 expression and blood FGF21 levels are strongly induced after birth in response to fat provided by milk ingestion. Moreover, preliminary data indicate that FGF21 is present in maternal milk. **Objective and hypotheses:** Our objective is to determine, using human samples and pre-clinical experimental models, the role of FGF21, both endogenously produced and transferred from the mother, in neonatal metabolism. **Methods:** Determination of the ontogeny of FGF21 levels and FGF21 gene expression in human early life, using blood samples as well as hepatic and adipose samples from necropsies. Determination of the alterations in neonatal metabolism in mice with targeted invalidation of the FGF21 gene. Characterization of FGF21 in maternal milk in humans and rodents. Determination of the physiological role of the FGF21 present in maternal milk on neonatal development. **Results:** FGF21 levels are induced after birth in human neonates, thus resulting in a surge of FGF21 from infra- to supra-adult concentrations in the neonate. Changes in FGF21 levels in blood appear to reflect mainly hepatic FGF21 expression changes in the neonatal period. Brown but not white adipose tissue expresses FGF21 in human neonates. Maternal milk, either from humans and rodents, contains FGF21 that is essentially originating in maternal blood. Rodent studies indicate that FGF21 from milk is essential for appropriate neonatal development. FGF21 in milk is retained in neonatal gut and does not cross to neonatal circulation. Small intestine is a target of FGF21 action in neonates, in contrast with adults in which intestine is not sensitive to FGF21. FGF21 acts on neonatal intestine promoting the expression of digestive enzymes, such as lactase, and intestinal hormones such as GIP and GLP-1. FGF21 in neonatal intestine induces lactose digestion. **Conclusion:** FGF21 is an important hormonal factor in neonates. The role of FGF21 involves both endogenous regulation of expression and levels in the neonate and the action of FGF21 present in maternal milk on neonatal intestine function and maturation. **Funding:** This work is supported by MINECO (Grant SAF2011-2636), Recercaixa Foundation, Instituto Danone and Generalitat de Catalunya (Grant 2009SGR00284), Spain.

PL6

The complex Relationship between the GH/IGF Axis and Aging and Longevity – the Interface with Diet and Mitochondrial Peptides

Pinchas Cohen[a,b]

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Background: Growth hormone (GH) has been used for over 50 years to benefit both children with GH deficiency (GHD) and other forms of short stature as well as to correct the metabolic abnormalities found in adults with GHD (AGHD). Moreover, low IGF levels have been associated with the risk of diabetes, heart disease and osteoporosis. On the other hand, epidemiological studies suggest that high IGF-1 levels may be associated with cancer risk in the general population. Furthermore, various animal models of reduced GH and IGF-1 have been demonstrated to have increased lifespan. **Objectives and hypotheses:** We wanted to establish the nature of IGF-1 and other GH-dependent factors as regulators of lifespan and healthspan in humans **Methods:** A series of human cohorts, as well as studies of animal models were employed **Results:** We have demonstrated that in human centenarians, rare polymorphisms of the GH and IGF receptors that confer mild resistance, are associated with exceptional longevity. However, our studies in Laron patients show that while they have improved healthspan and reduced incidence of cancer and diabetes, their mortality rates are similar to their normal relatives. We also observed a strong relationship between protein intake in humans and mice and subsequent effects on IGF levels and life expectancy. In several studies of large populations, a "U"-shaped curve of mortality versus IGF-1 levels suggested that both high and low IGF levels are potentially hazardous. Recently, we also demonstrated that GH and IGF-1 suppress the levels of the mitochondrial peptide, humanin, which is related to healthspan and lifespan. **Conclusion:** The practice of IGF-based dosing is a practical approach to maintain IGF levels in the normal range during GH therapy to reduce theoretical risks. We also propose that monitoring humanin levels during GH therapy may be potentially valuable. **References:** Suh et al. *PNAS* 2008; Guevara-Aguirre et al. *Science Translational Medicine* 2011; Levine et al. *Cell Metab*. 2014; Cohen et al. *Clin Endocrinol* 2014; Milman et al. *Aging Cell* 2014; Lee et al *Aging Cell* 2014. **Declaration of interest:** The author is a consultant to Teva, Ascendis, Opko, and Versartis. I am a Stock-holder and consultant to CohBar Inc. **Funding:** NIH, NIA.

Symposia

S1.1
The Effect of Thyroid Hormones on the Brain

Joanne Rovet

Toronto, Canada

Background: It is long been known that thyroid hormone (TH) is essential for brain development; however most evidence is based almost on rodent models. Since the advent of advanced neuroimaging techniques, it is now possible to study the manifestations of TH role in developing human brain. **Objective and hypotheses:** To examine findings from structural and functional MRI investigations of maternal hypothyroidism and congenital hypothyroidism (CH), which represent two human conditions involving a loss of TH at different stages of gestation and early life. We hypothesize that different brain regions have unique critical periods of TH need. **Method:** Participants were offspring of women with hypothyroidism in pregnancy (HYPO), children with CH, and controls with normal thyroid history, aged 10–14 years. All received extensive testing and structural and functional MRIs. Scans were examined for size of hippocampus (H) and corpus callosum (CC), cortical thickness, and fMRI response. **Results:** HYPO and CH show i) reduced size and atypical functioning of H, albeit in different hemispheres, ii) different patterns of cortical thinning and thickening, iii) abnormalities in different CC segments. Results are associated with weaknesses in memory, visual and verbal processing, and executive functions. **Conclusion:** As in rodents, the human brain critically needs TH for its early development while the particular processes that are disrupted by TH loss and their specific brain locations reflect the exact timing of the TH insufficiency. These findings have implications for specific weaknesses in cognitive functioning as well as everyday functional limitations.

S1.2
Diabetes Dysglycaemia, Cognition and the Developing Brain

Fergus Cameron

Royal Children's Hospital, Melbourne, Victoria, Australia

Glucose is the preferred metabolite of the brain with 25% of circulating blood glucose in adults destined for cerebral metabolism. It is intuitive then that type 1 diabetes mellitus (T1DM), a disorder characterised by perturbations in blood glucose ('dysglycaemia'), should cause acute and chronic brain dysfunction. These cognitive and affective impacts appear to be greatest in the developing brain of children and adolescents with T1DM. Aspects of diabetic dysglycaemia that appear to be most significant are hypoglycaemia, hyperglycaemia and diabetic ketoacidosis (DKA). Some early *in vitro* work suggest that glycaemic variability may also play a significant role in neural cell injury. Prospective observational data from the point of diagnosis to neuromaturation in the Royal Children's Hospital Diabetes Cohort Study revealed a rather lamentable 'rule of thirds'- one third of subjects developed a DSM IV threshold mental health disorder, one third did not complete secondary schooling and one third did not continue in adult care after transition. This was coincident with a 0.3 SD loss of full scale IQ and changes in regional brain volumes. More recent functional imaging studies have provided insight into some of the mechanistic aspects of dysglycaemia-induced brain injury. DKA at the point of diagnosis is associated with acute grey and white matter volume and spectroscopic changes that are associated with neurocognitive outcome in the medium term. Clamp studies combined with MRI have shown that hypo- and hyperglycaemia result in distinct regional changes in brain perfusion and metabolic activity. Potential synergies of chronic and additive dysglycaemic insults are difficult to quantitate largely due to an inability to fully record all aspects of glycaemic perturbation over a life course. In addition to this, pre-conditioning and programming may also play significant mediating roles. However, developmental age at the time of diabetes onset appears to have a critical influence upon outcome. A nascent understanding of mechanism of neural injury is providing some insights as to potential non-glycaemic interventions that might be used to protect the developing brain.

S1.3

Abstract unavailable.

S2.1

Abstract unavailable.

S2.2
Is Brown Adipose Tissue Relevant to Paediatrics?

Vicente Gilsanz

Children's Hospital Los Angeles, Los Angeles, California, USA

In this presentation, we will highlight areas of progress in pediatric brown adipose tissue (BAT) research over the past decade, including the general acceptance that this tissue is much more prevalent in children than adults and in infants than in children. Available longitudinal data in pediatric patients provide strong evidence in support of an inverse association between BAT activity and white adipose tissue (WAT) accumulation, most strikingly in the intra-abdominal depot. Emerging evidence also

suggests a possible link between BAT and musculoskeletal development. Adolescents and post-pubertal teenagers that depict BAT on positron emission tomography examinations have significantly greater muscle volume than those without identifiable BAT. Moreover, the volume of BAT is positively associated with the amount of bone and the cross-sectional size of the femur in children and adolescents. This relation between BAT and bone structure could, at least in part, be mediated by muscle. Infancy is another developmental stage associated with concurrent gains in skeletal muscle and large amounts of BAT, but low levels of physical activity. Although the lack of modalities to noninvasively measure BAT has limited our understanding of its relevance to human physiology, advances in magnetic resonance imaging techniques based on the cytological differences in lipid content and the degree of vascularization between brown and white adipose tissue allow for the quantification of BAT, even in healthy infants.
Funding: This work was supported by National Institutes of Health/NIDDK (R21DK090778).

S2.3
Lipodystrophies: New Approaches for Diagnostic Workup and Treatment

Corinne Vigouroux[a,b]

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Lipodystrophic syndromes are rare and heterogeneous diseases, characterized by a generalized or partial loss of adipose tissue (lipoatrophy) associated with metabolic complications usually associated with obesity: insulin-resistant diabetes, dyslipidemia, ovarian hyperandrogenism and non-alcoholic fatty liver disease.

Molecular genetic studies in different types of lipodystrophies showed that primary adipocyte alterations leading to impaired adipogenesis and/or defects of the metabolic functions of the adipocyte lipid droplet, were responsible for systemic metabolic alterations.

However, the broad spectrum of lipodystrophic clinical phenotypes, of genetic or acquired origin, and recent data have also pointed to important relationships between adipose tissue development, ageing, inflammation processes, DNA damage responses, and lipodystrophy and insulin resistance.

Non-specific therapeutic approaches aim to improve metabolic consequences of lipodystrophic syndromes. However, endocrine defects of lipodystrophic adipose tissue also participate to altered metabolic regulations, with leptin deficiency leading to increased appetite and ectopic storage of lipids in muscle and liver.

Leptin replacement therapy using s.c. injection of recombinant leptin (metreleptin) is the first specific therapy for lipodystrophies. Although it does not improve lipoatrophy itself, metreleptin was shown to significantly improve glucose and lipid alterations associated with lipodystrophies. Metreleptin was approved in 2014 by the FDA for generalized forms of lipodystrophies, and is available for the treatment of lipodystropic syndromes through compassionate programs in several European centers.

S3.1
Novel Genes Identified in Male and Female Sex Development

Kenneth McElreavey

Institut Pasteur, Paris, France

Next generation sequencing technologies are dramatically changing biomedical research and patient diagnosis. The reducing costs of sequencing as well as robust experimental and computational protocols mean that the technology is readily available to most research and diagnostic laboratories. However, the identification of disease-causing mutations in individuals with disorders of sex development (DSD) is challenging for several reasons. These conditions are very difficult to study using classical genetic approaches since many aspects of sex development are not well-conserved in evolution and familial cases of some forms of DSD are very rare. Excluding cases where the biochemical profile indicates a specific error in steroidogenesis, it is estimated that a specific molecular diagnosis is obtained in 20% of DSD cases and that only 50% of 46,XY children with DSD will receive a definitive clinical diagnosis.

We have now performed whole exome sequencing in >130 cases of DSD, including 13 familial cases, using the Illumina HiSeq2000 platform. In this talk I will summarise our main genetic findings and highlight some of the challenges and surprises that have resulted from this approach. In around 40% of cases a known or suspected pathogenic gene mutation was found. For the remaining 60% of cases several variants of uncertain significance (VUS) were identified. The challenge is to determine the pathogenicity of at least some of these rare VUS. This may only be possible through large-scale data-sharing initiatives such as the one currently being developed within the COST action DSDnet.

S3.2
Decision Making in DSD: Development of a Decision Support Tool

David Sandberg[a], *Nina Callens*[a], *Laura Siminoff*[b]

[a]University of Michigan, Ann Arbor, Michigan, USA; [b]Temple University, Philadelphia, Pennsylvania, USA

Background: Disorders/differences of sex development (DSD) differ from other rare conditions which are often accompanied by significant morbidity and mortality. With limited exceptions, DSD are not life-threatening and do not predict a given level of physical health or health-related quality of life across the lifespan. The birth of a child with DSD is anxiety-provoking. Stressors include weathering drawn-out diagnostic testing, difficulty absorbing complex medical information, and managing strains on family and other social relationships associated with potentially stigmatizing conditions. It is in this context, when usual social support systems are often perceived as inaccessible, that parents are called upon to make decisions having pervasive consequences for their child. **Objective:** This presentation describes the decision making

challenges health care providers and families face in DSD and the potential value of introducing a decision support tool that facilitates informed and balanced discussions. **Method:** A web-based decision-support tool for parents of newborns/young children with DSD, designed with input from scientists, clinical specialists, patients, parents and patient advocates. In the project's initial phase, clinician–parent discussions were audio-recorded without having presented the decision support tool. In the on-going phase, the tool is introduced and the clinical discussions continue to be recorded to assess whether the quality of the discussions change once parents have the opportunity to deliberate using the tool. Evaluation of the tool includes qualitative coding of the audio-recordings, quantitative questionnaires and a semi-structured interview. **Results:** Preliminary findings will be presented. **Conclusion:** As long as there is not strong evidence showing the superiority of one approach over another with regard to DSD decisions, there will be a strong need to develop strategies promoting informed and shared decision making in DSD. **Funding:** Patient-Centered Outcomes Research Institute (PCORI) Award #1360 and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (R01 HD068138; DSD-Translational Research Network).

S3.3
Genetic and Environmental Disruption of Testicular Function

Olle Soder

Karolinska Institutet, Stockholm, Sweden

Approximately 25 of 100 000 children are born with an atypical appearance of their genitalia as part of a more or less defined disorder of sex development (DSD). Due to improved medical knowledge and better classification, the aetiology and pathophysiology behind a growing number of these cases have been clarified, although a large number still remains obscure with respect to the underlying biology. In line with this, there are growing insights into the functional consequences for sex differentiation of chromosomal aberrations and defined genetic defects. However, many cases of DSD seem to be associated with environmental rather than genetic causes. Data to support this comes from recently observed trends of declines in human male fertility in parallel with reports on poorer semen quality in young adult males. Further, solid reports on recent increases of testis germ cell cancer also point to an environmental origin. Congenital abnormalities in boys such as cryptorchidism and hypospadias also appear to be increasing, at least in certain regions. Such geographical variations strengthen the possible association with environmental factors. Endocrine disrupting chemicals (EDCs) is the term used for an expanding number of exogenous chemicals with the ability to influence the endocrine system. EDCs have been firmly associated with observations made world-wide on malformations and dysfunctions of the reproductive system in different species of wild-life and there is emerging evidence of such associations also in humans. In experimental models EDCs have been found to disrupt gonadal maturation and function, with a particular vulnerability of the testis. Androgen production by Leydig cells is critical for normal male pre and postnatal testicular development and constitutes an important target of EDC actions. This presentation will give an overview of the concept of environmental disruption of testicular function with focus on the possible role of some defined EDCs. **Funding:** Swedish Paediatric Cancer Fund; Swedish Research Council.

S4.1
Management of Hyperthyroidism in Children

Scott Rivkees

University of Flroida, Gainesville, Flroida, USA

Background: The most prevalent cause of thyrotoxicosis in children is Graves' disease (GD), and remission occurs only in a modest proportion of patients. The treatment of GD involves the use of antithyroid medications (ATDs), radioactive iodine (RAI; (131I), or surgical thyroidectomy. **Objective and hypotheses:** This presentation will focus on the risks and benefits of the different treatment options for GD. **Method:** ATDs are the most common initial therapy for GD. When used, only methimazole should be used due to the risk of liver failure associated with propylthiouracil therapy in children. RAI is an acceptable form of therapy for older children. When used, the goal should be to ablate the thyroid gland. When surgery is performed, total thyroidectomy by an experienced surgeon is recommended. **Results:** Long-term data show that rates of spontaneous remission for GD with long-term ATD therapy range from 10 to 40%. With RAI or surgery, more than 95% of children are cured with initial therapy. **Conclusion:** Pediatric patients with GD who are not in remission following at least 1–2 years of methimazole therapy should be considered for treatment with RAI or thyroidectomy. Alternatively, if children are tolerating ATD therapy, ATDs may be used for extended periods. This approach may be especially useful for the child not considered to be a candidate for either surgery or RAI. Individuals on prolonged ATDs therapy (>2 years) should be re-evaluated annually and when transitioning to adulthood. **Funding:** This work is supported by the NIH (R01FD003707).

S4.2

Abstract unavailable.

S4.3

Abstract unavailable.

S5.1
Developmental Programming of Reproductive Function

Deborah Sloboda

McMaster University, Hamilton, Ontario, Canada

There is now considerable epidemiological and experimental evidence indicating that early life environmental signals, including nutrition, affect subsequent development. It is now quite clear that a relationship exists between the periconceptional, fetal and early infant phases of life and the subsequent development of chronic diseases including obesity and type 2 diabetes. This relationship, the 'developmental origins of health and disease' (DOHaD), suggests that the embryo/fetus/neonate makes adaptations in response to early life cues, resulting in adjustments in homeostatic systems that are maladaptive in postnatal life, leading to an increased risk of chronic disease and/or the inheritance of risk factors across generations. Reproductive maturation and function is similarly influenced by early life events. This should not be surprising, since the female primordial follicle pool is established early in life and is thus vulnerable to early life events. A multitude of 'modifying' cues inducing developmental adaptations have been identified that result in a decline in ovarian follicular reserve, changes in ovulation rates and altered age at onset of puberty. Both caloric restriction as well as caloric excess induces early life adaptations that produce long-term reproductive dysfunction that may have consequences for future reproductive fitness and may impact subsequent generations. Many pathways have been suggested to underpin these associations, where studies have investigated the maternal–fetal–placental relationship as well as events occurring in the early postnatal environment in modulating pubertal onset and ovarian function. But the underlying ovarian mechanisms regulating the relationship between the early life developmental environment and postnatal reproductive dysfunction remain unclear. Thus, it is clear that the perinatal environment provides a potential therapeutic target for intervention and prevention, and focusing on this developmental window of vulnerability may translate into improved interventional strategies for mediating long-term dysfunction. **Funding:** DMS is supported by the Canadian Research Chairs Program and by the Canadian Foundation for Innovation.

S5.2
Transgenerational Developmental Programming of Endocrine Disease

Susan Ozanne

University of Cambridge, Cambridge, UK

It has been recognized for over 20 years that there is an association between patterns of early growth and long-term risk of traditionally adult onset diseases such as type 2 diabetes. This has been observed both in human epidemiological studies and in animal models. This led to the concept of the developmental origins of health and disease that suggests that the environment to which an individual is exposed during critical periods of development, such as the *in utero* period, has a permanent impact on our long-term health.

One important early environmental factor known to have such programming effects is nutrition. Initial studies focussed on the detrimental effects of low birth weight and early under-nutrition. However in light of the growing epidemic of obesity, more and more focus is now being directed towards the detrimental effects of early over-nutrition. Fetal under-nutrition and fetal over-nutrition appear to have a very similar phenotypic consequence in terms of metabolic disease risk. However it is yet to be established if they mediate their effects through the same mechanistic pathways. In recent years considerable progress has been made in defining these mechanisms by which an event in early life can have a long-term phenotypic consequence. Three key programming mechanisms have emerged: i) permanent structural changes – the idea that if during a critical period of development an organ is exposed to a suboptimal level of a key hormone or nutrient required for its development this will permanent impact on organ structure and consequently function, ii) accelerated cellular ageing as a consequence of increased oxidative stress and iii) epigenetic programming of gene expression through changes in DNA methylation, histone modifications and/or miRNAs. Further understanding of these mechanisms may give us the potential to develop markers of disease risk and aid the design of rational intervention strategies.

S5.3
Intergenerational Programming of Metabolic Disease via the Paternal Lineage

Mary Elisabeth Patti

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Background: Common metabolic diseases, including diabetes and obesity, are the result of interactions between genes and environment. It is well-recognized that the maternal intrauterine environment is an important modifier of this risk. Thus, fetuses carried by women who are obese, diabetic or suffer from suboptimal nutrition are at increased risk of insulin resistance, obesity, type 2 diabetes (T2D), and cardiovascular disease as adults. Emerging data indicate that paternal environmental exposures also influence disease risk in offspring. **Objective and hypotheses:** The objective of our studies is to identify molecular mechanisms contributing to paternally-mediated intergenerational risk. To test our hypotheses that paternally-mediated intergenerational risk is mediated via epigenetic marks in male germ cells, we assessed DNA methylation in sperm using our mouse model of intergenerational nutritional risk. **Method:** Sperm were isolated from young male offspring exposed to maternal undernutrition in utero, and DNA methylation was assessed using MeDIP-sequencing. Selected differentially methylated regions were assessed by pyrosequencing. Functional analysis

was performed in tissues of second-generation embryos and adults. **Results:** *In utero* undernutrition results in perturbed DNA methylation in spermatozoa of adult males. This is associated with differential expression of genes neighboring these differentially methylated regions in F2 embryos. **Conclusion:** Both prior nutritional exposures *in utero* and current metabolic health of males can alter epigenetic marks in sperm, contributing to altered gene expression and disease risk in his offspring.

S6.1

Abstract unavailable.

S6.2

Abstract unavailable.

S6.3
From Obesity to Type 2 Diabetes

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With the ever escalating trajectory of childhood obesity, rates of prediabetes and type 2 diabetes (T2DM) are on the incline. Impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) constitute a state of prediabetes with high risk for the development of T2DM. Among U.S. adolescents 12–19 years of age, NHANES 2005–2006, the prevalence of IFG, IGT and prediabetes was 13.1, 3.4 and 16.1%, respectively. Overweight adolescents had a 2.6-fold higher rate than those with normal weight.

Glucose homeostasis is maintained by a delicate balance between insulin sensitivity and insulin secretion and is best described by a hyperbolic function called the disposition index (DI). This relationship which is an expression of β-cell function relative to insulin sensitivity is a constant for a given glucose tolerance in any one individual. When insulin sensitivity declines, insulin secretion must increase to maintain glucose tolerance. Overweight and obesity are major contributors to the development of insulin resistance. In the presence of robust pancreatic β-cell compensatory insulin secretion, glucose homeostasis remains normal. When β-cells are no longer able to secrete sufficient insulin to overcome insulin resistance, prediabetes ensues progressing to T2D.

Cross-sectional and longitudinal studies in youth along the spectrum of dysglycemia from obese-NGT, to obese-IFG/IGT, to obese-T2DM, show that it is β-cell failure that results in prediabetes and T2DM. However even prior to reaching the universally accepted glycemic cut-points for the diagnosis of prediabetes, youth demonstrate declining β-cell function relative to insulin sensitivity along the continuum of what is considered to be normal fasting and normal 2-h glucose concentrations during an OGTT. Not only insulin secretion is impaired in prediabetes and T2DM but also there is impairment in incretin effect and glucagon secretion. Lastly, data re progression over time from NGT to IGT and from IGT to T2DM are highly variable, 9–24 and 0–20%, respectively.

S7.1
Genetics of Congenital Hypogonadotropic Hypogonadism

Johanna Tommiska

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Congenital hypogonadotropic hypogonadism (CHH) is a rare disorder characterized by incomplete or absent puberty caused by the lack or deficient number of hypothalamic GnRH neurons, disturbed secretion or action of GnRH, or both. The association of CHH and a defective sense of smell (anosmia or hyposmia) found in approximately half of the CHH patients is termed Kallmann syndrome (KS). CHH is clinically and genetically heterogeneous, and >25 different causal genes have been identified to date. Genetic testing for CHH is useful for diagnosis, prognosis, and genetic counselling. In the majority of cases, however, the molecular genetic cause remains unresolved, implying there are still new genes to be found. Various patterns of inheritance have been observed in association with this condition, including X-linked, autosomal dominant, and autosomal recessive, as well as di- and oligogenic inheritance. Recently, CHH has been found to overlap both phenotypically and genetically with several other syndromes, which underlines the need for careful clinical examination and the importance of family background analysis before genetic testing. Next-generation sequencing techniques allow the simultaneous investigation of several genes, but identification of the real causal mutations among the variants detected poses another challenge, especially when the patterns of inheritance vary. In addition, many mutations display variable penetrance and variable phenotypic expressivity, and defining the contribution of each mutation involved in oligogenic inheritance is difficult. The genetic data must thus be interpreted with caution, and the real clinical value of the findings carefully evaluated before reported to the patient. **Funding:** This work was supported by the Academy of Finland (grant number 138124) and Jalmari and Rauha Ahokas Foundation.

S7.2

Early Therapeutic Approach to the Male Patient with HH

Claire Bouvattier

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In male fetuses, during the first 4–6 months of life, the 'mini-puberty' represents a period of intense hormonal activity of the hypothalamic–pituitary axis, reflected physically by an increase in testicular volume due to seminiferous tubule elongation and by an increase in penis length. During this period, pituitary LH and FSH levels rise, leading to an increase in circulating levels of testosterone, inhibin B and AMH. Concomitantly, Sertoli cells proliferate and a degree of germ cell development occurs. Congenital hypogonadotropic hypogonadism (CHH) could be suspected in a male neonate with cryptorchidism and micropenis, and easily confirmed by hormone assays before the age of 6 months. The best hormonal replacement in CHH newborns remains still unclear. Testosterone treatment has been traditionally successfully used to treat micropenis, and surgery is sometimes needed for cryptorchidism. The first patient with CHH and micropenis, treated with recombinant human subcutaneous LH and FSH during the first year of life, was reported 10 years ago, with an increased penile length and testicular volume. As the aim of the treatment was to re-establish the physiological postnatal gonadotropin peak, neonates with CHH were treated by our group, for 6 months, with recombinant human LH and FSH, delivered subcutaneously via a pump. Penile length and testicular volume increased, and the treatment was well tolerated. Spontaneous testicular descent occurred in a small number of patients during the treatment. This could represent a further benefit of neonatal treatment with gonadotropins, for children with CHH, as cryptorchidism is a factor of poor prognosis for adult fertility, as well as a risk factor for testicular malignancy.

S7.3

Abstract unavailable.

S8.1

Abstract unavailable.

S8.2

Abstract unavailable.

S8.3

Abstract unavailable.

S9.1

Abstract unavailable.

S9.2

Abstract unavailable.

S9.3

Abstract unavailable.

S10.1

Molecular Mechanisms of Growth Plate Adaptation During Undernutrition

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It is known that almost 180 million children in the world have stunted growth. Most of these children live in eastern and central Africa and in South-central Asia. Among multiple factors causing stunted growth in the developing world, malnutrition is the most important one. On the other hand, reduced caloric intake is also a cause of poor statural growth in developed countries.

Mammals, including humans, exposed to malnutrition experience poor bone growth through a number of adaptive mechanisms affecting endocrine factors as well as paracrine factors in the growth plate. For instance, malnutrition-related deficiencies of endocrine factors such as IGF1, insulin, and leptin lead to impaired statural growth. It has also been shown that microRNAs and enzymes like Sirtuin1 may be implicated in growth adaptation during malnutrition by regulating the activity of systemic and paracrine growth factors. Lastly, recent evidence indicates that the changes in expression of fibroblast growth factor 21 (FGF21) associated with caloric reduction can adversely affect growth plate chondrogenesis and bone growth both systemically and locally within the growth plate. Increased FGF21 action during chronic undernutrition causes GH resistance/IGF1 deficiency and, in turn, reduced growth plate function and bone growth.

S10.2

Molecular Response of the Growth Plate to Inflammatory Cytokines

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Background: Children with inflammatory diseases usually display abnormal growth patterns as well as delayed puberty. This is a result of several factors related to the disease itself, such as malnutrition, hypercortisolism, and elevated levels of pro-inflammatory cytokines. These factors in combination with glucocorticoid treatment contribute to growth retardation during chronic inflammation by systemically affecting the major regulator of growth, the GH/IGF1 axis. In conditions of chronic inflammation, pro-inflammatory cytokines are up-regulated and released into circulation. The most abundant of these, tumor necrosis factor-α (TNF-α), interleukin-1β (IL1β) and interleukin-6 (IL6). Recent studies show evidence of a direct effect of these factors at the growth plate level. **Objective and hypotheses:** To study the molecular response of the growth plate to inflammatory cytokines. **Method:** Cytokine actions in growth plate cartilage was studied in ex vivo cultures of fetal rat metatarsal bones. Molecular mechanisms were studied focusing on chondrocyte proliferation, differentiation and cell death. Furthermore, a retrospective clinical study was performed to investigate the potential for anti-cytokine treatment to rescue bone growth in children and adolescents with chronic juvenile rheumatoid arthritis. **Results:** TNF-α, IL1β, and IL6 were all found to directly act on growth plate cartilage to induce apoptosis and thereby suppress bone growth. Moreover, TNF-α and IL1β were found to act in synergy to suppress chondrocyte proliferation and differentiation as well as increase apoptosis. Clinical and experimental studies showed that growth retardation can partly be rescued when these cytokines are blocked. **Conclusion:** Therapy modulating the local actions of pro-inflammatory cytokines may be effective for preventing growth failure in patients with chronic inflammatory disorders. The current knowledge of inflammatory cytokines and their role in regulating bone growth will be reviewed in this presentation.

S10.3

Bone Health in Chronic Disease

Jarod S C Wong

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Abnormal bone development is commonly seen in children with chronic disease. However, fragility fractures in the young individual may be less common compared to older adults, which may be due to under recognition. The underlying chronic condition and medication can impact on bone turnover, modelling, bone mineral homeostasis, growth, pubertal development and muscle mass. The diagnosis and management of osteoporosis in children and adolescents with chronic disease remains contentious. In growing children, interpretation of densitometric results need to take into account the differences in stature, growth and pubertal development. There is little evidence on the predictive value of DXA BMD in children with chronic disease even when size corrected. pQCT BMD is not size dependent but the predictive value for fragility fractures in children with chronic disease is still unclear. The ISCD recommends that people up to the age of 19 years should not be diagnosed with osteoporosis solely based on low BMD by DXA and has placed a greater focus on the presence of pathological fractures, especially vertebral, such that the diagnosis of vertebral fractures alone is indicative of osteoporosis in the younger individual regardless of DXA parameters. A stronger emphasis on vertebral morphometry, is therefore, becoming more routine in the assessment of osteoporosis. With technological advances in imaging, it is also possible that identification of osteoporosis may rely on modalities that can provide a 'virtual bone biopsy' such as high resolution MRI or CT. Optimising growth, calcium vitamin D and weight bearing exercises where possible are important measures. Ensuring normal pubertal development with timely induction of puberty in these children is often ignored. Bisphosphonates therapy should only be reserved for those children with fragility fractures, although there remains numerous unanswered questions including duration of treatment and also treatment of asymptomatic/mild vertebral compression fractures.

New Perspectives

NP1.1

Abstract unavailable.

NP1.2

Optogenetic Control of Neuroendocrine Hormone Secretion

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Optogenetics represents a powerful new approach to modulate the activity of excitable cells in the body. Based upon the ability of specific wavelengths of light to activate newly discovered and engineered opsin-based receptors, optogenetics can be used to control the activity of cells with very high temporal resolution. Opsin-based receptors, most often channelrhodopsin (ChR), need to be expressed selectively in the cell type under investigation. This is achieved by generating genetically-modified rodent models in which ChR is expressed only in a specific cell phenotype or by using viruses to deliver Cre-dependent ChRs to genetically manipulated Cre-driver rodent lines.

In the field of experimental endocrinology, optogenetics has been extremely useful for investigating the neuroendocrine control of pituitary hormone secretion. For example, mice and rats with ChR expressed only in the GnRH neurons have been used to examine how these neurons generate pulsatile patterns of LH. By inserting optic fibres delivering 470 nm blue light into the brain regions of GnRH-ChR mice that contain the GnRH neuron cell bodies or their distal processes, it has been possible to remotely control the electrical activity of groups of GnRH neurons and determine the patterns of firing required to generate a pulse of gonadotropin (Campos & Herbison, 2014). By expressing ChR in other neuronal phenotypes it has also been possible to explore which cells in the brain innervate the GnRH neurons and are involved in generating their episodic activity. To date the most promising up-stream candidate has been the kisspeptin neurons of the hypothalamic arcuate nucleus.

Optogenetics provides a new research tool enabling the remote, high-fidelity, control of specific neuroendocrine cell populations *in vivo* and, thereby, an unparalleled means through which investigators can probe the cell networks underlying pituitary hormone secretion.

Campos P & Herbison AE. Optogenetic activation of GnRH neurons reveals minimal requirements for pulsatile luteinizing hormone secretion. *PNAS* 2014 111 18387–18392.

NP2.1

Engineering Cartilage

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Background: Articular cartilage is closely related to epiphyseal growth plate cartilage with one major discriminant: while epiphyseal growth plate cartilage is transformed into bone by endochondral ossification, epiphyseal growth plate cartilage remains stable in a healthy situation. In contrast in diseases like osteoarthritis articular cartilage acquires characteristics of epiphyseal growth plate cartilage. The underlying molecular pathophysiology is largely unknown. **Objective and hypotheses:** It is our aim to elucidate the molecular mechanisms responsible for the transformation of an healthy articular chondrocyte into a diseased epiphyseal growth plate like chondrocyte. Understanding these mechanisms may lead to highly needed biomarkers to assess joint homeostasis as well as protocols for the derivation of articular chondrocytes from mesenchymal stromal cells (MSCs) to engineer articular cartilage for therapeutic purposes. **Method:** In our studies we combine state of the art molecular and cellular biological techniques with advanced chemistry to develop methods for assessing joint homeostasis and injectable MSC based strategies to repair the damaged articular cartilage surface in osteoarthritis. **Results:** We have identified WNT and BMP signalling as driving forces in transformation of a healthy articular chondrocyte into a diseased chondrocyte with potential to serve as biomarkers. In addition we have developed strategies to derive stable articular cartilage like chondrocytes from MSCs *in vitro*. **Conclusion:** Increased understanding of the molecular pathways that differentiate the two types of hyaline cartilage, i.e. articular cartilage versus growth plate cartilage has provided new cues that can help in assessing osteoarthritis much earlier in the disease process which can be exploited to develop highly needed causal treatment.

NP2.2

Astrocytes and Neuroendocrine Control

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Glial cells are the most abundant cell type in the CNS. Although they were originally thought to only play a supportive role for neurons, it is now clear that glial cells are involved in all aspects of brain function. Understanding how glia, and in

particular astrocytes, tanycytes and microglia, participate in the neuroendocrine control of metabolic homeostasis has come to the forefront in recent years. This is largely due to the observation that high fat diet-induced hypothalamic inflammation and gliosis have been implicated in the development of obesity associated secondary complications such as central insulin and leptin resistance. However, in addition to participating in pathophysiological processes, glial cells are also involved in the physiological control of metabolic homeostasis. Glia are the first line of defense against any attack on neurons, including nutritional assaults. Tanycytes and astrocytes transport circulating nutrients and metabolic factors fundamental for neuronal viability and activity into and within the hypothalamus. Astrocytes also participate in the rewiring of hypothalamic metabolic circuits. Astroglia express receptors for diverse metabolic signals, including various forms of the leptin receptor. Not only does leptin induce cytokine production by astrocytes, but it stimulates morphological changes in these glial cells and this is associated with modifications in synaptic inputs to neurons involved in metabolic control. The capacity of astrocytes to transport glucose and glutamate is modified by both leptin and ghrelin, indicating an additional mechanism by which these hormones can modify neuronal metabolism and synaptic transmission. Indeed, knock-out of the leptin receptor specifically in astrocytes modifies an individual's metabolic response to this hormone. The aim of this talk will be to present our current understanding of how astrocytes participate in both the physiological and pathophysiological control of metabolic homeostasis. **Funding:** This work was funded by grants from Fondos de Investigación Sanitaria (PI1302195), Ministerio de Ciencia e Innovación (BFU2011–27492), Centro de Investigación Biomédica en Red Fisiopatología de Obesidad y Nutrición (CIBEROBN), Instituto de Salud Carlos III, and Fundación de Endocrinología y Nutrición.

New Technologies

NT1

New Technologies in Imaging

Chris Clark

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I will review the latest developments in imaging of the brain using magnetic resonance. Over the last twenty years imaging of the diffusion of water molecules in the tissue has emerged as the method of choice for measuring the structure of brain tissue. The development of so called diffusion tensor imaging had allowed measurement of anisotropy which reflects how aligned or coherent is the underlying structure of myelinated axons in white matter. For example we have shown in children with growth hormone deficiency that anisotropy is reduced. Despite the success of diffusion tensor imaging its limitations have long been recognised, namely that it lacks specificity. For example changes in anisotropy may be brought about by changes in axonal density and orientation. A new class of diffusion models have emerged under the name of 'microstructure imaging' which allow the inference of axonal density and diameter. A more recent advance is to couple this with magnetisation transfer imaging that is sensitive to myelin content, thereby allowing calculation of g ratio maps which represents the ratio of the axon to myelin diameter. I will describe the emergence of these new methods and the prospects for deploying them in patients with pathologies affecting the endocrine system in the brain.

NT2

Next Generation Sequencing: Implementing the 100,000 genome project for treatment of NHS patients

Abstract unavailable.

Prize Winners

HA1

Mutations in IGSF10 cause Self-limited Delayed Puberty, via Effects on GnRH Neuronal Migration

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Background: Timing of puberty is associated with height, cardiovascular health and cancer risk, with a significant public health impact. Previous studies estimate that 60–80% of variation in the timing of pubertal onset is genetically determined. Self-limited delayed puberty (DP) often segregates in an autosomal dominant pattern, but the underlying genetic background is unknown. **Methods:** We performed whole exome sequencing in 52 members of 7 families from our patient cohort with self-limited DP, with follow-up targeted re-sequencing of candidate genes in a further 42 families. For one candidate gene we defined tissue expression in human and mouse embryos by *in situ* hybridization and immunohistochemistry. The effects of gene knockdown were investigated via *in vitro* neuronal migration assays, and in vivo using a transgenic zebrafish model with fluorescently labelled GnRH neurons. **Results:** We identified four rare heterozygous mutations in IGSF10 in 29 members of ten unrelated families. All four variants were in evolutionarily conserved positions and were predicted by in silico analysis to have a deleterious effect on protein function. Statistical tests showed a significant difference in the prevalence of these mutations within DP cases compared to a general population ($P = 4.46 \times 10^{-3}$), and a significant association between these mutations and the delayed puberty trait within our cohort ($P = 3.47 \times 10^{-4}$). IGSF10 mRNA shows strong expression in the nasal mesenchyme in mouse and human embryos, during the time-period when GnRH neurons migrate from their nasal origin towards the hypothalamus. IGSF10 knockdown caused reduced migration of immature GnRH neurons in the *in vitro* analysis, and perturbed migration and extension of GnRH neurons in the transgenic zebrafish model. **Conclusions:** We present our novel finding that IGSF10 mutations contribute to the phenotype of self-limited delayed puberty in humans, at least in part through the mechanism of impaired migration of GnRH neurons during embryonic development.

HA2

A New Syndrome Associated with Mutations in the Gene for Pregnancy-Associated Plasma Protein A2 (PAPP-A2) Causing Proportionate Short Stature, High Circulating IGF-I, IGFBP-3, and ALS, Mild Microcephaly, thin Long Bones and Decreased Bone Mineral Density in two Unrelated Families

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Background: PAPP-A2 is a metalloproteinase that specifically cleaves IGFBPs 3 and 5. *Papp-a2* knock-out (KO) mice show a reduction in body size and skeletal abnormalities. **Objective and hypotheses:** Our objective is to report two affected families from Spain and USA. The Spanish family presents a homozygous frameshift mutation in exon 3 of the *PAPP-A2* gene (c.1927_1928insAT, p.D643fs25X) resulting in a premature stop codon, with 2 of 4 siblings affected. The American family has a homozygous missense variant in exon 8 (c.3098C > T), with three of five siblings affected. We hypothesized that the lack of IGFBP-3 and -5 proteolysis might increase in their circulating

levels and limit the release and access of IGF1 to its receptors. **Methods:** IGF-I, IGF-II, ALS, IGFBPs 1-6, fIGF-I, insulin, PAPP-A and PAPP-A2 levels were measured in serum by RIA/ELISA. Full exome, *PAPP-A2* sequencing, *in vitro* expression of PAPP-A2 wt and mutants and functional PAPP-A2 protease activity and ternay complex (TC) formation by cross-linking and chromatography were performed. A skeletal survey was done, as well as bone mineral density (DXA), trabecular structure (TBS) of the bones and 3D micro-CT in a tooth of one proband. **Results:** The 5 affected children exhibit a constant postnatal growth failure and high circulating IGF-I, IGF-II, IGFBP-3 and ALS levels. The Spanish children present high spontaneous GH secretion/8hr. PAPP-A2 was undetectable in the Spanish patients and very low in the American children. The TCs are very high. The Spanish mutation shows lack of proteolytic activity, while the American mutation results in expression of PAPP-A2, but at a much lower level than wt and the expressed protein is cleaved, probably by autoproteolysis. BMD in the lumbar area was decreased. TBS was into the normal range. The PAPP-A2 null patient showed decreased enamel and dentin density. **Conclusions:** i) A new syndrome involving *PAPP-A2* mutations is described; ii) PAPP-A2 levels should be measured in patients with short stature and elevated IGF-I; iii) Lack of PAPP-A2 activity results in reduced fIGF-I; iv) *PAPP-A2* is involved in short stature. **Funding:** This work was supported by Fondos de Investigación Sanitaria (FIS) PI13/02195 and CIBER-OBN. Instituto de Salud Carlos III. Madrid, Spain.

Working Groups

WG1.1

Short Stature: Blame the Chondrocyte

Jeffrey Baron

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Background: In the past, the GH–IGF1 axis was thought to be the central system regulating childhood growth and therefore responsible for short stature and tall stature. **Objective and hypotheses:** The objective of this talk is to conceptualize disorders of linear growth in terms of the underlying growth plate biology. **Method:** Powerful, new, unbiased tools have recently been developed to investigate the genetic control of childhood growth. These approaches include genome-wide association studies and exome sequencing. Concomitantly, cell culture, organ culture, and animal studies have helped elucidate the mechanisms regulating growth plate chondrogenesis. **Results:** Recent findings have revealed that the GH–IGF1 axis is just one of many regulatory systems that control chondrogenesis in the growth plate, the biological process that drives height gain. Consequently, normal growth in children depends not only on GH and IGF1 but on multiple hormones, paracrine factors, extracellular matrix molecules, and intracellular proteins that regulate growth plate chondrocytes. Mutations in genes encoding many of these local proteins cause short stature or tall stature. Similarly, genome-wide association studies have revealed that the normal variation in height appears to be due largely to genes outside the GH–IGF1 axis that affect growth at the growth plate through a wide variety of mechanisms. **Conclusion:** Growth plate chondrogenesis is the final common pathway through which many systems regulate childhood linear growth. Consequently, the primary genetic defects responsible for short and tall stature lie scattered throughout these many regulatory systems at multiple different levels.

WG1.2

The Role of NFkB in Growth Plate Chondrogenesis

Francesco De Luca

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Nuclear Factor kappa B (NF-κB) is a group of seven transcription factors, including p65 (RelA), c-Rel, RelB, p50/p105 (NF-κB1), and p52/p100 (NF-κB2). Upon activation by a wide variety of stimuli, NF-κB translocates to the nucleus, where it modulates the expression of target genes involved in cell growth, survival, and death.

Previous evidence indicates that NF-κB regulates bone growth and development. Mice deficient in both the NF-κB subunits p50 and p52 have retarded growth and shortened long bones. In addition, we have previously shown that the NF-κB subunit p65 is expressed in the growth plate and facilitates longitudinal bone growth by inducing chondrocyte proliferation and differentiation and by preventing apoptosis. Furthermore, we have demonstrated in rodents that NF-κB expressed in growth plate chondrocytes mediates the promoting effects of GH and IGF-1 on longitudinal bone growth and growth plate chondrogenesis. Lastly, functional studies carried out in two children with growth failure and GH insensitivity, and affected by two different mutations impairing NF-κB activation, indicate that NF-κB also mediates the growth-promoting effects of GH in humans.

WG1.3

Genetics of Juvenile Osteoporosis

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Genetic factors play an important role in osteoporosis. Several monogenic forms of osteoporosis have been recognized. The most common is osteogenesis imperfecta (OI) in which heterozygous mutations in the genes encoding type 1 collagen are responsible for ~90% of the cases. Several rare autosomal recessive forms of OI have also been described. In these the defects lie in proteins involved in posttranslational modification of type 1 collagen. Recent studies have also identified several forms not related to type 1 collagen. The WNT-signalling pathway is of key importance for skeletal health, activation leading to increased and inhibition leading to decreased bone mass. Mutations in *LRP5*, encoding a co-receptor for the pathway, cause the autosomal recessive osteoporosis–pseudoglioma syndrome or early-onset osteoporosis. Recently heterozygous loss-of function mutations in the *WNT1* gene were shown to lead to early-onset osteoporosis while homozygous *WNT1* mutations resulted in severe infancy-onset osteoporosis. The first X-chromosomal form of osteoporosis, resulting from mutations in the gene encoding plastin 3 (*PLS3*), was described in 2013. PLS3-osteoporosis has its onset in childhood and results in recurrent peripheral fractures, low BMD, vertebral compression fractures, and significant height loss in adulthood. Males are in more severely affected than females. PLS3 may be linked to osteocyte dendrite function and skeletal mechanosensing. Future studies are needed to elucidate the role of *WNT1* and *PLS3* in early-onset osteoporosis and to define optimal therapy for affected individuals.

WG1.4

Bone Tissue Characteristics in Pediatric Bone Disease

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Histomorphometric evaluation of transiliac bone samples represents a standardized tool for studying bone metabolism, yielding information on bone both static and dynamic parameters on bone formation and static resorption parameters. Beyond these routine evaluations, the identical bone biopsy sample can be further used to assess submicroscopic tissue characteristics of the bone matrix. At the material level, bone matrix can be considered as a mineral/organic matrix composite where mineral particles consisting of stiff carbonated hydroxyapatite platelets (2–4 nm in thickness) are embedded within long elastic fibrils of type 1 collagen. One important determinant of bone material quality is the bone mineralization density distribution (BMDD) that can be measured in the bone biopsy block, using quantitative Back-scattered Electron Imaging (qBEI). BMDD provides information on the mean calcium content within the mineralized bone matrix as well as the heterogeneity of the calcium distribution, reflecting bone turnover, mineralization kinetics and tissue age. The same biopsy block can further be used to characterize properties of the organic matrix by Raman microspectroscopy with a spatial resolution of $\sim$1 μm. In combination with fluorescence labeling, this offers the capability of characterizing properties of the organic matrix in addition to the mineral, both as a function of tissue age. The BMDD and matrix parameters assessed in children and adolescents are remarkably constant and normative data have been established that can now be used as references in pediatric osteology. Such data may be complemented by even higher resolution techniques, such as small-angle X-ray scattering that provide information on mineral particle size. Together with bone histomorphometry, multi-scale characterization of the bone tissue contributes to differential diagnosis in unclear bone fragility, in genetic diseases, including osteogenesis imperfecta, pycnodysostosis or X-linked hypophosphatemia or in metabolic disorders such as chronic kidney disease. These analyses also support the understanding of the underlying pathophysiological mechanisms and the effects of treatment.

WG1.5
Fracture Prevention in Cystic Fibrosis

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The pathogenesis of altered bone metabolism leading to bone mass loss and fractures in patients with cystic fibrosis (CF) is complex, and can involve malnutrition, malabsorption, lack of physical activity, vitamin D and K insufficiency, systemic inflammation, respiratory failure, liver disease, hypogonadism, and treatment with glucocorticosteroids. Many studies reported osteopenia, osteoporosis and fractures in adults with CF, with bone loss starting at an earlier age than in healthy subjects. The most common fracture sites are ribs and vertebrae (especially thoracic), with reported fracture rates as much as tenfold (ribs) and 100-fold (vertebrae) higher than in the general population. Less data are available for children, adolescents and young patients. Regular evaluation of bone mineral density (BMD) is now recommended in both adult and young CF patients to minimize the risk of fractures, with their consequent reduced mobility and increased risk of pulmonary infections. Prevention, early recognition, and adequate treatment of bone metabolic derangements are now possible and must be pursued. Nutritional aspects, vitamin D status, and physical activity are the key components of prevention. Regarding treatment, both oral and i.v. bisphosphonates (BPs) have been successfully used in adults with fragility fractures or significant BMD reduction, in particular patients starting long-term treatment with systemic glucocorticosteroids or waiting for lung transplantation. BPs have been rarely used in children and adolescents with CF, and essentially only in the presence of fragility fractures (mainly vertebral fractures), as suggested by the European Cystic Fibrosis Society. A recent multicenter randomized, placebo-controlled trial on 171 patients aged 5–30 years demonstrated the efficacy and safety of oral alendronate in improving BMD.

WG2.1
New Technologies in Treating Patients with Type 2 Diabetes

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Background: Technology applied to type 2 diabetes (T2D) is an area of investigation with important clinical applications. **Objective and hypotheses:** There are three issues which should be considered: is continuous subcutaneous insulin infusions (CSII) effective for treatment of T2D? What is the level of satisfaction and quality of life in T2D patients using CSII? Are CSII and glucose monitoring in T2D relevant from an economic perspective? **Method:** We conducted a comprehensive literature search on this topic. **Results:** Larger longitudinal trials showed a durable efficacy of CSII on glucose control accompanied by moderate weight gain. Diabetes satisfaction scores improved over time with both CSII and MDI treatments. A insurer cost-of-care study performed among T2D patients analyzed diabetes treatment costs from T2D patients on MDI or CSII therapy found a cost-saving reduction in insulin dose. To improve adherence to CSII therapy, it is recommended the use of a behavioural contract providing specific metabolic goals to patients; SMBG frequency and commitment by the patient to go to the diabetes centre for follow-up visits and fulfill a detailed list of responsibilities. **Conclusion:** Diabetes technology in T2D is an example of personalized therapy, where evaluation and use should be both appropriate and targeted.

Without a structured approach the new technologies are often started and maintained improperly with poor cost-effective results.

WG2.2
The Pros and Cons of Using Sulfonylurea before Genetic Testing in Neonatal Diabetes Mellitus

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Background: Very early onset diabetes mellitus (neonatal diabetes mellitus (NDM)) seems to be unrelated to autoimmunity in most instances. A number of conditions are associated with NDM, some of which have been elucidated at the molecular level. Among these, the recently elucidated mutations in the *KCNJ11* and *ABCC8* genes, encoding the Kir6.2 and SUR1 subunit of the pancreatic K_{ATP} channel involved in regulation of insulin secretion, account for one third to half of the PNDM cases.[1,2,3] Molecular analysis of chromosome 6 anomalies (found in more than 60% in 'transient' NDM), and the *KCNJ11* and *ABCC8* genes encoding Kir6.2 and SUR1 (found in around 50% of permanent NDM), provides a tool to characterized NDM in the neonatal period. **Objective and hypotheses:** Proof of concept of the action leading to endogenous insulin secretion by glibenclamide has been fully established when the potassium channel display an activating mutation which impairs membrane depolarization, insulin secretion and is responsible for neonatal diabetes mellitus. It is also important to understand that this glibenclamide effect leading to insulin secretion is also present when the potassium channel is normal and the cause of neonatal diabetes mellitus unrelated to potassium channel mutation. The use of glibenclamide is therefore possible to treat neonatal diabetes mellitus, providing that there are insulin secreting cell in the endocrine pancreas.[4] **Results:** Sulfonylurea therapy appears to be safe and often successful in neonatal diabetes patients before genetic testing results are available;[4] however, more cases must be studied. Given the potential beneficial effect on neurodevelopmental outcome, glycemic control, and the current barriers to expeditious acquisition of genetic testing, an empiric inpatient trial of sulfonylurea can be implemented. However, obtaining a genetic diagnosis remains imperative. **Conclusion:** The pros and cons of using sulfonylurea before genetic testing will be discussed.

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WG2.3
Are Genetic Tests Necessary before Starting the Treatment of a Patient with Neonatal Diabetes? CON

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Neonatal diabetes is defined by hyperglycemia either isolated or as a part of a syndrome, diagnosed within the first 6 months of life. This is a monogenic form of diabetes resulting from mutations in a number of different genes encoding proteins that play a key role in the normal function of the pancreatic β-cell. To date, over 20 genes have been identified in about 60–75% of cases. A significant breakthrough was the recognition that a large portion of patients can be treated with sulfonylurea instead of insulin. Those include the most common cases of sporadic neonatal diabetes caused by ATP-sensitive potassium channel mutations and sometimes other non-syndromic causes. This is an example of personalized genetic medicine where genetics is associated with long term prognosis (transient or permanent disease) and influences the choice of treatment (s.c. or oral). Nevertheless, genetic analysis is very costly and not available in all clinics. Furthermore, the laboratory testing may take time thus delaying the appropriate treatment for a large number of patients. Therefore, practical approach to treatment selection may be based initially on clinical judgment. That means, testing the clinical respond to p.o sulfonylurea shortly after diagnosis, even before genetic testing results are available. No damage will be done to those whose respond to p.o sulfonylurea will be tested, due to the safe profile of sulfonylurea (sulfonylurea is an 'old' medication, not expensive, well tolerated with few adverse events) and the continued treatment with insulin during the transition attempt. Early treatment with sulfonylurea has the advantages of improving metabolic control and reducing diabetes complications, reducing risk of hypoglycemia related to insulin treatment (especially important at this age), improving neurodevelopmental impairment that accompanies many cases of neonatal diabetes, improving quality of life and easy for use at this age, shortening hospitalization duration and reducing expenses. In summary, it seems that the benefits of early testing the response to sulfonylurea before the genetic testing outweighs the risks.

WG2.4
Blood Glucose Monitoring: Which is Better: Continuous Real-Time or Episodic Real-Time on Demand? PRO

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Background: The use of continuous glucose monitoring has been proven beneficial in improving glucose control. Nevertheless, its use by the patients is still limited with a high discontinuation rate, especially in the pediatric population. Real-life data showed a

30% adherence to treatment after 1 year of use. **Objective and hypotheses:** The most likely explanation for the sensor being underutilized is the significant burden related to its use fraught with tension and anxiety. The sensor necessitate continual attention and decision making by patients and caregivers, while some have difficulty responding to the large influx of data. Furthermore, it acts as a constant reminder of them being diabetic, reporting blood glucose levels at all times. The recording of high and low blood glucose may lead to confrontation between parents and their children. Others are frustrated by false alarms caused by sensor inaccuracy and although expected, evidence shows no reduction in fear of hypoglycemia with its use. Use of episodic real-time glucose sensor data on demand may improve patient adherence to sensor use, allowing patients access to data needed for appropriate decision making regarding insulin dosing. **Method:** Several studies showed that continuous glucose monitoring had no advantage over frequent blood glucose measurements. Indeed, a recent data from the exchange registry showed that the target HbA1c can be achieved with seven to nine measurements of blood glucose. Others studies showed that for each additional glucose testing the HbA1c is reduced by 0.2%. However, most patients avoid multiple finger sticks due to the accompanied inconvenience. A sensor that only shows glucose levels and trends on demand, when the patient needs the data and is willing to react, will decrease exhaustion related to sensor use, decrease the burden of monitoring diabetes and improve patient compliance and glycemic control. Episodic real-time data on demand would appear to have all the advantages of continuous monitoring while at the same time being much more convenient. Additional advantages of this sensor are the ease of use without the need for calibration, long use duration and no alarms. **Conclusion:** Compliance in management of a chronic disease depends largely on the ease of application of treatment measures. As long as the patient is the one that needs to react to the real-time sensor data, some patients will prefer other means of measurement. Glucose data on demand would appear to offer all the advantages of sensor monitoring without the burden and hassle.

WG2.5
Blood Glucose Monitoring: Which is Better: Continuous Real-Time or Episodic Real-Time on Demand? CON

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Background: Self-monitoring of blood glucose is an essential tool in the optimal management of childhood and adolescent diabetes. In the last 15 years, an extraordinary development of reliable devices for real-time continuous glucose monitoring (CGM) has taken place. Meanwhile, several trials in adults and children showed that CGM can be associated with improved glycaemic control, significant reduction of hypoglycaemia and better quality of life, particularly in those patients with a high adherence to continuous use. **Objective and hypotheses:** Hypoglycaemia fear is one of the leading obstacles to better glycaemic control. Fluctuating blood glucose levels have been shown to be associated with behavioural changes in children with diabetes as frequently reported by their parents. The continuous use of CGM devices, particularly in terms of sensor-augmented pump treatment, can help young patients with diabetes to overcome these challenges, achieve near-glycaemic control and improve their quality of life. **Method:** The advantages and limitations of real-time continuous glucose monitoring will be discussed. **Results:** While CGM is beneficial in both patients using multiple daily injections and insulin pump users, the latter combination is more effective. Moreover, new generation of pumps are combining a continuous glucose sensor with a mechanism of automatic shut-off in the presence of low glucose values (low glucose suspend (LGS)) or when a hypoglycaemia is predicted within 30 min (predictive low glucose management (PLGM)). The efficacy of the automatic suspension of insulin delivery was evaluated under challenging conditions both in adults (automation to simulate pancreatic insulin response (ASPIRE)) and in children (predictive low glucose management in realtime sensing insulin pump therapy (PILGRIM)) showing a significantly reduced duration and severity of induced hypoglycemia without causing rebound hyperglycemia. **Conclusion:** The implementation of real-time sensor in diabetes pump treatment (open loop) has definitively an advantage over episodic real-time on demand and can be helpful to increase the routine use of CGM. However, prerequisites for sustainable use of CGM are detailed knowledge, realistic expectations, high degree of self-control, ability to interact with negative feedback and maybe even early introduction of CGM in the management of diabetes.

WG2.6
Type 2 Diabetes Mellitus in Adolescence

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Type 2 diabetes mellitus (T2DM) is emerging as a new clinical problem within pediatric practice. Recent reports indicate an increasing prevalence of T2DM in children and adolescents around the world in all ethnicities, even if the prevalence of obesity is not increasing any more. There are great differences in T2DM prevalence worldwide. The majority of young people diagnosed with T2DM was found in specific ethnic subgroups such as African-American, Hispanic, Asian/Pacific Islanders, and American Indians. Clinicians should be aware of the frequent mild or asymptomatic manifestation of T2DM in childhood. Therefore, a screening seems meaningful especially in high risk groups such as children and adolescents with obesity, relatives with T2DM, and clinical features of insulin resistance (hypertension, dyslipidemia, polycystic ovarian syndrome, or acanthosis nigricans). However, there is an ongoing discussion whether and how to screen for T2DM (oGTT and HbA1c). The prospective value of impaired glucose tolerance in adolescence is low since the majority of obese adolescents demonstrated a normalization of impaired glucose tolerance after end of puberty. Treatment of choice is lifestyle intervention followed by pharmacological treatment (e.g.

metformin). New drugs such as dipeptidyl peptidase inhibitors or glucagon like peptide 1 mimetics are in the pipeline for treatment of youth with T2DM. Furthermore bariatric surgery is proposed as a therapeutic option especially in extreme obese adolescents with T2DM. Recent reports indicate a high dropout of the medical care system of adolescents with T2DM suggesting that management of children and adolescents with T2DM requires some remodeling of current healthcare practices.

WG2.7

The Rationale and Potential Role of Surgery in the Treatment of Adolescent Diabetes

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Background: Type 2 diabetes mellitus (T2DM) is a chronic and disabling disease affecting increasing numbers of adolescents. Conventional medical therapy presents unique challenges and seldom stalls progression. **Objective and hypotheses:** The objective of this presentation is to discuss the findings of contemporary, controlled, and prospective trials of surgical therapy for adult T2DM, which demonstrate dramatic early glycemic control, improvement in cardiovascular risk factors, and impactful weight loss. However, in adults, the durability of the treatment response to surgical treatment may be limited, and influenced by duration and severity of the disease at the time of operation, leading to the hypothesis that surgery may more affectively arrest or reverse beta cell failure, cardiovascular, and renal damages if used earlier in life. **Conclusion:** Based on the evidence in adults, it is appropriate to consider metabolic/bariatric surgery earlier in the treatment armamentarium for T2DM – and especially for select adolescents. However, well-designed prospective studies with hard endpoints that include a detailed assessment of target organ damage will be necessary to influence the place and timing of surgery in the treatment algorithm for adolescents.

WG3.1

Maternal, Placental, and Fetal Steroid Hormone Synthesis: The Key Facts for Understanding DSDs

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The human fetal adrenal comprises the fetal zone which produces adrenal androgens (predominantly DHEA and DHEAS) and the definitive zone which will give rise to the adult adrenal cortex after birth. Together with the fetal liver and the placenta, it forms the fetal-placental unit which produces a variety of estrogens from androgen precursors. Although steroid production by the fetal adrenal seems not essential for fetal survival during pregnancy, steroid biosynthetic defects (such as 3β-hydroxysteroid dehydrogenase, 21-hydroxylase or 11-hydroxylase deficiency, and P450 oxidoreductase or aromatase deficiency) may lead to virilization of 46,XX fetuses through unbalanced androgen metabolism in the fetal–placental unit. Even under physiologic conditions the normal fetal adrenal shifts from androgen to cortisol production during the critical window of the development of the external genitalia from 6 to 12 weeks gestation to safeguard the female phenotype. The fetal testis starts producing testosterone around 7 weeks gestation. Normal testosterone and dihydrotestosterone (DHT) production in the first trimester are crucial for proper virilization of the external genital organs in 46,XY fetuses. Therefore, any defect affecting testosterone/DHT synthesis or action will lead to lack of virilization or undervirilization in males. Such defects may affect overall steroidogenesis (e.g. StAR) or sex steroid synthesis only (e.g. HSD17B3 or SRD5A2). Moreover, recently identified human mutations in genes of the alternative, backdoor pathway for DHT production establish a role of this novel pathway for male sex development. By contrast, the ovary seems steroidogenic quiescent during fetal life and estrogens may not play a major role in (female) sex development. In addition to being part of the fetal-placental unit, the placenta is a barrier for maternal steroids reaching the fetus. Such as placental 11β-HSD activity inactivates maternal cortisol to cortisone to protect the fetus. On the other hand, the placenta itself produces CRH and promotes cortisol production in both mother and fetus in the last trimester. Placental CRH seems in a positive feedback loop with fetal cortisol forming a cascade for rapid adrenal growth and steroidogenesis during late gestation and is possibly responsible for the involution of the fetal zone after birth.

WG3.2

DSD in Indonesia: The Course of Psychological Development in Late Identified Patients

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Background: In Indonesia clinical management of DSD is challenged by limited knowledge and diagnostic and treatment facilities. **Objective and hypotheses:** We investigated patients' experiences of being raised in physical ambiguity and doubts about gender and it's consequences on gender development, social stigmatization, and quality of life. **Method:** 118 Indonesian patients, age 6–41, with 46,XX DSD ($n=27$), 46,XY DSD ($n=77$), and chromosomal DSD ($n=14$). 118 control subjects matched for gender, age, and living area. Questionnaires for gender behaviour and identity, social stigmatization, emotional problems, and quality of life were translated or developed. Reference data were collected in 5024 adults, children, adolescents and parents (web-based and paper and pencil surveys). Construct validity and reliability of questionnaires were tested with principal component analysis and Cronbach alpha procedures. Non-parametric and parametric statistical tests were applied for group comparisons.

Results: Construct validity and reliability were sufficient for all measures. Gender change was observed in 7% (6–11 years), 8% (12–17 years), and 44% (>18 years) of patients. Gender identity confusion was seen in girls with DSD (6–11 years, $P=0.004$ and 12–17 years, $P=0.01$). Adult men with DSD reported past cross gender behaviour ($P=0.01$) and identification ($P=0.01$) that disappeared after they changed gender (F/M). Children with genital ambiguity ($P<0.006$) and cross gender behaviour ($P<0.001$); adults with physical ambiguity ($P=0.001$), and adults who changed gender ($P<0.03$) suffered social stigmatization. Social stigmatization elicited depression and withdrawal in girls ($P=0.002$), women ($P=0.009$) and youngsters who had changed gender ($P=0.02$). Parents reported emotional problems in their sons with DSD ($P=0.05$); adult men with DSD reported anxiety/depression ($P=0.04$), women with DSD reported social isolation ($P=0.02$). On quality of life, parents reported more problems in social functioning ($P=0.001$) in children with DSD. **Conclusion:** High percentages of patients with progressive masculinization changed gender. Patients experienced social stigmatization and related emotional problems. Early identification and referral, providing medical care, patient education and enhancement of coping abilities will improve patients' wellbeing and should be promoted among Indonesian health practitioners.

WG3.3
European Reference Network: Accomplishments of the COST Action DSDnet

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Background: The European Programme on Cooperation of Science and Technology (COST) funds the formation of networking activities with Horizon 2020. In November 2013, the COST Action DSDnet was started and currently 22 European countries as well as six additional partner countries participate. The EU plans to instal European Reference Networks (ERN) by 2016 for defined rare conditions. **Objective and hypotheses:** DSDnet encompasses five working groups (WGs) which compile consented information on i) clinical approaches, ii) genetics and biology, iii) laboratory aspects, iv) perception of research, and v) dissemination of information. **Method:** We had a successful WG meeting in 2013 which laid the grounds for consented manuscripts on sharing of genetic information and laboratory assessement. A survey on the current status of centres of reference for DSD in the different countries was launched. And a proposal for clinical assessment is in preparation. The incorporation of young investigators was propelled forward by a Training School on 'Holistic Care in DSD' and the instalment of Short Term Scientific Missions (STSM). **Results:** The consented manuscripts are under preparation by the WGs and will be distributed shortly. The training school included 30 trainees from 18 countries and 20 international trainers. Four STSMs were already accomplished. **Conclusion:** The COST Action DSDnet is a tool to provide access to training, education and research for DSD. It aims to form a clinical ERN for urogenital rare conditions. Furthermore, it provides the basis for further structured international research grant applications.

WG3.4
I-DSD and I-CAH Registry Update

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Background: Whilst adhering to the highest standards of data governance and security, the International DSD Registry (www.i-dsd.org) and the International CAH Registry (www.i-cah.org) allow standardised collection of data and promote multicentre collaboration across national boundaries and across multiple clinical and research disciplines. **Results:** By April 2015, over 1600 cases had been added by registered users from 41 centres in 22 countries across four continents. A further 76 centres from another 24 countries covering all six habitable continents have registered as users. The median year of birth of cases entered is 1999 (range 1927–2014). The commonest disorder type is disorders of androgen action followed by disorders of gonadal development. The Registry has been developed into an optional modular structure for adding clinical data and supports the development of new primary research through generation of new modules (such as the newly launched CAH module which allows the collection of sequential clinic data) and also supports secondary research on the existing dataset. With the development of I-CAH, an increasing number of CAH cases have now been included and currently exceed 300. Other developments over the last year include the development of patient/participant access and the involvement of clinical users in a survey performed by DSDnet Details of current and past studies that have used the I-DSD Registry are available at its website. In addition to supporting research and surveys, the Registry also acts a database of experts and centres of expertise. **Conclusions:** The I-DSD and I-CAH Registries are open to new researchers and clinical users who can register at www.i-dsd.org (I-DSD) or www.i-cah.org (I-CAH). In addition to acting as a resource for performing studies, the I-DSD Registry is facilitating the development of a network of DSD centres and specialists and forms the backbone of initiatives such as DSDnet. In case of queries please contact the I-DSD Project Manager, J Bryce (Jillian.Bryce@glasgow.ac.uk).

WG3.5
EU-Study: DSD-LIFE

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DSD-LIFE is a comprehensive clinical outcome study investigating medical, surgical, psychosocial, and ethical issues to improve treatment and care of patients with the different diagnoses included in the umbrella term disorders/differences of sex development (DSD). The multidisciplinary DSD-LIFE consortium consists of 15 experienced European scientists in the areas endocrinology, psychology, surgery, gynaecology, urology, and ethics. In 2013 the study protocol and the online database have been developed in six languages. Patient support groups have contributed to the study protocol, physicians, psychologists, and nurses have received training on standard operating procedures (SOP) to perform the study in a standardized manner in all study centres. The study is conducted in Germany, UK, France, Sweden, The Netherlands, and Poland. The recruitment phase of participants has started in February 2014 (duration February 2014–30th September 2015). Patients >16 years with the following diagnoses are invited to partipate in the study: Turner syndrome, Klinefelter syndrome, congenital adrenal hyperplasia (CAH), impaired testosterone synthesis (e.g. 5α-reductase-2 deficiency, 17β-HSD3 deficiency, and LH-receptor defects), impaired androgen action (complete androgen insensitivity (CAIS) and partial androgen insensitivity (PAIS)), dysgenesis of the testes or ovaries, mixed gonadal dysgenesis, karyotype 46,XY/46,XX, 46,XX males, ovotestes, and hypospadias. Until June 2015 the consortium has recruited 1090 patients with the different diagnoses. A parents website was developed. Data analysis, publication and development of clinical recommendations will start in 2016 (http://www.dsd-life.eu).

WG4.1

The Endocrine Role of Brown Adipose Tissue

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Background: The endocrine role of white adipose tissue (WAT), as a site of release of the so-called adipokines, has been recognized for long. Brown adipose tissue (BAT) is the main site of adaptive thermogenesis in mammals, especially relevant in neonates and early infancy. The amount and activity of BAT are associated with a healthy metabolic profile and protection against obesity, type II diabetes and hyperlipidemia. This biological role of BAT is traditionally attributed to its capacity of oxidation of metabolic substrates to fuel thermogenesis. However, recent findings suggest that BAT activity could result in systemic effects due to the secretion of endocrine factors, distinct from white adipokines, the so-called BAT adipokines or batokines. **Objective and hypotheses:** Which are the current evidences for an endocrine role for BAT? **Method:** Summarizing currently available literature highlights two main sources of evidence for an endocrine role of BAT: i) the identification of endocrine factors preferentially released by BAT versus WAT, which expression and release is enhanced when BAT is activated and ii) the evidence for beneficial effects of BAT transplantation that cannot be attribute to the intrinsic thermogenic activity of the transplated tissue. **Results:** Recently reported endocrine factors released by BAT, specially under therogenic activation of the tissue, include FGF21, an anti-diabetic hormone, BMP8b and neuregulin-4. These factors usually combine autocrine action with endocrine effects, acting on tissues such as liver or WAT. Interleukin 6 and IGF1 are also proposed to be released by BAT and to account for the beneficial effects of BAT transplantation on glucose homeostasis and protection against diabetes. **Conclusion:** Although the endocrine role of BAT is an emerging concept, we are still far from a comprehensive identification of the endocrine BAT secretome. Identification of BAT adipokines will expand the current availability of potential therapeutic tools for obesity and associated metabolic diseases.

WG4.2

A Monomeric Peptide Triagonist for the Treatment of Obesity and Diabetes

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Encouraged by unimolecular dual incretin co-agonists (GLP1/GIP) to enhance glycemic efficacy (Finan et al. 2013, Sci Transl Med) and GLP1/glucagon co-agonists to enhance weight loss efficacy (Day et al. 2009, Nat Chem Biol) and to restore diet-induced leptin sensitivity (Clemmensen et al. 2014, Diabetes), we recently developed the first tri-agonist (GLP1/GIP/glucagon) for the treatment of metabolic disorders (Finan et al. 2014, Nat Med). Importantly, this concerted triple agonism outperforms the aforementioned co-agonists by synergistically harnessing the attributes of each constituent hormone, ultimately resulting in benefits that rival those of bariatric surgeries. Another strategy we are currently pursuing involves incretin-based delivery of nuclear hormones in order to gain synergistic effects while restricting hallmark toxicities of the nuclear hormone, all of which is

governed by the use of incretins as a chaperone to selectively target the nuclear hormones to certain tissues (Finan *et al.* 2012, *Nat Med*). In summary, incretin pharmacology can be enhanced or exploited through integration of complementary peptide agonism or through targeting of nuclear hormones. This pharmacological strategy may provide unprecedented opportunities in the personalized treatment of heterogeneous metabolic diseases.

WG4.3

Abstract unavailable.

WG4.4

Abstract unavailable.

WG5.1

Impact of Malignancies and Their Treatment on Reproductive Function in Girls

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Background: A 5-year survival rates for children/adolescents diagnosed with cancer are currently ~80%, with survival rates ~90% for those with acute leukaemia, the most common type of cancer in this population. It is estimated that there will be some 500 000 survivors of childhood cancer in the USA by the year 2020. These impressive survival rates are due, in large part, to the use of multi-modality therapy (i.e., surgery, multiagent chemotherapy, and surgery) in a large proportion of children with cancer. Moreover, a smaller percent require very intensive therapy such as stem cell transplantation (SCT). Ovarian dysfunction, including premature ovarian insufficiency (POI) and impaired fertility, is a known complication of certain cancer therapies, less commonly due to the cancer itself. **Objective and hypotheses:** Review prevalence and risk factors for POI and impaired fertility in survivors of childhood cancer. **Results:** Primary ovarian damage has most often been associated with exposure to alkylating agents (dose–response) and radiation (RT) that includes the ovary (dose–response). Early onset POI occurs commonly in girls exposed to ovarian RT at doses >10 Gy and following high-dose alkylating agents as is given for SCT. Late onset POI may be seen following modest doses of alkylating agents and low doses, <10 Gy, of ovarian RT. Recent data indicate that overall, female survivors have a modestly decreased risk a pregnancy (RR 0.8) 0.80 compared to population norms. Greatest risk of infertility observed after pelvic RT >5 Gy and/or exposure to high-dose alkylating agents. Pelvic RT also associated with adverse pregnancy outcomes, including SGA and preterm births as well as neonatal deaths. Because women are born with a finite number of primordial oocytes that decline over time, older age at treatment is associated with a greater risk for POI and impaired fertility **Conclusion:** Survivors of childhood cancer exposed to pelvic RT and high-dose alkylating agents are at high risk of developing POI and impaired fertility, especially if treated at an older age. Such individuals may benefit from fertility preservation techniques such as ovarian tissue cryopreservation and oocyte retrieval, ideally prior to start of cancer therapy.

WG5.2

Preservation of Fertility Pre-Therapy

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We are in an exciting and interesting time, when pediatricians and reproductive endocrinologists across the globe rise to the challenge of providing fertility services for people with a history of gonadotoxic diseases. Indeed, developments in numerous medical fields have improved long-term survival rates for many diseases that strike children and young adults. However, to survive is no longer enough. The emphasis is shifting, to enable people to live a life as normal as possible after cancer; this includes giving them the best possible opportunity to have their own biological children. However, recognition of the damaging effects of chemotherapy and pelvic irradiation, and sometimes of the disease process itself, in children and patients of reproductive age, is now common knowledge. As a consequence, innovative technologies and surgical procedures have been developed in order to give hope of preserving the potential for biological parenthood after healing. Though sperm cryopreservation before treatment is a well-established procedure, routinely performed for more than 20 years, the science and clinical practice of female fertility preservation remains at a pioneering level. This situation may be explained by the relative complexity of folliculogenesis and the large number of possible fertility-sparing treatments. Approaches to fertility preservation vary greatly, depending on the age of the patient, the type of disease and the reproductive medicine services available locally. Ovarian tissue cryopreservation (OTC), despite its experimental nature, may represent the main option in pre-pubertal girls. In addition, questions related to the potential of pre-pubertal ovarian tissue have been recently swept away with the first live birth reported in a patient having undergone OTC at 14 years old. However, the OTC procedure is relatively invasive and implies the reduction of the follicular ovarian stockpile, which is, in some

situations, as genetic premature ovarian failure, conceptually difficult to accept. In addition, the ovarian tissue may carry malignant cells that could contraindicate its future use. Therefore, oocyte vitrification, following controlled ovarian hyperstimulation or after *in vitro* maturation, should be discussed. Whatever the technique used, fertility preservation in prepubertal girl and adolescents remains a challenge. Ethical aspects and projections into the future use should be systematically considered.

WG5.3

Abstract unavailable.

WG5.4

Diagnosis and Management of Endometriosis in Adolescence

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The presence of endometriosis, from minimal/mild disease up to the rASRM classification for endometriosis stages III and IV, has been described repeatedly in adolescent women. The complaints are common and elicit compassion, but rarely stimulate a thorough research of the cause. The clinical reality is that common complaints of dysmenorrhea or acyclic pelvic pain – even before the onset of menstruation – may hide a disease the severity of which is not reflected by the degree of discomfort and that already may have reached a stage in which the future reproductive life of an otherwise healthy teenager is severely and irreversibly compromised. Especially in these young women, endometriosis remains a disease with an unacceptable delay of the diagnosis, mainly because non-invasive tools are unavailable for the reliable 'early-stage' diagnosis of the condition. And that delay is one if not the most important reason for its progression. The true incidence of adolescent endometriosis is indeed severely biased by the necessity of a laparoscopy for the diagnosis. This presentation intends to elucidate the clinical entity of adolescent endometriosis, including its pathogenesis and evolution. It also attempts to accelerate and improve the diagnosis and the treatment of this often neglected condition. Compared to adult endometriosis, adolescent endometriosis typically presents with a high percentage of subtle, yet active implants on the peritoneal surface and inside small endometriomas of the ovaries whereas the deeply infiltrating (adenomyotic) type, like in rectovaginal endometriosis, and the considerably large and/or bilateral endometriomas are rare. A first-line diagnostic approach includes the use of a high-resolution ultrasound and a CA-125 assay during menstruation. Non-steroidal anti-inflammatory drugs (NSAIDs) and/or a trial treatment with a monophasic contraceptive pill are the first-line therapeutic possibilities, provided there are no contraindications. Although the gold standard for the diagnosis is a standard transumbilical laparoscopy, transvaginal hydrolaparoscopy definitely offers a number of advantages in the sexually active adolescent, both diagnostic and therapeutic.

WG5.5

Uterus Transplantation with Live Births – An Update

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The last frontier to conquer in female infertility is absolute uterine factor infertility (AUFI), affecting more than 10 000 women in the UK. Uterine transplantation (UTx) is now the first available treatment for this large group of women. Adoption and gestational surrogacy are other means to obtain motherhood, but the acceptances of these arrangements in the society vary greatly between societies. Our research group initiated a step-by-step developmental animal-based research approach on UTx in 1999 and have optimized all aspects of the procedure in several animal species. Today 11 human UTx ttempts have been made, with the last nine of them performed by our team. The first two human UTx-attempts, which were unsuccessful, were done in Saudi Arabia in 2000 and in Turkey in 2011. In early 2013 our team completed the surgeries of a series of totally nine human UTx, with live uterus donors. Eight recipients were MRKH patients and one had undergone a hysterectomy because of cervical cancer. The mean age of the recipients was 31.5 ± 3.9 years. Five donors were mothers and others were close relatives and in one case family friend. The mean age of the donors was 53.0 ± 7.0 years. IVF treatments were done before transplantation. The donor surgery involved uterine isolation with pedicles of the uterine arteries and veins and including large parts of the internal iliacs. In the recipient bilateral end-to-side anastomosis was accomplished between the uterine artery and one major uterine vein on each side. None needed perioperative blood transfusion and the hospital stays were 3–9 days. The recipients received two ATG treatments perioperatively and corticosteroids for 4 days. They were then only on double immunosuppression with tacrolimus and MMF and the plan was tapered doses of tacrolimus and omission of MMF after 6 months, to avoid possible teratogenic effects of MMF. Two patients had to be hysterectomized during the initial months due to uterine complications. The other seven patients have shown regular menstruations from 2 months after UTx. The first live birth after UTx occurred in September 2014, when a baby was delivered by c-section in week $31 + 5$ because of maternal preeclampsia (PE) development. Since then two more births have taken place and these mothers did not develop PE. A fourth recipient is expected to deliver in July 2015. The four successful pregnancies after UTx are proofs-of-concept of UTx as an effective method to treat uterine factor infertility.

WG6.1

Incidental Prenatal Diagnosis of Turner Syndrome, Perspectives of Parents and Professionals

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In the light of technologic advances in prenatal testing, more genetic information about the fetus will become available, some of which may have uncertain clinical significance. In the light of all new genetic diagnosing technologies, professional guidance of patients to reliable, tailored, and accurate information is essential. In this presentation I analyze and discuss the various aspects of parental attitudes and dilemmas, as well as professional opinions about the benefits or disadvantages of an incidental finding of a fetal sex chromosome aneuploidy (SCA). I will focus on the incidental prenatal diagnosis of Turner syndrome. I will discuss how to provide accurate and balanced pre-test information to parents and to guide them to secure additional information. An incidental prenatal finding of Turner syndrome in routine prenatal testing procedures always comes as a shock to parents, as they are often not aware of the possibility of incidental findings and are not familiar with the syndrome. Moreover, the phenotypic prognosis is uncertain. Turner syndrome is associated with many diseases, but in prenatal incidental diagnosis and without any ultrasound abnormalities, the child might have a better prognosis. I will discuss a review of the literature. Prenatal pre- and post-test prenatal counseling should guide parents to a well-informed decision in whether or not to continue pregnancy and to assist them in this difficult period in pregnancy with many uncertainties. Shared decision-making after non-directive counseling by medical and psychological specialists after an incidental prenatal diagnosis of Turner syndrome, enhances patient empowerment and ultimately leads to more satisfaction with the decision to continue or to terminate. Professional opinions are explored on the (un) desirability of a prenatal diagnosis of Turner syndrome. It may lead to more understanding of the child's needs and a better parent-child relationship; but the risk of stigmatizing of the child must be kept in mind. Early medical testing and treatment as well as early psychological support is possible, which is beneficial for the prognosis of these Turner girls and may give them better chances and a better health status later in life.

WG6.2

The Challenges of Prenatal Diagnosis: The Experience of a Supportive Group for Parents of Children with TS

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Background: Prenatal diagnostics (PND), as any achievement in genetic research, brings ethical and moral dilemmas that need to be a subject of reflection and debate in modern societies. **Objective and hypotheses:** Once the expecting parents have undergone PND, data about abnormalities confront them with moral dilemmas regarding the decision on the life or death of the unborn child, the responsibility for it, and possible suffering during its future life. Psychological consequences may regard the relationship between parents and the newborn. Psychological effects of this experience sometimes do not appear until years after the decision. We would like to contribute to identifying the best practices when PND of TS occurs. **Method:** We describe the experience of a group for parents of children with TS conducted by a psychotherapist (with the collaboration of another psychologist writing a report). At first we invited all the couples of our clinics who had a girl with TS (0–10 years old) and new couples joining every year (overall 12 couples, five who received PND). We planned a Saturday encounter of 2 h per month (8–10 per year). The group has now been meeting for 6 years. **Results:** The group has allowed parents to name and share many hidden and unthinkable issues connected to PND of TS. In their own words: 'I have realized I'm looking at my child with 'TS lenses'', 'I feel guilty for my decision of giving her so many problems', 'I'm carrying a backpack full of bad news for her since the 'PND day': I don't know when, how and what to tell her!', 'After PND, I couldn't feel her moving in the uterus anymore'. **Conclusion:** Each individual who profits and suffers from PND, experiences it in a very idiosyncratic human way, however our experience underlies the necessity of supporting parents after a PND of TS with specific tools. We noticed some differences between PND and post-natal diagnosis. A supportive group has proved to be a good instrument.

WG6.3

Impact of Age at Start and GH Dose for Height Gain and Age at Adult Height in TS Girls

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Background: Early TS diagnosis permits early GH start and estradiol (E2) supplementation, approaching adult height (AH) at normal age and within normal range. However, higher age at diagnosis is still a challenge according to age for puberty induction and AH. **Objective and hypotheses:** The objective from our long term trials is knowledge enough for personalized treatment in order to obtain a psychological acceptable age at onset of puberty and still an attained AH within normal range. **Method:** Results from national multicenter studies with GH treatment (33/67 ug/kg per day) in combination with possible oxandrolone from 11 years and oral/transdermal estradiol will be presented: 132 prepubertal TS girls (3–9 or 9–16 years) were allocated into different treatment groups and followed until AH. **Results:** $Height_{S.D.S}$ at start was −2.8 (vs non-TS prepubertal reference) in all subgroups. Age at onset of puberty (years) and AH (cm) was for $GH_{33young}$ 14.7, 153.7; $GH_{67young}$ 13.0, 157.2; GH_{33old} 15.2, 156.5; GH_{67old} 14.1, 159.9. Oxandrolone was used in 94% of GH_{33} and in 54% of the GH_{67} group. Pubertal growth was 3.3, 7.7, 7.2 and 9.2 cm respectively. In multivariate analysis the factors GH dose, age and duration of puberty (+) all had high impact on AH.

Conclusion: Younger age at start with higher GH dose results in increased prepubertal height gain, permitting puberty at normal age (2 years before low dose) and an AH within normal range. The girl diagnosed at higher age can still attain an acceptable age for puberty onset and AH – by using higher GH dose, oxandrolone and slow E2 dose increment, thus optimizing the treatment tools GH dose, oxandrolone and E2 in a personalized approach.

WG6.4

Management of Middle Ear and Hearing Problems in Turner Syndrome – How Can We Do Better?

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Background: Otological problems in Turner syndrome (TS) are notoriously common and troublesome, often requiring intervention with adeno-tonsillectomy, insertion of ventilation tubes and occasionally resulting in serious disease such as cholesteatoma. **Survey of otological problems in the West of Scotland:** A case note review of 174 girls attending the Turner clinic in Glasgow, Scotland from 1989–2015 found that of 155 patients in whom data were available (current mean (range) age 26.9 (3.8–47.2) years), middle ear problems were documented in 85 (55%). Prevalence was higher with the 45, X (43/64 (67%)) and 45, X/46, XiXq (19/30 (63%)) karyotypes; lower with 45, X/46, XY (3/10(30%)) karyotype and zero in the seven patients with 45, X/46, XX. The type of middle ear problem encountered was age-related. Recurrent acute otitis media (AOM) and otitis media with effusion (OME) affected young girls – 31/60 girls with recurrent AOM were aged <5 years; while 42, 34 and 7 of 83 girls with OME were aged <5, 5–10 and >10 years. By contrast 22/32 patients with chronic perforation of tympanic membrane and 10/11 with retraction pocket were aged 5–15 years. Seven (4.5%) girls aged 11.9 (7.5–15.2) years developed cholesteatoma – a far higher prevalence than in the general population (3–6 per 100 000). Five (3.2%) girls aged <15 years were recorded as having sensorineural hearing loss, with 10 (6.5%) receiving hearing aids. However, data are incomplete for the adult population and a questionnaire-based survey is about to be launched. **Suggested strategies to improve management of ear problems in TS:** The UK TS Support Society reports that many girls present initially to the Ear Nose and Throat (ENT) clinic before TS is diagnosed, indicating the value of educating ENT specialists in early recognition. Otoscopy training should be offered to paediatricians caring for TS so that effusions, perforations and retraction pockets can be diagnosed promptly and accurately. Patients and families require written information, with clear guidelines as to when to seek medical advice (e.g. purulent/offensive ear discharge for >5 days). A prospective study examining the benefit of early antibiotic prophylaxis in girls at particular risk of middle ear sepsis (e.g. those with 45, X and 46, XiXq karotypes) should be discussed.

WG6.5

Report on the Progress and Difficulties on Transdermal Estradiol Supplementation in Europe

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Background: The Turner syndrome (TS) Working Group of the ESPE intends to start an international study comparing transdermal estradiol (E2) vs oral E2 in Europe in girls with TS. For this, stable and reliable products for children are needed, for use in different countries with different climates. It has previously been shown that E2 matrix patches for adults can be cut in smaller pieces to administer low doses for pubertal induction in girls. The Turner Working Group plan to extend the knowledge of the use of the (cut) patches for children, as no pharmacological company will perform this important work. Consequently, *in vitro* studies are necessary before going further to the clinical study. After this study, we expect to have the knowledge and experience to ask to the pharmacist to cut different patches in a standardized way and we can give advices to patients and parents about the storage conditions in different countries with different temperatures during the year. **Objective and hypotheses:** Assess the consequences of cutting the patch on the distribution of E2 over the surface and storage conditions of cut pieces. **Method:** The study will include five patches from different manufacturers in Europe. E2 concentrations in patches stored in sealed sachets and cut pieces after storage in $+30$C and $+35$C for up to 4 weeks will be determined in parallel with storage in $+21$–23C. **Results:** In a pilot study, one of the E2 matrix patches after cutting into pieces were stored together with the remaining patch in its foil-lined sachets, either in a plastic bag in the fridge i) in a plastic bag in room temperature ii) or just in room temperature iii). Storage for 0, 1, 2, 3, 4 and 5 days were compared. Our *in vitro* study showed that the patches contained the expected drug amount E2 and it was evenly distributed on the surface. After cutting the patches, E2 concentrations were stable in 22 C for at least 1 week in its sachet. **Conclusion:** The ESPE TS Working Group hopes to get the possibility to perform this *in vitro* study in order to obtain more knowledge about storage conditions of cut pieces from different estrogen matrix patches, and consequently a better way to induce puberty in TS.

WG7.1

Abstract unavailable.

WG7.2

Abstract unavailable.

WG7.3

Abstract unavailable.

WG7.4

Long-Term Outcome of a Male Preschooler Treated for Central Precocious Puberty

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Background: A 3.6-year-old Caucasian male presented with rapid onset of deep voice, facial hair, Tanner stage 2 testes, Tanner stage 3 pubic hair, penile length 9.5 cm, growth velocity (GV) 13.1 cm/year, and bone age 7 years. Evaluation was consistent with central precocious puberty and ruled out other pathology. Standard weight-based gonadotropin-releasing hormone agonist (GnRHa) therapy was initiated. GV increased to 16.6 cm/year, puberty advanced further, and bone age was 11 years at age 4.1 years. Predicted adult height was 28 cm $<$ mid-parental height (MPH). **Objective and hypotheses:** The objective was to suppress puberty. The hypothesis was that individualized GnRHa therapy would suppress puberty and optimize height potential. **Method:** Leuprolide acetate depot-ped IM injections were increased from 11.25 mg every 28 days to 15 mg every 28 days. Due to continued progression of puberty, leuprolide was increased to 15 mg every 25 days. Growth and pubertal development were monitored closely. **Results:** Individualized GnRHa therapy was well tolerated. Progression of puberty and bone age slowed significantly. When he was 11.8 years of age, bone age was 14.5 years, height was 14.2 cm below MPH, testes and pubic hair were T_4, and treatment was discontinued. Puberty progressed over the next 2 years. Near final adult height was 4.6 cm below MPH. **Conclusion:** This case demonstrates the long-term outcome of individualizing GnRHa therapy until pubertal suppression was achieved in a young male. No literature was identified on increasing GnRHa dose and frequency when standard therapy fails to suppress puberty, therefore further study is needed.

WG7.5

Pan-Canadian Experience of Pediatric Endocrine Nurses Assisting Youth Through Gender Transition

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Background: Increasing referrals for transgender youth demonstrated a lack of local interprofessional comprehensive programs for transgender youth. Pediatric endocrine clinics across Canada have collaborated with other disciplines to provide increasingly comprehensive assessment and treatment programs for transgender youth. **Objective and hypotheses:** Share a case study of a Canadian youth's experience with the Gender Dysphoria Assessment and Action for Youth (GDAAY) program. Review of pediatric endocrinology nurses roles within interdisciplinary teams in assisting youth through gender transition across Canada. **Method:** Review a case from first referral through telephone triage, intake, diagnosis and treatment with the support of the pediatric endocrine nurse. **Results:** An interprofessional team approach to gender dysphoria assessment and action for youth is a leading model of care for other clinics across the country. **Conclusion:** Canadian youth with gender dysphoria have increasing access to assessment and treatment programs through local interprofessional clinics with pediatric endocrinology nurses across the country.

WG7.6

Abstract unavailable.

Free Communications

FC1.1

A Genomic Atlas of Human Gonad and Adrenal Development

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Background: The adrenal glands and gonads develop from an area of intermediate mesoderm between 6 and 10 weeks post conception (wpc) in humans. Elucidating the genomic components and pathways in these processes could reveal novel aspects of human developmental biology and new factors implicated in adrenal insufficiency and DSD. **Objective and hypotheses:** To develop a unique genomic atlas of adrenal and gonad development during critical stages of human embryonic organogenesis. **Method:** In collaboration with the Wellcome Trust-MRC Human Developmental Biology Resource, RNA was extracted from 58 tissue samples between 6 and 10 wpc (22 adrenal, 20 testis, 10 ovary, 6 control). Gene expression was determined using Affymetrix Exon 1.0 ST arrays, generating 1.5 million data points. Global differences in gene expression between tissues were elucidated using Bioconductor and Partek. A novel phenomenological mathematical model was developed to investigate time-series changes across the dataset. Data were validated with qRT-PCR and immunohistochemistry. **Results:** The adrenal gland develops a specific genomic signature early in development with marked differential expression of known genes (e.g. *CYP17A1*, *CYP11A1*, *STAR*, *MC2R*) and novel genes (e.g. *OSAP*, *MAP3K15*, *ASB4*). In the developing testis, SRY was the differentially expressed Y-chromosome gene at 6 wpc. By modelling resultant SOX9 upregulation, several potential new testis development genes were identified (e.g. *CITED1*, *ZNF280B*). Known steroidogenic genes showed consistent upregulation around 8 wpc in the testis with a sigmoidal time-series pattern. By combining adrenal and testis datasets, several potential novel steroidogenic components were identified (e.g. *GRAMD1B*, *SLC16A9*). Ovarian genes were enriched for germ cell factors, olfactory receptors and NPY. Remarkably, the only transcription factor differentially expressed in adrenal, testis and ovary was SF-1/NR5A1. **Conclusion:** A unique, highly-validated genomic atlas of human adrenal and gonad development has been generated. This resource is revealing novel pathways in human development and new candidate genes for adrenal and reproductive disorders. **Funding:** JCA is a Wellcome Trust Senior Research Fellow in Clinical Science (098513). The human embryonic and fetal material was provided by the Joint MRC/Wellcome Trust grant number 099175/Z/12/Z Human Developmental Biology Resource (http://hdbr.org).

FC1.2

Involvement of the Wnt/β-catenin Pathway, *SF1*, *DAX1* and Stem/Progenitor Cell Markers in Paediatric Adrenocortical Tumors

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Background: Activation of the Wnt/β-catenin pathway is frequent in adrenocortical tumors (ACTs). This pathway and *DAX1*, a negative regulator of *SF1* expression, control adrenal stem/progenitor cells, which can be involved in ACTs formation. **Objective:** To analyse the association between the Wnt/β-catenin pathway and the expression of a stem cell marker (NANOG), STAT3, DAX1 and SF1 in ACTs. **Methods:** Patients: 70 paediatric and 18 adults with ACTs; Control adrenals: 13 children and 13 adults. mRNA expression of *DAX1*, *SF1*, *STAT3* and *NANOG* evaluated by qPCR. Protein expression of SF1 and DAX1 evaluated by immunohistochemistry. Copy number variation of *SF1* and *DAX1* evaluated by MLPA. *In vitro* the effect of inhibition of the Wnt/β-catenin pathway with PNU on *NANOG* expression was evaluated in H295 adrenal tumour cells. **Results:** Decreased expression of *SF1* mRNA was found in 84% of paediatric ACTs ($P=0.02$) but not in adult ACTs ($P=0.49$). Conversely, overexpression of *DAX1* mRNA was found in 89% of adult ACTs ($P<0.01$) but not in paediatric ACTs ($P=0.65$). *STAT3* mRNA expression was higher in adult than in paediatric ACTs ($P<0.01$). p.S45P *CTNNB1*/β-catenin mutated ACTs presented increased expression of *NANOG* ($P<0.01$). *In vitro* inhibition of the Wnt/β-catenin pathway impaired NANOG mRNA expression in a dose-dependent manner ($P<0.01$). At protein level, moderate or strong nuclear staining of SF1 was found in 78 and 19% of paediatric and adult ACTs, respectively. Moderate to strong nuclear staining of DAX1 was found in 48% of paediatric ACTs but not in adult ACTs, in which only weak nuclear staining was present. MLPA analysis revealed *SF1* gene amplification in 23 and 15% of paediatric and adult ACTs, respectively. **Conclusion:** Post-translational mechanisms, likely associated with the loss of inhibition exerted by DAX1, regulate the overexpression of *SF1* in paediatric ACTs. *NANOG* may play a role in Wnt/β-catenin activation in ACTs, particularly in the presence of the p.S45P β-catenin mutation. **Funding:** CAPES, FAPESP and CNPq.

FC1.3

Aldosterone and Mineralocorticoid Receptor as Inducers of Immune Markers in Peripheral Blood Mononuclear Cells: Beyond Elevating Blood Pressure

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Background: *In vitro* studies suggest a broader role for aldosterone, beyond elevating blood pressure. Clinical data support the notion that aldosterone can directly alter the function of the immune system and can participate in low-grade inflammation which leads to blood pressure elevation and end organ damage. **Objective and hypothesis:** To assess in humans, whether aldosterone plasma levels and mineralocorticoid receptor (MR) expression associate with immunological markers in peripheral blood mononuclear cells (PBMCs). **Methods:** We recruited 228 subjects (11-67 years, BMI 27.09 ± 4.8 kg/m^2, 61% female). We measured in blood samples: aldosterone, hsCRP, and IL17. Sodium was measured in serum and urine. We isolated mRNA from PBMCs and evaluated MR, pathogen-activated molecular patterns (PAMPs like TLR-4, TLR-2, CD-14), damage-activated molecular patterns (DAMPs like Hsp-90, NGAL) and IL17 expression by q-RT-PCR. Statistics was done by Spearman. **Results:** Aldosterone plasma levels were directly associated to CD-14 mRNA expression ($r=0.2998$ $P=0.0022$) and inversely associated with age ($r=-0.2904$ $P<0.00001$), Na_S ($r=-0.2150$ $P=0.0011$) and Na_U ($r=-0.1995$ $P=0.0025$). There was no association with hsCRP, TLR-4, TLR-2 nor DAMPs expression. Neither did IL17 levels or expression. MR mRNA expression in PBMCs was directly associated to IL17 levels ($r=0.2459$ $P=0.0217$) and IL17 expression ($r=0.4472$ $P=0.0002$). It was also directly associated to CD-14 ($r=0.6769$ $P<0.0001$) and NGAL ($r=0.3216$ $P=0.0024$) expression, and inversely associated to Hsp-90 ($r=-0.2591$ $P=0.0258$) expression. There was no association with TLR-2, TLR-4 expression neither hsCRP levels. **Conclusion:** Aldosterone plasma levels and/or MR-expression in PBMCs are associated to PBMC inflammatory activation markers, which could predispose to autoimmune disorder development.

FC1.4

Congenital Adrenal Hyperplasia due to 21 OH Deficiency: Final Height Before and After Newborn Screening Era in Emilia-Romagna Region, Italy

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Background: Final height (FH) in patients (pts) with congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (21OHD) is often under the genetic target, despite improvement of new therapeutic strategies. **Objective and hypotheses:** The aim of this study is to evaluate FH in a cohort of pts with CAH due to 21OHD diagnosed before and after newborn screening (NBS) era in Emilia-Romagna, Italy. **Method:** We evaluated final height, genotype and treatment of 103 21OHD-CAH pts, diagnosed and treated at our Pediatric Endocrinology Unit in the last 40 years, before (57 pts, 21 M-group A) and after (46 pts, 20 M-group B) NBS era. Our pts were subdivided in three sub-groups upon severity of genotype (salt wasting-SW, simple virilizing-SV, non classical-NC). Other than classical treatments (gluco and mineralocorticoids, NaCl salts), 14 cases underwent GnRH analogue (9 pts), GnRH analog + growth hormone (GH) (3 pts), GH (2 pts) for severely reduced projected adult stature. **Results:** FH of males of group B with severe forms (SW + SV) is higher than that of pts with severe forms of group A. FH has negative correlation ($P<0.001$) with age at diagnosis in severe forms (61 cases), in particular in SV males of group B ($P<0.01$). These pts show better final height ($P<0.005$) than SV males of group A. Glucocorticoid dose is lower in pts of group B than that of group A, with statistical significance in females only. Pts with NC forms, both males and females, diagnosed before and after NBS show similar final height. The three cases treated with GnRH + GH reached FH above mid-parental target height. **Conclusion:** In our study the introduction of NBS significantly improved FH only in males with severe forms. Further studies are needed to increase the number of pts with final height to extensively evaluate our results on a larger group of cases.

FC1.5

Atypical Presentation of Six Patients with Mutations in the Side Chain Cleavage Enzyme CYP11A1

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Background: Mutations in the side chain cleavage enzyme, (*CYP11A1)* cause congenital adrenal insufficiency, with complete or partial 46XY sex reversal. The disorder manifests with adrenal and gonadal insufficiencies along with derangements of the renin/angiotensin system. **Objective and hypotheses:** To obtain a genetic diagnosis in six patients with adrenal insufficiency of unknown aetiology. Patients 1 and 2 are sisters with ACTH resistance, having high ACTH levels, low glucocorticoids, no response to exogenous ACTH and no pigmentation. Patients 3 and 4 have FGD and subclinical hypothyroidism. The patients are adult now and female patient 4 has suffered three miscarriages. Patient 5, with a diagnosis of lipoid adrenal hyperplasia, presented with adrenal failure in early life with mineralocorticoid and glucocorticoid deficiency and had big adrenals in the neonatal

period. Patient 6 had a salt wasting early neonatal history and was hyperpigmented in infancy. He was treated as a case of Addison's disease despite normal renin and aldosterone levels. **Method:** Whole exome sequencing was undertaken on genomic DNA of the patients. Variants in seven genes; *MC2R, MRAP, STAR, CYP11A1, NNT, MCM4* and *TXNRD2* were assessed for causality. **Results:** All patients had *CYP11A1* mutations; homozygous A359V (patients 1 and 2), compound heterozygous mutations I279Yfs*9 and *122Rext*68 (patients 3 and 4), compound heterozygous R120Q and Q395K (patient 5) and compound heterozygous E314K and an exon5/intron5 splice site mutation (patient 6). The A359V and I279Yfs*9 mutations have been previously reported and in homozygosity shown to cause severe cases of CAH, all other variants were novel, with the exception of the E314K (aka rs6161 with a minor allele frequency 0.001). **Conclusion:** The presentation varied between cases, ranging from a patient with neonatal salt wasting/adrenal crisis and large adrenals to a pair of non-pigmented sisters aged 2 and 4 years on glucocorticoid replacement alone. These cases emphasize the utility of whole exome sequencing as a tool for improved diagnosis and therefore patient management/genetic counselling in the endocrine clinic.

FC1.6

An Update on Noninvasive Prenatal Diagnosis of Congenital Adrenal Hyperplasia Using Cell-free Foetal DNA in Maternal Plasma

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Background: Congenital adrenal hyperplasia (CAH) arises from mutations in *CYP21A2* gene, which encodes for the steroidogenic enzyme 21-hydroxylase. Currently employed chorionic villus sampling and amniocentesis provide genetic results at ~14 weeks of gestation at the earliest. At this time, the genitalia of the affected female foetuses have already become virilized. To prevent genital ambiguity, prenatal treatment with dexamethasone must begin on or before gestational week 9. This means that all mothers, even those pregnant with male and unaffected female foetuses, must receive dexamethasone before the genetic mutation are known, highlighting the need for earlier genetic diagnosis *in utero*. **Objective and hypotheses:** Massively parallel sequencing (MPS) on plasma from pregnant mothers at 6 weeks of gestation could potentially provide the diagnosis of CAH, noninvasively, before the 9th week of gestation. **Method:** Twenty families, each with a proband affected by classical CAH, were recruited. Cell free foetal DNA was obtained from 3.6 ml of maternal plasma. Using hybridization probes designed to capture a 6 Mb region flanking *CYP21A2*, targeted MPS was performed to analyze genomic DNA samples from parents and proband to determine parental haplotypes. Plasma DNA from pregnant mothers also underwent targeted MPS to deduce foetal inheritance of parental haplotypes. **Results:** In twenty families, the foetal CAH status was correctly deduced by targeted MPS of DNA in maternal plasma, obtained as early as 5 weeks and 6 days of gestation. **Conclusion:** MPS on 3.6 ml plasma obtained from pregnant mothers at 6 weeks of gestation could potentially provide the diagnosis of CAH, noninvasively, before the 9th week of gestation. Only affected female foetuses will thus be treated. Our strategy represents a generic approach for noninvasive prenatal testing for an array of autosomal recessive disorders.

FC2.1

Whole Exome Sequencing Analysis of Patients with Autosomal Recessive Hypophophatemic Rickets Identified Mutations in *DMP1*, *ENPP1* and *SLC34A3*

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Background: Hypophosphatemic rickets (HR) is most commonly X-linked or autosomal dominant, but autosomal recessive (AR) forms have been described. ARHR1 (*DMP1*) and ARHR2 (*ENPP1*) share identical biochemical characteristics of excessive renal phosphate wasting due to increased circulating levels of the phosphatonin FGF23 and low serum levels of $1,25(OH)_2D$. By contrast, in hereditary hypophosphatemic rickets with hypercalciuria (HHRH) phosphaturia is due to defects in the renal type 2c sodium phosphate cotransporter encoded by *SLC34A3*, with suppressed levels of FGF23 and consequently elevated levels of serum $1,25(OH)_2D$ and urine calcium. **Objective and hypotheses:** To use whole exome sequencing (WES) to identify the genetic basis for HR rickets in four kindreds with AR transmission. **Method:** We obtained clinical and biochemical data and performed WES for four kindreds. **Results:** The three affected boys of family 1 were initially diagnosed with HR based on severe signs of rickets of both knees but with elevated serum $1,25(OH)_2D$ levels; the parents were healthy first cousins of Arab-Bedouin descent. We identified a known frameshift variant, c.295_296delGG, in *DMP1*. Affecteds are homozygous, both parents are heterozygous and maternal grandmother is wild type. The affecteds from families 2 and 3 were also suspected to have HR, but they also had borderline to high PTH levels and very low 25(OH)D levels. WES revealed homozygous mutations in *ENPP1* in affecteds from family 2 (c.1499A > G:p.H500R) and family 3 (c.755A > G:p.Y252C). In family 4, two children had HR with elevated $1,25(OH)_2D$ and developed hypercalcemia after moderate vitamin D supplementation; we confirmed a homozygous variant, c.709G > A:p.D237N, in *SLC34A3,* that cosegregated with the phenotype. **Conclusion:** We report 2

novel mutations in *ENPP1* and 1 known mutation in *DMP1* in patients with ARHR2 and ARHR1, respectively. The HHRH phenotype is further extended by illustrating that patients with *SLC34A3* mutations have vitamin D sensitivity that can lead to hypercalcemia.

FC2.2

Identification of Mutations in *TBX1* and *AIRE* in Isolated Hypoparathyroidism Patients

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Background: Hypoparathyroidism may manifest either as an isolated disorder or as a component of a more complex syndrome. Molecular genetic studies indicate that mutations in *PTH*, *CASR*, *GCM2* and *GNA11* are causes of isolated hypoparathyroidism (IH) and mutations in *GATA3*, *TBCE*, *FAM111A*, *AIRE* and *TBX1* are associated with different complex syndromes with hypoparathyroidism. **Objective and hypotheses:** To identify the underlying genetic basis for IH two multigenerational families with negative *PTH*, *CASR*, *GCM2* and *GNA11* sequencing. **Method:** Whole exome sequencing (WES) was performed in three affecteds in family 1 and five affecteds from two generations in family 2. **Results:** WES analysis in family 1 revealed that affecteds were compound heterozygotes for two previously identified mutations (c.967_979delGCCTGTCCCCTCC:p.L323SfsX51 and c.995+(3_5)delGAGinsTAT) in *AIRE*, which is implicated in autoimmune polyglandular syndrome type 1 (PGA1). In PGA1 hypoparathyroidism is usually associated with adrenal insufficiency and candidiasis, which were not present in the three affected patients now aged 40-50 years. For family 2, all affecteds carried a novel heterozygous splice-altering mutation in *TBX1*, which is located at 22q11. This mutation showed reduced penetrance – 8 affecteds all have splicing mutation and some unaffecteds as well. Previously studies showed either gain of function or loss of function *TBX1* mutations can lead to DGS or a DGS-like syndrome with craniofacial features, but the prevalence of hypoparathyroidism is only about 30%. A similarly low prevalence of hypoparathyroidism occurs in DGS due to the 3Mb deletion. The limited phenotype of IH in family 2 suggests that manifestation of the splicing defect may be tissue-specific, a hypothesis we are now testing in zebrafish. **Conclusion:** Our identification of mutations in *AIRE* and *TBX1* in patients with IH refines the phenotypic spectrum of clinical and endocrine abnormalities associated with these genes, and extends the number of candidate genes that can cause IH.

FC2.3

High Success of a Next Generation Sequencing Panel for the Molecular Diagnosis of Rare Skeletal Dysplasias

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Background: A total of 456 skeletal dysplasias have been classified by molecular, biochemical and/or radiological criteria, into 40 groups. Despite this, the precise, final diagnosis is often difficult due to the high phenotypic and genotypic variability. **Objective:** To improve the molecular and clinical diagnosis of skeletal dysplasias using a custom-designed next-generation sequencing (NGS) panel. **Method:** A total of 56 skeletal dysplasia probands of unknown molecular etiology were clinically and radiologically evaluated. DNA from the probands and in some cases affected family members, was analysed using the SKELETALSEQ.V3 panel ($n=315$ genes) and sequenced on a MiSeq. All variants were confirmed by Sanger sequencing or arrayCGH. Functional analysis was undertaken where possible. **Results:** In 24/56 (43%) probands the causative mutation(s) was identified; 12/25 (48%) probands classified with a severe and 12/31 (39%) with a mild skeletal dysplasia. A total of 23 missense, stop or small deletions and one gene deletion were detected. Two heterozygous stop mutations were identified in aggrecan (*ACAN1*) in two families with disproportionate short stature, one with advanced bone age whilst the other not. Compound heterozygous functionally confirmed pathogenic *POP1* mutations were detected in the second case of spondylometaphyseal dysplasia with extreme short stature (−5.57 SDS) reported so far. Two novel homozygous *POCA1* mutations were identified in two families with remarkably similar clinical features of primordial dwarfism (SOFT syndrome). **Conclusion:** i) The SKELETALSEQ NGS panel is a powerful tool in determining the causative mutation in 43% of patients with skeletal dysplasias and extreme short stature. ii) Causative mutations were identified in genes in which only one or few mutations have been previously described. iii) The advancement in the genetic diagnosis of these disorders will not only improve the management, monitoring and

treatment of these patients but also permit prenatal and preimplantational genetic studies for the affected families. **Funding:** This work was supported in part by the following grants: MINECO (SAF2012-30871) and Comunidad de Madrid ENDOSCREEN (S2010/BMD-2396).

FC2.4

Asfotase Alfa: Sustained Efficacy and Tolerability in Children with Hypophosphatasia Treated for 5 Years

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Background: Hypophosphatasia (HPP) is the rare inherited metabolic disorder resulting from loss-of-function mutation(s) in the tissue-nonspecific alkaline phosphatase (TNSALP) gene. TNSALP deficiency can cause a spectrum of complications in children including premature deciduous tooth loss, rickets, poor growth, and compromised physical function. We previously reported that children, 5–12 years old, with HPP and treated with asfotase alfa, a recombinant bone-targeted human TNSALP, experienced rapid improvement in skeletal mineralization and physical function, sustained through 3 years (Madson, JBMR 2014). **Objectives:** Report data following 5 years of asfotase alfa treatment in these children. **Methods:** Phase II, open-label, ongoing extension study of asfotase alfa (6 mg/kg per week; SC). Outcomes include change in rickets severity (7-point Radiographic Global Impression of Change (RGI-C) scale; −3 = severe worsening, +3 = near-complete/complete healing); functional ability (6-Minute Walk Test (6MWT) :normal range = 80–120% predicted for healthy peers; Bruininks-Oseretsky Test of Motor Proficiency, 2nd Edition (BOT-2) Strength and Agility score:mean (S.D.) for healthy peers = 50 (10); Child Health Assessment Questionnaire (CHAQ) Disability Index:0–3, 0 = no disability); and safety. Data are presented as median (min, max). **Results:** 12 patients who entered the extension study were treated ≧5 years. At baseline, 6MWT was 61%(29%, 82%) predicted, BOT-2 was 28(20, 37), and CHAQ was 1(0, 2.25). Rapid and significant improvement in rickets was sustained through 5 years (RGI-C: +2.2(+1.7,+2.7); $P = 0.0005$). Normalization of physical function was also sustained: 83%(70%, 104%) predicted ($P = 0.0002$) on the 6MWT, and normal BOT-2 (46(33, 64); $P < 0.0001$). Most patients continued to report no detectable disability on CHAQ (0(0,1); $P = 0.0002$). Most common AEs were mild-to-moderate injection site reactions in all patients (eg erythema, macule, and lipohypertrophy; 1 injection site atrophy assessed as severe). There were no deaths or AEs leading to withdrawal. **Conclusion:** Normalization of HPP-related skeletal manifestations and functional ability is sustained through 5 years of asfotase alfa treatment in children with HPP. Treatment was well tolerated. **Declaration of interest:** TO and SM are employees of Alexion, which sponsored the study. KLM received honoraria from Alexion. MPW has received honoraria, grants, and travel fee from Alexion. CRG is clinical trials investigator and received honoraria and travel fee from Alexion.

FC2.5

Methyl Donor Deficiency Impairs Differentiation of Pre-Osteoblasts Through Disruption of Functional Interaction Between Peroxisome Proliferator-Activated Receptor-Gamma Coactivator-1 Alpha and Vitamin D Receptor

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Background: Folate and cobalamin are needed for synthesis of methionine, a substrate of methylation in epigenetic, and epigenomic pathways. Methyl donor deficiency (MDD) leads to hyperhomocysteinemia, which has been related to osteoporosis in humans and disruption of epiphyseal cartilage and bone development in rodents. Recent studies have revealed evidence for association between $25(OH)D_3$ and homocysteine levels, however, underlying mechanisms remain elusive. **Objective:** We aimed to elucidate molecular mechanisms linking MDD and VDR signalling, and the role of MDD in VDR-mediated transcription during osteoblast differentiation. **Method:** Proliferation and differentiation of MG-63 pre-osteoblasts were studied under normal conditions and under experimental conditions of MDD. **Results:** The $1,25(OH)2D_3$ and vehicle treated MDD cells displayed significantly decreased expression of VDR comparing to controls and impaired nuclear activation of the transcriptional co-activator PGC-1α, through its decreased methylation related to blunted expression of PRMT1 and ADMA, decreased S-adenosylmethionine:S-adenosylhomocysteine ratio, and increased cellular concentration of S-adenosylmethionine, a potent inhibitor of PRMT1. The mechanistic studies further revealed a markedly decreased interaction between VDR and PGC-1α and a strong interaction between protein chaperon HSP90 and VDR in MDD cells. We speculate that HSP90 sequestrates VDR and prevents the hormone binding to PGC-1α leading to altered expression of downstream

genes, in particular increased expression of pro-adipogenic PPARγ, adiponectin and ERRα, and significantly decreased expression and activity of bone ALP. **Conclusion:** The data presented here provide new mechanistic insights into regulation of human osteoblast differentiation demonstrating for the first time a crucial role of PGC-1α-VDR functional interaction, dramatic effect of MDD on the nuclear action of $1,25(OH)2D_3$ through hypomethylation of PGC-1α and sequestration of VDR in a form of the HSP90-VDR complex. This prevents the hormone binding to PGC-1α and leads to impaired expression of target genes ultimately directing cell differentiation toward a more adipogenic phenotype.

FC2.6

A Contextual Feature-Based Recognition Approach to Quantify Trabecular Microstructure Using 1.5T Axial-MRI: An Innovative Methodology

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Background: *In-vivo* skeletal MRI imaging remains challenging due to the extremely short MR relaxation times (<1 ms) of protons bound to water in bone. However, each MRI sequence contains properties identifiable through feature-based recognition, highlighting characteristics relating to skeletal configuration. We thus present a novel statistical method for clinical 1.5 Tesla (T) MRI in quantifying trabecular microstructure and use HRpQCT to determine its accuracy. **Objective:** To assess fifteen contextual image-based features of trabecular bone relating to pattern fragmentation, repeatability, complexity, and statistical variability of multiple axial-plane MRI sequences. **Method:** We compared HRpQCT and 1.5T MRI scans of the non-dominant ultradistal tibia in 96 13–16 year olds. Participants underwent two of the following axial-MRI sequences: T1-weighted fast spin echo, T2-weighted fast spin echo, T2*-weighted gradient echo, FIESTA, ultrashort time echo (UTE), UTE High Resolution. By relating HRpQCT-derived trabecular parameters to contextual image features contained within axial-MRI sequences we developed a statistical prediction model designed to predict trabecular microstructural parameters. Image descriptors included statistical variability (mean intensity, standard deviation, skewness, and kurtosis), pattern repeatability (using grey level co-occurrence matrices), and pattern complexity (using run-length analysis and fractal dimension). Kernel partial least squares defined an optimal non-linear predictor model from the data relating MRI sequences to HRpQCT parameters. By using the MRI sequences as the input of the prediction model: $((y_{mripredicted} - y_{hrpqct}/y_{hrpqct}) \times 100)$, percentage prediction errors for trabecular thickness, spacing and number were calculated. **Results:** FIESTA and UTE-HR image sequences demonstrated the highest accuracy in predicting all three trabecular parameters ($12.0 \pm 3.4\%$, $12.1 \pm 4.5\%$ respectively). T2w and T2×w most accurately predicted trabecular thickness (mean prediction error- 9.5%) and trabecular number (7.5%), respectively. T1w most accurately predicted trabecular spacing (7.4%). **Conclusion:** 1.5T MRI sequences can predict trabecular number, spacing, and thickness to within 10% of the values derived from HRpQCT using the established model, demonstrating the future potential of clinical 1.5T MRI in assessing trabecular bone. **Funding:** The British Society of Paediatric Endocrinology and Diabetes. The Sheffield Children's Hospital Charity, UK.

FC3.1

RNA-Based MAFA Over-Expression is Sufficient to Drive Human Pancreatic Duct-Derived Cells Toward a β-Cell-Like Phenotype

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Background: Pancreatic epithelial cells represent an attractive cell source for replacement therapy of type 1 diabetes. Previously, we designed a protocol for expansion of human pancreatic duct-derived cells (HDDCs) and showed their β-cell engineering potential. **Objective and hypotheses:** In this study, we reprogrammed HDDCs into β-cell-like lineage by over-expressing mRNAs of key pancreatic transcription factors (TFs). **Method:** Pancreatic duct cells ($n=6$) were purified and propagated into endothelial growth-promoting media. Synthetic modified (sm) RNAs were manufactured by unidirectional subcloning of *PDX1*, *NGN3* and *MAFA* into a plasmid containing 5′ and 3′ UTR regions. The UTR-flanked inserts were excised and poly(A)-tailed. The final smRNAs were synthesized through *in vitro* transcription followed by phosphatase and DNase treatments, before being daily transfected in HDDCs. **Results:** In all donors, transfection of *PDX1*, *NGN3* and *MAFA* led to upregulation of endogenous target (ex: *NGN3*) and β-cell marker (ex: *INS*, *synaptophysin*, *SLC2A2*, *GCK*) genes with the highest expression levels being reached after MAFA transfection. Co-transfection protocols failed to show significant improvement of β-cell differentiation. Acceptable impact on innate immune response and cell viability was noticed after seven consecutive daily smRNA transfections, based

respectively on minimal *IFNA* and *RIG-1* gene expression and on annexin-V/PI staining. After *MAFA* transfection, HDDCs stained positive for MAFA and insulin (19.3 ± 3.3%) proteins, while ELISA assays showed detectable amounts of C-peptide content and release (21.45 ± 2.42 pg/ml per 10^6 cells) under basal conditions. **Conclusion:** We showed that *MAFA* RNA over-expression is sufficient to efficiently reprogram HDDCs toward β-cell-like phenotype in a timely manner. Further research is mandatory to demonstrate a controlled insulin secretion capacity after differentiation.

FC3.2

Experience with Molecular Diagnosis in 48 Cases of Neonatal Diabetes Mellitus Using Targeted Next-Generation Sequencing

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Background: Neonatal diabetes mellitus (NDM) comprises a group of monogenic disorders caused by mutations in genes involved in pancreatic development or insulin secretion. Accurate and rapid molecular diagnosis of NDM is pivotal for making decision on the treatment strategy. Next-generation sequencing (NGS) allows simultaneos analysis of several candidate genes, which facilitates the diagnostic procedure in NDM. **Objective and hypotheses:** To summarise our experience with molecular diagnosis of NDM using targeted NGS. **Method:** 48 children with NDM were studied. Seven patients had transient NDM (TNDM), while 41 patients had permanent NDM (PNDM), five of which showed features of DEND-syndrome. In seven subjects *KCNJ11*, *ABCC8* and *INS* genes were initially analysed by Sanger sequencing, and no mutations were found. 'Diabetes panel' genes were sequenced using a custom Ion Ampliseq gene panel and PGM semiconductor sequencer (Ion Torrent). Bioinformatic analysis was performed using Torrent Suite (Ion Torrent) and ANNOVAR (annovar.openbioinformatics.org) Software packages. **Results:** Mutations were identified in 38 of 48 patients (79.1%). Distribution of mutations was as follows: *KCNJ11*, $n = 22$; *INS*, $n = 7$; *ABCC8*, $n = 3$; *INSR*, $n = 2$; *EIF2AK3*, $n = 1$; *FOXP3*, $n = 1$; and *HNF1B1*, $n = 1$. One patient showed digenic (*HNF1A* and *GLIS3*) mutatons. Nine mutations were novel. The patient with PNDM and *EIF2AK3* defect had no features of Wolcott-Rallison syndrome at the time of diagnosis. Seventeen children with *KCNJ11* defects were successfully switched from insulin to glibenclamide. **Conclusion:** The study shows that targeted NGS can be successfully used in infants with NDM. **Funding:** This work was supported by Alfa-Endo Program of Charities Aid Foundation (CAF) Russia.

FC3.3

Clinical Characteristics and Molecular Genetic Analysis of Six Patients with Pancreas Aplasia and Neonatal Diabetes: Predominance of PTF1A-Enhancer Mutations

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Background: Pancreas aplasia (PA) and neonatal diabetes mellitus (NDM) syndrome is a rare disease that usually presents in the 1st months of life. **Objective and hypotheses:** We aimed to characterize molecular genetic defects in a cohort of six NDM/PA patients with up-to-date unknown pathogenesis with optimum genetic testing. **Method:** As part of our ESPE-RU-project 'Understanding the molecular basis of diabetes mellitus associated with novel syndromes', we established a cohort of six patients with neonatal diabetes (five onset < 6 months of life, one at 2.5 years) and pancreas aplasia or hypoplasia. In detail, four of six individuals had consanguineous parents, two had complete pancreas aplasia, three pancreas hypoplasia and one had aplasia of the dorsal pancreas. For genetic analysis, we performed Nextera Rapid Capture exome assay, a custom-designing target enrichment (including 57 genes coding for monogenic diabetes, type 2 diabetes risk or pancreas development, including the PTF1A enhancer region). **Results:** We identified one homozygous PTF1A enhancer mutation (Hg19: Chr 10: 23508437 A > G) in four of our six individuals with three families having known consanguinity. All individuals had a reduced exocrine pancreas function, but applying pancreas imaging only two had complete pancreas aplasia while two had pancreas hypoplasia. From the additional two individuals the first had dorsal pancreas aplasia and a de-novo mutation V252M (c.G754A) in KCNJ11 explaining NDM but not PA. In the second individual from one consanguineous family, we could not identify any genetic cause, including NGS and haplotype mapping of his family. **Conclusion:** The known homozygous mutation in the distal enhancer region of *PTF1A* was the commonest cause of PA/NDM in our cohort and the novel KCNJ11 mutation could at least explain neonatal diabetes in the fifth case. The high rate detecting disease-causing mutations reflects the contribution of new genetic knowledge and systematic use of novel techniques (targeted enrichment, NGS). **Funding:** This work was supported by the ESPE-RU-project 'Understanding the molecular basis of diabetes mellitus associated with novel syndromes'.

FC3.4

Wolfram Syndrome: Natural History and Genotype–Phenotype Correlation Based on EURO-WABB Registry Show Gender Differences in Disease Severity

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Background: Wolfram syndrome (WS) is a rare autosomal recessive disorder, characterised by early-onset diabetes and optic atrophy. It is caused by mutations in *WFS1*. **Objective and hypotheses:** This study aimed to comprehensively review the natural history of WS in a large cohort of patients from the EURO-WABB registry. **Method:** Data from EURO-WABB patients with WS was analysed in conjunction with the Leiden Open Variation Database (LOVD) for genotype–phenotype correlation. **Results:** 174 WS patients (90M:84F) had standardised data available. Mean age of diagnosis was 8.39 years (S.D. 4.39). Most patients followed a classical sequence of clinical manifestations (deafness – median age of onset 1 (range 0–9 years); insulin-dependent diabetes – 5 (1–32 years); optic atrophy – 8 (0–32 years); diabetes insipidus – median age – 13 (3–34 years); urological abnormalities – median age 16 (12–20 years) and neurological abnormalities – median age 25.5 (7–40 years)). 11 patients (6.3%) had hypergonadotrophic hypogonadism. A proportion of patients had abnormalities not usually associated with WS: retinal dystrophy (4.6%, $n=8$), chronic renal failure (5.7%; $n=10$) and cardiomyopathy (2.8%, $n=5$). 91 patients had mutations found in both alleles. 16 patients had only one mutation identified. 56 patients had no mutation in either allele identified. 80.8% of all mutations were located within exon 8. Most mutations were nonsense with predicted effects of reduced or truncated WFS1 protein. There was no significant genotype-phenotype correlation for age of onset of diabetes or optic atrophy (nonsense vs missense mutations). There was a gender difference in disease severity with earlier age of onset of insulin dependent diabetes (M = 4 years; F = 5 years; $P=0.04$) and incidence of mental health disorders with males being more frequently affected (26M:15F) although this was not significant. **Conclusion:** Analysis of the core data from EURO-WABB, the largest standardised patient cohort to date, shows a sequence of clinical manifestations similar to published literature. The phenotypic spectrum of WS is much wider than previously reported. Of note, is the male preponderance with mental health problems including depression and psychosis. **Funding:** The EURO-WABB project has received funding from the European Union, in the framework of the Health Programme (Grant Agreement Reference: 2010 12 05).

FC3.5

C-Peptide Levels and Glycaemic Control in Children, Adolescents, and Young Adults with Type 1 Diabetes

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Background: C-peptide, an indicator of own insulin production, is usually very low in patients with type 1 diabetes (T1D). **Objective and hypotheses:** The aim of the study was to evaluate C-peptide levels in children and adolescents and young adults with T1D and to correlate them with glycemic control. **Method:** Fasting C-peptide levels were measured with RIA, in 118 children, adolescents and young adults (60 females, mean age 13.3 S.D. (5.9) years, median disease duration 5.8 years (range 0–25 years)). C- peptide was measured after a median period of 1.3 years (range 0–22). HbA1c, daily insulin requirements, height, and weight anti GAD65 anti IA2 autoantibodies were evaluated**.** Out of 118 subjects 65 were on continuous insulin infusion and 53 on a multiple injection regimen. **Results:** C-peptide was measured in 56 subjects <1 year after diagnosis, in 27 1–5 years and in 34 >5 years and found increased (>3 ng/ml) in 53% of subjects, even when measured >5 years after diagnosis vs 80.3% <1 year and 77.7% between 1 and 5 years ($P=0.014$). Out of 83 subjects with C-peptide >0.3 ng/ml 38.5% were <5 years old at T1D diagnosis, 37.3% between 5 and 10 and 24% >10 years old ($P=$NS). HbA1c was not different between two groups of C-peptide (>0.3 or <0.3 ng/ml) after exclusion of HbA1c values at the time of diagnosis. Furthermore there was no difference in age, daily insulin requirements and BMI between the two groups, however, subjects with C-peptide <0.3 ng/ml had longer disease duration vs those with higher C-peptide ($P=0.004$). Linear regression analysis showed no correlation between HbA1c levels at the time of last visit and previous C-peptide levels. Out of 19 subjects with negative autoantibodies 13 had higher C-peptide values. **Conclusion:** C-peptide levels higher than 0.3 ng/ml can be found in subjects with T1D, even years after diagnosis. Nevertheless these higher values do not seem to affect significantly glycaemic control.

FC3.6

First Report of Nationwide Incidence and Prevalence of Type 1 Diabetes Among Children in Turkey

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Background: Data on the epidemiology of type 1 diabetes among children in Turkey are limited. **Objective and hypotheses:** The aim of this study was to report, for the first time, the incidence and prevalence of childhood type 1 diabetes in Turkey using a nationwide registry. **Method:** Information on birth date, city of birth, diagnosis date and gender of all type 1 diabetes patients aged less than 18 years were obtained from the Turkish Social Security Institute from January 2011 through December 2013. **Results:** There were 17 175 prevalent cases of type 1 diabetes over the 3-year period. The prevalence of type 1 diabetes was 0.75/1000. There were 2465 incident cases in 2013. The female to male cases ratio was 1.02. The incidence was 10.4/100 000 for males and 11.3/100 000 for females. The age standardised incidence rate was (10.8/100 000) according to the World Health Organization standard population estimated using the direct method. The highest proportion of cases was diagnosed between the ages of 10 and 14. **Conclusions:** This is the first study to report the incidence and prevalence of type 1 diabetes in children in Turkey. The location of Turkey, as a bridge between Asia and Europe, is reflected in its incidence, which is higher than Asia but lower than Europe.

FC4.1

Heterozygous Dominant Negative *STAT5B* Variants associated with Short Stature and GH Insensitivity

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Background: Homozygous mutations in *STAT5B* result in GH insensitivity and immune dysfunction. Heterozygous dominant negative mutations have not been described. **Aims and objectives:** To characterize genomic *STAT5B* DNA in two families exhibiting short stature. **Methods:** Sanger sequencing of *STAT5B* from genomic DNA. Mutant *STAT5B* constructs were expressed in HEK293 cells. **Results:** *Family 1*: The index case grew at −2.9S.D. from the age of 2 years. Investigations revealed IGF1 <25 ng/ml, IGFBP3 1.29 ng/ml (NR0.8–3.9), prolactin 265–65 3 mU/l (NR59-271), GH-peak (glucagon test) 17.3 μg/l, and normal GH-peaks on overnight sampling. A standard and extended 3-step IGF1-generation test (2 weeks GH sc at 0.7, 1.4 and 2.4; mg/m^2 per day) showed a poor response. His brother had short stature (−2.9S.D.), mild speech delay, eczema, undetectable IGF1, a GH peak of 13.9 μg/l and poor response in the IGF1-generation test. Both brothers had elevated IgE concentrations. Family histories were positive for short stature, eczema and transient hyperprolactinaemia. A heterozygous missense variant c.1433C>T (p.Ala478Val) was identified within the conserved STAT5B DNA-binding domain, and segregated with the phenotype. *Family 2*: Male monozygotic twins presented at age 14 years with short stature (−5.3SDS), eczema and a history of mild respiratory infections. Investigations revealed a provoked GH peak of 16.2 μg/l, low IGF1 (56 μg/l) and elevated IgE concentrations. rhIGF1 therapy led to modest catch-up growth. A *de novo* heterozygous variant (c.530A>C; p.Gln177Pro) was identified. Neither of the *STAT5B* variants are listed in control databases. Functional evaluation of the FLAG-STAT5B mutants indicated normal protein expression and phosphorylation but severely compromised nuclear translocation and transcriptional function compared to WT. Both variants inhibited translocation and transcription activity of WT FLAG-STAT5B, suggesting a dominant-negative mode of action. **Conclusion:** This is the first description of dominant-negative *STAT5B* mutations in subjects with short stature and mild GH insensitivity. Eczema may also be related to impaired STAT5B function.

FC4.2

A Recurrent Homozygous *NDUFB3* Mutation, p.Trp22Arg Causes a Short Stature Disorder and Mitochondrial Protein Complex I Deficiency with a Variable Metabolic Phenotype

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Background: Many children with short stature (defined as height SDS <−2S.D.) have no identified cause for their growth impairment and are classified as either small for gestational age or idiopathic short stature depending on birth size. Whole exome sequencing (WES) is a useful tool to identify new genetic diagnoses in this group. Here we describe a recurrent *NDUFB3* mutation in children with intra-uterine growth retardation, short stature and a variable metabolic phenotype. **Patients and methods:** Two

siblings (one male aged eight birth weight 2.5 kg, one female aged seven birth weight 2.27 kg) presented with short stature and subtle dysmorphism. No diagnosis was reached despite extensive biochemical and genetic investigations. WES of the mother and affected siblings was undertaken. **Results:** One variant compatible with autosomal recessive inheritance with a minor allele frequency $<1\%$ and predicted to be deleterious by *in silico* analysis was identified. This missense variant (c.64T>C, p.Trp22Arg) in *NDUFB3* (NADH-ubiquinone oxidoreductase 1 beta subcomplex 3, a nuclear encoded component of complex I of the mitochondrial respiratory chain) was previously reported to be associated with a severe neurometabolic phenotype and death in infancy. Sanger sequencing confirmed parents and unaffected siblings were heterozygous and affected siblings homozygous for the mutation. A targeted next generation sequencing strategy identified a further seven patients, from six families, all homozygous for the p.Trp22Arg mutation. They comprise a clinically distinct group with intra-uterine growth retardation, postnatal growth impairment and characteristic facial appearance with frontal bossing, midface hypoplasia and poorly defined philtrum. Intelligence is normal and the metabolic phenotype is variable from no symptoms to life threatening episodes of lactic acidosis and cardiomyopathy in infancy. **Conclusions:** Patients with the *NDUFB3* p.Trp22Arg mutation may present with pre- and postnatal growth failure with a variable metabolic phenotype where some patients may present only with growth failure and subtle dysmorphism. **Funding:** This work was supported by a Society for Endocrinology Early Career Grant.

FC4.3

An Updated and Final Analysis of a Randomised Placebo-controlled Trial of the Effect of Oxandrolone and Timing of Pubertal Induction on Final Height in Turner Syndrome

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Background: While GH therapy forms the mainstay of growth promoting treatment for Turner syndrome (TS), adjunctive use of oxandrolone and optimal timing of pubertal induction remain controversial. The previously published interim analysis of this randomised double-blind placebo-controlled trial demonstrated that oxandrolone and pubertal induction at 14y vs 12y significantly increased final height. However, these effects were not additive. **Objective:** To update the analysis now the remaining participants have reached adult height. **Method:** Girls with TS aged 7–13y receiving GH (10 mg/m^2 per week) were randomised to oxandrolone (0.05 mg/kg per day, max. daily dose 2.5 mg) or placebo from 9y. At 12y, those with ovarian failure were further randomised to oral ethinylestradiol (year 1, 2 μg daily; year 2, 4 μg daily; year 3, 4 months each of 6/8/10 μg daily) or placebo (until the age of 14y, when puberty was induced using the same protocol). The primary outcome measure was final height. **Results:** 106 participants were recruited from 36 hospitals (1999–2003); 14 participants withdrew leaving 92 who completed therapy and reached final height by 2013. Mean (S.D.) final height was 151.8 (6.3) cm. As in the interim analysis, oxandrolone significantly increased final height – by 4.1 cm (95% CI 1.6 to 6.6 cm ($P=0.002$, $n=92$). Delaying pubertal induction to 14y increased final height by 2.7 cm (95% CI −0.8 to 6.1 cm) but this was no longer statistically significant ($P=0.13$, $n=56$). No excess virilisation was reported. **Conclusion:** This study confirms the positive effect of oxandrolone, consistent with other reports. Failure to demonstrate a similar effect of delaying pubertal induction may be due to the study being underpowered. However, since the effects in the interim analysis were not additive, there can be little support for delaying pubertal induction much beyond 12y (already relatively late compared to normal) when oxandrolone is available. **Funding:** Funding was provided by the Scottish Executive Chief Scientist Office (1999–2004) (K/MRS/50/C2713) and the British Society for Paediatric Endocrinology and Diabetes (2004–2013), with a contribution to funding of pharmacy staff from the Child Growth Foundation.

FC4.4

Modulation of *GH-1* Splicing as Potential Strategy to Rescue GH Deficiency Type II

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Background: Isolated GH deficiency type II (IGHD II), the autosomal-dominant form of GH deficiency, is mainly caused by specific splicing mutations in the human GH (hGH) gene (*GH-1*). These mutations, occurring in and around exon 3, cause complete exon 3 skipping and produce a dominant-negative 17.5-kDa GH isoform that reduces the accumulation and secretion of *wt*-GH. **Objective and hypotheses:** As the severity of IGHD II inversely correlates with the amount of 17.5-kDa produced and with the 17.5/22-kDa ratio, increasing the inclusion of exon 3 during splicing is expected to ameliorate disease symptoms. To test this hypothesis we modulated *GH-1* splicing by overexpressing ASF/SF2, the alternative splicing factor 2, known to promote GH exon 3 inclusion *in vitro* and *in vivo*. **Method:** Rat pituitary cell line stably expressing hGHRHR (GC-GHRHR cells) were transiently transfected with either *wt*-GH or with different GH-splice site mutants (IVS+2, IVS+6 and ISE+28), stimulated with GHRH (10 nM) and/or additionally transfected with ASF/SF2 for 24 h. The differences in the splicing pattern of *wt*-GH vs GH-splice site mutants were assessed by qRT-PCR and

western blot. Extracellular GH-secretion was measured in aliquots of cultured medium by DSL-GH ELISA. **Results:** At the mRNA level, overexpression of ASF/SF2, promoted exon 3 inclusion and increased the amount of full-length transcripts ($P<0.05$). At the protein level, we could observe an increased synthesis of the 22-kDa isoform ($P<0.05$) and therefore a decreased 17.5/22-kDa ratio ($P<0.05$). Overall, the switched balance between the two GH isoforms resulted in a statistically increase of GH secretion ($P<0.01$) in all GH-splice site mutants analysed. Moreover, the impact of ASF/SF2 overexpression was more pronounced in presence of GHRH ($P<0.01$). **Conclusion:** While rhGH replacement therapy in IGHD II patients helps growth, it does not prevent the development of other pituitary hormone deficiencies in many of these patients. In this study we propose an alternative approach to IGHD II and we showed that, targeting *GH-1* splicing, it is possible to significantly rescue the GH secretion and to reduce the 17.5/22-kDa ratio which has been established as a parameter of IGHD II clinical severity.

FC4.5

Stunted Growth after Inhaled Corticosteroid Use during the First 24 Months of Life

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Background: Inhaled corticosteroids (ICS) are used frequently in infants with recurrent wheezing. They may have potential adverse effects as treatment of childhood asthma with ICS decreases growth velocity and adult height. ICS treatment in infancy is thought to alter linear growth only little, but however, studies on ICS use in infancy and linear growth are practically lacking. **Objective and hypotheses:** To evaluate the impact of ICS on linear growth during infancy. **Method:** A population-based cohort of 6391 boys and 6091 girls with data on primary care height and weight measurements, parental heights and drug purchases from birth to 24 months was collected. Height-for-age deviation from the target height (TH) and height velocity (HV) were calculated, and expressed as *z*-scores (zTH and zHV) at the median age of 24 months (interquartile range 24–26 months). These were compared between ICS (fluticasone and budesonide) exposed and unexposed infants using the analysis of covariance with maternal, perinatal, auxological and medication factors as covariates. **Results:** ICS exposed infants were on average shorter than the unexposed infants ((adjusted zTH and zHV differences −0.16 (95% CI −0.22 to −0.11, $P<0.001$) and −0.28 (−0.37 to −0.19, $P<0.001$)). The effect was most pronounced after exposure to budesonide prior to 12 months of age (zTH −0.31 (−0.46 to −0.16) and zHV −0.34 (−0.58 to −0.09)) or lasting more than 6 months (zTH −0.63 (−0.89 to −0.37) and zHV −0.70 (−1.13 to −0.27)). **Conclusion:** Long-term treatment of ICS during infancy was associated with stunted growth at or after the age of 24 months in otherwise healthy children. Stunting of linear growth in infancy may cause permanent loss of growth potential with decreased adult height. These observations highlight the importance of appropriate use of inhaled corticosteroids in infants. **Funding:** This work was supported by the Päivikki and Sakari Sohlberg Foundation and the Kuopio University Hospital State Research Funding.

FC4.6

Positive Association between Height and Cancer in the Swedish Population

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Background: Previous studies have indicated that taller individuals have a higher risk of developing different types of cancer, including breast cancer and melanoma. **Objective and hypotheses:** Our goal was to study any association between height and the risk of cancer in general-, and breast cancer and melanoma specifically in a very large cohort composed of most Swedish women and men followed over a long period of time. **Method:** We have performed a cohort study of 5.5 million women and men born between 1938 and 1991 with adult heights ranging between 100 and 225 cm. They were followed from 1958 or from the age of 20 if occurring later until the end of 2011. Adult heights were collected from the Swedish Medical Birth-, the Swedish Conscription-, and the Swedish Passport Registers. Cancer data were retrieved from the Swedish Cancer Register. **Results:** Risks are presented as hazard ratios (HRs) with 95% CIs for every 10 cm increase in height. Adjustments have been made for education and income and the analyses are stratified by birth year. **Conclusion:** We found that total cancer risk and risks of breast cancer and melanoma were higher with increasing height in the Swedish population. This is in line with previous studies. Thanks to the extensive national registers in Sweden, we were able to obtain height and cancer data from the majority of the Swedish

	HR (CI)	
	Women	Men
Total cancer	1.18 (1.17, 1.19)	1.11 (1.10, 1.12)
Breast cancer	1.20 (1.18, 1.22)	NA
Melanoma	1.32 (1.28, 1.36)	1.27 (1.23, 1.31)

population. This association has never before been studied in such a large cohort including both genders. **Funding:** This work was supported by HKH Kronprinsessan Lovisas förening för Barnasjukvård and Stiftelsen Samariten.

FC5.1

Resveratrol Potentiates Growth Inhibitory Effects of Rapamycin in PTEN-deficient Lipoma Cells by Suppressing p70S6 Kinase Activity

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Background: Patients with PTEN (phosphatase and tensin homolog) hamartoma tumor syndrome and germ line mutations in *PTEN* frequently develop lipomatosis, for which there is no standard treatment. Rapamycin was shown to reduce the growth of lipoma cells with heterozygous PTEN deficiency *in vitro*, but concomitantly induced an up regulation of AKT phosphorylation. **Objective and hypotheses:** Since it was shown that resveratrol stabilizes PTEN, we asked whether co-treatment with resveratrol could suppress the rapamycin-induced AKT phosphorylation in *PTEN*-deficient lipoma cells. **Method:** *PTEN*-deficient lipoma cells and primary PTEN WT preadipocytes were treated with resveratrol, rapamycin or a combination of both. Cell viability was measured by WST-1. Analysis of cell cycle and apoptosis induction was done by staining with propidium iodie and annexin-V-FITC/propidium iodide, respectively, with subsequent flow cytometry. Expression of PTEN and phosphorylation of AKT, S6 kinase and mammalian target of rapamycin was analysed by western blot. **Results:** Resveratrol treatment resulted in decreased lipoma cell viability by inducing G1 phase cell cycle arrest and apoptosis. PTEN expression and AKT phosphorylation were not significantly changed, whereas p70S6 kinase phosphorylation was reduced in *PTEN*-deficient lipoma cells after resveratrol treatment. Rapamycin/resveratrol co-treatment significantly decreased viability further at lower doses of resveratrol and resulted in decreased p70S6 kinase phosphorylation compared to rapamycin treatment alone, suggesting that resveratrol potentiated the growth inhibitory effects of rapamycin by reducing p70S6 kinase activation. Both viability and p70S6 kinase phosphorylation of primary *PTEN* WT preadipocytes were less affected compared to *PTEN*-deficient lipoma cells by equimolar concentrations of resveratrol. **Conclusion:** These results support the concept of combining chemopreventive natural compounds with mTOR inhibitors in cancer therapy to increase the efficacy of chemotherapeutic drugs. **Funding:** We are grateful for the support and funding of the Integrated Research and Treatment Center (IFB) Adiposity Diseases MD Pro_1 and MD Pro_2 granted to J L, Clinical Research Units (KFO) 152 (K7-10) and 'Kompetenznetz Adipositas Seed Money' grant to A G.

FC5.2

MEN1 Syndrome Because of Combined Germline and Somatic Mosaicism, with Important Consequences for Relatives

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Background: Multiple endocrine neoplasia type I (MEN1) is characterized by the combined occurrence of tumours in several endocrine tissues such as parathyroid tumours, pituitary tumours (usually prolactinomas) and pancreatic neuroendocrine tumours. MEN1 is an autosomal dominant disorder caused by germline mutations in the tumour suppressor gene *MEN1*. First-degree relatives of a germline MEN1 mutation carrier have a 50% risk of the mutation. Intensive surveillance of germline carriers starts at age 5 years. **Case presentation:** The index patient in this family presented at age 16 years with primary amenorrhoea, caused by a prolactinoma. At the age of 26 years she had urolithiasis, because of primary hyperparathyroidism. Germline DNA testing showed a heterozygous deletion of the *MEN1* gene (c.-101-?_1848+?del). Surprisingly neither her father (known with urolithiasis), nor her mother appeared to carry the same germline *MEN1* mutation. Because somatic mosaicism in the parents could be present, her brother was tested and was found to have the *MEN1* mutation. Surveillance showed hyperparathyroidism and a thymus carcinoid. Then their father was diagnosed with a pancreatic neuroendocrine tumour. Tumour DNA analysis showed the same *MEN1* mutation as in the germline of both his children. **Conclusion:** This is the first reported case of combined germline and somatic mozaicism for a *MEN1* mutation. This family history shows that in families with an apparent de novo genetic mutation, germline mozaicism is important to consider. Especially in cancer syndromes, it has major implications for the family's surveillance, treatment and prognosis.

FC5.3

Screening in Children with Succinate Dehydrogenase B (SDHB) Mutations: a Single Centre's Family Clinic Experience

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Background: Germline mutations in *SDHB* gene are associated with the familial paraganglioma (PGL) syndrome that carries the highest malignant potential. Although penetrance is lower than initially described, lack of effective treatments for

metastatic PGLs makes screening essential for early tumour detection, surgical removal and improved outcome. However, no consensus exists in relation to timing and mode of screening. **Objective:** To assess published data and examine our cohort to produce screening recommendations for children with *SDHB* defects. **Method:** A retrospective review of children with *SDHB* mutations at Barts Hospital between 1989 and 2014 was undertaken. This cohort includes 21 patients who were either diagnosed with PGLs <18 years, or whose screening started <18 years (family members carrying *SDHB* mutation). **Results:** Within our cohort, seven children had PGLs, with one PGL identified on initial routine screening. This 15 years male was asymptomatic but found to have elevated catecholamines and a large retroperitoneal mass on MR scanning. The youngest two patients (both females) diagnosed with PGLs in our cohort were 10 years. One was successfully treated for an abdominal PGL, but aged 23yr developed metastatic disease. The other had a para-aortic PGL, which was successfully resected but recurred 17 years later with metastases in addition to a renal medullary carcinoma. **Conclusion:** We believe that initial clinical screening should be undertaken between the ages of 5–7. Our adult imaging surveillance includes biennial neck-to-pelvis MRI with abdominal imaging alone annually. Age at which each child enters adult surveillance regime should be determined on an individual basis and for most children this could be considered from 10 years old. Yearly abdominal USS should be considered <10 years if tolerated, but clinician should be aware of its limitations. We found that joint adult/paediatric family clinic works well for families in terms of convenience, anxiety reduction and to tailor screening to the individual child.

FC5.4

X Chromosome Gene Dosage and the Risk of Developing Congenital and Acquired Traits in Turner Syndrome: a Cross-Sectional Database Analysis of the French National Rare Disease Network

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Background: The broad spectrum of associated diseases underlying the diverse phenotypes of patients with Turner syndrome (TS) has been extensively described. However, the underlying pathophysiological mechanisms remain unknown. Few studies have analyzed congenital and acquired diseases as a function of karyotype, and conflicting results have been obtained, calling into question the role of haploinsufficiency for genes located on the X chromosome. **Objective:** To investigate the effect of X chromosome gene dosage on the risk of developing congenital and acquired diseases, analysing a large database of patients with TS as a function of karyotype subgroup. **Method:** Congenital and acquired diseases were evaluated in 1536 and 993 patients, respectively, and analyzed, by karyotype subgroup, at a median age of 18.9 (16.1–25.3) years (similar for all karyotype subgroups), in this large observational cohort study. **Results:** Congenital heart and kidney malformations were more prevalent among 45X (27 vs 15%) and 45X, XrX, isoXq (25 vs 14%) patients, respectively, than among patients with mosaicism or with a Y chromosome. The cumulative incidence of acquired traits increased with age, and at 20 years, the highest prevalences were associated with isoXq for autoimmune thyroid diseases (31% (24;38)), isoXq and XrX for celiac disease (10% (6–17)) and isoXq, XrX and 45X for hearing loss (31% (27;35)). Lipid abnormalities were most prevalent among patients with XrX or a Y chromosome (24% (17;34)) and glucose intolerance or type 2 diabetes most prevalent among patients with XrX (12% (6;24)). Patients with XrX were more likely to have poor academic skills and those with mosaicism (45X/46XX) were more likely to display spontaneous puberty. **Conclusion:** Phenotypic traits are related to karyotype in TS, highlighting the importance of the effect of gene dosage for genes located on the X chromosome. Further studies are required to determine the genetic mechanisms underlying TS pathogenesis.

FC5.5

Hereditary Turner Syndrome 46,X,rec(X)inv(p21q28) in Six Women and Four Generations: Estimation of Skeletal Effects of GH Treatment

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Background: Terminal Xp-deletion causes a variant of Turner syndrome (TS). Several studies described the associated phenotype: gonadal function is generally preserved and short stature is the major clinical feature. **Case presentation:** We present a family with vertical transmission of TS affecting six women in four subsequent generations. SNP-array indicates that the chromosomal aberration in this family includes terminal Xp-deletion and terminal Xq-duplication constituting a recombinant X-chromosome. The karyotype was defined as 46,X,rec(X) inv(p21q28). Major phenotypic feature of all affected women was short stature. Other characteristic somatic signs of TS were absent. The women developed spontaneous puberty and regular menses, had normal fertility and regular menopause. Exclusively generation IV received GH. We estimated the effect of GH-treatment on the skeleton by comparing auxological and pQCT data of 39-year-old mother to her 14-year-old daughter. We found expected height gain for the daughter (before//after GH-treatment: -2.5//-0.8 SD) and improved final height (160.3 cm) compared to her mother (150.0 cm/ -2.7 SD).

Disproportion progressed for the daughter (before//after GH-treatment: upper body segment: −1.1//1.8 SD; lower body segment: −2.4//−2.2 SD), which confirms major growth-promoting effect on the trunk for patients with SHOX-deficiency. Finally the mother's disproportion (upper body segment: −0.5 SD; lower body segment: −2.7 SD) was milder compared to the daughter. Peripheral quantitative computed tomography (pQCT) confirmed normal trabecular bone density (mother: 0.1 SD, daughter: 1.9 SD) as well as normal strength-strain index (mother: 2.2 SD, daughter: 1.9 SD). **Conclusion:** This rarely found family demonstrates the possibility of vertical transmission of TS spanning multiple generations. Our results confirm significant height gain after GH-treatment and normal bone strength for both, treated and untreated woman. However, our study puts into question the impact of GH-treatment on disproportion.

FC5.6

Anti-Müllerian Hormone Levels in Patients with Turner Syndrome: Relation to Karyotype, Pubertal Development and GH Therapy

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Background: Gonadal dysgenesis in Turner syndrome (TS) results in pubertal delay or failure and infertility in most patients. However, up to 30% of girls with TS have spontaneous pubertal development and 2–5% have regular menstrual cycles before the onset of premature menopause. Serum anti-Mullerian (AMH) levels reflect the ovarian reserve in females, even in childhood. **Objective and hypotheses:** To Asses serum AMH levels in patients with TS and its relation to karyotype, spontaneous puberty, and GH therapy. **Methods:** Fifty TS patients were subjected to history, auxologic assessment and Tanner staging. Karyotype was obtained from patients' records. In addition, serum AMH, FSH and LH and oestradiol (E2) were measured. Pelvic ultrasound was done to assess uterine and ovarian volumes and fundic:cervical ratio. **Results:** Serum AMH was detectable in 24% of all TS girls and correlated strongly with karyotypes. A measurable serum AMH was found in 75% of TS girls with karyotype 45X/46XX, in 21% with other karyotypes and in 8% of 45X TS girls. A measurable serum AMH was also associated with signs of spontaneous puberty such as breast development (OR: 18.4; 95% CI 3.1–117.6; $P=0.003$) and menarche (OR 37.5; 95% CI 5.6–401.9; $P=0.001$). Serum AMH correlated negatively with FSH and LH, but did not correlate with E2. GH therapy increased the odds of having measurable AMH in TS girls (OR 6.1; 95% CI 2.8–5.8; $P=0.002$). **Conclusions:** Serum AMH levels could serve as a useful marker of the follicle pool and therefore ovarian function in paediatric patients with TS. Further studies are warranted to confirm the effect of GH therapy on AMH levels.

FC6.1

Correlation of AR Expression and AR Transcriptional Activity in Cultured Human Genital Fibroblasts

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Background: The androgen receptor (AR) is essential for the development of primary and secondary male characteristics and is activated by its ligand dihydrotestosterone (DHT). Reduced AR activity can cause undervirilization and infertility. We recently developed an assay to test AR function as a ligand-dependent transcriptional activator in human genital skin fibroblasts (GF). So far it is unclear, if AR expression levels correlate with AR function in the male external genitalia. **Objective and hypotheses:** To analyse, if AR expression could be a surrogate for AR function in GF by correlating AR-expression levels with AR activity in GF from fertile adult males as well as children who have undergone orchidopexy. **Method:** Cultured GF were derived from scrotal biopsies taken during vasectomy from fertile males as well as from boys during orchidopexy. In these GF *AR* mRNA expression was analyzed and, in parallel, AR transcriptional activity was determined through DHT-dependent induction of the androgen regulated AR target gene apolipoprotein D (APOD). A correlation coefficient was calculated between APOD induction (AR activity) and AR expression. **Results:** Vasectomy patients (fertile males $n=29$) showed a three- to fivefold APOD induction upon DHT treatment. AR expression varied widely leading to a low correlation coefficient between AR expression and AR activity (0.12). In contrast, boys who had undergone orchidopexy ($n=10$) showed a wider range of APOD induction which correlated highly with AR expression (0.84). AR expression levels did not differ significantly between adults and children and did not correlate with age. **Conclusion:** Our data show that during childhood, AR activity is closely linked to *AR* mRNA expression levels while this interrelation gets lost in adulthood. This suggests a profound biological change in the mechanism of regulation of cellular androgen sensitivity in different developmental stages from childhood to adulthood in the male. Biologically, this difference may be linked to the existing growth potential of the external genitalia in boys in response to pubertal androgen while genital outgrowth comes to a fixed end in adult males despite the long-term presence of high androgen. **Funding:** German Research Council (DFG; HO2073/7-1 and AM343/2-1).

FC6.2

A Role for DMRT1 in Human Primary Sex-Determination

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Background: DMRT transcription factors are highly conserved regulators of metazoan sexual development. The role of DMRT1 in human primary sex-determination is unclear. Chromosome 9p deletions that remove one copy of DMRT1 are associated with 46,XY feminization and gonadal dysgenesis. While they suggest that DMRT1 is haploinsufficient for testicular development, these deletions usually remove other genes, including DMRT2 and DMRT3. Also, most 9p deletions cause incomplete gonadal dysgenesis so it has been unclear whether loss of DMRT1 alone can cause full sex reversal. **Objective and hypotheses:** Using an exome sequencing approach on a large cohort of 46,XY individuals with gonadal dysgenesis, we predicted that mutations in DMRT1 should occur if it is a primary sex-determining gene. **Method:** Exome sequencing was performed on >100 cases of 46,XY complete gonadal dysgenesis using the Illumina HiSeq2000 System at $\times 50$ average coverage. *In vitro* DNA-binding and transient transfection assays were performed using the WT and mutated DMRT1 proteins. **Results:** We identified a *de novo* missense mutation (p.R111G) in a sporadic case of 46,XY complete gonadal dysgenesis. This mutation was absent in 200 ancestry-matched controls as well as the publicly available SNP databases. The mutation affects an arginine residue that located in DM-domain and which is conserved in both *Caenorhabditis elegans* and *Drosophila*. The DMRT1p.R111G protein shows reduced DNA-affinity and altered sequence specificity indicating a loss-of-function. Moreover the mutant protein showed a dominant disruption of WT DMRT1 binding stoichiometry at some DMRT1 binding sites. This combination of haploinsufficiency and dominant disruption may explain the severe phenotype caused by the DMRT1R111G mutation. **Conclusion:** This is the first amino acid change described in human DMRT1, which results in a complete absence of testis-determination. This indicates that in the human DMRT1 plays a role in primary sex-determination. **Funding:** This work was funded by the US National Institutes of Health (GM59152, GM50399, AI087098, and GM095558), COST Action DSDnet BM1303 and Program Blanc Assistance Publique-Institut Pasteur.

FC6.3

Establishing the Role of the Steroid Backdoor Pathway for Androgen Biosynthesis in the Human Ovary

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Background: Recent work revealed two pathways in androgen biosynthesis, namely the classic and an alternative, the backdoor pathway. In this alternative pathway dihydrotestosterone is produced from 17-hydroxyprogesterone without the intermediacy of testosterone using mostly enzymes that are specific to the backdoor path. In the human ovary, regulation of androgen production plays a crucial role in normal physiology and in pathologies such as the polycystic ovary syndrome (PCOS). But the regulation of ovarian androgen production is poorly understood. Therefore, while in the foetal testis a role of the backdoor pathway in androgen production has been suggested, its role in the human ovary remains to be established. **Objective and hypotheses:** Characterisation of the backdoor pathway in human ovarian androgen biosynthesis in health and disease. **Method:** Pathway analysis was performed on fresh frozen paraffin embedded ovarian tissue samples obtained from the Institute of Pathology Bern, Switzerland. Genes involved in the backdoor pathway were assessed by quantitative RT-PCR (qRT-PCR). Testis and adrenal tissues served as control. For the comparison of normal to aberrant ovarian physiology, we analysed tissue samples of control ovaries and of patients diagnosed with PCOS and ovarian endometriosis. Same tissues were investigated by immunohistochemistry. **Results:** Backdoor pathway genes including the aldo-keto reductases AKR1C1 – 1C4, the 5α-steroid-reductases types 1 and 2 (SRD5A1 and SRD5A2), 3β-hydroxysteroid dehydrogenase type 2 (HSD3B2), and the 17β-hydroxysteroid dehydrogenase type 6 (RoDH) are differentially expressed in the human ovary compared to adrenal and testis. Ovarian expression of aldo-keto- and steroid-reductase genes is low. By qRT-PCR, we found no difference in gene expression between normal ovaries and PCOS or endometriosis ovaries. **Conclusion:** Genes involved in the backdoor pathway are expressed at low levels in normal and abnormal human ovaries compared to testes and adrenals. Immunohistochemistry experiments are ongoing to show their localization and expression in normal and PCOS ovaries. **Funding:** This work is fully supported by the Swiss National Science Foundation. Grant number is 320030-146127 (granted to Prof. C E Flück, University of Berne, Switzerland).

FC6.4

Severe 46,XY Disorder of Sex Development due to CBX2 Isoform 2 Mutation is Distinct from CBX2.1 Deficiency and is Likely due to EMX2 Dysregulation in the Human Developing Gonad

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Background: The process of sexual differentiation is central for reproduction of almost all metazoan. Recently, we identified CBX2.1 a chromatin architecture regulator, as an essential transactivator for human male gonadal development. CBX2 has a second isoform CBX2.2. Since nothing is known about the role of CBX2.2 in human sex development, we took advantage of the p.C132R mutation in CBX2.2 in a 46,XY disorder of sex

development (DSD) patient with complete female phenotype and dysgenetic gonads. **Objective and hypotheses:** To place CBX2.2 in the sex development cascade and gain insights in DSD mechanism of disease. **Method:** We used the DNA adenine methyltransferase identification and next-generation sequencing in the human testicular NT2-D1 cells. The validation was carried out by overexpression of either WT or mutated CBX2.2 and qRT-PCR of the candidates. **Results:** We identified 1901 CBX2.2 targets. We then selected a subset of six candidates unique targets of CBX2.2. for validation based on potential links to sex development (Pathway Studio 10.5): *EMX2*, *MAK*, *HOXA13*, *WDR77*, *TWIST1*, and *BNC2*. The most relevant for us is *EMX2*: Emx2 XY deficient mice have gonadal agenesis and patients with deletions encompassing *EMX2* have 46,XY DSD. *EMX2* and *CBX2* are expressed at 7 weeks of gestation in humans, suggesting a role in the formation of the early gonad. WT CBX2.2 increased the expression of *EMX2* (3.2×) whereas the mutated CBX2.2 protein was inactive, indicating that the effect is CBX2.2-specific. Thus, it is intriguing to hypothesise that a mutation in CBX2.2 impairing *EMX2* expression causes gonadal dysgenesis in 46,XY individuals similarly to EMX2 haploinsufficiency but distinct from 46,XY CBX2.1 deficient patients, whose gonads presented with apparent ovarian tissue. **Conclusion:** Taken together, using a novel approach we were able to identify targets of CBX2.2 in the human sex development cascade, which could help to gain insights in the biology of the process and help elucidate the molecular basis of DSD. **Funding:** This work was supported by Grant of the Swiss National Science Foundation (number 320030_130645).

FC6.5

Characterisation of Mutations in the Androgen Receptor Identified in 38 Brazilian Families with Complete or Partial Androgen Insensitivity Syndrome

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Background: Androgen insensitivity syndrome (AIS) is a genetic disease X-linked, caused by functional abnormalities of the androgen receptor (AR). Mutations in the AR are associated with broad phenotypic spectrum from partial insensibility (PAIS) to complete insensitivity (CAIS). **Objective and hypotheses:** To characterize the mutations (MUT) identified in the AR in 38 Brazilian families with AIS. The MUT were analyzed considering their type, location in the gene, functional domain and associated phenotype. **Method:** PCR amplification of the coding and promoter regions of the *AR* gene, followed by direct sequencing. The identified MUT were searched in the literature, genomic sites and the novel MUT were evaluated by prediction sites. We classify MUT according to the type (missense and nonsense), exomic location, the affected functional domain (NTD, LDB, DBD, and Hinge) and phenotype (CAIS and PAIS). **Results:** We identified 17 different AR MUT in 22 families with PAIS ($n=37$) and 13 in 16 families with CAIS ($n=23$). Of these, six (CAIS) and eight (PAIS) have not been described. These novel variants are not found in either 1000 Genome and ESP-6500 database and the all of them were considered deleterious. Missense MUT were identified in 90.5% of PAIS and in 83% of CAIS and nonsense MUT in 9.5% of PAIS and 17% in CAIS. The frequency of MUT by exon differ between CAIS and PAIS patients, being more frequent in exons 5 and 7 (18 and 17%) in PAIS and in exons 1 and 4 (27 and 21%) in CAIS. In functional domains, there was a lower frequency of MUT in the DBD (12.5% in CAIS and 20% in PAIS) followed by the NTD (25% in CAIS and 20% in PAIS) and LBD (62.5% in CAIS and 60% in PAIS). We describe for the first time, a large deletion in the promoter region of the *AR* gene in a family with PAIS, whose exonic region was normal. Mutations in AR were not identified in 18.2% of families with PAIS (4/22) and 6.25% of the families with CAIS (1/16). **Conclusion:** The identification of MUT related to different phenotypes of AIS in Brazilian families allows for greater insight into genetic defects. The strategy of seeking MUT in the promoter region, when there is clinical suspicion of AIS without MUT in exonic region of the AR may allow the identification of genetic alteration in patients without exomic mutations.

FC6.6

Frequency of Gonadal Tumour in Complete Androgen Insensitivity Syndrome: a Retrospective Case-Series Analysis

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Background: Complete androgen insensitivity syndrome (CAIS) is an X-linked recessive disorder of sex development (DSD) where affected individuals are phenotypically female but have a XY karyotype and testes. With increasing age there is an increased risk of malignant gonadal change, with incidence rates variously reported from 3.6 to 14%. Consequently, gonadectomy is recommended either during childhood or after puberty is complete, although there is no consensus on the optimal timing for this procedure. **Objective and hypotheses:** To establish the frequency of histological abnormalities in CAIS in relation to the age and timing of gonadectomy. **Method:** Data was collected from the Cambridge DSD database on patients with CAIS ($n=225$; age range 3–88 years) undergoing gonadectomy, including – age and pubertal status at gonadectomy, gonadal histology, and immunohistochemistry. **Results:** Evaluable data was obtained from 139 patients. At time of gonadectomy, median (range) age = 12.8 years (18 days – 68 years); pubertal status $n=63$ pre-puberty; 70 post-puberty; six unknown. Gonadal abnormalities were reported in 26 cases: benign tumour $n=18$ (seven sertoli cell adenoma (SCA); eight testicular hamartoma (TH); two mixed SCA/TH; and one sex cord tumour with annular tubules)/malignant changes $n=8$ (one Sertoli cell tumour; one sex cord tumour; one seminoma; and five intra-tubular germ cell neoplasia). Pre-malignant changes were all confirmed on immunohistochemistry. In malignant/pre-malignant cases, median (range) age at gonadectomy = 18 years (1–68 years) with two out of eight individuals undergoing this procedure

before puberty. **Conclusion:** In this large case-series of CAIS patients undergoing gonadectomy evidence of malignant or pre-malignant change was found in 5.7% of cases and occurred before puberty in 1.4%. Consequently, it may be advisable to perform gonadectomy before puberty in those who present in early childhood, if there is a lack of tumour marker evidence to exclude malignancy.

FC7.1

Safety and Effectiveness of Increlex® Therapy in Children with Laron Syndrome and Enrolled in the European Increlex® Growth Forum Database in Europe

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Background: The post-authorisation registry, European Increlex® Growth Forum Database (EU-IGFD), initiated in December 2008, collects data in children receiving Increlex (mecasermin (rDNA origin) injection) for growth failure, including Laron syndrome (LS) (severe primary IGF1 deficiency with confirmed GH-receptor mutation). **Objective and hypotheses:** Report safety and effectiveness data in children with LS. **Method:** Multicentre, open-label observational study, eCRF data collection. **Results:** As of 2nd October 2014, nine countries enrolled 205 patients (115 naïve-prepubertal), including 29 LS patients (13 naïve-prepubertal). In LS patients (vs non-LS), 45% were females (vs 34%), 48% treatment-naïve (vs 69%). Mean (95% CI) treatment duration (days): 1413 (1190; 1636) (vs 916 (837; 995)); median dose (μg/kg BID): 40 at treatment initiation (both subgroups), 105 (vs 120) at year 1, 120 at year 2. Naïve-prepubertal LS patients had significantly higher Δ height SDS at year 1, vs naïve-prepubertal non-LS (linear regression, $P=0.006$). Targeted adverse events (TAEs) were reported in 69% LS patients (vs 36% non-LS); most frequently hypoglycaemia (41% vs 13%), lipohypertrophy (21% vs 9%), tonsillar hypertrophy (17% vs 5%), and otitis media (14% vs 3%). LS was a predictive factor for hypoglycaemia (OR (CI 95%): 0.21 (0.09;0.50); $P<0.001$). **Conclusion:** Height SDS increase was higher in LS patients vs non-LS and this was significant at year 1 in the naïve-prepubertal subgroup; however, they remained shorter. TAEs were more frequent in LS patients; LS was identified as predictive factor for hypoglycaemia. **Declaration of interest:** A Houchard and C Sert: employees of Ipsen. M Polak and J Woelfle: advisory boards for Ipsen and Novo Nordisk. **Funding:** This work and the study on which it is based were supported by Ipsen.

	n[a]	Height SDS	n[a]	Δ Height SDS
LS patients				
Baseline	26	−5.22 (1.63)		
Year 1	23	−4.46 (1.88)	22	0.50 (0.61)
Year 2	22	−4.51 (1.72)	20	0.77 (0.79)
Naïve-prepubertal				
Baseline	12	−5.80 (1.60)		
Year 1	10	−4.76 (2.09)	9	0.77 (0.54)
Non-LS patients				
Baseline	163	−3.50 (1.04)		
Year 1	139	−3.19 (1.10)	134	0.32 (0.44)
Year 2	102	−2.99 (1.24)	99	0.57 (0.62)
Naïve-prepubertal				
Baseline	97	−3.42 (0.95)		
Year 1	84	−3.03 (0.95)	81	0.36 (0.40)

[a]Available at timepoint.

FC7.2

Topicon™ ThermoMatrix™-Mediated Passive Transdermal Delivery of IGF1 Across EpidermFT Full-Thickness Human Skin Equivalent: Towards an Extended-Wear IGF1 Patch

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Background: There is a need for a convenient and affordable alternative to twice daily s.c. injections for children with IGF1 deficiency (IGFD) and growth failure. We report a novel platform technology, *Topicon™ ThermoMatrix™*, applied to the transdermal delivery of IGF1 (7649 Da). **Objective and hypotheses:** We sought to develop a convenient, non-invasive, and affordable transdermal patch formulation capable of achieving passive delivery of large molecule drugs such as IGF1, insulin, and GH for multiple days. **Method:** Lyophilized IGF1 was reconstituted in a *Topicon™ ThermoMatrix™* formulation that transitions from solid at 25 °C (room temperature) to gel at 30–32 °C (skin temperature). Formulations containing IGF1 were applied as 50 μl gel to EpidermFT™ tissue inserts, which are barrier-enhanced, full thickness, and metabolically active human skin equivalents (HSEs) when cultured in maintenance medium at 32 °C. Equal volume of medium was sampled and replenished every 24 h. IGF1 concentrations were measured by using a Quantikine® ELISA Kit (R&D Systems). Steady-state IGF1 flux (J_{ss}) was calculated using Fick's first law of diffusion. **Results:** IGF1 *Topicon™ ThermoMatrix™* formulations over the dose range of

5–500 μg/0.6 cm^2 achieved and maintained a maximum J_{ss} of 0.8 μg/cm^2 per h for 7 days. We observed a dose–response effect over the tested dose range, which was non-saturating. The calculated steady-state plasma level in pediatric IGFD patients after twice daily 0.12 mg/kg s.c. injection of Increlex™ is 250 ng/ml. Extrapolated to 7.7 l volume of distribution (30 kg boy) for Increlex (mecasermin), a 64 or 25 cm^2 patch containing 500 μg/0.6 cm^2 of IGF1 would achieve the target steady-state plasma level of 250 ng/ml in 1.5 or 4.5 days respectively. MTT assays showed that epidermal cell viability was preserved, independent of dose or time. **Conclusion:** These rigorous *in vitro* studies support the feasibility of developing safe and effective extended-wear IGF1 *Topicon™ ThermoMatrix™* patches that replace daily injections and provide constant and consistent drug delivery. **Funding:** This work was supported by Prometheon Pharma, LLC, which has no formal business, commercial, or other relationship with the manufacturer (Ipsen) of commercially available IGF1 (Increlex).

FC7.3

IGF1 Levels, Complex Formation, and IGF-Bioactivity in GH-Treated Children with Prader–Willi Syndrome

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Background: Children with Prader–Willi syndrome (PWS) attain high serum immunoreactive IGF1 levels during standard dose GH treatment, which leads to concern, but lowering the dose, deteriorates their body composition. **Objective and hypotheses:** To evaluate serum IGF1, IGFBP3 and acid-labile subunit (ALS) levels, complex formation and IGF-bioactivity in GH-treated PWS children. We hypothesized that GH-treated children with PWS have a normal IGF-bioactivity, despite the high serum immunoreactive IGF1 levels. **Method:** We included 40 GH-treated PWS (1.0 mg/m^2 per day ≈ 0.035 mg/kg per day) children and compared them with 41 age- and sex-matched healthy controls. Main outcome measures were serum IGF1, IGFBP3 and ALS levels, complex formation and IGF-bioactivity by IGF1 receptor kinase activation assay (KIRA). **Results:** Serum IGF1, IGFBP3, ALS levels, and IGF1/IGFBP3 ratio were significantly higher in GH-treated PWS children than in healthy controls. The 150 kDa ternary complex formation was, however, also significantly higher than in controls, indicating that most of serum IGF1 is sequestered in the ternary 150 kDa complex with ALS and IGFBP3. Young GH-treated PWS children, median (IQR) age 5.2 (4.3–7.2) years, exhibited higher serum IGF-bioactivity than controls, but no difference was observed in IGF-bioactivity between older GH-treated PWS children, age 14.9 (13.8–16.2) years, and controls. The proportion of IGF-bioactivity of total serum IGF1 was, however, lower in GH-treated PWS children than in controls. Serum immunoreactive IGF1 levels did not correlate with IGF-bioactivity in GH-treated children with PWS, in contrast to a strong positive correlation in healthy controls. **Conclusion:** In GH-treated PWS children, most off serum IGF1 is sequestered in the 150 kDa complex. Higher IGF-bioactivity was only found in young GH-treated PWS children and not in the older ones. IGF-bioactivity during GH showed a wide variation and there was a disrupted correlation with immunoreactive IGF1 levels, which makes immunoreactive IGF1 levels an inappropriate indicator of GH-dosing in PWS children. **Funding:** This study was an investigator-initiated study, supported by an independent research grant from Pfizer.

FC7.4

A Novel Reversible Albumin-Binding GH Derivative Possesses a Promising Once-Weekly Treatment Profile in Children with GH Deficiency

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Background: GH administration restores normal growth in children with GH deficiency (GHD). However, current daily s.c. injection treatment regimens may be inconvenient leading to impaired adherence and subsequently suboptimal treatment outcomes. NNC0195-0092 is a novel, reversible albumin-binding GH developed for once-weekly administration. **Objective and hypotheses:** This was a randomised, open-label, active-controlled, dose-escalation trial (NCT01973244) investigating the safety, tolerability, pharmacokinetics, and pharmacodynamics of a single dose of NNC0195-0092 compared with once-daily GH for 7 days. **Method:** Four cohorts of eight prepubertal children (≥6 and <13 years) with GHD on GH therapy (≥3 months) were investigated ($n=32$). Within each cohort, children were randomised to receive either a single s.c. dose of NNC0195-0092 (0.02, 0.04, 0.08, or 0.16 mg/kg; $n=6$) or once-daily GH for 7 days (0.03 mg/kg; $n=2$). Each child was allocated to one dose level only. Current GH therapy was discontinued 7–10 days before randomisation. At each dose-level, the pharmacokinetics and pharmacodynamics (IGF1 and IGFBP3) were evaluated. **Results:** All doses of NNC0195-0092 were well tolerated, with no safety or local tolerability issues identified. Dose-dependent increases in IGF1 and IGFBP3 were observed for $AUC_{(0-168\ h)}$ and C_{max} after adjustment for baseline. IGF1 responses following 0.04 and 0.08 mg/kg NNC0195-0092 and daily GH were similar. Mean changes in IGF1 and IGFBP3 were within reference ranges, except for a peak in IGF1 SDS in the 0.08 mg/kg NNC0195-0092

dose-group that was slightly above the reference range (days 1–3). **Conclusion:** All doses of NNC0195-0092 were well tolerated in children with GHD with no clinically relevant short-term safety or local tolerability issues observed. A dose-dependent IGF1 response, similar to the IGF1 response observed after daily GH, was found. The present data indicate that NNC0195-0092 may potentially serve as a well-tolerated once-weekly treatment for children with GHD. **Declaration of interest:** N Zuckerman-Levin and Z Gucev, consultants (Novo Nordisk and Spring). M H Rasmussen and M B Olsen, employees Novo Nordisk. L Sävendahl, consultant (Ferring, Novo Nordisk, Merck Serono, Pfizer, and Sandoz); grants (Merck Serono, Novo Nordisk, and Pfizer). T Battelino, board member (Novo Nordisk, Sanofi, and Eli Lilly). Consultation fees from Ferring, Novo Nordisk, and Pfizer. **Funding:** This study was sponsored by Novo Nordisk A/S, Denmark. Dr J de Schepper.

FC7.5

12-Month Safety and Efficacy of a Weekly Long-Acting GH (MOD-4023) Compared to Daily Recombinant Human GH Therapy in Pre-Pubertal GH-Deficient Children; Phase 2 Study: Study CP-4-004 Summary

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Objective and hypotheses: To compare the PK/PD, safety, efficacy, and tolerability of three doses of once-weekly MOD-4023 to that of a daily recombinant human GH (rhGH) formulation in pre-pubertal children with growth failure due to GH deficiency (GHD). **Method:** The randomised, controlled phase 2 study was conducted in 53 pre-pubertal, hGH-naïve GHD children randomised to receive one of three MOD-4023 doses as a once-weekly s.c. injection (0.25, 0.48, and 0.66 mg/kg per week) or daily rhGH (34 μg/kg per day) as a control arm. Annual height velocity (HV) was evaluated at 12 months, accompanied by assessment of safety, including metabolic profiles. **Results:** Last subject, last visit is anticipated in June 2015. Data on 49/52 subjects who completed 12 months treatment indicated that baseline demographic and auxological characteristics were comparable among all groups. Twelve months PK/PD profile following administration of MOD-4023 in these subjects demonstrated a significantly extended half-life compared to daily rhGH. A dose-dependent PK/PD (IGF1) response was observed among MOD-4023 dose cohorts, reaching steady state with no accumulation or excessive levels by 10 weeks. All cohorts demonstrated expected 'catch-up' growth, with subjects on the two highest doses of MOD-4023, demonstrating HV comparable to those in the hGH arm and ranging from 10 to 12 cm/year. Sub-analysis of HV response based on baseline characteristics confirmed a comparable response in all sub-populations. The 12-month safety analysis indicates a safety profile comparable to daily rhGH, while IGF1 and metabolic parameters remained within the normal range. **Conclusion:** Available data on the PK/PD, efficacy, and safety analysis of MOD-4023 administration to GHD children confirmed its long acting properties and affirmed that a single weekly injection of MOD-4023 has the potential to replace seven consecutive daily injections of rhGH in pediatric GHD patients. Further, final study data, anticipated in June 2015, will provide the basis for dose selection for phase 3.

FC7.6

Pharmacokinetic and Pharmacodynamics Modelling of MOD-4023 (a Long-Acting Human GH) in GH-Deficient Children

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Background, objective, and hypotheses: OPKO Biologics has produced a long-acting human GH (hGH), MOD-4023, containing copies of a naturally-occurring C-terminal peptide (CTP) to markedly increase GH's *in vivo* residence. We describe the construction and validation of a pharmacokinetic (PK) /pharmacodynamics (PD) model to characterise the relationship between MOD-4023 dose, MOD-4023 serum concentrations (Cserum), and IGF1 responses in healthy adults, GH-deficient (GHD) adults and GHD children. The model was used to characterise the PK and PD profile of MOD-4023 as part of the on-going paediatric GHD clinical studies. **Method:** MOD-4023 PK and PD were studied following administration to healthy adults ($n=18$), GHD adults ($n=46$), and GHD children (3–11 years of age, $n=53$). In children, doses were 0.25, 0.48, or 0.66 mg/kg weekly; genotropin® (hGH 34 μg/kg daily) was the comparator. Data from healthy adults were used to develop PK and PD models; models were then applied to GHD adults and children. Serum concentrations were fit to a linear compartmental model with first-order absorption and an absorption lag. An indirect-response PD model was applied to IGF1 data. Covariates (age, body size, gender, and organ function) were entered into the PK and PD models if justified statistically. **Results:** In adults and children, a two-compartment PK model fit Cserum data well. For PD modeling, the indirect response model generally fit IGF1 data well. Systemic parameters scaled allometrically; baseline IGF1 increased with age in GHD children. **Conclusion:** We constructed and validated MOD-4023 PK and PD models which predict the relationship between administered dose, Cserum, and IGF1 response with various dosing regimens in paediatric GHD population. This model can assist in safety monitoring, including dose selection and dose modification in future clinical studies.

FC8.1

DLK1 Expression in Adipose Tissue Following Fetal Growth Restriction: Relation to Visceral Fat Expansion and Catch-Up Growth in Wistar Rats

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Background: *DLK1* (*PREF1*) is a key inhibitor of adipogenesis and adipocyte differentiation. Adipose tissue expansion depends on adequate adipocyte differentiation. However, whether lower *DLK1* expression facilitates adipose tissue expansion following fetal growth restriction is so far unknown. **Objective and hypotheses:** To study the expression of *DLK1* in the adipose tissue of prenatally growth-restricted rats and its relation to postnatal visceral fat and weight gain. **Method:** Calorie restriction during gestation was used to induce intrauterine growth retardation in Wistar rats. Dams on a 50% calorie-restricted diet delivered growth-restricted pups with low birth weight (R). Restricted offspring fed a standard rat chow after birth showed catch-up growth (RC) whereas restricted offspring kept on a calorie-restricted diet did not show catch-up growth (RR). Weight gain, visceral fat (including retroperitoneal fat) and relative expression of *DLK1* in retroperitoneal fat, as well as microscopic morphology of this fat pad, were postnatally assessed in the offspring ($n=14$ pups/group) at day 42 (prepubertal juvenile rats). **Results:** RC pups showed higher postnatal weight gain, percentage of visceral fat, retroperitoneal fat and adipocyte size, and lower *DLK1* expression in retroperitoneal fat compared with RR pups (all $P<0.0001$). In RC pups, *DLK1* expression was negatively related to body weight ($r=-0.863$, $P<0.0001$), weight gain ($r=-0.835$, $P<0.0001$), visceral ($r=-0.808$, $P<0.0001$), and retroperitoneal fat ($r=-0.800$, $P<0.001$). **Conclusion:** Our results show for first time that lower *DLK1* expression in retroperitoneal fat relates to postnatal catch-up growth and visceral fat expansion in prenatally growth-restricted rats. Deregulated *DLK1* expression in adipose tissue could be among the mechanisms involved in postnatal visceral fat accumulation following fetal growth restriction. **Funding:** This study was supported by a grant from the Ministerio de Ciencia e Innovación, Instituto de Salud Carlos III (ISCIII), Madrid, Spain (PI13/01257), project co-financed by Fondo Europeo de Desarrollo Regional (FEDER).

FC8.2

Apoptosis Inhibitor of Macrophages: an Anti-Inflammatory Adipocyte Factor in Mild Adolescent Obesity?

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Background: Adipose tissue (AT) in obesity is characterized by low grade inflammation. The apoptosis inhibitor of macrophages (AIM; also called CD5L) is incorporated into adipocytes leading to increased lipolysis. Excess AIM-dependent lipolysis induces adipose tissue macrophage recruitment. M1 (proinflammatory) macrophage infiltration, with surface marker CD40, correlates with metabolic complications. **Objective and hypotheses:** To study serum levels and AT expression of AIM in lean and obese children correlated with CD40 expression. **Method:** Paraffin embedded abdominal AT microarrays from 33 lean and 29 obese prepubertal children and adolescents were used. Intensity and distribution of AIM and CD40 were studied with immunohistochemistry, size and total adipocyte numbers by image analysis (adiposoft) and serum AIM by ELISA. **Results:** AIM serum levels were lower in males vs females (3.92 ± 1.38 vs 5.58 ± 1.51, $P=0.0005$) irrespective of BMI and pubertal status. Also, males with adipocyte size <33 μM had lower serum AIM levels compared to those with ≥33 μM (3.23 ± 1.27 vs 4.27 ± 1.31, $P=0.028$). Most obese males had higher AIM tissue distribution in the adipocytes (64.7%, $P=0.021$) and macrophages (88.2%, $P=0.024$) vs lean males. Particularly, most male obese adolescents (76.9%, $P=0.031$) had a large (≥33 μM) adipocyte size, small (<80) adipocyte number (83.3%, $P=0.023$), and lower intensity of macrophage CD40 ($P=0.043$) with high intensity of adipocyte AIM vs male lean adolescents. **Conclusion:** Our study shows the presence of AIM in the adipocytes of children even from an early age. Males showed lower AIM serum levels than the females that were further decreased when the adipocyte size decreased. Obesity in the males was associated with higher tissue AIM distribution in both adipocytes and macrophages. Obese adolescent males particularly showed an association of low CD40 (M1 macrophage marker) intensity with high AIM adipocyte intensity suggesting an anti-inflammatory role of AIM in the adipocytes in male adolescents with mild obesity possibly reflecting a protective mechanism against metabolic complications in this age group.

FC8.3

Testing the Appetite Suppressing Effects of Vitamin B12 Conjugates of Peptide YY

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Introduction: Anti-obesity drugs with increased efficacy and safety are urgently being sought. Peptide YY3–36 (PYY3–36) is an attractive drug target due to its anorectic effect and decreased circulation concentration, without drug resistance, in obese individuals. Its short half-life and required method of delivery are limiting factors in its clinical application. Transport and uptake mechanisms, including blood-brain barrier passage, of vitamin B12 (B12) is highly efficient in mammals. We tested the hypothesis that conjugation of B12–PYY3–36 will help to overcome major hurdles of PYY3–36 by improved efficacy and pharmacokinetics. **Methods:** B12–PYY3–36 conjugate was tested against native PYY3–36, and an inactive B12–PYYC36 (null control) on food intake, weight gain and peptide concentrations in lean male Sprague–Dawley rats (SD 9 weeks, mean weight 316 g) as well as genetic obese diabetic Zucker rats (ZD, mean weight 891 g). Daily treatments were delivered subcutaneously in five 1-h pulses, each pulse delivering 5–10 nmol/kg, by implanted micro-infusion pumps. **Results:** In SD rats, food intake was reduced during 5-day treatment by 24% in B12–PYY3–36 and by 13% in PYY3–36 treated groups relative to baseline. B12–PYY3–36 generated a significantly longer inhibition of food intake vs PYY3–36 treatment following the first two pulses (121 min vs 81 min, $P<0.05$). In ZD rats, food intake was reduced by 22.5% during 4 days of treatment with B12–PYY3–36 vs 13% during PYY3–36 ($P=0.012$ and 0.031 respectively). After 4 days of treatment, body weight was reduced by 10 g in B12–PYY3–36 ($P=0.049$) vs 4 g in PYY3–36 treated ZD rats. Pharmacokinetic parameters showed positive effects of B12 conjugation on volume of distribution, clearance, and improved half-life (1.4 h vs 0.8 h, B12–PYY3–36 vs PYY3–36). **Conclusion:** Our data demonstrate for the first time that conjugation of B12–PYY3–36 improved pharmacology, resulting in greater suppression of food intake and body weight in lean and obese rat models. **Funding:** Sources of research support: NIH R15DK097675-01A1 and support from W M Wrigley Jr company, Chicago, IL, USA.

FC8.4

Severe Early-Onset Obesity Caused By Bioinactive Leptin due to a N103K Mutation

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Background: Early-onset severe obesity due to leptin deficiency typically results from a defect of leptin production or secretion due to mutations in the leptin gene. Recently we described a new form of leptin deficiency caused by bioinactivity of the hormone and associated with high circulating leptin levels (*New England Journal of Medicine* 2015 **372** 48–54). **Method:** Serum leptin was measured by ELISA. The leptin gene was sequenced in patient DNA. The secretory behavior and the biological activity of the identified mutation was assessed using HEK293 cells. **Results:** We describe two siblings, a 9-year-old girl and a 6-year-old boy with severe early-onset obesity (BMI *Z*-score 3.5 and 4.1) and hyperphagia, both homozygous for a c.309C>A transversion in the leptin gene leading to a N103K amino acid exchange in the protein und high circulating levels of leptin being normal for body fat mass (59.7 and 74.6 ng/ml). Secretion studies in a HEK293 cells overexpressing either WT or mutant leptin demonstrated that the N103K is indeed released into the cell culture media. However, while the WT leptin was able to induce phosphorylation of Stat3 in HEK293 cells overexpressing the leptin receptor, the N103K mutant was unable to do so. Likewise, the mutant mCherry-tagged leptin did neither bind to nor internalize the leptin receptor, while the WT hormone exerted these functions. This set of experiments clearly demonstrates that the N103K leptin is secreted, but not functional. Treatment with metreleptin (0.03 mg/kg LBM per day) led to rapid improvement of eating behaviour and weight loss in both patients. **Conclusion:** We present here further cases with severe early-onset obesity due to bioinactive leptin, which are successfully treated with recombinant human leptin. We strongly recommend considering this new disease entity in hyperphagic and severely obese children. High immunoreactive levels of circulating leptin do not exclude functional leptin deficiency.

FC8.5

Adipocytokines in Placenta and Cord Blood in Relation to Maternal Obesity, and Foetal and Postnatal Growth of the Child

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Background: The nutritional and hormonal state *in utero* may be a link between maternal obesity and obesity in the offspring. The gene expression in placentae in pregnancies complicated by

diabetes is reduced for leptin, but increased for ghrelin. It is not known whether these genes' expressions in placentae are altered in maternal obesity. **Objectives and hypotheses:** To compare obese and normal-weight women and their children concerning gene expressions of leptin and ghrelin in placentae; leptin, ghrelin, adiponectin, and C-peptide levels in cord blood, birth size and postnatal growth. Changes in the expression of these adipocytokines may lead to an altered hypothalamic sensitivity to leptin and ghrelin resulting in an increased risk of obesity in the offspring. **Method:** 32 women with pre-pregnancy obesity, but otherwise healthy, were compared to 32 matched, normal-weight controls. Full-term placenta biopsies were analysed with qPCR for leptin mRNA and ghrelin mRNA. Cord blood samples were examined with ELISA for leptin, ghrelin, adiponectin, and C-peptide concentrations. Birth size and postnatal growth of the children were collected from clinical registers at the Child Health Care Units. **Results:** The leptin and ghrelin gene expressions in placentae did not differ between obese and normal-weight women. The leptin concentration in cord blood was higher in children of obese mothers ($P=0.021$). It correlated with birth weight Z-score ($r=0.467$, $P<0.001$) and C-peptide level in cord blood ($r=0.446$, $P<0.001$). Children of obese women were slightly heavier at birth, but postnatal growth did not differ between groups. Children with birth weight ≤ -0.67 Z-score had higher ghrelin levels in cord blood than heavier children ($P=0.042$). The leptin level in cord blood correlated negatively with weight gain at 6 months ($r=-0.332$, $P=0.009$). The ghrelin level in cord blood correlated with weight gain at 3 months in girls ($r=0.611$, $P=0.001$), but not in boys. The adiponectin level in cord blood correlated negatively with length gain at 3 years in the obese group ($r=-0.571$, $P=0.033$), but not in the normal-weight group. **Conclusion:** Leptin and ghrelin placental gene expressions are not altered in obese women, but foetal adipocytokine production may influence early postnatal growth, possibly by influencing hunger signalling or insulin levels. **Funding:** This work was supported by the Research Committee in Region Örebro County and the Key Fundation (Nyckelfonden) at Örebro University Hospital.

FC8.6

Metabolic Effects of ADP355, Protein-Based Adiponectin Receptor Agonist, on Mice with High-Fat Diet Induced Fatty Liver Disease

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Background: Adiponetin is considered a protective hormone exhibiting beneficial effects against insulin resistance, cardiovascular disease, and cancer. Non-alcoholic fatty liver disease (NAFLD) is considered the hepatic component of insulin resistance. Pharmacological activation of adiponectin signaling might be helpful for treatment of NAFLD, but it is difficult to develop the whole adiponectin protein as a drug because the C-terminal globular domain of adiponectin is extremely insoluble and the peptide fragments are large. ADP355 (H-DAsn-Ile-Pro-Nva-Leu-Tyr-Dser-Phe-Ala-DSer-NH2), a peptide-based adiponectin receptor agonist, inhibits the growth of AdipoR1/AdipoR2-positive cancer cell lines. **Objective and hypotheses:** ADP355 act through AdipoR1 mainly, we thought it would activate AMPK pathway in the liver and improve NAFLD. We treated ADP355 on mice with high-fat diet (HFD) induced fatty liver disease to investigate the metabolic effects of ADP355. **Method:** Twenty mice were randomly divided into standard diet (SD, $n=5$) and HFD ($n=15$) group. After 12 weeks, HFD-fed mice were randomized into three groups for ADP355 treatment (none, 0.5, and 1 mg/kg per day) for 4 weeks. Intraperitoneal glucose tolerance test (IPGTT) were done in all mice before and after 27 days of ADP355 treatment. One day after IPGTT, mice were sacrificed and livers were weighed. Hematoxylin and eosin-stained sections analysed to establish the type and the degree of steatosis. Hepatic mRNA expression level of sterol regulatory element binding protein 1c (SREBP1c), acetyl-CoA carboxylase (ACC), fatty-acid synthase (FAS), palmitoyl transterase 1 (CPT1), acyl-CoA oxidase (ACO), and aldehyde oxidase 1 (AOX1) were measured. **Results:** Body weights were significantly lower in ADP355 treatment group, but liver weight, liver weight/body weight ratio, and area under curve of glucose level in IPGTT showed no significant difference. Grade of steatosis, SREBP1c, FAS, ACC, and AOX were significantly lower in ADP355 treatment groups than HFD group. **Conclusion:** ADP355 ameliorate HFD induced weight-gain and steatosis of liver in mice by decreasing de novo lipogenesis and stimulating fatty acid oxidation through AMPK pathway, but have no effect on insulin resistance.

FC9.1

Islet δ-Cells Contribute to the Pathobiology of Atypical Congenital Hyperinsulinism

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Background: Atypical forms of congenital hyperinsulinism in infancy (CHI-A) represent a novel subgroup of patients who present later in the neonatal period; have poor responses to medical intervention; an unremarkable histopathology and no known genetic cause of disease. **Objective and hypotheses:** To compare the expression profiles of insulin and somatostatin in islets from patients with CHI-A, diffuse CHI (CHI-D) and age-matched control tissue. **Methods:** CHI tissues were obtained following pancreatectomy, and control tissue following autopsy.

CHI-D patients were positive for defects in *ABCC8*; CHI-A was not associated with defects in CHI-associated genes. Insulin- (INS^+) and somatostatin-expressing cells (SOM^+) were identified by immunohistochemistry and quantified following digitization of paraffin-embedded tissue samples; Ki67 is a marker of cell proliferation and NKX2.2 is a marker of cell fate determination in islets. **Results:** We examined $n=380$ islets from CHI-A and compared to control and CHI-D islets. In CHI-A, 49.5% of the islets ($n=188$) had a quiescent profile associated with condensed cytoplasm, nuclear crowding and reduced numbers of centrally-located INS^+ cells. In control and CHI-D, $>90\%$ of islets were composed of $>70\%$ INS^+ cells and $<20\%$ SOM^+ cells ($n=91$). In contrast, $>70\%$ of quiescent CHI-A islets had less than 30% INS^+ cells and $>65\%$ had more than 20% SOM^+ cells; with 30% of islets composed of $>50\%$ δ-cells ($n=20$). Surprisingly, 'quiescent islets' had twofold higher rates of proliferation than unaffected islets from the same tissue, and $>60\%$ δ-cells were positive for NKX2.2; a transcription factor that was only present in a limited number of δ-cells in control islets. **Summary/conclusion:** NKX2.2 maintains a β-cell phenotype and has a limited expression profile in δ-cells following birth. Marked increases in NKX2.2 expression in CHI-A δ-cells combined with increased numbers of SOM^+ cells and rates of proliferation, strongly imply that an immature δ-cell profile contributes to the pathobiology of CHI. **Funding:** National Institute of Health Sciences.

FC9.2

A Novel Source of Mesenchymal Stem Cells Lines from the Human Neonatal Pancreas of Patients with Congenital Hyperinsulinism in Infancy

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Background: Congenital hyperinsulinism in infancy (CHI) is a neonatal disorder of uncontrolled insulin release leading to profound hypoglycaemia. In addition to defects in pancreatic β-cell function, we have recently demonstrated that the CHI pancreas is highly proliferative, with rates of proliferation up to 14-fold higher than in age-matched controls. **Objective and hypotheses:** As patients require pancreatectomy to alleviate hypoglycaemia, our aim was to demonstrate that CHI pancreatic tissue could represent a novel source of pancreatic stem cells. **Method:** Proliferating cell lines were derived from the pancreata of three patients with CHI following surgery and from the islet-enriched digest of an adult donor. In two cases CHI was caused by *ABCC8* gene defects in association with focal- and diffuse disease. In the third case – atypical CHI, no mutations in CHI-associated loci have been found. RT-PCR was used to examine gene expression profiles; western blot, flow cytometry, and immunocytochemistry for protein analysis. **Results:** All three cell lines were found to express Islet1, MafB, Pax6, and Sox9, markers associated with pancreatic development, and low level insulin. Profiling by flow cytometry for mesenchymal stem cell (MSC) markers demonstrated cells to be positive for CD105, CD44 and CD90, and negative for CD45, as in published literature. The morphology of CHI-derived pancreatic MSCs (pMSC) lines was consistent and they were readily able to form islet-like clusters in low adherence culture. Differentiation to adipocyte-, chondrocyte-, and osteocyte lineages was achieved for all three lines indicating multipotency. CHI-derived pMSCs proliferated faster than adult pMSCs (doubling time of 90 h vs 195 h) and continued to proliferate beyond their adult counterparts. **Summary:** pMSCs have not been previously derived from CHI patients. We have shown this is feasible, reproducible and that this tissue source has advantages over adult pMSCs, including insulin gene expression and longer-term stability, viability, and differentiation capacity. **Funding:** The National Institute of Health Research.

FC9.3

Failure to Terminate Cell Proliferation Contributes to the Pathobiology of Congenital Hyperinsulinism in Infancy

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Background: Diffuse congenital hyperinsulinism in infancy (CHI-D) mainly arises from mutations in K_{ATP} channel genes. In addition, there are also several reports of increased cell proliferation in CHI-D. We hypothesised that the higher rates of proliferation in CHI-D are as a consequence of failure to terminate proliferation in the neonatal period. **Objective and hypotheses:** To test this we examined the proliferative index (PI) of CHI-D tissue and compared with focal CHI (CHI-F), which is associated with loss of cell cycle repression in β-cells within the focal domain. **Methods:** PI was assessed by Ki67 or phosphohistone-H3 immunohistochemistry using samples of whole pancreas from patients positive for mutations in *ABCC8* with CHI-D ($n=10$) or CHI-F ($n=6$) and foetal/neonatal ($n=12$), juvenile and adult control tissues ($n=5$). Analysis of digitized images was used to calculate the average PI (mean $\pm$ S.E.M.) from 45 000 cells/tissue section. **Results:** In controls there was an inverse correlation between the PI and age. At 10 weeks post-conception more than 27% of the total cells were $Ki67^+$. At term the PI was $\sim$7%, which declined sharply to $2.6\pm0.1\%$ ($n=3$) at 8 weeks and 0.5% from 6 to 10 months. From 8 years until adulthood, PI was $0.1\pm0.03\%$ ($n=5$). In CHI tissue – including non-lesion domains of CHI-F, there was a similar inverse correlation with age, but the rates of decline were markedly decreased. Thus, up to 8 weeks following birth $8\pm0.4\%$ ($n=5$) of cells were $Ki67^+$; $4\pm0.4\%$ ($n=3$) up to 7 months and 3% up to 10 months of age. Importantly, there was little overall difference in the PI between

CHI-F (non-lesion) and CHI-D; 4±0.4 vs 5±1 respectively. **Conclusion:** We suggest that enhanced rates of proliferation in CHI arise from failure to terminate proliferation by a mechanism that is not directly attributable to the genetic cause of disease. **Funding:** National Institute for Health Research.

FC9.4

Novel Molecular Mechanisms of Congenital Hyperinsulinism due to Autosomal Dominant Mutations in *ABCC8*

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Background: Dominant mutations in *ABCC8* can cause congenital hyperinsulinism (CHI), which is characterised by unregulated insulin secretion. **Objective and hypotheses:** To understand the molecular basis of medically unresponsive CHI due to dominant *ABCC8* mutations. **Method:** We investigated ten patients with diazoxide unresponsive CHI who required a near total pancreatectomy. DNA sequencing revealed seven dominant heterozygous missense mutations in *ABCC8* (one novel and six previously reported but uncharacterised mutations). Mutant cDNA constructs were transfected into HEK293 cells for functional studies. $^{86}Rb^{+}$ was used as a surrogate to measure the efflux of K^{+}. Electrophysiological techniques were used to measure whole-cell and single channel currents. Confocal microscopy was used to determine the subcellular location of mutant K_{ATP} channels, by co-transfecting with pDs-Red2-ER (endoplasmic reticulum marker) and $K_{ir}6.2$-GFP. **Results:** D1506E is a SUR1 mutation located in nucleotide binding domain 2 (NBD2). Homologous expression of D1506E under whole-cell patch-clamp, displayed only −2.88±1 pA/pF of current in the presence of 100 μM diazoxide. Similarly single channel data showed a current response of 4.5±1.8% in the presence of 1 mM ADP. Heterozygous expression of D1506E suggested a strong dominant negative effect on WT SUR1 subunits. Mutations in the transmembrane domain (TMD) were more responsive to channel activators. The A113V (SUR1 TMD0) mutant showed some activation to MgADP (83.5±7.3%). Confocal analysis demonstrated that the NBD2 mutations were not retained in the ER, which is indicative of membrane expression. The TMD mutations are relatively retained in the ER suggestive of a trafficking defect. **Conclusion:** We define two groups of mutations with different cellular mechanisms. In the first, channel complexes with mutations in the NBD2 traffic normally but are unable to be activated by MgADP. In the second with mutations in the TMD are retained in the ER and have variable functional impairment.

FC9.5

The Use of Glucagon for Management of Severe-Persistent Hypoglycaemia in Patients with Congenital Hyperinsulinism

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Background: Severe-persistent hypoglycaemia (SPH) in congenital hyperinsulinism (HI) can cause blindness and brain damage. First line treatment with diazoxide treatment can cause significant side effects, including fluid retention. Off-label use of i.v. reconstituted glucagon is also used but little safety and efficacy data have been reported. **Objective and hypotheses:** To evaluate the use of i.v. glucagon infusion for management of SPH in HI. **Method:** Anonymised data regarding age, duration, dose, responsiveness, and adverse events was collected retrospectively from three international HI centres, although not consistently. The duration of treatment was short-term (<14 days) or long-term (>14 days). Responsiveness was defined as reduction in glucose infusion rate (GIR) by 50% or achievement of euglycaemia (plasma glucose >3.5 mmol/l (63 mg/dl)), or a twofold increase in plasma glucose following an i.v. bolus of glucagon. **Results:** Information available in 135 patients with HI was collated. In one centre, 12 patients were treated short-term pre-operatively. Glucagon decreased GIR from 19.7 to 7 mg/kg per min in nine children of median (range) age 17.5 days (3–665) and weight 4.3 kg (2.6–10.3) Eight patients with transient HI due to perinatal stress were also treated at age 5 days (2–10) and birth-weight 3.1 kg (2.4–3.5) for a duration of 7 days (2–13) to achieve euglycaemia. Treatment complications included i.v. line occlusion due to glucagon precipitation in seven of 20 children. In other centres, a total of 115 children were treated with i.v. glucagon long-term pre-operatively, the duration of treatment varying between 2 and 6 weeks, with good response noted in 109 children, partial response in five children and one being non-responsive. One child developed severe diarrhoea, while two developed necrolytic migratory erythema as adverse events. **Conclusion:** I.v. glucagon therapy has been used effectively in short- and long-term treatment in 135 patients with HI. Severe drug reactions from prolonged use are few. Short-term complications included i.v. line occlusion from precipitation of reconstituted glucagon in 33% of those in whom data was available. **Declaration of interest:** J Kinzel works for Xeris, a company developing a form of soluable Glucagon and P Thornton has performed consulting work for Xeris Pharmaceuticals.

FC9.6

Pharmacokinetics of a New Suspension of Glibenclamide for Use in Young Patients and Infants with Neonatal Diabetes

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Background: Sulfonylurea therapy allows a better metabolic control than insulin in patients with neonatal diabetes secondary to mutation in potassium channel. Its galenic form (tablets) is not suitable for children, as the dosage can't be easily modulated and as it induces large pharmacokinetics (PK) variations when administer to young children. **Objective and hypotheses:** To measure relative biodisponibility of a new galenic form of glibenclamide and to assess its safety and tolerability. **Method:** Open-label, cross over randomised phase 1 study in 18 healthy male subjects. Single oral administration, in fasted conditions of two new oral glibenclamide suspensions (0.83 ml of a 6 mg/ml suspension (S6) and 8.33 ml of a 0.6 mg/ml suspension (S0.6)) and of 5 mg of Daonil crushed tablet (DCT). **Results:** When suspensions were administered, glibenclamide plasma concentrations peaked 0.5 h earlier than observed with a DCT (median value of 2.5 h post-dose vs 3.0 h post-dose). Mean plasma peak C_{max} values were similar for the two suspensions (S6: 201.71 ± 71.43 ng/ml and S0.6: 206.93 ± 67.33 ng/ml), ~40% higher than the DCT one (148.34 ± 46.74 ng/ml). Exposures were similar for the two suspension dosages (AUC0-∞ values: S6: 1120.9 ± 400.5 ng.h/ml and S0.6: 1172.3 ± 422.0 ng.h/ml), and superior to that observed after DCT administration. Relative bioavailability was 121.6% for the 0.6 mg/ml and 114.1% for the 6 mg/ml formulations when compared to the DCT. Elimination half-lives were similar for the two suspensions (close to 8 h) and a little shorter than that observed with DCT (10.45 h). No adverse events were reported. **Conclusion:** Suspension of glibenclamide appears to be more suitable for use in paediatric patients as its dosage can be adjusted to patients needs with great precision more easily. PK studies reported it to be better absorbed than glibenclamide tablets. Tolerance and acceptability are being evaluated in patients with neonatal diabetes (ClinicalTrials.gov Identifier: NCT02375828).

FC10.1

Effect of Sonic Hedgehog Signalling on Regulation the Expression of 11β-HSD2 in the Placenta

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Objective: Excessive exposure to glucocorticoids (GCs) during gestation period not only causes fetal growth retardation but also increases the risk of adult metabolic diseases. 11 Beta-hydroxysteroid dehydrogenase (11β-HSD2) is a kind of glucocorticoid metabolic enzymes, which plays a role to the placental GCs barrier during gestation period. The aim of this study is to investigate the effect and mechanism of sonic hedgehog (Shh) signalling on regulation the expression of 11β-HSD2 and the progress of syncytialization in the placenta. **Methods:** Cytotrophoblasts was extracted from normal full-term pregnancy placenta. They were induced to Shh conditioned medium, a specific inhibitor of Shh signalling pathways cyclopamine, and Smo agonist purmorphamine. The luciferase gene report was used to detect Shh conditioned medium activity. shRNA was used to knock-down of Gli1, Gli2, and Gli3. The Bewo cells were used as a human trophoblast cell model. PCR, western blotting, immunofluorescence, and ELISA were used to measure the levels of ZO-1, β-hCG, membrane fusion protein factor Synctin A, and transcription factor GCMa. **Results:** Gli was actived in Shh-conditioned medium. Shh-conditioned medium increased the protein levels of Gli1 as measured with western blotting. Shh antagonist cyclopamine decreased Shh pathway-stimulated expression of 11β-HSD2. In addition, knock-down of Gli with shRNA significantly decreased 11β-HSD2 mRNA and protein levels. Shh reduced the protein expression of ZO-1 while stimulated the production of β-hCG. Also, Shh increased the mRNA expression of Synctin A and GCMa. **Conclusion:** These results suggested that the Shh signal pathway was expressed in human placenta. Protein and mRNA levels of 11β-HSD2 increased with Shh and membrane receptor proteins Smo. Additionally, we also found that transcription factor Gli1 and Gli2, and Gli3 upregulated the expression of including 11β-HSD2, in which Gli1 played the main role. These indicated that Shh signalling pathways regulate the expression of 11β-HSD2. These also indicated that Shh signalling pathways regulate the process of trophoblast cells fusion. **Funding:** This work was supported by the National Natural Science Foundation of China (81170787) Zhejiang Provincial Program for the Cultivation of High-Level Innovative Health Talents(2015).

FC10.2

The Altered Circulating miRNA Profile in Maternal Obesity Associate with Pre- and Post-Natal Growth

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Background: Gestational obesity has not only adverse effects on the mothers' health but also on the developing fetus. Newborns

of obese pregnant women have increased birth weight and increased risk for obesity and associated diseases in adulthood. The mechanisms by which maternal nutrition induce these changes in the offspring may involve microRNAs (miRNAs) regulation. **Aims and objectives:** To study the associations between circulating miRNAs altered in obese pregnant women and pre- and postnatal growth-related parameters. **Methods:** Thirteen circulating miRNAs differentially expressed in maternal obesity were quantified in second trimester plasma samples of 42 pregnant women (20 with normal weight and 22 with pre-pregnancy obesity and/or gestational obesity, as defined by international references)). Patients with preeclampsia, gestational diabetes or with pathologies other than obesity were excluded. Placentas and newborns were weighed at delivery and the latter also at 1, 4 and 6 months of life. **Results:** Decreased levels of miR-340 and miR-652 associated with higher placental weight; and decreased levels of miR-423-5p and miR-652 associated with higher birthweight (all $P<0.05$ to $P<0.001$). On infants' follow-up, decreased levels of miR-128a associated with increased weight at 1, 4 and 6 months, and decreased levels of miR-29c and miR-221 associated with increased weight at 6 months. In multivariate analysis, miR-128a ($\beta=-0.474$, $-=0.001$; $R^2=19.1$), miR-29c ($\beta=-0.379$, $P=0.01$; $R^2=14.3$) and miR-221 ($\beta=-0.377$, $P=0.01$; $R^2=12.14$) were predictors of infant's weight at 6 months, independently of maternal obesity. Insulin/IGF signalling and chemokine signalling pathways were predicted targets of these miRNAs. **Conclusions:** We report new data on the potential role of miRNAs as modulators of pre- and post-natal growth. Interventions on these miRNAs might modulate the deleterious effect of maternal obesity in the offspring. **Funding:** This study was supported by grants from the Ministerio de Ciencia e Innovación, Instituto de Salud Carlos III (ISCIII), Madrid, Spain (MS12/03239 and PI13/01257), projects co-financed by FEDER (Fondo Europeo de Desarrollo Regional).

FC10.3
Circulating miRNA Expression Profile in Pregestational and Gestational Obesity

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Background: miRNAs are valuable circulating biomarkers and therapeutic targets for metabolic diseases. A differential pattern of miRNAs has been described in pregnant women with preeclampsia or gestational diabetes; however, it is unknown whether maternal obesity affects the profile of circulating miRNAs. **Aims and objectives:** To define the circulating pattern of miRNAs in pregestational and gestational obesity; and to explore their associations with maternal metabolic parameters. **Methods:** TaqMan Low-Density Arrays (TLDAs) were used to profile plasma miRNAs in 18 pregnant women (six with pregestational obesity (PregestOB), six with gestational obesity (GestOB) and six with normal pregnancies (Control)], during the 2nd trimester of gestation. The most relevant miRNAs were validated in 70 pregnant women (20 PregestOB, 25 GestOB and 25 Control). Maternal metabolic parameters including fasting glucose, HbA1c, HOMA-IR, C-peptide and lipids were assessed. **Results:** We identified 13 circulating miRNAs differentially expressed in maternal obesity, including decreased levels of miR-29c, miR-99b miR-103, miR-221, miR-340, and increased levels of miR-30a-5p, miR-130a and miR-150 in GestOB; and decreased levels of miR-122, miR-324-3p, miR-375, miR-652 and increased levels of miR-625 in both PregestOB and GestOB ($P<0.05$ to $P<0.0001$ vs control). Decreased levels of several of these miRNAs associated with a more adverse maternal metabolic status (more pregnancy weight gain, glucose, HbA1c, HOMA-IR, C-peptide, TG and less HDL) (all $P<0.05$ to $P<0.001$). These miRNAs have been heralded as 'ribo-regulators' of glucose homeostasis and lipid metabolism. **Conclusions:** This study provides the first identification of altered circulating miRNAs in maternal obesity. The next step will be to demonstrate whether interventions on these miRNAs can avoid the adverse effects of gestational obesity in the mother and/or her offspring. **Funding:** This study was supported by grants from the Ministerio de Ciencia e Innovación, Instituto de Salud Carlos III (ISCIII), Madrid, Spain (MS12/03239 and PI13/01257), projects co-financed by FEDER (Fondo Europeo de Desarrollo Regional).

FC10.4
Effect of P450 Oxidoreductase Variants on Metabolism by Cytochrome P450 Proteins

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Background: A broad spectrum of human diseases including abnormalities in steroidogenesis is caused by mutations in the NADPH P450 oxidoreductase (POR). POR transfers electrons from NADPH to several small molecules, non-P450 redox partners and all microsomal cytochrome P450 proteins. POR disruption affects all partners with disastrous consequences and POR knock-out mice are embryonically lethal. A number of POR mutations and polymorphisms have been characterized from patients and genome sequencing databases and tested for their abilities to support CYP17A1 and CYP19A1 activities. POR also interacts with drug metabolising CYPs such as CYP3A4 which is responsible for metabolism of about 65% of the drugs in the human liver. **Aim and objective:** We aim to evaluate the effect of mutations in POR on steroid and drug metabolising cytochrome P450 activities and study the functional basis of POR deficiency. **Method:** We analysed the ability of wild type POR and POR variants (A503V, P284L, P284T and some novel mutants) to

reduce ferricyanide, MTT, cytochrome $b_{5,}$ cytochrome c and P450s. POR variants were produced as recombinant N-27 form while P450s and Cytochrome b_5 were produced as His-tag recombinant protein and purified by ion-exchange and Ni^{2+} metal chelate chromatography. Reduction of ferricyanide, MTT and cytochrome c was monitored spectrophotometrically by measuring the change in absorbance. We also tested the interaction of POR variants with P450s using ELISA. **Results and conclusion:** Ferricyanide and MTT reduction activity of POR was mildly affected by the mutations. We found varied effect of different POR mutants on CYP17A1, CYP19A1 and cytochrome c reduction activity. However, we observed comparable binding of POR mutants with CYP19A1. Further it would be interesting to study interaction of POR variants with other redox partners. In conclusion, characterization of POR mutants provides valuable genotype-phenotype and structure-function correlation. **Funding:** This work was supported by the Swiss National Science Foundation(grant number 134926).

FC10.5

Lack of Association between Transient Hypothyroxinaemia of Prematurity and Neurodevelopmental and Behavioral Outcomes in Young Adulthood

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Background: Preterm newborns are at risk of becoming transiently hypothyroxinaemic, which has been associated with neurodevelopmental impairments in childhood. It is not known whether these associations persist into adulthood. **Objective and hypotheses:** We studied the relation between transient hypothyroxinaemia of prematurity and IQ, neuromotor functioning and problem behaviour at young adult age. **Method:** This was a prospective study among 473 19-year-old subjects born very preterm (i.e., <32 weeks) and/or with a very low birth weight (i.e., $<1{,}500$ g) from the project on preterm and small-for-gestational-age infants (POPS) cohort. Total thyroxine (T_4) concentrations were obtained through the national neonatal screening program for congenital hypothyroidism. Children with congenital hypothyroidism were excluded. We studied whether hypothyroxinaemia, defined as a total $T_4 < -3$ S.D., was associated with low IQ (<85), measured with the digital Multicultural Capacities Test-Intermediate Level; impaired neuromotor function (<10th percentile), using Touwen's examination of mild neurologic dysfunction; and behavioral problems, assessed with the Young Adult Self Report and the Young Adult Behavior Checklist for parents. **Results:** Hypothyroxinaemia did not influence the risks of low IQ score or impaired motor functioning, as evidenced by an odds ratio of 1.2 (95% CI: 0.5–2.5) and 0.7 (95% CI: 0.4–1.2) respectively after adjusting for perinatal and family background variables. Hypothyroxinaemia was associated with a 2.0 (95% CI: 1.1–3.7) – fold increased risk of parent-reported total problem behavior after correction for perinatal and family background variables. No associations were found for other parent-reported or self-reported problems. **Conclusion:** No associations between transient hypothyroxinaemia of prematurity and neurodevelopment or behavioural problems at the age of 19 years were found, except for parent-reported total problem behaviour. Therefore, this study adds to the evidence not to routinely screen for hypothyroxinaemia in preterm newborns.

FC10.6

Heterozygous Hypomorphic Mutation in the INS Gene could Cause Transient Neonatal Diabetes in Extremely Low Birth Weight Neonates

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Background: Approximately 70% of transient neonatal diabetes mellitus (TNDM) are caused by abnormalities in the imprinted locus at chromosome 6q24, and the remaining 30% are caused by heterozygous mutations in the K_{ATP}-channel genes, ABCC8 or KCNJ11. Only a few cases of TNDM are reported to be caused by biallelic, recessive mutations in the insulin (INS) gene. **Objective and hypotheses:** To explore the role of INS gene mutations as a cause of transient neonatal diabetes. **Method:** (Subjects) Ten Japanese patients with transient neonatal diabetes who previously tested negative for abnormalities in the imprinted chromosome 6q24 locus and for mutations in the ABCC8 and KCNJ11 genes. (Methods) All three exons, exon-intron boundaries, and the 5′ upstream region of the INS gene were amplified from genomic DNA and directly sequenced. Additionally, the presence of the A23T substitution were tested by the mismatch primer PCR-RFLP analysis on 202 controls without diabetes and on 285 patients with late-onset diabetes. **Results:** Out of the ten TNDM patients, we identified one patient with the heterozygous Q62* mutation and five patients with the A23T substitution in the signal peptide. On the contrary, the A23T was found in only 7/202 normal controls and in 25/285 of late-onset diabetes patients. Interestingly, fout patients with the INS gene alterations were born with an extremely low birth weight (ELBW, <1000 g) and the hyperglycaemia resolved spontaneously by 2 months of age. **Conclusion:** Heterozygous hypomorphic mutation in the INS gene could cause TNDM in ELBW neonates. The A23T substitution previously believed to be a rare polymorphism without functional significance was strongly associated with TNDM of ELBW neonates in Japanese. **Funding:** This work was suppoted in part by a Grant-in-aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan to TY (No. 15K09636).

FC11.1

Mutations in *BRAF* are Associated with Septo-Optic Dysplasia and Cardiofaciocutaneous Syndrome☆

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Background: Mutations in *BRAF* are a rare cause of cardiofaciocutaneous syndrome (CFC). Recently, *BRAF* mutations have been reported in papillary craniopharyngiomas, but have not been described in patients with other hypothalamo-pituitary abnormalities. We describe three patients with CFC and septo-optic dysplasia (SOD) associated with heterozygous *BRAF* mutations. **Cases:** Patients presented in childhood with clinical features of genetically proven CFC, short stature (height <0.4th centile) and MRI features of SOD. In 2/3 (Cases 1 and 2), GH deficiency was initially observed (see Table 1). Case 1 subsequently developed low normal T_4 and TSH requiring Levothyroxine replacement, and gonadotrophin deficiency, Case 2 TSH deficiency and primary gonadal failure and Case 3 partial ACTH deficiency. *In situ* hybridisation performed on human embryonic brain and hypothalamo-pituitary sections showed strong *BRAF* mRNA transcript expression at Carnegie stages (CS) 19, 20, 23 and 8 post-conception weeks in the hypothalamus/ventral diencephalon, Rathke's pouch, trigeminal ganglia, retina, spinal cord and ganglia, and partially at CS16. **Conclusion:** We report the first novel association of SOD and CFC secondary to *BRAF* mutations. Unifying features include GH deficiency, with evolution of other pituitary abnormalities. Patients with CFC should be screened for pituitary abnormalities as these may be associated with morbidity. *BRAF* therefore appears to be implicated in normal pituitary function.

FC11.2

Functional Characterisation of a *POU1F1* Mutation Unexpectedly Associated with Isolated Growth Hormone Deficiency (IGHD): A Novel Aetiology of IGHD

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Background: In humans, the *GHN* gene transcription is under the control of a Locus Control Region (LCR) enhancer, HSI, located 14.5 kb 5′ to the *hGHN* promoter. POU1F1, a pituitary-specific transcription factor, plays an essential role in the specification of the somatotroph, lactotroph and thyrotroph lineages and the activation of *GHN*, *PRL* and *TSH* gene transcription. All *POU1F1* mutations so far reported have been linked to a combined deficit in GH, PRL and TSH. The association of POU1F1 with three cognate sites in HSI has binding specificity and functions distinct from that to sites in responsive gene promoters. POU1F1 binding to HSI activates a domain of noncoding transcription that loops to the *hGH* promoter then triggers *GHN* transcription. **Objective and hypotheses:** To explore the molecular basis of an IGHD phenotype segregating as a dominant trait within a large three-generation family. **Methods:** Sequencing of candidate genes. Functional studies to decipher the mechanism underlying the consequences of the identified mutation: co-immunoprecipitation (CoIP), DNA-protein interaction by EMSA and kinetic studies by Surface Plasmon Resonance (SPR). Generation of a mouse 'knock-in' model of the *Pou1f1* missense mutation. **Results:** A *POU1F1* heterozygous missense mutation (P76L) was identified in the nine affected family members. This amino-acid is highly conserved within the transactivating domain of POU1F1. A low-yield mutant protein production was observed, suggesting an impact on protein conformation. As shown by CoIP, the P76L mutation increases interactions of POU1F1 with different cofactors (LHX3, PITX1, ELK1). SPR experiments revealed increased binding affinity of the P76L protein to LCR sites. EMSA studies on the LCR and the *GHN* promoter sites with a mix of wt and mutant POU1F1 revealed a pattern different from that with wt alone, whereas those patterns are similar on the *PRL* promoter. The mutation was 'knocked in' to the endogenous mouse *Pou1f1* locus. In heterozygotes, while levels of mutant mRNA were equivalent to wt, P76L protein was poorly expressed and failed to repress mouse GH as well as an hGH

Table 1. (for abstract FC11.1)

Case/gender (M/F)	Case 1 (M)	Case 2 (F)	Case 3 (F)
BRAF mutation	c.770 A>G (p.Q257R)	c.1403T>C (p.Phe468Ser)	c.721 A>C (p.T241P)
GH peak (μg/l) (age/years)	5.9 (2.5 years)*	5.1 (9.7 years)**	11 (6.2 years)**
IGF1 (μg/l), NR	61, 20–180	69, 111–551	74, 88–474
fT_4 (pmol/l age/years), NR	16.6 (3.4 years), 10.3 (3.8 years) 7.3–21.1	9.4 (9.8 years) 10.8–19.0	Normal
TSH mU/l (age/years), NR	0.7 (3.4 years), 0.58 (3.8 years) 0.34–0.56	3.0 (9.8 years) 0.4–4.6	
LH, FSH (IU/l (age/years)	Stimulated: 4.1, 8.0 (14.1 years)	Basal: 44.5, 53.5 (13 years)	–
Tanner stage	Testosterone 0.5 (nmol/l)	Oestradiol: <44 pmol/l	
	1	1	
Cortisol peak (nmol/l)	–	–	433***

NR, normal range; *, clonidine; **, glucagon stimulation; ***, modified synacthen.

transgene expressions. **Conclusion:** This is the first report of a *POU1F1* mutation associated with IGHD. The data obtained unveil a novel mechanism underlying a dominant form of IGHD in humans.

FC11.3

Next Generation Sequencing: Towards a new Clinical Frontier in the Diagnosis and Management of Pituitary Tumours

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Background: In the past few years, new genes involved with familial predisposition to pituitary tumour development have been recognised, including *AIP* and *SDHx*. These factors are likely to underestimate the occurrence of familial pituitary tumour predisposition, commonly thought to account for 5% of all pituitary tumours. Furthermore, the clinical management of aggressive pituitary tumours is challenging, particularly when tumours exhibit resistance to standard hormonal agents and temozolomide. While next generation sequencing panels have aided in the stratification of genetic aberrations in those who are afflicted with better studied cancers such as those of the breast, lung and melanoma and aided in defining new therapeutic options, those with poorly studied and/or rare tumours such as those of the pituitary, particularly in children, have yet to benefit from these new technologies. **Objective:** We have developed a pan-cancer genetic screening panel with a pituitary bias, with which we aim to demonstrate the clinical utility for stratifying the genomic landscape of disparate cancer types, thereby improving treatment options and prognoses through discovering new or repurposing existing therapeutics. **Method:** Our custom next generation sequencing (NGS) panel (Roche/Nimblegen) contains the eight known familial pituitary tumour genes, plus 25 genes implicated in embryonic pituitary development and a further 270+ genes that have been implicated in various cancers and cancer-related pathways (~0.9 Mb target sequence). Subjects recruited for testing include those with a sporadic pituitary tumour, or patients with a family history of pituitary tumours or other endocrine neoplasia. DNA extracted from blood is interrogated using our >300-gene panel (Illumina HiSDefault 2500 sequencing). Raw sequencing data was analysed by a custom bioinformatic pipeline, with mutations being functionally assessed *in silico* and *in vitro*. In addition, RNA sequencing was applied to blood and tumour of a patient with a highly aggressive ACTH-secreting pituitary tumour, who had failed all standard treatments including temozolomide. **Results:** We detected three patients with germline mutations in *AIP* (p.F269F, p.A299V, p.R106C), verified by Sanger sequencing. In addition our patient with an aggressive pituitary tumour indicated suitability for trial of Bevacizumab, an inhibitor of VEGF-A. **Conclusion:** Our cancer panel is novel in its applicability to poorly studied cancer types and is designed to uncover new, causative genes as well as potentially identify alternative treatment options. Such a panel could greatly benefit children who are afflicted with rare tumour types who have not yet benefited from cutting-edge technology.

FC11.4

Idiopathic Multiple Pituitary Hormone Deficiency (IMPHD): Radiological and Perinatal Factors

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Background: Most cases of multiple pituitary hormone deficiency (MPHD) are acquired and genetic aetiology is rare in the UK. We have investigated whether environmental factors are implicated in 'idiopathic' MPHD (IMPHD). **Objective and hypotheses:** In IMPHD to determine perinatal risk factors and radiological features; to identify the regional epidemiology. **Method:** Systematic analysis of paediatric IMPHD cases in the UK West Midlands region from 1998 to 2014. Diagnosis was based on two or more hormonal deficits. Patients with acquired hypopituitarism and also midline and/or optic nerve abnormalities (septo-optic dysplasia) were excluded. Districts with higher incidence of IMPHD was compared. **Results:** patients (33 (42%) female) were identified. Caucasian (78%), Asian (16%) and Afro-Caribbean (6%) ethnicities were comparable to the regional background population. 52% were normal vaginal deliveries, with 36 and 10% born via LSCS and instrumental deliveries respectively. Median maternal age was 27 years (UK mean 29.3) and 52% were primigravida (UK Default 43%). During pregnancy 27% smoked, 13% consumed alcohol, 13% required prescribed medications but none reported recreational drug use. 22% had 1st trimester antenatal bleeding (cf. 7% nationally). TSH, GH, gonadotropin, ACTH and ADH deficiencies occurred in 79, 67, 54, 36, and 12% respectively). 80% (n=62) of pituitary MRIs were abnormal: 49% involving the anterior pituitary and 62% the posterior pituitary (including 37% with ectopia (EPP)). 34 (43%) were born in Birmingham which has 20% of the regional population, with clustering in other urban areas with socio-economic deprivation. **Conclusion:** IMPHD appears associated with environmental risk factors implicated in structural and/or functional disturbance in foetal pituitary development. Association with young maternal age, primagravida birth and antenatal bleeding as with SOD along with clustering in areas of socio-economic deprivation raise the possibility that IMPHD also shares a similar aetiological background.

FC11.5

Endocrinopathy after Intracranial Germ Cell Tumours (IGCT) is Disease Not Radiation-Related: Two Decades of Surveillance in a Large Tertiary Paediatric Cohort

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Background: Childhood IGCT are rare, malignant tumours of the pituitary stalk and pineal region, highly curable (>90%) by multimodal therapies. Neuroendocrine outcomes are thus important. Deficits increase over time but, without longitudinal studies, it remains unclear whether they are primarily disease or treatment related. **Objective and hypotheses:** To determine, by longitudinal retrospective analysis in survivors, tumour- and treatment-related factors for neuroendocrine morbidity, including effects of anatomical tumour location and volumetric size. **Method:** We searched 'germinoma' in electronic document libraries from 01/01/1995 until 01/01/2015 at our split-site centre (UCLH/GOSH) and excluded cases where an IGCT was not confirmed by MRI and/or histopathology reports. We identified 30 survivors now aged 14.7 (8–26) years and 5.5 (0.2–14.7) years from diagnosis. Evolving endocrinopathies were analysed by Kaplan Meir statistics and correlated with radiological tumour location and mass (3D volumetric assessments (www.itksnap.org)) and treatment. **Results:** Patients were diagnosed at median age of 9.52 (5.83–14.57) years, pineal tumours presenting with shorter symptom duration (pineal vs pituitary:0.33 vs 0.67 years, $P=0.10$). 76.7% had presenting visual disturbance, 57.1% had two or more anterior pituitary deficits and 66.7% had central DI (CDI). Pineal disease was of smaller volume (pituitary vs pineal: 5.74 (0.96–13.99) vs 0.97 (0.24–2.89) cm^3 $P=0.02$). All (100%) pituitary cases eventually developed CDI (vs 0% pineal), GHD and one or more other anterior pituitary deficits, (vs 16.7% pineal). All seven surgical patients developed perioperative panhypopituitarism + CDI, but only 50% of irradiated patients, (neuraxial alone (CSI) vs ventricular (VI) + chemo), developed new anterior pituitary deficits. **Conclusion:** Contrary to prevailing dogma, late evolving endocrinopathy is predicted by pituitary disease at diagnosis rather than imposed pituitary radiation and escalated by surgery. Thus substituting CSI with VI + chemo will not avoid this complication and may add peripheral toxicity (ototoxicity, nephrotoxicity, gonadotoxicity).

FC11.6

Long-term Outcome of Patients Treated for Paediatric Cushing's Disease

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Background: Due to the rarity of Paediatric Cushing's disease (CD) there is limited data on the long-term consequences of treatment. **Objective and hypotheses:** We assessed recurrence, anterior pituitary function and psychiatric disorders in a group of paediatric CD patients treated in a single centre. **Method:** Retrospective review of 20 patients with CD, mean age 11.75 years (5.74–17.8), managed in our centre between 1986 and 2010. Mean follow-up from the first surgical treatment was 10.5 years (5.01–27.2). 'Cure' was defined as undetectable postoperative 09:00 cortisol level (<50 nmol/l) and 'cure' after radiotherapy (RT) by mean serum cortisol on 5-point day curve of <150 nmol/l and midnight sleeping cortisol <50 nmol/l. **Results:** 14 patients were 'cured' by transsphenoidal surgery (TSS) and five were 'cured' following TSS + radiotherapy (RT). One patient underwent bilateral adrenalectomy (BA) following failed TSS. CD recurrence was seen in 3 (15%) patients: two after TSS (2 years after TSS) and one following TSS + RT (2 years post RT). The former two patients were treated with TSS + RT successfully. The latter was treated by BA. One BA patient developed Nelson's syndrome requiring RT 0.5 years post surgery. GHD was documented in 11 patients (55%) (seven following TSS and four after TSS + RT) and three (15%) had long-term GHD. 15 patients were treated with hGH, nine have reached final height (FH) on treatment. Gonadotropin deficiency causing delayed or slow pubertal development was diagnosed in six patients (30%), only one needed treatment post-pubertally. There were no reproductive problems. two (10%) patients had TSH deficiency. Two (10%) had psychiatric problems and two (10%) have poor memory and concentration after treatment. **Conclusion:** Pituitary deficiencies occurred in 60% patients after treatment for CD but long term deficiencies were less common (25% patients). Relapse occurred in 15% of patients after apparent 'cure' of CD and emphasises the importance of continued surveillance.

FC12.1

Evaluation of Cardiovascular Risk in Childhood: Data from a Survey of Dyslipidaemic Children

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Background: Dyslipidaemia is a well-known risk factor in developing cardiovascular disease (CVD) already in childhood. **Objective and hypotheses:** To investigate the clustering of

cardiovascular risk-factors (anthropometric parameters, blood pressure and metabolic abnormalities) in different type of dyslipidaemia in children and adolescents. **Method:** All the subjects aging 2–18 years referred for dyslipidaemia to our endocrine outpatient clinic between April 1999 and June 2014 were included. Categories of dyslipidaemia comprise: genetic-confirmed familial hypercholesterolemia (FH), hypercholesterolemia (XH), isolated hypertriglyceridemia (hyperTG), combined hyperlipidaemia (CH), isolated deficiency of HDL (idHDL), dyslipidaemia not otherwise classified (NAS). Familial history of precocious CVD (F+), anthropometric parameters (BMI-SDS, waist circumference (WC), waist-to-hip ratio (WHR)), systolic blood pressure (SBP), lipid profile, fasting glycaemia (G), insulin (Ins) and liver enzymes (AST, ALT) were collected in all the enrolled patients. **Results:** Among 1245 included subjects (median age 9.8, range 2–17.6 years; 95.7% Caucasian), 813 (65.3%) were confirmed dyslipidaemic: 5.6% FH, 25.6% XH, 27.2% hyperTG, 28.5% CH, 1.8% idHDL, 11.3% NAS. Among categories, BMI-SDS was greater in CH and hyperTG ($P<0.000$) and WC was higher in XH, hyperTG and CH (P 0.001), even if WHR did not differ significantly. High levels of SBP were more frequently detected among FH, hyperTG and CH subjects (31.1, 31.5 and 30.4% respectively). TC and LDL-C were higher in FH ($P<0.000$), while hyperTG and CH presented elevated TG ($P<0.000$). HDL-C was lower in idHDL and hyperTG ($P<0.000$). FH showed greater TC/LDL, LDL/HDL and ApoB/ApoA-1 ratios. ALT, Ins levels and HOMA index were increased in hyperTG and CH (P 0.018, <0.000, <0.000 respectively). The odds ratio for F+ was 8.72 in FH, 0.76 in XH, 0.70 in hyperTG, 1.07 in CH and 3.63 in idHDL. **Conclusions:** We demonstrated the evidence of a specific cluster of pro-atherogenic conditions among different categories of dyslipidaemia increasing sinergically the cardiovascular risk already in childhood.

FC12.2

Soluble CD163, A Circulating Marker of Macrophage Activation, Associates With a Less Favourable Metabolic Profile in Children

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Background: Soluble CD163 (sCD163) is shed from the cell surface into the circulation as a specific marker of macrophage activation. Macrophages are involved in low-grade inflammatory states such as obesity. **Objective and hypotheses:** To investigate the relationships between circulating sCD163 and metabolic parameters in asymptomatic prepubertal children. **Method:** A population of 236 school-aged Caucasian children (111 girls and 125 boys) aged 8±1 year (81 normal weight (BMI-SDS<1); 74 overweight (1≤IMC-SDS<2) and 81 obese (BMI-SDS≧2)) were enrolled in a cross-sectional study of obesity in primary care. Body mass index (BMI), waist circumference, fat mass (bioelectric impedance) and visceral fat mass (high-resolution ultrasonography) were measured. Fasting serum sCD163, glucose, insulin (and HOMA insulin resistance index), highly sensitive C-reactive protein (hs-CRP), gamma glutamyl transpeptidase (GGT) and lipids (triglycerides (TG) and HDL-cholesterol) were quantified. **Results:** Circulating sCD163 concentrations were higher in overweight and obese children ($P<0.0001$). Increased circulating sCD163 was associated with a less favourable metabolic profile as judged by higher waist circumference, fat mass percentage, visceral fat, HOMA-IR, serum GGT and TG, and by lower HDL-cholesterol (all $P<0.005$ to $P<0.0001$). As expected, sCD163 associated also with hs-CRP ($\beta=0.230$, $P=0.002$). In multiple regression, circulating sCD163 levels were an independent predictor, together with age and visceral fat, of HOMA-IR ($\beta=0.159$, $P=0.015$; R^2 model=0.171) and HDL-cholesterol/TG ratio ($\beta=-0.151$, $P=0.035$; R^2 model=0.143). **Conclusion:** We report for the first time on the association between circulating sCD163 and markers of a poorer metabolic profile, including insulin resistance and a proatherogenic lipid profile, in children. Childhood obesity may increase the risk of developing metabolic diseases later in life through chronic macrophage activation having deleterious effects on metabolism. **Funding:** This study was supported by a grant from the Ministerio de Ciencia e Innovación, Instituto de Salud Carlos III (ISCIII), Madrid, Spain (PI13/01257), project co-financed by FEDER (Fondo Europeo de Desarrollo Regional).

FC12.3

Re-Classification of Childhood Obesity by Steroid Metabolomic Disease Signature

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Context: Analysis of steroids by gas chromatography – mass spectrometry (GC-MS) defines a subject's 'steroidal fingerprint'. Here, we clustered steroidal fingerprints to classify childhood obesity by 'steroid metabolomic signatures'. **Methods:** Urinary samples of 87 children (44 F) age 8.5–18.0 with obesity (BMI > 97%) underwent solid phase extraction, enzymatic hydrolysis and derivatization. 31 steroids metabolites were quantified by GC-MS and quantities were Z-transformed based on sex and age. MetaboAnalyst 3.0, a software tool designed for metabolic data analysis, provided five unique k-means clusters. Steroidal signatures and clinical data of patients in each cluster were analysed, and ANOVA was utilized to biochemically and clinically

characterize each cluster. **Results:** Cluster 1 subjects ($n=39$, 21F) have normal steroid metabolome and is clinically unique only in that 28% of males have gynecomastia. Cluster 2 ($n=20$, 11F) show mild, nonspecific elevation of C_{19}- and C_{21}-steroids. Females show resistance to PCO (9% vs 24, 43, 40% in Clusters 1, 3, 5, resp.), but have hirsutism (45% vs 14 and 40% in Clusters 1 and 5, resp.). Cluster 3 ($n=7$, F only), all with partial or full PCOS, show relative 21-hydroxylase insufficiency. Cluster 4 ($n=4$, M only), show markedly elevated steroids and shift to 11-oxidized metabolites suggesting an imbalance in the 11ß-HSD system, insulin resistance ($P<0.001$), high GGTP levels ($P=0.0015$), and high systolic BP ($P=0.027$); half of them present features of liver steatosis in ultrasonography. Cluster 5 ($n=17$, 5F) have elevated DHEA and 17OH-pregnenolone metabolites, suggesting 3ß-HSD insufficiency but no clinically unique phenotype. **Conclusions:** 1. We define a novel concept of 'steroid metabolomic signature' based on high throughput urinary steroidal GCMS data. 2. Clustering by software designed for metabolic data analysis re-classified childhood obesity into five entities with their unique steroid metabolomic signatures, which require further definition and may need cluster-specific therapy.

FC12.4

RM-493, a Melanocortin-4 Receptor (MC4R) Agonist, is Being Therapeutically Evaluated in Patients with Deficiencies in the Leptin – Proopiomelanocortin (POMC) – MC4R Hypothalamic Pathway, Including Prader–Willi Syndrome (PWS)

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Background: The hypothalamic leptin–melanocortin signalling pathway is a critical regulator of human appetite and weight regulation. Monogenetic defects in the POMC gene, the MSH ligand generating PC1 gene and the MSH receptor gene MC4R lead to severe early onset and leptin-resistant obesity. In PWS, where the function of genes such as *MAGEL2* are impaired, the *Magel2*$^{-/-}$ mouse model revealed decreased POMC neuronal functioning as one critical mechanism of severe obesity in PWS. *Magel2*$^{-/-}$ mice were responsive to pharmacological treatment with an MC4R agonist that by-passes this defect. **Objective and hypotheses:** Together, all leptin-resistant monogenetic obesity, including the more prevalent PWS, might be potentially treatable by MC4R agonists. **Method:** More than 15 years after the initial description of MSH-deficient monogenetic human obesity, the synthetic MC4R agonist peptide RM-493 is ideally positioned for the experimental treatment of PWS patients and other monogenetic defects of the POMC signaling pathway. Several Phase 1 and Phase 2 studies were conducted to assess RM-493 safety, efficacy, and pharmacokinetics. **Results:** RM-493 showed 13% weight loss in obese rhesus over 8 weeks of RM-493 treatment. Phase 1b studies in normal obese patients demonstrated ~1 kg/week weight loss *vs.* placebo. Extensive analysis of blood pressure showed little, if any of the increases seen with previous MC4R agonists. **Conclusion:** RM-493 is a first in class well-tolerated efficacious MC4R agonist that may be a treatment for MSH deficient severe obesity. As a consequence we initiated several studies, including a double-blind, placebo controlled, randomized, Phase 2 study in overweight to obese adult patients (>16 years) with PWS, and a non-randomized, Phase 2 open-label pilot-study to treat homozygous or compound heterozygous POMC-deficient patients. Preliminary results show very promising weight loss in the first treated POMC null patient. RM-493 represents a new treatment option for PWS and other monogenetic obesity forms in which POMC function is affected.

FC12.5

Link Between BMI and Insulin Requirement in Children and Young People with Type 1 Diabetes Mellitus

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Background: Prevalence of being overweight or obese is increasing in type 1 diabetes mellitus (T1DM). The recent UK National Paediatric Diabetes Audit (NPDA) 2013/14 reported that 36.6% of 0–11 year old children and 43.9% of 12 years and older children are currently overweight or obese. Childhood obesity in T1DM predicts long-term risk of adult diabetes complications. Previous studies have shown significant positive correlation between HbA1c and total insulin requirement by dose per kilogram body weight. **Objective and hypotheses:** The objective of our study was to evaluate factors associated with high BMI SDS in Children and Young People (CYP) with T1DM. **Method:** We examined the insulin requirement profiles defined by total daily insulin dose per kilogram body weight, BMI SDS, mean HbA1c over 12 months, age at diagnosis and pubertal status of 102 CYP with T1DM between April 2014 to March 2015 in a single paediatric centre. **Results:** There were 59 males. 42 were on continuous subcutaneous insulin infusion (CSII), 56 were on multiple daily insulin regimen and four were on twice daily insulin regimen. Mean age at diagnosis was 7.79 years (range 0.16–16.91), mean BMI SDS was 0.89 (range −3.7 to +3.32), mean height SDS was 0.02±2.97 and mean weight SDS was 0.73±3.75. Mean Diastolic blood pressure was 69 mmHg (range 51–89), mean insulin requirement was 1.01 units/kg per day (range 0.38–2.43) and mean HbA1c was 8.0 (range 5.3–13.4). Out of 102 CYP, 24 were pre-pubertal, 28 were pubertal and 50 were post-pubertal. There was significant positive correlation between insulin requirement (units/kg per day) and HbA1c ($r=0.59$, $P<0.01$) and significant positive correlation between insulin requirement (units/kg per day) and BMI SDS ($r=0.23$, $P=0.02$). BMI SDS was not correlated with HbA1c. Multivariable linear regression analysis of factors affecting BMI SDS (age at diagnosis, HbA1c, gender, pubertal status and insulin in units/kg per day) showed that insulin requirement (units/kg per day) was an independent factor affecting BMI SDS. **Conclusion:** There is a link between

increased total insulin requirement (units/kg per day) and increased BMI SDS. Higher insulin requirement was also associated with poorer metabolic control.

FC12.6

Initial Experience with Endoscopically Placed Duodenal–Jejunal Bypass Liner (Endobarrier) in Morbidly Obese Adolescents

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Background: The duodenal–jejunal bypass liner (DJBL) is an endoscopically placed and removable intestinal liner that creates a duodenal–jejunal bypass. Weight loss and diabetes improvement was reported in the adults. **Objective and hypotheses:** To evaluate clinical effects and safety of this device in severely obese adolescents with obesity complications. **Method:** Six morbidly obese adolescents (four female, mean age 18.2 years (range 16.1–19.3), BMI 44.7 kg/m^2 (range 40.4–48.8)) were included. Inclusion criteria were age >15 years, unsuccessful conservative therapy ($<10\%$ decrease in body weight) for >6 months, girls were not pregnant or planning pregnancy within next 12 months. All had prediabetes or type 2 diabetes and were receiving metformin, which was discontinued prior to DJBL placement. None had exclusion criteria described in detail at www.ClinicalTrials.gov (NCT02183935). DJBL was inserted under general anaesthesia, with no complications. Following the procedure subjects were symptomatically treated for nausea and abdominal pain and were discharged on day 2 post procedure. All were receiving esomeprazole 2×40 mg/day throughout follow up. **Results:** In all a significant decrease in body weight and waist circumference was determined at 1 month (-7.4% (range -4.7 to -10.7) and -3.4 cm (range -3 to -7.5), respectively), continued to decrease at 3 months (-13.1% (range -8.6 to -19) and -10.5 cm (range -3 to -16)) and 6 months (-20.8% (range -20 to -21.7) and -18.5 cm (range -16.5 to -21.5)). In two subjects that completed 6 months of treatment glucose metabolism significantly improved (HOMA-IR decreased by -3.6 and 4.5, HbA1c by -2 and -0.5%), blood pressure normalized, liver steatosis and dyslipidemia improved (with the exception of decreased HDL). One subject developed cholecystitis 1 month post procedure and one had mildly elevated pancreatic enzymes concomitant to a gastrointestinal infection. **Conclusion:** This is the first report on the use of endoscopically placed and removable DJBL in adolescents. In a limited number of subjects, being followed for up-to 6 months a significant loss of body weight with favorable metabolic outcome and no serious device-related side effects was observed. **Funding:** This work was in part supported by grant number J3-6798 from the Slovenian Research Agency.

FC13.1

Gain of Function *STAT3* Mutation in a Boy with Early Onset Autoimmune Diabetes and Thyroid Disease, Prenatal and Postnatal Growth Impairment and Lymphoproliferation

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Background: Recently, a new monogenic cause of multiple immune system disorders and short stature has been attributed to germline activating mutations in the *STAT3* gene encoding signal transducer and activator of transcription 3. Possible pathophysiological mechanisms include enhanced proliferation and activation of T-helper 17 cells and inhibition of regulatory T-cells by STAT3, as described in *in vitro* studies. **Case presentation:** The affected boy was born at 35th GW of a twin pregnancy with birth weight 1900 g (-1.74 SD) and birth length 44 cm (-2.06 SD). Both of his parents suffer from type 2 diabetes, his father has psoriasis and his mother autoimmune thyroiditis. He underwent transient neonatal hypoglycaemia and unconjugated hyperbilirubinaemia. After 2 months of age, he started to fail to thrive and then consecutively presented with ketoacidosis at onset of type 1 diabetes at 11 months, hepatosplenomegaly and generalized lymphadenopathy with non-specific chronic activation in the biopsy sample at 16 months, autoimmune thyroid disease at 2 years and immune thrombocytopenia at 3.5 years. He also suffered from recurrent respiratory infections. At current age 6.5 years, his height is 103 cm (-3.81 SD). His peak GH secretion is normal. He has decreased IgG (5.07 g/l) and IgM (0.29 g/l) levels as well as NK-cell count (5.5%) and higher B-lymphocyte count (22.9%). Direct Sanger sequencing of *STAT3* revealed a heterozygous *de novo* p.Pro715Leu mutation in a highly conserved region of *STAT3* gene. **Conclusion:** We revealed a previously unreported, heterozygous *de novo* p.Pro715Leu mutation of *STAT3* with a high probability of pathogenicity. We strongly recommend considering investigation for *STAT3* mutations in children with early onset multiple autoimmune endocrine and non-endocrine disorders, growth impairment and lymphoproliferation. **Funding:** The study was supported by grant NT 11402.

FC13.2

Analysis of Chosen Polymorphisms rs2476601 A/G – PTPN22, rs1990760 C/T – IFIH1, rs179247 A/G – TSHR in Pathogenesis of Autoimmune Thyroid Diseases in Children

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Background: Autoimmune thyroid diseases are multifactorial diseases with a genetic susceptibility and environmental factors. A potential role of the protein tyrosine phosphatase non-receptor type 22 (PTPN22) gene, the interferon induced helicase domain 1 (IFIH1) gene, the TSH receptor (TSH-R) gene polymorphisms on autoimmune thyroid diseases (AITDs) in children has not been established equivocally yet. **Objective and hypotheses:** To estimate the association of polymorphisms of PTPN22, IFIH1 and TSH-R genes with the predisposition to Graves' disease (GD) and Hashimoto's thyroiditis (HT) in children. **Method:** The study was performed in 142 patients with GD, 57 with HT and 160 healthy volunteers. The three single nucleotide polymorphisms (SNPs): rs2476601 – PTPN22, rs1990760 – IFIH1 and rs179247 – TSHR were genotyped by TaqMan SNP genotyping assay using the real-time PCR. **Results:** Rs2476601 A alleles were more frequent in GD patients in comparison to healthy subjects ($P=0.009$ with OR = 2.13). It means that risk for development of GD is exactly 2.13 higher for A allele in comparison to G allele. Rs2476601 A alleles were more frequent in HT patients in comparison to healthy subjects ($P=0.008$, OR = 2.48). Rs1990760 T alleles were more frequent in GD male patients in comparison to healthy males ($P=0.003$, OR = 3.00). In case of HT patients rs1990760 T alleles were also more frequent in males compared to healthy subjects ($P=0.086$, OR = 2.47). Rs179247 A alleles were more frequent in GD patients in comparison to healthy subjects ($P=0.039$, OR = 1.51). **Conclusion:** Rs2476601 A/G, Rs1990760 C/T and Rs179247 A/G polymorphisms could contribute to development of AITDs in children. The main risk factor for rs1990760 and rs179247 is allele A. In case of rs1990760 the main risk factor is allele T.

FC13.3

Targeted Next-Generation Sequencing Demonstrates High Frequency of 'Dyshormonogenesis Genes' Mutations in Severe Congenital Hypothyroidism

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Background: 80–85% of cases of congenital hypothyroidism (CH) are shown to be due to thyroid dysgenesis, while 15–20% are due to dyshormonogenesis. At least 12 candidate genes are associated with congenital hypothyroidism (CH), however its molecular basis is defined in fewer than 10% of the patients (ESPE consensus, 2014). Recent studies suggest that using a next generation sequencing (NGS) approach may increase the mutation yield in CH. **Objective and hypotheses:** To define molecular basis of severe CH using a targeted NGS. **Methods:** 198 CH patients (males, $n=70$; females, $n=128$; TSH level on neonatal screening more than 90 mU/l) and 35 control subjects were studied. 'Thyroid panel' genes were sequenced using a custom Ion Ampliseq gene panel and PGM semiconductor sequencer (Ion Torrent). Non-synonymous sequence variants were rated as 'probably pathogenic' if they had allele frequency $<1\%$ and pathogenic ljb database scores (ANNOVAR). **Results:** 129 pathogenic or probably pathogenic mutations were found in 51% of the patients ($n=100$) and in 11% of controls. 18 mutations (14%) were detected in genes associated with thyroid gland dysgenesis: *TSHR,* $n=6$; *PAX8,* $n=5$; *NKX2-1,* $n=4$; *NKX2-5,* $n=3$; *FOXE1,* $n=0$. 111 mutations (86%) were found in genes associated with dyshormonogenesis: *TG,* $n=39$; *DUOX2,* $n=29$; *TPO,* $n=27$; *SLC26A4,* $n=7$; *IYD,* $n=5$; *SLC5A5,* $n=3$; *DOUXA2;* $n=1$. 19 patients showed mutations in two or three genes. The majority of mutations in 'dyshormonogenesis genes' were monoallelic. **Conclusion:** The results demonstrate high frequency of mutations in genes associated with dyshormonogenesis. The molecular findings were consistent with the phenotype only in one third of the cases, which implies that other mutations/factors may play a role in development of CH. **Funding:** This work was supported by Alfa-Endo Program of Charities Aid Foundation (CAF) Russia.

FC13.4

Effects of Initial Levothyroxine Dose on Growth and Neurodevelopmental Outcomes During the First Year of Life in Children with Congenital Hypothyroidism

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Background: An important issue in the management of congenital hypothyroidism (CH) is the best initial dose of levothyroxine (L-T_4) in order to achieve optimal neurocognitive outcomes. Both European and American guidelines suggest an initial dose of 10–15 μg/kg per die but trials on long-term effects of

different doses within this range are lacking. **Objective and hypotheses:** This was a multicenter randomized trial to evaluate the effects of the initial dose of L-T_4 on growth and neurodevelopmental outcomes in children with CH. **Method:** Seventy-two children with CH diagnosed by neonatal screening were enrolled in the study. They were randomly assigned to receive an initial L-T_4 dose of 10–12.5 μg/kg per die (group A) or 12.6–15 μg/kg per die (group B). All patients underwent clinical examination and FT4 and TSH measurement after 7–10 days of treatment and at the age of 1.5, 3, 6, 9 and 12 months. At the age of 12 months they underwent Griffiths Mental Development Scales to evaluate cognitive development. Four patients were lost to the follow-up and two patients have not yet reached 12 months of age; therefore only 66 children (32 from group A and 34 from group B) concluded the first year of study. **Results:** No significant differences were detected in auxological parameters between the two groups (Table 1).

Table 1.

	3 months	6 months	9 months	12 months
Weight SDS				
Group A	0.50 ± 1.25	0.28 ± 1.36	0.13 ± 1.37	0.16 ± 1.29
Group B	0.66 ± 0.87	0.66 ± 0.98	0.55 ± 1.17	0.38 ± 1.09
Length SDS				
Group A	0.32 ± 1.07	0.31 ± 1.01	0.22 ± 1.08	0.08 ± 1.03
Group B	0.34 ± 1.11	0.47 ± 1.16	0.30 ± 1.23	0.20 ± 1.17

The intelligent quotient (IQ) at 12 months of age was similar in the two groups (104.79 ± 13.18 vs 104.77 ± 12.81). IQ correlated with age at diagnosis ($r = -0.03$, $P = 0.02$) and FT_4 levels after 7–10 days of L-T_4 therapy ($r = 0.33$, $P = 0.01$). **Conclusion:** Different initial doses of L-T_4 within the range of 10–15 μg/kg per die provide similar outcomes in growth and neurocognitive development in CH patients.

FC13.5

Effect of 2 Years of Treatment with Levothyroxine on Cardiovascular Risk Factors in Children with Mild Idiopathic Subclinical Hypothyroidism

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Background: The benefits of levothyroxine (L-T_4) therapy in subjects with mild SH (TSH between 5 and 10 mU/l with normal FT_4 values) are controversial. Current recommendations in adults suggest to start on treatment selected groups of subjects with mild SH and evidence of atherosclerotic CV disease. Data in children are lacking. **Objective and hypotheses:** To investigate the effect of L-T_4 treatment on CV risk factors in children with mild idiopathic SH. **Method:** Thirty-nine children (19 males) aged 9.32 ± 0.65 years with long-lasting idiopathic SH underwent waist circumference, lipid profile, homocysteine (Hcy) and asymmetric dimethylarginine (ADMA) measurements. Non-HDL-C and atherogenic index (AI) were also calculated. Waist to height ratio (WHtR) was used as indicator of visceral adiposity. Thirty-nine euthyroid children were enrolled as controls. **Results:** At baseline SH subjects compared to controls showed significantly higher WHtR (0.54 ± 0.01 vs 0.49 ± 0.01; $P = 0.0072$), ADMA (0.99 ± 0.02 vs 0.90 ± 0.02 μmol/l; $P = 0.002$), LDL-C (92.06 ± 3.65 vs 75.05 ± 5.76 mg/dl; $P = 0.0148$), non-HDL-C (106.41 ± 4.05 vs 86.44 ± 6.49 mg/dl; $P = 0.0109$), AI (3.18 ± 0.14 vs 2.75 ± 0.12; $P = 0.0232$) and Hcy levels (9.34 ± 0.41 vs 7.71 ± 0.32 μmol/l; $P = 0.0024$) and significantly lower HDL-C concentrations (52.30 ± 1.79 vs 61.06 ± 2.32 mg/dl; $P = 0.0038$). After 2-years of L-T_4 therapy SH subjects had a significant reduction in WHtR (0.54 ± 0.01 vs 0.50 ± 0.01; $P = 0.0414$) and ADMA concentrations (0.99 ± 0.02 vs 0.38 ± 0.06 μmol/l; $P < 0.0001$). Lipid profile and Hcy levels became comparable to controls, although the changes from baseline values did not reach a statistical significance. **Conclusion:** L-T_4 treatment in children with mild idiopathic SH is associated with a trend toward improvement of the subtle metabolic abnormalities in visceral adiposity, lipid profile, Hcy and ADMA levels observed in untreated children. Our data suggest the CV risk profile should be taken into account in the decision to treat or not a child with asymptomatic mild SH.

FC13.6

TRIAC Treatment of Allan-Herndon-Dudley Syndrome (AHDS) due to Defects in Thyroid Hormone Transporter *MCT8*

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Background: AHDS is a devastating disease caused by defects in the thyroid hormone (TH) transporter MCT8. Endocrine expression is heralded by systemic hyperthyroidism with elevated serum T_3, mildly increased TSH and decreased T_4. However, the brain is hypothyroid, causing severe psychomotor retardation. Therapeutic attempts with PTU + levothyroxine or the T_3-analogue DITPA could normalize TH derangements but without any neurological improvement. Recently, *in vitro* and mouse studies support the therapeutic utility of triiodothyroacetic acid (TRIAC) in MCT8 deficiency. **Objective:** To investigate the hormonal effects of TRIAC in AHDS. **Patients and methods:** Five children diagnosed with AHDS between 8 months and −6

years of age, harbouring various defects in *MCT8* (p.P215L, p.delF230, p.V254DfsX24, p.L304_I539del, p.G401R). TRIAC compassive treatment started with 10 μg/kg per day, doubling the dose every 2 weeks until normalization of TH parameters. Determination of serum TSH, FT_3, FT_4 by immunoassay, TRIAC and rT_3 by RIA and SHBG by ELISA. **Results:** At baseline, patients (9 mo–8 years old) showed high FT_3 (7.3 ± 2.4 ng/dl; $n < 4$) or T_3: (4.2 ± 0.2 nmol/l; $n < 3.8$), low FT_4 (0.6 ± 0.08 ng/dl; $n > 0.8$), borderline-high TSH (4.4 ± 2.6 mU/l; $n < 4.5$), low rT_3 (3/5) (8.6 ± 2.8 ng/dl; $n > 15$) and high SHBG (207.6 ± 55.8 nmol/l; $n < 100$). After mean 11.4 weeks and mean TRIAC dose of 33.3 μg/kg per day (20–40), FT_3 and T_3 normalised (3.8 ± 0.6 ng/dl -3/5-; T_3 3.14 nmol/l -1/5-) and TSH decreased (1.99 ± 1 μU/ml), but FT_4 and rT_3 remained low (7.8 ± 4.9 ng/dl, 0.39 ± 0.05 ng/dl) and SHBG elevated (221 ± 59 nmol/l). Serum TRIAC increased ten-fold from baseline to final dose (12.8–163.5 ng/dl). **Conclusions:** TRIAC normalises hyperthyroidism and hyperthyrotropinmia in AHDS, but not FT_4, rT_3 or SHBG. The required dose is inversely related to age, possibly due to larger distribution volume of drugs in early childhood. Effects of TRIAC on child neurodevelopment and brain myelination are being prospectively evaluated by psychometric tests and MRI in periodic follow-up investigation. **Funding:** This work was supported in part by the Paediatric Endocrinology Spanish Society, with the grant for Basic Research in 2014.

FC14.1

KLB, Encoding the Co-receptor for FGF21, is Mutated in Congenital Hypogonadotropic Hypogonadism

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Background: The hepatokine FGF21 signals through a dual receptor complex consisting of FGFR1c and the obligatory co-receptor β-Klotho to regulate glucose and lipid metabolism. Interestingly, female mice with *Fgf21* transgenic overexpression are not only resistant to high-fat diet induced obesity but also present with hypogonadotropic hypogonadism (HH) and infertility. Loss-of-function (LOF) mutations in *FGFR1* are a frequent cause of congenital HH (CHH). We previously reported a CHH patient with obesity and severe insulin-resistance who harboured a *FGFR1* L342S mutation. *In vitro* studies showed this mutation impaired association of β-Klotho with FGFR1c thereby diminishing FGF21 signalling through FGFR1c. **Objective and hypotheses:** We thus hypothesised that mutations in *FGF21* and *KLB*, which encodes β-Klotho, could also underlie CHH. **Method:** We screened 295 CHH patients for mutations in *FGF21* and *KLB*. The functionality of the mutants was assessed *in vitro* using cell-based reporter gene assays, expression studies, and *in vivo* assays in *C. elegans*. The reproductive phenotypes of $Klb^{-/-}$ mice were also evaluated. **Results:** No mutations were identified in *FGF21*. We identified nine heterozygous *KLB* mutations among 13/295 unrelated CHH patients (4%). Five patients harboured the identical *KLB* deletion (p.Phe777del). The other eight mutations were missense. All mutations have a minor allele frequency (MAF) $<1\%$ in the EVS and ExAC databases. All *KLB* mutants were loss-of-function *in vitro* and/or *in vivo*. Additional CHH gene defects were identified in 5/13 patients including two heterozygous *FGFR1* mutations, consistent with an oligogenic model of inheritance. Notably, 9/13 subjects also exhibited metabolic defects, such as overweight/obesity, impaired fasting glucose, and/or severe dyslipidaemia. Finally, $Klb^{-/-}$ mice exhibited pubertal delay and decreased fertility. **Conclusion:** FGF21/KLB/FGFR1 signalling is implicated in GnRH neuron biology as indicated by LOF *KLB* mutations in CHH and delayed puberty and infertility in $Klb^{-/-}$ mice. **Funding:** This work was supported by the SNF Sinergia (141960).

FC14.2

A Mutation in HS6ST1 Causes Self-limited Delayed Puberty

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Background: Self-limited delayed puberty (DP) often segregates in an autosomal dominant pattern, suggesting that inheritance is conferred by a small number of genes. However, the underlying genetic background is mostly unknown. By comparison, many genes have been identified where loss-of-function mutations lead to hypogonadotropic hypogonadism (HH). Despite likely overlap between the pathophysiology of delayed puberty and conditions of GnRH deficiency, few studies have examined the contribution of mutations in HH genes to the phenotype of self-limited DP. **Methods:** We performed whole exome sequencing in 52 members of seven families from our patient cohort with self-limited DP, and filtered the results for potentially pathogenic mutations in a list of 25 genes identified as

causal in HH from the published literature. After follow-up targeted re-sequencing in a further 42 families (288 individuals), one candidate gene was identified. Developmental tissue expression studies and assessment of the enzymatic function of the mutant protein were carried out. **Results:** A novel variant in heparan sulfate 6-*O* sulphotransferase 1 (HS6ST1) was identified, present in six affected members of one family and not present in 145 controls or unaffected family members. HS6ST1 codes for a member of the heparin sulfate biosynthetic family, and is involved in modification of extracellular matrix components critical for normal neural branching. It is thought to be required for the function of FGFR1 and KAL1 *in vivo*, both of which are vital for GnRH neuronal development and normal hypothalamic–pituitary–gonadal axis function. The mutated protein was shown to have reduced sulphotransferase activity *in vitro*. **Conclusions:** Mutations in HS6ST1 contribute to the phenotype of self-limited DP. However, although mutations in genes controlling GnRH neuronal migration and differentiation may cause both HH and DP, the overlap between the genetic basis for the two conditions appears from our study to be limited to a small number of cases. **Funding:** SRH: The Wellcome Trust (102745), Rosetrees Trust (M222) and the Barts and the London Charity (417/1551). LD: partly supported by the Academy of Finland (14135). MRB, HRW and CPC: the National Institutes for Health Research (NIHR).

FC14.3

The New Syndrome of Hypogonadotropic Hypogonadism, Arrythmogenic Right Ventricular Dysplasia, Facial Dysmorphism and Absence of Corpus Callosum is Associated to TAX1 Binding Protein 3 Gene Mutation

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Background: A growing list of genes has been implicated in the pathogenesis of congenital hypogonadotropic hypogonadism (HH). **Objective and hypotheses:** To identify the cause of a unique syndromic HH in a consanguineous Bedouin family. **Method:** Medical records of the patients were reviewed. Genotyping of the brothers and their parents and whole exome sequencing (WES) were performed. **Results:** Two brothers presented at 19 and 8 years of age. Both were normosmic, had facial dysmorphism with underdeveloped genitalia due to partial isolated HH. Brain MRI disclosed absence of corpus callosum in both patients. Renal US was normal. Recurrent pre-syncope events at 26 years of age lead to the diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVD) in the older patient and subsequently in his young brother who has recently died after heart transplantation. Genotyping done on the patients and their parents identified a total of 17.4 Mb of homozygosity larger than 5 cM. Assuming the disease is caused by homozygotisation of the causative mutation, WES identified only one variation segregating as expected in the family and not present in the public databases, Ile33Thr substitution in the Tax1 (human T-cell leukemia virus type I) binding protein 3 (TAX1BP3), The Ile at position 33 is evolutionary conserved, has the highest prediction to be deleterious by polyphene, additionaly the change is predicted to cause loss of the PDZ domain and affect the structure of all other domains. **Conclusion:** A new clinical syndrome combining HH, ARVD absence of corpus callosum and peculiar facial dysmorphism has been found to be associated to TAX1BP3 gene mutation.

FC14.4

Genetic Variation of AMH Signaling Affects AMH and Inhibin B Levels in Healthy Peripubertal Girls

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Background: Anti-Müllerian hormone (AMH) is produced by small growing ovarian follicles. It inhibits both FSH induced maturation of follicles as well as aromatase activity. Genetic variation of AMH signalling is associated with age at menopause and circulating oestradiol levels, i.e. *AMH* rs10407022 T>G (intragenic) and *AMHR2* rs11170547 C>T (putative enhancer). **Objective and hypotheses:** This present study aims to investigate the impact of the two SNPs on hormonal as well as morphologic parameters in healthy girls. **Method:** Participants were recruited as part of two population-based cohort studies of healthy children and adolescents: The longitudinal part of The COPENHAGEN Puberty Study (83 girls, 737 examinations) and The Mother-Child Cohort (nested cohort including TAUS and MRI of the ovaries, $n=121$). Subjects were genotyped for SNPs using KASP™ assays and grouped according to pubertal stages (Tanner's classification: B1/B2+3/B4+5). We assessed associations of the genotypes with circulating hormone levels (AMH, FSH, LH, oestradiol, inhibin B) and the number of ovarian follicles. **Results:** *AMH* rs10407022 T>G was associated with AMH levels in prepubertal girls: TT ($n=47$) vs GT+GG ($n=18$), AMH median (range) 18 (8–49) vs 30 (6–50) pmol/l, $P=0.038$ (Mann–Whitney *U*). This was not reflected in the number of AMH producing follicles (adjusted for Tanner stages): MRI follicles $\leq$6 mm (Effect size estimate β −0.073, $P=0.508$) and TAUS follicles $\leq$4 mm (β −0.155, $P=0.144$). *AMHR2* rs11170547 C>T was associated with inhibin B in mid-puberty (B2+3): CC ($n=87$) vs CT+TT ($n=33$), 41 (10–125) vs 57

(26–215) pg/ml, $P<0.001$. This was not reflected in the number of inhibin B producing follicles (adjusted for Tanner stages): MRI follicles ≥ 7 mm (β −0.067, $P=0.505$) and TAUS follicles ≥ 5 mm (β −0.089, $P=0.393$). **Conclusion:** Genetic variation of AMH signalling affects serum levels of AMH and inhibin B in peripubertal girls. The effect could not be explained by the number of ovarian follicles implying a direct effect on expression of AMH (*AMH* rs10407022 T>G) as well as inhibin B (*AMHR2* rs11170547 C>T).

FC14.5

Polybrominated Diphenyl Ethers (PBDEs) and Timing of Puberty in Girls

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Background: Polybrominated diphenyl ethers (PBDEs) are widely used as flame retardants and have shown endocrine disruption properties in experimental studies. Preliminary studies in animal models have suggested a link between exposure to PBDE and alterations of puberty and reproduction. **Objective and hypotheses:** To investigate the association between the exposure to PBDEs and alterations of puberty in girls, referred for idiopathic premature thelarche (IPT) and idiopathic central precocious puberty (ICPP). **Method:** A case control study was conducted in 124 girls, subdivided into three groups: 37 girls with ICPP (mean age 7.4±0.9), 56 with IPT (mean age 5.7±2.1) and 31 controls (mean age 5.4±1.9). PBDE (PBDE-47+PBDE-99+PBDE-28+PBDE-100+PBDE-153) serum concentrations, hormone levels and anthropometry were assessed. In a subgroup of 36 girls (11 ICPP, 13 IPT, 12 controls) urinary concentrations of PBDE were measured. Individual exposure was evaluated through 'ad hoc' questionnaires providing data life styles, diet and other potential determinants of exposure. **Results:** ICPP and IPT girls showed significantly higher levels of serum PBDEs (adjusted for BMI SDS) than controls ($P<0.01$): median 38.02 ng/g lipid (range 2.68–129.85), 44.65 ng/g lipid, (range 1.08–941.78) and 17.64 ng/g lipid (range 2.07–207.7), respectively. ICPP girls showed significantly higher levels of urine PBDEs than controls ($P<0.05$). No significant difference in serum and urine PBDE levels between ICPP e IPT girls was found. Questionnaires analysis showed significantly longer time spent at computer in ICPP girls compared to IPT and controls ($P<0.001$). No significant relationship between serum PBDEs and diet was found. **Conclusion:** Our findings suggest, for the first time, that high concentrations of serum PBDEs are associated with idiopathic precocious puberty and idiopathic premature thelarche in girls.

FC14.6

An Evaluation of Glandular Breast Tissue Development and Volume by MRI in 121 Healthy Peripubertal Girls

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Background: Since the late 1960's, pubertal breast staging has been based on Tanner's classification. Appearance of glandular breast tissue may be difficult to distinguish by palpation from the surrounding subcutaneous fat tissue, especially in obese girls. To our knowledge, validation of the clinical assessment of pubertal stages by MRI quantification of glandular breast tissue has never been performed. **Objective and hypotheses:** i) To report normative data of glandular tissue volume in healthy girls. ii) Validate the clinical evaluation of pubertal breast staging by MRI of breast tissue. iii) Evaluate circulating hormone levels and morphology of internal genitalia by transabdominal ultrasound (TAUS) as markers of glandular tissue. **Method:** Breast stage (Tanner B1–B5 by inspection and palpation) was performed in 121 healthy peripubertal girls from the Copenhagen Mother-Child Cohort (9.8–14.7 years). Glandular tissue volume was measured with MRI. Ovarian volume, follicle counts, uterine volume, and endometrial thickness were assessed by TAUS. Circulating levels of FSH, LH, inhibin B and oestradiol were assessed by immunoassays. **Results:** Glandular tissue volume by MRI was positively associated with Tanner stages ($r=0.858$, $P<0.001$), however, marked inter-individual variation occurred in late puberty (B4+B5): median (range): 74 (20–241) cm^3 and CV=51%. The sensitivity and specificity for breast palpation to detect the presence of glandular tissue using MRI as gold standard were 99 and 95%, respectively. The best parameters to distinguish between prepubertal girls (B1 and no glandular tissue on MRI) and girls with breast development (B2–B5 and visible glandular tissue on MRI) were: LH (area under the curve by ROC analysis=0.949), estradiol (AUC=0.935), FSH (AUC=0.879) and uterine volume (AUC=0.934), endometrial thickness (AUC=0.855) and ovarian volume (AUC=0.848). **Conclusion:** Clinical palpation reliably detects glandular breast tissue. In addition, unstimulated LH, oestradiol, and FSH as well as uterine volume, endometrial thickness and ovarian volume are valuable to distinguish prepubertal from pubertal girls.

FC-LB-1

RNA Sequencing Reveals the Pathways Perturbed by Redox Imbalance in Nicotinamide Nucleotide Transhydrogenase Null Mice

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Background: In humans, loss-of-function mutations in Nicotinamide nucleotide transhydrogenase (*NNT*) cause familial glucocorticoid deficiency, a potentially fatal, adrenal-specific disorder characterized by increased ACTH and reduced cortisol levels. NNT is a highly conserved inner mitochondrial membrane protein, which supplies high concentrations of NADPH for detoxification of reactive oxygen species (ROS) by glutathione and thioredoxin pathways. **Objective and hypotheses:** To determine how loss of NNT results in a steroidogenic phenotype and to identify pathways affected upon limited NADPH supply in adrenal cells. **Method:** Adrenal RNA was extracted from Nnt-WT, Nnt-KO, and Nnt-BAC (rescue) mice. RNA-sequencing (RNA-Seq) was performed as paired end reads on the Illumina HiSeq2000 platform. Differential expression levels were confirmed by SYBR-Green q-PCR and western blotting. **Results:** RNA-Seq analysis revealed no alterations in antioxidant genes of glutathione and thioredoxin pathways (*Prdx3*, *Gpx1*, *Sod2*, *Txnrd2*, and *Gr*) but that NNT loss affects expression of key mitochondrial steroidogenic enzymes (CYP11A1 and CYP11B1) with a 25% reduction in mRNA levels and a more pronounced decrease in protein expression. Comparison of RNA-Seq data from Nnt-WT and -MUT mice revealed differential expression (fold change ≥ 1.5; p value < 0.001) of 91 genes that was reversed in the Nnt-BAC suggesting these genes are directly affected by *Nnt* loss. The 91 genes fell into 12 biological processes by gene ontology analysis with significant enrichment (4.13-fold; $P < 0.05$) of genes involved in stress response including the heat shock proteins *Dnajb1*, *Hsph1*, *Hspa1a*, and *Hspa1b*. Interestingly α- and β-haemoglobins (*Hba-a1*, *Hba-a2*, *Hbb-b1*, and *Hbb-b2*) were highly upregulated in the knockout mouse, suggesting a compensatory mechanism to combat oxidative stress, with levels returning to normal in Nnt-BAC rescue mouse. **Conclusion:** Our data suggest loss of *Nnt* and the resultant reduction in NADPH production affects a number of gene networks within the adrenal. It reveals up- or down-regulation of important pathways presumably to combat the sustained adversity due to mitochondrial NADPH restriction and the concomitant increase in ROS that this causes.

FC-LB-2

Loss of Neuronal Dmxl2 Impairs the Maturation and the Activation of GnRH Neurons: a New Mechanism of GnRH Deficiency

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Background: *DMXL2* haploinsufficiency in humans was recently shown to cause the polyendocrine-polyneuropathia syndrome including a GnRH deficiency (OMIM #616113). The neuronal deletion of *Dmxl2* in mice (Nes::Cre;Dmxl2$^{loxp/wt}$) caused infertility and gonadotropic deficiency (*Plos Biology* **9** e1001952, 2014). *Dmxl2* encodes rabconnectin-3α (rbcn-3α), which participates in the control of the V-ATPase activity and regulatory secretion. The association between a defect in a synaptic protein and GnRH deficiency was novel and suggested a new mechanism. **Objective and hypotheses:** To characterize the mechanism of the GnRH deficiency caused by loss of neuronal *Dmxl2,* in mice. **Method:** An extensive analysis of GnRH neuron development and activation was performed in *Nes::Cre;Dmxl2$^{-/wt}$* mice as well as in a mouse line with a complete knock out of *Dmxl2* in GnRH neurons (*GnRH::Cre;Dmxl2$^{loxp/loxp}$*). **Results:** *Nes::Cre;Dmxl2$^{loxp/wt}$* mice exhibited 30% decrease of GnRH neurons in the hypothalamus but an increase of immature GnRH neurons as compared to WT mice. GnRH neurons did not respond to Kisspeptin stimulation in male *Nes::Cre;Dmxl2$^{loxp/wt}$* mice and female *Nes::Cre;Dmxl2$^{loxp/wt}$* mice did not respond to the estradiol-induced positive feedback. This defect of the GnRH maturation and activation was associated with an impaired glutamatergic signaling pathway in the hypothalamus. To delineate the role of rbcn-3α in GnRH neurons as compared to other hypothalamic neurons, we created a mouse line with a full deletion of *Dmxl2* in GnRH neurons. *GnRH::Cre;Dmxl2$^{loxp/loxp}$* male mice were subfertiles whereas *GnRH::Cre;Dmxl2$^{loxp/loxp}$* females were infertile. These mice exhibited a similar developmental defects of the GnRH neuron morphology than in *Nes::Cre;Dmxl2$^{loxp/wt}$* mice. *GnRH::Cre;Dmxl2$^{loxp/loxp}$* female mice exhibited advanced vaginal opening yet the time to first estrus was delayed associated with abnormal estrous cyclicity. **Conclusion:** Low neuronal expression of *Dmxl2* impairs the maturation and the activation of GnRH neurons, most likely by a defect in synaptogenesis. These results open new perspectives to understand mechanisms of puberty disorders.

FC-LB-3

Pharmacokinetic and Pharmacodynamic Studies of *Topicon*™ Mediated Patch Delivery of Insulin Glargine in a Streptozotocin-Induced Hairless Rat Model

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Background: The *Topicon*™ patch is a needle-free novel platform technology developed to achieve truly passive transdermal delivery of insulin. Here we report pharmacodynamic (PD) and pharmacokinetic (PK) studies comparing needle injection (s.c.) vs *Topicon*™ mediated patch delivery of the insulin analog glargine (LANTUS®) in streptozotocin-induced hairless rats. **Objective and hypotheses:** We sought to develop a convenient, affordable, and needle-free transdermal patch formulation capable of achieving passive delivery of large molecule drugs such as insulin and insulin-analogues for multiple days. **Method:** Male CD® hairless rats were induced with type 1 diabetes (T1DM) by i.p. injection of streptozotocin (65 mg/kg). Plasma insulin glargine was determined by ELISA (Mercodia Iso-Insulin Kit). PK calculations are based on extravascular non-compartmental analysis (NCA) using PKSolver 2.0 for Microsoft Excel. The first-order elimination rate constant (K_{el}) was calculated as $0.693/T_{1/2}$. Required input rate of insulin (k_0) to reach C_{max} was calculated by $C_{max}{}^{\star}V_d{}^{\star}K_{el})/(1-e\hat{}K_{el}{}^{\star}t)$. Amount of LANTUS® delivered by *Topicon*™ patch per unit surface area over time (t) was $J_{ss}{}^{\star}t$, where J_{ss} is the steady-state flux rate. **Results:** A single s.c. injection of 10 U/kg of LANTUS® resulted in an unexpectedly rapid rise to a peak plasma glargine concentration (C_{max}) of ~120 mU/ml at 1 h, rapid elimination with plasma half-life ($t_{1/2}$) of 2 h and a return to baseline level by 5 h. Blood glucose (BG) lowering was observed from baseline mean of ~375 mg/dl to ~70–80 mg/dl for 0.5–5 h. Administration of LANTUS® 20 U/kg in a 1 cm^2 patch resulted in a C_{max} of 5.3 mU/ml at 2 h, a $t_{1/2}$ of 1.7 h. Euglycemia was achieved in 4 h and maintained for 6–7 h. PK modeling was done to assess whether a *Topicon*™ glargine patch can achieve a clinically meaningful therapeutic response by combining *in vitro* EpidermFT™ permeation data with the reported C_{max} of 22 mU/ml at 12 h after injection of LANTUS® 0.4 mg/kg in T1DM. **Conclusion:** Our *in vivo* studies support the feasibility of developing an effective *Topicon*™ extended-wear basal insulin patch that can achieve BG lowering comparable to s.c. injection. Within 10 h, a 3×3 cm^2 patch containing ~200 U of LANTUS® can achieve and maintain a target C_{max} of 22 mU/ml continuously for >7 days.

FC-LB-4

Long-Term Cognitive Effects of Antenatal Dexamethasone Treatment in Swedish Adolescents with and without CAH

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Background: In order to prevent virilization in CAH female fetuses, physicians have during the last thirty years used the synthetic glucocorticoid dexamethasone (DEX) as a therapeutic approach administered during early pregnancy. Due to the fact that treatment has to be started before the genotype of the fetus is known, seven out of eight treated fetuses will be subjected to high doses of DEX during early embryogenesis without benefit. Therefore, negative side effects cannot be tolerated. **Objective and hypotheses:** To evaluate the long-term effects of prenatal DEX therapy in the context of CAH focusing on neuropsychological functions. **Method:** In Sweden, 77 cases were treated prenatally with DEX from 1984 through 2010. We evaluated cognitive functions in 135 subjects aged 7–17 years (mean 11.0 ± 2.8 years). The cohort comprises 45 prenatally DEX treated children (34 short-term treated healthy boys and girls, five short-term treated boys with CAH, and six long-term treated girls with CAH). The control group comprises 66 healthy children from the general Swedish population and 24 children with CAH. The children were assessed with standardized neuropsychological tests: vocabulary, coding, block design, digit span, processing speed (WISC-III); memory encoding and long term memory (NEPSY); and span-board test (WNV). We report significant and trend findings on a three-way ANOVA with factors CAH (no CAH and CAH), DEX (non-treated and treated), and sex (male and female) as well as specific contrasts of DEX or CAH vs healthy control subjects. Analyses were carried out with test age as covariate of no interest. Omitted main effects and interactions were not significant at $P>0.10$. Reported group scores are estimated marginal means ± S.E.M. for specific contrasts. **Results:** DEX treatment significantly affected performance for both, male and female subjects, on visuospatial working memory assessed with the span-board test (($F(1,124)=6.40$, $P=0.013$) and on speed of processing as measured by the stroop-speeded reading ($F(1,112)=5.90$, $P=0.017$). Moreover, DEX treatment significantly affected performance for females on all of the sub scores of the WISC-III scale, coding ($F(1,60)=3.60$, $P=0.063$), block design ($F(1,60)=4.55$, $P=0.037$), vocabulary ($F(1,60)=8.30$, $P=0.005$), and digit span ($F(1,48)=12.55$, $P=0.001$) but not for males. For verbal working memory, assessed with the test digit span, the effect was restricted to girls without CAH, but it should be noted that female CAH subjects without DEX treatment already performed poorer than healthy controls, pointing to a possible flooring effect ($F(1,47)=4.76$, $P=0.034$). In tests assessing long term memory, NEPSY-LTM for faces, DEX treatment did not affect performance, but CAH-patients performed significantly worse than healthy controls ($F(1,126)=8.94$, $P=0.003$). In conclusion, prenatal exposure to glucocorticoids has a negative impact on several cognitive functions, especially in girls. CAH-patients perform poorer than healthy controls regardless of prenatal DEX treatment.

FC-LB-5

Paternally Inherited *IGF2* Mutation Results in Intrauterine and Postnatal Growth Retardation

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Background: IGF1 and IGF2 are major regulators of somatic growth acting mainly through the IGF1R. Variants in IGF1 and in IGF1R were identified to cause intrauterine and postnatal growth retardation but variants in IGF2 have not yet been reported. **Method:** In a multigenerational family four affected members (two siblings, one first degree cousin and the daughter of one sibling) exhibited severe growth retardation with heights between −4.2 and −5.6 SDS in childhood and dysmorphism resembling Silver–Russell syndrome. Whole exome next generation sequencing was performed to identify the genetic cause. Serum IGF1, IGFBP3, and IGF2 were assayed by RIA and clinical characterization was carried out to confirm the pathogenicity of the identified variant. **Results:** We identified a heterozygote nonsense variant (c.191C > A) in the coding sequence of IGF2, resulting in a premature stop codon (p.Ser64Ter). *IGF2* mRNA from the variant allele was not detectable implying nonsense mediated decay. The clinical and endocrine phenotype cosegregated with the mutation. Affected had a birth length < −4 SDS, relative macrocephaly, no skeletal asymmetry, deficient IGF2 (< 5th percentile) and normal IGF1 levels. Mental retardation was present in only one of the three patients who had reached adulthood. The patients inherited the variant from their healthy fathers, and it originated from the paternal grandmother. **Conclusion:** This is the first report on a functional variant in the *IGF2* gene. As expected, it is associated with intrauterine growth restriction, but the severe growth retardation of variant carriers accompanied by IGF2 deficiency indicates that IGF2 is a key player in postnatal growth and development. The association of the phenotype with the sex of the parent inheriting the variant is in accordance with the imprinting status of IGF2. This observation and the additional dysmorphic features confirm the hypothesis that IGF2 is a major factor in the etiology of Silver–Russell syndrome.

FC-LB-6

PROP1 Mutations Cause Hypopituitarism by Disrupting the Transition of Pituitary Stem Cells to Differentiation

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Background: Congenital multiple pituitary hormone deficiency (MPHD) arises from defects in pituitary development and is sometimes associated with craniofacial abnormalities. Mutations in the transcription factor PROP1 are the most common known genetic cause of the disorder. In this case the course of disease is progressive, and can lead to life threatening adrenal insufficiency. **Objective and hypotheses:** Our objective is to understand the role of PROP1 in the generation of this disease and to improve molecular diagnosis of MPHD. Our hypothesis is that PROP1 promotes the transition of progenitors into differentiating cells and that new PROP1 target genes can be MPHD candidates. **Method:** We performed stem cell colony formation assays, RNA-Seq, immunohistochemistry and qPCR using *Prop1* mutant mice and their controls. We created a *Prop1*-expressing pituitary cell line to perform ChIP-Seq experiments for PROP1. **Results:** *Prop1* deficiency in mice causes elevated expression of the stem cell marker SOX2, and altered stem cell colony forming behavior including increased growth rate, abnormal cellular morphology, and misexpression of genes associated with the Notch pathway and cell cycle regulation. We identified novel PROP1 binding sites near *Gli2,* which is mutated in some cases of MPHD. PROP1 also bound at genes associated with cell junction signaling and regulation of epithelial–mesenchymal transition (EMT). We validated representative putative *Prop1* target genes by comparing expression in pituitaries of developing normal and *Prop1* mutant mice. *Prop1* mutants exhibit elevated expression of claudins, indicating that *Prop1* may normally suppress tight junction maintenance, promoting progenitor release from the stem cell niche. Genes that can induce EMT, like *Notch2* and *Zeb2,* had reduced expression in *Prop1* mutants, while the epithelial marker E-cadherin was increased. **Conclusion:** *Prop1* promotes the transition of progenitors into differentiating cells by driving an EMT-like process. Our results advanced our understanding of the mechanism of PROP1 action and MPHD pathophysiology.

Poster Presentations

P1-1

Evaluation of Glucose Metabolism and Cardiovascular Risk Factors and Hyperandrogenemia in Prepubertal Girls with Premature Pubarche

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Background: Premature pubarche (PP) is known to be a risk factor the development of metabolic syndrome (MS) and hyperandrogenism. **Aims:** To evaluate if glucose and insulin metabolism, cardiovascular risk factors and cardiovascular risk factors in family (FCVRF) create a risk for insulin resistance (IR) and if PP is a risk factor alone for MS and hyperandrogenism in normal weighted prepubertal PP girls. **Methods:** Prepubertal and non-obese 35 PP girls with normal birth weight (BW) and 35 healthy controls with same properties were evaluated for BW, gestation week (GW), FCVRF, anthropometric measurements, lipid profile, fasting blood glucose, fasting insulin, HbA1c, SHBG, leptin, adiponectin, TNFα, 17OHP, DHEAS, AS, testosterone, and bone age. HOMA-IR, fasting glucose/insulin ratio, atherogenic index (AI), and free androgen index (FAI) were calculated. OGTT was performed on PP cases. PP cases were also divided into two subgroups according to the presence of FCVRF. **Results:** The mean ages were 8.3 ± 1.1 and 8.1 ± 1 years in PP group and control group respectively. BW, GW, FCVRF, heightSDS, weightSDS, and bone ageSDS were similar between groups, whereas BMI SDS was significantly higher in PP group ($P = 0.026$). Fasting and postprandial glucose and insulin levels in PP group and fasting glucose, insulin levels in control group were normal. HbA1c, lipid profiles, testosterone, leptin, adiponectin, TNFα, HOMA-IR, and AI were all similar. In PP group SHBG was significantly lower ($P = 0.010$), whereas FAI was significantly higher ($P = 0.001$) than in control group. Mean leptin levels were significantly higher in FCVRF+ group than in FCVRF− group ($P = 0.016$). **Conclusion:** This study results indicate that PP is not a risk factor alone for impaired glucose metabolism and IR in non-obese girls with normal BW before puberty. Additionally, low SHBG levels can be a predictive marker of hyperandrogenism in prepubertal girls with PP and high leptin levels in FCVR+ subgroup of upcoming obesity in the future. **Funding:** This work was supported by the Trakya University School of Medicine Research Council.

P1-2

Ontogeny of the Synchronisation between Adrenal Clock Genes, Adrenal Steroidogenesis-Related Genes and the Circadian Rhythm of the HPA Axis in Rats

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Introduction: The circadian rhythmicity of the hypothalamic–pituitary–adrenal (HPA) axis depends on the synchronization of the clock molecular systems in the suprachiasmatic nucleus and in the adrenals. When and how this process occurs in the adrenal is unknown. **Objective:** To assess the ontogeny of daily variation of the expression of the adrenal clock genes (*Clock, Arntl, Per1, Per2, Per3, Cry1, Cry2, Rora*, and *Nr1d1*), steroidogenesis-related genes (*Star* and *Mc2r*), and plasma corticosterone (B). **Material and methods:** Male Wistar rats were kept under a 12 h light:12 h darkness cycle (lights on at 0700 h, Zeitgeber time, ZT0). Plasma and adrenal tissue samples obtained every 4 h over a 24 h period on postnatal days P3, P6, P14, P16, P21, and P24 were used for plasma B measurement (RIA) and mRNA expression by qPCR. The results were analysed using the Kruskal–Wallis test. **Results:** From P14 until P24 there was a progressive nocturnal increase of B concentrations, with peak at ZT20 and nadir at ZT0 ($P < 0.01$), characterising the establishment of the circadian rhythm of the HPA. There was a daily variation in the mRNA expression of *Clock, Arntl, Per2, Per3, Cry1, Nr1d1*, and *Star* since P3 ($P < 0.05$), with attenuation between nadir and peak at P6 and reversal of these parameters from P14, reaching adult patterns at P24. Synchronisation between the expression of the clock genes and adrenal steroidogenesis was observed from P14 and thereafter when the mRNA expression pattern of *Per2, Per3*, and *Cry1* genes became concordant with that of the *Star* gene. **Conclusions:** In the adrenal, there is a gradual synchronization of the molecular mechanisms modulating the ontogeny of the HPA axis circadian rhythm. From P14, the expression of the adrenal clock genes and the genes involved in adrenal steroidogenesis are synchronised resulting in the appearance of the circadian rhythm of the HPA axis. **Funding:** Supported by FAPESP (Säo Paulo State Research Agency) grant number 2012/22164-2.

P1-3

Are Heterozygous Carriers of *CYP21A2* Less Vulnerable to Psychological Stress?

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Background: Congenital adrenal hyperplasia (CAH), due to 21-hydroxylase deficiency is one of the most common monogenic

autosomal recessive disorders with an incidence of one in 15 000, and even more common in some populations. Do carriers have a survival advantage? **Objective and hypotheses:** The HPA axis has been reported to be more active in *CYP21A2* carriers, and possibly enable a more rapid return to homeostasis. A compensatory increase in CRH secretion could result in vulnerability to anxiety and depression. Carriers had lower 24 h cortisol excretion but higher ACTH in response to CRH stimulation. **Method:** We investigated vulnerability to psychological stress in obligate carriers through the national CAH registry ($n=395$). The birth or diagnosis of the child was used as the psychological stressor. Psychiatric diagnoses of the parents, in the national diagnosis registry, before and after the birth of a child with CAH were investigated. Parent in general population, with child with hypospadias or with diabetes type 1 were controls. **Results:** Parents of children with CAH had less risk of receiving a psychiatric diagnosis of affective disorder or substance miss-use after the diagnosis of the child, compared to the general population, odds ratio (OR) 0.3 (95% CI 0.2–0.7) and 0.3 (0.1–0.8) respectively after the child's birth. Compared to parents with a child with hypospadias OR 0.5 (0.2–0.9) and 0.3 (0.1–0.7), and parents of a child with T1DM OR 0.4 (0.2–0.9) and 0.2 (0.1–0.6) respectively. **Conclusion:** Parents of children with CAH had less risk of receiving a psychiatric diagnosis of affective disorder or substance miss-use after the diagnosis of the child, compared to the general population, OR 0.3 (95% CI 0.2–0.7) and 0.3 (0.1–0.8) respectively after the child's birth. Compared to parents with a child with hypospadias OR 0.5 (0.2–0.9) and 0.3 (0.1–0.7), and parents of a child with T1DM OR 0.4 (0.2–0.9) and 0.2 (0.1–0.6) respectively.

P1-4

Effect of CYP17A1 Inhibitors Orteronel and Galeterone on Adrenal Androgen Biosynthesis

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Background: The cytochrome P450 CYP17A1 plays a vital role in regulating adrenal androgen production. The 17,20 lyase activity of CYP17A1 is key for androgen regulation. The orteronel and galeterone are known to inhibit 17,20 lyase activity however the detailed mechanisms of the inhibition of CYP17A1 activities remain unknown. These inhibitors have been developed to treat the castration resistant prostate cancer (CRPC) but little is known about their effects on adrenal androgen biosynthesis. **Objective and hypotheses:** The objective of this study is to study the effect of inhibitors on CYP17A1 enzyme activity and adrenal androgen biosynthesis. **Method:** We used NCI-H295R adenocarcinoma cell model to study the effect of orteronel and galeterone. We treated the H295R cells at 0–2 μM orteronel and galeterone for 24 h. Steroid production was labeled with [^{3}H] pregnenolone for 90 min. Steroids were extracted and resolved by thin layer chromatography. For specific analysis of the P450c17 activities, cells were treated with 1 μM trilostane (a specific blocker of HSD3B) before adding [^{3}H] pregnenolone. **Results:** The drugs orteronel and galeterone were able to inhibit CYP17A1 activity in H295R cells. Both drugs have more potency towards the 17,20 lyase activity but we also observed that they partially affected 17α-hydroxylase activity. From our results, we observed that orteronel seems to be more potent and selective towards 17,20 lyase activity than galeterone. However, we also found that DHEA, cortisol, and androstenedione were drastically decreased by both compounds at 1 and 2 μm concentration. **Conclusion:** Based on these results we can conclude that orteronel is a more potent inhibitor of 17,20 lyase activity and also has partial effect on 17α-hydroxylase activities. Detailed mechanisms that alter the CYP17A1 enzyme activities need further investigation. The discovery of these drug actions on CYP17A1 activity would be of great clinical value for understanding adrenal androgen regulation. **Funding:** Swiss National Science Foundation (grant number 31300-134926).

P1-5

Genetic Heterogeneity in Triple A Syndrome: Discrimination of the Classic Syndrome from Two Triple A-Like Syndromes

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Background: Triple A syndrome is a rare autosomal recessive disorder characterized by adrenal failure, alacrima, achalasia, and a variety of neurological features. In 70% of the families it is caused by mutations in the *AAAS* gene. Linkage analyses indicated genetic heterogeneity and exome sequencing revealed two further genes causing triple A-like syndromes. **Objective and hypotheses:** To summarise the genotypes and phenotypes of classic triple A syndrome in comparison to two novel triple A-like syndromes. **Method:** Clinical and genetic analysis of more than 250 patients with suspected triple A syndrome. **Results:** In classic triple A syndrome due to AAAS mutations adrenal insufficiency occurs in 77.1%, achalasia in 85.1%, and alacrima in 89.7% of all patients. Most patients (72.8%) display neurological impairment, most frequently distal muscular weakness, hyperreflexia, nasal speech, and autonomic dysfunction. Mutations in GDP-mannose pyrophosphorylase A (GMPPA) cause a triple A-like syndrome characterized by alacrima, delayed developmental milestones, and speech delay (each 100%), intellectual disability (91.6%) and achalasia (84.6%). None of the worldwide 13 known patients developed adrenal insufficiency. The disorder caused by GMPPA mutations represents a novel congenital disorder of glycosylation. Recently we identified a homozygous splice mutation in a novel gene in four patients from two independent families. These

patients suffer from achalasia, alacrima, short stature, developmental delay, seizures, and cerebral atrophy, but also lack adrenal insufficiency. The protein product seems to be important for an intact Golgi apparatus. **Conclusion:** There are at least two novel diseases who display overlapping features with classic triple A syndrome. Protein products are involved in different cellular pathways. Clinicians should be aware of this genetic heterogeneity in terms of genetic and clinical counselling. All known patients with triple A-like disorders are still young so that we cannot exclude that they develop adrenal failure at a later time. **Funding:** This work was supported by the German Research Society (HU 895/3-3, 3-4, 3-5, 4-1, 5-1, 5-2).

P1-6

Genetic Diagnosis of Congenital Primary Adrenal Insufficiency by Massive Parallel Sequencing

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Background: Congenital primary adrenal insufficiency (PAI) can occur as three types: isolated glucocorticoid or mineralocorticoid deficiency, or global adrenal insufficiency, with combined mineralo and glucocorticoid deficiency. Once the most frequent genes (*CYP21A2, ABCD1*…) have been discarded by biological tests, many other genes may be involved in each type, and one gene may be responsible of different types. Consequently, there is no real decision tree in the gene analysis order. **Objective and hypotheses:** The aim is to replace Sanger sequencing by massive parallel sequencing (MPS) in order to get a rapid, confident, and costless diagnosis. Instead of studying the genes one by one, they are analysed all at once. But do we get the same results? **Method:** An AmpliSeq™ custom panel was designed including 17 genes: *AAAS, AIRE, CDKN1C, Cited2, CYP11A1, CYP11B2, GPX1, MC2R, MCM4, MRAP, NNT, NR0B1, NR5A1, PBX1, PRDX3, StAR*, and *TXNRD2.* To evaluate the MPS strategy, 20 patients, previously studied by Sanger sequencing (up to ten genes), were sequenced on an Ion Torrent PGM™ System. The bio-informatics pipeline used was the one implemented in the Torrent Suite™ Software. Statistical tools (log-linear and logit models) were used to compare the results, considering Sanger as the 'gold standard'. **Results:** 90% of our targets are well sequenced. The average read depth is 250×. The sensitivity is 80% and specificity 99.9%. No detectable variations were in GC rich regions within the 10% targets not covered or in *CYP11B2,* because mapping quality was at 0 due to its high homology with *CYP11B1.* **Conclusion:** Complete molecular investigation by MPS was faster and cheaper. All regions insufficiently covered by MPS still need to be studied by Sanger sequencing. Taking this into account, no variations would have been missed except in *CYP11B2.* This underlines problem of pseudogenes or homologous genes in MPS.

P1-7

Carriers of 21-Hydroxylase Deficiency Demonstrate Increased Psychological Vulnerability to Stress

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Background: Carriers of congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (21-OHD) demonstrate increased secretion of cortisol precursors following ACTH stimulation, suggestive of impaired cortisol production, and compensatory increases in hypothalamic CRH secretion. Both cortisol and CRH have behavioural effects, and hypothalamic CRH hypersecretion has been associated with chronic states of anxiety and depression. **Objective and hypotheses:** To perform endocrinologic and psychologic evaluation in carriers of 21-OHD and matched control subjects. **Method:** Twenty-nine parents of children with classic CAH (14 males and 15 females; age (mean ± S.E.M.): 41.76 ± 1.07 years), and hence obligate 21-OHD carriers, and 13 normal subjects (five males and eight females; age: 43.77 ± 1.69 years), were recruited to participate in the study. The carrier state of 21-OHD was confirmed by genotype. All subjects underwent a formal oCRH test for measurement of ACTH, cortisol, 17-hydroxyprogesterone (17-OHP), and androstenedione concentrations, which was preceded by determination of urinary free cortisol in two 24-h urine collections. Psychometric assessment was performed by administering the State-Anxiety Inventory (STAI), Beck Depression Inventory, Profile of Mood States, Symptom Checklist-90R, and Temperament and Character Inventory. The study was approved by the Ethics Committee and written informed consent was obtained in all cases. **Results:** Carriers of 21-OHD had significantly higher 17-OHP concentrations following CRH stimulation (peak 17-OHP: 3.97 ± 0.62 ng/ml vs 1.9 ± 0.26 ng/ml, $P < 0.001$), and higher STAI1 (440.86 ± 31.66 vs 359.65 ± 17.71, $P = 0.03$) and STAI2 (879.85 ± 63.2 vs 716.76 ± 34.98, $P = 0.03$) scores compared with control subjects. ACTH, cortisol, and androstenedione responses were similar in the two groups. Stepwise multiple linear regression analysis revealed that in control subjects, peak stimulated cortisol concentrations predicted predisposition to paranoid ideation ($r = 0.294$, $P = 0.049$). **Conclusion:** Carrier state of 21-OHD may predispose subjects to psychopathology.

P1-8

Cortisol:Cortisone Ratio and Metalloproteinase 9 Emerging as Risk Factors Associated with Paediatrics Hypertension

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Background: Paediatric hypertension is increasing and has been associated with obesity and insulin resistance. Recently, cortisol:cortisone ratio and the metalloproteinase 9 (MMP9), which is a marker of vascular remodelling, have been syndicated as new risk factors associated with hypertension. **Objective and hypotheses:** To analyse the association between paediatric hypertension with clinical, biochemical, inflammation, and vascular remodelling biomarkers **Method:** A cross-sectional study was designed. We selected 320 subjects (4–16 years old, female 49.4%), anthropometric parameters, serum aldosterone (SA), plasma renin activity (PRA), cortisol, cortisone, HOMA-IR, hsCRP, adiponectin, IL6, TNFα, PAI1, MMP2, and MMP9 activities were measured. We calculated SA:PRA ratio (ARR >10, as screening of hyperaldosteronism) and serum cortisol:-cortisone ratio as 11β-HSD2 activity estimation. The systolic and diastolic blood pressure indexes were calculated (SBPi and DBPi = observed/50th percentile blood pressure). **Results:** According the Fourth Report of Task Force and JNC7, 59 children were hypertensive. Cortisol and cortisol:cortisone ratio were higher in hypertensive ($P<0.001$). No hyperaldosteronism was found. A positive linear correlation was observed between SBPi and DBPi with: BMI–SDS, HOMA-IR, cortisol:cortisone ratio, MMP2, and MMP9 activities. However, correlations with SA, PRA, and ARR were not significant. The variables associated with hypertension in the multivariate logistic model were: serum cortisol:cortisone ratio (OR: 4.73; CI = 2.32–9.65), BMI–SDS (OR: 3.74; CI = 1.91–7.32), MMP9 (OR: 3.48; CI = 1.79–6.78), and HOMA-IR (OR: 2.20; CI = 1.10–4.38). The other variables we did not correlate with blood pressure. **Conclusion:** Novel biomarkers such serum cortisol:cortisone ratio and MMP9 activity emerged associated with paediatric hypertension. Further studies are needed to know the role of these markers in hypertensive patients. **Funding:** This work was supported by Fondecyt 1130427 and 1150437, CORFO 13CTI-21526-P1 and IMII P09/016-F (ICM) Chilean Grants.

P1-9

Founder Effect and the Clinical and Molecular Characteristics in a Cohort of Classical and Non-Classical Congenital Lipoid Adrenal Hyperplasia Due To *StAR* Mutations

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Background: Classical and non-classical congenital lipoid adrenal hyperplasia (CLAH) are extremely rare condition caused by mutations in *StAR*. The degree of enzyme activity impairment determines the clinical phenotypes. **Objective and hypotheses:** To identify the genetic cause of primary adrenal insufficiency in a cohort of patients from 13 unrelated families with classical and non-classical CLAH, to correlate genotype to phenotype and to identify a possible founder effect of these mutations. **Results:** All ($n=15$) affected individuals with classical CLAH in Israel and the Palestinian territories had the same N-terminal c.201_202delCT mutation due to a founder effect and presented neonatally with severe Addissonian crisis and XY-DSD (in cases of XY karyotype) responding well to full replacement therapy. Three patients with non-classical CLAH had the G221S mutation (novel in the homozygous state), again with a founder effect. These patients presented during early childhood with addisonian crisis during a severe infection requiring just glucocorticoid replacement therapy. Characterization of the pubertal development in XX and XY patients of this cohort is underway. **Conclusion:** Classical and non-classical CLAH due to *StAR* mutations are extremely rare but are significantly more common in the Palestinian population, given the founder effect of the two mutations characterized here. The different clinical phenotype of patients with classical and non-classical reflects the degree of StAR protein dysfunction caused by these mutations. To our knowledge, this is one of the largest cohorts studying the clinical and molecular characteristics of CLAH patients. The actual prevalence of mutations in the *StAR* gene in the general Palestinian population remains to be determined.

P1-10

Use of a Cord Blood Fluorescein Labeled Dexamethasone Monocyte Binding Assay to Study the Glucocorticoid Receptor in Neonates

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Background: Glucocorticoids play an important role in the developing fetus, the most important of which is lung maturation

by increasing surfactant production and release. Glucocorticoid receptor (GR) functioning changes throughout the fetal period, especially during the transition to extrauterine life. Given the importance of glucocorticoids in lung development and functioning, studying glucocorticoid sensitivity in this population would be helpful, especially in the preterm population, to determine steroid treatment for better lung outcomes. Few groups have characterised the GR and its sensitivity using cord blood monocytes. **Objective and hypotheses:** We propose to use cord blood monocytes to characterise the GR and its sensitivity in term neonates using a fluorescein labeled dexamethasone (F-Dex) monocyte binding assay. **Method:** Twenty cord blood samples were collected from term neonates (37–40 weeks gestation) born to mothers with no pregnancy complications and no labor (scheduled C-section). We compared the F-Dex binding in this group to 50 healthy pediatric pts (5–22 years old). **Results:** We found that the F-Dex binding of the studied neonatal population was similar (within 1 S.D.) to the pediatric population through the initial concentration ranges of F-Dex. However, there was an increase in binding in the neonatal population in comparison to the pediatric population at the highest concentration. **Conclusion:** A cord blood F-Dex monocyte binding assay can be used to characterise the GR in neonates. It showed that there is a difference in F-Dex binding at the highest concentrations in the neonate population, as compared to our pediatric population, most likely related to changes in the GR in the process of adaptation to extrauterine life. Our future studies will use this assay to study the GR in preterm neonates to help us determine appropriate steroid dosing and better lung outcomes in these patients.

P1-11

Steroid 11β-Hydroxylase Deficient Congenital Adrenal Hyperplasia with a Reversible Cardiomyopathy Caused by a Novel *CYP11B1* Mutation: Report of Three Cases

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Background: Congenital adrenal hyperplasia (CAH) due to steroid 11β-hydroxylase deficiency is the second most common form of CAH, resulting from a mutation in the *CYP11B1* gene. Steroid 11β-hydroxylase deficiency results in excessive mineralcorticoids and androgen production leading to hypertension, virilisation, and ambiguous genitalia of genetically female infants. **Objective:** The aim of the study was to identify the molecular detect causing steroid 11β-hydroxylase deficiency in two patients from a Saudi family. **Methods:** Two brothers aged 21- and 10-month-old presented with penile enlargement, progressive darkness of skin, hypertension, and cardiomyopathy. Their elder brother had the same family history and died at age of 30 months due to heart failure with severe dilated cardiomyopathy. All coding exons and intron–exon boundary of *CYP11B1* gene were amplified by PCR from peripheral leukocyte DNA of two patients and sequenced. **Results:** A novel biallelic mutation in exon 4 of the *CYP11B1* gene was found in both patients. The mutation c.780 G>A created a premature stop codon at amino acid 260 (p.W260*), resulting in a truncated protein devoid of 11β-hydroxylase activity. Interestingly, a somatic mutation at the same codon (c.779 G>A, p.W260*) was reported in a patient with papillary thyroid cancer (COSMIC database).Clinically, both patients were treated with hydrocortisone and anti-hypertensive medication. Nine months following treatment, cardiomyopathy disappeared with normal blood pressure and improvement in the skin pigmentation. **Conclusions:** We have identified a novel nonsense mutation in the *CYP11B1* gene that causes classic steroid 11β-hydroxylase deficient CAH. Cardiomyopathy and cardiac failure can be reversed by early diagnosis and treatment.

P1-12

Genetic Diagnosis Using Whole Exome Analysis in Two Cases with Malign Infantile Osteopetrosis

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Aim: Osteopetrosis is caused by autosomal mutations occurring in nine genes (*TNFRSF11A, TNFSF11, TCIRG1, CLCN7, OSTM1, SNX10, PLEKHM1, CA2*, and *LRP5*). Detecting the aetiology and providing genetic counselling via individual mutation analysis of all these genes is expensive and time consuming. Whole exome sequencing is currently increasingly used given that the cost and the time needed are similar to that of single gene sequencing analysis. Here, two newborns, genetic evaluations of whom were made with whole exome analyses, are presented. **Methods:** A 9-day-old male case, who was born to nonconsanguineous parents, with bicytopenia and hypocalcaemia and a 6-day-old female patient with hypocalcaemia, whose parents are first cousins and elder brother had died due to osteopetrosis, were studied. They were diagnosed with malignant infantile osteopetrosis on clinical and radiological grounds. Their DNA samples were extracted from peripheral blood. Exome sequencing data generated in Genotypic (India) using HiSDefault 2500 sequencer were analysed in İntergen Genetics Center. **Results:** 31 382 variants were detected in the first case. Among the possible genes in aetiology, a novel heterozygous mutation (c.718G>A), which was predicted to be most likely a disease-causing mutation with *in silico* analyses, was detected in CLCN7. Another mutation was also detected using whole gene Sanger sequencing (compound heterozygous c.398_401delTTGG/c.718G>A). 32 529 variants were detected in the second case. A previously reported homozygous nonsense mutation c.2236C>T in TCIRG1 was detected and confirmed using Sanger sequencing. **Conclusion:** Whole exome analysis is a useful method for diseases in which multiple genes play role in the aetiology. It should be kept in mind

when heterozygous mutations are detected in autosomal recessive diseases that exome sequencing may not evaluate 5% of coding regions and relevant gene should be reanalysed by Sanger sequencing.

P1-13

Osteogenesis Imperfecta: A Pilot Trial on Treatment with the RANKL-Antibody Denosumab

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Background: Osteogenesis imperfecta (OI) is a rare disease leading to an increased bone fragility due to a reduced bone mass. Pathological fractures are the most severe symptom. More than 85% of patients are affected by mutations in *COL1A1*/A2 impairing quantity and quality of collagen. No approved drugs for OI treatment in childhood are available. **Objective and hypotheses:** A prospective pilot study was performed to assess safety and efficacy of an antiresorptive therapy with the RANKL-antibody denosumab in children 5–10 years with OI caused by mutations in *COL1A1/A2*. **Method:** Ten children (male $n=7$, mean age 7.48 years) with genetically confirmed OI (COL1A1: seven patients) were included. All children were treated at least 2 years with neridronate before trial entry. Denosumab was applicated after a washout phase of 6 months every 3 months with 1 mg/kg body weight s.c. for 1 year. Weight adjusted vitamin D/calcium substitution was given 4 weeks after each application. Primary efficacy endpoint was change of areal bone mineral density at the lumbar spine assessed by GE lunar iDXA. Mobility was evaluated by gross motor function measurement (GMFM-88) and 1-min walking test if applicable. Bone metabolism markers were evaluated continuously for safety monitoring. **Results:** After 40 applications of denosumab no severe side effects were observed. A slight hypocalcemia without clinical relevance was seen in all children after each application. DXA assessment showed a mean increase of lumbar spine *Z*-scores of +0.9 S.D. ($n=10$) and total body less head *Z*-scores of +0.6. Mobility improved in all children (mean percent change of: GMFM-88 = 3.1% ($n=10$); 1-min walking distance = 20.1% ($n=8$)). **Conclusion:** Denosumab is effective to reduce bone resorption and increase bone mineral density in children with classical OI. Denosumab seems to be safe in the short-term application at least if a close monitoring/substitution of calcium is guaranteed. Finally, long-term observation and a higher sample size are essential to assess risk:benefit ratio more detailed. **Funding:** Work was supported by a grant from the 'Forschungspool' University of Cologne 2012 and a grant from 'Care for brittle bones'.

P1-14

No Secular Trend in Vitamin D Levels Over the Past 30 Years in Swedish Children

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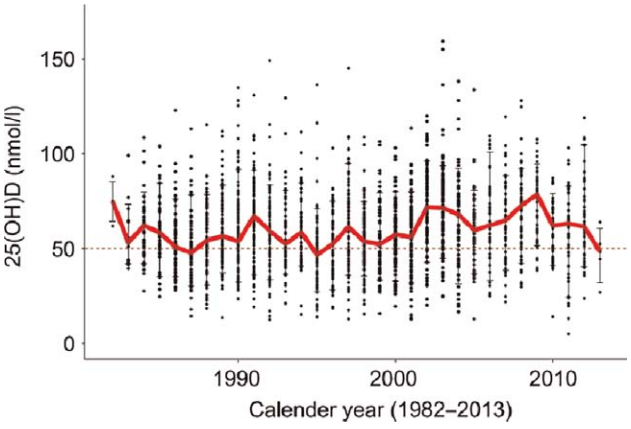
Background: The importance of vitamin D for skeletal health is well established and many recent reports indicate that vitamin D deficiency is linked to chronic diseases. Vitamin D status is defined by serum 25-hydroxyvitamin D (25(OH)D), and although there is no consensus on optimal levels of 25(OH)D concentrations of 50 nmol/l (20 ng/ml) meet the requirements in 97.5% of the population. In Sweden, sun cannot synthesize vitamin D during the winter, therefore supplementation is recommended in Sweden during infancy. **Objective and hypotheses:** Will increased indoor activities and obesity during the three last decades contribute to decreased vitamin D levels in children? **Method:** We analysed serum collected 1982–2013 at GP-GRC from 2048 Swedish children (mean age ± S.D., 8.59 ± 3.68 years; 1197 boys). 25(OH)D was determined with the IDS-iSYS 25-hydroxy vitamin DS automated chemiluminescence immunoassay. Studies of decades-old sera have revealed that 25(OH)D is stable. **Results:** A median (10th–90th percentile) of 58 (29–96) was found and 704 (34.4%) subjects had serum 25(OH)D levels below the recommended level of 50 nmol/l over the 32 years study period. Interestingly, only 3.1% of the children had 25(OH)D levels below 25 nmol/l defined as vitamin D deficiency. We found that younger children had higher levels of 25(OH)D, possibly due to the general supplementation in infants. **Conclusion:** In this unique study over 30 years in a large group of children, there was no trend for decreased vitamin D levels. Information that will be of high value for future cost–benefit analyses in preventive health care. **Funding:** These investigator-initiated and sponsored studies (TRN 88-080; TRN 88-177; TRN 89-071; and TRN 98-0198-003) were supported by unrestricted research grants from Pharmacia/Pfizer, the Swedish Research Council grant number 7509, the Foundation Växthuset for Children, Sahlgrenska University Hospital (ALF), West Sweden Region (VGR) grants, and the County Council of Östergötland.



P1-15

Lithium Chloride Prevents Glucocorticoid-Induced Growth Failure in Cultured Foetal Rat Metatarsal Bones

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Background: Glucocorticoids (GCs) are frequently used to treat numerous chronic diseases in children. Beside their desired anti-inflammatory and immunosuppressive effects, GCs are well known to cause osteoporosis and impaired linear bone growth. These serious side effects of GCs have at least partially been linked to impairment of Wnt/β-catenin signalling. There is no therapy available to rescue from the undesired skeletal effects of GCs. **Objective and hypotheses:** Our aim was to test whether lithium chloride (LiCl), an activator of non-canonical Wnt/β-catenin signalling, can rescue from GC-induced bone growth impairment. **Method:** Foetal (days E19–20) rat metatarsal bones (seven to nine bones per group) were dissected out and cultured with control medium (C), 1 μM dexamethasone (Dexa), 1 mM LiCl (L1), 10 mM LiCl (L10), or combination of drugs (Dexa + L1 and Dexa + L10) for 12 days. Pictures were taken at days 0 and 12 and the percent increase in bone length was calculated using Image J Software. Statistics was computed in R. **Results:** Bone length increased by 141 ± 12% when exposed to control medium. In contrast, Dexa-treated bones grew significantly less (115 ± 12%; $P = 0.001$ vs control). The growth of LiCl-treated bones was similar as in the control group (147 ± 15 and 146 ± 16% in the L1 and L10 groups respectively). When combining L10 and Dexa, bone growth was 147 ± 20%, which was significantly better than in bones treated with Dexa only (115 ± 12%; $P = 0.004$). At a lower concentration (L1), LiCl did not rescue from Dexa-induced growth failure (121 ± 19% vs 115 ± 12% in Dexa only; $P = 0.44$). **Conclusion:** LiCl (10 mM) has the capacity to prevent GC-induced growth failure in cultured foetal rat metatarsal bones, an effect likely to be mediated through the non-canonical Wnt/β-catenin signalling pathway. As LiCl is already available for clinical use, our data could potentially open up for a new approach to prevent GC-induced growth failure in children. **Funding:** This work was supported by ESPE Research Fellowship, sponsored by Novo Nordisk A/S.

P1-16

Diverse Presentations of Hypophosphatasia in Paediatric Patients: A Review of the Case Literature

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Background: Hypophosphatasia (HPP) is the rare inherited metabolic disease resulting from loss-of-function mutations in the tissue-nonspecific alkaline phosphatase (TNSALP) gene. Understanding of the clinical presentation is largely based on single case reports, which presents challenges for the recognition and diagnosis of HPP. **Objective:** To better understand disease presentation, we surveyed the literature to characterize clinical features and presentation for children under the age of 18 with HPP. **Methods:** English-language cases were identified through searches of PubMed using the keywords 'hypophosphatasia' AND ('case report' OR 'case study') and reference lists of identified articles. Cases were then filtered for those reporting patients under age 18. Available information captured for each case included: age of patient, presenting features, predetermined systemic manifestations of interest including craniosynostosis, respiratory compromise, and nephrocalcinosis, and age at death if applicable. **Results:** 293 publications were identified, dating from 1939; of which, 166 publications reported 365 cases <18 years of age. 141 cases had perinatal onset, 68 infantile onset (<6 months of age), and 78 juvenile onset (6 months, <18 years) of HPP; 23 had dental manifestations only (odontohypophosphatasia) and 55 did not provide enough information to determine age at onset. 142 patients were reported as deceased (range of age at death: prenatal to 16 years). Common first reported symptoms included skeletal deformities, failure to thrive, respiratory difficulties, seizures, or premature tooth loss. Overall, the most frequently reported manifestations of interest were premature tooth loss ($n = 114$), respiratory complications ($n = 108$), craniosynostosis ($n = 77$), and muscle weakness ($n = 73$). Other commonly reported complications included delayed walking/motor development and failure to thrive. 40 patients had undergone surgery for craniosynostosis and 12 for correction of deformity or fracture fixation. **Conclusion:** Recognition of these common symptoms as characteristic of hypophosphatasia will facilitate proper diagnosis of this rare disease. **Declaration of interest:** E K Sawyer and K Anderson are employees of Alexion Pharmaceuticals, Inc.

P1-17

Humanin Prevents Undesired Apoptosis of Chondrocytes without Interfering with the Anti-Inflammatory Effect of Dexamethasone in a Model of Arthritis

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Background: Glucocorticoids (GCs) are widely used for treatment of inflammatory and autoimmune conditions. Prolonged use of GCs, however, has several negative side effects, including bone growth impairment in children. Previous studies have shown that GC-induced apoptosis in growth plate chondrocytes is mediated by inhibition of the PI3K–Akt signaling pathway and activation of the pro-apoptotic protein Bax. Humanin, a small mitochondrial derived peptide, has shown promising effects in rescuing chemotherapy-induced apoptosis in growth plate chondrocytes by suppressing Bax. Here we have

extended our findings in combination with GCs in a disease specific mouse model of arthritis. **Aim and objective:** The aim of this study was to investigate if the synthetic analog to humanin, [Gly^{14}]-HNG (HNG), prevents apoptosis of growth plate chondrocytes without interfering with the anti-inflammatory effect of dexamethasone (Dexa) in an *in vivo* model of collagen type II-induced arthritis (CIA). **Methods:** CIA was induced in DBA/1 mice and the animals were treated with Dexa (0.25 mg/kg per day) with/without HNG (100 μg/kg per day) for 14 days. The animals were observed daily for the presence of arthritis including signs of erythema and swelling of the joints and the paws were scored based on the severity of the swelling. Sections of femur growth plate were also analyzed for cell death using TUNEL assay. **Results:** Based on the clinical scoring we observed that humanin in combination with Dexa does not interfere with the desired anti-inflammatory effect of Dexa in the CIA model. Most importantly, we found that humanin protects chondrocytes from GC-induced cell death in femur growth plates of these mice. **Conclusion:** Our results suggest that the combination of humanin and GCs may provide a new treatment strategy for preventing bone growth impairment in children.

P1-18

Response to Vitamin D Replacement is Determined by Body Surface Area in Children with Vitamin D Deficiency

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Background: The serum 25-hydroxyvitamin D (25OHD) levels are known to be lower in obese children, probably due to sequestration of vitamin D in the adipose tissue. However, there is no consensus on the dose adjustment for vitamin D supplementation in obese children with vitamin D deficiency (VDD). **Aims:** To compare the response to vitamin D replacement in normal weight vs overweight children with VDD, and to investigate the determinant for increment of 25OHD level (Δ25OHD) after vitamin D replacement. **Methods:** Participants were 65 Korean children between 8 and 15 years of age diagnosed with VDD between December 2013 and February 2014. VDD was defined as serum 25OHD <20 ng/ml and vitamin D sufficiency as 25OHD ≥ 30 ng/ml. Overweight was defined as BMI $\geq$85th percentile ($n=20$), and normal weight as BMI 5th–84th percentile ($n=45$). All participants received vitamin D3 supplementation (2000 IU/day) for 8 weeks. The levels of 25OHD and biochemical parameters were measured before and after treatment. Body fat was measured by bioelectrical impedance analysis. **Results:** After 8 weeks of treatment, 33.3% of overweight children and 68.9% of normal weight children attained vitamin D sufficiency ($P=0.02$). The Δ25OHD was higher in normal weight group than in overweight group (20.6 ± 7.2 ng/ml vs 15.0 ± 7.6 ng/ml, $P=0.006$). Calcium creatinine ratio was lower than 0.2 in all participants before and after vitamin D replacement. Body surface area (BSA) was the determinant of Δ25OHD ($\beta = -0.644$, $P=0.034$) in a regression model including age, gender, body fat, BSA, and being overweight ($R^2=0.219$). **Conclusion:** The response to vitamin D replacement seems to be influenced by the size of the body rather than adiposity. To achieve vitamin D sufficiency, dose adjustment for vitamin D supplementation is required according to the patient's BSA. **Funding:** This work was supported by the FNDnet research council.

P1-19

Bone–Muscle Unit Assessment with pQCT in Children with Inflammatory Bowel Disease Following Treatment with Infliximab

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Background: Biologic therapy may improve bone health, body composition, and muscle function in children with inflammatory bowel disease but the extent of improvement are unclear. **Objective and hypotheses:** To evaluate bone and muscle mass in children with inflammatory bowel disease (IBD) following infliximab (IFX) therapy. **Method:** Prospective longitudinal study of 19 children (12M), 17 Crohn's disease (CD), one ulcerative colitis (UC), one inflammatory bowel disease unclassified (IBDU) of bone evaluation commencing treatment with IFX. Bone and muscle parameters were measured by pQCT at the non-dominant distal radius at 4 and 66% at baseline and 6 months. pQCT parameters for area were adjusted for height. **Results:** At baseline 7/19 (37%) had moderate/severe disease activity whereas at 6 months this was 1/19 (5%). Nine children (47%) who were on oral prednisolone at baseline discontinued at 6 months. Seven children (37%) were not on oral prednisolone at baseline and 6 months. One child (5%) who was not on oral prednisolone at baseline was on prednisolone at 6 months whereas two children were on oral prednisolone at baseline and 6 months. For all cohort median volumetric BMD Z was -1.4 (-2.8, -0.4) at baseline and -1.4 (-2.8, -0.4) at 6 months ($P=0.64$) and muscle area Z score were -1.8 (-4.3, -0.3) and -2.1 (-3.5, -0.5) ($P=0.93$). Total alkaline phosphatase (U/l) increased from 97 (37, 259) at baseline to 153 (29, 391) at 6 months ($P=0.001$). In the seven children who were not on oral prednisolone at baseline and 6 months, volumetric BMD Z score were -0.9 (-2.1, 0.0) and -0.7 (-2.2, -0.3) ($P=0.79$); muscle area Z score were -0.9 (-3.2, -0.3) and -1.0 (-3.3, -0.9) ($P=0.79$). In the nine children who discontinued oral prednisolone at 6 months, volumetric BMD Z score were -1.2 (-2.8, -0.4) and -1.6 (-2.9, $+0.5$) ($P=0.90$); muscle area Z score were -2.5 (-4.3, -0.6) and -2.2 (-2.9, -0.5) (0.44). In the 12 children who showed progression in puberty, volumetric BMD Z score were -1.4 (-2.8, -0.4) and -1.2 (-2.6, 0.5) at baseline and 6 months ($P=0.65$); muscle area Z score were -1.6 (-3.4, -0.3) and -1.3 (-3.5, -0.5) ($P=0.10$). **Conclusion:** Despite improvement in disease activity, reduction in oral steroid, progression in puberty and increase in plasma alkaline phosphatase following therapy with IFX, muscle bone assessment using pQCT in children with IBD over the short period did not show improvement.

P1-20

24-Hydroxylase Polymorphism as a Possible Contributor to the Increased 1,25(OH)2D in African Americans

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Background: States of vitamin D insufficiency are important determinants of rickets, as well as osteoporosis and other common complex disorders like diabetes, cancer, and infectious diseases. Although, serum concentrations of the vitamin D metabolites are primarily driven by vitamin D supply (by diet or cutaneous synthesis), there is emerging evidence to suggest that single nucleotide variants (SNVs) are important genetic determinants. **Objective and hypothesis:** The aim of this study was to determine whether a functional SNV in the 24-hydroxylase gene promoter (c.-686A > G in CYP24A1) shows significant association with blood levels of vitamin D metabolites. **Methods:** Genomic DNA from 776 inner-city New Haven children aged 6 months to 3 years with different ancestries (African American, Caucasian, and Hispanic) was genotyped for the c.-686A > G SNV. Serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D (1,25(OH) 2D) were measured by RIA. Ancestry was assessed using a validated panel of 108 ancestry informative markers (AIMs) and data from well-characterized African, Native American, and European population samples. **Results:** The main outcome measures were significance of associations between the c.-686A > G CYP24A1 SNV and vitamin D metabolites, with modeling to adjust for age, season, vitamin D intake, and other co-variates. Secondarily we examined the strength of these associations in relation to SNV frequency in the three major ancestral groups. Subjects with the variant allele of CYP24A1 SNV (and decreased 24-hydroxylase activity) had a significantly higher mean 1,25(OH)2D ($P < 0.001$), but all variants were found in African Americans who, as a group, had higher mean 1,25(OH)2D ($P < 0.0001$). Since the effect was not significant when the association was AIMs-adjusted for ancestry, we cannot exclude confounding by stratification. **Conclusion:** Further studies of the CYP24A1 SNV are warranted, but the 24-hydroxylase polymorphism may be considered as one possible contributor to the increased 1,25(OH)2D that is widely observed in African Americans.

P1-21

Effects of Inorganic Phosphate and FGF23 on C2C12 Myoblast Cells

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Background: Dysregulation of phosphate homeostasis in diseases such as tumor-induced osteomalacia and chronic kidney disease are often associated with impairment of musculoskeletal tissue function. While various factors such as intracellular calcium levels and dysegulated endocrine mechanisms are thought to contribute, the role of single factors such as phosphate and its main regulating hormone FGF23 are only partly revealed. **Objective and hypotheses:** Inorganic phosphate and FGF23 have been shown to act via similar signalling pathways in several cell types but we are not aware of any detailed investigations into their effect on the differentiation and viability of skeletal muscle cells. We therefore investigated their effect on skeletal muscle cells in a murine *in vitro* model. **Method:** Murine C2C12 cells were differentiated under single and combined treatments with inorganic phosphate and/or FGF23 and Klotho. Expression of differentiation markers (myogenin, MyHC, MyoD, Myf5) were analysed by RT-PCR and Immunohistochemistry. Proliferation rate was analysed by measurement of BrdU incorporation. Metabolic activity was examined by EZ4U assays. **Results:** Phosphate treatments inhibited the expression of differentiation markers in C2C12 cells in a dose-dependent manner. The altered expression profile was associated with increased proliferation rates and metabolic activity. FGF23/Klotho treatments did not alter gene expression of C2C12 cells or change the effects observed under phosphate treatment. **Conclusion:** High phosphate loads inhibited muscle cell differentiation dose-dependently in a C2C12 model system. FGF23/Klotho treatments did not influence these effects. Knowledge of the distinct effects of phosphate could help us to optimize treatment of hyperphosphataemia and ultimately to prevent musculoskeletal diseases.

P1-22

Evaluation of Bone Mineral Density and Microarchitectural Parameters by DXA and HR-PQCT in 36 X-linked Hypophosphatemic Rickets Patients from a Single-Centre Study

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Background: Previous studies evaluating bone quality and microarchitecture in X-linked hypophosphatemic rickets (XLH) have produced conflicting data. **Objective and hypotheses:** To evaluate the bone mineral density (BMD) and microarchitecture in

36 XLH patients (13 children and 23 adults) with confirmed *PHEX* mutations compared to healthy controls. **Method:** The areal BMD (aBMD) at lumbar spine (L1-L4), femoral neck, total hip and distal radius was evaluated by dual-energy x-ray absorptiometry (DXA). The volumetric BMD (vBMD) and the microarchitectural parameters were evaluated at the distal radius and tibia by high resolution peripheral quantitative computed tomography (HR-pQCT). **Results:** XLH patients presented with a higher aBMD at L1-L4 ($P<0.01$), a lower aBMD at the distal third of the radius ($P<0.01$) and a trend towards lower aBMD at the total radius ($P=0.12$). There were no differences between groups at the femoral neck, total hip and ultradistal radius ($P=0.49$, $P=0.90$ and $P=0.57$, respectively). No differences were observed in vBMD at the radius ($P=0.50$), although the patients presented with a lower total vBMD ($P<0.01$) at the tibia compared to the controls, likely resulting from a decreased trabecular vBMD ($P<0.01$). Regarding the microarchitectural parameters, XLH patients presented a lower trabecular number ($P<0.01$), a greater trabecular separation ($P<0.01$) and a more inhomogeneous trabecular network ($P<0.01$) at both sites. In summary, HR-pQCT analysis showed microarchitectural changes in XLH patients at the radius and tibia; moreover, decreased trabecular vBMD was found mainly at the tibia. On the other hand, DXA analysis presented heterogeneous results at the different sites probably due to the influence of anatomical and anthropometric factors. **Conclusion:** HR-pQCT was more informative than DXA in the bone evaluation of XLH patients. In contrast, DXA results should be interpreted carefully in this group of subjects.

P1-23

Safety and Efficacy of Treatment with Long-Acting Lanreotide Autogel® in Early Infancy in Patients with Congenital Hyperinsulinism

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Background: Long-acting somatostatin analogues have been reported to be an effective treatment option to prevent severe hypoglycaemia in children with severe diffuse congenital hyperinsulinism (CHI). Possible side effects include gallstones, growth retardation and necrotizing enterocolitis (NEC), the latter occurring in particular cases of newborns treated with octreotide. So far only short-acting octreotide is being used in early infancy, requiring multiple injections daily or continuous infusion. Long-acting lanreotide autogel® (LAN-ATG), that has to be applied only once a month, has not been reported as a treatment option in early infancy. **Objective and hypotheses:** To assess safety and efficacy of treatment with LAN-ATG in early infancy in patients with CHI, that did not sufficiently respond to diazoxide, octreotide and nutritional treatment. **Method:** Off-label use of LAN-ATG (5–10 mg/kg body weight) in four infants with CHI without any risk factors for NEC, starting at an age of 2–3 months. CHI was due to homozygous K-ATP-channel mutations ($n=2$) and due to Beckwith-Wiedemann syndrome ($n=2$). Evaluation of blood glucose concentrations, incidence of hypoglycaemia and need of concomitant drugs. **Results:** Mean blood glucose concentrations, 7 days before compared to 7 days after the first LAN-ATG administration increased by 13.5 mg/dl (range 7–15 mg/dl). Frequency of hypoglycaemia <60–mg/dl decreased by 13% (range 0.1–27%). Glucose infusions, octreotide and glucagon treatment could be successfully stopped in all cases 3–20 days after first LAN-ATG injection. In all but one patient, carbohydrate intake could be reduced, by a mean of 6 g/kg body weight/d (range 1.75–12.8 g/kg body weight/d). Over an treatment period of in total 26 patient-months of LAN-ATG application, no serious adverse effects occurred. **Conclusion:** During treatment of CHI with LAN-ATG in early infancy no severe side effects were observed and treatment was efficacious in patients not responding to current treatment regimen as alternative to surgery.

P1-24

The Influence of miR-125b in Pancreatic β-Cell Apoptosis

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Background: Type 1 diabetes is characterised by destruction of islet β cell by autoimmune insulitis and islet cell apoptosis. This study analysed the microRNA 125b how to regulate pancreatic β-cells dysfunction, aiming to elucidate the association between miRNA125b and type 1 diabetes. **Objective and hypotheses:** Recent study indicate miRNA may have role in the development of type 1 diabetes, so this study analyse the miRNA expression profile in the pancreas of type 1 diabetes model NOD mouse, By microarray analysis, clustering analysis indicate a different miRNA profile in insulitis. miR-125b have significant alteration, which is validated by qRT-PCR. we investigated the influence of miR-125b in pancreatic β-cell dysfunction. **Method:** In vitro study, we established the PA (palmitic acid) induced apoptosis model in NIT-1 islet cell line. we found mir-125b expression upregulated during apoptosis. After transient transfection with mimics and inhibitor of mir-125b in NIT-1 cell cells, we found mir-125b inhibit Bak1 expression, then subsequently downregulate Cytochrome C and caspase-3 expression, contribute to its inhibition effects on apoptosis. The bioinformatic analysis show the Bak1 is predict target of miR-125b, dual luciferase reporter assay preliminarily validate Bak1 is target gene of miR-125b. We studied the effect of miR-125b on proliferation?apoptosis and insulin secretion in β-cells through flow cytometry, CCK8 assay and

ELISA, discovered the molecular mechanism behind these phenomena by RT-PCR, Western blot and luciferase reporter gene technology. **Results:** In addition to low viability and increased apoptosis rate, prolonged exposure of the β-cell lines to palmitate caused a dose-dependent decrease of miR-125b.Over-expression miR-125b dramatically suppressed the expression of Bak1 and inhibit cells apoptosis. High miR-125b level also promoted insulin secretion by increasing cell viability. In diabetic mice, low expression level of miR-125b was detected, indicated that miR-125b may be involved in mechanisms of type 1 diabetes. **Conclusion:** Our findings suggest that miR-125b participate in pancreatic β-cell dysfunction and involve in the molecular mechanism of type 1 diabetes, maybe as a novel target for the treatment of this disease.

P1-25

Lower Bone Mineral Density in Type 1 Diabetes Mellitus (T1DM) is Probably Associated with Wnt/β-Catenin Pathway Downregulation Through Increased Dickkopf-1 Levels

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Background: Disruption of many bone metabolic pathways and reduced bone mass are associated with diabetes mellitus. Increased fracture risk and elevated Dickkopf-1 and sclerostin levels, which are inhibitors of Wnt/β-catenin pathway, have been found in adult T2DM patients, but no relevant data exist on childhood T1DM. **Objective and hypotheses:** We aimed at studying plasma Dickkopf-1 and sclerostin concentration in children and adolescents with T1DM and controls. We subsequently correlated Dickkopf-1 and sclerostin levels with metabolic bone markers and bone mineral density (BMD). **Method:** We evaluated 40 children and adolescents with T1DM (mean ± SD age:13.04 ± 3.53 years, T1DM duration:5.15 ± 3.33 years), along with 40 healthy matched controls (age 12.99 ± 3.3 years). Dickkopf-1, sclerostin, receptor activator of Nuclear factor-KappaB Ligand (s-RANKL), osteoprotegerin, osteocalcin, C-telopeptide crosslinks-CTX, electrolytes, PTH, total 25 (OH) D were measured and lumbar spine along with total body BMD were evaluated. **Results:** Patients with T1DM had lower values of L1-L4 (−0.17 ± 1.08 vs 0.23 ± 0.96, $P=0.035$) and total body BMD z-score (0.23 ± 1.01 vs 0.56 ± 0.77, $P=0.04$) than matched controls and higher Dickkopf-1 levels (13.56 ± 5.34 vs 11.35 ± 3.76 pmol/l, $P=0.0194$). A trend for lower Dickkopf-1 values was found in girls (13.36 ± 4.04 vs 11.72 ± 5.14 pmol/l, $P=0.06$) and in pubertal children (13.61 ± 4.87 vs 11.83 ± 4.56 pmol/l, $P=0.054$). Dickkopf-1 correlated with Sclerostin and L1-L4 BMD z-score only in controls and with Osteoprotegerin and i-Phosphorus only in patients, indicating bone metabolism alterations in T1DM. In both groups a significant correlation with log (CTX) and √ALP was found. A significant association of Dickkopf-1 with IGF1 and insulin dose was also found in patients. **Conclusion:** Higher levels of Dickkopf-1 were found in T1DM children and adolescents, indicating a downregulated Wnt signaling system and possible lower osteoblast activation that could be associated with T1DM osteopathy.

P1-26

Human Placenta-Derived Mesenchymal Stem Cells: A Novel Protocol for Pancreatic Differentiation

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Background: Placenta tissue hold great promise as a source of cells for regenerative medicine due to its plasticity and easy availability. Amniotic Mesenchymal Stem Cells (AMSC) represent a potentially unlimited source of functional pancreatic endocrine lineage cells, used to replenish the islet mass in diabetic patients. **Objective and hypotheses:** The aim of our study is to culture AMSC in serum-free condition preserving their phenotypic traits. These cultures could differentiate into pancreatic lineage on exposure to lineage-specific cocktails of growth factors. **Methods:** Different placenta samples of segment cesarean section deliveries of full term pregnancies were collected and AMSC were isolated and cultured in serum-free optimized media with human platelet lysate (HPL). Cell growth was analyzed by direct cell count to determine the log, lag and stationary phases. Differentiation was carried out in three stages and nicotinamide, taurine and retinoic acid were added to each medium. Pancreatic markers expression was assessed with fluorescence-activated cell sorting (FACS) analysis. **Results:** Serum-free media sustained AMSC growth. Cell colonies from placental tissue began to appear after 4 days of cells isolation. The induction of AMSC has microscopically shown progressive cell clustering from day 2 and this led to a spheroidal structure similar to a typical Islet-Like cell formation at the end of day 10. Preliminary pancreatic induction assessed with FACS revealed expression of insulin and c-peptide. **Conclusions:** The present study shows that placenta-derived mesenchymal cells can be isolated and expanded in medium supplemented with HPL. Due to the easy accessibility, lack of ethical concerns and abundant availability AMSC might be an attractive, alternative source of progenitor/stem cells for basic or translational research and a reliable source of insulin producing cells in clinical applications.

P1-27

Activation of Insulin Signaling in Gastrocnemius after Central Leptin Infusion is Associated with an Increase in Proliferation and Muscle Fibre Size

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Background: Skeletal muscle is the largest tissue involved in the insulin-stimulated disposal of glucose, with its size being controlled by hormonal status, among other factors. Leptin plays a primary role in the regulation of glucose homeostasis with a substantial degree of insulin and leptin cross-talk in muscle. However, the relationship between the leptin's central effects on insulin sensitivity in muscle and associated structural changes remain unclear. **Objective and hypotheses:** We hypothesised that chronic central leptin infusion modifies muscle proliferation and fibre size through activation of insulin sensitivity. Thus, we analysed whether the possible changes in insulin signalling and glucose uptake in the gastrocnemius of rats infused with leptin are associated with structural modifications. **Method:** 18 male Wistar rats were divided into control (C), intracerebroventricular leptin infusion (12 μg per day) for 14 days (L) and pair-fed (PF) groups. We analyzed serum levels of insulin by ELISA, muscle glucose concentrations by a colorimetric method, insulin signaling by a multiplexed bead immunoassay, as well as glucose transporter 4 (GLUT4) and insulin receptor (IR) levels by Western blot. Proliferating cell nuclear antigen (PCNA) in gastrocnemius was studied by immunohistochemistry and the area of fibers by haematoxylin-eosin staining. **Results:** Serum insulin concentrations were unaltered in the PF and L groups. Muscle levels of glucose, GLUT4 and IR were unchanged in PF and augmented in the L group. Phosphorylation of IR substrate-1, Akt and mammalian target of rapamycin (mTOR) were enhanced in L, whereas phosphorylation of phosphatase and tensin homolog (PTEN) was reduced in the same group. The number of PCNA-positive nuclei and area of fibers in the gastrocnemius were also increased in L group. **Conclusion:** Central leptin promotes an increase in muscle proliferation and size that could be associated with improved insulin sensitivity.

P1-28

Clinical Characterisation of a Novel RFX6 Mutation – A Rare Cause of Neonatal Diabetes Syndrome

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Background: Mitchell Riley syndrome is a rare syndrome caused by mutations in the *RFX6* gene, resulting in neonatal diabetes, intestinal atresia, pancreatic abnormalities, and biliary hypoplasia. *RFX6* is a winged helix transcription factor that is expressed in the developing pancreas and in the gut endoderm. Previous eight case reports highlight poor outcomes with usually a fatal course in infancy. **Case presentation:** Twin 2 of a dichorionic diamniotic IVF pregnancy was antenatally diagnosed with duodenal atresia. On day 2 of life, at planned repair of this defect, she was noted to have an annular pancreas and absent gallbladder. Preoperatively, pigmented stool and bile were noted, but postoperatively she became acholic with rising conjugated hyperbilirubinaemia. Subsequent investigation revealed a patent but hypoplastic biliary tree with absence of gallbladder. She was also diagnosed with neonatal diabetes and difficult to control initial blood glucose levels. Feed intolerance and poor weight gain were also problematic, complicated by stricture formation at the site of the duodenal atresia repair. Pancreatic exocrine insufficiency was excluded. Surgical intervention helped to improve feed tolerance but she remains PN-dependent due to presence of malabsorptive diarrhoea to achieve adequate nutrition. Genetic analysis identified a novel homozygous intronic mutation, c.1556-40T>G in *RFX6*. This mutation is predicted to create a cryptic splice acceptor site in intron 14 and cause aberrant splicing. Currently, aged 1 year, conjugated hyperbilirubinaemia has resolved, weight gain is improving, and neuro-development is appropriate. Diabetes is well controlled with insulin pump therapy (HbA1C of 6.3%). **Conclusion:** Mutations in *RFX6* are a rare cause of neonatal diabetes associated with poor prognosis. Death within 6 months of life has been reported in 5/8 cases reported so far, mostly due to end stage liver disease and multi-organ failure. This report describes the clinical characteristics of a new case due to a novel homozygous splice site mutation in *RFX6*. It also illustrates that careful management of the critical phase in early infancy may be followed by a relatively favourable outcome than previously reported.

P1-29

Is Reduced Heart Rate Variability Associated with Arterial Stiffness in Youth with Childhood-Onset Type 1 Diabetes Mellitus?

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Background: Increased arterial stiffness may precede cardiovascular complications in patients with type 1 diabetes (T1DM). As the autonomic nervous system is responsible for regulating

heart rate and vascular tone, autonomic dysfunction may contribute to increased arterial stiffness in patients with T1DM. **Objective and hypotheses:** We investigated whether decreased heart rate variability (HRV) was associated arterial stiffness index (ASI) in patients with childhood-onset T1DM without chronic complication. **Method:** Measurements of HRV and ASI, cardio-ankle vascular index (CAVI), were performed in 77 patients with T1DM (19.3 ± 4.3 years, males 38 (49.4%)). Standard deviation of mean NN intervals (SDNN) and root mean squared difference of successive NN intervals (RMSSD) as estimates of overall HRV were obtained using a 5-min ECG recording using SA-2000E (Medicore Co. Korea). CAVI was measured using VaSera VS-1000 (Fukuda-Denshi, Tokyo, Japan). BMI z-score, history of smoking, duration of DM, systolic and diastolic blood pressure (SBP and DBP), HbA1c, HDL and non-HDL cholesterol were also evaluated. **Results:** In youth with T1DM (diabetes duration 10.6 years (2.0–25.0) and mean HbA1c 7.9% (5.5–11.5)), CAVI correlated negatively with both SDNN ($P = 0.044$) and RMSSD ($P = 0.032$) and positively with age ($P < 0.001$) and cholesterol ($P = 0.019$). In multivariate analysis adjusting for demographic characteristics and traditional cardiovascular disease risk factors (age, sex, DBP, cholesterol, smoking, BMI *z*-score, diabetes duration, HbA1c), RMSSD were negatively correlated with CAVI ($\beta = -0.049$, $P = 0.024$). **Conclusion:** Reduced HRV, especially decreased RMSSD was independently associated with increased arterial stiffness in patients with T1DM. Early testing and treatment for cardiac autonomic neuropathy may be effective in preventing cardiovascular morbidity and mortality. **Funding:** This study was supported by grant from the Seoul National University College of Medicine Research Fund 2013.

P1-30

A Novel Mutation in the *abcc8* Gene Causing a Variable Phenotype of Impaired Glucose Metabolism in the Same Family

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Background: Dominantly acting loss-of-function mutations in the *ABCC8* gene, encoding the sulfonylurea receptor 1 (SUR1) subunit of the β-cell potassium channel (KATP), are usually responsible for mild diazoxide-responsive congenital hyperinsulinism (CHI). In rare cases dominant *ABCC8* mutations can cause diffuse diazoxide-unresponsive CHI. Recent reports suggest that medically responsive CHI due to a dominant *ABCC8* mutation may confer an increased risk of diabetes mellitus (DM) in adulthood. The mechanism is not clear at present; possible explanations include a progressive failure in β-cell function due to 'exhaustion', increased β-cell beta cell apoptosis as a result of raised intracellular calcium concentration and the influence of other genetic or environment factors. **Method:** The index patient was born at term to non consanguineous parents with a birth weight of 3900 g. Pregnancy was complicated by gestational diabetes. Biochemical diagnosis of CHI was performed during the first week of life. The patient started diazoxide when he was 3 months old because the drug was not available in his country. He showed a good response to the drug. Molecular genetic analysis revealed a novel heterozygous ABCC8 missense mutation (p.A478T). F-DOPA PET/CT scanning was not conclusive. The patient's mother had gestational diabetes and after delivery she fulfilled the criteria for DM. She did not present hypoglycemia during childhood. The patient's grandfather developed DM at 45 years of age and he also had no past history of hypoglycaemia. Patient's mother and grandfather were heterozygous for the p.A478T mutation. **Conclusion:** Our experience confirms that dominantly acting ABCC8 mutations can cause CHI during childhood and/or gestational diabetes and DM later in life. The novel mutation identified in our patient was not previously reported in diazoxide-responsive forms of CHI; nevertheless a different mutation at the same residue has been reported in a family with CHI. The p.A478T ABCC8 mutation seems to be associated to an incomplete penetrance of hypoglycaemia in infancy.

P1-31

Type 1 Diabetes Onset: A Story of Innate and Adaptive Immune Cells?

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Background: Type 1 diabetes (T1D) is a T cell-mediated autoimmune disease. A more complex immunological picture is being unraveled, with a key role of innate immune cells at disease onset and maintenance. For new therapies based on immune-modulation to be possible, immune characterization of T1D patients is crucial. **Objective and hypotheses:** We aimed to characterise innate and adaptive immune cells of T1D children at a well-defined 'onset-window' of disease, and to correlate with the metabolic status of patients at this stage. **Method:** Blood samples from 41 T1D children, followed at a Paediatric Central Hospital, were evaluated by flow cytometry, <14d after diagnosis and were matched to controls. HbA1c was also evaluated by HPLC at the same time point in T1D. Statistical significance was defined by a P-value of <0.05. **Results:** At disease onset, T1D children presented significantly higher T and B cell percentages and lower

NK cells compared to controls. Within T cells, T1D children exhibited significantly decreased Th17 and Tc17 cells. Regarding leukocytes, monocytes were significantly impaired in T1D children. However, neutrophils and IL17-producing cells correlated inversely with HbA1c. Separating T1D patients in high- and low-HbA1c ($\geq$12%vs$<$12%), high-HbA1c patients showed significantly reduced neutrophils, Th17 and Tc17 cells, compared to low-HbA1c and controls. **Conclusion:** T1D onset presented lower circulating innate cells (NK cells, monocytes) and IL17-producing cells, which may reflect increased migration of these cells to pancreatic tissue at this stage, associated with tissue damage. Longer pre-clinical hyperglycemic patients presented even less circulating IL17-producing cells, and also less neutrophils, which can be due to the capacity of Th17 to attract neutrophils to the site of inflammation. These results suggest that metabolic status influences the migration pattern of immune cells. Our data point toward a relevant role of neutrophils and IL17-producing cells as future targets for immune response modulation.
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P1-32

Aetiological Diagnosis of Diabetes in Italian Diabetic Children and Adolescents

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Background: Type 1 diabetes (T1D) is the most frequent etiology in Italian diabetic children and adolescents. Data on type 2 (T2D) and monogenic diabetes (MD) prevalence are scanty. **Objective and hypotheses:** To estimate the prevalence of T1D, T2D, secondary diabetes, and MD in a pediatric population of Italian diabetic patients. **Method:** Data on 3,076 patients (diabetes onset January 2007–December 2012, age at diagnosis $<$18 years) were collected from 13 Italian Tertiary Centers. Genetic testing was performed when required. Diabetes was categorized as T1D, T2D, MD or as syndromes associated with diabetes (if confirmed by genetic testing), and secondary diabetes (i.e. cystic fibrosis). **Results:** 2813 patients (51.8% males) were diagnosed with T1D (91.4%), 35 T2D (1.1%), 196 MD 6.4% (180 MODY = 5.8%, (2.8% MODY1, 88.3% MODY2, 7.2% MODY3, 1.7% MODY5; neonatal diabetes 0.6%)). Nine cases (0.3%) were diagnosed with other genetic conditions (Wolfram syndrome, mitochondrial diabetes, severe insulin resistance, other), and 23 (0.7%) with secondary diabetes. **Conclusion:** Similarly to other countries, T1D is the most frequent diagnosis in Italian diabetic patients $<$18 years, while a striking disparity, likely due to different lifestyle and genetic background, is observed between the rate of T2D of this study (1.1%, in keeping with European reports of 0.24–1.4%) and the SEARCH data from US (about 11%). At further variance with other Western countries (e.g. Norwegian registry, the DPV-Wiss study, the SEARCH study), the prevalence of MD in Italy is very high. This could depend on the fact that broader attention is devoted to MD in Italy than in the US, and also on the fact that genetic testing is easily accessible and free of charge. The close follow-up of patients with incidental hyperglycemia likely accounts for the very high rate of GCK/MODY2 mutations, the most frequent MODY type in Italy.

P1-33

Improved Genetic Testing for Monogenic Diabetes in the Swiss Population by Targeted Next Generation Sequencing

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Background: Monogenic diabetes is a heterogeneous group of diabetes due to a single gene mutation and includes neonatal diabetes (NDM), MODY and rare forms of syndromic diabetes. These forms of diabetes remain undiagnosed in probably more than 90% of patients. The aim of the study was to identify mutations causing monogenic diabetes using a single test. **Method:** Swiss endocrinologists were proposed to participate in the study and to send blood samples of their patients with suspected monogenic diabetes. Inclusion criteria were NDM, autoantibody negative type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM) diagnosed before the age of 45 without

metabolic features and syndromic diabetes regardless to treatment. The analyses were performed by a targeted next-generation sequencing (NGS) assay sequencing 323 diabetes genes using the Haloplex technology. All the variants were confirmed by Sanger sequencing. **Results:** So far we have analysed 142 diabetic probands by NGS. We identified 73 variants (51%) in the selected 323 genes, compatible with neonatal diabetes and MODY, we also found, variants in genes associated with T_1 or T_2 diabetes. 55% (40/73) of the mutations were found in one of the 13 putative MODY genes (*HNF4A, GCK, HNF1A, PDX1, HNF1B, NEUROD1, KLF11, CEL, PAX4, INS, BLK, ABCC8, KCNJ11*). The most frequent MODY mutations were found in the *GCK* gene (42%, 31/73). 17 different mutations of *GCK* could be identified and 16% (12/73) of the probands carry the p.Val203Ala mutation. **Conclusion:** This study shows that monogenic diabetes can easily be diagnosed by NGS. In 51% of the probands, changes in diabetes genes were found; several variants will need functional validation. 42% of the positive patients had *GCK* diabetes and the Val203Ala mutation is the most prevalent in the Swiss population. Introducing the targeted next generation sequencing as a clinical diagnostic testing could clearly improve the identification of this kind of diabetes. **Funding:** This work was supported by the Fond National Suisse and Schweizerische Diabetes Stiftung.

P1-34

Low Bone Mineral Density is Associated to Poor Glycemic Control and Increased Dickkopf-1 (DKK-1) Serum Levels in Children and Adolescents with Type 1 Diabetes

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Background: Decreased bone mineral density (BMD) and increased fracture risk have consistently been observed in type 1 diabetes mellitus (T1DM). The influence of T1DM on BMD seems to depend on gender or patient's age and to occur early after T1DM diagnosis. The mechanisms of decreased BMD in T1DM patients are still unknown. **Objective and hypotheses:** To investigate the serum levels of dickkopf-1 (DKK-1), a Wnt signaling inhibitor which decreases bone formation and increases bone resorption, in children and adolescents with T1DM and to evaluate the relationship with glycemic control and bone biomarkers. **Method:** This cross-sectional study included 53 T1DM children and adolescents (mean age 12.1 ± 3.3 years) and 50 sex and age-matched controls. Phosphorus, total and ionized calcium, osteocalcin, alkaline phosphatase, PTH and 25 (OH)-vitamin D values were determined. DKK1 was measured in the sera of T1DM patients and controls by ELISA. Bone mineral status was measured by quantitative ultrasonography (QUS). **Results:** T1DM patients showed a significant reduction of BTT-*z*-score compared to controls ($P=0.01$). Higher DKK-1 levels were found in patients than in controls (3344 ± 961 vs 2450 ± 684 pg/ml, $P<0.001$). The DKK-1 levels positively correlated with HbA1c values ($r=0.353$, $P=0.01$). Furthermore, with adjustment for age HbA1c inversely correlated with BTT-*z*-score, AdSos-*z*-score, osteocalcin, alkaline phosphatase, 25 (OH)-vitamin D, as well as directly correlated with daily insulin dosage and T1DM duration. We also found that in T1DM patients DKK-1 serum levels inversely correlated with PTH, osteocalcin, and AdSos-*z*-score. Additionally, the T1DM duration was indirectly correlated with alkaline phosphatase, 25 (OH)-vitamin D and BTT-*z*-score. Multiple regression analysis showed that DKK-1 serum levels were best predicted by AdSos-*z*-score, alkaline phosphatase, 25 (OH)-vitamin D and HbA1c ($r=0.61$, $P<0.0001$). **Conclusion:** In conclusion, children and adolescents with T1DM presented a reduction of bone mineral status associated to poor glycemic control and increased DKK-1 serum levels.

P1-35

Effect of 6 Months Therapy with Metreleptin in an African American Boy with Congenital Generalised Lipodystrophy

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Background: Congenital generalised lipodystrophy (CGL) is a rare autosomal recessive disorder which presents with near total lack of adipose tissue and extreme insulin resistant diabetes. Metreleptin, an analogue of leptin was made through recombinant DNA technology. It was approved to treat CGL from February 2014.Our case represent successful use of Metreleptin in a child with diabetes developed secondary to CGL. **Case presentation:** A 14-years-old African-American boy was referred for evaluation of insulin dependent diabetes at 11 years of age. He was diagnosed with diabetes at 9 years of age. Clinically, he was noted to have significant acanthosis nigricans, muscular extremities, acromegaloid features of the face and normal intellectual development. His BMI 23.2 kg/m^2 and blood pressure were normal. Leptin level was decreased 0.5 ng/ml (Nl. 1.4–16.5), Triglycerides (TG), ALT, AST were elevated and Hemoglobin A1c was 14.7%. Islet cell antibodies were negative. MRI revealed generalized muscle hypertrophy with markedly decreased subcutaneous and intra-abdominal fat, periarticular and intramedullary lytic bone lesions, and hepatomegaly. *AGPAT2* gene analysis revealed homozygous c.IVS4-2A>G

mutation. Treatment with high doses of insulin up to 3 u/kg/day with addition of metformin was unsuccessful. After starting Metreleptin treatment within 1 month we were able to stop insulin therapy. At first it was necessary to increase Metreleptin dose from 2.5 mg to 10 mg per day but within 2 months of therapy dose was decreased to 2.5 mg per day and without any other medications his glucose levels became normal. HbA1c improved from 14.7 to 6.3% after 6 months of therapy. His TG, ALT and AST became normal as well. **Conclusion:** Diabetes secondary to CGL can be misdiagnosed in children as type 1 diabetes. Clinical keys were acanthosis nigricans and acromegalic facial features and muscular extremities. Metreleptin therapy may dramatically improve the metabolic complications in patients with CGL.

P1-36

Somatic Paternal UPD on Chromosome 11p15 in Focal Form of Congenital Hyperinsulinism (CHI) Causes Monoallelic Expression of Mutant ABCC8 and KCNJ11

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Background: Congenital hyperinsulinism (CHI) is a disorder characterised by dysregulation of insulin secretion that leads to severe hypoglycaemia in neonates and infants. The focal form of CHI is caused by an autosomal recessive mutation in the genes ABCC8 or KCNJ11 inherited from the father and a second somatic event in the affected islet of Langerhans. **Objective:** We report molecular genetic examination of focal pancreatic lesions of patients receiving therapeutic surgery in order to discover the genetic mechanisms in focal form of CHI. **Method:** Patients were selected from the German Registry for Congenital Hyperinsulinism with proven *ABCC8* or *KCNJ11* mutations. Loss of heterozygosity (LOH) and gene expression levels were analysed by PCR, RT-PCR and Sanger sequencing in 11 patients with focal form of CHI. Deletions, duplications and uniparental isodisomy (UPD) were tested by methylation-specific MLPA (MS-MLPA). **Results:** Complete and partial LOH was found in 10/11 focal lesions and monoallellic expression of the mutant *ABCC8/KCNJ11* alleles was observed in all lesions. In contrast, there was no LOH detected in surrounding pancreatic tissue or blood cells. This supports somatic mosaicism specific in pancreatic beta cells. Both, *ABCC8* and *KCNJ11*, are located in proximity to the Beckwith-Wiedemann imprinting control region on chromosome 11p15 that is also known for UPD. By MS-MLPA paternal UPD at 11p15 was detected in all samples showing LOH, whereas no deletion or duplication was found of this region. **Conclusion:** In focal form of CHI monoallelic expression of mutant *ABCC8/KCNJ11* is mainly caused by somatic paternal UPD 11p15. **Funding:** MicroDissect GmbH (Spende:Somatische Mosaike # 995040).

P1-37

Hyperthyroidism in 276 Children and Adolescents with Type 1 Diabetes from Germany and Austria

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Background and aims: Little is known about the incidence and clinical consequences of hyperthyroidism in paediatric patients with type 1 diabetes mellitus (T1DM). **Methods:** We analysed the DPV database to investigate the rate of hyperthyroidism in paediatric T1DM patients, its impact on metabolic control, and potential associations with other autoimmune diseases. **Results:** Hyperthyroidism was found in 276/60,456 patients (0.46%) and was associated with younger age, shorter diabetes duration, female sex, and reduced body mass index. Diabetic ketoacidosis (DKA) and hypoglycaemia were more frequent in T1DM with comorbid hyperthyroidism, while long-term metabolic control (HbA1c) was similar in both groups. Absolute blood pressure and arterial hypertension rate were elevated in the hyperthyroid patients. Rates of microalbuminuria and diabetic retinopathy were not different. Thyroid-specific antibodies (TPO, TG, TR) were associated with hyperthyroidism. Thyroid volume and rates of cysts and nodules were higher and echogenicity was decreased. **Conclusion:** Prevalence of hyperthyroidism is low in diabetic children with T1DM but increased compared to children <18 years without diabetes. Hyperthyroidism is primarily associated with acute diabetes complications (DKA and hypoglycaemia) and affects blood pressure regulation. Long-term metabolic control or insulin requirement were not different.

P1-38

Metabolic Syndrome Frequency in Longitudinally Followed Children with Premature Adrenarche During Pubertal Ages

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Objective: To evaluate metabolic syndrome parameters in children with premature adrenarche (PA) during presentation in prepuberty and afterwards in puberty. **Methods:** 54 (48 femals, six males) patients (mean age 12.5 ± 2.4 years) diagnosed with PA and followed until puberty were included in our study; as the control group 28(22 females, six males) (age, sex, puberty matched) healthy children (mean age 13.5 ± 2.2 years) were taken. CAH was ruled out in all PA children. Anthropometric measurements, lipid levels, hormonal parameters, adipocytokines (adiponectin, leptin, ghrelin, visfatin, resistin, RBP-4, TNF-α, IL-6) were evaluated and OGTT was done. Pelvic US (female) and Carotid Doppler US were performed in all patients. Different indices for insulin resistance (IR) were calculated. In PA children, prepubertal and pubertal results and also pubertal PA and control cases were compared. **Results:** In PA cases; onset of adrenarche was 7.0 ± 0.9 years, onset of puberty was 9.7 ± 0.8 in girls, 10.7 ± 0.9 in boys and menarcheal age was 11.8 ± 0.9 years. Mean BMI SDS was normal in PA at presentation and in puberty but was significantly higher than the controls. Waist circumference (WC) SDS was significantly higher in pubertal PA than the controls. IR parameters were higher in puberty in PA than in prepuberty and higher than the controls. At first presentation, 25.9% of the patients had IR and 15.4% had dyslipidemia; during the study 63% had IR, 11.1% had impaired glucose tolerance, 3.7% had diabetes, 27.5% had dyslipidemia and PCOS was present in 33.3%. Lipid profiles, except for cholesterol, and adipocytokine levels were similar between the groups. Carotid Intima-media thickness was positively correlated with BMI SDS ($r=0.281$; $P=0.043$) and WC ($r=0.287$; $P=0.043$). The most important factors for the development of IR in pubertal PA were WC SDS, birth weight and exaggerated adrenarche. **Conclusion:** Hyperinsulinaemia is common in children with PA in prepuberty and increases with age especially with increasing BMI, even within normal ranges, and WC. **Funding:** This work was supported by Scientific Research Projects: Istanbul University (42752).

P1-39

Evaluation of Ability of Urinary Podocalyxin, Nephrin and Liver type Fatty Acid Binding Protein for Early Diagnosis in Renal Injury in Adolescents with Type 1 Diabetes

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Background: Biomarkers other than microalbuminuria are needed to detect early kidney injury in adolescents with type 1 diabetes. **Objective and hypotheses:** We aimed to determine diabetic nephropathy in normoalbuminuric and normotensive diabetic adolescents with biomarkers related different segments of the glomeruli (podocalyxin, nephrin and liver type fatty acid binding protein (L-FABP)), and to assess the relationship among these biomarkers and glomerular filtration rate (GFR). **Method:** 109 diabetic adolescents and 30 healthy controls were enrolled in the study. Diabetics were divided into subgroups according to long-term mean HbA1c levels, diabetes duration as 1–5 years, 5–10 years and ≧10 years, allowing further assessment of association of biomarkers with study variables. **Results:** Urinary podocalyxin, nephrin, L-FABP levels and GFR were higher in subjects with diabetes compared with nondiabetics. Urinary podocalyxin was found to be correlated with diabetes duration ($r=0.752$, $P<0.001$). Urinary nephrin and L-FABP levels were found to be correlated with HbA1c levels ($r=0.45$, $P=<0.001$ vs $r=0.69$, $P=<0.001$). Urinary nephrin, podocalyxin and L-FABP levels were found higher in normoalbuminuric diabetic patients with than healthy subjects and in diabetics with microalbuminuria than normoalbuminuric diabetics (P values, respectively 0.002, <0.001 vs <0.001). **Conclusion:** The present study demonstrates that elevated urinary podocalyxin, nephrin and L-FABP excretion may determine early kidney injury before microalbuminuria occurs. Besides, these biochemical markers may be useful for staging kidney injury, predicting kidney injury progression. Closer monitoring of diabetic patients with elevated urinary podocalyxin, nephrin, L-FABP levels and protective measures may prevent chronic kidney disease development.

P1-40

Efficacy and Safety of a Fixed Combination of Insulin Degludec/Insulin Aspart in Children and Adolescents with Type 1 Diabetes

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Background: Insulin degludec/insulin aspart (IDegAsp) is the first soluble co-formulation that combines two insulin analogues. **Aims and objectives:** To assess the efficacy and safety of IDegAsp administered once-daily (OD) plus meal-time IAsp for

remaining meals in controlling glycaemia as assessed by change in HbA_{1c} from baseline in a paediatric population. **Methods:** A 16-week, 1:1, open-label, parallel group, randomised, treat-to-target trial. **Results:** Children aged 1–5 years ($n=82$), 6–11 years ($n=122$), 12–17 years ($n=158$) with a diabetes duration of 1.6–6.0 years, HbA_{1c} of 7.9–8.3% and fasting plasma glucose (FPG) of 8.1–8.6 mmol/l (all range of means at baseline) were randomised to receive either IDegAsp OD + meal-time IAsp for remaining meals ($n=182$) or insulin detemir (IDet) + meal-time IAsp ($n=180$). IDegAsp was non-inferior (limit 0.4%) to IDet for change in HbA_{1c} (estimated treatment difference (ETD) -0.04 $(-0.23; 0.15)_{95\%CI}$), which was accomplished with a numerically lower basal insulin dose: IDegAsp + IAsp: 0.36 vs IDet + IAsp; 0.5 U/kg. ETD for FPG at Week 16 was 0.31 $(-0.70; 1.33)_{95\%CI}$. Rates of confirmed hypoglycaemia were 46.2 (IDegAsp + IAsp) vs 49.6 (IDet + IAsp) events/patient-years of exposure (PYE) (estimated ratio (ER) 0.95 $(0.76; 1.17)_{95\%CI}$). Rates of nocturnal hypoglycaemia were 5.77 (IDegAsp + IAsp) vs 5.40 (IDet + IAsp) events/PYE (ER 1.09 $(0.81; 1.48)_{95\%CI}$). Rates of severe hypoglycaemia were 0.26 (IDegAsp + IAsp) vs 0.07 (IDet + IAsp) events/PYE (ER 3.20 $(0.88; 11.66)_{95\%CI}$; $P=$ ns). Rates of hyperglycaemic episodes with ketosis were 0.11 (IDegAsp + IAsp) vs 0.22 events/PYE (IDegAsp + IAsp) (ER 0.44 $(0.11; 1.74)_{95\%CI}$) and ETD for body weight SD scores was 0.07 $(0.02; 0.12)_{95\%CI}$. Adverse event profiles were similar. **Conclusions:** IDegAsp + IAsp was non-inferior to IDet + IAsp for change in HbA_{1c}, at a numerically lower basal insulin dose. There were no significant differences in rates of confirmed or severe hypoglycaemia between IDegAsp + IAsp and IDet + IAsp. IDegAsp + IAsp offers an alternative to basal–bolus treatment with one injection of combination insulin per day. **Disclosures:** TB has been a board member for Novo Nordisk, Sanofi, Eli Lilly, Medtronic and Bayer Health Care. His institution has received research grants and/or travel and accommodation expenses from Abbott, Medtronic, Novo Nordisk, GluSense, Sanofi, Sandoz and Diamyd. He has served on speakers' bureaux for Eli Lilly, Bayer, Novo Nordisk, Medtronic, Sanofi and Roche. He has stock in DreamMed. LD has served on advisory panels for Novo Nordisk, Sanofi and Bayer. He has also received research support from Novo Nordisk and Locemia. PDR and TMG are employees of Novo Nordisk A/S. GK has served as a consultant for Novo Nordisk. M Kocova and M Kovarenko have no conflicts to disclose. NS has served on advisory panels and speakers' bureaux for Novo Nordisk. **Conflict of interest:** TB has been a board member for Novo Nordisk, Sanofi, Eli Lilly, Medtronic and Bayer Health Care. His institution has received research grants and/or travel and accommodation expenses from Abbott, Medtronic, Novo Nordisk, GluSense, Sanofi, Sandoz and Diamy. **Funding:** The work was supported by Novo Nordisk A/S.

P1-41

Current Care and Outcomes for Children and Young People with Diabetes in England and Wales: Results from the National Paediatric Diabetes Audit

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Background: Assessment of care and outcomes in children with diabetes requires on-going monitoring to ensure improvement. **Objective and hypotheses:** To assess the current quality of care and outcomes for children and young people with diabetes in England and Wales. **Method:** The National Paediatric Diabetes Audit (NPDA) collates data on the demographic characteristics, care processes and outcomes of all children and young people with diabetes under the care of paediatric diabetes units in England and Wales. **Results:** In the 2013/14 data was collected on 26 598 children and young people with diabetes. Almost all (98.3%) had at least one HbA1c measurement in the audit period. However, only 16.1% (12 years and older) received all seven recommended care processes (HbA1c, BMI, BP, cholesterol, urinary albumin, eye screening and foot examination) compared to 12.1% in 2012/13. Mean (SD) HbA1c was 71.6 (17.4) mmol/mol falling from 73.0 (18.0) mmol/mol in 2012/13. 18.4% had a HbA1c <58 mmol/mol (cf. 15.8% in 2012/13) and 23.9% had a HbA1c >80 mmol/mol (cf. 25.9% in 2012/13). 14.1% (12 years and older) had abnormal eye screening and 7.1% were known to have albuminuria. 27.9% had a systolic and/or a BP above the 98th centile. $<$ half (45.2%) were recorded as having received structured education in the past year. **Conclusion:** Despite improvements in the care processes received and mean HbA1c in children and young people with diabetes most are not meeting recommended targets. Early warning markers of microvascular and cardiovascular disease are present. International benchmarking of mean (SD) HbA1c in 2011/12 showed Germany/Austria 64 (18) mmol/mol, USA 67 (15) mmol/mol cf. with England and Wales 74 (18) mmol/mol. Further progress is needed to improve long term outcomes for children and young people with diabetes in England and Wales as they progress into adulthood. **Funding:** This work was supported by funding from the Healthcare Quality Improvement Partnership.

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Dynamics Perceptions of Their Own Health in the Process of Learning Self-Control Adolescents with Type 1 Diabetes Mellitus

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Background: Psychological characteristics of patients with type 1 diabetes mellitus (DM1) factor significantly into the effectiveness of disease self-control training. An important part of I-concept of child with DM1, along with internal picture of disease, is internal picture of health (IPH). IPH is an individual's special attitude towards his/her health, represented by recognizing its value and taking active and positive effort to improve it. **Objective and hypotheses:** To determine the nature of changes in internal picture of health while teaching self-control of the

disease to adolescents with DM1. **Method:** in 157 children 4–18 years old (84 girls and 73 boys) with DM1 a research of IPH was conducted before and after the self-control training cycle (3 months), using psycho-semantical method (content-analysis of mini-essay: «My health»). Structural components (behaviour, self-assessment, values, emotions, will, interpersonal relations, etc.) and dynamic characteristics (desire to preserve and maintain health, disease presence denial, destructive behaviour, etc.) were defined. **Results:** Among the hierarchy of structure and content components of IPH in adolescents with DM1, both before and after training, the top three are self-assessment, behavioral and cognitive-declarative components. After the exercise, faith and hope for cure component moved up to the 4th place, previously held by control component. One half of teens displayed lack of defined locus of control, while the other half displayed dominating internal locus of health control, understanding that health depends on one's own efforts. Therapeutic studies with adolescents with DM1 led to decreased percentage of patients with ambivalent position (from 63 to 11%) and increased percentage of children whod is closed IPH, concerning only the pole of health (from 31 to 78%), meaning reduced fixation on disease. These changes of IPH were accompanied by improved metabolic compensation, seen in indicators H_BA1C (from (9.80 ± 0.02)% to (8.14 ± 0.13)%, $P < 0.05$). **Conclusion:** While teaching self-control to adolescents with DM1 it is necessary to give attention to the formation of such IPH components as control, faith in cure, motivation and will. Formation of internal locus for one's health control while teaching self-control to adolescents with DM1 determines the efficiency of treatment of disease.

P1-43

Evaluation of Median Nerve in Children with Type1 Diabetes using Ultrasonographic Imaging and Electrophysiology

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Background: Diabetic neuropathy is recognised as the most common clinical picture of nervous system disorders caused by DM and is considered the most common type of neuropathies. **Objective and hypotheses:** To evaluate the relationship between the sonographically measured cross-sectional area (CSA) of the median nerve and nerve conduction study (NCS) in children with type1 diabetes (T1DM) complaining of DPN. **Method:** 40 children withT1DMand 20 age-matched healthy subjects were enrolled in this study. The diabetic children were divided into two groups (without and with DPN). All participants underwent NCS and sonographic measurement of CSA for the median nerve in the carpal tunnel. All NCS were done on both median nerves measuring the motor nerve conduction velocity (MNCV) and the motor latency from the elbow to the wrist joint. **Results:** Patients with T1DM (mean age 15.2 ± 2.9 years, duration 8.4 ± 4.1 years, all participants were on intensive insulin therapy in a dose ranging from 0.5 to 2.5 IU/kg per day with a mean of 0.4–1.8 IU/kg per day. The CSA of the median nerve in children with DPN was higher than that in the control subjects yet with no significant difference with that of children without DPN. The mean value of median nerve motor latency was diminished in patients with DPN in comparison to patients without DPN and controls (3.5, 3.4, 2.96 ms respectively, $P = 0.005$). The mean value of median nerve MNCV in the control individuals showed no significant difference ($P = 0.085$) compared to that of children without DPN and statistically significant difference ($P = 0.016$) compared to that of children with DPN as it was 54.6 m/s vs 52.9 m/s and 54.6 m/s vs 51.5 m/s respectively. The increased median nerve CSA in the carpal tunnel was considerably correlated with the median nerve motor latency and duration of diabetes, nevertheless, with no correlation with median nerve motor conduction velocity (MNCV). The best cut-off value of the sonographically measured median nerve CSA for discrimination between control individuals and children with DPN is (0.046) with sensitivity = 100%, specificity = 80%, PPV = 83.3%, NPV = 100%. **Conclusion:** Our data implicate that sonographic measurement of CSA is a good alternative to NCS results of motor latency and MNCV for the diagnosis and follow up of diabetic neuropathy. Moreover, the duration of disease and impaired glycaemic control play an important role in the development of peripheral neuropathy. Sonographic measurement of CSA of the median nerve in the carpal tunnel serves as a good discriminator for diabetic children from healthy individuals. Moreover, it has significant positive correlation with duration of disease and the nerve motor latency.

P1-44

Is Metabolic Control Affected by Military Service in Young Adults with Type 1 Diabetes?

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Background: Young adults with type 1 diabetes (T1D) are exempt from conscript military service due to risk of severe hypoglycaemia and metabolic compromise. Nevertheless, there are patients who volunteer to military service. **Aims and objectives:** To evaluate the effect of military service on metabolic control and incidence of acute diabetes complications. **Methods:** Study design: retrospective, comparative analysis. Data of 145 T1D patients born between 1984 and 1992 and followed at the National Center of Childhood Diabetes was retrieved from the institutional registry. The study group included 76 (36 males (47.4%)) T1D conscript volunteers and 69 (38 males (55.1%)) T1D non-volunteers served as controls. Clinical and laboratory data was collected from medical records one year prior to enlistment to military service, at enlistment, after 1 and 2 years of service. Outcome measures: HbA1c, occurrence of severe hypoglycaemia or diabetic ketoacidosis (DKA), BMI-SDS and insulin dosage.

Results: Metabolic control was comparable in volunteers and non-volunteer controls (mean HbA1c (1 year prior to enlistment 7.83±1.52% vs 8.07%±1.63; at enlistment 7.89±1.36% vs 7.93±1.42%; 1 year after enlistment 7.81±1.28% vs 8.00±1.22%; 2 years after enlistment 7.62±0.8% vs 7.79±1.19%)); with no significant changes from baseline throughout follow-up. BMI status and insulin requirements were similar and remained unchanged in volunteers and controls (mean BMI-SDS (1 year prior 0.23±0.83 vs 0.29±0.95; at enlistment 0.19±0.87 vs 0.25±0.98; 1 year after 0.25±0.82 vs 0.20±0.96; 2 years after 0.20±0.87 vs 0.16±0.90) and mean insulin dose in U/kg per day (1 year prior 0.90±0.23 vs 0.90±0.37, at enlistment 0.90±0.28 vs 0.93±0.33, 1 year after 0.86±0.24 vs 0.95±0.33, 2 years after 0.87±0.23 vs 0.86±0.28)). There were no severe hypoglycaemia episodes and DKA events in both groups. **Conclusions:** Our data suggests that young adults with T1D can maintain appropriate metabolic control during military service without significant weight change or severe acute diabetic complications.

P1-45

Immune/Inflammatory Profile in Children with Type 1 Diabetes Mellitus and Celiac Disease and/or Autoimmune Thyroiditis

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Background: Most studies examined immune/inflammatory parameters in type 1 diabetes mellitus (T1D) showing discrepant results and not yield definitive conclusions. A study carried out by our group in 2013 compared meta-immunologic profiles of three groups: high-risk children, newly diagnosed children affected by T1D and controls. **Objective and hypotheses:** To compare metabolic profile in three groups: children affected by T1D and an additional autoimmune disease; children affected by T1D; control subjects. The aims of this study are: i) to verify if metabolic profile of children affected by T1D is significantly different respect to ones with additional autoimmune disease and ii) if it might reveal possible predictors of disease severity. **Method:** 134 consecutive T1D-children, recruited in the Department of Pediatrics at Univeristy of Naples 'Federico II', were analyzed for a wide range of metabolic parameters. Metabolic profile was verified at baseline (T_0, after a first glycemic stabilization by insulin) and 12 months after diagnosis (T_1). 64/134 had at least one autoimmune disorder besides T1DM: 44 celiac disease (CD) and 20 autoimmune thyroiditis (TAI) (group 1) and 70 only T1DM (group 2). 56 healthy children were enrolled using the following criteria: fasting blood glucose of <5.5 mmol/l (100 mg/dl), personal and family history negative for autoimmune disorders, negative islet autoantibodies (group 3). The three groups were matched for sex, age and BMI. We evaluated the following metabolic variables: leptin, sLepR, MCP-1, sCD40L, OPG, MPO, sICAM, sTNFr, resistine. Variables were preliminary evaluated by means of T-test. **Results:** Preliminary results: at T0 group 1 presented statistically significant sTNFr lower than other groups ($P=0.0025$ vs group 3 and $P=0.0004$ vs group 2); sICAM-1 lower than group 2 ($P=0.038$); leptin lower than group 3 ($P=0.0024$); sLepR lower than group 3 ($P=0.0001$). At T_1 group 1 presented statistically significant sICAM-1 and sTNFr lower than group 2 ($P=0.04$ and 0.08 respectively). **Conclusion:** Patients with T1D and CD and/or TAI present more immune/inflammatory markers than patients with only T1D and controls. Further results are needed to verify if these results are useful to predict disease severity.

P1-46

Trends in Insulin Therapy in 50 861 Children and Adolescents with Type 1 Diabetes from Austria and Germany Between 2000 and 2014

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Background: Over the last two decades, treatment of type 1 diabetes became more intensified and changes in the type of insulin used were reported. **Objective and hypotheses:** We hypothesised that there are also changes in insulin dosage and in the ratio of prandial to basal insulin. Our aim was to analyse potential trends in paediatric subjects with type 1 diabetes from Austria and Germany between 2000 and 2014. **Method:** 50 861 subjects (<20 years of age) with type 1 diabetes from the Diabetes-Patienten-Verlaufsdokumentation (DPV) – database documented between 2000 and 2014 were included. Regression models were applied for insulin dosage/kg body weight in patients on intensified conventional insulin therapy (ICT) and in patients on continuous s.c. insulin infusion (CSII) as well as for the ratio of prandial to basal insulin in patients on ICT. Additionally, sex- and age-specific analyses (0–5; 5–<10; 10–<15; 15–<20 years of age) were conducted. Confounders: sex, age, BMI, and diabetes duration. *P* values for trend (SAS 9.4). **Results:** Insulin dosage increased in ICT from 0.88 IU/kg per day in 2000 to 0.94 IU/kg per day in 2014 and in CSII from 0.71 IU/kg per day to 0.80 IU/kg per day (both $P<0.0001$). Stratification by sex and age-groups revealed a significant increase in ICT and CSII (all $P<0.01$).

Only in 5–10 year old subjects on CSII, insulin dosage decreased from 0.71 IU/kg per day to 0.68 IU/kg per day ($P<0.0001$). The ratio of prandial to basal insulin in ICT rose from 1.25 in 2000 tov 1.37 in 2014 ($P=0.0056$). In girls and in younger age-groups (0–5; 5–<10), an increase was present (all $P<0.0001$). In other subgroups, this trend was lacking ($P>0.05$, respectively). **Conclusion:** Insulin dosage and ratio of prandial to basal insulin both increased over the last 15 years. Possibly, these findings might be explained by an increase in sedentary lifestyle or by changes in the quantity/quality of nutrition. **Funding information:** The work was supported by the German Competence Network Diabetes mellitus funded by the Federal Ministry of Education and Research (FKZ 01GI1106), now integrated into the German Center for Diabetes Research (DZD). Further financial support was provided by the European Foundation for the Study of Diabetes (EFSD).

P1-47

Relative Hypoaldosteronism in a Patient with WOLCOTT-Rallison Syndrome

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Background: Wolcott–Rallison syndrome (WRS) is an autosomal recessive, multi-system disorder with early onset diabetes in infancy. It is associated with clinical features that show variability between WRS cases. Clinical data are still scarce. **Patient data:** A 9 year old girl followed-up due to diabetes and growth failure since 2 months of age from another centre presented with ketoacidosis and multi-organ failure. After resolution of her decompansated status, evaluation for short stature revealed epiphyseal dysplasia. A homozygous mutation in EIF2AK3 gene confirmed the clinical diagnosis of WRS. She was euthyroid on L-thyroxine therapy. Endocrine work-up for potential adrenal dysfunction due to persistent need for i.v. 0.9% NaCl therapy with elevated serum potassium (range 5.9–6.3 mEq/l) and low serum sodium levels (range 126–130 mEq/l) 3 weeks after resolution of ketoacidosis and multi-organ failure yielded normal findings with respect to basal and post-standard corticotropin (250 μg ACTH) cortisol levels. Plasma aldosterone (upright: 241.3 pmol/l) was within normal ranges, and plasma renin (39 pg/ml (range: 5.41–34.53 pg/ml)) was slightly elevated. Transtubular potassium gradient was 1.39 (normal value: >4.1). The patient was diagnosed with relative hypoaldosteronism, and was started on a diet rich in sodium and low in potassium. Failure of response to dietary intervention prompted a trial of oral fludrocortisone with subsequent normalisation of electrolyte levels. **Conclusions:** This is the first case report of WRS complicated with relative hypoaldosteronism. Increased life span of patients with WRS may be associated with emergence of new endocrine dysfunctions in these patients.

P1-48

Structured Education Programmes for Children with Type 1 Diabetes: a Systematic Review

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Background: Type 1 diabetes mellitus (T1DM) is a complex chronic condition common in children and young people. Structured age-appropriate life-long education for patients and their carers is very important to manage this complex condition. **Objective:** To critically evaluate the available Structured Education Programmes (SEPs) including psychosocial interventions in children and young people (CYP) with T1DM and its impact on medical and psychosocial outcomes. **Method:** 9 electronic databases were searched for studies published between January 2007 and March 2014. 38 relevant papers from 30 studies were analysed. **Results:** Of these 30 studies, 1 (3%) was a systematic review, 17 (57%) were randomised controlled trials (RCT), 4 (13%) were case–control studies and 8 (27%) were Before and After (BA) studies. 18 out of 27 studies showed decrease in HbA1c after the intervention, ranging from 0.28% to 1.3%, with a mean of 0.59% (SD 0.28%). In five out of seven studies, quality of life (QOL) improved and in 18 out of 21 studies psychosocial outcomes improved after an intervention. A wide variety of interventions including general education programme, family therapy and motivational interviewing were used for varied duration in different settings. Although family-centred interventions and motivational interviewing produced promising results, the results couldn't be replicated in larger samples. **Conclusion:** As the results of different interventions used were not consistent, none of these interventions on its own could be strongly recommended for current clinical practice. Hence more high quality studies with combination of interventions are needed.

P1-49

Can Hypothalamic Obesity be Treated with Stimulants? Follow Up

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Background: Published case reports and anecdotal experience suggest a positive effect of dexamphetamine, a CNS stimulant on impetus and weight in patients with hypothalamic obesity. Based on these observations, patients presenting to our obesity clinic with hypothalamic obesity are offered off-label treatment with dexamphetamine. **Method:** Between 2010 and 2015, patients starting dexamphetamine treatment were enrolled in a prospective observation study. A retrospective chart review was conducted to establish BMI-SDS development prior to treatment initiation. Impetus was rated on a scale from 1 to 5 at baseline and every 3 months. Dexamphetamine administration was initiated at a

single dose of 5 mg/day, and titrated to effect up to a dose of 20 mg/day in 2–3 single doses. Side effects were recorded in a standardized fashion. **Results:** Nine patients (three males) mean age 17.2 years (range: 13.0–23.8) were included in the study. The primary diagnosis was craniopharyngeoma in 6 patients, gangliglioma WHO °I in one patient, neonatal meningitis in one patient and astrocytoma in one patient. Time from initial CNS insult to initiation of dexamphetamine treatment was 5.7 years on average (range 4 months to 17.4 years). All patients demonstrated a steady increase in BMI-SDS from the time of initial diagnosis up until the initiation of treatment. Of the nine Patients, two were excluded from the evaluation because of proven non-compliance. Baseline BMI-SDS of the remaining seven patients was +3.1 (1.9–4.4). After a mean treatment duration of 1.8 years (0.2–4.1), BMI-SDS decreased on average by 0.5 (0–1.36) and the mean score for impetus improved from 1.3 to 2.8. No significant side effects were reported. **Conclusion:** Dexamphetamine lead to improved impetus and stabilisation or reduction of BMI-SDS in a cohort of seven patients with hypothalamic obesity. Considering the projected increase in BMI-SDS according the natural course of the disease, these findings are promising and warrant further study.

P1-50

A Feasibility Study of Intra-Gastric Balloons (Supported By a Lifestyle Programme) for the Treatment of Severe Adolescent Obesity: the (Bob) Study

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Rationale: Although many adolescents meet the NICE criteria for bariatric surgery in the UK, there is a reluctance to undertake or commission irreversible procedures in young people. Balloons are temporary, reversible, safer and in adults have been shown to promote a clinically significant change in BMI of between 4.0 and 9.0 kg/m^2. However due to subsequent weight regain, bypass surgery is preferred in adults. In adolescents, more amenable to change, balloons may potentially be more effective. **Objectives:** i) To assess the efficacy of the intragastric balloon (*in situ* for 6 months) supported by a lifestyle intervention to promote weight loss in severely obese adolescents. ii) To assess the impact of the weight loss on biomedical outcomes such as glucose metabolism, lipid profiles, bone density and architecture, and on psychosocial health. **Methodology:** A cohort study of 12 adolescents (BMI >3.5 SD, Tanner stage 4 or above) with a 2-year follow up. All subjects took part in a comprehensive medical assessment including OGTT's, measurement of basal and stimulated incretins, bone turnover markers, DEXA scans and high resolution peripheral quantitative CT scans at 0.6 and 24 months. **Results:** Twelve young people (seven girls) were recruited. The median age, weight, BMI and BMI SDS were 15.7 years, 136.55 kg (range 107.6–178.9), 46.6 kg/m^2 (range 39.2–56.3) and +4.1 (range 3.6–4.5) respectively. Mean weight loss at 6 months (balloon removal) was 7.1 kg, whilst the mean weight loss was 5% of total body weight (range −12.7% to 1%). Balloon removals were completed in March 2014 and 24-month follow up is on-going. Improvement in co-morbidities (blood pressure and insulin resistance) and in quality of life was been noted. Bone density was unaffected. **Funding:** CLAHRC-Collaboration for Leadership in Applied Health Research and Care for South YorkshireBSPED-British Society of Paediatric Endocrinology and Diabetes.

P1-51

Distribution of Obesity Indices Among European Preschool Children and Associated Risk Factors: The ToyBox-Study

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Background: Childhood obesity is a serious health problem, related to an increased risk of adult morbidity and mortality. Evidence indicates that central adiposity increases this risk to a higher degree compared to the general obesity indices. **Objective and hypotheses:** To evaluate the distribution of anthropometric obesity indices among preschool children aged 3.5–5.5 years, from six European countries, and to examine their associations with certain obesity-related risk factors. **Method:** 7576 children (mean age 4.74±0.44 years; 51.9% boys) from six European countries (Belgium, Bulgaria, Germany, Greece, Poland and Spain) participated in a baseline survey, conducted in 2012. Body weight, height and waist circumference (WC) were measured; BMI and waist-to-height ratio (WHtR) were calculated. The prevalence of overweight (OW) and obesity (OB) was defined according to the IOTF criteria. WHtR values over 0.5 were used as a definition of abdominal obesity (AO). A standardized questionnaire was used to collect information on risk factors. **Results:** The OW and OB rate were 11.0 and 3.5%, respectively, with a significantly higher prevalence among girls compared to boys ($P<0.01$). AO was found in 23.7% (21.8% boys vs 25.7% girls, $P<0.001$). Greek preschool children had the highest mean BMI and WC (16.1±1.7 kg/m^2 and 53.3±4.4 cm, respectively). Anthropometric indices correlated significantly with the pre-gestational maternal weight ($r_{BMI}=0.215$, $r_{WC}=0.221$, $r_{WHtR}=0.147$, $P<0.01$), maternal BMI ($r_{BMI}=0.217$, $r_{WC}=0.176$, $r_{WHtR}=0.153$, $P<0.01$) and children's birthweight ($r_{BMI}=0.139$, $r_{WC}=0.147$, $P<0.05$). Children from the low SES group had higher BMI, WC and WHtR compared to high SES ($P<0.001$). In the group of obese children we found significantly higher parental BMI and pre-gestational maternal weight ($P<0.001$), with higher maternal weight gain during pregnancy ($P=0.048$). **Conclusion:** Obesity prevalence among preschoolers in Europe is of concern highlighting the need to identify

cost-effective strategies to decrease it. **Funding:** This work was supported by the Seventh Framework Programme (CORDIS FP7) of the European Commission under grant agreement n° 245200.

P1-52

A Randomised Trial of the Effects of Perinatal Education of Overweight Pregnant Women to Prevent Childhood Overweight: The ETOIG Study

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Background: Early-life risk factors of childhood obesity include maternal obesity; smoking, diabetes and high weight gain during pregnancy for the mother; short duration of breastfeeding and poor quality of early feeding in the infants. Perinatal life thus may be a good period for primary prevention. **Objective and hypotheses:** We aimed to evaluate whether perinatal education of overweight pregnant women would reduce childhood overweight. **Method:** Four French centers included before 20 weeks of gestation 268 pregnant women who were overweight before pregnancy (BMI 32.5 ± 5.4 kg/m^2, obesity 62%, age 30.4 ± 5.0 years). They were randomized into either a control group ($n=136$: routine care including at least one dietary consultation) or an interventional group ($n=132$: intervention based on patient therapeutic education with four collective sessions at 18, 26, 33 weeks of gestation and 2 months after delivery and two individual ones) which aimed to educate the future mother for infant and maternal nutritional aspects, without weight objectives. The primary endpoint was postnatal excess weight gain from birth to 2 years ((weight SD 2 years – weight SD birth) $> +0.67$), which is associated with obesity in childhood. Loss to follow-up was considered as a failure in the intention to treat (ITT) analysis. **Results:** Events during pregnancy were similar in both groups, including incident gestational diabetes mellitus, gestational weight gain and birth weight. The rate of postnatal excess weight gain was similar in interventional and control groups: in ITT ($n=268$; 59.1 vs 60.3% respectively, $P=0.84$), and in available data (AD, $n=206$; 47 vs 48% respectively, $P=0.88$). Children feedings habits didn't significantly differ between both groups. Overweight 2 years after delivery was less likely to occur in the interventional group than in the control group for the mothers (ITT: 93.2 vs 97.8% respectively, $P=0,07$; AD: 87.1 vs 96.2% respectively, $P=0.04$) and for the children (ITT: 23.5 vs 29.4% respectively, $P=0.27$; AD: 0 vs 6.8% respectively, $P=0.014$). **Conclusion:** An intervention based on patient collective therapeutic education for overweight pregnant women has no effect on postnatal excess weight gain but seems to prevent overweight in mothers and children 2 years after delivery. **Funding:** French PHRC Necker K070102.

P1-53

Perypheral Neuroblastic Tumours and Immunological Studies in ROHHADNET Syndrome (Rapid-Onset Obesity With Hypothalamic Dysfunction, Hypoventilation, Autonomic Dysregulation and NEural Tumour)

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Background: ROHHADNET syndrome affects children with normal development until 2–4 years. A paraneoplastic/autoimmune etiology has been suggested because of the association with neural crest tumours. **Objective and hypotheses:** Aim of this study was to describe the phenotype of ROHHADNET patients, and to evaluate a possible role of autoimmunity in this disorder. In spite of a suspicion for genetic etiology, disease-associated genetic variations have not been identified yet. **Method:** Seven patients with ROHHADNET underwent clinical and instrumental studies; serum levels of several antibodies against neural receptors were assessed in six patients. CSF was tested for oligoclonal bands in 6/7 patients. **Results:** All patients had uneventful history until 2–4 years, when they developed rapid weight gain, hyperprolactinemia, water/salt balance disruption and behavioral problems or EEG alterations (five patients). Central apneas were diagnosed in six patients and non-invasive ventilation was started in five patients (one patient borderline apneas). Central adrenal insufficiency was found in four patients (partial or total); all patients had GH deficiency, two patients had central precocious puberty, six patients had central hypothyroidism (one transient). Brain MRI was not significant in all patients. A retroperitoneal mass was found in four patients, and biopsy led to ganglioneuroma diagnosis in three of them. Serum neural receptors autoantibodies were undetectable in all tested patients. CSF and serum tested positive for oligoclonal bands in 3/6 patients. **Conclusion:** We aimed to evaluate whether markers of autoimmune encephalitis could be detected in serum of patients with ROHHADNET, whose possible autoimmune etiology has been suggested based on the association with neural crest tumors and a partial response to intravenous immunoglobulin, or immunosuppressants. The results of our study were negative, but CSF tests have shown autoimmune activation in three patients so far. Further studies are ongoing in order to better evaluate the autoimmune status of these patients.

P1-54

'BestPWS EU': A Phase 3 Study in Adolescent and Adult Patients With PWS in Europe

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Background: Prader–Willi Syndrome (PWS) is a complex genetic disease; one hallmark of the disease is failure to regulate hunger and metabolism. Hyperphagia and severe obesity contribute significantly to the morbidity and mortality of this disease. Methionine aminopeptidase 2 (MetAP2) inhibition reduces fat biosynthesis and stimulates fat oxidation and lipolysis. Beloranib is a selective and potent MetAP2 inhibitor. In a 4-week phase 2, placebo-controlled, proof-of-concept study in obese, adult PWS patients, beloranib resulted in dose-dependent decrease in body mass and reduction in total fat mass (DXA) despite 50% increase in total daily calorie intake. There was meaningful reduction in food related problem behaviors typical of PWS. Beloranib appeared safe and well-tolerated in this patient population. **Objective and hypotheses:** To provide the study design of a phase 3 study being conducted in Europe in adolescent and adult PWS. Primary Objectives include assessment of changes in hyperphagia-related behaviors and total body weight, and safety and tolerability of beloranib over 52 weeks. **Study design:** Randomised, double-blind, placebo controlled; 150 obese subjects with PWS 12–50 years old; placebo vs 2.4 mg beloranib (2:3 ratio); a 26 week open-label extension will be offered to patients at the end of the 52 week blinded study period with all patients receiving beloranib. **Results:** Dual primary efficacy endpoints include: change in hyperphagia related behavior based upon the Hyperphagia Questionnaire for Clinical Trials (HQ-CT) total score; percent change from baseline in total body weight; key secondary endpoints will be reported including total body fat mass (DXA), LDL and HDL cholesterol; Safety and tolerability will be assessed. **Conclusion:** Beloranib shows promise for further development in the treatment of obesity and hyperphagia related behaviors in PWS. A phase 3 study is underway in Europe in adolescent and adult PWS patients. **Conflict of interest:** Three authors are employees of Zafgen. **Funding:** This work was funded by Zafgen.

P1-55

Intrauterine Growth Restriction is Associated with Greater Severity in Childhood Obesity-Associated Metabolic Impairment and Poorer Adult Height Prediction

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Background: Intrauterine growth influences the risk of childhood obesity and its associated metabolic derangement. **Objective and hypotheses:** To investigate the effect of intrauterine growth (as shown by newborn anthropometry) on physical and metabolic features in obese children and adolescents. **Method:** A retrospective study of 1049 obese children and adolescents (46.8% females/53.2% males; age: 10.31 ± 3.23 years; BMI: +4.00 ± 1.95 SDS; 54.9% prepubertal/45.1% pubertal) was performed. Groups were compared according to gestational age adjusted newborn anthropometry: adequate (AGA, $n=810$), small (SGA, $n=73$) or large (LGA, $n=166$). *Studied variables*: age at obesity onset, age at first visit; bone age (Greulich & Pyle), adult height prediction (Bailey & Pinneau); IGF1, IGFBP-3, BMI-SDS, glucose, insulin, HOMA, cholesterol (total, HDL, LDL, VLDL), triglycerides, area under the curve (AUC) for glucose and for insulin in the OGTT ($n=638$); LDL/HDL and triglyceride/HDL ratios. **Results:** SGA prevalence was 6.3%. No patient received rGH treatment (spontaneous catch-up growth). No inter-group differences were observed in age, BMI-SDS, sex or pubertal distribution. LGA were taller and SGA smaller than AGA ($P<0.001$) with the later showing more advanced skeletal maturation ($P<0.05$) that resulted in a poorer adult height prediction ($P<0.001$), despite similar IGF1 and IGFBP3 levels. No other differences were found between LGA and AGA. In contrast, SGA had lower 25-OH-vitamin D levels ($P<0.05$) and more severe impairment of carbohydrate metabolism with higher fasting glucose ($P<0.01$), HOMA and AUCs for glucose and insulin in the OGTT than the two other groups (all $P<0.05$). When compared exclusively with AGA, SGA patients also had higher triglycerides and triglyceride/HDL ratio (both $P<0.05$). **Conclusion:** i) Restriction of intrauterine growth, as shown by SGA anthropometry, and spontaneous catch-up growth are associated to a higher frequency and severity of obesity-associated metabolic comorbidities. ii) Obese children born SGA with spontaneous catch-up growth exhibit poorer adult height prediction than those born AGA or LGA. **Funding:** This work was supported by the CIBER Fisiopatología de la Obesidad y Nutrición (CB06/03) and the Instituto de Salud Carlos III, Fondo de Investigación Sanitaria (FIS: grant number PI10/00747 and PI13/02195).

P1-56

Immunohistochemical Detection of Estrogen α and Androgen Receptors in Genital Tissues in Girls with Congenital Adrenal Hyperplasia

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Background: Introital stenosis in CAH girls could occur due to poor estrogenisation of vaginal tissue. It is unknown whether CAH genital skin is equally capable of responding to estrogens and androgens, depending on form and degree of external virilisation. **Objective and hypotheses:** To determine the levels of oestrogen α (ERa) and androgen receptors (AR) immunoreactivity in genital tissues of girls with CAH. **Method:** Surgical waste tissues obtained from girls with CAH (Prader III-IV) undergoing clitoroplasty ($n=13$; 2.4 years (2.1; 4.0), SW/SV = 11/2) and vaginoplasty ($n=8$; 16.7 years (15.2; 17.6), SW/SV = 3/5) were screened for ERα and AR using immunohistochemistry. All patients received adequate replacement therapy. Proportions of immunopositive

nuclei were calculated for each specimen. **Results:** In clitorophallic tissue (labia minora) ERα were localized in parabasal and basal epidermal cells and in dermal fibroblasts, whereas AR were observed only in parabasal cells. There was no difference between SW and SV forms in ERα levels (16.8% vs 15%) and in AR level (9.7% vs 15.2%), $P > 0.05$. No difference was observed in ERα and AR expression between patients with Prader III and IV (15.4% vs 20.8% for ERα and 15.6% vs 10.4% for AR), $P > 0.05$. In vagina ERα were localised in basal, parabasal and intermediate epithelial cells and in stromal fibroblasts. AR were observed only in basal epithelial cells. There was no difference between SW and SV forms in ERα levels (55.8% vs 46.6%) and in AR levels (5.4% vs 7.9%), $P > 0.05$. No difference was found in ERα and AR expression between patients with Prader III and IV (54.1% vs 43.9% for ERα and 9.2% vs 3.9% for AR), $P > 0.05$. **Conclusion:** The distribution of ERα and AR in genital tissues in girls with CAH is similar to its distribution in healthy adult women. Expression of these receptors doesn't depend on form of CAH and degree of external virilisation.

P1-57

Attitudes of Parents of Klinefelter Boys and Flemish Paediatricians Towards Neonatal Screening and Fertility Preservation Techniques in Klinefelter Syndrome

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Background: Preserving spermatogonial stem cell (SSCs) in Klinefelter syndrome (KS) adolescents by testicular tissue banking to safeguard their fertility potential is under debate. While diagnosis of KS is frequently made in late adolescence or young adulthood, when testicular fibrosis is already present, this strategy may be an option when associated with *in vitro* culture and maturation of SSC. **Objective and hypotheses:** To evaluate the attitude of the parents of KS boys as well as of the Flemish pediatricians with regard to early detection of KS and the different fertility preservation options in pubertal KS boys. **Method:** A specific questionnaire investigating the acceptability towards neonatal screening for KS and the use of testicular biopsy and sperm collection was designed. The responses of 49 pediatricians and 18 parents of KS boys were evaluated. **Results:** All parents and 67% of the pediatricians consider neonatal screening for KS to be a good option, in view of early detection and treatment of medical and psychosocial complications. 83.3% of the parents agree on performing a testicular biopsy in their pubertal KS boy, 72.2% would be in favor of spermatozoa banking after masturbation, and 77.7% agree on spermatozoa banking after penile vibrostimulation or rectal electrostimulation under general anesthesia. Parents of boys presenting behavioral or mental problems tended to be less in favor of fertility preservation. 69% of Flemish pediatricians would counsel their KS patient in favor of early detection and cryopreservation of spermatozoa after masturbation, and 71.2% agrees on testicular biopsy to detect spermatozoa or eventually SSC's for cryopreservation in minor KS patients. **Conclusion:** The majority of KS parents and Flemish paediatricians, who completed the questionnaire, were in favour of neonatal screening of KS. Both sperm collection and SSC collection are highly appreciated by parents and paediatricians, despite the currently experimental character of these fertility preservation strategies.

P1-58

Long-term Endocrine Outcome in Men with Partial Androgen Insensitivity Syndrome

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Background: Partial Androgen insensitivity syndrome (PAIS) is a rare condition which is associated with a variable phenotype. To date, there are limited data reporting long-term endocrine outcome for this condition. **Aims:** To determine the outcomes and clinical characteristics for 46, XY males with PAIS, using information from the International DSD (I-DSD) Registry and its clinical users. **Methods:** The I-DSD Registry and its users were approached to identify all male participants over the age of 14 years and registered as having PAIS. Data were collected regarding date of initial presentation with PAIS, presence/absence of an AR mutation, clinical characteristics, biochemical characteristics and treatment received. **Results:** A total of 60 men with a median age of 24 years (range, 15–60) were reported as having PAIS at the time of data collection. Of these 60, 37 (62%) had a confirmed AR mutation. Of those with a confirmed AR mutation, median external masculinisation scores at first and last presentation were seven and nine (3–12), respectively. Median FSH levels at first and last presentation were 2.0 IU/l (0.1–50) and 5.2 IU/l (1.15–89) respectively. Median LH at first and last presentation were 4.8 IU/l (0.04–36) and 9.3 IU/l (1.15–89). 18 (49%) of these men received testosterone therapy at some point between diagnosis and data collection. Regards surgical intervention, 7 (19%) had 1 or 2 hypospadias operations in childhood, whilst 7 (19%) had >2 hypospadias operations. Two (5%) and 11 (30%) males, had unilateral orchidopexy and bilateral orchidopexy, respectively. Although, gynaecomastia was a universal finding, 4 (11%) required mastectomy. Only one subject (2%) was reported to have required treatment for testicular cancer. **Conclusion:** Over

50% of boys with PAIS and a confirmed AR mutation virilise without the need for testosterone therapy but many have a high likelihood of multiple operations for hypospadias and biochemical evidence of primary gonadal failure in adulthood. Gynaecomastia that is severe enough to require mastectomy is not uncommon. These data will aid in the long-term management of boys and men with PAIS and a confirmed AR mutation. **Funding:** International DSD Registry Travel Grant.

P1-59

Novel Genetic Associations in Children with Disorders of Sex Development and Neurodevelopment Disorders – Insights from the Deciphering Developmental Disorders study

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Background: Collaborative project to review the phenotypic and genotypic data from children recruited to the UK wide deciphering developmental disorders (DDD) study. **Objective and hypotheses:** To report the frequency and range of disorders of sex development (DSD) phenotypes observed in DDD participants who have one or more associated 'neurodevelopmental delay' diagnostic human phenotype ontology (HPO) term. **Method:** Retrospective review of anonymized data from participants in the DDD study. **Results:** Of 7439 DDD participants recruited, 603 (8%) had at least one HPO term in the 'abnormalities of the genital system' and 6621 individuals had neurodevelopmental delay. Of these 603 children, 370 (61%) had at least one 'neurodevelopmental delay' diagnosis with an overall frequency of 6%. DSD phenotypes in individuals with neurodevelopmental delay. The 370 patients had a total of 447 DSD phenotypes, the majority, 420 (94%) abnormalities of the external genitalia. Of the male external genitalia abnormalities, 212 (54%) were testicular, 74 (19%) were hypospadias, 57 (15%) were penile and 47 (12%) were other abnormalities. Testicular abnormalities included unilateral cryptorchidism, bilateral cryptorchidisms, hydrocele and other phenotypes. Causative mutations were found in 14 genes already listed on the Developmental Disorders Genotype To Phenotype (DDG2P) database (https://decipher.sanger.ac.uk/), confirming a range of syndromic diagnoses with associated DSD, including: KBG syndrome, Meier-Gorlin syndrome, (α – thalassemia/mental retardation syndrome, Kabuki syndrome and Donnai-Barrow syndrome. Of these likely pathogenic mutations, 6 of 14 (43%) were found in DDG2P genes not previously associated with DSD. **Conclusion:** The association of DSD with learning difficulties is not uncommon and a range of DSD phenotypes may be encountered. Recognition of these associations should not be overlooked in the management of patients with complex conditions. Exomic sequencing through projects like DDD increases diagnostic yield and the identification of mutations in developmental genes may improve our understanding about the pathogenesis of DSD.

P1-60

Insight into the Human Ovarian Sex Development Networks

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Background: Ovarian sex differentiation network involves a panoply of interacting factors. Yet, no single sex-determining factor has been identified to be an equivalent of SRY or SOX9 in the testis. Recently, data suggested CBX2 as a pioneer regulator promoting testis development. In addition to its implication in ovary pathway differentiation which remains unclear. **Objective and hypotheses:** To deepen our understanding of the regulatory network that underpins the molecular basis of ovary development. Within, we light up whether CBX2 is a putative regulator. **Method:** i)We evaluated genes modulation effects on specific female-markers by RT-qPCR following WT/MTCBX2 forced-expression and knock-down assay. ii) DamID/RNAseq approaches performed under overexpression and down-regulation of CBX2 to screen for new female-determining genes. **Results:** We established an *in vitro* cell system suitable for the screening of new ovarian-determining genes. In addition, forced-expression and RNA interference of CBX2 isoforms (CBX2.1 and CBX2.2) showed divergent effects on the expression of FOXl2/WNT4/RSPO1/FST ovarian-specific genes. CBX2.1 was a repressive actor vis-à-vis the female cluster. However, a preferential bidirectional interaction relating CBX2.2 and RSPO1 has been highlighted. Likewise, we assume a positive regulatory feed-forward loop relating the two markers. CBX2.2 expression seems to be enhanced upon WNT4 overexpression, suggesting that CBX2.2 may be positively regulated through the WNT4 pathway. In the same context, we showed an antagonistic interaction between FOXL2 and the two CBX2 isoforms mirroring the FOXl2 vs SOX9 picture. Of utmost importance, substantial number of novel CBX2 targets has been identified. Eight candidates (DKK1, DOK5, BMP5, SIRT5, BMP2, AMIGO2, FZD7, and RSPO3) have been selected basing on their potential link to sex process. Surprisingly, DKK1 an identified mice pro-male marker, turned out to be preferentially expressed in human KGN and found to be positively regulated by the female players. **Conclusion:** Few steps have been made in the human ovary differentiation-regulatory network. Further information of this molecular pathway will doubtlessly be provided by the ongoing genome-wide high throughput analysis to rationalise the potential role of CBX2 and its partners within the ovary gene repertoire. **Funding:** Swiss National Science Foundation Grant Nr 320030_130645/1 to ALB.

P1-61

Current Models of Practice & Professional Development of Clinicians in DSD Centres – Results from an International Survey of Specialist Care for DSD

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Background: In the optimal care of children with DSD, it is considered good practice to work within a multidisciplinary team (MDT) and engage in opportunities for professional development. **Method:** To explore the current models of MDT practice and the extent of professional development in specialist DSD centres, an international survey of 124 paediatric endocrinologists, identified through DSDnet and the I-DSD Registry, was performed in 2014. **Results:** A total of 77/124 (62%) clinicians, in 74 centres, from 38/42 (91%) countries responded to the survey. In 61 (82%) centres, the lead of the team that provided DSD care was a paediatric endocrinologist with the next commonest being a clinical geneticist in 5 (7%) centres. The surveyed clinicians responded that the paediatric specialists routinely involved in the initial evaluation of a newborn were: endocrinologist (98%), surgeon/urologist (95%), radiologist (94%), neonatologist (90%), clinical geneticist (81%) and clinical psychologist (69%). However, a team consisting of paediatric specialists in endocrinology, surgery/urology, clinical psychology, neonatology and nursing was only possible in 29/74 (38%) centres. During the first three months after presentation, a team comprising of paediatric specialists in endocrinology, surgery/urology, clinical psychology, nursing and clinical genetics was only possible in 33/74 (43%) centres. A nationally organised network/plan for managing rare conditions such as DSD was reported to exist in 14/38 (37%) countries. Of the 77 clinicians, 28 (36%) kept a local DSD registry only, 40 (52%) shared their data in a multicentre DSD registry and 9 (12%) did not record any data. Participation in audits/quality improvement exercises in DSD care was reported by 13/74 (18%) centres. Attendance in local, national or international DSD related educational programs was reported by 69, 78 and 82% clinicians respectively. **Conclusion:** Although an increasing number of DSD centres have access to specialist staff, the actual delivery and quality of care provided by these staff requires further exploration. Professional development and engagement in activities leading to improved care need further attention.

P1-62

Prediction of Germ Cell Cancer Occurrence in Postpubertal Individuals with Androgen Insensitivity Based on Pathological Findings and Cancer Predisposition SNPs

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Background: Gonadectomy is generally postponed until early adulthood in complete androgen insensitivity syndrome (CAIS) and close surveillance of gonads *in situ* proposed in males with partial AIS (PAIS). Delaying gonadectomy further is controversial given the lack of data regarding germ cell cancer (GCC) development in adulthood and the absence of biomarkers for noninvasive GCC screening. **Aims and objectives:** To study the prevalence of invasive GCC, carcinoma *in situ* (CIS), or signs of pre-malignancy (combined aberrant OCT3/4 and KITLG expression) in genetically confirmed AIS cases at a (post)pubertal age and study the correlation with a genetic predisposition for GCC based on allele sequencing of 13 GCC-associated SNPs. **Methods:** Immunohistochemical study of 96 samples (CAIS: 72 gonadectomy, seven biopsy; PAIS: ten gonadectomy, seven biopsy). All surgical procedures were performed at or after the age of 14 years (median 17, range 14–54). Allele sequencing of 13 GCC-associated SNPs. **Results:** No invasive GCC were encountered. Changes suggestive for premalignancy were found in 8/79 (10.1%) CAIS samples from five women (5/41; 12.2%) at a mean age of 16.6 (14–21) years; three women had bilateral changes. CIS was detected in one girl with PAIS (1/10; 10%) gonadectomised at 15 years. Preliminary analysis in 47 samples reveals a significant association between the occurrence of (pre)malignancy and a high genetic relative risk for GCC ($P = 0.003$). **Conclusions:** The prevalence of premalignant lesions in CAIS women in this cohort was 12%. Lesions are already present during adolescence and often bilateral. No prospective data exist regarding progression of such lesions to

GCC. A comparable prevalence was seen in PAIS, with possibly a higher risk of malignant progression given the residual AR activity. Preliminary data suggest a significantly higher risk of (pre) malignancy in individuals with a genetic predisposition for GCC. **Funding:** This work was supported by a Senior clinical investigatorship grant from the Research Foundation Flanders.

P1-63

Gender Identity Prediction in Adulthood by HTP Test (House-Tree-Family) in 46, XY DSD Patients

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Background: Patients with 46, XY DSD present conflicts and issues related to gender identity (GI) and change to male social sex in patients registered in the female social sex is not rare. The HTP test is a projective psychological test, which assesses aspects related to sexual identification. GI in this test is defined as female (F), male (M) or ambiguous. **Objective and hypotheses:** To evaluate GI in patients with 46, XY DSD by the HTP test and compare the results among individuals who maintained the social sex with those who changed the social sex. **Method:** We used the HTP test in 96 subjects with 46, XY DSD before and after treatment (psychological, surgical and clinical). The first HTP test (HTP1) was performed on 90/96 patients. The second HTP (HTP2 – after treatment) was applied in 81/96 patients (all > 16 years old) **Results:** 20 patients changed social sex in adulthood and 76 kept the social sex (56/76 = 73.68% in F social sex and 20/76 = 26,31% in M social sex). In the group that changed the social sex in adulthood, all patients (18 F to M and two M to F) showed inappropriate HTP results before treatment. In these cases, the HTP2 was consistent with the final social sex in all of them. Among those who maintained the F social sex in adulthood, the HTP1 was adequate in 67.8% (38/56) and inadequate in 32.2%. After treatment, the HTP2 showed 81.1% of agreement with F social sex. In male social sex, HTP1 was discordant in 50% of cases (10/20), After treatment, the HTP2 was adequated in 80% (16/20) and inadequated in 20%. **Conclusion:** In 46, XY DSD who changed social sex in adulthood the HTP test was able to identify a discordant GI before treatment in 100% of the cases. Among the patients who kept the social sex, inadequate GI was found in 1/3 of F social sex and in 1/2 of M social sex. After multidisciplinary approach the social sex adequacy had a marked improvement. The HTP test proved to be a useful tool for diagnosis and treatment of patients with 46,XY DSD.

P1-64

MAMLD1 Mutations Seem Not Sufficient to Explain a 46, XY DSD Phenotype. What else?

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Background: The *MAMLD1* gene (Xp28) is thought to cause disorder of sex development (DSD) in 46, XY patients, mostly presenting with hypospadias, and, recently, also gonadal dysgenesis. However, there is some controversy about the role of *MAMLD1* in sex development because i) some *MAMLD1* variants are also detected in normal individuals, ii) others are not present in all affected DSD individuals of the same family; iii) several *MAMLD1* mutations have wild-type (WT) activity in functional studies; iv) the male *Mamld1* knockout mouse has normal genitalia and reproduction; and v) other species with or without DSD harbor also *MAMLD1* variants in the genome. **Objective and hypotheses:** We searched for *MAMLD1* sequence variations in 108 46, XY DSD individuals presenting with a wide spectrum of DSD phenotypes. Identified variations were functionally tested *in vitro*, and findings were compared with reported cases and the literature of MAMLD1 focusing on sex development. **Method:** Sanger sequencing was performed to detect *MAMDL1* gene variations/mutations. Functional experiments were completed in non-steroidogenic HEK293, adrenal NCI-H295R and Leydig MA-10 cells. MAMLD1 transcriptional activity was tested on the *Hes3* and *CYP17A1* promoters. Effect of MAMLD1 on androgen production was assessed by testing the CYP17A1 activity. WT and mutant MAMLD1 expression was also assessed. **Results:** We found nine *MAMLD1* mutations (seven novel) in 9/108 46,XY DSD patients. *In vitro* assays revealed that most MAMLD1 variants acted similarly to the WT. Only the L210X mutation showed loss of function in all tests, while variants L724V and S730S showed a decrease in *CYP17A1* promoter activation. We found no effect of either WT or any MAMLD1 variant on CYP17A1 enzyme activity. Also, no difference for MAMLD1 protein expression was found, except for a shorter L210X. **Conclusion:** Our data support the notion that *MAMLD1* sequence variations may not suffice to explain the DSD phenotype in carriers. **Funding:** This work was supported by the Swiss National Science Foundation (320030–146127), the Instituto de Salud Carlos III, Madrid, Spain CIBERER U-712, the AGAUR (University and Research Management and Evaluation Agency), Barcelona, Spain (2009SGR31), and by the private Foundation Bangerter-Rhyner, Basel, Switzerland.

P1-65

Subcutaneous Continuous Administration of Recombinant Human Luteinizing and Follicle-Stimulating Hormones is an Effective Treatment for Micropenis During the Mini-Puberty

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Background: Early postnatal administration of recombinant human gonadotropins can be an effective way to mimic mini-puberty, and thus increase penile growth in infants with congenital hypogonadotropic hypogonadism (CHH). We report for the first time its efficacy on an infant with partial androgen insensitivity syndrome (PAIS). **Objective and hypotheses:** To evaluate the benefits of a continuous subcutaneous infusion of recombinant human gonadotropins (CSCI-HGon) on penile length and hormonal response, in a group of infants with micropenis and cryptorchidism. **Method:** Six male patients (isolated CHH, $n=4$, panhypopituitarism, $n=1$, PAIS, $n=1$) were treated at a mean age of 3.8 months with continuous recombinant LH (Luveris, Merck Serono) and FSH (Gonal-F, Merck Serono) delivered *via* a pump. Clinical (stretched penile length (SPL), testicular position and volume), hormonal (testosterone, LH, FSH, anti-Mullerian hormone, AMH and inhibin B) and radiological (testicular position and size) parameters were evaluated at baseline, during and at the end of the treatment. **Results:** CSCI-HGon was administered during a mean duration of 4.3 months. In CHH patients, CSCI-HGon increased serum testosterone concentration at 3.5 ± 4.06 ng/dl, and thus, SPL (from 13.8 ± 4.5 to 42.6 ± 5 mm, $P < 0.0001$). At the end of the treatment, micropenis was corrected in all patients, except one, who therefore received intramuscular testosterone. Inhibin B (from 94.8 ± 74.9 pg/ml to 469.4 ± 282.5 pg/l, $P=0.04$) and AMH (from 49.6 ± 30.6 to 142 ± 76.5 ng/ml, $P=0.03$) also increased, reflecting the efficacy of the treatment on Sertoli cells. For PAIS patient, final SPL significantly increased (from 13 to 38 mm) under higher doses of LH. **Conclusion:** Early CSI-HGon is an effective and safe treatment, mimicking the physiological neonatal activation of gonadotropic axis restoring a normal penile length. Furthermore, we report for the first time its effectiveness at a patient with PAIS. Long-term follow-up is needed in order to evaluate the consequences in future fertility and reproductive function.

P1-66

46, XX Ovotesticular DSD in the Absence of SRY Gene Associated to SOX3 Duplication

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Background: Ovotesticular DSD is a rare disorder defined by the presence of both ovarian and testicular tissues in the same individual. *SRY* is present in approximately 1/3 of patients with 46, XX ovotesticular DSD. In *SRY*-negative ovotesticular DSD, the mechanism responsible for the presence of testicular tissue is not yet understood. **Case presentation:** A male patient was referred to us for hypospadias and bilateral cryptorchidism at 2.5 years of age. He had a trophic phallus (32×13 mm) with coronal hypospadias and hypoplastic scrotum. Right gonad was palpable in the inguinal region; no gonad was palpable on the left side. Basal AMH (216 pmol/l) and hCG-stimulated testosterone (30 ng/dl) were low, indicating that dysgenetic testicular tissue was present. Gonadotrophins were not elevated, with FSH predominance (LH $<$ 0.10 U/L, FSH 0.73 U/L). Karyotype was 46, XX. These results were suggestive of the presence of ovarian tissue. Diagnostic laparoscopy was performed, and the histopathological study confirmed the presence of bilateral ovotestes. Absence of *SRY* in peripheral leukocytes was documented by QF PCR analysis (Devyser Kit). A genome-wide copy number analysis, performed by single-nucleotide polymorphism using CytoSNP-850K microarray (Illumina), confirmed the absence of *SRY* and of Y chromosome sequences. Furthermore, a *de novo* duplication of 502, 127 bp at Xq27.1 chromosomal region encompassing *SOX3* gene was evidenced. Metaphase FISH analysis using a BAC probe hybridizing on both X homologues demonstrated a tandem duplication of this region. **Conclusion and discussion:** This is the first case of SRY-negative 46, XX Ovotesticular DSD in whom a genetic association (*SOX3* duplication) is reported. These results are in line with evidence in mice indicating that, in the absence of *SRY*, gain-of-function of *SOX3* induces testis differentiation in the XX bipotential gonad. SOX3, as a surrogate of SRY, would act synergistically with SF1 to upregulate SOX9 expression and stimulate testicular organogenesis. **Funding:** This work was partially financed by Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Argentina.

P1-67

miR-146a-Mediated Suppression of the Inflammatory Response in Human Adipocytes

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Background: microRNAs (miRNAs) are a class of small (18–25 nucleotides), non-coding RNA molecules. They play an important role in the regulation of gene expression by either suppressing translation of genes or inducing their mRNA degradation. Several miRNA species are expressed in adipose tissue and involved in adipocyte function. **Objective and hypotheses:** Obesity leads to the infiltration of macrophages into adipose tissue causing local inflammation. In an Affymetrix miRNA array we found miR-146a expression strongly upregulated in adipocytes under inflammatory conditions. The aim of this project was to elucidate the biological function of miR146a in adipocytes. **Method:** SGBS adipocytes were cultured with human THP-1 macrophage conditioned medium (MacCM) to mimic adipose tissue inflammation. Gain-of-function experiments were performed by transfection of miR146a mimics into SGBS adipocytes. **Results:** miR146a is down-regulated during adipogenic differentiation of SGBS cells as well as human primary preadipocytes. However, the expression of miR146a was significantly upregulated in SGBS adipocytes treated with 10% MacCM (24 h: 16.9-fold vs vehicle control). Transfection of miR146a mimic into adipocytes resulted in a down-regulation of IRAK1 and TRAF6 expression, two known target genes of miR146a. Upon MacCM stimulation adipocytes transfected with miR146a mimic showed a significantly reduced activation of the NFkB signalling pathway and a reduced upregulation of IL-8 secretion (24 h, ctrl + MacCM: 7.0 ng/ml, miR-146a mimic + MacCM: 3.1 ng/ml). **Conclusion:** miR146 is a fine tuner of immune responses in many cell types. We show here for the first time that miR146a operates in a negative feedback loop in adipocytes to control the inflammatory response caused by macrophage-secreted factors. **Funding:** This work was supported by an ESPE-RU collaborative project grant.

P1-68

Leptin Resistance Alteration after Modulation of Dopamine System Funcional Activity in Rat's Diet-Induced Obesity

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Background and aim: High caloric diet (HCD) in diet-induced obesity (DIO) can be caused by central mechanisms regulating reward-seeking behaviour. Leptin modulates the dopamine system and vice versa. We supposed D2 dopamine receptor agonist and dopamine neurons toxin to influence weight gain and leptin level, mobility and behaviour in wild type rats (GUR) with HCD. **Materials and methods:** Male rats ($n=64$, 183.0 ± 14.0 g) were divided into HCD group ($n=36$) and standard caloric diet (SCD) ($n=36$). HCD and SCD rats had daily intraperitoneal injections of Bromocriptin (B) (1 mg/kg), Rotenone (R) (0.3 mg/kg), dimethyl sulfoxide (DMSO – vehicle, 1 ml/kg) ($n=8$, respectively) during 3 months. Eight rats from both groups weren't injected. Length, weight and caloric intake were recorded twice a week. Leptin levels (immunoenzyme analysis and leptin/weight ratio (L/WR)) and rodents' speed (S), distance (D), open and closed arms visits and time (plus maze test) were discovered at the 1st and 3rd months. Nonparametric analysis was performed (SPSS 16.0, $P<0.05$). **Results:** HCD rats showed similar weight gain in 1st and 3rd months compared to SCD rodents irrespective to injected agent with lowest weight gain in HCD rats received R ($P<0.05$). S and D had no changes in HCD group after 1 month but open arm visits significantly decreased in HCD rats injected with B ($P<0.05$). S reduced after 3 months in HDC rats compared to the same group after 1 month ($P>0.05$). Leptin and LWR decreased after 3 months of Br injections in HCD rats relative to the HCD rodents ($P=0.05$ and 0.005 comparatively). Leptin and LWC levels were extensively lower in Br injected HCD rats in 3 month concerning to the 1st one. **Conclusion:** Long-term Bromocriptin injections prevent leptin resistance and neurotoxic Rotenone effect leads to weight gain diminishing in HCD DIO rats. **Funding:** The work was supported by Belorussian republican foundation for fundamental research (grant number 20122542, 2012).

P1-69

Abstract unavailable.

P1-70

Outcome of Adolescents Undergoing Bariatric Surgery – 1 Year Follow-Up

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Background: Adolescent obesity has been steadily increasing all over the developed world for the past several decades. Bariatric surgery in morbid obese adolescents is gaining popularity. The main surgical technique that is used on adolescents in Israel is a gastric sleeve. **Aims:** To study clinical and laboratory outcomes of adolescent patients 1 year after they underwent bariatric surgery. **Methods:** Anthropometric, clinical and laboratory data were obtained from all patients' ages 13–19 years who had bariatric surgery in the years 2010–2015 in Edmond and Lily Safra Children's hospital at Sheba Medical Center before and after the surgery. **Results:** 27 adolescents (16 females) underwent bariatric surgery. Their mean age was 16.9 ± 1.5 (range 13.7–18.60, weight 129 ± 16 kg, BMI 46.6 ± 5.8 kg/m^2, BMI-z-score 2.8 ± 0.27. Seven

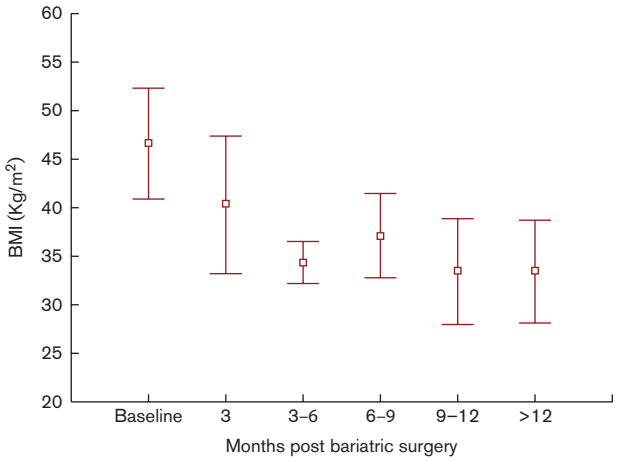

Figure 1 BMI at baseline and after bariatric surgery.

adolescents had obstructive sleep apnea, two had pseudo tumor cerebri, three had hypertension, two had type 2 diabetes, 13 had fatty liver in ultrasound and four had elevated liver enzymes. BMI changes throughout the first year of follow-up are presented in Figure 1. There was a significant weight reduction 3 months after the surgery, BMI 40.3 ± 7.1 kg/m^2 ($P < 0.001$), Most of the weight loss occurred during the first 6 months. Thereafter there was no significant change. 1 year after the surgery, only 14 adolescents continued to come for follow-up. Two of them gained weight and were re-scheduled for operation, two adolescents developed eating disorder requiring referral to eating disorder clinic. four patients developed gall stones requiring cholecystectomy. One was hospitalized in rehabilitation because of paralysis secondary to severe vitamin deficiency. **Conclusions:** Despite significant weight loss, bariatric surgery in adolescents is associated with significant long-term morbidity.

P1-71

Identifying Critical Periods for Maintaining Weight Loss in Obese Children

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Background: Adults have a weight that is normal for them. This is referred to as their 'set-point' for weight. Studies have shown physiological protection of this set-point, explaining why most obese adults who diet eventually regain weight. **Objective and hypotheses:** We hypothesised that set-points for weight, and their physiological defence, are flexible in childhood but become fixed sometime around puberty. We aimed to show that obese children who lost weight had less 'reflex' changes in satiety hormone profiles that would drive weight regain, compared with adolescents who had lost weight. **Method:** Prospective cohort study. 41 subjects; 21 obese pre-pubertal children (age 3–7 years; 11 males) and 20 obese adolescents (age 14–18 years; ten males). Obesity defined as BMI > 2.4 SDS. Subjects recruited as either 'reducers' (relative or absolute weight loss of ≧10% in the preceding 9–15 months) or maintainers (controls). Resting energy expenditure (REE), impedance and fasting and post-prandial satiety hormone profiles with subjective assessments of appetite were taken every 30 minutes over 3 h. Multilevel methods were used to model post-prandial hormone and satiety profiles. **Results:** Post-pubertal adolescents had 31% lower Ghrelin concentrations (4–51%, $P = 0.03$) and 50% higher Amylin concentrations than pre-pubertal children (18–91%, $P = 0.001$). Children reducing weight reached maximum GIP slower than weight maintainers ($P = 0.05$). The association between Ghrelin, Amylin and GIP concentration and weight change was similar for both pre- and post-pubertal children ($P = 0.79$, $P = 0.39$, $P = 0.79$ respectively). No associations were found for Peptide YY, PP, active GLP1. Regarding satiety, post-pubertal adolescents who lost weight reported less hunger ($P < 0.001$) and higher satiety ($P = 0.03$) than pre-pubertal children. REE in pre-pubertal weight reducers and maintainers were similar (50 kcal lower, −143 to 242, $P = 0.6$) but post-pubertal reducers had 250 kcal lower REE compared to post-pubertal maintainers (−68 to 572, $P = 0.1$). **Conclusion:** Satiety hormone profiles were similar between pre- and post-pubertal subjects, and appeared to contrast with previously published adult data, where weight reduction leads to sustained increases in Ghrelin and reductions in the other hormones. These findings indicate that the physiological mechanisms which act to protect against weight change, may develop later than in the adolescent years. **Funding:** Murdoch Children's Research Institute, Melbourne, Australia.

P1-72

Use of Topiramate in Severe Hyperphagia Associated to Neuropsychiatric Features in a Boy with Congenital Proopiomelanocortin Deficiency

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Background: Congenital proopiomelanocortin deficiency (POMC) gene mutations cause early-onset obesity, hyperphagia and ACTH deficiency. In the subjects with this picture, neuropsychiatric (NP) features were rarely reported. Many Authors described an appetite loss during the topiramate treatment. **Objective and hypotheses:** To discuss NP features observed in a POMC deficient patient and to propose a therapeutic attempt to reduce the hyperphagia. **Method:** Case report and literature discussion. **Results:** We describe an 8-month old male infant who was referred for severe early-onset obesity due to severe hyperphagia. In this patient isolated ACTH deficiency was

detected. The MRI was normal. Direct sequencing of the POMC gene revealed a homozygous single substitution C6902T determining a Gln68X substitution. Therefore congenital POMC deficiency was diagnosed. The child spoke his first words and walked alone at 2 years of age. Since 2.5 years, he was followed for neurocognitive development and psychiatric features. At the first evaluation, a neurodevelopmental delay was noticed by the Griffiths Mental Development Scale (Developmental Quotient 64 with disharmonic profile for greater impairment of locomotor, hearing and speech domains) and by a parent-report measures. When the boy was 3.5-year-old, due to the worsening hyperphagia associated with an oppositional defiant disorder, a treatment with topiramate was started with a good response on hyperphagia and behaviour disorder; no side effects were reported. At 6 yrs, an attempt to stop topiramate caused a rapid worsening of NP symptoms leading to a resumption of the therapy. At last NP evaluation at 6.5 years, WPPSY-III cognitive test evidenced a borderline total IQ (87) and significant discrepancy between verbal and performance IQ (verbal IQ: 70, performance IQ: 111). Psychiatric features revealed attention problems and confirmed the oppositional defiant conduct. During topiramate therapy, BMI has not increased. **Conclusion:** In patients with congenital POMC deficiency hyperphagia can contribute or be associated to NP problems. Topiramate therapy could be considered.

P1-73

Circulating miR146a and 486-5p are Altered in Obese Children with and Without Non-Alcoholic Fatty Liver Disease (NAFLD) and Correlate with Abdominal Fat and BMI

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Background: MicroRNAs (miRNA) are small non coding RNA molecules, key regulators of metabolic pathways. Obesity is characterised by many metabolic changes. NAFLD is seen as a complication of obesity. FOXO-1, key regulator in insulin signalling, has been shown to be implicated in NAFLD. We previously identified miRNAs regulators of the FOXO-1 gene. **Objective and hypotheses:** To assess in serum whether the regulation of miR-146a and miR-486-5p, FOXO1 gene regulators, changed in obese subjects, and whether any changes were related with measurements of adipoity and indexes of insulin sensitivity. Relationships with NAFLD were investigated also. **Method:** 83 obese children were consecutively enrolled (CA: 11.35 ± 0.33 years-range: 3.78–16.83 years; BMISDS: 3.17 ± 0.10; males: 40; females: 43) with (N: 37) and without (N: 46) NAFLD. A group of 23 healthy controls comparable for age, sex and pubertal stage (CA: 12.1 ± 1.3 years; BMISDS: 0.56 ± 0.66; males: 12; females: 11) was used for comparison. NAFLD was diagnosed by liver ultrasound. Total RNA from serum was extracted using the MirVana PARIS kit. MiRNAs were quantified by TaqMan microRNA Assays and normalized with respect to miR-16 and miR-93, as housekeeping miRNAs. dCts were normalized with respect to the pool of dCt controls. Relative gene expression was then presented as fold change (Log10). **Results:** Obese subjects having NAFLD had a larger waist circumference(96.63 ± 2.58 cm vs 88.58 ± 1.87 cm, $P < 0.05$). MiR146a and 486-5p were similar in females and males. In the obese children, miR146a was down-regulated (−2.06 ± 0.05) and miR486-5p upregulated (0.56 ± 0.11) compared with controls. No significant difference was detected based on the presence of NAFLD. MiR-146a was correlated with BMISDS ($P = 0.013$; $R = -0.3$), with waist circumference ($P = 0.006$; $R = 0.35$), and with the HOMA-IR index ($P = 0.015$; $R = 0.3$). **Conclusion:** Specific circulating miRNAs show changes in obesity and miR-146a shows clear relationships with BMI, distribution of adiposity and parameters of insulin sensitivity.

P1-74

Abstract withdrawn.

P1-75

Ghrelin and Brain-Derived Neurotrophic Factor in Children with Prader-Willi Syndrome

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Background: Prader-Willi syndrome (PWS) is a complex multisystem genetic disorder arising from lack of expression of paternally inherited imprinted genes on chromosome 15q11–q13. Hyperphagia represents one of the most serious symptoms of the PWS, leading to develop premature mortality. **Objective and hypotheses:** To compare orexigenic (ghrelin) and anorexigenic factor (brain derived neurotrophic factor (BDNF)) concentration in non-GH-treated obese patients with genetically confirmed PWS with age, sex and BMI-matched obese controls (OC) and lean controls (LC). **Method:** Fasting and postprandial levels of plasma ghrelin and serum BDNF during mixed meal testing (370 kcal: 20% protein, 50% carbohydrate and 30% fat) were evaluated in obese children with PWS in comparison with OC and LC. All patients were prepubertal (Tanner 1). Data are reported as medians (interquartile range), Manne–Whitney test was used for between-group. **Results:** Fasting ghrelin concentration was significantly higher in 17 (six males: 11 females) PWS children in comparison with 15 (four males: 11 females) OC and ten (four males: six females) LC (1.0 (0.5 ÷ 1.0) ng/ml vs 0.23 (0.13 ÷ 0.30) ng/ml and 0.23 (0.11 ÷ 0.45), $P < 0.01$). Postprandial ghrelin levels on 60 and 120 min (0.75 (0.4 ÷ 1.0) vs 0.18 (0.11 ÷ 0.31) and 0.17

(0.13÷0.35), $P<0.01$ and 0.5 (0.4÷1.0) vs 0.16 (0.13÷0.28) ng/ml, $P<0.01$) were also elevated in PWS. There were no significant differences between 29 PWS (20 males: nine females) and 27 OC (16 males: 11 females) in basal (20.7 (15.77÷24.8) vs 18.49 (12.99÷24.45) ng/ml, $P>0.05$) and postprandial BDNF levels on 60 and 120 min (22.1 (12.1÷30.27) vs 18.02 (12.97÷25.32), $P>0.05$ and 24.62 (15.68÷27.75) vs 16.05 (12.29÷22.42) ng/ml, $P=0.07$). However the concentration of BDNF was significantly higher in PWS compared with 14 LC (12 males: two females) on 0 min (20.7 (15.77÷24.8) vs 14.16 (10.87÷19.34), 60 min (22.1 (12.1÷30.27) vs 13.25 (10.37÷16.02)) and on 120 min (24.63 (15.68÷27.75) vs 13.44 (11.28÷17.4)), $P<0.05$ respectively. **Conclusion:** Fasting and postprandial ghrelin levels were significantly higher in PWS subjects compared to obese and lean controls. The level of BDNF postprandial secretion is significantly higher in PWS patients in contrast to lean controls.

P1-76

Endothelial Progenitor Cells in Obese Non-Diabetic Children and Adolescents: Relations to Some Metabolic Parameters, Echocardiographic Parameters and Tissue Doppler Imaging

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Background: Endothelial progenitor cells (EPCs) are involved in the regeneration of the endothelial lining following blood vessel injury. The reduction in the number of EPCs was postulated to be associated with the initiation and progression of cardiovascular disease. **Objective and hypotheses:** This study aimed at exploration of the number of EPCs in obese non-diabetic children and adolescents and their relation to the fasting lipid levels, fasting glucose, fasting insulin, homeostasis model assessment for insulin resistance (HOMA-IR), carotid intima media thickness (CIMT), echocardiography as well as parameters of cardiac dysfunction on tissue doppler imaging. **Method:** 56 children and adolescents (5–14 years) were chosen randomly from patients seeking medical advice for obesity management at the Obesity Clinic of the Paediatrics Hospital, Ain Shams University. Another group of 32 age and sex matched children and adolescents served as a control group. All underwent anthropometric evaluation, measurement of fasting lipids, glucose, insulin, HOMA-IR, CIMT, echocardiography and tissue doppler imaging. EPCs are the cells expressing CD34 CD144. EPCs were calculated as a percentage of the mononuclear cells. **Results:** EPCs were significantly lower in patients compared to controls ($P=0.00$) and CIMT was significantly higher in patients ($P=0.00$). Despite showing non-significant correlations with the fasting lipid parameters, fasting insulin, fasting glucose and HOMA yet tissue doppler imaging across the mitral valve showed a significant positive correlation with the EPCs ($r=0.283$, $P=0.034$). **Conclusion:** Obese non-diabetic children and adolescents have impaired endothelial regeneration and diastolic dysfunction independent of dyslipidaemia or hyperinsulinaemia.

P1-77

Evaluation of Adiponectin Concentrations in Obese Children and Its Correlation with Lipid and Carbohydrate Parameters

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Aims: The aims of the study was to evaluate the plasma adiponectin levels in obese children depending on children age, gender, stage of puberty and its relationship with lipid and carbohydrate metabolism parameters. **Material and method:** The study were involved 122 obese children (52 girls, 70 boys), aged 5.3–17.9 years (11.6±3 years), 52 children in prepubertal, and 65 in pubertal period. Obesity was defined using IOTF criteria. The control group consisted of 58 healthy children (11.7±3 years). In each patient anthropometric measurements including bioelectrical impedance analysis (BIA) method was taken. Adiponectin concentration were determined by radioimmunoassay (RIA) method. In obese children oral glucose tolerance test was performed (OGTT). In 26 obese patients adiponectin were taken during OGTT. HOMA was calculated. **Results:** The plasma adiponectin levels were significant lower in obese children than in control group (13.1 vs 15.9 μg/ml; $P=0.004$). Slightly lower values were found in obese boys compared to obese girls (12.9 μg/ml vs 13.4 μg/ml; $P=0.77$) and in pubertal children compared to prepubertal children (12.5 μg/ml vs 13.8 μg/ml; $P=0.238$) with the lowest values of adiponectin at Tanner stage 3 (9.56 μg/ml). According to gender and pubertal period the changes in adiponectin concentration were observed in the obese boys. The linear regression models showed the negative correlation adiponectin with pubertal period, at Tanner stage 3. Adiponectin correlates with HDL cholesterol ($r=0.183$, $P=0.047$). Logistic regression analysis showed that an increase of 1 unit in adiponectin reduces the risk of lowered <40 mg/dl HDL-C levels by 0.9 times. Adiponectin levels did not appear to be modulated by glucose challenge during OGTT. **Conclusion:** Sex related differences between plasma adiponectin levels were dependent on puberty stage. Hypoadiponectinemia in obese children is a risk factor for low HDL-C level.

P1-78

Influence of Genetic Variation on the Response to Recombinant Human Growth Hormone Treatment in Children with GH Deficiency: An Analysis of 13 Single Nucleotide Polymorphisms and the GH Receptor Exon 3 Deletion

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Background: Growth hormone deficiency (GHD) is the most common endocrine cause of impaired growth. Recombinant human GH (rhGH) therapy does not always achieve complete catch-up growth or final height within the genetic target height despite standardised treatment guidelines. The factors causing the considerable variability in responsiveness to rhGH have not yet been fully elucidated. Apart from a number of auxological and clinical parameters, genetic factors also appear to play an important role. **Objective and hypotheses:** We analysed 13 single nucleotide polymorphisms (SNPs) located in genes of the GH axis, the growth plate, and the cell cycle, as well as the exon 3 deletion of the GH receptor (GHR) to explore their potential influence on patients' responsiveness to rhGH therapy. **Method:** The study involved 101 children treated with rhGH for GHD. Thirteen SNPs were genotyped using high resolution melting analysis and sequencing. Furthermore the frequency of the growth hormone receptor exon 3 deletion was determined by PCR using a combination of different primers. The index of responsiveness (IoR) was used as an objective measure of response to rhGH therapy. IoR values were compared by genotype for each SNP using one-way ANOVA. **Results:** For the rs2888586 SNP in the SOS1 gene, the TT genotype was associated with increased IoR values compared to CT and CC. For rs2069502 in the CDK4 gene, the G allele was associated with increased IoR values compared to the A allele. Furthermore, patients with the exon 3 deletion in the GHR gene had higher IoR values. **Conclusion:** The results of our study indicate that genetic analyses are a starting point for the individualised treatment of GHD. Thus, the genetic variations investigated may serve as predictive markers of response to rhGH treatment in GHD. **Conflict of interest:** T R Rohrer is a member of the Nordinet® IOS International study committee and has received consultation fees and speaker's honoraria from Ferring, Novo Nordisk, MerckSerono and Pfizer. Research grants from MerckSerono, Novo Nordisk, and Pfizer. **Funding:** This study was funded by an unrestricted grant from Pfizer WI172376.

P1-79

Decrease of Jumping Power in Adolescents with Severe GHD After Stop of GH-Therapy

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Background: Recently we demonstrated that male adolescents with severe GHD (sGHD) had a significant decrease of lean body mass and increase in fat mass after stop of GH-therapy. The functional consequence of this observation is unknown. **Objective and hypotheses:** The aim was to study the changes in parameters of jumping mechanography in adolescents with GHD in the transition period (end of growth) after stop of GH-therapy. **Patients and method:** We studied 64 (N = 17 girls) patients with idiopathic childhood-onset GHD. GH-therapy was stopped at the end of growth to retest the GH-axis (age 16.4 ± 1.5 years, height −0.5 ± 0.9 SDS). We performed jumping mechanography with the Leonardo ground-reaction-force-plate (NovoTec Medical, Germany) at the end of GH-therapy and 6 months thereafter. We analyzed peak jump power (PJP in W), PJP/kg body weight (in W/kg) and time in air (tAir in sec.). sGHD was defined as GH peak in Arg-GHRH-Test < 16 ng/ml and IGF1 < −1 SDS. **Results:** 13 patients had sGHD and in 51 patients GHD was transitory (tGHD). Prior to stop of GH in both patient groups PJP, PJP/kg and tAir were similar (2.7 vs 2.5 W and 46.6 vs 43.0 W/kg and 0.467 vs 0.447 sec. in tGHD vs. sGHD). After stop of GH in sGHD patients PJP, PJP/kg and tAir decreased significantly ((Δ = −0.17 W, −3.33 W/kg and −0.019 sec, $P < 0.01$) in tGHD patients PJP, PJP/kg and tAir did not change significantly (Δ = 0.01 W, −0.69 W/kg and 0.000 sec.). There were no significant differences in changes between boys and girls. Peak GH did not correlate significantly with change in PJP, PJP/kg and tAir, but it correlated significantly with PJP/kg ($r = 0.27$, $P = 0.0332$) and, only in boys, with tAir ($r = 0.33$, $P = 0.021$) 6 months after stop of GH. **Conclusion:** In severe GHD decrease of muscle mass results in a significant decrease of jumping performance after 6 months. **Conflict of interest:** Schweizer und Binder got presentation fees from Lilly, Novo Nordisk, Pfizer.

P1-80

Good Clinical Response to the Growth Hormone Therapy in the Patient with Familiar Short Stature Caused by Novel p.Val478Serfs*14 Mutation in ACAN Gene and Isolated Growth Hormone Deficiency

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Background: Recently a heterozygote mutations in the gene ACAN coding the protein aggrecan has been described as a cause of familiar short starture combined with accelerated bone age. The aggrecan is an extracellular proteoglycan in cartilage of growth plates and plays an important role in biological and biomechanical properties of cartilage. **Objective and hypotheses:** To provide a genetic screening of ACAN within the families with familiar short stature and describe the potential effect and risks of growth hormone therapy in this patients. **Method:** The direct sequencing of the exon and exon – intron boundaries of ACAN. **Results:** Novel heterozygote frameshift mutation p.Val478Serfs*14 has been found in the 10-years-old male proband and his father from the family with familiar short stature inherited by the male line (the father has 155 cm (−3.6 SD), his father −4.3 SD (150 cm), fathers brother −3.6 SD and his son −4.3 SD). The mother of the proband has 162 cm (−0.84 SD). The proband was born as SGA for birth length (2920 g/45 cm in 40 GW, −? SD) without any perinatal problems. At the age of 7 years has been found the slightly lower IGF1 level (−1.59 SD) and lower levels of growth hormone in stimulation tests (maximum peak in clonidine test was 3.54 ug/l and in insulin test 3.05 ug/l in the time of glycaemia 2.5 mmol/l). The MRI scan showed the pituitary area without pathology. The growth hormone treatment was started at the age of 7 years and 4 months with the high −3.7 SD (108 cm) at the

dosage 0.028 ug/kg/den. After 3.5 years of treatment the high is −2.5 SD, the growth velocity in 1 year of treatment was 10 cm per year, in 2 and 3 years 8 cm per year. The proband had accelerated bone age of 1.5 year at the age of 6 years and the acceleration is stable on the growth hormone therapy. No adverse events has been detected after 3.5 years of treatment. **Conclusion:** This is a first description of a novel mutation in ACAN gene as a cause of familiar short stature in the Czech population. The patient has a combination of isolated growth hormone deficiency and FSS. The reaction to the growth hormone is excellent and the bone age remains stabile accelerated.

P1-81

The Growth Response to Growth Hormone Treatment is Greater in Patients with *SHOX* Enhancer Deletions Compared to SHOX Defects

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Background: Short stature caused by point mutations or deletions of the short stature homeobox (SHOX) gene (SHOX haploinsufficiency, SHI) is a registered indication for growth hormone (GH) treatment. Patients with a SHOX enhancer deletion (SED) have a similar phenotype, but their response to GH is unknown. It is uncertain if duplications of SHOX or its enhancer (SDUP) can cause short stature. **Objective and hypotheses:** To describe the clinical characteristics and growth response to GH treatment in patients with aberrations of *SHOX* and its enhancers. **Method:** In this retrospective observational multi-center study (2002–March 2014) clinical information was available from 130 patients (72 SHI, 44 SED, 14 SDUP) and from 52 patients treated with GH. Height, sitting height, arm span, dysmorphic features and indicators of the growth response to GH (delta height SDS, height velocity and index of responsiveness) were collected. **Results:** Patients with SEDs showed similar height SDS to patients with SHI (−2.3 and −2.6 respectively, $P=0.2$) and have a similar frequency of Madelung deformity, but they were less disproportionate (sitting height/height ratio SDS 2.0 vs 3.1 ($P<0.01$), and extremities-trunk ratio 2.57 vs 2.43 ($P=0.03$)). Parents carrying SEDs are less short and disproportionate than parents with SHI. Height SDS and body proportions varied widely in both groups. The first year growth response to GH treatment was significantly greater in prepubertal patients with SEDs than SHI. None of the patients with a SDUP was disproportionate and SDUP cosegregated poorly with short stature; their growth response to GH treatment ($n=3$) was similar to the other groups. **Conclusion:** This is the first study to assess the effect of GH in patients with SEDs. Patients with SEDs are equally short, but less disproportionate than patients with SHI, and show a greater response to GH treatment.

P1-82

Assessment of Primary Cancers in Growth Hormone–Treated Paediatric Patients Compared with General Population Registries: An Epidemiological Analysis of a Large, Multinational, Prospective Observational Study

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Background: Concern remains regarding the potential influence of growth hormone (GH) treatment on neoplasia because of the general growth-inducing effect of GH and associations between high serum IGF1 concentrations and certain cancers in adulthood. Many studies that evaluated risk for primary cancer in GH-treated patients without previous malignancy found no increased rates of primary neoplasia. A higher risk for colorectal cancer was observed in a single-country cohort treated with cadaveric GH. **Objective and hypotheses:** To assess primary cancer occurrence in the prospective, multinational GeNeSIS observational study of paediatric GH use and compare observed cases with rates from general population cancer registries (USA: SEER; other countries: GLOBOCAN). **Method:** Study data and serious adverse event reports for patients with ≧1 follow-up visit were examined to identify and exclude those without previous history of malignancy and to ascertain incident cases of primary cancer. 19054 GH-treated patients without previous cancer were identified (40% female; 63% with GH deficiency, 13% idiopathic short stature, 9% Turner syndrome, 6% born small for gestational age, and 9% other diagnoses; mean ± SD baseline age 9.5 ± 4.0 years; mean follow-up time 3.4 ± 2.5 years). **Results:** Thirteen incident primary cancers were ascertained, with mean ± SD age at cancer onset of 13.5 ± 2.7 years. The standardized incidence ratio (SIR) (95% CI) for primary cancers was 1.02 (0.54–1.75) for all countries combined; no individual country had a significantly elevated SIR. Ten of the affected patients (four lymphoma cases, three germ cell tumours, Ewing sarcoma, osteosarcoma, and skin cancer) had no neoplastic history. Three patients had neoplastic history/predisposition (rectal adenocarcinoma in a patient with neurofibromatosis and Gardner syndrome, pancreatic neuroendocrine tumour in a patient with neurofibromatosis, and malignant schwannoma in a patient with previous pilocytic astrocytoma). **Conclusion:** Risk for all sites primary cancers in GH-treated patients without previous cancer was no higher in GeNeSIS than in general population cancer registries. **Conflict of interest:** The author is an employee and stockholder of Eli Lilly and Company. **Funding:** Sponsored by Eli Lilly and Company.

P1-83

Genetic Markers Contribute to the PREDICTION of Response to GH in Severe but not Mild GH Deficiency

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Background: Single nucleotide polymorphisms (SNPs) associated with the response to GH therapy have previously been identified in growth hormone deficient (GHD) children in the PREDICT long-term follow-up (LTFU) study (NCT00699855). **Objective and hypotheses:** To assess the effect of GHD severity on the predictive value of genetic markers of growth response. **Method:** We used pre-pubertal GHD children (peak GH <10 μg/l) from the PREDICT LTFU study ($n=113$) and PREDICT validation (VAL) study (NCT01419249, $n=293$). Single nucleotide polymorphisms (SNP) previously identified to be associated with first year growth response to GH ($n=22$) were genotyped. Random forest classification (RFC), a prediction method based on decision trees that is not sensitive to variable inter-dependency, was undertaken to identify variables associated with growth response (change in height (cm)) using the baseline clinical variables of gender, age, GH dose, distance to target height SDS (DTH) and mid-parental height SDS (MPH). Accuracy ((true positives + true negatives)/total population) of the RFC models was assessed and a variable importance score (VIS) calculated by permutation. GH peak was used to stratify GHD patients into severe (≤ 4 μg/l) and mild (>4 & <10 μg/l). **Results:** Growth response in GHD severity-stratified sub-populations can be predicted by random forest classification with high levels of accuracy; in mild GHD an accuracy of 74.9% ($P<3.0\times10^{-17}$), in severe GHD an accuracy of 74.0% ($P<7.3\times10^{-15}$). Only baseline clinical variables were important in mild GHD with only GH dose and MPH (ranked by VIS) contributing to prediction. However in severe GHD VIS ranked important variables as followed: DTH, SNP rs1024531 (*GRB10*), age, SNP rs7101 (*FOS*), MPH, SNP rs3213221 (IGF2), and GH dose. **Conclusion:** Growth response to GH therapy can be predicted by RFC using baseline clinical parameters alone in mild GHD. Three genetic markers (SNPs) can be used to improve growth response prediction in severe GHD. **Conflict of interest:** Dr Adam Stevens has received honoraria as an investigator from Merck Serono. **Funding:** The PREDICT study was supported by Merck Serono S.A – Geneva, Switzerland.

P1-84

Disease and Treatment Burden in Children and Adolescents with Growth Hormone Deficiency

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Background: Children with growth hormone deficiency (GHD) may experience physiological symptoms as well as social and emotional problems. **Objective and hypotheses:** This qualitative study explored the burden of GHD and treatment for children and their parents. **Method:** 70 interviews were conducted with 39 children (age 8–12) and 31 parents of children with GHD (age 4–12) in Germany, UK and USA. Interviews were analysed using grounded theory to identify themes/sub-concepts and a conceptual model of burden of disease was developed. **Results:** Children and parents reported similar disease and treatment burdens. Disease burden domains and the most frequently reported subtheme by parents and children were symptoms (poor appetite: 48%), physical impacts (reduced performance in physical activities/sports: 58%), social impacts (being mistaken for being younger: 58%) and emotional impacts (worry: 55%). The most frequently reported child treatment burden domains and subthemes reported by children and parents were physical (pain: 33%), emotional impacts (worry about injections: 37%), and interference with daily life (overnight activities: 29%). For parents, most frequently reported treatment burden domains and subthemes were emotional impacts (worry about treatment/administration: 58%) and interference with daily life (time needed to administer injection: 42%). Treatment was associated with improvements for all impacts. Findings did not differ substantively among countries. The conceptual model describes the full range of disease and treatment impacts, and factors that may modify impact severity. **Conclusion:** The overall burden of disease for GHD children and their parents is considerable and not limited to short stature. A well-designed measure of the full range of impacts identified in this study is not currently available and will be developed based on this conceptual model. Accurate and reliable assessment of symptoms and impacts, on both children and parents, may help clinicians to better address the burden of disease, assess treatment effect, and may improve the quality of doctor-patient communications. **Conflict of interest:** Dr. Brod, Ms. Alolga, and Ms. Nacson are consultants to Novo Nordisk. Drs. Højbjerre, Nordholm, and Højby Rasmussen are employees of Novo Nordisk A/S. **Funding:** This study was funded by Novo Nordisk A/S.

P1-85

Effects of Growth Hormone Treatment on Immunity

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Background: As well as acting on longitudinal growth, growth hormone (GH) also has a number of metabolic effects, and is involved in the regulation, functioning and development of the immune system. **Aims:** To evaluate the immune profile in GH-deficient children after 6 months' GH treatment. **Method:** A total of 44 children were examined before and after a six-month course of treatment with rhGH (0.03 mg/Kg per day). Levels of IGF1 and IGFBP3 were measured, and both the humoral immune profile (IgM, IgG, IgA, C1-inhibitor y serum complements C3 and C4) and the cell immune profile (WBC, differential leukocyte formula: lymphocytes, monocytes, total neutrophils, and CD3+, CD19+ and NK lymphocyte subpopulations) were investigated. A study was also made of CD4+ and CD8+ lymphocyte subpopulations grouped by positive cell counts above and below normal values. Data were subjected to Student's t test and to Wilcoxon's T-test for parameters exhibiting non-normal data distribution (total lymphocytes and NK cells), with a significance level of $P<0.05$. **Results:** After 6 months' GH therapy, a significant reduction was observed in IgG and IgM, together with a significant increase in IGF1 ($P<0.05$). A moderate decline in CD3+, CD4+, CD8+, CD19+ and NK cell levels was also recorded. Analysis of CD4+ and CD8+ lymphocyte subpopulations grouped by positive cell counts above normal values revealed significantly elevated levels prior to treatment; after 6 months' treatment, values had fallen to levels not significantly different from normal. Subpopulations grouped by positive cell counts below normal values also rose to near-normal values after treatment. **Conclusions:** These findings confirm changes in the immune system of GH-deficient children treated with rhGH. GH exerts immunomodulatory effects, and plays an important role in homeostasis, affecting the immune system; GH therapy normalises peripheral-blood CD4+ and CD8+ levels. The precise mechanism through which GH modulates the immune system remains unknown, and should be addressed in future, broader-based research.

P1-86

The Growth Hormone Treatment Results in the Increase of Irisin Concentration in Plasma

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Background: Brown adipose tissue metabolism is of remarkable pathophysiological interest, because it could be a target for therapies for obesity and metabolic syndrome. Irisin (Ir), recently identified adipomyokine is essential in a white-to-brown fatty tissue transdifferentiation, and mediates some of the positive influences on metabolic disorders through increase of energy expenditure. The exact regulation of Ir secretion and action is unknown but positive associations of circulating Ir with growth hormone and IGF1 were found. **Objective and hypotheses:** We studied Ir response in a group of patients treated with supraphysiological doses of growth hormone (rGH). **Method:** The study group consisted of 36 turner syndrome (TS) patients aged 3.2–16.07 years (mean 8.2 years) diagnosed by karyotyping. The rGH was applied in a dose 0.05 mg/kg per day prior to and following the treatment anthropometrical data were recorded as well as biochemical parameters were measured: Ir, OGTT, insulin, IGF1, and IGFBP3. **Results:** The increase of IGF1 concentration at the end of observation was significant (from 119.4 ± 62.46 to 413.37 ± 204.38 ng/ml, mean $\pm$ SD, $P=0.000$). The rise of Ir level was recorded on rGH treatment (2.1 ± 1.03 vs 2.47 ± 0.79 µg/ml, mean $\pm$ SD, $P=0.035$). The GH treatment influenced insulin resistance revealed by increased HOMA values (median 0.64 ± 0.45 before and 0.92 ± 0.97 after, $P=0.02$). The correlation between Ir and IGF1 levels was not significant neither before nor on the treatment ($P=0.22$ and $P=0.95$ respectively). At the end of observation Ir was negatively related to % weight to height ratio ($P=0.04$). The correlation between Ir and insulin ($r=-0.44$, $P=0.01$) and Ir and HOMA ($r=-0.46$, $P=0.007$) was significant. **Conclusion:** Result of the study showed an increase in Ir level following GH application. It seems to be not IGF1 mediated. Ir may mediate some metabolic effects of GH treatment. We are unable to conclude whether Ir rise is connected with direct GH stimulation, their influence of body composition, or with altered insulin sensitivity.

P1-87

A Novel OTX2 Gene Mutation in a Child with Growth Hormone Deficiency

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Background: OTX2 is expressed in the human brain and plays a key role in the eye development. OTX2 mutations are reported in patients with ano/microphtalmia, optic nerve or optic chiasm hypoplasia, ocular coloboma and retinal dystrophies, associated in some cases with brain or pituitary abnormalities. **Objective and hypotheses:** Most of *OTX2* mutations are nonsense or frameshift, more rarely missense mutations occur.

Method: We describe a child with microphtalmia and GH deficiency carrying a novel *OTX2* heterozygous mutation. **Results:** At birth, she presented right microphtalmia, absence of retinal vascularization, vitreal spots and optic nerve hypoplasia in the right eye and mild macular dystrophy in the left eye. Electroretinogram and p-VEP confirmed the right nerve hypoplasia. A brain MRI showed normal midline structures and cerebral parenchyma, mild hypoplasia of the anterior corneal segment, dysmorphic cristalline with increased posterior convexity and thin optical nerve in the right eye. Left nerve eye was normal. When 20 months old, after excluding other causes of microphtalmia, *OTX2* gene sequencing was performed and showed a heterozygous c.402del mutation. At the age of 3.8 years, height was −2.1 SDS (TH −0.6 SDS), BMI-1.0 SDS, bone age 3 years. Routine biochemistry was normal as well as thyroid and adrenal function, while GH peaks after arginine and clonidine test were 5.24 and 3.46 ng/ml respectively. IGF1 level was 47.5 (10th-25th). Recombinant GH treatment was started (33 mcg/kg per day). **Conclusion:** In this paper we report on a novel *OTX2* heterozygous mutation (c.402del), never described before, in a patient with microphtalmia and growth hormone deficiency. This frameshift mutation (p.S135Lfs*43) causes a premature codon stop 43 amino-acids downstream which is predicted to generate a premature truncation and thus a non-functional protein. Parental analysis indicated that the mutation was absent from the healthy parents (*de novo* mutation). Follow-up to evaluate furtehr pituitary deficiency is ongoing.

P1-88

The Dose Dependent Effect of Growth Hormone Therapy in Patients with IGF1 Receptor Haploinsufficiency due to Heterozygous Deletion

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Background: The IGF1 receptor (IGF1R) gene is located on the distal long arm of chromosome 15 (15q26.3). Heterozygous inactivating mutations of the IGF1R gene cause intrauterine and postnatal growth failure and mental retardation. **Objective:** The purpose of this research is to determine the most effective GH treatment for patients with IGF1R haploinsufficiency due to heterozygous deletion. **Method:** We investigated the clinical course of four patients with IGF1R haploinsufficiency due to heterozygous deletion diagnosed by array CGH analysis. **Results:** All four patients were born with severe intrauterine growth failure. One female patient at 7 years of age, with height 101.3 cm (−4.2 SD), was administered 0.18 mg/kg per week of GH and increased to 0.20 mg/kg per week. Her serum IGF1 was 375 ng/ml before GH treatment. Her adult height was 141.1 cm (−3.2 SD). During GH treatment, high levels of IGF1 persisted (380–730 ng/ml before the development of secondary sexual characteristics and 648–1030 ng/ml since then. The other three patients (two female and one male) at 3 years of age, with height SDS ranging from −4.7 SD to −6.4 SD, were administered 0.25 mg/kg per week of GH and increased to 0.35–0.47 mg/kg per week. The serum IGF-1 was 128–260 ng/ml before GH treatment. One female patient improved from −6.4 SD to −3.5 SD after 5 years of GH treatment. Her maximum IGF1 was 877 ng/ml during GH treatment. The male patient improved from −5.1 SD to −4.1 SD after 1 year of GH treatment. His maximum IGF1 was 513 ng/ml during GH treatment. The other female patient improved from −4.7 SD to −1.9 SD after 4 years of GH treatment. Her maximum IGF1 was 701 ng/ml during GH treatment. However, there was no obvious improvement of mental retardation in the four patients. **Conclusion:** Long-term GH therapy causes growth acceleration during childhood in a dose-dependent manner. Earlier onset of therapy may provide better results.

P1-89

Royal Jelly Supplementation Induces the Growth Plate Development and Increases Plasma Growth Hormone and Oestradiol Levels in Prepubertal Rats

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Background: In recent years families, especially in the children's growth and development, often use alternative treatments as growing more healthy individuals. **Objective and hypotheses:** The purpose of the present study was to examine the hormonal, histomorphometric and immunohistochemical effects of Royal Jelly (RJ), which was a growth supplement commonly used by parents for their children, on growth plate of young rats. **Method:** 7-day-old female Sprague-Dawley rats were randomly divided into two groups each containing 15 animals. RJ group was administered 50 mg/kg of RJ for 15 days. At the end of the study, the height of the growth plate and numbers of proliferative and hypertrophic chondrocytes per column were determined. The expression of Ki-67 proliferation, oestrogen and IGF1 receptors of proximal tibial growth plates were investigated. Oestrogen, growth hormone (GH) and IGFI were measured. **Results:** Mean weight change in the RJ group was significantly higher than the control group (41.4 ± 7.1 vs 31.5 ± 4.8 g, $P < 0.001$) at the end of the study. Mean change of the tail length measurement was significantly higher in RJ group compared to the control group (3.7 ± 0.6 cm vs 3.6 ± 0.3 cm, $P = 0.04$). Oestrogen levels (708 ± 353 pg/ml vs 582 ± 85 pg/ml, $P = 0.03$) and GH levels (2.8 ± 5.7 vs 1.05 ± 0.6 ng/dl, $P = 0.04$) were significantly higher in RJ group than the control group. Total length of growth plate in RJ group was measured significantly higher than the control rats (5.2 ± 0.1 vs 2.7 ± 0.8 mm, $P < 0.001$). Oestrogen receptor expression on growth plate was stated as 38% in hypertrophic zone and 81.3% in proliferative zone, however; in control group, it was stated as 0% in hypertrophic zone and 14.3% in proliferative zone ($P < 0.001$). In addition, compared with the control group, Ki-67 proliferation staining and IGF1 receptors were highly expressed in growth plate zones ($P < 0.001$ and $P < 0.001$). **Conclusion:** Our findings suggested that oestrogen and IGF1 receptors were expressed in the growth plate zones following RJ administration. The RJ was

found here at a relatively low dose to have some potential estrogenic effects on growth plate of young rats.

P1-90

Silver-Russell Syndrome without Body Asymmetry in Three Patients with Duplications of Maternally Derived Chromosome 11p15 Involving *CDKN1C*

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Background: Silver-Russell syndrome (SRS) is a congenital developmental disorder characterised by pre- and post-natal growth failure, relative macrocephaly, hemihypotrophy, and fifth-finger clinodactyly. Recent studies have shown that gain-of-function mutations of CDKN1C result in IMAGe syndrome (IMAGeS) characterized by intrauterine growth restriction, metaphyseal dysplasia, adrenal hypoplasia congenita, and male genital abnormalities, whereas less severe gain-of-function mutations of CDKN1C have been identified in a large family with maternally inherited SRS. Thus, it has been suggested that relatively severe and mild CDKN1C gain-of-function effects lead to IMAGeS and SRS, respectively. Notably, IMAGeS patients satisfy the diagnostic criteria for SRS proposed by Nechine *et al.*, and IMAGeS and SRS patients with CDKN1C mutations invariably lack hemihypotrophy characteristic of SRS. **Results:** We report duplications of maternally derived chromosome 11p15 involving CDKN1C in three Japanese patients (cases 1 and 2 from family A, and case 3 from family B) with SRS phenotype lacking hemihypotrophy. Chromosome analysis showed 46, XX, der (16) t (11; 16) (p15.3; q24.3) mat in case 1, 46, XY, der (16) t (11; 16) (p15.3; q24.3) mat in case 2, and a *de novo* 46, XX, der (17) t (11; 17) (p15.4; q25.3) in case 3. Genomewide oligonucleotide-based array comparative genomic hybridization, microsatellite analysis, pyrosequencing-based methylation analysis, and direct sequence analysis revealed the presence of maternally derived extra copies of the distal chromosome 11p involving the wild-type CDKN1C (a ~7.98 Mb region in cases 1 and 2, and a ~4.43 Mb region in case 3). **Conclusion:** The results, in conjunction with the previous findings in patients with similar duplications encompassing CDKN1C and in those with intragenic mutations of CDKN1C, imply that duplications of CDKN1C as well as relatively mild gain-of-function mutations of CDKN1C lead to SRS subtype that usually lack hemihypotrophy. **Funding:** This work was supported by Grants-in-Aid for Scientific Research (A) (25253023) and Research (B) (23390083) from the Japan Society for the Promotion of Science, Grants for Research on Intractable Diseases (H22-161) from the Ministry of Health, Labor and Welfare, and Grant for National Center for Child Health and Development (25–10).

P1-91

Mutation in RTTN, a Regulator of Ciliary Function, Causes a Complex Syndrome Characterized by Severe Congenital Microcephaly, Lissencephaly and Profound Growth Failure in Two Siblings

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Background: Primordial dwarfism (PD) is a phenotype characterized by profound growth retardation and microcephaly that is prenatal in onset. Recently mutations in genes involved in ciliogenesis have been described in patients with primordial dwarfism phenotype. In 2012 mutations in rotatin (RTTN), a protein involved in cilia structure and function, have been described in in individuals with bilateral diffuse polymicrogyria, but not growth failure. **Case presentation:** We report on a consanguineous Moroccan family with two siblings with a severe congenital microcephaly syndrome with growth failure resembling PD. The affected individuals in this family were born to consanguineous parents. The two affected children, a 21 months old boy and 11 months old girl, presented with severe microcephaly, failure to thrive and are also very short and microcephalic (the boy, at 21 months was 6.5 kg (<2th) and 68.7 cm (<4 SDS), W/L<2th; head circumference 34 cm; the girl months was 4.559 kg (<2th) and 57 cm (<4 SDS), W/L<2th; head circumference 31 cm); they had both dermatitis from newborn period and have very high level of IgE. Brain MRI showed lissencephaly of frontal lobe. They both had severe development delay. We identified by next generation sequencing a new homozygous mutation in exon 23 of RTTN gene (Arg985Gly). We analysed cDNA from leukocytes of the patients and found an abnormal splicing with two different transcripts: one lacking the entire exon 23 and one lacking exons 22 and 23. **Conclusion:** For the first time we describe a new phenotype characterized by primordial microcephaly, severe growth failure, cortical malformation and severe dermatitis caused by a mutation in RTTN, a gene involved in ciliary function. We suggest that our mutation, more severe than the ones described till now affecting splicing, causes a more extreme phenotype disrupting cortical differentiation, growth and skin formation. Thus, our study adds PD to a growing list of ciliopathy phenotypes in humans.

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Chronic Effects of Bisphenol A Administration on Growth Hormone Activity

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Background: Bisphenol A (BPA), a plastic byproduct, is a known endocrine disruptor and is types of cancers, such as prostate and ovaries, and some other health conditions, for

instance diabetes and obesity. It has direct effect on reproductive system through its strong oestrogen agonist activity. **Objective and hypotheses:** BPA has a strong oestrogen agonist activity. And oestrogen antagonize cellular activity of growth hormone (GH), however, the effect of BPA on growth hormone has been never investigated. The aim of this research is to study the *in vivo* effect of chronic BPA administration on body growth and cellular GH signalling. **Method:** CD-1 male mice were given 1.75 mM BPA in drinking water for three months starting form weaning age. Every week for three months, the weight, body length and tibia length of each mouse was measured. At end of 3 months, liver tissues were excised and measurement of STAT5, SOCS2 and GHR protein expression was done. Plasma GH and IGF1were measured by commercial ELISA **Results:** Mice given BPA for 3 months showed lower rate in total body and tibia length compared to control mice. The phenomenon of catch-up growth was observed. The Inhibitory effect of BPA on GH was also observed in reduced expression of STAT5 protein in mice given BPA. SOCS2 is a known feedback inhibitor of GH signalling. The levels of hepatic SOCS2 protein were higher in mice given BPA. We have not observed significant differences in plasma IGF1 and GH between BPA treated and untreated mice. **Conclusion:** We noticed there is an adverse effect of chronic administration of BPA on growth hormone activity. This provides further evidence of the endocrine disruptive effect of BPA and novel inhibitory effect on GH signalling pathway. **Funding:** This work was supported by the FURAP of the research council in oman.

P1-93

Severe IGF1 Deficiency and Multi-Organ Autoimmune Disease Associated with Novel Germline *STAT3* Mutations

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Background: Primary IGF1 deficiency can result from molecular defects in genes encoding for the GHR, IGF1, STAT5b and ALS. Heterozygous, activating mutations in the *STAT3* gene have been recently described in children with severe growth failure associated with a spectrum of early-onset autoimmune disease. **Case presentation:** We report the molecular diagnosis in two unrelated patients with severe growth failure and IGF1 deficiency: P1, a 3.6 year old girl, born at term with normal weight (3155 g). She presented congenital hypothyroidism, descamative eczema, chronic diarrhea, recurrent candidiasis and severe respiratory infections. At 3 years, she presented height −6.0 SD, lymphocytic interstitial pneumonia with no-necrotizing granulomas. She had normal IgG and IgM with elevated IgA and no-detectable IgE levels. Lymphocyte subset was normal, presenting normal FOXP3 and Treg CD127, but low Th17. P2, a male, 6 years, height SD of −5.36, who had a history of IPEX-like syndrome with dermatitis, chronic diarrhea, colitis, and thyroiditis (*FOXP3* mutation negative). Whole-exome sequencing (WES) was performed on both patients, and parents and sister of P1, using Illumina HiSDefault 1500. P1: elevated GH (20 ng/ml), low IGF1 (20 ng/ml), normal IGFBP3 (2.2 μg/ml) and elevated prolactin (30.6 ng/ml) levels were noted. After 17 months of rhGH treatment IGF-I increased (240 ng/ml) with a partial recovery of height (−4.8 SD). WES analysis identified private heterozygous *de novo STAT3* variants as candidate variants: c.1847_1849delAAG (p.Glu616del) in P1, and a missense p.Cys426Arg, in P2. Both variants are predicted to be activating, since inactivating *STAT3* mutations are associated with hyper-IgE syndrome without growth failure. **Conclusion:** Activating *STAT3* mutations represent a novel monogenic defect presenting multi-organ autoimmune disease associated with severe growth retardation as the result of marked IGF1 deficiency. In contrast to STAT5b deficiency, patients carrying activating *STAT3* mutations appear to preserve partial GH responsiveness. **Funding:** This work was supported by grants from the Agencia Nacional de Promoción Científica y Tecnológica (PICT-2010 Nro.1916), and SANDOZ International GmbH, Business Unit Biopharmaceuticals.

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Abstract unavailable.

P1-95

Various Imprinting Disorders Underlying Silver-Russell Syndrome-Compatible Phenotype

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Background: Silver-Russell syndrome (SRS) is a rare congenital developmental disorder characterised by pre- and postnatal growth failure, relative macrocephaly, triangular face, hemihypotrophy, and fifth finger clinodactyly. Hypomethylation of the H19-DMR and maternal uniparental disomy chromosome 7 (UPD(7)mat) were identified in about 30 and 10% of SRS patients respectively. Genetic causes of the remaining 60% of the patients are unknown. Growth failure, small hands, and hypotonia in neonate and early infancy which are observed in SRS patients are also identified in patients with the other imprinting disorders such as Temple syndrome (TS14) and Prader-Willi syndrome (PWS). **Objective and hypotheses:** To clarify the relevance of imprinting disorders other than SRS to SRS-like phenotypes. **Method:** We examined the methylation status of the six differential methylated regions (DMRs); KvDMR on chromosome 11, the IG-DMR and the MEG3-DMR on chromosome 14, the SNRPN-DMR on chromosome 15, the PLGLA1-DMR on chromosome 6, and the GNAS exon A/B-DMR on chromosome 20, using pyrosequencing methods. We studied 81 Japanese patients who satisfied the SRS diagnostic criteria proposed by Netchine et al in 2007 and had neither epimutation of the H19-DMR nor UPD(7)mat. For patients with abnormal methylation status in these six DMRs, we performed microsatellite analysis, aCGH, and MLPA to determine the genetic causes of the imprinting disorders in each patient. **Results:** We identified three TS14 patients with epimutation, two PWS patients with maternal uniparental disomy chromosome 15 and one patient with maternal uniparental disomy chromosome six in 81 patients with SRS-like phenotypes. These results suggest that the imprinting disorders other than SRS also demonstrate SRS-compatible phenotype. **Funding:** This work was supported by Grants-in-Aid for Scientific Research Research (B) (23390083) from the JSPS, and by Grants for Research on Intractable Diseases (H22-161) from the MHLW, and by Grants from the NCCHD (25–10).

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Ligase IV Deficiency Syndrome as a Cause of Microcephalic Primordial Dwarfism in Dizygotic Twins

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Background: Microcephalic primordial dwarfism (MPD) is a group of rare genetic disorders defined by severe growth restriction of both prenatal and postnatal weight (W), height (H), and particularly head circumference (HC). **Objective and hypotheses:** To elucidate the genetic origin of the MPD in dizygotic twins. **Method:** Exome sequencing of 19 genes known to be implicated in microcephaly was performed. **Results:** Dizygotic twins (a male and a female) were issued from non-consanguineous healthy parents of normal height and had two healthy 4 years- and 2 years-old siblings. Intrauterine growth restriction of both twins was noted during the 2nd trimester of pregnancy and confirmed at birth (at 36 1/7 weeks of gestation, ♂/♀: W 1500/1490 g, H 41.5/40 cm and HC 28/26.7 cm (< -2 SD). Both twins had feeding difficulties. They were hospitalized at the age of 5 months to investigate their poor growth. W, H and HC remained well below -2 SD (♂/♀: W 3710/3150 g, H 55/54 cm, HC 36/35 cm). Developmental skills and physical exam was normal except for a small penile length (1 cm) in the boy. Extensive work-up showed hypogammaglobulinemia and neutropenia. Thyroid function tests, growth factors, brain MRI, skeletal x-rays, blood standard karyotype and array-CGH were normal. Genetic analysis revealed compound heterozygous mutations of the ligase IV gene (chromosome 13) in both twins: *c.2321T>C,p.(Leu774Pro)/c.2440C>T,p.(Arg814*)*, the parents being each heterozygous carriers of one of the mutations. **Discussion:** Ligase IV is an enzyme implicated in the nonhomologous end-joining repair of DNA double-strand breaks. To date, 27 cases of ligase IV deficiency have been reported. Major clinical features are severe prenatal and postnatal growth restriction (H and HC), immunodeficiency, pancytopenia and lympho-reticular malignancies. Other inconstant characteristics include feeding difficulties and hypergonadotropic hypogonadism. **Conclusion:** Ligase IV deficiency syndrome has to be considered in the differential diagnosis of patients with MPD, especially if associated with immune and haematological anomalies. The diagnosis is important for the follow-up of the patients, since they are at risk for cancer development due to a constitutive hypersensitivity to ionising radiations.

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High Frequency of Hypomorphic Allelic Haplotypes of the *gh1* Proximal Promoter in Patients with Proportional Undergrowth and Isolated GH Deficiency

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Background: Although isolated GH deficiency (IGHD) is one of the most frequent causes of postnatal proportional undergrowth, up to 85–90% of IGHD cases are still classified as idiopathic. On the other hand, previous reports identified up to 40 different *GH1* proximal promoter haplotypes, some of which show hypomorphic effects, significantly reducing *GH1* expression levels. **Objective and hypotheses:** To investigate the frequency of *GH1* proximal promoter hypomorphic allelic haplotypes in a cohort of patients with IGHD. **Method:** Subjects: 53 children with proportional undergrowth and IGHD (height <-2.5 SDS and peak GH <10 ng/ml). Molecular studies: Mutation screening/genotyping of the coding sequences, intron/exon boundaries and regulatory regions of *GH1*; *GH1* proximal promoter haplotype classification was performed according to Horan *et al.* (2003) and Wolf *et al.* (2009). **Results:** We identified a total of 19/53 (35.8%) patients presenting with hypomorphic allelic haplotypes of the *GH1* proximal promoter. Three out of 53 patients (5.7%) presented also with three known *GH1* mutations c.291+1G>A, p.Arg42Cys and p.Arg209His, in heterozygosis, located in *GH1* intron 3, and exons 2 and 5 respectively. **Conclusion:** Up to 36% of the examined patients with proportional undergrowth and IGHD present with hypomorphic allelic haplotypes of the *GH1* proximal promoter. These novel data suggest that the hypomorphic allelic haplotypes of the *GH1* proximal promoter represent an important causative/contributing factor of IGHD, which has been underestimated or overseen so far. Furthermore, according to the clinical information submitted by the referring endocrinologists, most of the patients presenting with *GH1* promoter hypomorphic allelic haplotypes who were treated with rhGH showed a positive response. Previous reports have shown that the *GH1* proximal promoter haplotype diversity is the consequence of a very high rate of interlocus gene conversion, which is caused by the high degree of sequence homology (>92%) between the 5 genes present in chromosome 17 GH cluster. **Funding:** This work was supported by grants: PI09/01266 and PI12/00643 from the Spanish Ministry of Health (ISCIII) to A.C-B; S22010/BMD ENDOSCREEN-CM to A.C-B and I.G-C., and by an Investigator Initiated Research Grant from Pfizer (IIR WI181614) to A.C-B and I. G-C.

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GH Excess in McCune–Albright Syndrome

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Background: McCune–Albright Syndrome is a combination of polyostotic fibrous dysplasia (BFD), café'-au-lait skin pigmentation and hyperfunctioning endocrinopathies. It results from postzygotic mutations in a-subunit of the Gsalfa protein and the consequent phenotype is a mosaic with high degree of clinical variability. **Objective and hypotheses:** The aim of the study is determine prevalence and characteristics of GH hypersecretion (GHH) in MAS. **Method:** 31/142 (21.8%) patients with GHH are identified. In all we study auxological data, biochemical GHH (IGF1 *Z*-score, random GH, GH after OGTT), association with prolactine hypersecretion (PH), possible abnormal pituitary MRI, BFD, other endocrinopathies and response to medical and other treatment. **Results:** Average age at diagnosis is 13.9 y.o. (from 3 to 36). Male are 18/31 (58%), female are 13/31 (42%). PH occurs in 27/31 (87%). Pituitary adenoma is evidenced in 16/31 (52%), while craniofacial and long bone FD are evidenced in 100%. Medical treatment was performed in 25/31: in 17 ocreotide 10–30 mg i.m./month, in 5 ocreotide 30 mg i.m./month and pegvisomant 20 mg s.c./day, in 1 ocreotide 30 mg i.m./month, pegvisomant 20 mg s.c./day and pipuitary irradiation, in 2 ocreotide 30 mg i.m./month and transphenoidal pituitary surgery (one died for post-operative complications). 19/24 (79%) have complete control of GHH ($-2<$IGF1 *Z*-score$<+2$), three patients are non-compliant to therapy. **Conclusion:** GHH can occur from childhood to adulthood above in 20% of MAS patients and when present is always associated with BFD. Micro or macro-adenoma is evidenced only in half of cases because the pituitary gland is often diffusely involved with areas of somatotroph hyperplasia. Medical therapy (ocreotide and pegvisomant) realize a good control of disease that is important to prevent a higher risk of BFD morbidity. Pituitary surgeon and irradiation are respectively the second and the third options due to thickness of BFD, post-operative complications and possible malignant transformation of BFD.

P1-99

GH Hypersecretion in Children with NF1 and Optic Pathway Gliomas

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Background: The association of NF1 with optic pathway glioma (OPT) and GH hypersecretion was initially described in some isolated cases, while the presence of PP was more frequently reported in these patients. Association of gigantism and

precocious puberty (PP) in five children with OPT (isolated in two and associated with NF1 in three cases) has been recently published. **Aims:** To evaluate the frequency of GH hypersecretion in children with NF1 and OPT, to verify the association of gigantism and PP in these patients, to find a possible correlation of GH hypersecretion and the MRI patterns of OPT. **Methods:** We selected all patients with NF1 and OPT followed in our hospital. All of them underwent auxological evaluation. Children with clinical signs of gigantism (height >2 S.D. and/or growth velocity >2 S.D.) were submitted to biochemical study, including IGF1, IGFBP3, FT_4, TSH, PRL, OGTT for glucose, insulin and GH levels, and bone age. Children with clinical signs of PP underwent GnRH test for LH and FSH and testosterone/estradiol levels, bone age, pelvic ultrasound in girls. MRI patterns of gliomas was reassessed by the same neuroradiologist. **Results:** Sixty one patients with NF1 and OPT (35 boys, age 2.1–17.9 years) were included in the study. Seven out of 61 (11.5%) presented clinical signs of gigantism. All of them showed IGF1 and IGFBP3 levels >2 S.D. and lack of GH levels suppression after OGTT was demonstrated in four cases. PP was confirmed in four children, isolated in three cases and associated with gigantism in one boy. MRI in all children with gigantism showed extension of OPT at least to pre-chiasmal region. **Conclusion:** GH hypersecretion is often associated with OPT in NF1 children and it is more frequent than PP. There is evident correlation between extention of glioma and presence of GH hypersecretion.

P1-100
Atypical Features in Patients with Leprechaunism Suggesting a Wide Clinical Spectrum of Disease

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Background: Donohue syndrome (DS) is the most severe form of insulin-resistance due to autosomal recessive mutations in the insulin receptor gene. Typical features include pre-/postnatal growth impairment, hyperinsulinaemic hyperglycaemia with fasting hypoglycaemia, nephrocalcinosis, recurrent sepsis, little adipose tissue, soft tissue overgrowth, hirsutism, acanthosis nigricans and facial dysmorphism. However, additional comorbidities may be present, affecting prognosis. **Case series:** We describe four males with DS, treated with bolus rhIGF-1. Patients 1 and 3 were treated for three months, but manifested severe comorbidities (liver and respiratory failure) and sudden death. Patient 1 received a 3-year rhIGF-1 trial until age 5 years, and was referred at age 11.5 years with diabetes mellitus and recurrent ketoacidosis. Patient 2 received rhIGF-1/IGFBP3 until age 8 years and was then started on rhIGF-1. Table 1 summarizes the clinical picture of our cohort. **Conclusion:** We report for the first time the presence of clotting abnormalities, diffuse psoriatic skin rashes and protein-losing inflammatory enteropathy in patients with DS. The relationship between additional comorbidities and genotype needs to be defined.

P1-101
Does Type 1 Childhood Diabetes Start *In Utero*?

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Background: In the last decades a rapid increase in the incidence of childhood type I diabetes (TIDM) has been reported worldwide. To stop the progressively advancing process immunosuppressive and nutritional trials have been made, but failed. Epidemiological studies by our group performed in several countries have shown that the season during which children who developed TIDM were born differed from that in the general population; suggesting that the initial trigger for TIDM was more likely to occur during the yearly viral epidemics. **Objective and hypotheses:** To test the above

Table 1. (for abstract P1-100)

Patient	1	2	3	4
Mutation	Homozygous p.R1092Q	Paternal c.576C>G, p.I119M and maternal c.334C>T, p.R1039X	Homozygous p.G84Q	Homozygous c.1924T>C, p.W642R
Age rhIGF-1 start (years)	13.3 (second course)	1.6	0.1	0.1
RhIGF-1 duration (years)	0.3	10	0.3	0.5
Age (years)/cause of death	14.7/unknown (recurrent sepsis and ketoacidosis)		1.3/liver dysfunction: respiratory infection	
Thyroid			Secondary hypothyroidism	Secondary hypothyroidism
Skin		Diffuse psoriatic skin rashes	Hyperkeratosis	Hyperkeratosis
Liver			Progressive cirrhosis	Mild cholestasis/hypoalbuminaemia
Clotting abnormalities		Low factor IX	Prolonged coagulation, deficits in factors II, IX, XI, fibrinogen, ATIII, Prot C	Prolonged coagulation, deficits in factors II, IX, XI, fibrinogen
Eyes	Bilateral cataract probably secondary to hyperglycaemia	Divergent squint astigmatic myopia		
Heart	Mild bi-ventricular hypertrophy		Biventricular hypertrophy	Mild pulmonary valvar stenosis, patent foramen ovale and ductus arteriosus, left ventricular hypertrophy
Gut			Protein losing inflammatory enteropathy	
Electrolyte disturbancies			Hypokalaemia	Hypokalaemia and hyponatreamia

hypothesis we collected maternal and cord blood sera from 107 healthy pregnant women (mean age 30.7 years) in winter during a viral season. **Method:** We tested for GAD 65 autoantibodies, and anti-rota and cox B3 antibodies. **Results:** GAD 65 Ab and rotavirus Ab present in both maternal and cord blood correlated with an odd ratio of 6.89 (95% CI: 1–46.7). For five, 22 and 17 pregnancies antibodies to GAD 65, rotavirus and CoxB3, respectively, were detected in cord blood only and not in the maternal serum. In ten pregnancies, rotavirus antibody titres in the cord blood exceeded those in the corresponding maternal serum by 2.5–5-fold. **Conclusion:** The concurrent presence of GAD 65 antibodies in cord blood and their mothers may indicate autoimmune damage to islet cells during gestation, caused by cross-placental transmission of viral infections, or antibodies. If the continuing study will confirm our findings pregestational antiviral vaccination will cause prevention or at least reduction in the incidence of childhood TIDM.

P1-102
The Role of HNF1B in Human Pancreas Development and Diabetes

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Background: Diabetes mellitus is a heterogeneous disorder with multiple aetiologies. Monogenic diabetes accounts for an estimated 2–5% of cases and is often associated with impaired pancreas development and β-cell dysfunction. Heterozygous mutations in the transcription factor, HNF1B, result in multisystem disease including diabetes due to β-cell dysfunction, hepatic insulin resistance and pancreatic hypoplasia. However, the mechanisms that underlie development of diabetes in HNF1B mutation carriers are still not fully understood due to lack of an appropriate model system. Human pluripotent stem cells (PSCs) are capable of self-renewal and have the potential to differentiate into any cell type in the body. They are therefore ideally suited to model human developmental diseases. **Objective and hypotheses:** We propose to use a human pluripotent stem cell-based model system to determine the molecular mechanisms by which HNF1B mutations cause pancreatic hypoplasia and diabetes. **Method:** Human PSC models of HNF1B-associated diabetes will be created through knockout of HNF1B in human embryonic stem cells (ESCs) and generation of induced pluripotent stem cells (iPSC) from patients. HNF1B deficient PSCs will be differentiated along pancreatic and hepatic lineages to investigate the effect of HNF1B mutations on human pancreas and liver development and function. **Results:** Initial experiments analysed the normal expression pattern of HNF1B and showed upregulation of HNF1B at the foregut stage, and during pancreatic and liver specification. Preliminary experiments also showed that hPSCs-derived hepatocyte-like cells can potentially be used to study insulin-mediated regulation of metabolism in hepatocytes. **Conclusion:** Human cellular models can be used to study the molecular mechanisms by which specific genotypes and epigenetic factors cause diabetes. The differentiation of PSCs along the pancreatic and hepatic lineages presents a unique tool to identify new genes that contribute to diabetes pathogenesis and novel therapeutic targets. **Funding:** This work was supported by funding from the Wellcome Trust.

P1-103
Molecular Characterization of a Novel Non-stop KCNJ11 Mutation Associated with a Dual Focal and Diffuse Hyperinsulinaemic Hypoglycaemia Phenotype

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Background: Hyperinsulinaemic hypoglycaemia (HH) has two main histological subtypes: diffuse and focal. Diffuse HH are most commonly due to recessive or dominant *ABCC8/KCNJ11* mutations. Focal HH results due to somatic loss of the maternal 11p allele involving the *ABCC8* and *KCNJ11* region in patients with paternally inherited *ABCC8* or *KCNJ11* mutation. **Aim:** To molecular characterise a novel non-stop *KCNJ11* mutations associated with a unique dual clinical phenotype of focal and diffuse HH. **Patients and methods:** A female infant with paternally inherited heterozygous *KCNJ11* mutation (c.1171T>C; p.*391Rext*94 Kir6.2), presented with diazoxide unresponsive HH. First ^{18}F-DOPA-PET suggested focal lesion in tail, which was resected. Tissue histology and microsatellite analysis confirmed focal HH. Post-resection, HH persisted and repeat ^{18}F-DOPA-PET suggested diffuse disease. A second limited pancreatectomy was undertaken. Tissue histology and microsatellite analysis confirmed diffuse HH. After second resection, the patient was diazoxide responsive. Point mutation of Kir6.2 was introduced in the human Kir6.2 cDNA in the pcDNA3.1 plasmid by site-directed mutagenesis. HEK293 cells were transfected with WT hamster SUR1 cDNA and mutant human Kir6.2 cDNA using FuGENE. Functional properties of channels were studied using whole-cell patch-clamp recordings. Both homogenous and heterozygous expressions of the mutants were studied. **Results:** Currents equivalent to endogenous HEK293 cells currents were noticed when mutant p.*391Rext*94 Kir6.2 subunit was expressed with WT SUR1 subunit (53 ± 10pA/pF vs. 80 ± 33pA/pF). This suggested negligible K_{ATP} current, consistent with the diazoxide-unresponsive clinical picture before the resection of focal lesion. With heterozygous p.*391Rext*94 Kir6.2 expression (1:1 molar ratio of WT and mutant Kir6.2 units, with WT SUR1 subunits) to simulate the situation in the rest of the pancreas, significantly reduced but diazoxide responsive K_{ATP} currents were observed (325 ± 54pA/pF vs. 147 ± 43pA/pF; $P=0.03$). **Conclusion:** This study describes the first reported dual focal and diffuse HH phenotype with *KCNJ11* mutations. Molecular characterization supports the observed clinical phenotype. **Funding:** This work was supported by MRC UK.

P1-104

Diazoxide Responsive Congenital Hyperinsulinism in a Patient with Dual Genetic Aetiology (*HNF4A* and *ABCC8* Mutation)

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Background: Congenital hyperinsulinism (CHI) results from unregulated insulin secretion from pancreatic β-cells, which leads to persistent hypoglycaemia. Mutations in nine different genes are reported and phenotypic variability exists both within and between the genetic subgroups. Variable penetrance has been described in some families with the same mutation; for example HNF4A mutations cause neonatal hypoglycaemia and/or maturity onset diabetes of the young (MODY). **Case:** A male born at 35 weeks gestation with a birth weight of 4.3 kg (+3.6 SDS) had recurrent hypoglycaemic episodes from day one of life. Investigations revealed a raised plasma insulin (1357 pmol/l) and C-peptide (3280 pmol/l) with supressed plasma free fatty acids and β-hydroxybutyrate during hypoglycaemia (glucose <0.5 mmol/l). Diazoxide (5 mg/kg per day) was started with a progressive increase to 20 mg/kg per day to maintain euglycaemia. His father was slim, had been diagnosed with diabetes mellitus in his thirties and was on Metformin. The paternal grandmother was also diabetic. There was no family history of hypoglycaemia. Sequence analysis identified a heterozygous HNF4A mutation (p.R245P) and two heterozygous ABCC8 mutations (p.G92S; p.A1185V) in the proband. The p.A1185V ABCC8 mutation had been inherited from his unaffected mother and the p.R245P HNF4A and p.G92S ABCC8 mutations from his father. All three mutations are novel, affect conserved residues, and are predicted to be pathogenic by *in silico* analysis. It is therefore likely that the CHI in the proband is resulting from a dual aetiology. Identification of a HNF4A mutation in the father is consistent with a diagnosis of MODY. He has subsequently switched treatment to Gliclazide resulting in improved glycaemic control. **Conclusion:** HNF4A CHI is often transient and responsive to diazoxide. In contrast recessively inherited ABCC8 mutations usually cause diazoxide-resistant CHI. Interestingly, our patient is responsive to diazoxide despite the dual genetic aetiology. The mechanism(s) underlying the molecular interaction between HNF4A and ABCC8 mutations are unclear.

P1-105

Fluoxetine Induced Hypoglycaemia in a Patient with Congenital Hyperinsulinism on Lanreotide Therapy

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Background: Lanreotide is a long acting somatostatin analogue that has been used successfully in the treatment of congenital hyperinsulinism (CHI) in patients who are unresponsive or intolerant to diazoxide. Antidepressant drugs are reported to cause alterations in blood glucose homeostasis in adults with diabetes mellitus. We report a patient with persistent CHI on Lanreotide therapy, who developed recurrent hypoglycaemia following Fluoxetine therapy. **Case:** A 15-year-old girl with persistent CHI was initially managed with diazoxide therapy. Genetic analysis revealed a *de novo* heterozygous novel ABCC8 mutation. 18-Fluro DOPA PET CT scan revealed a diffuse disease. She developed troublesome hypertrichosis on diazoxide therapy. This had a major impact on her quality of life and there were episodes of deliberate self-harm needing psychological assistance. A trial off diazoxide revealed persistent hyperinsulinaemic hypoglycaemia. Hence Lanreotide was commenced subcutaneously (30 mg, once monthly). The continuous blood glucose monitoring on monthly Lanreotide injections revealed good glycaemic control. Her quality of life improved and hypertrichosis reduced. Six months later, she developed depression due to psychosocial problems at school. She was commenced on Fluoxetine (20 mg/day) by the psychiatry team. She subsequently developed recurrent hypoglycaemic episodes (blood glucose <3.5 mmol/l) and hence Fluoxetine was discontinued, following which the hypoglycaemic episodes resolved within a week. She is currently maintaining normoglycaemia on monthly Lanreotide injections. **Conclusion:** Fluoxetine has been associated with hypoglycaemia, hypoglycaemia unawareness, and increased insulin sensitivity in patients with diabetes mellitus. We report, for the first time, hypoglycaemia secondary to Fluoxetine in a patient with CHI. Hence, close blood glucose monitoring should be undertaken in patients with disorders of glucose homeostasis (CHI and diabetes mellitus) who are commenced on antidepressants.

P1-106

Influence of Nocturnal Glycaemia on Ventricular Repolarisation and Heart Rate Variability in Prepubertal Children with Type 1 Diabetes

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Background: 'Dead in Bed syndrome' mechanism in childhood diabetes remains unknown. The hypothesis is that a nocturnal hypoglycaemia could lead to arrhythmias related to abnormal ventricular repolarisation. **Objective and hypotheses:** To look for a relationship between spontaneous fluctuations of nocturnal glycaemia, ventricular repolarization and heart rate variability (HRV) in prepubertal children with type 1 diabetes. **Method:** Continuous glycemic together with electrocardiographic

monitoring were performed for 1–2 nights at home in 29 prepubertal children with type 1 diabetes. QT apex length and HRV (linear and non linear methods) were compared between hypoglycemic and normoglycaemic periods and between hyperglycemic and normoglycaemic periods. We evaluated correlations between HRV and ventricular repolarization parameters recorded in a stable euglycaemic period and clinical and biological variables (age, sex, BMI, duration of diabetes, HbA1c, percentage of hypoglycemia over the past 3 months). **Results:** No difference for QT length or HRV parameters were found between periods of hypoglycemia ($n=6$) and hyperglycaemia ($n=17$) compared to euglycaemic phases. During euglycaemic phases ($n=21$), lower low frequency (LF) was significantly correlated with the frequency of hypoglycemia over the past 3 months ($P=0.03$). Tiertile comparison analysis confirmed it and found significant differences between children with high and low hypoglycaemias frequency in LF, SD2 ($P<0.05$). There was a negative correlation between Alpha 1 and HbA1c ($P=0.03$) and high frequency (HF) tended to be positively correlated with HbA1c ($P=0.05$). Tiertile comparison analysis found significant differences between children with high and low HbA1c in HF, rmssd, SD1 ($P<0.05$). **Conclusion:** We did not find that spontaneous nocturnal glycemic variations, including hypoglycemia, induced changes in ventricular repolarization and heart rate variability in prepubertal children with type 1 diabetes. However, frequent hypoglycaemias over the past 3 months could have an influence on nocturnal autonomic balance. **Funding:** This work was supported by the COREC Grant (CHU Rennes) (2010).

P1-107

Changes in Serum Protein Expression in Small-for-Gestational-Age Newborn Infants at Different Gestational Ages

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Background: Small-for-gestational-age (SGA) newborn infants (NB) may present long-term comorbidities influencing their metabolism, growth and/or development. Although their serum proteome is unknown, altered expression of the proteome profile may provide information on their physiopathology and lead to the discovery of biomarkers for postnatal complications. **Aim:** To detect changes in the serum proteome in SGA-NB vs adequate-for-gestational-age (AGA) newborns during the first month of postnatal life. **Population and method:** A total of 43 SGA-NBs and 45 AGA-NBs were divided into three groups (15 SGA/15 AGA, respectively): Group 1, 29–32 weeks; Group 2, 33–36 weeks; Group 3, ≧37 weeks. Inclusion criteria: signed informed consent, weight at birth <p10 (Carrascosa curves), and absence of congenital genetic abnormality, malformation or infection. Three samples were taken: at birth, 7–10 and 28–30 days. For proteome techniques (2DE-PAGE) to assess differential expression of proteins, spot analysis was carried out using the Proteomweaver v 4.0. software package; proteins were identified by MALDI-TOF/TOF, and Western Blot was used for validation purposes. **Results:** Differences were found in the expression of 33 proteins, all identified. One (LPIAT1) was present only in SGA-NBs. Seven (SUMO3, APOL1, ICLC6, DEFB108A, IGLC2 KRT9 and CCDC51) were found only in AGA-NBs. A total of 20 were overexpressed (five Albu, GSN, APOE, KRT10, SLC41A2, ANAPC2, APOA1, UPG2, two SERPIN1, DNAH6, Apoh, Prdx2, FGB, and two TFS) and 5 were underexpressed (FCN2, two VTNs, RAB35, and Apoh-fragment) in SGA-NBs. LPIAT and SERPIN1 were found in all SGA-NB groups at all stages. **Conclusions:** Significant differences between SGA-NBs and AGA-NBs at different ages were found for the expression of proteins involved in phospholipid synthesis, protein ubiquitination, lipid transport, antimicrobial activity and the innate immune response. In SGA-NBs, expression of LPIAT1 and SERPIN1 may be an adaptive response to protect the brain in an adverse foetal environment, recalling Barker's foetal programming theory. This is the first study to evaluate changes in the serum proteome of SGA-NBS as a function of gestational age: 1, 7 and 30 days after birth.

P1-108

Liver ER Stress and Intrauterine Growth Retardation in Rats

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Background: Endoplasmic reticulum (ER) is the site where proteins are folded. Perturbation of ER homeostasis activates a set of ER-to-nucleus signaling reactions known as the unfolded protein response (UPR). Metabolic stress causes UPR activation which contributes to the development of insulin resistance and metabolic syndrome. As UPR can be activated by nutrient and oxygen starvation, we postulated that intrauterine growth restriction may trigger UPR signaling and thereby contribute to the metabolic risk of IUGR subjects. **Objective and hypotheses:** i) to evaluate liver UPR and ii) to determine the functional

consequences of UPR in IUGR rat pups. **Method:** Sprague-Dawley pregnant rats underwent surgery for uterine artery ligation at day 19 of gestation. Approximately 8 h after delivery, pups were weighed and killed. Tissue was immediately harvested and stored at $<80°C$. The expression of genes that regulate liver UPR and their metabolic targets were investigated in 14 SHAM and 14 IUGR pups. **Results:** IUGR animals had significantly lower birth weight than controls ($P<0.001$). No significant differences were observed in blood glucose and insulin levels at birth. IUGR animals showed significantly higher NEFA blood levels ($P<0.001$). A significant increased expression of XBP1s mRNA ($P<0.01$), Erdj4 mRNA ($P<0.05$) and Bip mRNA ($P<0.05$) was observed in liver of IUGR pups. In IUGR pups the gene expression of Pck1 and G6pc (gluconeogenesis genes) and Acc2, Dgat2 and Scd1 (lipogenesis genes) was significantly upregulated ($P<0.05$). **Conclusion:** We document hepatic UPR activation by uteroplacental insufficiency in newborn animals. Specifically, the IRE1α and ATF6 UPR signalling branches display higher levels of activation. In IUGR newborn pups, UPR activation correlates with the increased levels of mRNAs encoding lipogenic and gluconeogenic enzymes. Our findings suggest that hepatic ER stress/UPR signalling may play a role in the metabolic risk associated to intrauterine growth retardation.

P1-109

Continuous Subcutaneous Infusion of Recombinant LH and FSH During Early Infancy Promotes Testicular Descent in Congenital Hypogonadotropic Hypogonadism

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Context: Cryptorchidism, a common consequence of HH, is treated with orchiopexy. We previously observed that continuous subcutaneous infusion of gonadotropins restored normal serum testosterone and inhibin B concentrations in two infants with hypogonadotropic hypogonadism (HH) and was associated with testicular descent in one. **Objective:** Test if subcutaneous gonadotropin infusion within the first year of life can allow testicular descent in eight boys with HH and bilateral cryptorchidism, aged 0.25–11 months. **Methods:** Continuous subcutaneous infusion of rhLH and rhFSH at a daily rate of 50 and 75–150 UI, respectively, aiming at AMH and inhibin B levels normally observed during postnatal mini-puberty. **Results:** In response to gonadotropin infusion, serum LH and FSH increased to 4.6 ± 1.3 and 33 ± 9 UI/ml, inhibin B 369 ± 145 pg/ml, AMH 748 ± 361 pmol/ml, testosterone 3.6 ± 1.4 ng/ml. Testicular descent was bilateral in 6/8 patients after 3.6 ± 1.7 months of treatment and unilateral in 1/8. Testes re-ascension in one case was treated by surgery. Testes and penis reached normal dimensions. **Conclusion:** Gonadotropin infusion in early infancy seems able to induce complete testicular descent in most cases of cryptorchidism due to HH. If confirmed, this may allow infants to avoid surgical correction.

P1-110

Neonatal Screening Program for Central Congenital Hypothyroidism

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Background: Congenital hypothyroidism (CH) comprises a heterogeneous group of disorders that includes diseases of the hypothalamo-hypophyseal system. The latter are missed on TSH based screening programs leading to increased morbidity and mortality. Additional T_4 determinations, allows an early detection of CH of central origin (CH-C). **Objective and hypotheses:** To report the findings of a neonatal screening program based on determination of TSH and T_4 for early detection of CH-C. **Method:** Between June 2014 to March 2015, 29 100 term newborns aged 2–7 days, were included. Screening strategy included TSH (IFMA Delfia), cutoff 10 mU/l and T_4 (FIA Delfia), cutoff 4.5 μg/dl serum, (-2.3 SDS) in filter paper blood samples. Infants suspicious of CH-C were referred to a paediatric endocrinologist. They underwent a thorough clinical assessment and determination of serum TSH, T_4, fT_4, T_3, thyroglobulin, antithyroid-antibodies, cortisol, GH, prolactin, LH, FSH, testosterone (boys), glycaemia and electrolytes. Serum TBG was performed in patients likely to have hypoTBGemia. Brain imaging was performed. **Results:** Nineteen patients with low T_4 and TSH <10 mU/l were recalled (mean age 3.1 days). Of these, ten infants had transient hypothyroxinemia (nine non-thyroidal illnesses; one healthy). Five boys had hypoTBGemia (mean T_4 2.6 μg/dL; TBG <3.5 μg/dl). Three had permanent CH-C (mean T_4 3.9 μg/dl) due to a hypothalamo-hypophyseal disorder (1:9700). These patients remained hospitalized due to morbid conditions (one hypernatremia; two hypoglycaemias). All of them had multiple pituitary hormone deficiency. MRI showed midline defects. One additional patient with poor weight progression and cholestasis normalized T_4 but remained with isolated ACTH deficiency. Hormonal replacement was instituted at a mean age of 12.2 days. **Conclusion:** Inclusion of T_4 determination allowed us to identify CH-C as a prevalent condition, to detect T_4 transport defects and transient hypotiroxinemia due to systemic diseases. In CH-C infants additional detection of other life-threatening hormone deficits, facilitated a timely treatment preventing mayor morbidity. **Funding:** This work was supported by the Fundación de Endocrinología Infantil a non profit organization.

P1-111

Serum Neurokinin B Level can be Used to Differentiate Central Precocious Puberty from Premature Thelarche

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Background: Neurokinin B and kisspeptin appear to play main roles in puberty. **Aims and objectives:** The aim of the present study was to investigate the diagnostic role of kisspeptin and neurokinin B in central precocious puberty (CPP) and premature thelarche (PT). **Methods:** The girls who presented with breast development (between 5 and 8 years) were included in the study. All cases underwent bone age (BA) assesment. Basal serum FSH, LH and E2 and peak FSH, LH were measured after GnRH test. Patients who had peak LH >5 mIU/ml and a bone age/chronological age (CA) ratio >1 were diagnosed as CPP, while cases who did not have these criteria were as PT. Organic pathologies were excluded. Healthy, similar age prepubertal girls were included as control group. Neurokinin B and kisspeptin levels were measured by ELISA method. **Results:** The study included 25 CPP (7 ± 0.8 years), 35 PT (6.8 ± 0.7 years) and 30 controls (6.7 ± 0.7 years). BA, BA/CA ratio, basal LH, peak LH were significantly different between CPP and PT groups ($P<0.05$). Serum kissppeptin and neurokinin B levels were detected as (2.36 ± 0.47 pg/ml and 2.61 ± 0.32 ng/ml) in CPP, (2.23 ± 0.43 pg/ml and 2.24 ± 0.23 ng/ml) in PT and (1.92 ± 0.33 pg/ml and 2.03 ± 0.24 ng/ml) in controls. Kisspeptin and neurokinin B levels were significantly higher in CPP and PT group compared to controls ($P<0.05$). While neurokinin B level was significantly different between CPP and PT groups ($P<0.01$), no significant difference was found in kisspeptin level. Neurokinin B value of 2.42 ng/ml provided the most appropriate level with a sensitivity of 84% and specificity 77.1% differantial diagnosis of CPP and PT. **Conclusions:** Increased serum levels of kisspeptin and neurokinin B in patient with PT and CPP suggest that they play role during the initiation of puberty. Neurokinin B could be used to differentiate with CPP from PT.

P1-112

Aetiological Spectrum and Clinical Characteristics of 129 Children with Gonadotropin Independent Precocious Puberty: A Nationwide Cohort Study

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Background: Gonadotropin independent precocious puberty (GIPP) is caused by a heterogenous group of disorders. With the exception of congenital adrenal hyperplasia (CAH), disorders causing GIPP are uncommon, and there are no studies evaluating the etiologic distribution of GIPP in a large cohort. **Objective and hypotheses:** To find out the relative frequencies of each etiological group in patients with non-CAH GIPP and also to evaluate the clinical and laboratory features of these patients.

Table 1. Aetiological spectrum, clinical and laboratory features of each diagnostic group. (for abstract P1-112)

Diagnosis	Ovarian cyst	McCune Albright Syndrome	Testotoxicosis	Hypothyroidism	Adrenocortical tumor	HCG secreting tumor	Leydig cell tumor	Ovarian tumor	Sertoli call tumor	Undetermined
Patient Number (%)	47 (37%)	34 (26%)	5 (4%)	7 (5.5%)	12 (9%)	7 (5.5%)	5 (4%)	5 (4%)	3 (2%)	4 (3%)
Sex F/M	47/0	34/0	0/5	5/2	7/5	0/5	0/5	5/0	0/3	4/0
Mean Age at diagnosis (year)	5.4 (0.4–10.1)	5.2 (0.8–9.6)	4.1 (1.4–8.3)	6.8 (2.8–9.6)	3.4 (0.8–7.7)	7 (0.3–10.6)	6.1 (4.6–8.8)	7.3 (4–11.3)	6.1 (4.6–7.2)	4.3 (3.3–6.5)
Height SDS	0.55 (–1.72/3.11)	0.76 (–4.01/5.97)	3.06 (0.9/6.26)	−0.76 (−4.47/2.88)	0.91 (−1.54/3.66)	1.1 (−0.18/4.68)	1.69 (−0.41/3.96)	−0.11 (−0.66/1.02)	0.9 (0.03/1.4)	1.18 (0.5/1.73)
BA-CA (year)	0.6	1.6	3.1	−1.7	2	2.2	4.1	1.6	0.6	3
Basal FSH (mIU/ml)	0.6 (0.01–3.6)	0.7 (0.01–3.1)	0.4 (0.05–1.03)	4 (0.3–11.7)	0.3 (0.09–0.7)	0.2 (0.05–0.6)	0.5 (0.1–0.8)	1.5 (0.1–4.8)	0.12 (0.1–0.2)	0.2 (0–0.7)
Basal LH (mIU/ml)	0.1 (0–0.72)	0.1 (0–0.65)	0.1 (0.07–0.2)	0.1 (0–0.23)	0.1 (0–0.6)	0.1 (0.01–0.2)	0.2 (0.1–0.2)	1 (0.1–4.8)	0.08 (0.05–0.1)	0.06 (0.01–0.2)
E2 (pg/ml)	211 (6.2–879)	193.5 (5–2792)		80.5 (40.7–163.7)	25 (10–73.9)			20 (28–48)	29 (9–48)	74.6 (30–170.4)
Peak LH (mIU/ml)	0.6 (0.07–4.9)	0.9 (0–5.1)	1.83 (0.4–2.7)							
Peak FSH (mIU/ml)	2.1 (0.2–8.7)	3.8 (0.1–16.6)	4.4 (1–6.7)							
Testosterone (ng/ml)			15.6 (2.6–32)	0.5 (0.2–0.84)	4.3 (1.08–8.79	10.9 (0.1–23.9)	4.7 (0.9–1.6)	1.7 (0.1–4.4)	0.1 (0.03–0.2)	
DHEAS (ng/ml)					827 (30–1543)		77.9 (21.8–152)			

*Values are given as mean (range).

Method: In this multicenter, nationwide, web-based study; data regarding the patients presenting with GIPP (excluding those with CAH) were gathered. **Results:** 129 patients (104 females, 25 males) from 28 centres were registered. Functional ovarian cysts were the most common aetiology and constituted 37% of all cases. 55% of the cysts were located in the right ovary, average cyst size was 37 mm (10–88 mm). McCune Albright syndrome (MAS) was the second most common aetiology. Cafe au lait and fibrous dysplasia were seen in 32 and 44% respectively in MAS patients, 18% had both. HCG secreting tumours were choriocarcinoma of the liver, hepatoblastoma and germ cell tumors of sellar-suprasellar region. Patients with adrenocortical tumours presented at an earlier age than other aetiologies. Ten were carcinomas and both adrenals were affected equally. Ovarian tumours were mature cystic teratoma, dysgerminoma, juvenile granulosa tumour and steroid cell tumour. **Conclusion:** This largest cohort of non-CAH GIPP demonstrates that ovarian cysts and MAS predominates over the other aetiologies. Detailed clinical features of each diagnostic group will be discussed at the meeting. **Funding:** Turkish Pediatric Endocrinology Society Favor Group.

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Relevance of Astrocytic Signals for GnRH-Neuronal Function

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Background: Gonadotropin releasing hormone (GnRH)-secretion is not only regulated by neuronal factors but also by astroglia cells *via* growth factors (transforming growth factor α (TGFα), neuregulin (NRG)), prostaglandin E2 (PGE2) and the erbB receptor family. Mutations of TGFα and erbB1 result in an impaired reproductive capacity. Mice show a characteristically skin phenotype with wavy hair and curly whiskers. The rat strain SPRD-Cu3 (curly) shows a similar phenotype but the underlying dysfunction has not been elucidated so far. **Objective and hypotheses:** This study investigates the significance of the erbB signalling pathway in regulating GnRH neuronal function in curly rats. **Method:** Pubertal timing, estrous cyclicity and reproductive performance were analyzed in curly and Sprague Dawley Crl: CD (SD) (control) rats. Primary hypothalamic astrocytic cell cultures were utilized to analyze PGE2 secretion after stimulation of the TGFα-erbB1/erbB2 or NRG-erbB2/erbB4 signalling pathway. **Results:** Puberty is delayed in curly compared to control rats (41 ± 0.4 d vs 35 ± 0.3 d, $P < 0.0001$). Their estrous cycle is irregular, experiencing seldom ovulation demonstrated by rare phases of proestrous ($10\% \pm 1.3$ vs $22\% \pm 0.8$; $P < 0.0001$) and significantly lesser pups per litter compared to controls (6 ± 0.3 vs 11 ± 0.5 pups/litter, $P < 0.0001$). Stimulation of erbB1/erbB2 with TGFα did not show a different release of PGE2 in cell cultures from both rat strains. Moreover, no mutations were present in *erbB1* or *TGFα*. In contrast, stimulation of erbB2/erbB4 signalling pathway with the NRG isoform NRGß2 did not elicit a sufficient PGE2 release in astrocytic cell cultures from curly animals. Whereas, the PGE2 response in controls was significant ($P < 0.001$). **Conclusion:** The impaired reproductive capacity and GnRH neuronal function of curly rats is due to a disrupted NRG-erbB2/erbB4 receptor pathway. Further phosphorylation analysis of the erbB4 receptor will proof the functional relevance.

P1-114

Screening of Mutations in Idiopathic Hypogonadotropic Hypogonadism Using a Targeted Next-Generation Sequencing Approach

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Background: To date at least 30 genes are known to be associated with idiopathic hypogonadotropic hypogonadism (IHH). Analysis of all these gene candidates by Sanger sequencing would be expensive, labour-intensive and time-consuming. Recent introduction of next-generation sequencing (NGS) enables simultaneous analysis of multiple gene targets making it an attractive approach in such conditions as IHH **Objective and hypotheses:** To study the spectrum of molecular defects in IHH using a targeted NGS approach. **Method:** 25 patients with IHH (males, $n = 23$; females, $n = 2$) were studied. five subjects showed features of Kallmann syndrome (KS), 20 were normosmic. 'Hypogonadotropic hypogonadism panel' genes were sequenced using a custom Ion Ampliseq gene panel and PGM semiconductor sequencer (Ion Torrent). Bioinformatic analysis was performed using Torrent Suite (Ion Torrent) and ANNOVAR (annovar.-openbioinformatics.org) software packages. Non-synonymous sequence variants were rated as 'probably pathogenic' if they had allele frequency less than 1% and pathogenic *ljb* database scores. **Results:** 21 heterozygous pathogenic or probably pathogenic mutations were found in 13 of 25 patients (52%). Distribution of mutations was as follows: *CHD7*, $n = 4$; *GNRHR*, $n = 3$; *POLR3A*, $n = 3$; *POLR3B*, $n = 2$; *KAL1*, $n = 2$; *PROKR2*, $n = 2$; *FGFR1*, $n = 1$; *HS6ST1*, $n = 1$; *WDR11*, $n = 1$; *FGF8*, $n = 1$; *SPRY4*, $n = 1$. Mutations were identified in four of five KS cases, and in nine of 20 subjects with normosmic IHH. nine of 21 mutations were novel. In two patients mutations were found in more than two genes. **Conclusion:** The results confirm predominance of mutations associated with defects of development and migration of GnRH neurons. The targeted NGS method can be successfully used for differential diagnosis of IHH. **Funding:** Alfa-Endo Program of Charities Aid Foundation (CAF) Russia.

P1-115

Clinical Guidance on 17β-Oestradiol and LH Serum Levels in Girls with Premature Thelarche Based on Clinical Outcome of 129 Girls Aged up to 4 Year with Premature Thelarche in West Sweden

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Background: Simple clinical investigations to differ harmless premature thelarche (PT) from pubertal precocity and other pathological conditions are needed as PT is a common condition in girls under the age of 3–4 year. **Objective and hypotheses:** Since 17β-oestradiol (17β-E2) is the major driver of breast development, the hypothesis is, that it is possible to define an upper serum 17β-oestradiol (17β-E2) level for harmless PT in girls under the age of 4 year. **Method:** All determinations of 17β-E2 in West Sweden are sent to Gothenburg Pediatric Growth Research Center Laboratory (GP-GRC) as this is the only laboratory that can analyse paediatric 17β-E2 levels (using a high sensitive extraction RIA). Together with the result of the 17β-E2 levels there was sent to the responsible paediatrician a request to ask the parents for participation in a study on evaluation of the clinical outcome of PT. Two standard-deviations (SD) above the mean for girls with benign PT was considered as the upper limit for serum 17β-E2 for harmless PT. **Results:** Totally 236 17β-E2 serum analyses were made for girls (age 1–48 months) with Tanner breast stage 2–3 during the 10-year study period. 129 of these patients participated in the follow up study on evaluation of clinical outcome of PT. In the follow up study 125 of 129 girls had a benign PT and their mean serum 17β-E2 level was 15 pmol/l with an SD of 8 pmol/l. The mean serum 17β-E2 plus 2SD was 32 pmol/l and considered as an upper limit for serum 17β-E2 in girls with benign PT. All five girls with harmful PT had17β-E2-levels above 70 pmol/l. **Conclusion:** This is the first study to define an upper 17β-E2 level that is associated with benign PT, 17β-E2 levels below 32 pmol/l is associated with benign form of PT. Support are concomitant serum LH levels under the detection limit, determined with IRMA methods. **Funding:** This work was financially supported by grants from the Swedish Medical Research Council, LUA/ALF and regionala grants from NÄL/VG.

P1-116

FSHB/FSHR Genetic Variants alter Serum FSH Levels and Prepubertal Ovarian Follicular Growth in Healthy Girls

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Background: Single nucleotide polymorphisms (SNPs) related to genes encoding the FSHβ subunit and FSH receptor (*FSHB*/*FSHR*) affect FSH production (*FSHB* c.-211G>T) and receptor sensitivity/expression *in vitro* (*FSHR* c.2039A>G & *FSHR* c.-29G>A). *FSHR* c.2039A>G, but not *FSHR* c.-29G>A, is associated with increased FSH levels in adult women, while there are conflicting results on *FSHB* c.-211G>T. We previously revealed that *FSHB* c.-211G>T and *FSHR* c.-29G>A delay pubertal onset in girls. **Objective and hypotheses:** This present study aims to investigate the impact of the three SNPs on hormonal as well as morphologic parameters in healthy girls. **Method:** Participants were recruited as part of two population-based cohort studies of healthy children and adolescents: The COPENHAGEN Puberty Study (8–13 years) & The Mother-Child Cohort (9–15 years) ($n=574$). In a subgroup, ovarian transabdominal ultrasound) was performed ($n=91$). Subjects were genotyped for SNPs using KASP assays and grouped according to pubertal stages (Tanner's classification: B1/B2+3/B4+5). We compiled genetic, hormone and morphologic data of which minor parts have previously been reported. We assessed associations of the genotypes with circulating hormone levels and ovarian morphology. **Results:** When evaluated separately, *FSHR* c.2039A>G, but not *FSHR* c.-29G>A, affected FSH levels in B2+3: $r=0.1$, $P=0.02$ and B4+5: $r=0.2$, $P=0.01$. In a combined model, cumulative minor allele counts of both *FSHR* SNPs were associated with FSH levels ($r=0.2$, $P=0.01$). *FSHB* c.-211G>T did not affect FSH levels. AMH, inhibin-B and estradiol levels were not associated with the SNPs. In prepubertal girls (B1, $n=11$), cumulative minor allele counts of all three SNPs were negatively correlated with the number of large ovarian follicles (≧5 mm) ($r=-0.8$, $P=0.004$) and positively correlated with small vs. large follicles ratio (1–4 vs ≧5 mm) ($r=0.7$, $P=0.02$) (relative underrepresentation of large follicles). **Conclusion:** *FSHR* variants were associated with FSH levels in healthy early- and late-pubertal girls. We further reveal a combined negative effect of *FSHB*/*FSHR* minor allelic variants on follicular growth in prepubertal girls. We hypothesize that this represents the morphologic parallel to the previously observed delay of pubertal onset in girls. **Funding:** Danish Agency for Science, Technology and Innovation (09-067180), Danish Ministry of the Environment, CeHoS (MST-621-00065), Capital Region of Denmark (December 2011), Ministry of Higher Education and Science (DFF–1331-00113).

P1-117

Transient Breast Budding in Healthy Girls is a Frequent Phenomenon: Description of Pubertal Progression and Associations to Gonadotropins, Estradiol and *FSHB/FSHR* Genetic Polymorphisms

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Background: Intermittent breast budding (girls entering stage B2 and then subsequently regressing to B1) in healthy girls is a frequent phenomenon observed by most clinicians. However, little is known of normal progression of female puberty, and the phenomenon of transient breast development has, to our knowledge, never been studied in details. **Objective and hypotheses:** We present and validate the female Puberty Nomogram indicating age specific SD scores for Tanner breast stages (based on Van Buuren *et al.*'s stage-line diagram). Moreover, we evaluate pubertal progression, longitudinal reproductive hormone profiles, and genetic polymorphisms affecting FSH signalling in girls with transient breast budding. **Method:** The Puberty Nomogram was based on 1375 healthy, Caucasian girls from cross-sectional studies in Copenhagen and Randers, and was validated using data from 98 girls from the longitudinal part of the COPENHAGEN Puberty Study. DNA was isolated from blood and *FSHB* c.-211G>T, *FSHR* c.-29 G>A and *FSHR* c.2039 A>G were assessed by KASP genotyping assays. **Results:** Thirteen (out of 98) girls (13%) from the longitudinal cohort presented with transient breast budding. On the Puberty Nomogram it is apparent that after a variable period of time, pubertal development progresses normally in girls with intermittent breasts (median +1.7 years, range 1.14–4.29). Transient breast budding was associated with lower concentrations of hormones, significantly for LH ($P=0.016$) and inhibin B ($p=0.019$), at the time of the initial B2 compared to girls who initiated and progress normally. The distributions of *FSHB* and *FSHR* SNPs were not associated with transient breast budding. **Conclusion:** Transient breast development is a clinical phenomenon observed in 13% of healthy girls and is not associated with a pubertal rise in gonadotropins and reproductive hormone concentrations at the initial breast development. Genetic polymorphisms affecting FSH signalling did not appear to be associated with the phenomenon in this pilot study.

P1-118

Specific Hypothalamic Activation Pattern by mGlu5 Receptor Blockade *in vivo* During Pubertal Development in Female Mice

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Background: Puberty is characterised by important changes of brain networks. The glutamate system plays a main role in modulating the onset of puberty as shown for NMDA receptor agonists. However, the underlying mechanisms are poorly understood. Metabotropic mGlu5 receptors (mGluR5) are tightly linked to NMDA receptors. The effect of mGluR5 blockade on neurohormonal mechanisms in puberty initiation were not studied yet. **Objective and hypotheses:** To investigate the role of pharmacological blockade of mGluR5 on neuronal activation during puberty in order to identify neuroendocrine signals involved in gonadarche and pubertal progression. **Method:** We used profiling of the expression of the immediate early gene c-fos, as marker of neuronal activity, triggered by the selective mGluR5 antagonist 2-Methyl-6-(phenylethynyl)pyridine (***MPEP***). Female mice at postnatal day (P) 16 to 40 ($n=4$-6) were treated i.p. with 30 mg/kg MPEP. Coronal brain sections (50 μm) were obtained and c-fos immunohistochemistry was performed. Serum levels of LH and FSH were measured in P26 female mice ($n=5$) after 7 days of MPEP or normal saline treatment by non-magnetic bead immunoassay. Mice growth, weight and uterus weight were analysed. **Results:** We found a remarkably specific activation of the paraventricular nucleus of the hypothalamus (PVNH) by MPEP, starting at P16 and continuing throughout puberty (P16–P40). MPEP reduced LH and FSH levels (pg/ml) as compared to normal saline (LH 38.43 ± 7.65–26.68 ± 4.18, for FSH 119.08 ± 45.66–86.38 ± 17.45). **Conclusion:** Our data provide new insights into the role of mGluR5 in pubertal development of female mice. Chronic MPEP treatment reduced LH and FSH levels. MPEP administration activates c-fos specific in the PVNH a key regulator of the hypothalamic-pituitary-adrenal (HPA) axis. Our data support a role of mGluR5 in regulating glutamatergic control of the hypothalamic-pituitary-gonadal (HPG) axis probably by early activation of collateral glutamatergic neurons.

P1-119

Lipid Profiles in Gender Dysphoric Adolescents Treated with GnRH Agonists Alone and in Combination with Cross-Sex Hormones

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Background: In gender dysphoric adolescents GnRH agonists can be used to suppress pubertal development of the natal sex. Subsequently cross sex hormones can be given to induce pubertal development of the experienced gender. Only few data are available on the safety of this treatment. Lipid levels are known to increase during puberty and pubertal suppression may alter this increase. In gender dysphoric male-to female (MtF) adults oestrogens has been shown to result in a more favourable lipid profile, whereas testosterone treatment in female-to-males (FtM) results in a decrease of HDL cholesterol and an increase of triglycerides. **Objective and hypotheses:** This study aimed to determine if GnRH agonist and cross sex hormone treatment of gender dysphoric adolescents influences lipid levels. **Method:** During treatment with GnRH agonists and cross sex hormone treatment fasting blood samples were drawn yearly to monitor lipid levels (total cholesterol, LDL- and HDL-cholesterol, and

triglycerides). 51 MtF and 67 FtM gender dysphoric adolescents were included at the start of GnRH agonist treatment and 34 MtF and 39 FtM at start of cross sex hormone treatment. **Results:** During the 2 years GnRHa treatment a significant increase in total and HDL-cholesterol was found in both sexes. LDL-cholesterol and triglycerides did not change during GnRHa treatment. During the cross-sex hormone treatment a significant decrease in HDL-cholesterol in the FtM group and significant decrease in LDL-cholesterol in the MtF group was found. The other lipid levels did not change significantly. **Conclusion:** In gender dysphoric adolescents puberty suppression during 2 years an increase of total and HDL-cholesterol was found. Oestrogen treatment led to a decrease in LDL-cholesterol levels, while testosterone treatment led to a decrease in HDL-cholesterol levels. **Funding:** An unrestricted educational grant from Ferring Pharmaceuticals BV, Hoofddorp, the Netherlands.

P1-120

A Novel *LHX4* Mutation is Associated with Hypogonadotropic Hypogonadism, Not Combined Pituitary Hormone Deficiency

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Background: Mutations in *HESX1*, *SOX3* responsible for combined pituitary hormone deficiency (CPHD) have been identified in a small number of hypogonadotropic hypogonadism (HH), suggesting that the genetic overlap between CPHD and HH. **Case presentation:** A 2-month-old boy was referred because of micropenis (stretched penile length 1.0 cm) with intrascrotal testes (1 ml). Hormone assays revealed very-low plasma testosterone levels (0.06 ng/ml). LHRH stimulating test performed at the age of 3 months revealed LH peak 7.3 mIU/ml, and FSH peak 20.7 mIU/ml, suggesting pre-pubertal response. Plasma concentrations of thyroxine and insulin-like growth factor-1 were within normal ranges. No episode of hypoglycemia was noted. Clinical diagnosis was HH. Brain MRI showed a normal size anterior pituitary with a visible stalk. **Method:** Using a next-generation sequencing strategy, we sequenced 9 genes implicated in CPHD, including *POU1F1*, *PROP1*, *LHX3*, *HESX1*, *OTX2*, *SOX3*, *SOX2*, *GLI2*, *LHX4*, and 12 genes implicated in HH, including *CHD7*, *FGFR1*, *FGF8*, *GNRH1*, *GNRHR*, *KAL1, KISS1*, *KISS1R*, *PROK2*, *PROKR2*, *TAC3*, and *TACR3*. Transcriptional activity of identified LHX4 variant was evaluated by luciferase reporter assays constructed by inserting the *POU1F1* or *αGSU* promoters. We also performed subcellular localization analyses and EMSA assays. **Results:** We identified a novel heterozygous LHX4 sequence variation, c.661C>T (p.R221W). R221W LHX4 had reduced transactivation and no dominant negative effect. Subcellular localization revealed no significant difference between wild-type and mutant LHX4. EMSA experiments showed that the R221W LHX4 abrogated DNA-binding ability. **Conclusion:** The R221W was proven to be loss-of function mutation. We showed for the first time that *LHX4* mutation is associated with HH, not CPHD. This study extends our understanding of the phenotypic features, molecular mechanism, and developmental course associated with mutations in LHX4. **Funding:** This work was supported by a Grant-in-Aid for the Health Science Research Grant for Research on Applying Health Technology (Jitsuyoka (Nanbyo)-Ippan-014 (23300102)) from the Ministry of Health, Labour and Welfare of Japan.

P1-121

A Missense Mutation in MKRN3 in a Danish Girl with Central Precocious Puberty and Her Brother with Early Puberty

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Background: Idiopathic central precocious puberty (ICPP) results from the premature reactivation of the hypothalamic-pituitary-gonadal axis leading to development of secondary sexual characteristics prior to 8 years in girls or 9 years in boys. Mutations in the maternally imprinted MKNR3 gene are the most common identified genetic cause of ICPP to date. Expression of MKRN3 in the arcuate nucleus is presumed to be inhibitory to GnRH secretion, but the exact mechanism remains unknown. **Objective and hypotheses:** We wanted to investigate whether mutations in MKRN3 contribute to the premature onset of puberty in Danish ICPP patients. We also wanted to find out if MKRN3 is expressed in adult human hypothalamus. **Method:** We screened 29 Danish girls with ICPP for mutations in MKRN3 by Sanger-sequencing. Expression of MKRN3 in a human hypothalamic cDNA library was investigated by PCR and gel electrophoresis. **Results:** We identified one paternally inherited variant (c.1034G>A (p.Arg345His)) in MKRN3 in one girl with ICPP and in her brother with early puberty. The variant was predicted to affect protein function by all three prediction programs used, and it has been reported once in 4 300 individuals in the European American population in the NHLBI ESP database. Expression of MKRN3 was confirmed in the hypothalamic cDNA library. **Conclusion:** Our results are in line with previous studies where paternally

inherited MKRN3 mutations have been found both in males and females with ICPP or early puberty. Our report further expands the set of MKRN3 mutations identified in ICPP patients across diverse populations. Expression of MKRN3 in adult human hypothalamus is in contrast to previous findings in the mouse arcuate nucleus and suggests MKRN3's hypothalamic function is not limited to inhibition of GnRH secretion. **Funding:** This work was supported by the Academy of Finland, the Helsinki University Central Hospital Research Funds, Foundation for Pediatric Research, the Danish research council (AJ), and the Capital Region of Copenhagen (AJ).

P1-122

Congenital Hypothyroidism in Twin Couples and Triplets

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Background: Over the years special screening procedures for preterm and twin babies (re-screening at 2–4 weeks of life) have been adopted by many screening laboratories worldwide. However, no extensive studies have been performed to verify how many co-twins with negative test at first screening (3–5 days) become positive at re-screening, and the utility of a long-term follow-up also in co-twin with negative test at screening and re-screening. **Objective and hypotheses:** i) to estimate the concordance rate for CH by the first month of life in twin couples/triplets discordant for CH at the first screening; ii) to verify whether a long-term follow-up of co-twins with negative test at screening and re-screening may be useful to verify the occurrence of thyroid hypofunction in these children during development; iii) to characterize probands and co-twins by NGS analysis of a panel of candidate genes. **Method:** 39 twin couples and four triplets discordant for CH at first screening (43 CH probands) were recruited for the study. The range of the long-term follow-up in the couples/triplets was 2–21 years. Pairwise concordance rate (PWCR) for CH by the first month of life and for occurrence of thyroid hypofunction during development, was calculated as the proportion of concordant pairs over the sum of concordant and discordant pairs. **Results:** Among the couples/triplets discordant at first screening six co-twins resulted positive at re-screening and the PWCR for CH confirmed at birth was 14.3%. During the long-term follow-up a thyroid hypofunction was observed in four co-twins and L-thyroxine treatment was started at the age of 2 mo, 9 mo, 12 years. The PWCR for thyroid hypofunction among couples discordant at screening was 21.3%. The systematic NGS analysis revealed variations consistent with the observed phenotype in 50% of concordant and 44% of discordant couples. Most of the discordant MZ cases remain unexplained by NGS analyses. **Conclusion:** These results confirm the importance of the re-screening at 2–4 weeks of life in twins, the possible benefit of a long-term follow-up also in co-twin with negative test at screening and re-screening, and the need of further studies in order to uncover the largely unexplained pathogenesis of CH. **Funding:** This work was supported by Ministry of Health Grant n. RF2010-2309484.

P1-123

Th17 Cells in Children with Graves' Disease During Methimazole Treatment

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Background: Graves' disease (GD) is the most common cause of hyperthyroidism in the pediatric population. T helper 17 (Th17) IL-17A+CD3+CD4+ cells represent a novel subset of T helper cells that play an active role in inflammatory and autoimmune diseases. Although methimazole (MMI) lowers the levels of thyroid autoantibodies, little is still known about its influence on cell-mediated immune response. The role of Th17 cells in GD pathogenesis remains uncertain and the impact of MMI treatment on these cell subset has not been investigated. **Aims and objectives:** The aim of this research was to describe the percentages and absolute counts of Th17 lymphocytes in children with GD and to assess changes in the amount of these cell subset during MMI treatment. The relationships between Th17 and selected clinical parameters were also assessed. **Methods:** The frequencies of Th17 cells were measured by flow cytometry in 60 adolescents at the time of GD diagnosis and after achieving MMI-induced euthyreosis. The control group consisted of 20 healthy volunteers. **Results:** Higher absolute counts of Th17 lymphocytes were found in hyperthyroid adolescents before the treatment initiation and after achieving euthyreosis than in healthy individuals ($P=0.0001$ and $P=0.047$). Treatment with MMI caused a significant decrease in the percentages and absolute counts of Th17 lymphocytes ($P=0.047$ and $P=0.043$). Before the treatment, the serum concentration of TSH correlated inversely with the absolute counts and percentages of Th17 cells (absolute count: $r=-0.3514$, $P=0.001$; percentage: $r=-0.3731$, $P=0.001$). **Conclusions:** Despite the observed high frequencies of Th17 cells in GD adolescents in comparison with controls, and its tendency to decrease after MMI administration, treatment with MMI did not lead to the normalization of Th17 levels. Obtained results suggest also that severe immune system deregulation in the form of extremely high numbers of Th17 cells may lead to rapid GD relapse after the treatment.

P1-124

Thyrocytes are Particularly well Protected Against Oxidative Stress Induced by H_2O_2

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Background: H_2O_2 produced in large quantities in the thyroid may play a role in the pathogenesis of thyroid nodules and cancer. *In vitro*, moderate amounts of H_2O_2 are able to cause similar DNA damage compared to irradiation and even to induce RET/PTC rearrangements. **Objective and hypotheses:** We compared the defence mechanisms against H_2O_2 and irradiation in human thyrocytes, T-cells and other cell types. **Method:** Human thyrocytes in primary culture were compared to other cell types: human T-cells in primary culture, a human thyroid epithelial cell line (Nthy-ori 3-1), non-transformed rat fibroblasts (F208) and a human myeloid cell line (PLB-XGCD) in terms of ability to degrade H_2O_2, glutathione peroxidase (GPx) activity, heme oxygenase-1 (*HO-1*) expression, cell survival and capacity to repair DNA damage after H_2O_2 exposure or irradiation. **Results:** Thyrocytes rapidly degraded extracellular H_2O_2. Addition of BSO increased DNA damages in thyrocytes but not in T-cells. In the presence of H_2O_2, only the thyrocyte was able to increase GPx activity. Four to eight hours after treatment with H_2O_2, *HO-1* expression was up-regulated in the thyrocyte. No significant regulation in *HO-1* expression or GPx activity was observed after irradiation in all tested cell types. Finally, kinetics of repair performed after treatment with H_2O_2 or irradiation demonstrated that damages caused by irradiation are repaired more rapidly than those caused by H_2O_2 in all investigated cell types. T-cells were totally unable to repair damages caused by H_2O_2. **Conclusion:** Thyrocyte have developed multiple mechanisms of protection against oxidative stress induced by H_2O_2. Our results suggest that deficiency of one of these mechanisms could promote the appearance of sporadic thyroid cancer. Due to their extreme sensitivity to H_2O_2, T-cells are probably not a good surrogate tissue to study individual susceptibility to H_2O_2. **Funding:** This work was supported by the « Fonds Erasme pour la Recherche Médicale », The Belgian Kids' Fund, FRS-FNRS, the Association Vinçotte Nuclear and the « Actions de Recherches Concertées de la Communauté Française de Belgique », the « Fonds Docteur J.P Naets » and Fondation Rose et Jean Hoguet.

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Thyrocyte is Particularly Well Protected Against Oxidative Stress Induced by H_2O_2

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Background: H_2O_2 produced in large quantities in the thyroid may play a role in the pathogenesis of thyroid nodules and cancer. *In vitro*, moderate amounts of H_2O_2 are able to cause similar DNA damage compared to irradiation and even to induce RET/PTC rearrangements. **Objective and hypotheses:** We compared the defence mechanisms against H_2O_2 and irradiation in human thyrocytes, T-cells and other cell types. **Method:** Human thyrocytes in primary culture were compared to other cell types: human T-cells in primary culture, a human thyroid epithelial cell line (Nthy-ori 3-1), non-transformed rat fibroblasts (F208) and a human myeloid cell line (PLB-XGCD) in terms of ability to degrade H_2O_2, glutathione peroxidase (GPx) activity, heme oxygenase-1 (*HO-1*) expression, cell survival and capacity to repair DNA damage after H_2O_2 exposure or irradiation. **Results:** Thyrocytes rapidly degraded extracellular H_2O_2. Addition of BSO increased DNA damages in thyrocytes but not in T-cells. In the presence of H_2O_2, only the thyrocyte was able to increase GPx activity. Four to 8 h after treatment with H_2O_2, *HO-1* expression was up-regulated in the thyrocyte. No significant regulation in *HO-1* expression or GPx activity was observed after irradiation in all tested cell types. Finally, kinetics of repair performed after treatment with H_2O_2 or irradiation demonstrated that damages caused by irradiation are repaired more rapidly than those caused by H_2O_2 in all investigated cell types. T-cells were totally unable to repair damages caused by H_2O_2. **Conclusion:** The thyrocyte has developed multiple mechanisms of protection against oxidative stress induced by H_2O_2. Our results suggest that the disability of one of these mechanisms could promote the appearance of sporadic thyroid cancer. Due to their extreme sensitivity to H_2O_2, T-cells are probably not a good surrogate tissue to study individual susceptibility to H_2O_2. **Funding:** This work was supported by the «Fonds Erasme pour la Recherche Médicale», The Belgian Kids' Fund, FRS-FNRS, the Association Vinçotte Nuclear and the «Actions de Recherches Concertées de la Communauté Française de Belgique», the «Fonds Docteur J.P Naets» and 'Fondation Rose et Jean Hoguet'.

P1-126

Characteristics and Outcome of Neonates with Congenital Hypothyroidism Born After *In Vitro* Fertilisation

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Background: *In vitro* fertilisation (IVF) has been widely used during the last decades. Increased susceptibility to birth defects and a higher cardiometabolic risk in children born after IVF than naturally conceived (NC) children have been reported. Also, a higher incidence of hyperthyrotropinemia has been noted in children born after IVF with respect to NC children and has been attributed to an epigenetic modification of the TSH set-point. **Objective and hypotheses:** To retrospectively evaluate the main characteristics and outcome of children born after IVF and diagnosed with CH. **Method:** Data from the medical records of children diagnosed with CH by the Greek national screening program were reviewed. **Results:** A total of 1 051 children with CH were analyzed. Of these, 152 neonates (14.5%) were born following IVF (88 boys and 64 girls; ratio 1.4:1). 89.5% of neonates born after IVF were premature ($<$37 gestational week) and 79.5% had a birthweight below 2500 g With respect to TSH values at diagnosis, 10% had a TSH $>$20 mIU/ml, 11% between 10 and 20 mIU/ml and 79% between 6 and 10 miU/ml. With respect to thyroid ultrasonography, only 4% had absence of or a very small thyroid gland. Pertinent longterm data were available in 62 boys and 48 girls. With respect to the outcome, LT_4 substitution therapy was discontinued only in 50% of boys and 37% of girls. **Conclusion:** Children born after IVF constitute a relatively large subgroup of children with CH, with a notable male predominance. Anatomical thyroid defects are rare. Although hypothyroidism at diagnosis is mild based on TSH values, in 50% of boys and 63% of girls born after IVF, a certain degree of dysfunction of the Hypothalamic-Pituitary-Thyroid-axis seems to persist. The reason of the gender dimorphism is not apparent.

P1-127

Transient vs Permanent Congenital Hypothyroidism: The Use of Baseline Characteristics and Long-Term Data Can Help Formulate a Practical Prognostic Algorithm

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Background: Implementation of neonatal screening programs for congenital hypothyroidism (CH) has reduced related nosologies and has eradicated CH-associated mental impairment. With the decrease of the TSH cut-off limits employed to avoid false negative results, milder cases of CH are diagnosed. Obviously, in a number of patients, especially among milder CH cases, thyroid dysfunction is transient. The diagnosis of transient vs. permanent CH is established in time. No specific prognostic factors have been introduced allowing prediction of the outcome. **Objective and hypotheses:** To identify the baseline characteristics influencing the outcome in neonates with CH. To formulate an algorithm that estimates the probability of transient CH in a given neonate based on specific data. **Methods:** Data from the medical records of children diagnosed with CH by the Greek national screening program were analysed retrospectively. Patients were diagnosed during the last 35 years using variable TSH cutoff limits ranging from 30 to 6 mIU/ml. Laboratory, clinical and ultrasonographic data, as well as family history and geographical origin, were recorded and evaluated. **Results:** A total of 1 051 children with CH were included in our study (569 male and 482 female, ratio 1.2:1). Of these, informative data were available in 844 patients. 15 children were diagnosed with a specific syndrome. In 20% of patients, a severe anatomical thyroid defect was disclosed. Among patients in whom an evident reason for permanent CH was not established (anatomic thyroid defect, known syndrome, etc), CH was transient in 33%. Percentage varies significantly among specific subgroups (e.g., 54% in premature IVF-conceived boys, 36% in premature normal-conception girls, etc). **Conclusion:** The use of baseline characteristics and long-term data (e.g. sex, birth weight, mode of conception, initial TSH value, family history etc) from representative CH subgroups can help formulate a practical algorithm calculating the probability of CH being transient.

P1-128

Diverse Genotypes and Phenotypes of Three Novel Thyroid Hormone Receptor α Mutations

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Background: Recently, T_3 receptor alpha (TRα) mutations have been identified in a number of patients with varying degrees of growth impairment, delayed development, constipation, increases in serum T_3 and decreases in T_4 and rT_3. **Objective:** To determine the spectrum of clinical and functional consequences of novel TRα mutations. **Method:** Clinical assessment and biochemical, imaging, and genetic analyses were performed in the three index patients and their relatives. Functional consequences of TRα mutations were investigated *in vitro*. **Results:** We studied 22 individuals from three families and identified nine

patients (five children, four adults; five females, four males; age range 11 months–55 years) with heterozygous TRα mutations: C380fs387X, R384H, and A263S, respectively. These mutations were associated with decreasing severity of the clinical phenotype: the patient in family 1 showed severe defects in growth, mental and motor development, whereas the six patients in family three had only mild clinical features. The patient in family 1 had been treated with LT_4 from the age of 2 years without obvious benefit. The most frequent abnormalities were thickened skull vault (100%), normocytic normochromic anemia, constipation, a delay in at least one of the developmental milestones (78% each). Only two patients (22%) had short stature and three cases (33%) demonstrated disproportionate body ratios. Serum (F)T_3 ranged from high-normal to elevated, and serum (F)T_4 and rT_3 from normal to decreased. TSH levels were all normal. Creatinine kinase levels were elevated only in affected children. The frame-shift mutation completely inactivated TRα, whereas the missense mutations produced milder defects. **Conclusion:** We report the largest case series with TRα mutations expanding the clinical spectrum. Lateral cranial x-ray findings, normocytic normochromic anemia, and, particularly in children, high creatinine kinase levels strengthen the diagnosis when clinical signs of hypothyroidism are present along with near-normal thyroid hormone levels.

P1-129

Intelligence and Behaviour in Children and Adolescents with Hashimoto's Thyroiditis

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Background: Hashimoto's thyroiditis (HT) is an autoimmune-mediated disorder, and is the most common cause of thyroid disease and acquired hypothyroidism in children and adolescents. In adults with HT, concentration problems, memory disorders and an increased rate of depression have been reported. **Objective and hypotheses:** To investigate, whether children and adolescents with HT have more behaviour and emotional problems, and/or lower intelligence than healthy subjects. **Method:** Psychometric testing was performed in 31 patients with HT (mean age 14.9, range 8.0–18.0 years) recruited *via* our paediatric-endocrine clinics and in 28 healthy controls (mean age 14.3, range 10.0–18.0 years). Intelligence was assessed by the Cultural-Fair-Intelligence-Test (CFT-20-R), physical complaints by the Gießener complaint questionnaire (GBBKJ), emotion regulation by the Toronto-Alexithymia-Scale (TAS26) and behavioural problems by the child-behaviour-checklist (CBCL). Student's *t*-test was used to compare the findings. In addition, we determined serum antibodies against thyroperoxidase and thyroglobulin in both groups and TSH and fT_4 in HT patients. **Results:** Age, gender, and parental educational differed not between both groups. All patients showed fT_4 values within the age-appropriate normal range. 19 patients had normal TSH values, while seven had values marginally above, and five slightly below the normal range. No thyroid antibodies were found in the controls. HT patients had more problems concerning emotion regulation and showed increased CBCL scores ($P < 0.05$ each). HT patients had also lower intelligence quotients and more family conflicts, but these differences did not reach statistical significance. As for physical complaints no difference between patients and controls could be detected. **Conclusion:** Children/adolescents with HT show especially more behavioural problems than healthy subjects of the same age, but do not show more intellectual problems. Further investigations should clarify whether the socio-emotional problems are specifically related to HT, or are due to affection by a chronic disease *per se*.

P1-130

Brain-Lung-Thyroid Syndrome – Update on the Clinical Spectrum of a Heterogeneous Disorder

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Background: Brain-lung-thyroid syndrome (BLTS, OMIM# 610978) is caused by mutations in the NK2 homeobox 2 (*NKX2-1; TTF1*) gene affecting the three NKX2-1 expressing organs brain, lung and thyroid. The syndrome is characterized by benign hereditary chorea (BHC), infant respiratory distress syndrome (IRDS) and congenital hypothyroidism (CH). However, the clinical spectrum and severity of symptoms vary widely. Regarding the increasing number of published mutations and heterogeneous phenotypes a clinical synopsis is needed for all involved specialists. **Objectives:** Summarising all available published cases of NKX2-1 related disorders to provide a detailed clinical overview of BLTS. **Methods:** We performed a systematic review of literature in MEDLINE and EMBASE. All subjects with proven NKX2-1 mutations and description of symptoms were included. For genotype-phenotype association studies, we compared different functional domains of the protein with specific phenotypes by Pearson's chi-square test. **Results:** We identified 243 subjects with 137 different mutations. Brain was affected in 91% of cases, lung in 56% and thyroid in 68%. Patients with brain involvement showed choreoathetosis (87%), developmental delay (61%) and muscular hypotonia (36%). Patients with lung disease showed IRDS (38%), recurrent lower respiratory tract infection (57%) and chronic interstitial lung disease (25%). Only 60% of patients with CH were detected by neonatal screening (mean TSH 130 mU/l), while 40% were diagnosed later (mean TSH 29 mU/l). In 202 subjects, information on all three organs was available for phenotype analysis: Only 44% suffered from the complete triad of BLTS, brain-thyroid-phenotype occurred in 29 and 15% showed isolated brain involvement. Further a detailed genotype-phenotype analysis revealed significant correlations between specific phenotypes and affected gene domains. **Conclusion:** We provide a

detailed clinical and genetic overview of BLTS with new insights in the heterogeneous symptoms and genotype-phenotype correlation of the syndrome.

P1-131

Increased Detection Rate of Paired Box Domain Gene Mutations by Application of Multiplex Ligation-Dependent Probe Amplification Analysis in Patients with Primary Congenital Hypothyroidism and Thyroid Dysgenesis

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Background: The contribution of mutations in paired box domain (*PAX8*) gene in children with congenital hypothyroidism (CH) and thyroid dysgenesis (TD) still remains a subject of interest of researchers. While quantitative PCR and direct sequencing concentrate on single gene fragment analysis and identification of point mutations, multiplex ligation-dependent probe amplification (MLPA) analysis might improve the detection rate of *PAX8* mutations in patients with congenital CH caused by TD. **Objective and hypotheses:** To determine if MLPA could improve the detection rate of *PAX8* gene mutations in patients with CH and TD. **Method:** The study included 45 children from south-eastern Poland selected *via* already established neonatal screening for primary CH. DNA was extracted from peripheral blood samples with the use of Master Pure DNA Purification Kit (Epicentre Biotechnologies). DNA samples were used in two types of genetic analysis of *PAX8* gene: Sanger sequencing method (promoter region and 12 exons with their exon-intron boundaries were sequenced) and MLPA technique (SALSA MLPA kit P319-A1 THYROID). **Results:** Sanger sequencing method revealed *PAX8* mutations in 5 out of 45 (11.1%) patients with CH and TD. In two of them heterozygous substitutions with the amino acid change in the coding sequence (c.700G>A, p.E234K and c.1225C>T, p.P409S respectively) were detected. In remaining three children missense variant within the promoter sequence of *PAX8* gene (456C>T) was revealed. Application of MLPA analysis allowed identification of heterozygous deletion of exon 7 of *PAX8* gene in two more (4.4%) patients in the examined group. In total, heterozygous *PAX8* mutations were detected in seven out of 45 patients (15.5%). **Conclusion:** In the study MLPA analysis increased *PAX8* mutation rate from 11.1 to 15.5%. Application of MLPA analysis, in addition to direct sequencing, both improves and expands genetic analysis for CH and TD. **Funding:** The work was funded in part by the Fritz-Thyssen-Stiftung and MAIFOR.

P1-132

Severe Hyperthyroidism in an Infant Revealed a Familial Non-Autoimmune Hyperthyroidism with Novel Heterozygous Thyrotropin Receptor Gene Mutation

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Background: The familial non-autoimmune hyperthyroidism (FNAH) is a hereditary disease caused by dominant activating mutations of the TSH receptor (TSHR) gene and rare in the paediatric population. **Case presentation:** A 20-month girl was referred for tachycardia. In personal history, she was delivered at 35 weeks of gestation by caesarean for fœtal tachycardia; she had been hospitalised at 1 and 5 months for diarrhoea and tachycardia was noticed. Clinically she presented with advanced growth (+2 SDS) and bone age (5 years), hypotrophy, craniostenosis, hyperactivity but motor delay by proximal amyotrophy. Discrete ophthalmopathy was observed. Lab tests revealed severe hyperthyroidism with free T_3 >20 pg/ml, free T_4: 52 pg/ml and TSH: 0.005 μU/ml. No anti-TSHR antibody was identified. Ultrasonography showed diffuse enlargement of thyroid gland (volume: 4 cm^3, normal <2.5 cm^3 for age). In familial history, father and father's mother have been treated for hyperthyroidism: surgery was performed once for father with total thyroidectomy (with papillary microcarcinoma) and twice for grandmother for voluminous and recurrent toxic goiter. Because of similar advanced growth, her 5-year old sister was tested and presented less severe hormonal (fT_3: 15.3 pg/ml, fT_4 40 pg/ml, TSH 0.006 μU/ml) and ultrasonography presentation. Treatment with thiamazole was initiated (1 mg/kg per day) and hyperthyroidism was partially controlled. We identified in the proband, her sister, father and grandmother a germinal heterozygous mutation in exon 10 of the TSHR gene; mutation C678W resulting for a cysteine to tryptophan substitution. Functional *in vitro* studies are on-going to explore the role of this residue in the modulation of TSHR activity. Interestingly, these four family members presented with mitral valve prolapse, as previously described in FNAH patients with C639 mutation. **Conclusion:** We report a French family with severe FNAH caused by a new germinal mutation in TDM7 of TSHR gene.

P1-133

Improved Determination of Total Serum Estrogenic Bioactivity: Characterisation of Oestrogenic Activity Modulators

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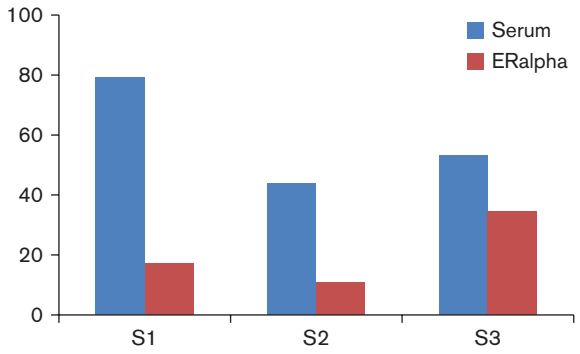

Figure 1 EBA is expressed as the percentage of luciferase activity; the value measured in the presence of 10 nM E2 was taken as 100%.

Background: Several years ago, we developed a recombinant cell bioassay to determine serum estrogenic bioactivity (EBA). In addition to its physiological interest, EBA could be a good marker of endocrine-disrupting compounds (EDCs) with estrogenic activity and thus would be useful in the field of environmental-related endocrine diseases. **Aims and objectives:** To characterise the type of substances that mediate estrogenic activity. **Methods:** We evaluated EBA before and after incubation with the estrogen receptor-α (ER-α) ligand-binding domain. Since ER-α was used in limited amounts, it preferentially captured compounds of high affinity like endogenous estrogens, with a residual EBA being related to low-affinity estrogenic compounds like EDCs. This measure was performed on three sera (S): two from young women during the ovulatory period (S1) and under estroprogestative contraception with 30 µg of ethinyl estradiol (S2), and the third was fetal bovine serum (S3). Radioimmunological determinations of plasma estradiol (E2) were 870, <9 and 25 pg/ml for S1, S2 and S3 respectively. **Results:** EBA fell after ER-α incubation for S1 and S2, whereas it remained at 65% of the basal value for S3 (Figure 1). **Conclusions:** We confirmed the usefulness of EBA evaluation in physiological conditions to measure both endogenous estrogens and ethinyl estradiol. The evaluation on total serum probably better reflects physiological status than the isolated evaluation of steroids. In addition, the EBA bioassay is able to detect other compounds of lower estrogenic activity and thus may be useful in evaluating environmental-related endocrine diseases.

P1-134

Co-Existing Variants of *FOXE1* and *BMP15* Genes in Young Females with Primary Ovarian Insufficiency: Evidence of Digenic Inheritance

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Background: FOXE1 gene variants containing alterations in the alanine tract length may confer susceptibility to primary ovarian insufficiency (POI). BMP15 gene variants have also been related to POI. **Objective and hypotheses:** To evaluate the contribution of *FOXE1* and *BMP15* variants in the pathogenesis of POI and to investigate the hypothesis of digenic inheritance in this disorder. **Method:** *FOXE1* and *BMP15* genes were directly sequenced in 35 young females with idiopathic POI (mean age at presentation 17.7 ± 5.91 years) and in 50 female controls from the general population. **Results:** In four out of the 35 POI cases, presenting at the age of 14, 25, 24 and 14 years respectively, a shorter alanine tract of the *FOXE1* gene was detected (genotypes: 8/16, 8/14, 8/8 and 12/12 respectively). Two of the patients were siblings. Thus, the frequency of *FOXE1* variants was 11.4% in patients vs 2% in the controls. In two out of the four patients (8/16, 8/14), variants of the *BMP15* gene (c.-9G/G, C>G), were also detected. These *BMP15* variants have been previously implicated in POI. No similar *BMP15* variants were present in controls. The mother of the two siblings with the shorter *FOXE1* alanine tract was also affected with POI (at age <30 years), after the birth of her children (mother's genotype 8/14). **Conclusion:** Data strongly indicate that i) *FOXE1* gene variants with a shorter alanine tract are causatively related to POI, ii) co-existence of variants in other POI-related genes (in this study *BMP15*) is possibly required in certain cases, for the clinical expression of an ovarian defect (digenic inheritance). These data are in accordance with our previous report on *FOXL2* also suggesting digenic inheritance in POI.

P1-135

Sex Hormones and Gonadal Size in Pubertal Girls Born Small or Appropriate for Gestational Age

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Background: Small for gestational age (SGA) birth size has been associated with various metabolic, hormonal and reproductive problems in later life. **Objective and hypotheses:** We aimed to compare differences in sex hormones, uterine and ovarian sizes in SGA and appropriate for gestational age (AGA) adolescent girls. **Method:** 23 SGA and 47 AGA pubertal 11–14 years old girls (median age 13.2 ± 1.94 years, median pubertal stage 4 ± 1) were recruited from the prospective newborn cohort. Sex hormones and gonadal size were analysed in both groups, adjusting for age and pubertal stage. Data are presented as mean and standard deviation. **Results:** No significant differences in LH, FSH, oestradiol and SHBG concentrations were found between SGA and AGA groups (4.26 ± 3.80 vs 3.35 ± 2.63 IU/l, $P=0.157$; 3.79 ± 1.75 vs 4.08 ± 2.33 IU/l, $P=0.983$; 326.86 ± 208.01 vs 427.45 ± 309.91 pmol/l,

$P=0.616$; 40.83 ± 16.46 vs 44.11 ± 20.76 nmol/l, $P=0.881$ respectively). SGA girls had significantly higher Testosterone levels (2.27 ± 1.25 vs 1.81 ± 1.00 nmol/l, $P=0.007$) and Free Androgen Index (FAI, 6.98 ± 6.72 vs 5.67 ± 5.26, $P=0.048$). Uterine size was significantly smaller in girls born SGA (42.19 ± 28.45 vs 64.45 ± 32.58 cm^3, $P=0.032$). Ovarian volume tended to be smaller as well in girls born SGA (9.15 ± 5.52 vs 12.38 ± 7.47 cm^3, $P=0.078$). Both uterine and ovarian sizes correlated directly with Estradiol levels ($r=0.344$, $P=0.008$ and $r=0.321$, $P=0.014$). Direct relationship between ovarian size and SHBG levels was also found in both groups combined ($r=0.522$, $P=0.001$). **Conclusion:** Pubertal SGA girls have higher markers of biochemical hyperandrogenism and smaller uterine size, which might influence future reproductive function in these girls. **Funding:** This study was funded by Lithuanian Research Council (grant No. MIP-103/2011) and the Swedish Research Council (No. 7509).

P1-136

The Eap1 Promoter is Differentially Methylated at the Onset of Puberty in Normal Weight and Obese Female Rats

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Background: Mammalian puberty is initiated by the pulsatile release of gonadotropin-releasing hormone (GnRH) from hypothalamic neurons. Enhanced at puberty (*Eap*) 1 is a transcription factor within this regulatory network integrating exogenous and endogenous informations, e.g. weight. Recent studies indicate an epigenetic regulation of the pubertal process. **Objective and hypotheses:** This study investigates if overweight modifies epigenetic marks in the *Eap1* promoter resulting in an altered function. **Method:** Female rats were raised in small ($n=3$) and normal litters ($n=12$). Weight, vaginal opening (VO) and estrous cycle were recorded. At different developmental time points methylation and expression profiles were analysed. **Results:** Rats growing up in small litters are significantly heavier than control rats. Furthermore obese rats show an earlier VO by one day and are significantly heavier at VO (151g ± 2.3 vs 131g ± 1.8, $P<0.001$). Within the first CpG island of the *Eap1* promoter region (−4028bp to −3703bp upstream TSS) the methylation level differs significantly between prepubertal and pubertal phases (11% ± 0.6 vs 26% ± 1.0, $P<0.001$, $n=6$). In obese rats the methylation level at the beginning of puberty is significantly blunted compared to normal weight rats (16% ± 1.5 vs 26% ± 1.0, $P<0.001$). The expression level of *Eap1* increases at PND 30 in normal weight and obese rats. **Conclusion:** These results show differences in the methylation level between pre- and pubertal phases influenced by endogenous factors, like weight. This might explain why moderate obesity advances pubertal onset. Further studies utilising luciferase promoter assays in CpG free vectors will proof the functional relevance. **Funding information:** This work was supported by the German Research Council (HE3151/4-2).

P1-137

Normalization of Puberty and Adult Height in Girls with Turner Syndrome, Randomised Trials vs Age and Dose at GH-Start

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Background: Early TS diagnosis permits early GH start and estradiol (E^2) supplementation approaching adult height (AH) at normal age and within a normal range. However, higher age at diagnosis is still a challenge. **Objective and hypotheses:** The hypothesis from our long-term trials will result in knowledge for personalized treatment in order to obtain a psychological acceptable age at onset of puberty and still an attained AH within normal range for TS girls. **Method:** 132 prepubertal TS girls (3–9/9–16 years) were randomised into national multicenter studies with GH treatment (33/67 µg/kg per day) in combination

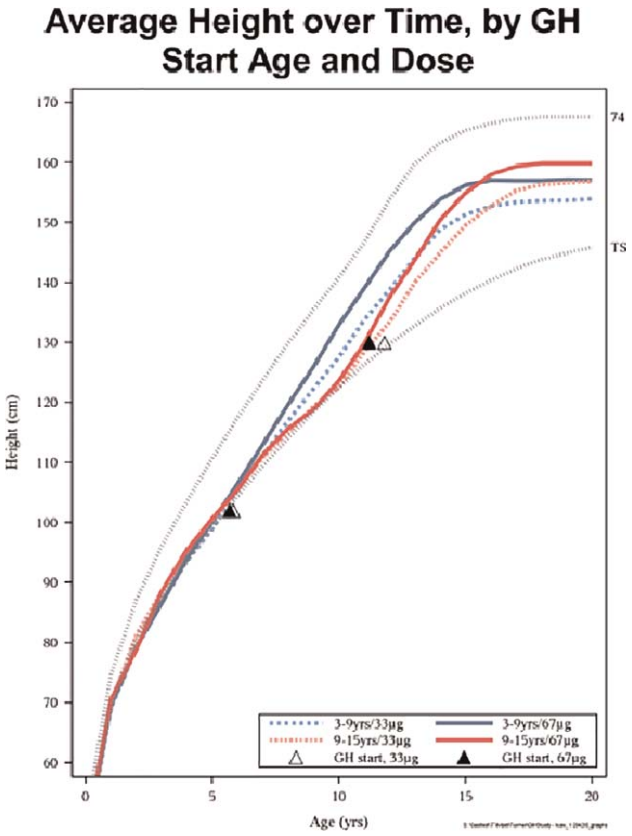

Figure 1 Average Height over Time, by GH Start Age and Dose.

with possible oxandrolone from 11 years and oral/transdermal estradiol. Subjects were followed until AH. **Results:** $Height_{SDS}$ at start was -2.8 (vs non-TS) in all subgroups. Age at onset of puberty (years) and AH (cm) was for $GH_{33young}$ 14.7, 153.7; $GH_{67young}$ 13.0, 157.2; GH_{33old} 15.2, 156.5; GH_{67old} 14.1, 159.9. Oxandrolone was used in 94% of GH_{33} and in 54% of the GH_{67} group. Pubertal growth was 3.3, 7.7, 7.2 and 9.2 cm, respectively. In multivariate analysis the factors GH dose, age and duration of puberty(+) all had high impact on AH. **Conclusion:** Younger age at start with higher GH dose results in increased prepubertal height gain, permitting puberty at normal age (2 years before low dose) and an AH within normal range. The girl diagnosed at higher age can still attain an acceptable age at puberty onset and AH – by using higher GH dose, oxandrolone and slow oestradiol dose increment. Thus it is now possible to optimise the treatment tools GH dose, oxandrolone and estradiol in a personalised approach. **Conflict of interest:** BK has received lecture fee from Sandoz, Pfizer and Novo Nordisk. **Funding information:** Growth hormone was partly provided (higher than standard dose) by Pharmacia/Pfizer.

P1-138

Weight Gain in Turner Syndrome: Association to Puberty Induction?

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Background: We have recently reported a BMI-SDS increase in girls with Turner syndrome (TS) treated with growth hormone (GH) (1). **Objective and hypothesis:** We hypothesise that puberty induction in TS is associated with weight gain. **Method:** We analysed the weight changes (BMI-SDS) of 888 girls with TS in the Pfizer International Growth Database (KIGS). Overweight was defined by a BMI >90th percentile and obesity by a BMI >97th percentile. For univariate statistical comparisons, Wilcoxon rank sum test was used. For proportions, χ^2 or Fisher Exact test was used for comparisons. **Results:** Puberty was induced in 618 (70%) girls. The changes of weight status over time are shown in the Table. BMI-SDS did not change between onset of GH treatment and 1yr later, but increased afterwards (+0.2 until onset of puberty, $P<0.05$; +0.2 between onset of puberty and 2 years later, $P<0.05$). Girls with spontaneous (S) and induced (I) puberty showed similar BMI-SDS changes (increase until start of puberty (S:+0.2;I:+0.2,$P=0.61$)) and in first 2 years of puberty (S:+0.1;I:+0.2, $P=0.11$)). BMI-SDS changes did not differ between early (E:<12 years, $n=89$) and late (L:>12 years; $n=529$) induced puberty (increase until onset of puberty (E:+0.2,L:+0.1, $P=0.57$) and in first 2 years of puberty (E:+0.2;L:+0.2, $P=0.80$)). **Conclusion:** Nearly half of BMI-SDS increase was recorded before puberty onset and weight changes did not differ between girls with induced and spontaneous puberty. These findings do not support the hypothesis that administered estrogens had a significant impact on weight gain in TS girls. **Conflict of interest:** Anders Lindberg, Jose Cara and Cecilia Camacho are employees of Pfizer Inc. Thomas Reinehr and Dionisis Chrysis act as members of KIGS Steering Committee. **Funding information:** This work was funded by Pfizer Inc. New York USA.

P1-139

A Study of Arterial Stiffness in Turner Syndrome Patients Using Cardio-Ankle Vascular Index

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Background: A large proportion of the increased mortality in Turner syndrome (TS) is related to cardiovascular complications. Increased arterial stiffness may be an important predictor related to cardiovascular complications. A novel method of evaluating arterial stiffness, relatively independent of changes in blood pressure (BP), is the cardio-ankle vascular index (CAVI). **Objective and hypotheses:** The aim of this study was to compare arterial stiffness using CAVI between TS patients and healthy controls and to evaluate for possible factors affecting arterial stiffness within the patient group. **Method:** Known TS patients ($n=24$) with confirmed karyotypes were recruited and patients with type 2 diabetes or hypertension requiring medication were excluded. Anthropometric data, fasting blood lab and measurements of CAVI and pulse wave velocity were collected. A healthy control group ($n=23$) matched for age and BMI were recruited for comparison. **Results:** The mean age and BMI of the TS patients were 27.0 years and 22.8 kg/m^2 respectively while that of the control were 28.2 years and 22.04 kg/m^2. CAVI was

Table 1. (for abstract P1-138)

Variable	Baseline (GH start)	1 year on GH	Puberty onset	Puberty at 2 years
Age (years)	9.1 (4.9–12.7)	10.1 (5.9–13.7)	13.0 (11.0–15.0)	15.0 (13.0–17.0)
BMI-SDS	0.1 (−1.2–1.6)	0.1 (−1.1–1.4)	0.4 (−0.9–1.8)	0.6 (−0.7–2.0)
Overweight	13.9%	11.8%	17.3%	20.4%
Obese	3.4%	3.2%	4.1%	5.3%

Data as percentage or median (10/90 percentile).

significantly higher in the TS patients compared to controls (6.05 vs 6.65, $P < 0.001$), while there was no significant difference in pulse wave velocity. Univariate analysis for factors affecting CAVI within the TS patient group showed that CAVI was associated with waist circumference ($P=0.04$) and systolic BP ($P=0.045$). There were no significant factors related to CAVI using multivariate regression analysis including age, systolic BP, waist circumference, HOMA-IR and presence of cardiac anomalies. **Conclusion:** TS patients showed an increased arterial stiffness compared to age- and BMI-matched controls using CAVI measurement. Further prospective studies in larger TS patient group are mandatory in order to find significant factors related to increased arterial stiffness.

P1-140

Impaired Motor Function in Turner Syndrome: What is the Relationship to Performal Intelligence Scores?

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Background: Although motor performance is often impaired in patients with Turner syndrome, the exact prevalence of motor problems is unknown. Detailed studies on specific motor profiles are lacking and the exact relationship between performal IQ and motor function is unknown. **Aims and objectives:** 1. To describe motor performance in our population of children and adolescents with Turner syndrome including the differentiation in specific motor skill domains. 2. To identify the relationship between motor performance and performal intelligence scores. **Methods:** Participants were enrolled at the Radboudumc Turner Centre of Expertise, Nijmegen, the Netherlands. For the evaluation of motor performance, the Movement Assessment Battery for Children-2 (MABC-2) was used. The MABC-2 includes a total score and 3 domain scores on 1) Manual Dexterity, 2) Ball Skills and 3) Static and Dynamic Balance. The WPSSI-III (for children) and the WISC-III (for adolescents) was used to measure total IQ (tIQ), verbal IQ (vIQ) and performal IQ (pIQ). **Results:** More than half (53.1%) of the 65 participants (age 11.8±4.3 SD years) scored below the 15th percentile for total motor performance. Patients showed slightly better results on Manual Dexterity compared with Balls Skills and Static and Dynamic balance (respectively 32.2% vs 57%% and 42.9% of the patients had a score below the 15th percentile; $P<0.001$). There was no significant correlation between motor performance and tIQ, vIQ or pIQ. **Conclusions:** Remarkably impaired motor performance is present in more than half of the girls with Turner syndrome. Patients showed slightly better test results on Manual Dexterity and had more difficulties with time related tasks. We found no correlation between motor function tests and pIQ which confirms earlier studies of our group.

P1-141

Adult Height after Growth Hormone Treatment and its Association with X Chromosome Dosage in Turner Syndrome: a Cross-Sectional Database Analysis of the French National Rare Disease Network

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Background: In Turner syndrome (TS), Shox haploinsufficiency accounts largely, but not entirely, for the short stature of patients, which has been estimated at a mean loss of 20 cm with respect to target height. GH treatment has been shown to improve adult height (AH), although individual outcomes vary markedly. Little is known about the relationship between the dosage effects of the X-linked gene and responsiveness to GH. **Objective:** To determine whether AH deficit with respect to target height (TH) after GH treatment is associated with karyotype subgroup. **Method:** TH minus AH (SDS) was analyzed, by karyotype, after a median of 5.8 (3.6;8.5) years of GH treatment at a median dose of 50 µg/kg/day, in a national cohort of 465 patients with TS, with all karyotype groups treated similarly. **Results:** Height before

Table 1. (for abstract P1-141)

	XrX $n=48$	IsoXq $n=110$	45,X $n=224$	45,X/46,XX $n=47$	Presence of Y $n=36$
Age at adult evaluation (y)	18.7 (16.5;22.9)	19.4 (18.3;21.8)	19.3 (18.0;21.9)	20.1 (18.3;22.8)	20.1 (18.4;24.1)
Height SDS before GH*	−3.13 (−3.90;−2.59)	−3.18 (−3.82;−2.59)	−2.89 (−3.65;−2.13)	−2.60 (−3.23;−2.01)	−2.81 (−3.26;−2.13)
Adult height SDS	−2.21 (−2.95;−1.66)	−2.28 (−3.05;−1.38)	−2.09 (−2.95;−1.34)	−2.05 (−2.77;−1.00)	−1.60 (−2.34;−1.03)
Δ TH minus AH SDS**	2.20 (1.21;2.59)	2.02 (1.41;3.04)	1.84 (1.07;2.55)	1.52 (0.95;2.07)	1.13 (0.68;2.10)

median (Q1; Q3); *$p=0.0001$; **$p=0.02$ adjusted for the duration and dose of GH treatment.

treatment and AH deficit with respect to TH SDS after GH treatment were associated with karyotype subgroup. Patients with structural abnormalities of the X chromosome (isoXq and ring X formation) or monosomy X were more severely affected than patients with mosaicism or with a Y chromosome. **Conclusion:** These data suggest that haploinsufficiency for unknown Xp genes increases the risk of a larger AH deficit with respect to TH both before and after GH treatment in TS.

P1-142

Fracture Incidence is Not Associated with the Six-Year Development of Trabecular BMD in Paediatric Turner Syndrome Patients

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Background: Increased fracture risk and decreased bone mineral density (BMD) have been demonstrated by several studies in Turner syndrome (TS). However, longitudinal data on BMD development in childhood and adolescence and a reliable densitometric predictor of fractures in TS are still lacking. **Objective and hypotheses:** Our aim was to longitudinally assess BMD in paediatric TS patients and test whether trabecular BMD development over six years of observation can predict fracture incidence in these patients. **Method:** Peripheral quantitative CT (pQCT) scans of the forearm were performed in 33 girls with TS (median age 12.1 year, range 6.0–16.4 year) every second year over a period of six years. Trabecular volumetric BMD (vBMD) and cortical thickness were assessed at the 4 and 65% site, respectively. Z-scores were calculated based on published references. Participants' fracture history was acquired through an interview. **Results:** Three girls sustained fracture during the follow up. Mean six-year decrease in trabecular vBMD Z-score was 1.0 ± 1.2 ($P < 0.001$). Girls with incident fractures didn't have larger six-year decrease in trabecular vBMD Z-score when compared to girls without a fracture (-0.35 ± 0.37 and -1.09 ± 1.20; $P = 0.051$). Cortical thickness Z-score remained the same over the six-year period (-0.31 ± 0.94, $P = 0.09$) and this didn't differ between girls with and without an incident fracture (-0.30 ± 0.52 and -0.31 ± 1.08; $P = 0.97$). **Conclusion:** Our study demonstrates that trabecular vBMD decreases with age in paediatric patients with TS, an effect possibly related to the hypergonadotropic hypogonadism, while cortical thickness seems to be stable over the childhood and adolescence. None of the two pQCT-derived parameters proved to be useful in the incident fracture prediction over the six-year observation duration. **Funding information:** This work was supported by the Project for Conceptual Development of Research Organisation 00064203 (University Hospital Motol, Prague, Czech Republic), sponsored by Ministry of Health, Czech Republic.

P1-143

Is Aortic Stiffness Increased in Young Turner Syndrome Patients?

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Background: Bicuspid aortic valve and aortic dilation are common in Turner Syndrome (TS). Aortic dissection is a well recognised cause of cardiovascular death, with an estimated incidence of 1.4 per 100 patients with TS. The biophysical properties of the aorta, including pulse wave velocity (PWV), characteristic impedance (Zc), input impedance (Zi), elastic pressure-strain modulus (Ep), and beta index (β-index), have not been well studied in TS. PWV is considered the most sensitive measure of aortic stiffness. **Objective and hypotheses:** The purpose of this study was to measure aortic stiffness and aortic dilation in TS. Our hypothesis was that aortic stiffness would be increased in TS patients compared to healthy control subjects (C). **Method:** TS patients were recruited from the Endocrinology Clinic at British Columbia Children's Hospital. C were recruited from family and friends of staff at the Hospital. An echo Doppler method was used to measure the aortic dimensions, PWV, Zc, Zi, Ep and β-index. Values were compared to C. **Results:** There were 14 TS patients and 28 C. Median ages, weights and body surface areas were similar; TS patients were shorter (150 vs. 161 cm, $P = .009$). Blood pressure and aortic dimensions were similar. PWV (451 vs. 372, $P < .001$) and Zc (259 vs 204, $P = 0.002$) were increased for TS. Zi. Ep and β-index were similar. **Conclusion:** This study shows that young patients with TS have stiffer aortas than C. This occurred without resting hypertension or aortic dilation. Further studies are needed to determine the aetiology of this stiffening and if this is the underlying cause of aortic dilation and dissection in TS. **Funding information:** Rare Disease Foundation, Vancouver, Canada (project number KRZ38144) Department of Pediatrics, University of British Columbia, Vancouver, Canada (grant number N/A).

P1-144

Primary Adrenal Insufficiency in Children without Congenital Adrenal Hyperplasia: Molecular and Clinical Characterisation of a Nationwide Cohort

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Background: Primary adrenal insufficiency (PAI) is a potentially life-threatening condition that requires accurate diagnosis and urgent treatment. Congenital adrenal hyperplasia is the most common cause of PAI in children. Non-CAH causes of PAI are relatively rare. Although several molecular causes have been found, it is emerging that considerable overlap in the clinical and biochemical features of these conditions exists. **Objective and hypotheses:** We investigated the clinical and molecular characteristics of a national cohort of 96 children (45 females, aged between 0–18 years, eight familial) with non-CAH PAI of unknown aetiology recruited from 22 paediatric endocrinology clinics in Turkey. **Method:** A structured questionnaire was used to evaluate clinical, biochemical and imaging data. A custom Haloplex panel-based next generation sequencing approach was used to study all known PAI-associated genes. Patients with clinical or biochemical findings suggestive of CAH, adrenoleukodystrophy, autoimmune adrenal insufficiency or known syndromic causes of PAI (e.g., Triple A syndrome) were excluded. **Results:** A molecular genetic diagnosis was obtained in 78 (81%) patients. The range of genetic aetiologies found in this cohort was:*MC2R* ($n=25$), *NR0B1* ($n=12$), *StAR* ($n=11$), *CYP11A1* ($n=9$), *MRAP* ($n=9$), *NNT* ($n=7$), *ABCD1* ($n=2$), *NR5A1* (1), *AAAS* ($n=1$), *HSD3B2* ($n=1$).Of note, recurrent mutations in several genes were detected, such as c.560delT and p.C251W mutations in *MC2R*, the p.R451W mutation in *CYP11A1*, *MRAP* c.IVS3ds+1delG, and *StAR* p.S13P. The incidence of childhood non-CAH PAI was approximately five in 1.000.000, with geographical enrichment of certain mutations due to founder effects. Several novel clinical and molecular insights emerged. **Conclusion:** This is the largest cohort study of PAI in children to date. Establishing a specific diagnosis of PAI is extremely valuable for counselling family members and for identifying presymptomatic children.Knowing the genetic aetiology can also help modify treatments, such as the need for long-term mineralocorticoid replacement, and can predict potential co-morbidities, such as impaired puberty or fertility and neurological dysfunction. **Funding information:** J.C.A. is a Wellcome Trust Senior Research Fellow in Clinical Science (098513) and T.G is a European Community, Marie-Curie research fellow (PIEF-GA-2012-328959). This study is also supported with Turkish Pediatric Endocrinology Research Grant.

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Clinical Follow-up of the First SF-1 Deficient Female Patient

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Background: Steroidogenic factor 1 (SF-1/NR5A1) plays a crucial role in regulating adrenal development, gonad determination and differentiation, and in the hypothalamic-pituitary control of reproduction and metabolism. In men (46, XY) mutations in SF-1/NR5A1 gene cause a wide phenotypic spectrum that ranges from complete testicular dysgenesis with Müllerian structures and amenorrhea, through individuals with mild clitoromegaly or genital ambiguity, to severe penoscrotal hypospadias or even anorchia and oligospemia. In recent years the role of SF-1 in the ovarian function was controversially discussed, some reports suggesting a relationship of mutation in SF-1 with primary ovarian insufficiency. **Case presentation:** We report the follow-up of the first case of a SF-1 deficient 46, XX girl in whom adrenal insufficiency was the only clinical sign of the loss-of-function mutation (AJHG 2000, 67:1563). During infancy ovarian development and function seemed normal on the base of normal ovarian morphology at US and repeatedly normal gonadotropins and ovarian markers. To date, this young woman aged 16.5 years shows normal growth, normal BMI and psychomotor development, has a normal puberty and regular menstruation. The current treatment of her adrenal insufficiency consists of hydrocortisone (17.4mg/m^2 per day) and fludrocortisone (0.05mg/day). **Conclusion:** This report shows one, to date uniquely described phenotypic variant of SF-1 mutation in a 46, XX affected person with adrenocortical insufficiency but no ovarian dysfunction nor disturbance of pubertal development. By following the patient during adolescence and transition to adulthood, this case will help us to follow natural history of SF-1 mutation in 46, XX patient and will shed light on its role in the ovarian function.

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Salt Sensitivity of Blood Pressure at Age 7–8 Years in Preterm Born Children

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Background: Preterm birth is associated with hypertension and increased fat contents in later life. Salt sensitivity (SS) could be a mechanism underlying this relationship. In adults SS has been recognised as a cause of hypertension that is related to low birth weight and obesity. **Objective and hypotheses:** We studied the prevalence of SS in 7–8-year old children born <32 weeks of gestation and/or with a birth weight <1500 g as well as its relation with birth weight, infant growth and body composition. **Method:** Subjects were recruited from a cohort ($n=152$) that participated in a nutritional randomized controlled trial during the first 6 months of life. Birth weight, gestational age and height at 0, 3, 6, 12 and 24 months were available. Of the original cohort, 79 children (40 males) aged 7.9 (IQR 7.6–8.3) years were enrolled. After an overnight fast, anthropometry, venipuncture and dual-energy X-ray absorptiometry (DEXA) were performed. Blood pressure (BP) was measured at baseline and after a 7-day high-salt diet (0.12 g/kg per day salt supplements in addition to regular diet) . SS was defined as delta mean arterial BP $\geqq 5\%$. HOMA-IR was calculated; (glucose (mmol/l)*insulin (mIU/l))/22.5. **Results:** Sixty-three children completed the study and were included in the analyses. The prevalence of SS was 15.9% ($n=10$). SS subjects had lower BMI (13.8 vs 15.5 kg/m^2), fat mass (at ages 0 and 6 months and 7–8 years) and systolic (95.0 vs 105.5 mmHg) and diastolic (51.1 vs 61.7 mmHg) BP at baseline compared with the non-SS subjects (all $P<0.05$). Birth characteristics, height and HOMA-IR were similar in both groups. **Conclusion:** Children with SS had lower fat mass from infancy onwards, lower baseline BP and showed no signs of the metabolic syndrome. Associations between SS and cardiometabolic parameters as found in adults, may only become manifest after fat accretion and increased salt intake later in life.

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A New LC-MS/MS Assay for the Analysis of Sulfated Steroids in Human Serum: Quantification of Cholesterol Sulfate, Pregnenolone Sulfate, 17-Hydroxypregnenolone Sulfate and Androgen Sulfates

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Background: Steroids are found in human blood predominantly as sulfated steroids. Conjugation of steroids increases their solubility in blood, facilitating their physiological regulation and excretion. Chromatographic separation and quantification of an extensive number of sulfated steroids is challenging. For instance, androgen sulfates are structurally related and their signals are very similar in mass spectrometry. **Objective and hypotheses:** Some of the most abundant sulfated steroids are cholesterol sulfate (CS), dehydroepiandrosterone sulfate (DHEAS) and androsterone sulfate (AnS). So far, no assay has been developed for the simultaneous quantification of such compounds present in higher concentrations. **Method:** We developed a novel assay for the quantification of the aforementioned compounds and other eight sulfated steroids in human serum by LC-MS/MS. The method uses 300 µl volume of serum, and the sulfated steroids are analyzed independently from free steroids, which are isolated during the sample preparation too. The method allows for the quantification of CS, DHEAS, AnS, pregnenolone sulfate, 17-hydroxy-pregnenolone sulfate, 16-α-hydroxy-dehydroepiandrosterone sulfate, androstenediol sulfate, epiandrosterone sulfate, testosterone sulfate, epitestosterone sulfate and dihydrotestosterone sulfate. **Results:** The performance of the method has been studied at three different concentration levels for each compound, allowing for the study of a broad range of concentrations. The method is sensitive and the quantification parameters are reliable. The average recovery was 97.6%. Averaged intra and inter-assay accuracies were 8.0 and 6.3%, respectively, and precision was always lower than 20% at all the concentration levels. **Conclusion:** We present a reliable method to quantify sulfated steroids in human serum. The study of serum from patients with steroid sulfatase deficiency has proven the utility of this assay for the diagnosis of this condition by analysing the levels of CS. **Funding:** This work was supported by the Selbsthilfe Ichthyose e. V., the Medical Faculty (OJ111409) of the University of Münster, and by the German Research Foundation (DFG) within DFG Research Group 1369 "Sulfated Steroids in Reproduction" to subproject 7.

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The Analysis of Occurrence the Zinc Transporter Antibodies ZnT8 in Children with Graves' Disease and Hashimoto's Thyroiditis

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Introduction: Recent studies have revealed the presence of zinc and the expression of zinc transporter (ZnT) family members in most endocrine cell types. Moreover it was demonstrated that the ZnT family plays an important role in the synthesis and secretion of many hormones like insulin. We studied the prevalence of ZnT8 Ab in patients with autoimmune thyroid diseases (AITD). **Material and methods:** The study was performed in the group consisting of 20 Graves' disease (GD) patients (mean age, 17.8 ± 1.4 years), 44 Hashimoto's thyroiditis (HT) patients (mean age, 13.8 ± 3.5 years) and 57 controls (mean age, 13.1 ± 3.5 years). Patients were recruited from few endocrine centers.GAD,IA-2,IAA,ZnT8,21-OH and AChR antibody concentrations were evaluated in the sera using RSR kits. **Results:** In our study, ZnT8Ab were found in four patients (20%) with GD while three patients (15%) were positive for GADAb, one patient (5%) was positive for IAA and one patient (5%) was positive for IA-2Ab. Of these, one GD patient was positive for all four diabetes associated antibodies. In the case of HT patients, 4 (9%) were positive for ZnT8Ab, while three patients (7%) were positive for GADAb, 2 (4.5%) were positive for IA-2Ab and 1 (2.3%) was positive for IAAAb. Of these, one HT patient had three diabetes associated antibodies (ZnT8,GAD & IA-2Abs) and one had two diabetes associated antibodies (GADAb and IAA). Out of 57 controls studied, 2 (3.5%) controls were positive for ZnT8 Ab, one (1.8%) was positive for GADAb and none of them was positive for IA-2Ab or IAA. Furthermore, one GD patient (5%) and two HT patients (4.5%) were positive for 21-OHAb only.None of the patients with AITD and controls studied was positive for AChRAb. **Conclusion:** In conclusion, these results suggest that the presence of ZnT8Ab can be associated with other autoimmune diseases other than T1DM in particular Graves' disease and Hashimoto's thyroiditis.

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Recombinant Parathyroid Hormone (1-34) Replacement Treatment of Hypoparathyroidism in the Alfacalcidol-Resistant Patient with Severe Autoimmune Polyendocrinopathy Syndrome Type 1

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Background: Hypoparathyroidism (HPT) is present in 80% of patients with Autoimmune Polyendocrinopathy Syndrome type 1 (APS-1) – rare monogenic complex disease characterized also by adrenal failure, chronic candidiasis and a spectrum of other autoimmune disorders, including enteropathy and malabsorbtion. Active vitamin D and calcium are currently used for HPT treatment to maintain normal serum calcium levels. **Objective and hypotheses:** To describe a severe case of APS-1 with HPT and a role of parathyroid hormone therapy in controlling normal calcium level. **Clinical case:** A 26-year-old female patient with confirmed APS type 1 has been followed up in our department since she was 10. She manifested with chronic candidiasis at 4 years, thereafter she developed other APS-1 components: HPT and adrenal insufficiency at 10 years, malabsorbtion and alopecia areata at 20 years, ovarian failure at 21 years. She was diagnosed with acquired pigmented retinopathy at 26 years. Two heterozygous mutations, R257Xand W78R, were found in *AIRE* gene. Alfacalcidol and calcium therapy was effective to maintain near normal serum calcium levels, however, calcium fluctuations were seen. Severe malabsorbtion was observed since 20 years and has led to clinically significant hypocalcemia. Progressive increasing of alfacalcidol doses up to 20 mcg/day did not normalize calcium level. Gastroscopic study showed an atrophy of the mucosa of the stomach and small intestine. The patient had cholelithiasis and cataracta. Parathyroid Hormone (PTH 1-34) treatment was initiated and normocalcaemia was achieved in two weeks on the dose 40 μg per day (twice a day) without vitamin D and calcium supplementation. Calcium level remained within normal range and was controlled several times a day first three weeks of PTH treatment, once a week for the next three months and once in two weeks during further eighteen months follow-up period. Urinary calcium excretion was measured on PTH therapy at 8 and 12 months and was in normal range (2.8 mmol/day). **Conclusion:** Hypocalcemia in severe APS-1 cases could be difficult to control with vitamin D metabolites. PTH replacement therapy of HPT could be a treatment of choice in case of severe malabsorbtion.

P1-150

Severe Immunodysregulation Phenotypes Including Infancy-Onset Type 1 Diabetes Mellitus in Two Siblings with a Homozygous Mutation in the LPS-Responsive Beige-Like Anchor (LRBA) Gene

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Background: Type 1 diabetes mellitus (T1DM) is caused by autoimmunity against the pancreatic beta-cell. Although a significant number of T1DM patients develop further autoimmune disorders during lifetime, coexisting severe immunodysregulation is rare. **Objective and hypotheses:** Presuming autosomal-recessive inheritance in a complex immunodysregulation disorder including T1DM in two siblings born to consanguineous parents, we performed whole exome sequencing (WES). **Method:** WES. **Results:** Patients 1 and 2 are born to consanguineous Libyan parents. In patient 1, T1DM was diagnosed at age 2 years. From early infancy the girl suffered from recurrent pneumonic infections, merging into severe chronic restrictive lung disease, resembling lymphocytic interstitial pneumonia. FACS analysis revealed B-cell deficiency, going along with decreased IgG levels. $CD4^+/CD25^+$ and $CD25^{high}/FoxP3^+$ cells were diminished, while an unusual $CD25^-/FoxP3^+$

population was detectable. In addition, she presented with short stature (<-4 SDS), GH-deficiency and mild symptoms of enteropathy. Her younger brother (patient 2) also suffers from infancy-onset T1DM. He has no history of respiratory problems but chronic diarrhea since infancy, leading to severe electrolyte disturbance and growth failure. Another sibling, who was diagnosed to have T-cell deficiency and Evans-syndrome, died before the family immigrated to Europe. By WES and filtering for autosomal-recessive disease-genes, we identified a homozygous truncating mutation (c.2445_2447del(C)3ins(C)2, p.P816Lfs*4) in the *LPS-responsive beige-like anchor* (*LRBA*)-gene in both patients. *LRBA*-mutations have previously been reported to cause autoimmunity and immunodysfunction presumably due to alteration of T*reg* cell function and, very recently, have been identified in two patients with IPEX-like syndromes. **Conclusion:** We identified a homozygous truncating *LRBA*-mutation in two siblings with T1DM and severe immunodysregulation disease. In light of the variable phenotypes reported so far in *LRBA*-mutant individuals, LRBA-deficiency should be considered in all patients presenting with T1DM and signs of severe immunodysregulation linked to altered Treg-cell function.

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A Case of Autoimmune Polyglandular Syndrome Type I Presenting as Progressive Generalised Lipodystrophy in a 15-month-old Child

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Background: Autoimmune polyglandular syndrome type 1 (APS1) is a monogenic autoimmune disease caused by defects in autoimmune regulator gene (AIRE). The classic clinical triad is composed of Addison disease, hypoparathyroidism, and chronic mucocutaneous candidiasis, however other endocrine and non-endocrine features of APS1 may occur. **Objective:** To describe an unusual clinical manifestation of APS1. **Methods:** Congenital lipodystrophy candidate genes (*ZMPSTE24, LMNA, BSCL2, PLIN1, PTRF, LMNB2, POLD1, AKT2, CIDEC, PIK3CA, PPARG, PSMB8, CAV1, PPP1R3A, AGPAT2)* were sequenced using a custom Ion Ampliseq panel and PGM semiconductor sequencer (Ion Torrent). p.R257X mutation in *AIRE* gene was analysed by real-time PCR. **Results:** A boy presented at the age of 15 months with progressive weight loss and subcutaneous fat disappearance, most evident on the limbs. Sequencing of congenital lipodystrophy candidate genes showed no mutations. During his fourth year of life autoimmune hepatitis (with rapid progression to hepatic cirrhosis Child-Pugh class C) and oral candidiasis were diagnosed consequently. Immunosuppressive therapy with prednisone normalised liver function, and the dose was reduced to 10 mg per day. At the age of 4.5 years the patient presented with symptoms of adrenal crisis, his renin was >500 mcIU/ml, ACTH >300 pg/ml. APS1 was suspected, which was confirmed by detecting a homozygous p.R257X mutation in *AIRE* gene. **Conclusion:** Acquired generalised lipodystrophy is known to be associated with autoimmune disorders. To our knowledge, however, this is the first time when generalised lipodystrophy is described as initial manifestation of APS1. **Funding:** This work was supported by Alfa-Endo Program of Charities Aid Foundation (CAF) Russia.

P1-152

Noonan Syndrome-Causing SHP2 Mutants Inhibit Murine Growth Plate Chondrogenesis and Bone Development: Role of Ras/MAPK Hyperactivation

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Background: Growth retardation affects more than 80% of patients with Noonan syndrome (NS; MIM#163950), one of the most common developmental disorders, but its origin remains poorly understood. We have demonstrated that mutations of the tyrosine phosphatase SHP2, that are responsible for half the cases of NS, impair the systemic production of Insulin-like growth factor 1 (IGF1), the biological mediator of GH acting on growth plate, through a hyperactivation of the Ras/Mitogen-Activated Protein Kinase (MAPK) signalling pathway. This is in accordance with clinical data suggesting partial GH insensitivity in NS patients. However, the direct impact of NS-causing mutations on growth plate and bone has never been explored. **Objectives:** To evaluate the impact of NS-causing mutations on growth plate and bone development and to determinate the contribution of GH insensitivity. **Methods:** *In vivo* and *in vitro* analyses were performed in a mouse model of NS (SHP2 D61G/+ mice) and in chondrogenic ATDC5 cells expressing NS-causing SHP2 mutants respectively. **Results:** Compared with their WT littermates, male SHP2 D61G/+ mice exhibited homogeneous postnatal growth retardation and alteration of trabecular bone of femur and vertebra. At the growth plate level, the length of the hypertrophic zone was decreased in SHP2 D61G/+ mice, whereas the length of the proliferating zone was unaffected. Proliferation and apoptosis were similar in WT and SHP2 D61G/+ mice. Expression of NS-associated SHP2 mutants results in ERK1/2 hyperactivation in chondrocytes *in vitro* and *in vivo*. Chronic inhibition of ERK1/2 activation in young mice alleviates growth plate abnormalities, which is associated with significant growth improvement in NS mice. Interestingly, IGF1 treatment of SHP2 D61G/+ mice increased the length of the proliferating zone

without modifying hypertrophic zone abnormalities. **Conclusion:** In conclusion, NS-causing SHP2 mutants inhibit chondrocyte differentiation through Ras/MAPK hyperactivation, a mechanism that could contribute to growth retardation. This also provides interesting insights into the development specific therapeutic options targeting the Ras/MAPK pathway to improve growth in NS patients. **Funding:** This work was supported by the 2012 ASPIRE Young Investigator Research Awards in Endocrinology from Pfizer (reference number WS2385803, 2012).

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Growth Curves for Height, Weight, BMI and Head Circumference in Children with Achondroplasia

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Background: Close monitoring of growth is vital when following children with achondroplasia yet existing growth curves suffer from a simple chart format and their clinical use is therefore limited. Also, references for body proportions; i.e. sitting height, relative sitting height and arm span, are lacking. **Objective and hypotheses:** The aim of this study was to construct age-specific growth curves for height, weight, BMI, head circumference and body proportions in children with achondroplasia. **Method:** A combination of longitudinal and cross-sectional measurements were collected from about 550 children and adolescents with achondroplasia aged 0–20 years. Standard deviation curves were estimated using the generalized additive models for location, scale and shape (GAMLSS). **Results:** Retrieved averages for these four variables were similar to the existing growth references by Horton *et al.* and Hoover-Fong *et al.* To better capture growth development during the first 4 years of life, the curves for head circumference, height and weight were combined on the same page by using logarithms for all axes. Similar approaches were used for the design of a separate BMI and a separate head circumference chart, both covering 0–20 years of age. **Conclusion:** Sex- and age-specific curves for height, weight, BMI and head circumference were constructed and designed in a format that makes it easy to follow growth development of the individual. The body proportion references are under construction.

P1-154

Novel Compound Heterozygous BMP1 Variants Associated with Osteogenesis Imperfecta

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Background: Osteogenesis imperfecta (OI) includes a group of disorders with a susceptibility to bone fractures, the presentation ranging from slightly increased fracture frequency to death in the perinatal period. **Objective and hypotheses:** Autosomal-dominant inheritance with type I collagen biosynthesis defects is the most common, but many autosomal-recessive genes have been previously reported. **Method:** Whole-exome sequencing was performed to simultaneously examine multiple genes associated with autosomal-recessive OI in a Korean patient with umbilical hernia, frequent fractures, scoliosis, markedly short stature and dislocation of the radial head. **Results:** Two novel variants in the BMP1 gene: c.808A>G and c.1297G>T were identified. The former variant caused a missense change p.(Met270Val) and the latter caused skipping of exon 10. Functional studies of the two variants demonstrated in a zebrafish assay showed a hypofunctional nature. **Conclusion:** Demonstration of hypofunction of the two novel variants in zebrafish supports the involvement of these variants in causing abnormal bones. These results emphasise the importance of BMP1 as a contributing factor in autosomal-recessive OI.

P1-155

Prospective Cognitive Assessment in Children with Craniopharyngioma Identifies Dysfunction at Diagnosis, After Conservative Surgery and Before Adjuvant Radiation

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Background: It has been previously reported that with current management, 9/10 children with craniopharyngioma will survive 10 years. Though most suffer both chronic neuroendocrine and cognitive impairments from disease and/or treatment, few prospective cognitive assessments have been reported which might separate the contributions of each. **Objective and hypotheses:** i) To prospectively evaluate the prevalence of cognitive dysfunction, before and after a conservative surgical and radiation strategy, avoiding hypothalamic morbidity. ii) To determine aetiology, incidence and severity of any deficits. **Method:** 21 children (14 males, seven females) presenting with craniopharyngioma between 09/07/2009 and 25/02/2014, of median age 7.8 (range 1.9–17.18) years underwent Wechsler assessments of IQ (full scale (FSIQ), verbal (VIQ), performance (PIQ) and working memory (WMI) and processing speed index (PSI)), after conservative surgery and before adjuvant proton ($n=7$) or IMRT ($n=7$) radiation to any residual. eight subjects underwent a repeat assessment 1–3 years after radiotherapy. Tumours were graded for hypothalamic involvement (Paris 0–2). There were no baseline demographic, tumour or cognitive differences between those who did and did not undergo reassessment ($P=0.16$). Data are shown as means and 95% CI and analysed using non parametric statistics. **Results:** Baseline IQ data on all parameters was available for only 16/21 patients assessed at 9.40 (2.80–17.50) years of age. At diagnosis, the majority (12/16)

had hypothalamic Grade 2 tumour involvement, but two had Grade 1 involvement and two had none. The overall median score for FSIQ was 105.5 (73–128), no different from age and sex standardised norms, and without any difference between individual domains (VIQ, PIQ, PSI, WMI, $P=0.121$). A significant number of patients, 13/16 (81%) had behavioural problems (limited adaptation, peer interaction and emotional distress) at diagnosis. Eight patients-7 Grade 2 and one Grade 1 assessed 2.05 (0.60–3.30) years later, tended to a decline though still normal FSIQ (105.5 vs 97.0 95 ci; $P=0.48$) not seen in VIQ $P=0.26$), PIQ ($P=0.916$), WMI (0.292) or PSI ($P=0.528$) Behaviour remained unchanged, only one out of eight patients seem to be coping better. **Conclusion:** Children with craniopharyngioma are of average intelligence at diagnosis but experience significant behavioural difficulties, which precede radiotherapy and are not changed by it, possibly due to hypothalamic tumour involvement. The trend to decline, seen after radiotherapy, can be found in FSIQ, but not in VIQ or other parameters, even in the youngest children. Proactive targeted schooling support may prevent significant decline, arguably due as much to behavioural difficulties, failed community reintegration and lost schooling, as to brain injury of multiple aetiology.

P1-156

Cushing Syndrome due to Adrenocortical Carcinoma in a 3-month-old Infant with a Large Interstitial Deletion of Chromosome 5q Including the APC Gene

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Background: Childhood adrenocortical tumours (ACT) are rare and have well been described as part of familial cancer susceptibility syndromes which are caused by single gene mutations including P53, MEN1, PRKAR1A, CTNNB1 and APC. Adenomas are the most common ACT, but adrenocortical carcinomas (ACC) occur as well. Childhood ACC can be part of the Li-Fraumeni Syndrome and Beckwith-Wiedemann syndrome. ACC can also occur in familial adenomatous polyposis coli (FAP). FAP is a colon cancer predisposition syndrome caused by germline inactivation of the adenomatous polyposis coli tumour-suppressor gene (APC) located on the long arm of chromosome 5 (5q21–5q22). The main feature of FAP is polypogenesis beginning in early adulthood, ACC have been reported only in adult patients. **Case report:** We report on a male infant, offspring from non-consanguineous german parents, who presented with clinical signs of Cushing syndrome at the age of 3-months. Additionally the child had unilateral club foot and micropenis. Diagnostic work-up revealed ACTH-independent hypercortisolism due to unilateral adrenocortical tumour. Tumour resection was performed at the age of 4 months, the tumour was classified as adrenocortical carcinoma (T2 N0 M0). Clinical signs of hypercortisolism resolved, but the child's facial features remained dysmorphic. Poor growth in association with micropenis as well as IGF1 and IGF BP3 levels far below the normal range led to further endocrinological evaluation at the age of 10 months. Severe growth hormone neurosecretory dysfunction was diagnosed. Subsequent growth hormone substitution led to catch-up growth, but the child's severely retarded psychomotor development and muscle hypotonia remained unaffected. At the age of 12 months comparative genomic hybridization identified a large interstitial deletion of chromosome 5q expanding over a 19.4-Mb region (5q21.3–5q23.3) including the APC gene. Other genes within the deleted region may be responsible for psychomotor retardation und muscle hypotonia. **Conclusion:** ACT caused by deletion of the ACC gene may occur even in childhood and infancy. Chromosomal deletions including known cancer susceptibility genes should be suspected in children with ACT and unexplained additional features.

P1-157

How do Adolescent Minors Banking Sperm Before Cancer Therapy Subsequently use the Fertility Service? A Post Banking Re-Evaluation

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Background: Gonadotoxic cancer therapy may cause adult male infertility. We previously reported that, of 2/3rds of underage males agreeing to pre-treatment sperm cryopreservation before cancer treatment, 2/3rds succeeded. **Objective and hypotheses:** i) To evaluate how many patients banking sperm successfully (GP1) returned for post treatment re-evaluation compared with those who attempted but failed (GP2). ii) To compare intergroup survival and fertility rates by prior gonadotoxicity risk. **Method:** Retrospective collection of post treatment survival, semenalysis (sperm count and volume), biochemical (LH/FSH/testosterone) and clinical (testicular volumes) parameters in 93 patients attempting to bank sperm between 2000 and 2010. 'Infertility' was defined as FSH >15 IU/l, azoospermia or adult testicular volume <10 ml. **Results:** Of 75 GP1 patients aged 15.11 (13.04–22.08) years, 68 banked sperm at cancer diagnosis (GP1A) and seven during 2nd remission (GP1B). 18/75 patients (17 GP1A) died 2.63 (0.98–6.00) years after banking. 27 (24 GP1A) survivors returned 8.02 (3.70–14.00) years later, for fertility ($n=17$), biochemical ($n=16$) and/or clinical ($n=9$) re-evaluation and five are now infertile (all GP1A: three medium, two high gonadotoxicity risk). Fertility is preserved in all returning low risk ($<20\%$) patients ($n=12$) but a significant minority at highest

risk (>80%) died (14/45, 31%). Of 18 patients (GP2) who failed to bank at diagnosis (GP2A, $n=13$) or 2nd remission (GP2B $n=5$), five died after 1.75 (0.05–3.94) years (one medium, four high risk) and six (4 GP2A) all still azoospermic, returned 8.72 (6.60–11.20) years later. There were no intergroup differences in risk, survival or fertility rates. **Conclusion:** Low gonadotoxicity risk patients, at low priority for fertility preservation, were correctly identified before treatment. High risk patients need prioritising but were least likely to survive. GP2 survivors were unlikely to recover fertility up to 11 years later. The low survivor re-evaluation rates suggest improved post treatment endocrine/fertility assessments are required to properly assess the cost-benefit of fertility preservation to underage patients.

P1-158

The Expression of Related Neuroendocrine Factors with Puberty Onset in Rat at Different Developmental Stages

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Introduction: Kisspeptin is well known gatekeeper of puberty onset to date. However, several neuroendocrine factors are also discovered to be associated with puberty onset and, especially neuropeptide Y (NPY) and neurokinin B, participate in the neuronal network integrating reproduction. However, the interactions between neuroendocrine factors and the reproductive axis have not yet been fully explored. We report herein the expression profile of NPY gene and neurokinin B gene in the rat at different developmental stages. **Methods:** Spraque-Dawley (SD) strain female rats were used. To analysis expression of NPY mRNA, samples were obtained from hypothalamus in female rats at 4, 8, 14, 23, 27, 34, 38 and 40 days. At the same time, blood samples were collected for analysis serum level of kisspeptin and luteinizing hormone (LH). The expression of NPY mRNAs and neurokinin B mRNAs were assessed by RT-PCR and the serum levels of kisspeptin and LH were analyzed by ELISA. **Results:** The expression of NPY mRNAs in hypothalamus was high in neonate and infant stages, while abruptly decreased prepubertal and pubertal stages (between day 23 and day 34). However, serum LH level was increased from prepubertal stage, especially day 23 and peak at pubertal stage (at day 38), reversely NPY mRNAs expression. In adult stage, both NPY mRNA expressions in hypothalamus and serum LH level were increased. Meanwhile, the expression of neurokinin B mRNA in hypothalamus was increased according to developmental stages as KiSS-1 gene mRNA expression and serum kisspeptin level and was peaked at adult stages. **Conclusion:** The expressions of NPY mRNA were decreased in hypothalamus at prepubertal and pubertal stages in rat, while serum levels of LH were increased at those developmental stages. Although both NPY mRNA expression and serum LH level were high in adult stage, NPY may inhibit LH release in prepubertal and pubertal stages, and it can be one of the explanations why puberty is delayed in fasting or low BMI conditions. In addition, the expression of neurokinin B mRNA was increased in hypothalamus according to developmental stages, with similar pattern in the expression of KiSS-1 gene mRNA and serum kisspeptin level.

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FOXL2 Gene and Combined Pituitary Hormone Deficiency: A Possible Link

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Background: Congenital hypopituitarism is a rare disease. Although our understanding of the involved transcription factors is improving, mutations in candidate genes are rarely identified. Extra-pituitary symptoms can point towards new genes of interest. FOXL2 is mutated in blepharophimosis/ptosis/epicanthus inversus syndrome (BPES), a rare affection that combines congenital alterations of eyelids with ovarian dysgenesis in some families. Moreover, we have previously reported the association of BPES with combined pituitary hormone deficiency (CPHD) in some rare non-related cases. **Objective and hypotheses:** The main objective was to better define the possible molecular association between anomalies of eyelids, including BPES, but also other oculo-optic anomalies, and CPHD. Patients presenting these specific syndromes were selectively tested not only for FOXL2 mutations, but also for mutations in a series of genes already linked with CPHD. **Method:** Our cohort consisted of 22 patients with CPHD and various ocular anomalies (of the eyelid, eyeball, and/or optic nerve), and presented various anomalies of pituitary gland documented by RMI. FOXL2 was screened in the patients with eyelid anomalies including BPES. HESX1 and OTX2 were screened for all patients. GH1, GHRHR, POU1F1, PROP1, LHX3, LHX4, PITX2, SOX3, PROKR2, GLI2, and/or ARNT2 were selected for screening by the GENHYPOPIT network based on clinical and radiological signs. **Results:** A FOXL2 mutation was identified only in the two BPES patients among nine patients with eyelid anomalies. In addition, OTX2 was mutated in one patient presenting with septo-optic dysplasia and microphtalmia. **Conclusion:** This study indicates a possible role of FOXL2 in hypothalamus and pituitary development. FOXL2 mutation is indeed the most frequent molecular anomaly within our cohort of patients with hypopituitarism and ocular anomalies. Further studies are necessary to determine if FOXL2 should be sequenced in CPHD patients presenting eyelid anomalies distinct from those observed in BPES.

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Septo-Optic Dysplasia Associated with Koolen-de Vries Syndrome: A Case Report

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Background: Septo-optic dysplasia (SOD) is a rare congenital anomaly, clinically heterogeneous, combining optic nerve and pituitary gland hypoplasia, midline abnormalities of the brain, including absence of the corpus callosum and septum pellucidum. The diagnosis is made when two or more features of the classic triad are present. HESX1, SOX2, SOX3, FGF8, FGFR1, PROKR1, SHH, are implicated in the etiology of SOD. **Objective and hypotheses:** Description of a patient with SOD, negative in the *HESX1*, *SOX2*, *SOX3* mutational screening. **Method:** Case report, direct sequencing of *HESX1*, *SOX2*, *SOX3*, *aCGH array*. **Results:** Girl, born after 1st uneventful pregnancy, SGA, with jaundice, hypotonia, feeding difficulties as neonate; mild developmental delay during infancy. Referred because of short stature (SDS_h–2.46) at 9.8 years. Diagnosed additionally with: optic nerves and macula hypoplasia, nystagmus, strabismus, absent septum pellucidum, hydrocephalus, anterior pituitary hypoplasia (MRI), growth hormone deficiency (GH peak 1.5 mU/ml after Arg-HCL); start of rhGH and development of central hypothyroidism thereafter, treated by L-T4. A 599 kb deletion 17(q21.31)(44188501-44787179)x1(hg19), containing the pseudogene LOC644246 and the gene KANSL1, known to cause Koolen-de Vries syndrome (KDVS) were found. mental retardation (MR), facial dysmorphism, hypotonia, developmental delay, SGA, short stature, brain and refraction anomalies, strabismus, and hypopituitarism due to PSIS (only one reported case) are described. A 551 kb duplication X(p11.3p11.3)(45838699-46389900)x3(hg19) was also found, including ZNF673, ZNF674 genes. Duplications/deletions are known to cause MR, retinal dystrophy and short stature. **Conclusion:** This is the first case of KDVS without MR and only the second case with hypopituitarism. Analogous to the x-linked SOX3, duplication/deletions in ZNF673 and ZNF674 could result in short stature without MR and may be implicated in the etiology of hypopituitarism. The patient's phenotype is probably a result of combination between the two aberrations. **Funding:** Supported by the Medical University Sofia, Grant 'Mlad issledovatel' Nr 41-D, contract 30-D.

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Screening of *IGSF1* in Patients with Central Hypothyroidism and GH Deficiency, Participating in the Dutch HYPOPIT Study

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Background: The Dutch HYPOthalamic and PITuitary gene (HYPOPIT) study investigates the genetic and non-genetic causes of isolated growth hormone deficiency (IGHD) and combined pituitary hormone deficiency (CPHD). Former projects within the HYPOPIT study showed that only a small minority of the Dutch IGHD and CPHD cases could be explained by mutations in *GH1, GHRHR, HMGA2* and *CDK6* in IGHD patients and *PROP1*, *HESX1*, *POU1F1*, *LHX3*, *LHX4*, *OTX2*, *SHH* and *HHIP* in CPHD patients. **Aims and objectives:** In the current project, we chose to study immunoglobulin superfamily gene 1 (*IGSF1,* highly expressed in pituitary and testis) as a new candidate gene. Mutations in *IGSF1* have recently been associated with central hypothyroidism. Initially, *IGSF1*-related central hypothyroidism was only described in combination with macro-orchidism. Later on, *IGSF1* mutations were also reported in patients with central hypothyroidism without macro-orchidism, with or without additional pituitary hormone deficiencies. Therefore, we chose to study *IGSF1* as a new candidate gene for patients with the rare combination of central hypothyroidism and growth hormone deficiency. **Methods:** We screened 80 males and 14 females patients with the combination of central hypothyroidism and GH deficiency for genetic defects in exons 10–17, encoding the extracellular region of *IGSF1.* **Results:** A total of six SNPs, one known mutation and one known deletion were identified in the extracellular regions of *IGSF1*. We will present the genotypic and phenotypic data of the patients with variants in *IGSF1*. **Conclusion:** Central hypothyroidism combined with growth hormone deficiency is explained by *IGSF1* defects in a small minority of the patients.

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Congenital Hypothyroidism: Reduction in the Female to Male Ratio Following the Decrease of the TSH Cut-off Point Used for Neonatal Screening

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Background: Since the initiation of neonatal screening-programs for congenital hypothyroidism (CH) in the 1970's, an increase in the incidence of CH has been observed. This change has been attributed to the gradual use of lower TSH cut-offs that lead to the detection of milder cases of CH. Based on currently used screening cut-offs, CH occurs in approximately 1:2 000 to

1:4 000 newborns, varying by geographic location and ethnicity. A female predominance, approaching a 2:1 female to male ratio, has been consistently reported. **Objective and hypotheses:** To assess whether the gradual decrease in the TSH cut-off limits has affected the female to male ratio in neonates with CH. **Method:** The yearly records from 1980 to 2014 of the Greek National Neonatal CH screening program were thoroughly reviewed. For each year, the TSH cut-off point was noted and the percentage of female neonates diagnosed with CH was calculated. **Results:** The National Greek Neonatal CH screening program was initiated in 1980. Over the following 35 years, more than 3 690 000 neonates were screened. The TSH cut-off point was gradually lowered from 30 mIU/ml in 1980 to 6 mIU/ml in 2006 and moved back to 8 mIU/ml as of 2012. The proportion of female neonates diagnosed with CH was 78% in 1980 but showed a progressive decrease to lower than 50% in the last decade. In fact, the use of a 6–8 mIU/ml TSH cut-off point led to marginal male predominance. **Conclusion:** Change of the TSH cut-off point used in the CH screening program alters the female to male ratio. Specifically, lowering the TSH limit results in a decrease of female percentage among neonates with CH. When a 6–8 mIU/ml TSH cut-off point is applied, an inversion of the female to male ratio is observed and male preponderance is noted.

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Paediatric Thyroid Nodule Score: Derivation and Validation of a Predictive Score for Thyroid Nodule Assessment in Children

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Background: Differentiated thyroid carcinoma has an incidence of 15.2 per 100 000 in adolescents. The clinical challenge is identifying nodules requiring further intervention. Current modalities, in isolation, have poor ability to reliably differentiate benign from malignant nodules. **Objective and hypotheses:** To derive and validate a predictive score that integrates clinical, laboratory, radiological and cytopathological parameters to define malignancy risk of a pediatric thyroid nodule. **Method:** With research ethics approval, a retrospective analysis of patients <18 years with histopathologically confirmed diagnoses of papillary/follicular thyroid carcinoma (88 patients) and benign thyroid nodular disease (37 patients) between 1987 and 2014 was performed at tertiary care institution A. Relevant clinical, laboratory, ultrasound and cytopathological variables were retrieved from hospital records. Bivariate analyses identified variables ($P<0.2$) that will undergo logistic regression to derive a predictive score. Variance inflation factors will be consulted for multicolinearity. Construct and predictive validity and reliability will be independently confirmed in a second cohort from institution B. **Results:** Patients with malignant and benign nodules had similar ages at presentation (12.8 ± 2.8 vs 11.7 ± 3.5 years) and female patients predominated (70%) in both groups. Variables identified to undergo logistic regression analysis for possible incorporation in the score: i) *clinical*: palpable thyroid nodule ($P=0.09$); palpable lymph nodes ($P=0.02$); ii) *laboratory*: TSH level ($P<0.01$); iii) *ultrasound*: nodule size ($P=0.02$), calcifications ($P<0.01$), focality ($P=0.14$), echogenicity ($P=0.13$), margins ($P=0.12$), $>50\%$ cystic ($P<0.01$), lymphadenopathy ($P<0.01$); iv) *cytopathology* ($P<0.01$). **Conclusion:** We hope to derive a clinical tool to predict the likelihood of malignancy of a thyroid nodule based on integration of clinical, biochemical, radiological and cytopathological features. This tool has the potential to improve diagnostic accuracy. **Funding:** This work is supported by a $3 500 microgrant from the Rare Disease Foundation and the BC Children's Hospital Foundation (no grant number has been assigned).

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Practical Application of Elastography in the Diagnosis of Thyroid Nodules in Children

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Background: Elastography is non-invasive ultrasound method of imaging based on estimation of mechanical properties (elasticity) of the tissue. Recent data has shown its ability to differentiate benign from malignant tumours. Decreased flexibility in comparison to around tissue is characteristic for malignant tissues, like most thyroid carcinoma (except follicular thyroid carcinoma). Analysis of the image gives the result presented as a ROI1/ROI2 index. **Objective and hypotheses:** The purpose of our study was to assess the deformation of the thyroid nodules during elastography in comparision to the results of fine needle aspiration cytology of the nodule. **Method:** We examined 47 children between February 2013 and February 2015 with nodular goiter. All patients underwent elastography and fine needle aspiration cytology (FNAC). Both data were compared in order to determine any correlations. Elastography parameters were acquired with Toshiba Aplio MX SSA-780A system and analysed while comparing of the stiffness of ROI 1 (of the nodule) to ROI 2

(of healthy tissue). **Results:** In the study 39 girls (83%) and 8 boys (17%) were involved. ROI index below two was observed in nine patients (19.2% of the study group). In 27 patients (57.4% of the study group) ROI1/ROI2 was between two and 4.9. ROI index above five was observed in 11 patients (23.4% of the study group). In three patients (6.4% of patients) histopathological examination confirmed thyroid carcinoma. In all of cases it was papillary thyroid carcinoma. ROI index: five and above was present in two patients with thyroid cancer, while one of the patients had ROI index two. **Conclusion:** Our results suggest, that elastography can be complementary to classic ultrasonography and useful while taking decision about fine needle aspiration cytology. At the same time it should not replace histopathological assessment of the nodule in the thyroid.

P1-165

Higher Urinary Iodine Levels Iodine Correlates with Lower Systolic Blood Pressure in Chilean Schoolchildren

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Background: Iodine concentrations in Chilean schoolchildren are the highest in South America. This may be related to excessive sodium intake, which is associated with hypertension. However, iodine decreases blood pressure (BP), which would be a cardiovascular protective factor. **Objective and hypotheses:** The objective of this study is to evaluate the effects of iodine on BP and cardiovascular risk factors, despite salt intake. **Method:** Cross-sectional study. Seventy schoolchildren in Santiago, Chile were recruited (54.3% female, median age 13 (12.1–16.1)). Anthropometry, BP, and pubertal stages were evaluated, and a salt questionnaire was applied; salt intake was *ad libitum*. Samples were obtained of ultra-sensitive C reactive protein (hsCRP), glucose, triglycerides, LDL, creatinine, microalbuminuria, TSH, fT_4, aldosterone and plasma renin activity (ARP). Iodine, creatinine, and sodium were measured in 24-h urinary samples and urinary iodine/urinary sodium ratio was calculated. Pearson correlation was performed for continuous variables; Mann–Whitney test for independent samples. **Results:** Urinary iodine (medium; (interquartile range)) was 298.5 ug/l (168.5–416.8). 65.7% presented iodine levels above requirements. A negative correlation was observed between urinary iodine and age ($r=-0.4$; $P=0.001$), systolic BP ($r=-0.3$; $P=0.01$), even when corrected for sodium excretion ($r=-0.32$; $P=0.01$). No statistically significant correlation was observed between urinary iodine and hsCRP ($P=0.13$), glycemia ($P=0.3$), cholesterol ($P=0.93$), triglycerides ($P=0.76$), LDL ($P=0.34$), TSH ($P=0.98$), aldosterone ($P=0.59$), ARP ($P=0.19$), neither with diastolic BP ($P=0.09$). **Conclusion:** Schoolchildren in Santiago have much higher urinary iodine than recommended by the WHO (adequate iodine nutrition between 100–199 ug/l). It decreases with age. Higher levels of urinary iodine corrected for urinary sodium excretion correlated with lower systolic BP, which could represent a cardiovascular protective factor. **Funding:** This work was supported by Fondecyt 1130427 and 1150437, CORFO 13CTI-21526-P1, IMII P09/016-F (ICM), School of Medicine, Catholic University of Chile 2013 Chilean Grants.

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Late Diagnosis of Adrenal Insufficiency Caused by Novel Compound Heterozygous Mutations in Proopiomelanocortin

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Background: Proopiomelanocortin (POMC) deficiency is characterised clinically by adrenal insufficiency, obesity and red hair. As a rule, such patients present early in life with severe hypoglycemia, which leads to initiation of glucocorticoid therapy. We describe here a case of POMC deficiency, where adrenal insufficiency was not diagnosed until the fourth year of life. **Objective and hypotheses:** To present a case of late diagnosis of POMC deficiency and characterise novel mutations in *POMC* gene. **Method:** *POMC* gene was analysed by Sanger sequencing. **Results:** The boy initially presented with prolonged neonatal jaundice. By the end of his first year the growth acceleration was evident. There were two episodes of severe hypoglycemia (glucose level 1.7 mmol/l) at ages of 1.5 and 3 years. In addition, there were recurrent episodes of cholestasis with bilirubin level 101 mcmol/l, ALAT 276 U/l, ASAT 444 U/l. At presentation at 3.6 years his height was at 4.1 SD, the BMI at 3.0 SD. He had red hair and light skin. Plasma ACTH and serum cortisol were undetectable. Replacement with hydrocortisone was initiated. Sequencing of *POMC* gene revealed two novel heterozygous mutations: p.W84X and c.-11C>A. The latter mutation is predicted to create an alternative initiation codon, which results in a frameshift. **Conclusion:** A case of late diagnosis of POMC deficiency is presented. It is not yet clear whether c.-11C>A mutation is compatible with partial inframe POMC translation, which could explain less severe adrenal insufficiency in infancy. **Funding:** By Alfa-Endo Program of Charities Aid Foundation (CAF) Russia.

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Hyponatraemia Secondary to Exudative Eczema

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Background: Classically adrenal insufficiency presents with hyponatraemia and hyperkalaemia, however the differential may be of alternative origin. Atopic dermatitis is a common inflammatory skin disease of infancy and childhood. In severe cases, the exudation from wet lesions can produce serious complications such as infection + very rarely electrolytes abnormalities as seen in this case. **Case report:** A 6-month-old female infant was referred for endocrine review due to hyponatremia (129 mmol/l) and hyperkalaemia (6.6 mmol/l) with a suspected diagnosis of adrenal insufficiency and possible congenial adrenal hyperplasia (CAH). She was not virilised and blood pressure was normal. She had a background of severe eczema. Initial bloods showed normal glycaemia, no acidosis. Cortisol 183 nmol/l, ACTH 10 ng/l, 17-OH-progesterone 14.5 nmol/l (<6) with a highly elevated aldosterone >2.700 pmol/l and renin levels >500.00 mU/l with normal sodium level urine <10 mmol/l. She also underwent a synacthen test (peak cortisol 1975 nmol/l) and urine steroid profile both of which excluded CAH. Her eczema was infective with widespread exudate and was treated with oral flucloxacillin, topical emollients and steroids. The hyponatraemia was treated with sodium supplementation. The hyponatraemia and abnormal biochemistry completely resolved with improvement of the eczema on repeat testing. **Conclusion:** The cause of this patient's hyponatraemia, hyperkalaemia, hyperaldosteronemia and hyperreninemia were secondary to oozing exudation due to severe atopic dermatitis associated with loss of fluid and electrolytes, which resolved on appropriate dermatological treatment. The raised aldosterone and renin levels associated with hyponatraemia, led to consideration of both CAH and pseudohypoaldosteronism type I (PHAI-I). CAH was excluded as described above and PHA-1 which results from renal tubular unresponsiveness or resistance to the action of aldosterone resulting in elevated Aldosterone and Renin levels and a similar biochemical picture with renal salt losing was excluded due to an appropriately undetectable urinary sodium level; thus type I (PHAI-I) was ruled out.

P2-168

The Natural Mutant Receptor hGRαT556I Causes Primary Generalised Glucocorticoid Resistance Through Decreased Affinity for the Ligand and Impaired Interaction with the GRIP1 Coactivator

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Background: Primary generalised glucocorticoid resistance (PGGR) is a rare condition characterised by tissue insensitivity to glucocorticoids owing to inactivating mutations of the *hGR* gene. A new case of PGGR was reported in a patient with an adrenal incidentaloma harboring a novel heterozygous point mutation in the *hGR* gene, which resulted in threonine (T) to isoleucine (I) substitution at amino acid position 556 of the receptor. **Objective and hypotheses:** To elucidate the molecular mechanisms of action of the hGRαT556I. **Methods and results:** Compared with the wild-type receptor (hGRαWT), the mutant receptor hGRαT556I demonstrated a 50% reduction in its ability to transactivate the glucocorticoid-inducible MMTV promoter in response to dexamethasone, and did not exert a dominant negative effect upon the hGRαWT. Transrepression assays showed that the hGRαT556I displayed enhanced ability to transrepress the nuclear factor (NF)-κB signaling pathway. Dexamethasone-binding assays demonstrated that the affinity of the hGRαT556I for the ligand was 50% lower than that of the hGRαWT (Kd: 21.3 ± 4.09 nM vs 10.8 ± 0.99 nM, $P<0.05$). *In vitro* binding assays revealed no significant difference in the association of hGRαT556I with the glucocorticoid-response elements (GREs) following exposure to dexamethasone. In subcellular localization and nuclear translocation studies, both the hGRαWT and the hGRαT556I were predominantly localized in the cytoplasm of cells in the absence of ligand. Addition of dexamethasone resulted in slower nuclear translocation of the hGRαT556I compared with the hGRαWT (53.3 ± 1.8 min vs 15.5 ± 0.46 min, $P<0.05$). GST pull-down assays showed that the hGRαT556I interacted with the GRIP1 coactivator mostly through its AF-1 domain. Structural biology studies demonstrated that the T556I mutation affected mildly the local 3D arrangement of the receptor and the electrostatic surface of the region. **Conclusions:** The mutant receptor hGRαT556I impairs glucocorticoid signal transduction through multiple molecular mechanisms.

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References Values Under Synacthen Test for Six Steroids in Serum by LC-MS/MS

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Background: The response to ACTH test (synacthen®) is a very useful for the screening of steroidogenesis enzymatic deficiency. With the development of steroid quantification by LC-MSMS more specific than most of immunoassays, the determination of reference value is required at basal and under stimulation time. **Objective and hypotheses::** The aim of this

Table 1. (for abstract P2-169)

N = 66 Normal	21 DF pmol/l	11 OH nmol/l	DOC nmol/l	Cortico nmol/l	Delta4 nmol/l	OHP nmol/l
Mean ± 1SD	0.606 ± 0.436	4.57 ± 5.46	0.54 ± 0.37	58.68 ± 17.29	4.37 ± 2.9	4.43 ± 1.99
Range value	< 0.125–2	1.1–29.35	0.130–2.3	16.24–105	0.4–13	1.41–8.85

study is the determination in the same extraction and chromatography after Synacthen references values for 6 steroids: 21-deoxycortisol (21DF), 11-deoxycortisol (11OH), deoxycorticosterone (DOC), corticosterone, Delta4 androstenedione (Delta4), 17-hydroxyprogesterone (17OHP) in serum by LC-MS/MS method. **Method:** Agilent Technology 1290® Infinity was used for HPLC coupled to a mass spectrometer Agilent technology® triple quadrupole 6460. Samples and calibration curve are extracted using SLE after addition of deuterium internal standard. This method was validated according to the Norm (linear response, CV less than 10% for the repetability, less than 15% for the reproducibility). The limit of quantification for 11OH is 0.135 nmol/l, 0.125 nmol/l for 21DF, DOC, Corticosterone (Cortico), Delta4, OHP. Reference values were performed for these six steroids after Synacthen® (T0, T30, T60) in a cohort of patients previously studied in radioimmunoassay for 17OHP and 21DF and genetic status (normal, heterozygous, non- classical form) for mutation of CYP21A2 confirmed by sequencing. In the normal group (normal response to Synacthen determined in radioimmunoassay), steroids were quantified at T0 and T60 min (peak of stimulation for 17OHP and 21DF). **Results:** For this study, we analyzed 66 patients. We choose the peak of secretion of steroids at 60 min of this test. We determined normal values for the 6 different steroids (see Table 1). The results for 21 DF exclude a heterozygote form of the the gene CYP21A2 then lower than 0.6 nmol/l and a non-classical form if lower than 9 nmol/l. **Conclusion:** An evaluation of normal values for these six steroids may be useful to diagnose affected parents and prevent risk of congenital adrenal hyperplasia for children. The utilisation of LC-MS/MS method showed a sensitive and specific method to detect steroidogenesis enzyme deficiency when multiple precursors were high.

P2-170

Usefulness of Salivary Cortisol Levels in Secondary Adrenal Insufficiency in Paediatric Population

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Background: The main cause of secondary adrenal insufficiency (SAI) in children is prolonged treatment with exogenous corticosteroids. plasma cortisol (PC) levels after administration of ACTH is the most used indicator of adrenal function in clinical practice. However, salivary cortisol (SC) levels is emerging as an alternative technique in the diagnosis of adrenal pathology, especially useful in the paediatric population because it is a simple noninvasive test. **Objective and hypotheses:** To evaluate the correlation between PC and SC, to assess the usefulness of salivary determination as a diagnostic parameter in children with suspected iatrogenic SAI. **Method:** Prospective 2 years study (January 2014–January 2016) in patients 0–18 years of age treated with corticosteroids for more than 15 days. Determination of PC and SC at baseline and after administration of ACTH 1 mcg intramuscular (at 30, 60 and 90 min). **Results:** We analysed 60 samples (plasma and salivary) of 15 studies of ten patients (two ♂ / eitht ♀) with a mean age of 12 years (range: 3.6–16.5), with different underlying pathologies, studied for suspected SAI in the context of prolonged corticosteroid therapy. The Pearson coefficient showed a direct correlation between plasma and SC levels ($r = 0.649$, $P < 0.001$). All our patients with any determination of PC > 18 mcg/dl ($n = 5$) had a peak SC > 0.58 mcg/dl (ROC curve, specificity 99.9%, sensitivity 99.9%). **Conclusion:** SC – is a less invasive test, easier and quicker to realise that PC – appears to reflect the levels of free PC – it could replace the PC as diagnostic method for iatrogenic SAI in children. In our study, a value of SC > 0.58 mcg/dl was able to discriminate patients without SAI.

P2-171

Acute Adrenal Failure in a Term Newborn with Congenital Cytomegalovirus Infection: Case Description and Review of the Literature

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Background: Bilateral adrenal haemorrhage is rare in the neonates and more rarely does it manifest itself as acute adrenal insufficiency (AI). Cytomegalovirus (CMV)-associated AI is a well-known in adults with acquired immunodeficiency syndrome. AI is not a common finding in children with congenital CMV infection. We describe herein the case of a newborn infant presenting with adrenal hematomas (AH), AI and congenital CMV infection. **Case report:** A 20 day-old female was referred to Neonatal intensive Care Unit with lethargy, poor feeding, paleness and hypotension. She presented metabolic acidosis, hyponatremia, hyperkalemia and anaemia. The abdominal US revealed bilateral heterogeneous soft-tissue mass lesion in adrenal glands, consistent with AH. Hormonal evaluation revealed: altered circadian rhythm of cortisol, markedly elevated plasma adrenocorticotropic

hormone levels; reduced cortisoluria; normal *17-hydroxyprogesterone* level. Replacement therapy with gluco- and mineralocorticoids was rapidly initiated, followed by resolution of clinical picture of AI. Serial ultrasound examination showed complete regression of AH within 5 weeks. Cranial US revealed the picture of 'candlestick' lenticulostriate vasculopathy, commonly found in infants with congenital CMV infection. Anti-CMV IgM and IgG antibody index values were elevated and quantitative CMV viral load in blood and urine showed significant viremia. Maternal serology was negative for anti-CMV IgM but positive for anti-CMV IgG. Serology was negative for human immunodeficiency virus (HIV). Chorioretinitis was observed on ophthalmologic examination and hearing loss was diagnosed by auditory brainstem evoked response testing. Ganciclovir therapy was started and continued for 6 weeks. The steroid dosage was tapered over the course of 3 months and gradually discontinued. **Conclusion:** This is, to our knowledge, the first reported case of acute AI in a HIV negative newborn with bilateral AH and congenital CMV infection. On the basis of this case history, we suggest to investigate adrenal function in CMV-infected newborns who present with unexplained electrolyte imbalances, weight loss, or hypotension.

P2-172

Resveratrol Disrupts Steroidogenesis in Human Foetal Adrenals

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Background: The phytoestrogen resveratrol found in grapes and other plants has attracted considerable interest due to its proposed ability to extend lifespan, attenuate the development of metabolic syndrome in obese subjects and protect against cardiovascular disease. Among other functions resveratrol has been reported to affect the endocrine system. Self-medication with high pharmacological doses of this polyphenol with the aim to improve metabolic parameters and health cannot be excluded in some health-seeking populations of humans. Prenatal involuntary foetal exposure to resveratrol due to consumption by pregnant women may negatively influence development of endocrine homeostasis and stress responsiveness in human foetuses. **Objective and hypotheses:** The aim of this project was to explore the potential of resveratrol to affect human foetal adrenal steroidogenesis and mitochondrial function at the end of the first trimester. **Method:** Cells were isolated from gestational week 9–12 human foetal adrenals and cultured *in vitro* for 24 h with resveratrol, with or without stimulation with ACTH. DHEA, androstenedione, progesterone, 17OH-progesterone, cortisol and testosterone were analysed by ELISA. Expression of steroidogenic enzymes was measured by qPCR and Western Blotting. Cell proliferation and mitochondrial function were also analysed. **Results:** Resveratrol significantly suppressed the production of DHEA and androstenedione but elevated the release of progesterone and 17OH-progesterone by primary cultures of ACTH stimulated human foetal adrenocortical cells. These alterations of steroidogenesis were associated with down-regulation of CYP17A1 expression. No significant effects of resveratrol on cell proliferation and mitochondrial function were found. **Conclusion:** Resveratrol has potential to disrupt steroidogenesis in human foetal adrenals at the end of the first trimester. Since this is a critical period for the development of many steroid-dependent organs, our data constitute a warning for self-medication with resveratrol especially during pregnancy. **Funding:** This work was supported by the Swedish Research Council; the Finnish Academy; the Children's Cancer Fund; Frimurare Barnhuset Foundation; Kronprinsessan Lovisas Foundation; the 'Sällskapet Barnavård'; the 'Stiftelsen Samariten'; the 'Stiftelsen Olle Engkvist Byggmästare' and the 'Stiftelsen Gunvor och Josef Anérs'.

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Normal Ranges of Basal and Glucagon-Stimulated Free Cortisol in Children

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Background: Standard assays for serum cortisol measurements determine total cortisol (TC) concentrations but not the unbound biologically active serum free cortisol (sFC). Measurement of TC would be greatly influenced by alteration in cortisol-binding globulin (CBG) concentrations. It is, therefore, important to determine sFC levels when CBG levels are either decreased or increased. **Objective and hypotheses:** To determine basal and glucagon-stimulated sFC in relation to TC, GH and glucose levels in children. **Method:** Infants and children referred for evaluation of GH and cortisol reserve, underwent glucagon test. Baseline and stimulated serum TC, FC, GH and glucose levels were measured before and every 30 min for 180 min after IM administration of Glucagon (30 mcg per kg, max of 1 mg). Serum TC and GH were determined by chemiluminescence and serum FC was measured by the same method following equilibrium dialysis. A TC response of 20 mcg/dl was considered normal. **Results:** The study group consisted of 62 subjects (26 girls), median age 3.9 years (range, 0.5–13.8). Mean baseline TC and sFC levels were 12.9 ± 6.5 mcg/dl and 0.78 ± 1.1 mcg/dl respectively. Mean peak TC and sFC levels (150 min) were 29.2 ± 9.5 mcg/dl and 1.7 ± 1.3 mcg/dl respectively. Mean fractions of sFC at baseline and at peak were $4.3 \pm 1.6\%$ and $5.2 \pm 1.7\%$ reflecting a lower increase in TC (200%) compared to sFC (250%). peak TC and sFC levels were positively correlated ($r = 0.5$ $P < 0.001$). The girls had a higher peak TC and Peak sFC $P = 0.004$ and $P = 0.03$ respectively. There was a negative correlation between peak TC and age $r = -0.3$, $P = 0.02$, however no correlation was found between peak sFC and age $r = -0.06$, $P = 0.7$. **Conclusion:** Based on these findings, we suggest pilot normal ranges for basal and glucagon-stimulated sFC for children. These norms might serve as a reference when cortisol binding globulin are abnormal. The finding that TC is age dependent while

the sFC is not may suggests that the sFC is superior to TC measurement in paediatric population. The higher TC and FC in girls compared to boys might suggest an survival advantage.

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Clinical, Biochemical and Molecular Characteristics of the Patients with Nonclassical Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency in Croatia

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Background: Nonclassical congenital adrenal hyperplasia (NCCAH) due to mild 21-hydroxylase deficiency is caused by mutations of the *CYP21A2* gene located on chromosome 6p21.3. **Objective and hypotheses:** To determine cut-off for basal and stimulated 17-hydroxyprogesterone (17-OHP) levels, to evaluate *CYP21A2* gene mutations frequency among Croatian NCCAH patients, to determine correlation between 17-OHP levels and genotype and to evaluate correlation between 17-OHP levels, *CYP21A2* gene mutations and phenotype. **Method:** A cohort of 49 patients (38 unrelated) with NCCAH (31 females/18 males) was studied (eight female/14 male patients discovered through family studies). The subjects were evaluated for signs of hyperandrogenism, basal and ACTH-stimulated 17-OHP levels were measured and *CYP21A2* gene molecular analysis were performed. **Results:** The 17-OHP cut-off levels of best sensitivity and specificity are 8.8 nmol/l for baseline and 39.2 nmol/l for ACTH stimulated 17-OHP levels. Only one patient had baseline 17-OHP levels below 6 nmol/l. Among 40 fully genotyped patients, 12 carried two 'mild' *CYP21A2* mutations, 27 were compound heterozygotes for one 'mild' and one 'severe' mutation, and one had two 'severe' mutations (I172N/ I2G). The commonest mutation in our study group is pV281L (83.87%) and 70.87% patients carry one 'moderate/severe' mutation. Genotype severity did not correlate with 17-OHP levels. No correlation was found between phenotype and 17-OHP levels or grading of genotype. **Conclusion:** Patients with basal 17-OHP levels above 8.8 nmol/l should be further evaluated for NCCAH. Phenotype and 17-OHP levels do not correlate with severity of genotype suggesting that modifier factors my modulate phenotypic expression. Thus molecular analysis of *CYP21A2* gene should be done in all patients, especially due to high frequency of patients with one 'moderate/severe' mutation. Considering the high incidence of heterozygotes in the general population, it is important to genotype the partners of the patients with one severe mutation to offer genetic counselling.

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Abnormal Circadian Blood Pressure Profile in Patients with Congenital Adrenal Hyperplasia without Overt Hypertension

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Background: An abnormal blood pressure (BP) circadian rhythm, and in particular a non- dipping phenomenon is associated with increased cardiovascular and cerebrovascular health risks. In patients on steroid replacement therapy non physiological substitution may affect the BP profile. **Objective and hypotheses:** i) to evaluate the circadian BP profiles of patients with congenital adrenal hyperplasia (CAH) on steroid replacement therapy, ii) to compare BP profiles of patients receiving hydrocortisone (HC) and fludrocortisone in different dosing schedules. **Method:** The study included 60 patients (32 girls) with classic CAH due to 21-hydroxylase deficiency (mean age 9.4 years, range 1.7–17.9). Patients received a mean of 17.1 mg/m^2 of HC in the following dosing schedules: 25 patients in three equal doses, 15 patients 40% of their daily dose in the morning (M) and in the afternoon (A) and 20% in the evening (E), the remaining 20 patients: 50%M + 25%A + 25%E. Fludrocortisone (FC) was given to 40 patients: in 26: in two equal daily doses (a), in 11: 2/3M + 1/3E (b), and in 3: 1/3M + 2/3E(c). The standard 24-h BP monitoring was performed using an Ambulatory BP Monitor (Spacelabs 90217, USA). **Results:** 24 h systolic (SBP) and diastolic (DBP) loads > 30% were found in 18.3 and 15% of patients. Night SBP and DBP loads > 30% were found in 36.6 and 31.6% of patients. 40 (66.6%) patients presented with an abnormal 24-h BP profile with no significant night dip (dip < 10%). The results were not dependent on the HC dosing schedule but were dependent on the total HC dose in kg/m^2 (dip < 10%: 17.9 vs dip > 10%: 15.3 kg/m^2, $P < 0.05$), FC dose (dip < 10%: 67 mcg vs dip > 10%: 59 mcg) and FC dosing schedule: (a) vs (b): mean dip: 12% vs mean dip: 6.3%, $P < 0,04$. **Conclusion:** Abnormal 24-h BP profile in CAH patients is not associated with HC dosing schedule but with the HC and FC dose and also FC dosing schedule.

P2-176

Triple A Syndrome – the Second Most Common Cause of Chronic Adrenal Insufficiency in North Africa?

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Background: Triple A syndrome (AAAS, OMIM#231550) is a very rare inherited disease characterized by the association of chronic adrenal insufficiency, achalasia, alacrima and central and peripheral neurological disorders. It is caused by mutations in the AAAS gene which encodes the nuclear pore complex scaffolding protein ALADIN. The relative prevalence and genotype of AAAS in the Maghreb countries has not been ascertained. **Objective and hypotheses:** To estimate the prevalence, clinical features and genetic findings of triple A syndrome among children with chronic adrenal insufficiency in Algeria. **Method:** Clinical data were collected retrospectively from the medical records of patients attending a single center between 2007 and 2014. Written informed consent was obtained from patients and family members for genetic testing. **Results:** Of 160 children and adolescents with chronic adrenal insufficiency, 25 (15.6%) were diagnosed with Triple A syndrome, rendering it the second most common cause of chronic adrenal insufficiency after congenital adrenal hyperplasia. The 25 patients (15 males: ten females) were from 20 families, the parents being consanguineous in 17 (68%) cases. There was a family history of unexplained sibling death in seven patients. Mean $\pm$ SD (range) age at diagnosis was 4.34 ± 2.80 (1–10.8) years, height at diagnosis (WHO 2007 data) was -1.26 ± 1.5 SDS, BMI 0.74 ± 1.36 SDS. All patients were initially diagnosed because of adrenal insufficiency, 19 with isolated glucocorticoid deficiency, six with combined glucocorticoid and mineralocorticoid deficiency. All patients had alacrima, all but one had achalasia and nine patients had neurological disorders. Genetic analysis of the AAAS gene was performed for seven families. The previously reported IVS14+1G>A splice donor mutation was found in six patients, the EVS9 mutation in one patient. **Conclusion:** Although rare, Triple A syndrome is the second most common cause of chronic adrenal insufficiency in our patients as well as being a cause of unexplained death in young undiagnosed children.

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Analysis the Relationship between Clinical Characteristics and Genotype of Six Cases of Bartter Syndrome and Gitelman Syndrome in Children

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Background: In developing countries, due to the lack of medical resources, it is necessary to do the preliminary diagnosis of Bartter syndrome and Gitelman syndrome according to the existing clinical data rather than the genetic testing. Is clinical diagnosis consistent with the gene diagnosis? **Objective and hypotheses:** To summarise the children's clinical features, furosemide/hydrochlorothiazide loading test and genotype of Bartter syndrome and Gitelman syndrome; To guide the clinical diagnosis and selecting the target gene examination of Bartter and Gitelman syndrome through the clinical features and furosemide/hydrochlorothiazide loading test. **Method:** Retrospective analysis of clinical and biochemical characteristics, furosemide/hydrochlorothiazide loading test and genetic testing results of six cases (all of them were confirmed by gene examinations) of Bartter syndrome and Gitelman syndrome in the period from 2012 to 2014. **Results:** Six patients came from six families, newly diagnosed at the age of 0.91–15.72 years old, and median age was 5.37 years. All patients had hypokalemic alkalosis with the normotensive, hyperreninemic hyperaldosteronism. Most of them had polydipsia, polyuria, and various degrees of growth retardation. The clinical diagnosis of Batter syndrome patients had hypercalciuria and the $\triangle$FEcl $<$ 2.3% in Furosemide loading test. Meanwhile the Gitelman syndrome patients had hypomagnesemia and the $\triangle$FEcl $<$ 2.3% in hydrochlorothiazide loading test. All the initial clinical diagnosis and genetic diagnosis is consistent at last. **Conclusion:** According to the results of furosemide/hydrochlorothiazide loading test and clinical deta (hypomagnesemia, hypercalciuria), we can better carry out the preliminary diagnosis, and guide the selection of a target gene detection to save costs and medical resources.

P2-178

Genotypic Heterogeneity and Clinical Phenotype in Two Patients with Triple A Syndrome (AAAS)

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Background: AAAS is an autosomal recessive disorder characterized by adrenal insufficiency, alacrimia, achalasia and neurological symptoms. The disease-causing AAAS gene encodes for the ALADIN nuclear pore protein. **Case presentation:** Case 1: A girl (born to unrelated parents) presented at age 3.9 years with fatigue and hyperpigmented skin. Clinical examination was normal, clumsy gait was noted. Endocrine studies confirmed adrenal insufficiency (F = 9 mg/ml, ACTH = 563 pg/ml), and glucocorticoid therapy was started. Diagnosis of AAAS was made later at age 15, when she developed muscle weakness, hypereflexia and ataxia. Electromyoneurography demonstrated motor-sensitive polyneuropathy. Alacrimia was diagnosed by Schirmer test. During follow-up (at age 18), she developed feeding difficulties that led to diagnosis of achalasia. Molecular analysis showed a compound

heterozygosity for previously known AAAS mutations 43C→A(GlnLyS)/IVS14+IG>A. Case2: a boy born to unrelated parents presented at age 14 years because of important weight loss (BMI=14 kg/m^2) and fatigue. He had been diagnosed with achalasia one year earlier. Past history revealed congenital twisted feet and dysphagia since 4–6 months of age. On clinical examination, cutaneous-mucosal hyperpigmentation, muscle weakness and nasal speech were noted. Endocrine studies confirmed adrenal insufficiency (F=12–mcg/L, ACTH>1250–pg/ml); elettromyoneurography demonstrated axonal polyneuropathy and Schirmer test was indicative for alacrimia. Glucocorticoid therapy was immediately started. Molecular analysis revealed a novel homozygous intronic variant (IVS11-2), inherited from the heterozygous parents (both from Sardinia). The molecular characterization of this novel variant, based on mRNA analysis, showed that this variant affects the splicing site of the exon 11 into the ALADIN gene, causing the production of an aberrant protein with a premature stop codon. **Conclusion:** Our finding of a novel causative IVS in AAAS gene supports the notion of genetic heterogeneity for this disorder, although other genetic mechanisms cannot be excluded. The variable presentation/progression of disease manifestations observed in our two patients with AAAS could support this hypothesis.

P2-179

Primary Adrenal Insufficiency: About a Paediatric Series

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Background: Adrenal insufficiency in children is rare and potentially serious because of the risk of acute adrenal insufficiency. This complication is lethal in the absence of prompt and appropriate treatment. Aetiologies are dominated by the genetic causes. **Objective and hypotheses:** Report diagnostic circumstances,phenotypic forms and causes of adrenal insufficiency in children and adolescents. **Method:** This is a retrospective study of 54 cases of children and adolescents with adrenal insufficiency hospitalised between 1988 2014 we evaluated the clinical, biological, etiological and evolutive features of adrenal insufficiency. **Results:** 54 cases were reported (44% boys, 56% girls) The average age was six years ±1.2 (2–18). The consultation Reason: ADS: 59%; adrenal insufficiency: 20%; Congenital adrenal hyperplasia: 5% melanodermia: 5% salt wasting syndrome: 3.7% early puberty: 1%. A familial form was observed in 14% (10% PEA, 4% HCS). Clinical feature was typical 42% (emaciation, asthenia, anorexia, hypotension melanodermia, digestive disorders). Paucisymptomatic in 58%. Biologically, the Serum potassium was high in 44.44% serum Na was low in 42.59%. glucose was low in 12.94% and symptomatic in 50%. The aetiologies were HCS 73% (21 OH 67% 11 OH 3% B OL 2% 17 βOH 1%) IS autoimmune 22.6% Allgrove sd 1.4%, tuberculosis 1.8%, adrenoleukodystrophy 1.8%. Replacement therapy has helped improve symptoms in all cases. The evolution was complicated iterative decompensation of 45% and difficulties of balancing (overdose 30%). **Conclusion:** Adrenal insufficiency is rare in children. Genetic diseases dominated by HCS are the most common causes in infants and very young children. Dehydration with a salt-losing syndrome should suggest this aetiology. In the older child, the autoimmune origin is predominant. It can be isolated or associated with a polyendocrinopathy that it will identify early. Replacement therapy started quickly should be reviewed and monitored to prevent under and overdoses.

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High-Dose Hook Effect in 17- Hydroxyprogesterone Assay in 21-Hydroxylase Deficiency

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Background: False-negative results can occur an extremely high level of substrate at the assay system. This is called the 'high-dose hook effect'. **Case presentation:** 14 year-old female patient was referred with short stature, amenorea and hirsutism. Height, weight and blood pressure were 140.5 cm (SDS:−3.5), 43.4 kg (SDS:−1.6) and 120/80 mmHg. She had stage 1 Tanner breast, stage 5 pubic hair and hirsutism (mFG scale: 28) with android distribution. The clitoris was enlarged 4 cm in longitudinal axis and 1.5 cm in transverse diameter of the glands. Laboratory: Sodium 138 mmol/L, potasium 4.3 mmol/L, 17-OHP <0.04 ng/ml (0.2–1.3), DHEA 720.6 ug/dL (35–430), androstenedione 13 ng/mL (0.3–3.3), testosterone 4,4 ng/ml (0.1–0.7), ACTH 319 pg/mL (4.7–48.8), cortisol 7.8 ug/dL (6.7–22.6), renin 69.7 mIU/mL (2.8–39), aldosterone 664.1 pg/mL (25–315), LH 3.1 mIU/ml, FSH 6.3 mIU/ml, estradiol <20 pg/mL, progesterone 31.9 ng/ml (25––315), prolactin 12.6 ng/ml. Pelvic ultrasonography was normal (uterus 8 ml and ovaries 2/2.3 ml). The karyotype was 46, XX. Unexpected result of low serum 17-OHP level led to the suspicion of a 'high-dose hook effect'. The measurement was repeated after 1/10 dilution of serum, and high level of 17-OHP was detected (115.4 ng/ml) with ELISA test (DiaMetra, Segrate, Italy). Homozygous p.I173N (c.518T>A) mutation was detected in the CYP21A2 gene. These values confirmed the diagnosis of 21-hydroxylase deficiency and hydrocortisone therapy was iniated. **Discussion:** Excessive accumulation of steroid precursors are occur due to the shunt throught the adrenal androgen biosentetic pathway. Large quantities of antigen impair antigen-antibody binding, resulting in low antigen levels (false negative result) in laboratory assays which can be satisfied by dilution of the sample or a change of sample antigen to antibody ratio either by assay reformulation. **Conclusion:** This is the first case of the hook effect

for 17-OHP immunoassay in 21-hydroxylase deficiency. Hook effect needs to be suspected in patients with CAH when steroid precursors are incompatible.

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Baseline Cortisol Concentrations Predict Positively and Negatively Anti- and Pro- Oxidation, Respectively that are Measured Following an Acute Aerobic Exercise Bout in Pre- and Early Pubertal Normal-Weight and Obese Boys

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Background: Little data exist regarding the hypothalamic-pituitary-adrenal (HPA) axis activation and the interplay between the HPA axis and markers of pro- and anti-oxidation in children, following an acute aerobic exercise bout in children. **Objective and hypotheses:** To investigate the changes of HPA axis hormones following an acute bout of aerobic exercise and their respective association with markers of pro- and anti- oxidation in normal weight and obese pre- and early- pubertal boys. **Method:** The present experimental study involved two visits at an ergophysiology laboratory. At the first visit 76 healthy pre- and early- pubertal, normal weight and obese boys, underwent a maximal aerobic exercise bout on a cycle ergometer for VO2max measurement. At the second visit subjects underwent a baseline blood sampling, followed by an aerobic exercise bout until exhaustion at 70% VO2max and a subsequent (post-exercise) blood sampling. Samples were taken for the measurement of HPA axis hormones (ACTH and cortisol), pro-oxidation markers (thiobarbituric-acid reactive species (TBARS), protein carbonyls (PCs)) and anti-oxidation markers (glutathione (GSH), oxidized glutathione (GSSG), glutathione peroxidase (GPX), catalase, and total anti-oxidant capacity (TAC)). **Results:** No difference was found between baseline and post exercise ACTH and cortisol concentrations in all subjects groups. Baseline cortisol concentration was the best predictor of post exercise catalase concentrations ($P<0.05$; $b=0.47$). Waist circumference followed by baseline cortisol concentrations were the best positive and negative predictors, respectively, of post exercise TBARS concentrations ($P<0.05$; $b=0.74$, $b=-0.37$). **Conclusion:** Baseline cortisol concentrations predict positively and negatively anti- and pro- oxidation, respectively that are measured following an acute aerobic exercise bout in pre- and early pubertal normal-weight and obese boys. This finding might imply an additional protective role of this anti-inflammatory hormone against excessive oxidation. Aerobic exercise bouts of greater duration and/or intensity are required to activate the HPA axis than the one employed in the present study.

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Insulin Sensitivity and Adipocytokynes in Children with Classical Congenital Adrenal Hyperplasia

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Background: Recent studies demonstrate that children with Congenital Adrenal Hyperplasia (CAH) may develop visceral adiposity and insulin-resistance. Data on adipocytokines are scanty and contradictory. **Objective:** To evaluate leptin and adiponectin concentrations in CAH adolescents and investigate their correlation with glucocorticoids and hormonal and metabolic profile. **Methods:** Leptin, adiponectin, insulin and HOMA were evaluated in 21 classical CAH patients, aged 13.5 ± 2.5 years, and 21 healthy subjects matched for age, sex and pubertal status. Anthropometric and hormonal parameters were also measured. **Results:** CAH patients exhibited higher BMI SDS, waist circumference and waist-to-height ratio than controls (1 ± 0.9 vs -0.2 ± 1.4, $P=0.002$; 83.6 ± 11 vs 73 ± 13 cm, $P=0.01$; 0.55 ± 0.07 vs 0.4 ± 0.06 cm, $P=0.008$), thus suggesting a visceral pattern of adiposity. Compared to controls, CAH patients had higher fasting insulin (11.4 ± 7.5 vs 9.4 ± 14 uU/ml, $P=0.01$), HOMA (2.3 ± 1.3 vs 1.2 ± 0.9, $P=0.05$), leptin (15.06 ± 8.9 vs 7.23 ± 6 ng/ml, $P=0.003$) and leptin/adiponectin ratio (1.9 ± 2.2 vs 0.76 ± 0.74, $P=0.03$). This difference in leptin and leptin/adiponectin ratio did not persist after correction for waist circumference, but they were still significantly higher after correction for BMI SDS. Adiponectin levels and lipid profile were comparable between the two groups. Leptin and leptin/adiponectin ratio in CAH patients were positively correlated BMI SDS ($r=0.5$, $P=0.03$ and $r=0.6$, $P=0.007$, respectively) and weist-to-height ratio ($r=0.67$, $P=0.001$ and $r=0.7$, $P=0.0009$, respectively); and negatively correlated to the current hydrocortisone dosage ($r=-0.5$, $P=0.02$ and $r=-0.6$, $P=0.003$, respectively). No correlation was found between leptin or leptin/adiponectin ratio and androgens or cumulative hydrocortisone dosage in the last three years. **Conclusion:** Children and adolescents with CAH may develop visceral adiposity, hyperinsulinism and insulin-resistance. Our results show that high leptin levels in CAH reflect increased adiposity; however the impact of sex and gender needs to be further investigated on larger cohorts. Finally, our data suggest that long-term hydrocortisone treatment does not affect leptin levels.

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24-H Urinary Free Cortisol as a Screening Test for Cushing's Syndrome in Children

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Background: Cushing's syndrome (CS) in children remains a challenge to diagnose and exclude. Published diagnostic guidelines for CS are heavily based upon adult data. The use of 24-h urinary free cortisol (UFC) measurements in the diagnosis of adult CS may have limited use. There is little data on the utility of 24-h UFC in children. **Objective and hypotheses:** We hypothesised that 24-h UFC is a robust and reliable screening test in children. The study aims to assess its screening accuracy in paediatric patients referred for evaluation of possible CS. **Method:** Retrospective study of children referred to our centre between 1982-2014 was undertaken. 68 patients: 19 controls (9M) and 49 CS cases (30M), which included: Cushing's Disease (CD) (39 patients, 25M), bilateral micronodular adrenocortical disease (BMAD) (8 patients, 4M), ectopic ACTH secreting tumours (two patients, 1M). All patient groups had either one or several 24-h UFC collections analysed by radioassay, immunoassay or liquid chromatography-mass spectrometry. Data was measured using the Receiver Operating Characteristics (ROC) analysis and expressed as area under the curve (AUC) and by an independent 2 tailed *t*-test. **Results:** The diagnostic accuracy of 24-h UFC was excellent (0.98, 95% CI 0.946-1.00), with sensitivity and specificity for CS being 94% and 90%, respectively. 24-h UFC levels were higher in CS secondary to peripheral causes (ectopic CS or BMAD) as compared to CD (mean: 1430 vs 885 nmol/24-h; $P=0.025$). For CD, the mean 24-h UFC values were higher in males compared to females ($P=0.02$). **Conclusion:** 24-h UFC is a reliable and practical screening tool with excellent diagnostic accuracy for paediatric CS. Children with a single high 24-h UFC, despite a normal overall mean, should be thoroughly investigated for CS. UFC measurements were significantly higher in male compared to female CD patients and in peripheral causes of CS compared to CD.

P2-184

Familial Hyporeninemic Hyperkalemia and Hypertension (Pseudohypoaldosteronism Type II) in Infancy and Childhood

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Background: Pseudohypoaldosteronism type II (PHAII), is a rare renal tubular disease with an autosomal dominant inheritance characterized by hyperkalemic, hyperchloremic acidosis and hyporeninemia. Mutations in WNK4 and WNK1 were found initially. Recently have shown that KLHL3 and CUL3 are also causative genes. **Objective and hypotheses:** Hypertension, an essential symptom of PHAII, manifest in adolescents and young adults. In the absence of family history the disease may remain undiagnosed in infancy and childhood. Manifestations such as hyperkalemia may also be overlooked. **Results:** We evaluated two families with 23 subjects. PHAII was diagnosed in ten patients. The index cases were twin brothers and an infant. All patients carried a heterozygous mutation in KLHL3 (Q309R and R528H) gene. Family I: Identical twins, presented at age 8 years, because of short stature. Investigations revealed persistent hyperkalemia (6.4–7.1 mmol/l) in both. Three years of follow-up in another medical center failed to diagnose PHAII. Family history of hyperkalemia (the mother) and hypertension (mother, maternal grandmother) were overlooked. A sister, mother and maternal grandmother carried the same mutation. Family II: A 2 years old male born by Cesarean section after 38 week of gestation. B.W.: 3400 g. Four hours after birth he developed respiratory distress requiring ventilation. At age of seven days, he had hyperkalemia (7.0 mmol/l) and hyperchloremia (110 mmol/l) that persisted. Plasma renin activity (PRA) was <0.3 ng/ml per h. Hypertension appeared at 17 months of age (146/95 mm Hg). Thiazide diuretics normalized hyperkalemia and blood pressure. At age 2 years, mutation analysis revealed KLHL3 mutation. Three of four sisters (8, 13, 15 years old) and the mother also carried the mutation. All had hyperkalemia, hyperchloremia and acidosis. Except one, all had very low PRA. Sistolic blood pressure was elevated in all (>95 P). **Conclusions:** To diagnose PHAII in pediatric age group high index of suspicion is required. Early diagnosis is crucial for appropriate therapy (thiazides) and genetic counseling.

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Severe Craniosynostosis Syndrome Associated to Salt Wasting Congenital Adrenal Hyperplasia

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Background: Craniosynostosis, defined as the premature fusion of the cranial sutures, presents many challenges in aetiology. One known form associated to steroid biosynthesis

impairment is the Antley-Bixler Syndrome (ABS). ABS-phenotype and normal steroidogenesis have FGFR mutations, whereas those with ambiguous genitalia and altered steroidogenes should be recognized as possibly having P450 oxidoreductase deficiency, with mild do moderate 17 OH progesterone (17HOP) elevation and basal normal cortisol levels. **Case presentation:** A term newborn, 46 XY, normal weight, male phenotype, with a severe craniosynostosis (turribrachycephalic skull shape), extreme ocular proptosis (unable to close eyelids), hand an feet malformation presented early respiratory insufficiency and needed mecanic ventilation. At 15 days of life, had clinical supection of adrenal insufficiency due to skin pigmentation and lowering of serum sodium. Hydrocortisone (HC) was initiated and 3 days later also fludrocortisone, with further normalization of eletrolytes. Neonatal screening was collected after 1 dose of HC and 17 OHP levels were 733 ng/ml. Salt-wasting congenital adrenal hyperplasia (CAH) diagnosis was made. At 42 days of life, do to upper respiratory distress, was transfered to a terciary complexity hospital. No signs of radioumeral or oder multiple synostoses and skeletal fractures were clinical or radiological observed in this patient. Cranial CT and MR showed severe medium face hypoplasia, corpus callosum and septum pellucidum absence, posterior fossa with Arnold -Chiari type 1 and cloverleaf skull, suggesting Crouzon or Pfeiffer Syndrome aspects. To avoid compressive complications of craniosynostosis, an early neuro-surgical approach was performed. Clinical signals of macro-genitossomia and cutaneous hyperpigmentation atenuatted after glucocorticoid doses were ajusted. **Conclusion:** We presented a patient with a severe syndrome with clinical aspects of FGFR mutations craniosynostosis and classical salt losting CAH in a different clinical presentation than in ABS, the first hypothesis advented, when features of craniosynostosis and steroidogenesis impairment are present.

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Testicular Adrenal Cell Rest Tumours are not Associated with 21 Hydroxylase Mutations or Therapy Compliance in Boys with Classic form of CAH

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Background: Testicular adrenal cell rest tumours (TART) are common in adult males treated for congenital adrenal hyperplasia (CAH) and contribute to reduced fertility. Their prevalence varies between 6-50%, and the incidence raises during adolescence. **Aim:** To explore the appearance of TART in a group of 25 male children in the age group 3-18 years who were treated for CAH. **Methods:** Compliance to the treatment was assessed through 17OHP values at 4 months intervals. Gene analysis for the CYP21A2 gene was performed using amplification creation restriction site (ACRS) method. Ultrasound examination was performed at yearly intervals. If positive for TART, it was followed by the MRI. Two boys underwent biopsy of the testes. **Results:** TART was detected by ultrasonography in 6 children (24%) at the age 6-16 years (14.2 years average). Four had a classical salt wasting form, two had simple virilising form of CAH. Molecular analysis confirmed homozygous I2S mutation in 3 patients, Q318X in one, and late onset form homozygous mutations P30L in one, and I172 in one. Ultrasonography confirmed tumours 8–25 mm in diameter and consecutively decreased normal testicular tissue. MRI confirmed TART, and clarified the exact distribution of the tumours. Histology was diagnostic of TART in two patients. Three of the patients had non-compliance, however in remaining 3, 17 OHP was always within the normal range. Surprisingly, one of the boys with TART developed mixed phenotypic leukaemia at the age of 16 years. **Conclusion:** TART is not rare in boys with salt wasting or simple virilising form of CAH. It is not associated with the genotype or the therapeutic compliance. Therefore, it might be advisable to perform systematic testicular ultrasonography since childhood at yearly intervals in all boys with classical form of CAH. Search for better treatments that will improve fertility in these patients is warranted.

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A Large Family with a Novel Mutation in the *SCNN1A* Gene Causing a Mild and Transient form of Autosomal Recessive Pseudohypoaldosteronism Type 1 (PHA1)

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Background: PHA1 is a rare inherited disease characterized by resistance to aldosterone action and distinguished in two forms: the autosomal dominant renal form caused by mutations of the *NR3C2* gene (MR) and the autosomal recessive systemic form caused by mutations of the subunit genes *SCNN1A, SCNN1B, SCNN1G* of the epithelial sodium channel (ENaC). The classic phenotype of the autosomal recessive form of PHA1 is usually severe, lifelong, and expressed with multiorgan symptoms, whereas the autosomal dominant form is milder, transient and restricted to the kidneys. **Objective:** In this study we describe the clinical and biochemical manifestations and genetic analysis in nine children diagnosed with PHA1, all members of a large consanguineous family. **Patients and methods:** Nine patients and their parents were studied. Clinical and biochemical data were analysed. The coding regions of the genes *NR3C2* and *SCNN1A* were bidirectionally sequenced. A structural model of the SCNN1A was constructed based on the protein threading method. *In silico* analysis was carried out. **Results:** Patients were diagnosed between 5 and 60 days of age presenting with failure to thrive or during the course of a respiratory illness, with hyperkalaemia, hyponatremia, elevated renin and aldosterone levels and a positive sweat test. All patients responded well to sodium supplementation

with decreasing requirements with age until discontinuation of treatment. All patients were homozygotes, whereas their parents were heterozygotes for the mutation F226C. The *in silico* analysis of the mutation revealed that it is pathogenic. The structural model constructed revealed that F226 is located at the extracellular domain of the α subunit and possibly affects the formation of the epithelial Na^+ channel by disrupting its interactions with the β and γ subunits that form it. **Conclusions:** We present a large family with a mild and transient form of autosomal recessive PHA1 due to a novel homozygous mutation in the *SCNN1A* gene.

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Phosphoglucomutase-1 Deficiency Presented as Adrenal Insufficiency

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Background: The congenital disorders of glycosylation (CDG) are a group of genetic diseases owed to defects in the biosynthesis of glycoproteins and other glycoconjugates. Phosphoglucomutase type 1(PGM1) deficiency is classified among the CDG. Varied range of clinical manifestations recently described includes hepatopathy, bifid uvula, malignant hyperthermia, hypogonadotropic hypogonadism, growth retardation, hypoglycaemia, myopathy, dilated cardiomyopathy, and cardiac arrest, ACTH deficiency has been reported but this finding is uncommon. **Objective and hypotheses:** To report the clinical picture of seven patients with PGM 1 deficiency from a consanguineous family presented with ketotic hypoglycaemia. **Method:** Medical records of the patients were reviewed for clinical details and endocrine evaluation. Whole exome sequencing (WES) was performed. **Results:** Seven patients ages between 2 and 29 are included, one patient died at 13 years old when gets off the school bus. All patients have abnormal palatine structure (cleft palate, bifid uvula) and bnormal liver function 6/7 patients, 4/7 had short stature (< -2.5SD) one was diagnosed with growth hormone deficiency. Recurrent episodes of ketotic hypoglycaemia were present in 6/7 patients. Hypoglycaemic episodes have been spontaneously resolved in two of them later in life, while 3/5 patients have deteriorating adrenal function with abnormally low cortisol and ACTH levels during hypoglycaemia and subnormal response of cortisol to low dose ACTH test. Serum electrolytes were within normal range. Hydrocortisone replacement therapy improved but not entirely eliminated hypoglycaemic episodes. Pubertal development appeared normal including the older patient who fathered an affected patient. WES revealed previously described homozygous mutation c.112A$>$T, p.Asn38Tyr in the PGM1 gene. **Conclusion:** ACTH deficiency may be a common manifestation in patients with PGM1 deficiency having recurrent hypoglycaemia.

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The Aetiological Spectrum of Congenital Adrenal Hyperplasia Based on Molecular Genetic Analyses

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Background: Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders characterized by a defect in cortisol biosynthesis. The most common form of CAH is the 21-hydroxylase deficiency (21-OHD), however, the incidence and the etiologic spectrum of other forms of CAH were not reported. **Objective and hypotheses:** This study describes the etiological distribution and clinical characteristics of CAH in a single academic centre. **Method:** This study included 190 patients with all forms of CAH. The diagnosis was confirmed by the clinical features, biochemical data, and molecular genetic analysis for the *CYP21A2*, *StAR*, *CYP17A1*, and *POR* genes. **Results:** Of a total of 190 patients, 138 patients (72.6%) from 128 families were 21-OHD (104 salt-losing, 33 simple-virilizing, and 1 non-classic forms), 44 (15.2%) from 41 unrelated families had *StAR* defect, six (3.2%) had 17-hydroxylase/17,20-lyase deficiency, and two (1.1%) had P450 oxidoreductase (POR) deficiency. Ninety seven patients with salt-losing 21-OHD (97/104, 93.3%) were diagnosed in the neonatal period. Most girls of 21-OHD (75/76, 98.7%) presented with genital virilisation, whereas most boys (38/62, 61.3%) presented with salt-losing phenomenon within the first month of life. Four genetic female (46,XX) with simple virilizing form of 21-OHD were assigned as male because of delayed diagnosis. Most patients (42/44, 97.7%) with *StAR* defect presented with adrenal crisis in the neonatal period, while two late-onset patients showed skin hyperpigmentation after age two years. Six patients with *CYP17A1* defect manifested with hypertension and primary amenorrhea during adolescent period. Two girls with POR deficiency displayed adrenal insufficiency, ambiguous genitalia, and craniosynostosis. **Conclusion:** The most common cause of CAH was 21-OHD. Interestingly, lipoid CAH is the second common because of the founder mutation (p.Q258X) in Korea. Nationwide surveillance is needed to estimate the incidence and precise distribution of diverse aetiology of CAH, though newborn screening for 21-OHD is introduced.

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Higher Serum DHEAS Concentration is Associated with Lower Plasma LDL Cholesterol Concentration in Children

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Background: Premature adrenarche is associated with overweight and insulin resistance, but the associations of serum dehydroepiandrosterone sulphate (DHEAS) concentration with other cardiometabolic risk factors are uncertain. **Objective and hypotheses:** We studied whether cardiometabolic risk factors and their clustering differ between children with higher and lower serum DHEAS concentration. **Method:** We studied 432 healthy children (207 girls and 225 boys; age 7.6 ± 0.4 years) participating in the Physical Activity and Nutrition in Children (PANIC) Study. Serum DHEAS concentration was determined by enzyme immunoassay. Children were divided into those with DHEAS <1.0 µmol/l ($n=354$) and $\geqq 1.0$ µmol/l ($n=78$). Cardiometabolic risk score was calculated summing the Z-scores of waist circumference, fasting serum insulin, fasting plasma glucose, triglycerides and high-density lipoprotein (HDL) cholesterol (multiplied by -1) and the mean of systolic and diastolic blood pressure. Also total cholesterol and low-density lipoprotein (LDL) cholesterol were measured from fasting plasma samples. Body fat percentage (BF%) and lean mass (LM) were assessed using dual-energy X-ray absorptiometry. Differences in cardiometabolic risk factors between the DHEAS groups were studied by general linear models adjusted for age, sex, BF% and LM. **Results:** Plasma LDL cholesterol was lower in children with higher serum DHEAS than in those with lower DHEAS adjusted for age and sex (2.25 vs 2.39 mmol/l, $P=0.029$). Other cardiometabolic risk factors or cardiometabolic risk score did not differ between the DHEAS groups. However, children with higher DHEAS had higher LM than those with lower DHEAS adjusted for age and sex (21.18 vs 20.46 kg, $P=0.008$). The difference in LDL cholesterol between the DHEAS groups weakened slightly after further adjustment for LM ($P=0.040$) but remained after additional adjustment for BF% ($P=0.017$). **Conclusion:** Higher serum DHEAS concentration is associated with lower plasma LDL cholesterol concentration in healthy prepubertal children. This relationship may be partly explained by increased skeletal muscle mass. **Funding information:** This work was supported by the Foundation for Pediatric Research, Research Committee of Kuopio University Hospital Catchment Area (State Research Funding) and Kuopio University Hospital (EVO funding number 5031343), Finnish Medical Foundation, Päivikki and Sakari Sohlberg foundation, Rauha and Jalmari Ahokas foundation.

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Central Adrenal Insufficiency is not a Common Feature in CHARGE Syndrome

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Background: CHARGE syndrome (acronym for coloboma of the eye, heart defects, atresia of the choanae, retardation of growth and/or development, genital hypoplasia, and ear abnormalities) is caused by a mutation in the CHD7 gene. CHARGE syndrome shares features with Prader-Willi syndrome, especially regarding hypothalamic-pituitary abnormalities. In Prader-Willi syndrome, central adrenal insufficiency (CAI) during stressful conditions has been described in a large number of patients. The presence of CAI in CHARGE syndrome has never been thoroughly studied, although unexpected mortality has been observed. **Objective and hypotheses:** The aim of our study was to assess the presence of CAI in patients with CHARGE syndrome. **Method:** Patients (ages between 20 months and 18 years) with genetically confirmed CHARGE syndrome were recruited from our national multidisciplinary outpatient clinic. To detect CAI, a low-dose ACTH test (LDAT) (0.5 µg/1.73 m^2 body surface area Synacthen®) was performed. Blood samples for determination of cortisol were taken at −15, 0, 30, and 60 minutes. A maximum cortisol concentration $>$ 500 nmol/l excluded CAI. In case of suspected CAI, a glucagon test (0.05 – 0.1 mg glucagon per kg body weight, maximum 1 mg) was performed on a separate occasion. Blood samples for determination of cortisol were taken at baseline and then every 30 minutes during 3 consecutive hours. Cut-off levels to detect CAI were similar as in the LDAT. **Results:** From 83 eligible patients, 27 were included in the study. In three patients, the LDAT could not be performed due to technical reasons, and 1 patient withdrew from the study. In total, 23 patients were tested (14 male, mean (SD) age 9.3 (5.0) years). Seven patients showed an insufficient maximum cortisol concentration in the LDAT (mean (SD) 425 (71) nmol/l), and underwent a glucagon test (1 patient underwent a standard dose ACTH test). Out of these seven patients, one patient was diagnosed with CAI (maximum cortisol concentration 415 nmol/l). **Conclusion:** CAI is not a common feature in CHARGE syndrome. Further studies in a larger number of patients are required to confirm our findings. **Funding information:** This work was supported by Fonds NutsOhra (grant number 1202-023).

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Baseline Adrenal Function by Measurement of Long-term Cortisol Levels in Scalp Hair of Asthmatic Children Using Inhaled Corticosteroids Equals Healthy Controls

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Background: Inhalation corticosteroids (ICS) as treatment for asthma can interfere with the hypothalamic-pituitary-adrenal axis and could lead to hypocortisolism. The frequency of this systemic side effect and the correlation to ICS usage is still unclear. Given that the cortisol excretion is pulsatile and determined by acute stress and circadian rhythms, the usefulness of tests based on momentary measures, such as saliva or serum are therefore

limited. Cortisol levels measured in scalp hair provide a marker for long-term cortisol exposure and seems promising for diagnosing hypercortisolism. **Objective and hypotheses:** The aim of this study is to determine the long-term hair cortisol concentrations (HCC) in children with asthma and corticosteroids usage compared to healthy controls. **Method:** A case-control study was conducted at the Groene Hart Hospital, Gouda, 2014. All asthmatic children (4–18 years of age) using ICS for more than three months and visiting the general hospital were eligible as cases. Healthy controls were voluntarily enrolled children (4–18 years of age) from schools or from healthy siblings attending the pediatric outpatient clinic Erasmus MC, Rotterdam. Anthropometric characteristics and hair samples from the posterior vertex were obtained from cases and controls. HCC in three cm scalp hair was analyzed by Liquid chromotography-tandem mass spectrometry. **Results:** 80 cases and 258 controls were enrolled for analysis. Median age of cases 10.8 (range: 4.1–17.6) and controls 11.5 (range: 4.3–18) were comparable ($P=0.56$). The use of budesonide equivalent dose by cases was 200–1 200 μg/day; with a median of 17.26 μg/kg (range 6.03–54.55) per day. Mean HCC-levels did not differ between cases and controls (F (1.336) = 0.005, $P=0.94$) which did not change after adjusting for age, gender, height-SDS, and weight-SDS (F (1.332) = 0.21, $P=0.65$). No correlation was found between budesonide doses and HCC levels. **Conclusion:** Assessment of long-term cortisol levels by hair cortisol showed no difference in baseline adrenal function in children with asthma and ICS to their healthy controls. This study suggests that the HPA-axis dysfunction, found in adrenal stimulation tests in children with asthma on ICS may not lead to clinical relevant HPA-axis changes in day-to-day life.

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Adrenal Function in Children Born Small for Gestational Age

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Background: Subjects born small for gestational age (SGA) were shown to be at higher risk to metabolic consequences later in life and this might be related to changes in hypothalamic–pituitary–adrenal axis. **Objective and hypotheses:** We aimed to investigate DHEAS and cortisol levels in adolescents born SGA or appropriate for gestational age (AGA) and their relationship with perinatal and postnatal factors. **Method:** A prospective cohort of 46 SGA and 94 AGA children was followed-up from birth to adolescence (75 boys and 71 girls). At the time of the investigation, study subjects were 11–14 years old (median 13.2 ± 2.1 years). Statistical analyses of DHEAS concentration were adjusted for sex, age and pubertal stage, and that of Cortisol concentration – for sex and BMI SDS. **Results:** SGA children had higher DHEAS levels than those born AGA (4.49 ± 2.65 μmol/l vs 4.15 ± 2.29 μmol/l; $P=0.007$). Analysing boys and girls separately, the difference was significant only in SGA boys (4.97 ± 2.82 μmol/l vs 4.27 ± 2.22 μmol/l; $P=0.017$). DHEAS levels were inversely associated with birth weight, birth length and gestational age ($r=-0.241$, $P=0.004$; $r=-0.230$, $P=0.006$; $r=-0.241$, $P=0.004$, respectively), and in the AGA group directly associated with current BMI SDS ($r=0.244$, $P=0.018$). There was no difference in cortisol levels between SGA and AGA groups. Analysing by gender, SGA girls had lower cortisol concentration than AGA girls (254.4 ± 82.4 nmol/l vs 382.1 ± 224.7 nmol/l; $P=0.01$). **Conclusion:** Small size at birth and higher BMI at puberty is related to higher DHEAS levels in pubertal children. **Funding information:** This study was funded by the Lithuanian Research Council (grant No. MIP-103/2011 and the Swedish Research Council (No. 7509).

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Cushing's Syndrome in Children and Adolescents: About a Paediatric Series

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Background: Cushing's syndrome in children and adolescents is rare. Its clinical and biological symptoms are severe with a significant impact on growth and puberty and poor prognosis. **Objective and hypotheses:** Report clinical, etiological and evolutionary characteristics of Cushing's syndrome in children and adolescents. **Method:** This is a retrospective study of 45 children and adolescents with Cushing's syndrome hospitalised at the department of endocrinology between January 1988 and December 2014. We have evaluated the clinical, biological, aetiological and evolutionary Cushing's syndrome in children and adolescents. **Results:** The mean age at diagnosis was 11.4 years (6–19), 2/3 of them will have an age > 10 years. The sex ratio F/G is 2.25. Clinical presentation was characteristic and significant in all cases. We observed complications In 22.5% (Diabetes mellitus 40% hypertension 30% dyslipidaemia 30% osteoporosis 20%). Aetiologies were iatrogenic causes 60%, Cushing diseases 33.3% adrenal corticosurrenaloma 6.6%. The transsphenoidal surgery has allowed a sustained remission of Cushing's disease in 30%. In 70% of relapse revision surgery + radiotherapy resulted in a adrenocorticotropic insufficiency. Adrenal surgery of carcinoma resulted in a good evolution. After a mean follow-up of six years, a Cushing disease recurrence was observed in 15%. **Conclusion:** The clinical and biological Cushing's syndrome in children and adolescents is often severe and complicated. Aetiological, Cushing's disease is more common in adolescents while malignant adrenal tumour most is often the prerogative of younger children. Their management is tricky with initial failures and high incidence of recurrence requiring monitoring the long course. Concertation

between doctors endocrinologists, paediatricians, radiologists and surgeons is essential.

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Serum Cortisol and Cortisone Ratio as Sensitive Tool to Identify Subjects With Severe or Partial 11β-Hydroxysteroid Dehydrogenase Type 2 Deficiency

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Background: Severe deficiency of 11β-hydroxysteroid dehydrogenase type 2 (11βHSD2) triggers activation of mineralocorticoid receptor (MR) by cortisol and causing apparent mineralocorticoid excess (AME) syndrome characterized mostly by low-renin arterial hypertension and hypokalemia. In 2003, we studied a patient with AME (3 years-old) having two homozygous mutation, D223N (rs121917833) and a SNP C>T in intron 3 (rs376023420) (Carvajal et al. JCEM 2003). **Objective and hypothesis:** To study the current clinical and biochemical status of the same AME patient including his mother and sister, and to evaluate serum cortisol/cortisone as a biomarker of partial 11βHSD2 deficiency. **Method:** We have recently evaluated the AME index case (17 years old), his mother (33 years old) and sister (8 years old). In all of them, we measured serum potassium, aldosterone, plasma renin activity (PRA) and microalbuminuria. Serum cortisol and cortisone were measured by LC-MS/MS, and cortisol/cortisone ratio was calculated. Genetic analyses of HSD11B2 gene were performed by PCR-HRM and DNA-sequencing. **Results:** The medical record of the AME index case indicated he was not under treatment. His clinical evaluation showed: hypertension (165/110 mmHg (>p99)), stunting (53 kg; 153 cm (−2.92DS); BMI: 22.6 Kg/m2 (p69), cardiac abnormalities (LVH), microalbuminuria (112 mg/24 h), severe hypokalemia (2.1 mEq/l), low aldosterone (1 ng/dl), suppressed PRA (<0.2 ng/ml*h) and a high cortisol/cortisone ratio (28.8 (Reference value (RV): 1.63–5.15)). Evaluation of his mother and sister indicated that both were normotensive and heterozygous for the same mutations, without biochemical abnormalities (normal aldosterone, PRA, potassium) but with high cortisol/cortisone ratios (13.1 (RV: 2.58–7.8) and 7.4 (RV: 1.63–5.15), respectively). **Conclusion:** Serum cortisol/cortisone ratio could be a sensitive tool to identify subjects with severe or partial 11βHSD2 deficiency. Since partial 11βHSD2 deficiencies -identified by high serum cortisol/cortisone ratio- may have no evidence of low-renin hypertension, low aldosterone or hipokalemia, is highly necessary to identify other complementary biomarkers to evaluate the progression of this condition. **Funding information:** Supported by FONDECYT 1130427, 1150437; FONDEF-IDEA CA12i10150, CORFO 13CTI-21526-P1 and the IMII P09/016-F (ICM) Chilean Grants.

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The Role of the Nurse Practitioner in Optimising Care for Children with Congenital Adrenal Hyperplasia

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Background: Congenital Adrenal Hyperplasia (CAH) is a rare group of congenital adrenal diseases with an estimated prevalence of about ten newly diagnosed patients in the Netherlands per year. Morbidity and mortality improved significantly in the last 20 years mainly due to improvement of multidisciplinary care and education of patients and parents. In the last years the role of the nurse practitioner (NP) as case manager in the care and follow up of patients with chronic diseases became more clear and is frequently described. **Presentation:** In our centre we provide outpatient care within the Radboud Adrenal Centre for about 90 children and 100 adults with CAH. The care for children and adolescents with CAH consists of frequent personal contact and follow up, medication control/ check-up and education of patients, parents andother care providers. The provided care is multidisciplinary and includes a team of medical specialists i.e. pediatric endocrinologist, pediatric urologist, gynecologist and clinical psychologist, all experienced in the field of physical and mental development of children with CAH. Easy accessibility for questions is a key factor to improve the care and reduce complications for these children. To improve our multidisciplinary care, we added a NP to our CAH team in 2012. The NP currently functions as case manager, coordinating the whole process of care and collaborates within the multidisciplinary team. Main tasks are: Organisation multidisciplinary outpatient clinic; training and education to prevent addison crisis; easy accessibility for parents, children and other care providers; providing information for school; coordinating transitional care; attention for quality of life by using annual questionnaires; contact with patient support group. **Conclusion:** We believe that the NP plays a key-role in improving care of children with CAH within a multidisciplinary team.

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Evaluation of Medical Treatment in the First 2 Years of Life with a New Dutch National Longitudinal Registry for Children with Congenital Adrenal Hyperplasia (CAH)

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Background: Recently, a national database has been developed to register yearly data from all children detected with CAH in the neonatal screening program from 2002 onwards. So far longitudinal data of 105 children have been registered (roughly 65% of Dutch CAH patients) to evaluate medical treatment and long-term effects in CAH. A national CAH work group developed guidelines for diagnostics and follow up in CAH. **Objective and hypotheses:** Aim of our current study is to evaluate the dosage of hydrocortisone, fludrocortisones and salt supplementation in CAH children in the first 2years of life. **Method:** This is a descriptive study in 105 children. The hydrocortisone, fludrococrtisone and salt medication was evaluated at the age of six months (T 0.5), 12 months (T1) and 24 months (T2). The treatment approaches of different centers was compared. **Results:** T 0.5: ($n=95$): median HC dosage ($n=89$) 4 mg/day. Interquartile range (IQR) 2 mg/day. FC ($n=82$) median 93.75 mcg/day; IQR 37.5 mcg/day and NaCl ($n=46$) median 500 mg; IQR 400 mg/day. T 1: ($n=90$) median HC dosage ($n=88$) 4 mg/day; IQR 1 mg/day, FC ($n=84$) median 62.5 mcg/day; IQR 30.3 mcg/day and NaCl ($n=25$) median 375 mg/day; IQR 400 mg/day. T2: ($n=88$) median HC dosage ($n=84$) 5.4 mg/day; IQR 2.14 mg/day, FC ($n=78$) median 62.5 mcg/day; IQR 37.5 mcg/day. No salt medication was used after the first year of life. No significant differences between centers are observed. **Conclusion:** Our analysis showed a stable slightly supraphysiological HC dosage over the first 2 years of life. FC shows a more widespread range in dosage suggesting a more individualized treatment approach without a clear difference between national centres. Further studies will focus on the relation between medication dosage and biometrical data. Our longitudinal database gives the opportunity to establish a more standardized care and long-term treatment evaluation.

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Incidence of Nonclassical 21-Hydroxylase Deficiency in Russian Population as Estimated by the Carrier Frequency of V281l Mutation

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Background: Nonclassical 21-hydroxylase deficiency (NC21OHD) is one of the most common monogenic diseases. Its frequency varies significantly among different ethnic groups. In Russians the frequency of NC21OHD is unknown. **Objective and hypotheses:** To estimate the incidence of NC21OHD in Russia based on the carrier frequencies of the two most common mutations associated with this disease (V281L and P30L). **Method:** A total of 998 randomly selected dried blood spot samples were obtained from a regional neonatal screening laboratory. All samples were collected within one calendar year. Each sample was analysed for V281L and P30L mutations in *CYP21A2* using allele-specific PCR. PCR-positive samples were reanalyzed by Sanger sequencing. The frequency of homozygotes was calculated by Hardi-Weinberg equation. **Results:** Heterozygous V281L mutations were detected in 39 of 998 samples (carrier frequency, 1:24), while P30L mutation was detected in none. Minimal frequency of NC21OHD, as estimated by theoretical frequency of V281L homozygotes, was 1:2206. In contrast, the incidence of NC21OHD suspected by dried blood spot 17OHP levels on the neonatal screening was 1:27990. **Conclusion:** The study provides an estimate of the population frequency of NC21OHD in Russians and demonstrates that the majority of NC21OHD cases remain undiagnosed.

P2-199

Cardio-Metabolic Risk Factors in Children and Adolescents with Classical 21-Hydroxylase Deficiency

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Background: Recent studies suggest patients with congenital adrenal hyperplasia (CAH) have adverse cardiovascular risk profile and other long-term health problems in adult life. However, there are limited data of these comorbidities in paediatric CAH patients. **Objective and hypotheses:** To evaluate the cardio-metabolic risk factors in children and adolescents with classical 21-hydroxylase deficiency (21-OHD) compared with age, sex and puberty-matched healthy controls. **Method:** A cross-sectional study of 21 Thai patients (females, $n=17$) with CAH aged 15.2 ± 5.8 years and 21 healthy matched controls. Anthropometric, biochemical and inflammatory markers were measured. Bone mineral density (BMD), fat mass and lean mass were measured using dual-energy x-ray absorptiometry (DXA). **Results:** Obesity was observed in 33% of the patients (7/21). The waist/hip ratio and waist/height ratio were significant higher in CAH patients when compared with controls. Three patients (14%) of 21 patients were noted to have prehypertension and two patients (9.5%) had hypertension. Fasting blood glucose levels in CAH patients were lower than normal subjects but HOMA-IR was not different. There were no significant correlations between HOMA-IR and glucocorticoid dose, age or 17-hydroxyprogesterone levels. Silent diabetes and metabolic syndrome were diagnosed in one patient (4.8%), but none in the control group. Lipid profiles were not different between patients and healthy controls except lower HDL to cholesterol ratio in CAH patients than in normal subjects. CAH patients had significantly higher AST levels than controls. Serum leptin concentrations were not different between groups, and positively correlated with BMI and HOMA-IR. Interleukin-6 levels

in CAH patients did not differ from controls, but hs-CRP levels tended to be higher in patients compared with controls. No significant differences in BMD *z*-score, fat mass and lean mass were found between CAH and healthy subjects. **Conclusion:** Children and adolescents with CAH appear to have an increased risk of obesity and cardio-metabolic risk factors. Close monitoring, early identification, and secondary prevention should be implemented during paediatric care to prevent metabolic complications and improve the long-term health outcomes in CAH patients. **Funding:** This work was supported by the Ratchadapiseksompotch Fund, Faculty of Medicine, Chulalongkorn University and the Thailand Research Fund.

P2-200

A Novel Mutation (c.delG209) in the Proopiomelanocortin Gene in a Child with Early-onset Obesity

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Background: Proopiomelanocortin (POMC) deficiency is characterized by early-onset obesity, adrenal failure, red hair and pale skin. The first genetic mutation in the POMC gene was demonstrated in 1998. This disorder is rare, but has increased our insight into the important role of the leptin-melanocortin pathway in energy balance. POMC deficiency causes obesity due to the inadequate production of alpha and beta MSH from POMC, which normally activate the melanocortin 3 receptor (MC3R) in the arcuate nucleus and the melanocortin 4 receptor (MC4R) in the paraventricular nucleus and antagonize the action of agouti-related peptide (AgRP). The hypocortisolism and hypopigmentation are due to inadequate stimulation of MC2R and MC1Rs by POMC-derived peptides in the adrenal gland and skin, respectively. **Case presentation:** The patient presented at 2 months with cyanosis and convulsions after 4 h of fasting. Her blood sugar was 31 mg/dl. She was born to non-consanguineous healthy parents after an uneventful 39-week pregnancy with a birth weight of 3 000 g. Physical examination revealed a weight of 3 700 gr ($<$3rd percentile), height of 51 cm ($<$3rd percentile) and red hair. There was no clinical or laboratory evidence of infection and she was admitted for blood sugar monitoring. Blood glucose level was 20 mg/dl, insulin 0.11 μIU/ml, ACTH $<$5 pg/ml and cortisol $<$0.2 μg/dl. The peak cortisol response during standard dose ACTH stimulation test was 0.44 μg/dl. Hydrocortisone treatment was initiated for secondary adrenal failure. There was no hypoglycemia under treatment. At 12 months, the patient's weight was 12 kg (1.99 SDS), height 76 cm (0.29 SDS) and the BMI 20.78 kg/m^2 (2.21 SDS) while these values at 15 months were 14.7 kg ($+$2.5 SDS), 83 cm ($+$0.24 SDS), and 22.4 kg/m^2 ($+$2.9 SDS) respectively. A novel homozygous c.delG209 mutation was found causing a frameshift at codon 69 (exon 4) of the POMC gene. **Conclusion:** POMC gene mutations should be considered among the rare causes of hypoglycemia in newborns and early infancy. Rare causes of monogenic obesity will help to elucidate POMC-AgRP-MC3R-MC4R interactions, and crosstalk between hypothalamic and peripheral signals in the development of obesity.

P2-201

Improved Linear Growth in Patients with Classical Congenital Adrenal Hyperplasia

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Background: Poor linear growth is still one of the main concerns in children with congenital adrenal hyperplasia (CAH). An impairment of linear growth, adversely affecting final height, has been related both to overtreatment with glucocorticoid replacement therapy and to poor control of adrenal androgen levels. **Objective and hypotheses:** To define factors that influence linear growth and final height in patients with classical CAH. **Method:** The medical records of 25 patients (12 females, 13 males) followed from early infancy until adulthood in our clinic were analysed and the clinical observations were divided into four groups according to age and puberty (0–2 years, 2 years up to puberty onset, pubertal years, post-pubertal years). Differences in the mean dose of hydrocortisone and average levels of Δ4-androstenedione and 17-hydroxyprogesterone between the four groups were evaluated using one-way ANOVA. Multivariate analysis was used to study factors independently affecting final height. **Results:** Mean final height was 167.8$\pm$7.1 cm in males ($-$1.3$\pm$1.1 SDS) and 158$\pm$6.5 cm in females ($-$0.8$\pm$1 SDS). Final height corrected for parental height was $-$1.01$\pm$1.3 in males and $-$0.37$\pm$0.5 in females. Mean total pubertal growth spurt was 23.1$\pm$4.6 cm in males and 19.8$\pm$6.5 cm in females. Significantly higher doses of hydrocortisone were required during the first 2 years of life and during puberty ($P<0.05$). Final height was adversely affected by the average dose of hydrocortisone ($P<0.001$) and by the level of Δ4-androstenedione ($P<0.045$) during follow up. **Conclusion:** The main goals of therapy in children with CAH are the control of glucocorticoid deficiency and the suppression of adrenal androgen hyper-secretion. Particularly during puberty, the daily dose of hydrocortisone should be maintained as low as possible to obtain a normal pubertal growth spurt and optimize final height. Final height of CAH patients followed from early infancy, particularly females, seems to be now less impaired than previously reported.

P2-202

Autoimmune Polyglandular Syndrome Type 1 in Russia: Clinical Experience in 112 Patients

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Background: Autoimmune polyglandular syndrome type 1 (APS-1) is a rare disease associated with mutations in the autoimmune regulator (AIRE) gene and characterized by mucocutaneous candidiasis (CMC), hypoparathyroidism (HP) and primary adrenal insufficiency (AI). Two of these three components are required for diagnosis. **Objective and hypotheses:** To describe Russian patients in terms of clinical, genetic, and immunological parameters. **Method:** We have recruited patients with at least one of the major clinical components of APS-1 from all over Russia. Eligible patients were phenotyped, *AIRE* sequenced, and typical autoantibodies assayed. **Results:** We recruited 112 patients (63 females, mean age 19.4 (2.7–44.6) years) from 102 families who fulfilled either the clinical diagnostic criteria or had at least one disease-causing *AIRE* mutations. 96 had two or three major components and sixteen had one; six -CMC, seven – HP, two – AI. 106 patients were AIRE sequenced, and twenty different AIRE mutations were found, ten of them novel *(A58V; p.Leu 323serfs*51; A390P;821delG;A399P; del>500Stopp*; K221X;C302(C,Y);L13(P,L); C434(*,C).* The Arg257Stopp AIRE mutation was present in 74% of the alleles (63 pts were homozygouse, 27 patients – heterozygous). Novel A58V AIRE mutation was found in six patients. Neutralizing autoantibodies against INFω were positive in all but one investigated patient. **Conclusions:** We have collected the largest cohort of patients with APS-1 published to date. Arg257STOPP AIRE mutation was the most frequent in Russian population. Ten novel AIRE mutations were found. Autoantibodies to INFω are useful for early diagnosis.

P2-203

Autoimmune Encephalitis – A Newly Recognised Clinical Manifestation of Autoimmune Polyendocrine Syndrome Type 1?

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Background: Autoimmune polyendocrine syndrome (APS) type 1 is a rare autosomal recessive disease. The classic features are chronic mucocutaneous candidiasis, hypoparathyroidism and adrenocortical failure. Several non-classic presentations of the disease has been described over the last few years. Authors present a case of 14-year old girl with a new serious non-classic presentation. **Case presentation:** Patient was diagnosed with a mucocutaneous candidiasis and hypoparathyroidism at the age of 3 years. APS 1 was diagnosed at 9 years of age shortly after diabetes mellitus type 1 had been recognised. Mutational analysis of the AIRE gene showed R257X (c.769C>T) mutation. Typical symptoms of Addison disease – weakness, fatigue and hyperpigmentation – developed at 13 years of age. At 14 years she was admitted to hospital for prolonged seizures. Hypoglycemia and hypocalciemia were excluded as a cause of the seizures. EEG showed finding non-specific for epilepsy. Examination of the CSF was performed to exclude infection (herpetic viruses, etc.). MRI angiography did not show vaculitis or other organic changes of cerebral vessels. Specific autoantibodies for autoimmune encephalitis turned out to be positive in CSF (antiGAD65 >2000 MU/l) as well as in blood (>2000 MU/l). Immunosupresive treatement (glucocorticoids and i.v. imunoglobulins) with antiepileptics resulted in a clinical course without seizures. **Conclusion:** This is the first documented case of APS type 1 in Slovakia. To the best of our knowledge this is the first described case of autoimmune GAD65-positive encephalitis as a component of APS1. Autoimmune GAD65-positive encephalitis should be considered a new component of the clinical spectrum of APS 1.

P2-204

Children with Coeliac Disease on Gluten Free Diet have Normal Bone Mass, Geometry and Muscle Mass

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Objective: To evaluate musculoskeletal development using pQCT in children with coeliac disease (CD) on gluten free diet (GFD) compared with age and gender matched healthy controls. **Method:** Prospective cross sectional study. 38 children (18 males) with CD on GFD for a duration of 3.6 years (0.6, 12.5) and 38 age and sex matched healthy controls underwent pQCT at 4, 38 and 66% tibial sites. Bloods were collected in CD children only. Results reported as median (range). **Result:** Median age for CD healthy controls were 10.3 years (4.8, 14.8) and 9.3 years (4.9, 15.7) respectively. Median height SDS for CD and healthy controls were −0.2 (−1.5, 2.3) and +0.2 (−2.0, 2,4) respectively ($P=0.01$). Median grip strength adjusted for height SDS for CD and healthy controls were 0.7 (−1.4, 3.4) and 1.1 (−2.0, 3.3) respectively. Median TTG was 1.8 IU/L (0.1, 114) with 30/38 (79%) children with TTG< 8 IU/. Median biagi score that verifies compliance to GFD was 3 (0.0, 4.0) with 32/35 (91.4%) scoring 3 and 4 (score of

3 and 4 = good compliance). Median 25-hydroxyvitamin D was 49.5 nmol/l (21, 82). 1/34 (2.9%) had 25-hydroxyvitamin D <25 nnmol/l. All children had normal serum calcium, phosphate, PTH and thyroid function. A history of fracture was reported in 7/38 (18%) of CD and 5/38 (13.2%) of healthy controls. In adjusted regression model (age, height SDS), there were no differences between CD and controls for pQCT bone area (95%CI -341.1 to $+204.6$, $P=0.62$), muscle area (95%CI -27.8 to $+284.1$, $P=0.97$), periosteal circumference (95%CI -4.6 to $+1.7$, $P=0.37$), endosteal circumference (95%CI -6.0 to $+1.8$, $P=0.28$) and cortical thickness (95%CI -0.1 to $+0.4$, $P=0.33$). There were no significant associations between pQCT bone parameters with TTG, Biagi score, 25-hydroxyvitamin D or calcium in CD. There were no significant associations between pQCT bone parameters and grip strength in CD and healthy controls. **Conclusion:** This first report of bone mass and geometry using pQCT in a group of children with CD on GFD demonstrates normal volumetric BMD and bone geometry compared with healthy controls. Our data questions the need for routine bone surveillance in children with CD who are compliant with GFD.

P2-205

Mechanism of Bone Disease in Prader-Willi Syndrome

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Background: Low bone mineral density (BMD) is found in up to 50% of adolescents and adults with Prader-Willi syndrome (PWS). High fracture risk has been described in adult PWS patients. This bone fragility could be due to inadequate gonadal hormones levels during pubertal development, and to relative growth hormone insufficiency during childhood and adolescence. However, the mechanism/s of low BMD in PWS have not been clarified. **Objective and hypotheses:** i) to study the osteoclastogenic potential of peripheral blood mononuclear cells (PBMCs) of PWS subjects and controls; ii) to evaluate the alteration of RANKL/OPG axis. **Method:** PBMCs of 26 PWS patients and 26 age and sex-matched controls were cultured in presence/absence of M-CSF and RANKL. Mature multinucleated osteoclasts (OCs) were identified as TRAP+ cells. RANKL and OPG levels were measured in the sera. RANKL expression was also evaluated by flow cytometry. Bone status was assessed by DXA. **Results:** A high number of multinucleated TRAP+ OCs were identified in the unstimulated PBMC cultures of PWS patients, while few OCs appeared in cultures of controls (OC number/well 60 ± 5 vs 10 ± 4, $P<0.01$). In the stimulated cultures the same OC number developed in cultures of patients and controls. Flow cytometry on lymphomonocyte circulating fraction of PWS patients showed higher levels of RANKL than controls ($32\%\pm5$ vs $5\%\pm2$, $P<0.01$), Significant higher RANKL and lower OPG levels were found in PWS patients than controls. The RANKL/OPG ratio resulted significantly elevated in patients compared with controls ($P<0.001$). BMD z-score was between <-1 and <-2 in 30% of PWS patients, and <-2.5 in 20% of them. **Conclusion:** We demonstrated a high osteoclastogenic potential of PBMCs of PWS patients, which could be due to increased RANKL/OPG ratio. This condition could contribute to bone disease affecting PWS patients.

P2-206

Hereditary Vitamin D-Resistant Rickets: Report of Four Cases with Successful Use of Intermittent Intravenous Calcium *Via* Peripheral Route

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Background: Hereditary vitamin D-resistant rickets (HVDRR) is a rare disease caused by mutations in vitamin d receptor (VDR). Patients with HVDRR are usually treated with intravenous calcium (i.v.-Ca) therapy *via* a central catheter. However, central catheter-related complications can cause important morbidity. In this report, we described four patients with HVDRR from different families. In three of these cases we used a novel therapeutic regime of intermittent IV-Ca therapy *via* peripheral vein. **Cases:** Four unrelated patients born to consanguineous parents, presented with inability to walk, leg deformities, and alopecia totalis. Diagnosis of HVDRR was established based on clinical and laboratory features (Table 1) and high 1.25 $(OH)_2$ D levels. High dose oral calcium and calcitriol treatment failed to achieve significant improvement. Intermittent i.v.-Ca treatment (2–5 times per week) was begun in four patients by peripheric route. In one patient, parents preferred central venous route and hence treated that way. No complications such as infection, extravasation of Ca or arrhythmias were detected with peripheral infusion. After normalization of PTH and ALP ('saturation of bone') with i.v.-Ca (which varied 1–22 months), physiological doses of oral Ca (200–400 mg/kg per day) and calcitiriol (0.5 µg/kg per day) were sufficient to maintain PTH levels within the normal ranges in all patients. Molecular studies showed that patient #1 and #2 had a homozygous *Q152X* mutation. Patient#3 had a novel homozygous mutation at intron 5, *IVS8 as-2 A > G*, which effects the splice acceptor site. Patient #4 had a novel homozygous *c.67insG* mutation, which causes a frameshift and result in a premature stop (p.Ile23Asp fsX20). **Conclusion:** Here we reported four HVDRR patients with three

Table 1. (for abstract P2.206)

	P#1	P#2	P#3	P#4
Age of 1st symptoms (months)-Sex	8 (F)	Nk (M)	6 (F)	12 (M)
Alopecia	+	+	+	+
Age of presentation (years)	4.3	9.8	2.7	1.5
Ca mg/dl (mmol/l)	8.2	7.5	8.6	8.2
PO4 mg/dl (mmol/l)	2.5	3.4	2.9	2.2
ALP (U/l)	6168	1303	1606	1655
PTH (pg/ml)(12–88)	1240	304	762	590
Age at initiation of IV Ca (years)	5.2	9.8	4.8	1.9
Route of i.v. therapy	periphery	periphery	periphery	Central
i.v. Ca dose (mg/kg/week)	18	90	60	18
Duration of i.v. Ca therapy (months)	10	1	22	10
VDR mutation	Q152X	Q152X	IVS8 as-2 A>G	p.Ile23Asp fsX20

different mutations and, their successful treatment with intermittent intravenous Ca therapy, *via* either peripheric or central route. Peripheral i.v.-Ca treatment seemed to be an effective alternative treatment mode with dramatic clinical benefit and a minimal cost in patients with HVDRR.

P2-207

A Novel *PRKAR1A* Gene Mutation with Mild Brachydactyly

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Background: Acrodysostosis is a rare skeletal dysplasia with severe brachydactyly, facial dysostosis and nasal hypoplasia. Some patients show hormone resistance whose phenotypes are similar to pseudohypoparathyroidism (PHP). In 2012, PRKAR1A gene was identified as one of the responsible genes of Acrodysostosis with hormonal resistance (ADOHR). Generally, brachydactyly is severe and hormone resistance is mild in Acrodysostosis patients. **Objective and hypotheses:** To report a novel heterozygous mutation of *PRKAR1A* gene in an ADOHR patient with mild brachydactyly. **Method:** Mutational analyses: We sequenced three genes associated in PHP using the next generation sequence strategy. Functional assay: We generated PRKAR1A expression vectors containing wild type and mutant type. Using the constructs, we are going to perform CRE-Luciferase activity to analyse the Protein Kinase A activity. **Case:** A 5-year-old boy who presented with short stature was referred to our hospital. He had mild brachydactyly and undescended testis of right side. Mild TSH and PTH resistance were shown; TSH 8.649 μIU/ml, fT_3 3.95 pg/ml, fT_4 1.25 ng/dl, iPTH 95 pg/ml, Ca 9.7 mg/dl and P 4.8 mg/dl. Urinary cAMP sharply elevated after injection of PTH, while urine P did not. Phenotypical features suggest PHP, but the response to PTH indicates an abnormality in the downstream of GNAS. **Results:** We identified a novel heterozygous mutation of c.511G>A, p.G171R in *PRKAR1A* gene. G171 is highly conserved among PRKAR1A protein. G171 is located in cAMP-binding domain B. Only one patient with severe brachydactyly is reported to carry mutation in the cAMP-binding domain B. **Conclusion:** This is the first report of ADOHR patient who carry *PRKAR1A* mutation with mild brachydactyly. Our finding expands the phenotypic features of *PRKAR1A* gene mutations.

P2-208

Bone Mineral Density in Children and Adolescents with Vertical HIV Infection

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Background: Chronic diseases are the main causes of bone mass reduction in childhood and adolescence. Different aspects related to the process of bone acquisition and maintenance may be affected. Studies had point out the presence of bone mass reduction in children and adolescents with HIV infection with association to antiretroviral use, chronological age (CA), weight and serum CD4 T-cell counts. However, others do not. **Objective:** To evaluate bone mineral density (BMD) in children and adolescents with vertically HIV infection and associated factors. **Methods:** Observational study in 46 vertically HIV-infected children and adolescents aged 7.7±3.5 years (17 males). Age, sex, weight, height, CDC clinical categories, BMD at lumbar spine (DXA), blood calcium, phosphorus, alkaline phosphatase (AP), CD4 and CD8 T-cell counts, IGF1, viral load and uCa/Creat were evaluated. BMD, weight and height were expressed in *z*-score. Reduced BMD was defined as *z*-score <-2 DP. Linear regressions, Mann–Whitney U, Kruskal–Wallis and Fisher tests were used in statistical analyses. Human Ethics Comity approved the study. **Results:** Reduced bone mass occurred in 13.0%. These patients had higher CA (12.3 vs 7.5; $P<0.01$), AP (232.7 vs 165.4; $P<0.01$) and IGF1 (464.8 vs 195.4; $P<0.01$); and lower CD4 (356.8 vs 761.8; $P<0.01$) and uCa/Creat (0.1 vs 0.6; $P<0.01$).

BMD correlated positively with CD4 and negatively with CA and IGF1. In multivariate analysis BMD correlated with CD4, CA, AP, uCa/Creat and IGF1 ($r=0.950$; $P<0.001$). Adolescents had higher proportion of reduced BMD (66.7% adolescents (10–19 years) vs 33.3% schoolers (6–10 years); $P<0.01$) and lower BMD (-1.91 adolescents vs -1.11 schoolers *vs* -0.31 preschoolers (2–5 years); $P<0.001$). **Conclusion:** Vertical HIV infection are associated with reduced bone mass, especially during adolescence. The association of low bone mass to low CD4 and higher CA suggests that duration of infection and clinical conditions affects bone mineral acquisition in this group. **Funding:** This work was supported by CNPq and FURB research grants (PIBIC CNPq and PIBIC FURB).

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Sclerostin and Its Associations with Energy Metabolism in Children and Adolescents

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Background: The recent evidence has shown that the skeleton can in turn affect carbohydrate metabolism. **Objective and hypotheses:** To analyse associations between serum level of sclerostin and as well other bone-related molecules as adipokines and some markers of glucose and lipid metabolism in children and adolescents. **Method:** 57 patients, 40 with type 1 diabetes mellitus (T1DM), 17 with obesity, and 11 control, healthy age- and BMI-matched children were included in the study. Fasting blood samples for measurement of bone derived sclerostin, osteocalcin (OC) and receptor activator of nuclear factor NF-κB ligand (RANKL), fat tissue-derived leptin and adiponectin, as well as vitamin D, lipid profile, glucose, HbA1c concentrations were taken at 0800 h. Hormones were measured by immunochemistry, vitamin D by HPLC and other parameters by routine chemistry methods. Statistical analysis was performed in all groups using ANOVA with post-hoc Turkey test and multiple regression analysis. **Results:** Sclerostin levels did not differ among the examined groups. In multiple regression analysis sclerostin was positively related to OC and negatively related to HbA1c level ($P<0.001$, $P=0.04$ respectively). In the group of patients with T1DM the partial regression coefficient of sclerostin for OC was strong ($r=0.62$, $P<0.001$). Moreover in T1DM patients sclerostin was negatively related to as well HbA1c as leptin levels ($P=0.036$, $P=0.038$ respectively). In obese patients multiple regression analysis did not find any relationships between sclerostin and other parameters. In the control group sclerostin was positively related to C-peptide level ($P=0.02$). **Conclusion:** The results of our study suggest that sclerostin could play an important role in the energy metabolism in children and adolescents. Its action seems to be associated with other bone-derived molecules as OC, but also fat-derived leptin. Moreover their relationships could be modified in different metabolic stages. **Funding:** This study was supported by a grant nr K/ZDS/001812, from Medical College, Jagiellonian University in Cracow.

P2-210

Genetic and Epigenetic Alterations at the GNAS Locus and Clinical Consequences in Pseudohypoparathyroidism: A New Healthcare Pathway

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Background: Genetic and epigenetic alterations at the GNAS locus are responsible for the Gsα protein dysfunctions causing Pseudohypoparathyroidism (PHP), a heterogeneous disease characterized by multiple hormone resistances and AHO signs (short stature, obesity, round face, brachydactyly, subcutaneous ossifications and mental retardation). A clinical overlap among molecular subtypes of the disease (Ia, Ib, Ic and II) makes the current classification inadequate; furthermore a common clinical approach still needs to be defined. **Objective and hypotheses:** In the largest Italian case series of (epi)/genetically characterized PHP patients, this work attempts to review and update the clinical data, correlating them to the molecular diagnosis, and to develop a healthcare pathway for patients with AHO/PHP. **Method:** The molecular analysis of the GNAS gene and locus identified the causal alteration in 74 subjects (46 genetic and 28 epigenetic mutations). The clinical data at the diagnosis and their evolution during up to 15 years follow-up, were collected using two different cards. **Results:** We observed that in all patients the growth impairment increases during the time, while overweight/obesity decreases. Subcutaneous ossifications were detected in patients with gene mutations only, which show also a higher prevalence of brachydactyly. In subjects with epigenetic alterations the disease seems to overt later in life, often with symptomatic hypocalcemia. A temptative healthcare pathway for patients with AHO/PHP has been drawn based on the collected clinical data in our series. **Conclusion:** A dedicated healthcare pathway addressing all these aspects in a systematic way would improve the management of the disease, allowing an earlier diagnosis of PHP, which is fundamental to optimize the medical treatment and its timing, (i.e. rGH therapy); however, the different prevalence and features of some AHO signs need to be confirmed by follow-up data, and in the future may lead to a better clinical-oriented molecular analysis. **Funding:** This work was supported by the Italian Society of Pediatric Endocrinology and Diabetology (ISPED) on behalf of the dedicated Study Group on Gsα-related diseases.

P2-211

Fibrous Cortical Defects and Non-Ossifying Fibromas in Patients with Precocious Puberty

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Background: Fibrous cortical defects (FCDs) and non-ossifying fibromas (NOFs) are the most common benign lesions of the skeletal system, with an estimated incidence of up to 30% in children and adolescents. **Objective and hypotheses:** Although their aetiologies are unknown, FCDs and NOFs develop mostly in regions of intense bone growth. We hypothesized that patients with precocious puberty (PP) would have a higher prevalence of FCDs and NOFs than age-matched patients without PP. **Method:** A retrospective radiological assessment of 607 patients with PP diagnosed between 2003 and 2014 was performed. The number of FCDs and NOFs and their location and morphology were determined on x-ray images of the area surrounding the knee joint. X-ray images of the corresponding area, taken to evaluate the condition of the growth plate, from 911 age-matched patients without PP served as the control. **Results:** Among the 607 patients with PP, 56 had FCDs or NOFs, resulting in a significantly higher prevalence in the PP patients than in the age-matched controls without PP (9.2% vs 2.3%). Most (71.4%) of the lesions were located in the distal femoral metaphysis; none of the patients had multifocal lesions. The mean age at discovery was 9.9 ± 2.4 years. The follow-up period was between 3 months and 10.5 years. Based on the radiological findings, 32 of the 56 patients had FCDs, all of which resolved completely during the follow-up period. In five of the remaining 24 patients with NOFs, the lesion either did not change in size or became much larger. **Conclusion:** The prevalence of FCDs and NOFs was lower in our study population than in the reported populations. FCDs and NOFs occurring in the condition of PP might be related to the intensive bone growth associated with this condition. Lesions that fail to regress spontaneously should be followed until they regress.

P2-212

The Effect of High Dose Oral 17ß Estradiol on Bone Mineralization and Body Composition in Young Women with Turner Syndrome – A 5 Year Randomized Controlled Clinical Trial

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Background: Reduced bone mineral density (BMD) is seen in Turner syndrome (TS) with an increased risk of fractures and osteoporosis. Body composition in TS is characterised by increased body fat (FM) and decreased lean body mass (LBM), even with a normal BMI. Oestrogen replacement therapy for attaining and preserving normal bone mass is necessary in most TS girls. There is a potential role of age-specific estrogen doses, with lower doses used in the early puberty and higher doses at the end of adolescence. Oestrogen also affects the accrual and preservation of LBM positively. **Objective and aims:** To evaluate the effect of two different doses of oral 17ß-oestradiol in young women with TS on BMD, bone markers, hormones related to bone metabolism, and body composition. **Method:** A double-blind 5 year randomized controlled clinical trial. The lower-dose (LD) group took 2 mg 17ß-oestradiol/day orally and placebo. The higher-dose (HD) group took $2 + 2$ mg 17ß-estradiol/day orally. 20 young TS women (19.2 ± 2.5 years, range 16.0–24.9) participated. DXA scan (BMD, FM, LBM), CTX, PINP, BSAP, PTH, IGF1, and IGFBP3 were performed yearly. **Results:** BMD increased over time with a tendency of attenuation towards the end of the study and bone markers decreased over time, both with no differences between the groups. IGF1 decreased in both groups. The rate of change of IGF1 was constantly lower in the HD group. LBM increased significantly in the HD group over time, whereas FM remained stable in both groups. **Conclusion:** We show a distinct pattern of changes in BMD in TS over time with a steady increase in BMD in accordance with the findings in the general population of healthy young women. The higher estrogen dose did not affect BMD or bone markers. The positive effect on body composition may have long ranging health benefits in TS. **Funding:** Novo Nordisk supplied the study medication.

P2-213

Comparison of Cost Benefits and Efficacy of Zoledronic Acid and Pamidronate in the Treatment of Osteogenesis Imperfecta in Children

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Background: i.v. Pamidronate (PAM) has been used in the treatment of osteogenesis imperfecta (OI) and is known to increase bone mineral density (BMD) and reduce the incidence of fractures. However an attractive alternative is the more potent i.v. Zoledronic acid (ZOL). **Objective and hypotheses:** To determine the clinical efficacy of i.v. PAM vs ZOL in children with mild to moderate OI and compare the cost benefits of the two drugs. **Method:** A retrospective review of patients aged $\geqq 5$ years with type I or i.v. OI, who started either PAM or ZOL (2001–2014)

at a tertiary centre was conducted. PAM was administered in cycles of 1.5 mg/kg per day over 2 days every 3 months and ZOL as a single dose of 0.05 mg/kg 6 monthly. Lumbar spine (LS) DXA was performed pre and 1 year post treatment. Cost analysis was performed for a 5 year period based on drug cost, nursing and medical time, equipment and days in hospital per year (8 vs 2 days/year, for PAM vs ZOL). **Results:** A total of 40 patients were identified, 20 in each group. LS BMAD *z*-scores increased significantly in both groups ($P<0.001$). The median (interquartile range) increase in LS BMAD *z*-score for the PAM group (1.67 (1.46–2.21)) and the ZOL group (1.75 (1.46–2.00)) was not significantly different. Total cost per treatment cycle per patient was £498 for ZOL and £1157 for PAM. Annual costs for bisphosphonate therapy (BP) per case since the introduction of ZOL halved from £1128 in 2008 to £540 in 2013. **Conclusion:** ZOL is a significantly cheaper alternative to PAM with comparable efficacy, resulting in substantial annual savings for health care providers. ZOL is also a more convenient option for patients due to fewer hospital visits, less time off school for patients and leave from work for carers.

P2-214

TmP/GFR is a Useful Marker in Making a Clinical Diagnosis of X-Linked Hypophosphataemic Rickets Caused by the PHEX Gene Mutation

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Background: The clinical diagnosis of x-linked hypophosphatemic (XLH) rickets is based on a number of biochemical observations. These include a reduction in the percentage of tubular reabsorption of phosphate (%TRP), and in the maximal tubular phosphate reabsorption capacity corrected for glomerular filtration rate (TmP/GFR). However, it is important to maintain sufficient renal blood flow in order to accurately calculate TmP/GFR. **Objective:** The aims of this study were to compare the normal reference values of %TRP and TmP/GFR with the values detected in XLH patients with and without pre-examination water loading, and to compare the time-dependent alterations in %TRP and TmP/GFR values in XLH patients who performed water loading either from the beginning of the test or the day before testing. **Results:** i) In the analysis of %TRP and TmP/GFR, calculated in 286 samples from 26 XLH patients without water loading, 64 samples for %TRP and four samples for TmP/GFR showed values within the reference ranges. ii) A time-dependent decrease in %TRP and TmP/GFR was observed in cases of XLH patients who performed water loading from the beginning of the test. However, time-dependent alterations in %TRP and TmP/GFR were not identified in patients who performed water loading from the day before testing. iii) In the analysis of %TRP and TmP/GFR, calculated in 48 samples from 22 XLH patients after water loading, 25 samples for %TRP showed values within the reference range, and all samples for TmP/GFR showed values lower than the reference value. **Conclusion:** TmP/GFR is a more useful marker than %TRP in making a clinical diagnosis of XLH caused by the PHEX gene mutation. Furthermore, it is important to maintain sufficient renal blood flow in order to accurately calculate TmP/GFR.

P2-215

Whole-Body Vibration Training Improves Physical Function and Increases Bone and Muscle Mass in Youngsters with Mild Cerebral Palsy

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Background: Adolescents with cerebral palsy (CP) have decreased muscle mass resulting in impaired mobility and osteopenia. There is a void in therapeutic interventions aimed at increasing muscle mass, muscle function as well as osteopoenia in this population. Whole body vibration training (WBVT) has the potential to fill this therapeutic void by maintaining/increasing muscle mass and bone mineral accrual during growth. **Objective and hypotheses:** We aimed to evaluate the effect of 20 weeks of WBVT on muscle function and bone health of adolescents with CP. **Method:** 40 adolescents (16.2 ± 2.1 years) with mild to moderate CP (10–20 years, Gross Motor Function Classification System – GMFCS II and III) were recruited to perform 9 min/day, $4\times$week of WBVT. Data was collected at baseline and after 20 weeks of vibration training on a Galileo platform. The assessments included Six-minute walk test, whole-body dual-energy x-ray absorptiometry, peripheral quantitative computed tomography of the non-dominant tibia, muscle force and power using a ground reaction force plate. **Results:** 20 weeks of vibration therapy increased lean mass overall ($+770$ g; $P=0.0003$), in the trunk ($+410$ g; $P=0.004$), and in the legs ($+240$ g; $P=0.012$). There were also consistent improvements in bone mass, with bone mineral content increasing in whole body ($+48$ g; $P=0.0001$), spine ($+2.7$ g; $P=0.0003$), and legs ($+13$ g; $P<0.0001$). Similarly, bone mineral density also increased in whole body

(+0.008 g/cm^2; $P=0.013$), spine (+0.014 g/cm^2; $P=0.003$), and legs (+0.023 g/cm^2; $P<0.0001$). Participants reduced the time taken to perform the chair test ($P=0.0004$) and improved the distance walked in the 6-min walk test by 11% on GMFCS II and 35% on GMFCS III participants. **Conclusion:** Whole body vibration significantly increases muscle mass and bone health and improves mobility, thus improving the health and well-being of children with CP. **Funding:** This work was supported by the Jubilee Trust, Australasian Paediatric Society Group and Maurice & Phyllis Paykel Grants.

P2-216

A Case with Acrodysostosis and Hormone Resistance

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Aim: Acrodysostosis is a rare genetic syndrome characterized by small hands and feet with short, stubby fingers and toes, cone shaped epiphyses, broad nasal root, various abnormalities of mandible, skull, and vertebra, short stature, and mental retardation. Because of the hormone resistance that would accompany, acrodysostosis can be confused with pseudohypoparathyroidism. Mutations of *PRKAR1A* and *PDE4D* are reported to be responsible for the disease in less than 50 cases. **Method:** A case considered to have acrodysostosisis discussed regarding clinical and laboratory findings. **Results:** A 12-year-old male patient was referred due to short hands and feet. These complaints were present since birth without a history of regular drug use or major disease. Motor and mental development was delayed compared to his peers. His parents were not relatives but from the same village. Physical examination disclosed followings: weight 45 kg (0.50 SDS), height 143.7 cm (−0.83 SDS), synophrys, arched eyebrows, low-set ears, and small squared hands. Upper/lower segment ratio was normal (0.95). Optic atrophy was bilateral but predominantly affected the left side. Skeletal survey was normal except short tubular bones in hands and feet and cone-shaped epiphyses. Calcium was 9.5 mg/dl, phosphorus 6 mg/dl, alkaline phosphatase 304 IU/l, parathormone 303 pg/ml, 25 (OH) vitamin D 22.4 ng/ml, thyroid-stimulating hormone 11.5 mIU/ml, fT_4 1.02 ng/dl, fT_3 4.7 pg/ml, and anti-thyroid peroxidase and anti-thyroglobulin antibodies negative. Thyroid ultrasonography revealed a volume of 2.79 ml (−1.52 SDS) and low echogenicity but no nodule. Bone age was compatible with chronological age. L-thyroxine 50 μg per day were administered. In our patient who had both parathormone and thyroid hormone resistance, the heterozygous cytosine-to-thymidine mutation was identified in *PRKAR1A gene* (c.1101C3T). **Conclusion:** Acrodysostosis should be kept in mind and appropriately evaluated when hormone resistance is detected in cases who presented with small hands and feet as well as pseudohypoparathyroidism.

P2-217

The Spectrum of Molecular Defects in 64 Patients with Hypophosphatemic Rickets Identified by Targeted Next-Generation Sequencing

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Background: Hypophosphatemic rickets (HR) comprises a group of inherited forms of rickets characterised by renal phosphate wasting. To date more than 10 genes are associated with HR, and a comprehensive molecular diagnosis in these disorders is technically difficult to perform. **Objective and hypotheses:** To assess the value of targeted next-generation sequencing (NGS) used for molecular analysis of candidate genes of HR. **Method:** 64 patients (aged, of 3 months to 45 years; females, $n=32$; males, $n=32$) with clinical and radiological findings of rickets, low serum phosphate and low tubular reabsorption of phosphate were included. There were 29 familial and 35 sporadic cases from 58 families. 'Rickets panel' genes were sequenced using a custom Ion Ampliseq gene panel and PGM semiconductor sequencer (Ion Torrent). Bioinformatic analysis was performed using Torrent Suite (Ion Torrent) and ANNOVAR (annovar.openbioinformatics.org) software packages. **Results:** Mutations were identified in 100% of familial and 88,5% of sporadic cases. In 60 probands mutations were detected in *PHEX*, 38 of which were novel. Out of the 54 *PHEX* mutations there were deletions ($n=7$), missense ($n=13$), nonsense ($n=11$), insertion and deletions ($n=16$) and splice site mutations ($n=7$). One subject had both *DMP1* and *PHEX* mutations. No mutations were detected in *FGF23*, *SLC34A1*, *SLC34A3*, *SLC9A3R1*, *ENPP1*, *CLCN5* and *SLC2A2* genes. **Conclusion:** The study confirmed predominance of *PHEX* mutations among the patients with HR. Nevertheless, the large size and complexity of *PHEX* gene makes the targeted NGS a feasible tool for diagnostics of HR. **Funding:** This work was supported by Alfa-Endo Program of Charities Aid Foundation (CAF) Russia.

P2-218

Nephrocalcinosis and Nephrolithiasis in 36 X-Linked Hypophosphataemic Rickets Patients: Diagnostic Imaging and Evaluation of Risk Factors in a Single-Centre Study

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Background: X-linked hypophosphatemic rickets (XLH) is caused by inactivating mutations in the phosphate-regulating gene with homologies to endopeptidases on the X chromosome (*PHEX*). In this group of patients, data about renal calcifying disorders are scarce. **Objective and hypotheses:** To determine the prevalence of nephrocalcinosis and nephrolithiasis and their risk factors in XLH patients. **Method:** 36 patients (15 children and 21 adults; 27 women and nine men) with confirmed *PHEX* mutations were followed for 5 years at regular intervals. Associated metabolic factors were evaluated by 24-h urinary samples. Blinded radiologists performed renal ultrasonography (US) and computed tomography (CT) and graded nephrocalcinosis using a 0–3 scale with 0 meaning no nephrocalcinosis and 3 meaning severe nephrocalcinosis. The NC confirmation was determined with a positive result in both US and CT while the NL diagnosis was confirmed by CT. **Results:** Besides hyperphosphaturia, present in all XLH patients, hypocitraturia was the most common metabolic factor found (30.5%), while hypercalciuria occurred in two patients (5.5%) and no one had hyperoxaluria. US diagnosed NC in 34 (94.4%) patients: 33 (97%) as grade 1 and one (3%) as grade 2. Meanwhile, CT identified medullary NC in 15 (41.6%) patients: 10 (66.7%) as grade 1 and five (33.3%) as grade 2. CT identified NL in 4 (11.1%) adults. Stratification by age showed a higher prevalence of NC in children than adults (60% vs 28.5%). The pediatric group, in intensive use of phosphate, started treatment earlier ($P<0.01$) and presented a greater phosphaturia than the adult group ($P<0.01$). **Conclusion:** In our cohort, nephrocalcinosis was more prevalent than nephrolithiasis. The main metabolic factor was hyperphosphaturia and intensive phosphate treatment appears to be a mitigating factor to kidney calcifications.

P2-219

Early Increase of the Bone Formation Marker PINP is in a Higher Degree Related to Growth Response Compared to Bone Mineralization in GH Treated Prepubertal Children

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Background: It has been reported that short-term increases of the bone formation markers intact amino-terminal propeptide of type I procollagen (PINP), bone-specific alkaline phosphatase (BALP) and osteocalcin display different temporal patterns. In adults, the biphasic model of GH action in bone remodelling shows that GH treatment results initially in an increased bone resorption with a concomitant bone loss, which later on is followed by increased bone formation. In children, little is known how bone remodelling takes place. **Objective and hypotheses:** Bone formation markers reflect different events during osteogenesis, and respond with different time courses during anabolic GH treatment. **Method:** The study population comprised 128 short prepubertal children (age range 3−11 years; 90 boys, 38 girls) who participated in a longitudinal, prospective, multicenter study in individual GH dosing[1], TRN 98-0198-003. The investigated children had either normal or reduced levels of GH secretion. Data from the first 2 years of GH treatment were analyzed. The bone markers were measured using the IDS-iSYS automatic system (immunodiagnostic systems)[2]. The DXA derived variable bone mineral density (BMD) was measured by Lunar DPX-L or Lunar Prodigy. **Results:** The bone markers PINP, BALP, osteocalcin and 25-hydroxyvitamin D (25(OH) D) at start and deltaPINP at 3 months of GH treatment explained 63% of the growth response at 2 years ($P<0.0001$), while only 26% of the variation in BMD response after 2 years of treatment was explained ($P<0.0001$). **Conclusion:** Bone markers at start of GH treatment, and the 3 months increase of PINP were associated with both growth response and bone mineralization after 2 years of treatment, but with different magnitude of impact on these anabolic GH effects.

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Genotype and Phenotype Characteristics in 22 Patients with Vitamin D Dependent Rickets Type I

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Background: Vitamin D dependent rickets type I (VDDR1) is an autosomal recessive disorder caused by mutations in the 25-Hydroxyvitamin-D_3 1-α-hydroxylase gene(*CYP27B1*). **Objective and hypotheses:** To evaluate clinical characteristics and molecular genetic analysis of the pediatric patients with VDDR1 who were being followed at Diyarbakir Children's State Hospital, Turkey. **Method:** VDDR1 diagnosis was considered in course of clinical, biochemical and radiological characteristics of rickets with a normal or high 25(OH) vitamin-D level. Genomic DNA was extracted from peripheral blood leukocytes using a standard procedure. Mutation analysis was performed on all affected cases and subsequently on the unaffected family members where DNA

was available. *In silico* analysis of the novel variants was performed using online available protein prediction software's. **Results:** In total 22 patients (11 females) from 13 families with VDDR1 recruited. The most common mutation which was detected in ten VDDR1 patients was a previously described, c.195 + 2T > G, splice donor site mutation. The novel missense p.192K > E(c.574A > G) mutation was detected in five patients, and a novel missense p.197G > D(c.590G > A) mutation was found in four patients. Previously reported 7 bp duplication mutation 1319–1325dupCCCACCC(Phe443Profs*24) in exon 8, was detected in one patient in the homozygous state. One patient was compound heterozygote for the novel p.192K > E and the previously described 1319–1325dupCCCACCC mutations. We also observed in one patient a novel single bp deletion, c.171_171delG, which causes a frame shift from protein 58 l and downstream, leading to an early stop. From the 36 unaffected family members, 28 were mono-allelic for the mutation detected in their family, and eight were biallelic for the normal reference allele. **Conclusion:** In this study on the largest VDDR1 cohort, we identified three novel and two previously described mutations in the *CYP27B1* gene. Mutation analysis, patient characteristics and sequencing results of unaffected family members revealed a good phenotype and genotype correlation.

P2-221

Evidence of a Link Between Resting Energy Expenditure and Bone Remodelling, Glucose Homeostasis and Adipokine Variations in Adolescent Girls with Anorexia Nervosa

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Purpose: Low areal bone mineral density (aBMD) is a well-known consequence of anorexia nervosa (AN). However, the impact of reduced energy expenditure on bone metabolism is unknown. This study assessed the effects of energy deficiency on bone remodelling and its potential interactions with glucose homeostasis and adipose tissue-derived hormones in AN, a clinical model for reduced energy expenditure. **Methods:** 50 women with AN and 50 age-matched controls (mean age 18.1 ± 2.7 and 18.0 ± 2.1 years respectively) were enrolled. aBMD were determined with DXA. Resting energy expenditure (REEm), a marker of energy status, was indirectly assessed by calorimetry. Bone turnover markers, undercarboxyated osteocalcin (ucOC), parameters of glucose homeostasis, adipokines and growth factors were concomitantly evaluated. **Results:** AN patients presented low aBMD at all bone sites. REEm, bone formation markers, ucOC, glucose, insulin, HOMA-IR, leptin and, IGF-1 were significantly reduced, whereas the bone resorption marker, leptin receptor (sOB-R) and adiponectin were elevated in AN compared with CON. In AN patients, REEm was positively correlated with weight, BMI, whole body (WB) fat mass, WB fat-free soft tissue, markers of bone formation, glucose, insulin, HOMA-IR, leptin, and IGF1, and negatively correlated with the bone resorption marker and sOB-R. Biological parameters, aBMD excepted, appeared more affected by the weight variation in the last 6 months than by the disease duration. **Conclusions:** The strong interrelationships between REEm and bone remodelling, glucose homeostasis and adipokines underscore the importance of preventing energy deficiency to limit short- and long-term bone demineralisation and hormonal alterations in AN patients. **Funding:** This work was supported by the Centre Hospitalier Regional Universitaire (CHRU) of Montpellier (AOI UF 8751 and UF 8854) and a grant from the Société Française d'Endocrinologie Pédiatrique (SFEDP).

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Bone Density, HIV Infection and Antiretroviral Treatment: A 10-Year Follow-Up in Young Patients

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Background: The success of highly active antiretroviral therapy (HAART) has dramatically increased life expectancy for human immunodeficiency virus (HIV)-positive patients, revealing a range of chronic problems associated with HIV. Among others, low bone mineral density (BMD) has been described in HIV-infected youths. Little is currently known about the changes of BMD over time in these patients. **Objective and hypotheses:** The aim of the study was to assess BMD changes over a ten-year period in a large cohort of HIV-infected young patients and to compare the results to the data obtained on a healthy control group of children and adolescents. **Method:** We report the 10 year follow-up data of 26 patients (13 girls), on HAART containing

tenofovir disoproxyl fumarate (TDF). The age at entry of the study ranged from 5 to 17 years. BMD measurements were compared to those obtained in 201 healthy subjects (3–25 years). BMD was measured at the lumbar spine (L1–L4 vertebrae) and in the whole skeleton. Analysis of the data were performed nonlinear mixed effect regression models for longitudinal data for both patients and controls. **Results:** HIV-infected patients did not differ from controls subjects in anthropometric measurements. Comparisons between the curves of healthy controls and HIV-infected patients showed significant differences at lumbar spine ($P < .0001$) and in the whole skeleton ($P < .01$) in boys and girls. However, further analyses showed that the difference between patients and controls did not change over time. **Conclusion:** Our long-term follow-up of BMD measurements demonstrate that the initial deficit in BMD does not worsen over time in patients receiving HAART. Moreover, the use of TDF appears to be safe as opposed to adult patients with HIV infection.

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Refractory Hypercalcaemia of Malignancy: Responsiveness to Denosumab and Zoledronate

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Background: Hypercalcaemia secondary to malignancy is rare in children and adolescents. Parathyroid hormone related peptide (PTH-rP) secreted by malignant cells increases bone resorption and renal calcium retention causing hypercalcaemia. We report 2 cases of hypercalcaemia of malignancy refractory to treatment with pamidronate and corticosteroids but responsive to treatment with Denosumab and Zoledronic acid. **Case 1:** A 17-year-old boy with epidermolysis bullosa and advanced squamous cell carcinoma of the left leg presented with symptomatic hypercalcaemia (serum adjusted calcium, 4.2 mmol/l). PTH was suppressed at 0.7 pmol/l. Serum 25 hydroxy vitamin D level was 31 nmol/l (normal range $>$ 50 nmol/l). PTH-rP and 1, 25 dihydroxy vitamin D levels were elevated at 2.1 pmol/l (0.0–1.8) and 173 pmol/l (43–143) respectively. The hypercalcaemia was initially managed with hyperhydration, prednisolone and i.v. pamidronate (1 mg/kg per dose $\times$ two doses), following which only transient improvement was noted. As symptomatic hypocalcaemia persisted (serum calcium 3.39 mmol/l), a trial dose of subcutaneous Denosumab (60 mg) was given, following which the calcium fell to 2.86mmol/l within 24 h and normocalcemia was sustained a week later. **Case 2:** A 17-year-old girl with pelvic rhabdomyosarcoma was hypercalcaemic (serum adjusted calcium, 3.19 mmol/l) with suppressed PTH of 0.3 pmol/l. Serum 25 hydroxy vitamin D was 28 nmol/l and renal profile was normal. The initial treatment comprised hyperhydration, furosemide, prednisolone and intravenous pamidronate (1 mg/kg). As symptomatic hypercalcaemia persisted (serum calcium 4.04 mmol/l), intravenous Zoledronic acid (2 mg) was administered, following which the serum calcium dropped to 2.79 mmol/l within 24 h with sustained normocalcemia. **Conclusion:** Denosumab is a monoclonal antibody, which neutralises RANKL (receptor activator of nuclear factor κ-B ligand), inhibiting the function of osteoclasts thereby preventing generalized bone resorption. Zoledronic acid blocks osteoclast resorption and has a more potent calcium-lowering effect than pamidronate. These two drugs widen the treatment options for patients with resistant hypercalcaemia of malignancy.

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Fractures in Boys with Duchenne Muscular Dystrophy and their Relationship to Age

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Objective and hypotheses: A retrospective review of bone morbidity in a contemporary cohort of boys with Duchenne muscular dystrophy (DMD) managed in a Scottish tertiary neuromuscular centre. **Method:** Clinical details and results of bone surveillance were obtained in 47 boys, aged 9 years (2–16). DXA bone mineral content (BMC) at total body (TB) and lumbar spine (LS) were adjusted for bone area. Fractures were classified based on radiological confirmation. Results are in median (range). **Results:** 39/47(82%) were on steroid therapy and 26/47 (55%) were ambulant. All were treated with vitamin D (800–1000 units/day). Of 35 who had vitamin D measured, 5 (14%) had a level $<$ 25 nmol/l. 5/10 (50%) of those $>$ 14 years had delayed puberty and had testosterone therapy. 12 (26%) sustained a total of 15 symptomatic fracture events. 12/15 (80%) were appendicular fractures (AF) and 3/15 (20%) were vertebral fractures (VF). AF occurred at a median age of 6 years (2.5, 14). The fracture distributions were 7 (58%) tibia/fibula, 3 (25%) femur and 2 (17%) humerus/radius/ulna. Mechanisms of injuries were 11 (92%) minor fall and 1 (8%) occurred while being lifted. Median length of steroid exposure was 4 years (0, 10). 7/9 (75%) were ambulant prior to fracture. 2/7 (29%) lost ambulation after fracture. 3/12 (21%) of AF occurred in steroid naïve ambulant boys $<$ 3 years. DXA and vitamin D level within 1 year of AF showed TB BMC SDS 0.1($-$0.8, 1.0) and LS BMC SDS $-$0.2 ($-$1.2, 1.0). Vitamin D level was $<$ 25 nmol/l in 2/10 (20%). VF occurred at a median age of 11 years (9, 13). 2/3 were ambulant. Median length of steroid exposure was 6 years (5, 8). DXA within 1 year of VF showed TB BMC SDS 0.3 ($-$0.2, 1.1) and LS BMC SDS $-$0.1 ($-$0.6, 0.8). None had vitamin D $<$ 25 nmol/l. **Conclusion:** Symptomatic VF occur in older children, with longer duration of steroid therapy. AF occur in younger boys and can also present in very young, ambulant, steroid naïve boys. Coincidental severe vitamin D deficiency or reduced BMC were not common findings at a fracture event.

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Early Detection of Increased Bone Turnover among Children and Adolescents with Type 1 Diabetes Mellitus

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Background: Most organs including bone are affected in type 2 Diabetes (T1D) mechanisms. The exact mechanism of bone derangement is still unknown. **Aim of work:** i) Assessment of Pyridinoline crosslinks as a bone resorption marker and alkaline phosphatase as a bone formation marker in T1D in children & adolescents. ii) To determine the effect of glycemic control and disease duration on bone turnover. **Subjects and methods:** 39 T1D patients, together with 39 age and sex matched non-diabetic healthy controls. The disease duration has to be at least 2 years. Exclusion criteria included autoimmune diseases, renal diseases, hyperparathyroidism, hypertension or medications that interfere with bone metabolism. The study was approved by the Ethical Committee. The entire group was subjected to history taking and through clinical examination. Lab. investigations included: Hb A1C by quantitative colorimetric determination of glycohaemoglobin in whole blood. Parathyroid hormone assayed by ELIZA kits,alkaline phosphatase quantitative determination by kinetic method as per recommendation of German Society for clinical chemistry.Urine sample for pyridinoline cross links (PYD) by ELIZA. **Results:** T1D had a mean Hb A1C of $10.7 \pm 1.6\%$, receiving 1.08 ± 0.27 units of insulin per kilogram per day. All had normal parathyroid hormone, while one third of them had high levels of alkaline phosphatase. PYD in diabetics was significantly higher than controls (49.06 ± 9.85 nmol/l vs 13.46 ± 6.69 nmol/l, $P=0.001$). PYD/creatinine was significantly higher than controls (12.64 ± 4.31 nmol/mmol vs 2.90 ± 1.50 nmol/mmol, $P=0.001$), In T1D there was no significant correlation between PYD/creatinine or PYD alone and BMI, age, disease duration, Hb A1C or ALP. **Conclusion:** Urinary PYD crosslink is markedly higher in diabetics than non-diabetics. Bone turnover (resorption and formation) in T1D is neither dependent on glycaemic control nor on the disease duration.

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Association between Oxidative Stress and Bone Turnover Markers in the Obese Children

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Background: Recent data have been showed that free radicals are involved in either bone resorption and atherosclerosis development in adults. In paediatric population the important risk factor for the early atherosclerosis development is obesity, which can be also associated with the disturb bone turnover. **Objective and hypotheses:** The aim of the study was to evaluate the interrelationship between oxidative stress and bone turnover markers in obese children vs lean controls and correlated them with the anthropometrical status and metabolic activity of adipose tissue. **Method:** Bone turnover markers (osteocalcin (OC), N-terminal telopeptide of type I collagen (NTx)), oxidative stress markers (total antioxidative capacity (TAC), glutathione peroxidase, oxLDL) and leptin were determined in 50 obese children and 79 healthy controls. Anthropometrical status by BMI calculation and body composition parameters as: fat mass (FAT), fat-free mass (FMM), predicted muscle mass (PMM) and total body water (TBW) were evaluated using bioelectrical impedance analyzer (BIA) in all children. **Results:** OC was significantly lower in obese children and correlated significantly (negatively $P<0.01$) with BMI in the lean group. There was also significant positive correlation between OC and TAC in obese children. NTx correlated significantly with oxy-LDL (positively) in either, obese and lean group ($P<0.05$ and $P<0.01$ respectively). In the lean group only, there were significant relations between NTx vs leptin and body composition parameters ($r=0.245$ vs leptin, $r=0.245$ vs FAT%, $r=-0.252$ vs PMM%, and $r=-0.245$ vs FFM% respectively). **Conclusion:** Bone turnover seems to be disturbed in the obese children and pathophysiological factor with can be involved in that mechanism may be an increase oxidative stress level. Osteocalcin and NTx levels seem to be related to the anthropometrical status and adipose tissue activity (leptin level). **Funding:** This work was supported by Polish Ministry of Science (grant number: KNW-1-112/P/2/0).

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Longitudinal Bone Development in Patients with Classical Congenital Adrenal Hyperplasia: Data Using Peripheral Quantitative Computed Tomography

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Background and aims: Glucocorticoid treatment may influence bone and muscle development in patients with congenital adrenal hyperplasia (CAH). This study evaluated bone mineral density (BMD), bone geometry and muscle mass longitudinally throughout childhood. **Methods:** 18 patients (ten males, eight females) with classical CAH were included. BMD, bone geometry and muscle mass were measured using peripheral quantitative computed tomography (pQCT) in prepubertal, midpubertal and postpubertal years. **Results:** Mean age at first measurement was 9.70 ± 1.95 years., at second 13.94 ± 0.98 years. and at third 17.03 ± 1.11 years. The corresponding bone ages were within a range of ± 1 years for chronological age. In all, mean SD score for trabecular BMD decreased (from 0.77 ± 1.24 to -0.32 ± 1.12), whereas mean cortical BMD increased (from -0.40 ± 1.39 to 0.74 ± 1.18). Mean SD scores at first measurement for total (0.86 ± 1.12) and medullary

cross-sectional area (CSA) (2.10 ± 1.17) were significantly elevated, also at all further time points, but decreased with time (−0.802 and −0.61 respectively; $P < 0.001$). In all patients, SD score for relative cortical CSA (−1.32 ± 01.16) was stable on a reduced level throughout childhood. After adjustment for lower height, muscle CSA was normal in all. **Conclusion:** From childhood to adolescence we observed a reduction of trabecular BMD. There is an enlarged total and medullary CSA in CAH patients that decrease with time. Relative cortical CSA was reduced in all CAH patients. These longitudinal changes in bone geometry may have a long-term impact on bone stability.

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Online Survey to Characterise the Burden of Illness in Children with X-Linked Hypophosphatemia

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Background: X-linked Hypophosphatemia (XLH), the most common heritable form of rickets, is a disorder of renal phosphate wasting caused by high circulating levels of fibroblast growth factor 23 (FGF23) that impairs normal phosphate reabsorption in the kidney and production of the active form of vitamin D. Affected children present with hypophosphatemia resulting in rickets, bowing of the legs and short stature. Limited information is available about the disease burden in children with XLH. **Objective and hypotheses:** The objective was to characterize the clinical condition of children with XLH and assess the impact on function and quality of life. **Method:** An IRB-approved, web-based questionnaire was completed by parents on behalf of children with XLH. English and French versions were available. **Results:** 70 paediatric surveys were completed for children from 1–17 years of age with a median age of 8 years. The median age at diagnosis was 2 years. Nearly all children were being treated with a standard of care (SOC) regimen that includes multiple daily doses of oral phosphate and active vitamin D (69/70 (99%)). Most children were diagnosed prior to 3 years of age (53/70 (76%)). Reported skeletal abnormalities and resulting complications included bowing of the femur, tibia/fibula (61/70 (87%)), gait disturbance (60/70 (86%)), joint pain (45/70 (64%)), bone pain (41/70 (59%)) and restricted range of motion (29/70 (41%)). Over 30% of responders had undergone at least one surgery to correct a skeletal defect. Diminished height was reported for (57/70 (81%)) of children with the majority of boys under the 25th percentile and the majority of girls under the 50th percentile for height. Scores on two PROs, the PODCI and the SF-10 were >1 SD below the US general population norms indicating significant issues with pain, mobility and quality of life. **Conclusion:** Children with XLH experience significant complications despite SOC treatment highlighting the need for more efficacious therapies. **Funding:** This work was supported by Ultragenyx Pharmaceutical Inc, the study sponsor.

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Comparison of the Response to Bisphosphonate Treatment between Acute Lymphoblastic Leukaemia and Osteogenesis Imperfecta Type I

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Background: Osteoporosis in children with osteogenesis imperfecta type 1 (OIT1) and acute lymphoblastic leukaemia (ALL) is characterised by high bone turnover. However the ability of spontaneous healing and reshaping of bone is retained in ALL even in the absence of bisphosphonate (BP) therapy, but impaired in OI. **Objectives:** To compare the response to BP therapy in children with ALL and OI. **Methods:** Retrospective review of children with ALL and OIT1 (2008–2013) managed at a single tertiary centre. Clinical data and dual energy x-ray absorptiometry (DXA) results were collected at baseline and following first year of intravenous BP therapy. **Results:** Ten (seven males) ALL patients were compared to 12 (seven males) OIT1 patients. Four of ten and 5/12 received zoledronic acid in ALL and OI respectively and the others received pamidronate. The median age at start of BP treatment for ALL and OI groups were (9.6 vs 10.2 years, $P=0.86$). The median height SDS of OI group was significantly lower compared to ALL group at the start of treatment (−1.38 vs 0.29, $P=0.001$). Growth during therapy (Δ height SDS) was not different between ALL and OI groups (−0.28 vs 0.045, $P=0.49$). Compared to baseline, the lumbar spine bone mineral apparent density (LSBMAD) z-scores improved significantly in both groups (ALL: −2.45 (range −3.6 to −0.90) to −0.45 (range −2.5 to 0.5), $P=0.005$; OI: −2.70 (range −4.20 to −0.29) to −1.1(range −2.15 to 1.17), $P=0.003$)). The 1-year change in LSBMAD z-score during treatment was similar between groups (ALL 1.34, OI 1.64, $P=0.92$). However, at the end of 1-year of treatment the median LSBMAD z-score in ALL patients (−0.45) was not different from normal (zero), but that for OI was significantly lower than normal (−1.1, $P=0.010$). **Conclusion:** LSBMAD improvement in ALL is comparable to that in children with type I OI. Although both groups responded similarly to BP treatment, LSBMAD was closer to normal in ALL patients after 1 year of therapy. **Funding:** No funding has been received for this work.

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The Relationship between Serum 25-Hydroxy Vitamin D and Parathyroid Hormone in Children

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Background: The lack of agreement in the definition of vitamin D deficiency may be due to differences in the study populations or in the assays used to measure 25OHD.

Objective and hypotheses: The aim of this study is to evaluate the relationship between 25OHD and PTH, and define the level of vitamin D deficiency in a paediatric population. **Method:** Retrospective medical record of children (age: 0.1–18years, $n=193$) who visited to EUMC and underwent simultaneous measurement of serum 25-OHD and PTH levels was reviewed. **Results:** Serum 25OHD was positively correlated with serum calcium ($r=0.359$, $P<0.001$), phosphorus ($r=0.359$, $P<0.001$). The serum PTH was negatively correlated with serum 25OHD level ($r=-0.406$, $P<0.001$). The best inflection point of serum 25OHD for maximal suppression of PTH was a level of 18.0 ng/ml (CI 14.2–21.7 ng/ml). Median PTH level of children with 25OHD <18.0 ng/ml was higher compared to children with 25OHD $\geqq 18.0$ ng/ml (62.1 (5.6–445.1) ng/l vs 24.2 (4.4–201.8) ng/l, $P<0.0001$). Median calcium level of children with 25OHD <18.0 ng/ml was lower compared to children with 25OHD $\geqq 18.0$ ng/ml (9.1 (5.6–10.5) mg/dl vs 9.4 (7.9–10.8) mg/dl, $P=0.0001$). Median phosphorus level of children with 25OHD <18.0 ng/ml were lower compared to children with 25OHD $\geqq 18.0$ ng/ml (4.9 (2.3–7.8 mg/dl)mg/dL vs 5.2 (2.1–8.2) mg/dl, $P=0.0460$). The children with 25OHD <18.0 ng/ml had 49.2% hyperparathyroidism, 39.3% hypokalemia, hypophosphatemia 24.6 and 9.8% rickets. **Conclusion:** These data suggest that vitamin D level of 18.0 ng/ml should be the deficiency level of 25OHD in children which is based on PTH elevation.

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Cinacalcet Treatment in Girls with Hereditary Vitamin D Resistant Rickets

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Background: HVDRR is characterised by hypocalcaemia, secondary hyperparathyroidism and severe early-onset rickets in infancy and is diagnosed easily especially associated with alopecia. **Objective and hypotheses:** Successful treatment requires reversal of hypocalcaemia and secondary hyperparathyroidism and is usually failed by high dose calcitriol but sometimes accomplished by administration of high doses calcium. Some patients need enteral or parenteral continuous calcium replacement that has low compliance or high complication risk. **Method:** Cinacalcet trial for HVDRR in 3-year-old girl who failed with high dose calcium and calcitriol. **Results:** The patient has been administered conventional treatment for 2.5 years and did not response to therapy. Metabolic and clinical deterioration progressed. Parathormone and alkaline phophatase levels could not reach to normal levels during treatment (about 400 pg/ml and above 1 000 U/l). Cinacalcet 16 mg/d was given and parathormone level decreased to normal at 4th day. Calcium and calcitriol doses were reduced and the phosphate replacement was ended. *Metaphyseal* cupping and fraying were improved, PTH and ALP was decreased to 36 pg/ml, 675 U/l respectively in 5th month of cinacalcet. **Conclusion:** Cinacalcet should be considered in HVDRR patients who were not responsive to conventional treatment.

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Regulation of Bone Growth *Via* Ligand-Specific Activation of Oestrogen Receptor α

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Background: Oestrogens are well known for their capacity to promote bone maturation and at high doses to induce growth plate closure and thereby stop further growth. High-dose oestrogen treatment has therefore been used to limit growth in extremely tall girls. However, recent data suggest that this treatment may have severe side effects, including increased risk of cancer and reduced fertility. **Objective and hypotheses:** We hypothesised that oestrogenic effects in bone are mediated *via* ERα signalling which could open up for more selective treatment of extreme tall stature using selective oestrogen receptor modulators. **Method:** 12-weeks-old ovariectomised female C57BL/6 mice were subcutaneously injected for 4 weeks with E2 or a selective ERα (PPT), ERβ (DPN) or GPER1 (G1) agonist. Tibiae and femur lengths were measured and growth plate morphology was analysed. **Results:** E2 and PPT treated mice had shorter tibiae and femur bones when compared to vehicle treated controls while those animals treated with DPN or G1 had similar bone lengths as controls. Growth plate height and hypertrophic zone height were reduced in animals treated with E2 or PPT but not in those treated with DPN or GI further supporting that the effect was mediated *via* ERα. **Conclusion:** Our data show that the oestrogenic effects on bone growth and growth plate maturation are mainly mediated *via* ERα. Our findings may have direct implications for the development of new more selective treatment modalities of extreme tall stature using selective oestrogen receptor modulators that may have less side effects than high-dose E2 treatment.

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Teriparatide (rhPTH) Therapy in a Boy with Hypoparathyroidism-Deafness-Renal Dysplasia Syndrome due to GATA3 Mutation

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Background: Hypoparathyroidism is usually treated with calcium and vitamin D analogues. Replacing the deficient hormone using recombinant human parathormone Teriparatide (rhPTH) has not yet become a common practice. We report a 3-year-old boy with hypoparathyroidism-deafness-renal dysplasia (HDR) syndrome who has been successfully treated with Teriparatide (1–34 rhPTH), who to our knowledge is only the second child reported in the literature to be successfully treated with Teriparatide. **Case:** A term male infant born to non-consanguineous Asian parents presented with hypocalcaemic

seizures at 1 month of age needing intensive care support and treatment with calcitriol and calcium supplements. Parathyroid hormone (PTH) level was inappropriately low at the time of hypocalcaemia suggesting hypoparathyroidism. He had bilateral sensorineural hearing loss from 5 months and his motor milestones were delayed. His hypocalcaemia was managed with calcium supplements and calcitriol. At 3 years of age, the patient moved to UK from India. His 25-hydroxy-vitamin D level and echocardiogram were normal. FISH for 22q11 deletion was negative. Despite treating with increasing doses of alfacalcidol (72 ng/kg per day) and calcium supplements (8 mmol/kg per day), the plasma calcium remained between 1.8–1.9 mmol/l with a high urinary calcium/creatinine ratio. Genetic evaluation revealed a heterozygous *GATA3* mutation confirming HDR syndrome. He was commenced on Teriparatide subcutaneously at a dose of 4 μg twice daily resulting in normalisation of plasma calcium levels. This enabled the alfacalcidol and calcium supplements to be weaned and stopped quickly. Half the initial dose of Teriparatide (2 μg twice daily) is currently maintaining normocalcemia and parents report a noticeable improvement in the motor function. **Conclusion:** rhPTH is an effective alternative treatment for patients with hpoparathyroidism which may avoid the potential side effects of conventional therapy and may also improve the motor function.

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Variable Degree of Hormonal Resistance in Patients with Progressive Osseous Heteroplasia

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Background: Progressive Osseous Heteroplasia (POH) is characterised by heterotopic ossifications in a deep muscle and fascia. To date, GNAS1 gene loss-of-function mutations on paternal allele were reported as responsible for POH. Unlike other GNAS1 related diseases such as pseudohypoparathyroidism 1a (PHP1a) or pseudopseudohypoparathyroidism (PPHP), patients with typical POH do not show hormonal resistance (HR) or Albright hereditary osteodystrophy (AHO). But some patients diagnosed as POH with HR and/or AHO were reported previously as overlapping syndrome with POH/PHP1a or POH/PPHP. **Objective and hypotheses:** The aim of this study is to investigate the degree of HR in four patients with clinically diagnosed as POH in our hospital. **Method:** We checked medical records retrospectively and evaluated HR with focuses on TSH and PTH. We also performed gene analyses of the patients and/or their parents. **Results:** Patient 1 showed no abnormality with TSH or PTH. Patient 2 showed transient increase in PTH without abnormalities in Ca, P and thyroid function from the age of 3–5 years. Patient 3 showed persistent elevation of PTH without abnormalities in Ca, P and thyroid function from the age of 8 years. Patient 4 showed TSH elevation from neonatal mass screening and PTH elevation with hypocalcaemia from the age of 5 years. All of four patients have heterotopic ossifications in a deep muscle of the shoulder, elbow, calf or heel. Patients other than patient 1 showed some symptoms with AHO. All of them have mutation of GNAS1 gene and the mutation was proved on the paternal allele in patient 1. **Conclusion:** POH patients could be accompanied with variable degree of HR. Further study other than GNAS1 gene mutation analyses might be necessary to understand the mechanisms for these variable HR with POH patients.

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Assessment of Foramen Magnum in Early Infancy is Efficient for Patients with Achondroplasia

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Background: Achondroplasia is the most common form of human short-limbed dwarfism. The most serious complication in individuals with achondroplasia is narrowing of foramen magnum (FM) that results in cervicomedullary compression and sudden infant death. To avoid sudden infant death, early monitoring and implementation of the necessary medical intervention are important. However, the optimal method of screening for cervicomedullary compression continues to be debated. **Objective and hypotheses:** To avoid severe complications that arise from narrowness of FM in achondroplastic infants, we assess narrowness of FM of our patients with achondroplasia and examine the timing and frequency of screening. **Method:** Children with achondroplasia who were born at or referred to our hospital between April 2002 and June 2014 was collected. Retrospective analyses were done for age at first screening MRI scan, age at presented radiological cervicomedullary compression, neurological or respiratory symptoms, surgical history for FM decompression and VP shunting. **Results:** 18 children ranging from 4 months to 12 years 5 months of age were analyzed. FM decompression was performed in six patients (33.3%) who had severe neurological symptoms including sleep apnea and quadriparesis, and VP shunting was performed in one patients (5.6%) with severe hydrocephalus. Radiological cervicomedullary compression presented in 17 of the 18 children between the ages of 1–13 months, and as many as 12 (66.6%) patients appeared to have cervicomedullary compression at their first MRI scan. Fifteen patients had their first MRI scan in 4 months, nine of which (60%) presented with cervicomedullary compression. **Conclusion:** To avoid the risks of complications due to cervicomedullary compression, careful monitoring of any rapid changes in head size and observations of neurological and respiratory symptoms is important in patients with achondroplasia. As for formal screening of all children with achondroplasia, we advocate a first MRI scan at 4 months of life.

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Body Composition Measures on Different DEXA Scanners are not the Same

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Background: Body composition measures differ between DEXA scanners. If an old DEXA is replaced a transition period for double measurements on the old and the new scanner is needed. **Objective and hypotheses:** To evaluate differences between the old (Hologic QDR 2000) and new (Hologic Discovery Wi) scanner and to calculate formula transforming measurements. **Method:** 51 double measurements were performed on a group of 41 children and adults (mean (SD) age 18.57 (10.06) y, BMI x (y) kg/m^2). Results for fat, lean, BMD and BMC were compared using Bland-Altmann plots. Linear regression analysis was used for transformation formula. Least significant change (LSC) was calculated using triple measurements of a separate group of 15 healthy adults. **Results:** LSC on the Discovery Wi for fat, lean, BMD and BMC was 0.76 kg, 0.83 kg, 0.02 g/cm^2 and 0.065 kg. The individual's mean of QDR 2000 and Discovery Wi measurements for fat mass was 4.6–34.9 kg; the mean ($\pm$2 SD) difference being 1.9 (4.3) kg, this difference was increasing as fat mass increased. Mean lean mass was 19.2–72.7 kg; independent of lean mass, the mean (SD) difference between QDR2000 and Wi was $-$1.5 (4.2) kg. Mean BMD was 0.7–1.5 g/cm^2; the mean (SD) difference between QDR2000 and Wi was $-$0.02 (0.06) g/cm^2; this difference was increasing as BMD increased. Mean BMC was 0.78–3.8 kg; independent of BMC the mean (SD) difference between QDR2000 and Wi was 0.04 (0.14) kg. Using transformation formula, maximum differences between true and calculated measurements for fat, lean, BMC and BMD are 11.8, 12.8, 11.9 and 22.5% respectively. **Conclusion:** Except for BMC and BMD, mean differences between the DEXA scanners exceed LSC two-fold. Exchanging DEXA scanners, an overlapping period with double measurements is mandatory. Transforming formulas induce significant variability.

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Intrauterine Growth Restriction, Gestational Age, Steroidal Prophylaxis and Breastfeeding Influence Bone Mass in Prepubertal Children

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Background: The impact of prematurity on skeletal health later in life is not well elucidated. **Objective and hypotheses:** In order to address this topic we evaluated bone mass in ex-preterm (PT) and born at term (BT) prepubertal children and potential risk factors for bone health. **Method:** DXA measures of total body less head and lumbar spine mineral density (TB/L1-L4 BMD, g/cm^2 and *z*-score), bone mineral content (TB-BMC, g), fat mass (FM%, kg) and free fat mass (FFM kg) were obtained in 100 PT ($n=42$ females, $n=58$ males, median age at study 6.7$\pm$1.3 years; gestational age-GA-range 26–36 weeks) and 51 BT ($n=28$ females, $n=23$ males) healthy children. Patients underwent height (HT SDS), BMI SDS and biochemical measures of 25OHD, PTH, CTx, BAP. 27 subjects ($n=21$ PT, $n=6$ BT) were intrauterine growth restriction (IUGR) and 55 PT underwent prenatal steroid prophylaxis. Forty-three children ($n=20$ PT and $n=23$ BT) were breastfed. **Results:** There were no significant differences in anthropometrics, DXA parameters and bone markers between PT and BT children. However, positive correlations were found between GA or birth weight and BMC, BMD or BMD *z*-score both at the TB and the L1–L4. Steroid prophylaxis and breast feeding were respectively negatively (*r*'s between -0.16 and -0.39; all *P*'s <0.04) and positively (*r*'s between 0.18 and 0.29; all *P*'s <0.02) associated to all bone parameters. The IUGR group (17.9%) was shorter and presented significantly lower DXA bone measures (all *P*'s <0.05) compared to no IUGR children. Multiple regression analyses showed that, independently of age at visit, gestational age was predictive of bone mass (4.8%) in PT but not in BT children. **Conclusion:** Our study demonstrates comparable bone mass parameters in PT and BT prepubertal children. Breastfeeding seems to have a positive impact on bone parameters, while gestational age, IUGR and steroid prophylaxis might represent long-lasting risk factors for bone health.

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Can Vitamin D Deficiency Cause Prolongation in Visual Evoked Potentials?

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Objective: It is known that vitamin D has differential roles in cell proliferation, differentiation, neurotransmission and neuroplasticity in nervous system and exerts neurotrophic and neuroprotective effects. In recent studies, it was shown that vitamin D could be protective against in age-related macular degeneration and optic neuritis related to demyelinating disorders. Here, we aimed to perform visual evoked potential (VEP) studies before treatment in patients with rickets. **Material and method:** This study included pretreatment VEP evaluations of 30 patients (aged 0–15 years) who were diagnosed as rickets in Child Endocrinology department of Yüzüncü Yıl University, Professor Dr Dursun Odabaş Medical Center between January, 2014 and July, 2014. **Results:** Mean age was 2.15$\pm$4.12 years (min-max: 0.07–15.13) in 30 patients with rickets. There were eight girls (25.8%) and 23 boys (74.2%). When biochemical and hormone values were studied in patients with rickets, the following results

were observed: mean calcium value, 8.09 ± 1.52 mg/dl; mean phosphor value, 4.24 ± 1.53 mg/dl; mean magnesium value 1.95 ± 0.23 mg/dl; mean alkaline phosphatase value 838.23 ± 627.86 U/l; mean parathormone value, 314.82 ± 310.76 pg/ml; mean creatinine kinase value, 173.58 ± 239.73 U/l; mean albumin value 4.05 ± 1.41 g/dl; and mean 25 OH vitamin D level 5.52 ± 3.20 ng/ml. When VEP results were assessed, mean P2 latency was 177.39 ± 37.87 (min-max: 115.80–228) in left eye whie 177.0 ± 932.30 (min-max: 120–230.4) in right eye in 27 patients. When LP 100 latency was evaluated in three patients, it was found that mean P100 latency was 113.50 ± 3.25 (min-max: 109.80–115.80 in left eyes. The prolongation was detected in left eyes of six patients (20%) and right eyes of four patients (13.3%) in VEP studies. **Conclusion:** We intended to emphasise that there could be prolongation in VEP studies in patients with rickets and that there should be need for detailed examination to monitor this prolongation in subsequent years.

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Novel *CYP27B1* Gene Mutations in Children with Vitamin D-Dependent Rickets Type 1A

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Background: The *CYP27B1* gene encodes 25-hydroxyvitamin D-1α-hydroxylase. Mutations of this gene cause a rare autosomal recessive disorder, vitamin D-dependent rickets type 1A. **Objective and hypotheses:** To investigate *CYP27B1* mutations in children when rickets was associated with normal or high vitamin D levels and low or inappropriately normal calcitriol levels. **Method:** All coding exons and intron-exon boundaries of *CYP27B1* gene from eight patients and their parents from seven unrelated families were sequenced. RNA extraction and mini-gene analysis were performed. **Results:** Clinically, all the patients (M/F:4/4, age range 12 months-11 years) required continued calcitriol treatment and the clinical presentations were consistent with the complete loss of vitamin D1α-hydroxylase activity. Biallelic mutations in the *CYP27B1* gene were found in all the patients and monoallelic mutations were present in their asymptomatic parents. Four novel mutations were identified: c.1215 T > C (p.R379R) in the last nucleotide of exon 7, a splice donor site mutation (c.1215 + 2T > A) in intron 7, a 16-bp deletion in exon 6 (c.1022-1037del16, p.T341Rfs*346), and a 2-bp deletion in exon 5 (c.934_935delAC, p.T312Rfs*331). Both c.1215 T > C and c.1215 + 2T > A were present together in two unrelated patients, and caused exon 7 skipping. However, c.1215 T > C alone has no effect on RNA splicing. The skipping of exon 7 resulted in a shift of the downstream reading frame and a premature stop codon 57 amino acids from L380 (p.L380Afs*437). The intra-exon deletions of c.1022-1037del16 and c.934_935delAC also resulted in frameshift and the creation of premature stop codons at p.T341Rfs*346, and p.T312Rfs*331, respectively, leading to the functional inactivation of the *CYP27B1* gene. **Conclusion:** Four novel mutations have been identified. Three of them caused frameshift and truncated proteins. The silent c.1215 T > C has no effect on pre-mRNA splicing and may be considered as a novel SNP.

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Size-Corrected Bone Mineral Density is not Affected by Haematopoietic Stem Cell Transplantation and Total Body Irradiation in Leukaemia Survivors

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Background: Childhood haematopoietic stem cell transplantation and total body irradiation (HSCT/TBI) survivors have multiple risk factors for reduced bone mineral density (BMD) and poor growth. Reduced *z*-scores from dual energy x-Ray absorptiometry (DEXA) have been reported, but are unreliable in patients with short stature/abnormal body composition. **Objective:** To investigate the influence of HSCT/TBI on size-corrected BMD in childhood leukaemia survivors. **Method:** Post-pubertal age- and gender-matched leukaemia survivors treated with HSCT/TBI (10–14.4 Gy) ($n = 21$, 11 males, aged 21 (16.1–26.1)) at mean aged 9.3 (1.0–10.8) years were compared with patients treated with chemotherapy-only ($n = 30$, 12 males, aged 21.5 (16.2–26) years) at (7.0 (1.6–18.0) years). Patients on long-term steroids were excluded. All had had endocrine evaluations and were on replacement hormones where appropriate. Assessments: height, weight, DEXA scanning (Lunar prodigy® fan beam) (BMD-*z*-scores, bone mineral content (BMC), bone area (BA) & width) and vitamin D levels. BMD was corrected for size as bone mineral apparent density (BMAD): Total-BMAD (BMD_T) = BMC/total body BA_2/height; Lumbar spine-BMD ($BMAD_{L2\text{-}4}$) = $BMD_{L2\text{-}4}$ x $(4/(\pi \times \text{width}))$. **Analysis:** student's *t*-tests and Pearson's correlations (5% significance). **Results:** HSCT/TBI survivors had lower total-BMD *z*-scores (−0.74 vs 0.19, $P = 0.012$), but were lighter ($P < 0.001$) and shorter ($P < 0.001$) than chemotherapy only patients. Total-BMD correlated positively with height-SDS, weight-SDS, fat and lean masses (all $P < 0.001$). Size corrected BMD showed no mean (SD) differences between HSCT and chemotherapy-only patients: BMD_T (0.089 (0.008) vs 0.086 (0.007), $P = 0.13$); $BMD_{L2\text{-}4}$ (0.38 (0.057) vs 0.37 (0.056), $P = 0.33$). There were no relationships between $BMAD_T$ or $BMDL_{2\text{-}4}$ with age at or time from primary diagnosis in both groups; or with age at and time from HSCT/TBI in HSCT/TBI group. The HSCT/TBI group showed no differences in $BMAD_T$ or $BMD_{L2\text{-}4}$ in HSCT/TBI patients treated < or >8 years, and no relationships between $BMAD_T$ or $BMD_{L2\text{-}4}$ with serum Vitamin D(p = 0.13,p = 0.21) or presence of endocrine disorders (growth hormone deficiency

($P=0.16$, $P=0.46$), hypothyroidism ($P=0.53$, $P=0.58$), gonadal failure ($P=0.33$, $P=0.43$)). **Conclusions:** Size of patient must be taken into account to avoid over diagnosis of osteopenia when assessing BMD in cancer survivors. Treatment effects on peak bone mass in survivors need further evaluation. **Funding:** The work was supported by the IPSEN clinical research fellowship, BSPED research Award, David Telling Research funds and Peel Medical research award.

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Quantitative Sonometeric Bone Age as a Function of Height and BMI

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Background: We have previously shown that bone age (BA) assessment by SonicBone BAUS^{TM}, measuring the speed of sound (SOS) of US waves propagating along measured bone, is reproducible and comparable to both GP and TW3 x-ray assessment of BA. This provides a safe and irradiation-free method to the assessment of BA in healthy children. **Objective and hypothesis:** We aimed to understand the dependency of BA on a child's height and BMI using sonometeric bone age (SBA), and hypothesized positive correlations. **Method:** SBA was analysed separately and averaged for the wrist (radius-ulna epiphyses), metacarpal epiphyses and the phalanx' ossification centers in 317 healthy girls and 333 boys, age range 4–15/4–17 resp., and the difference from chronological age was regressed onto their height SDS and BMI SDS. **Results:** A child's height SDS is strongly and positively correlated with the SBA deviation from the chronological age in the wrist ($r^2=0.30$, $P<0.0001$), metacarpals ($r^2=0.29$, $P<0.0001$), phalanx ($r^2=0.47$, $P<0.0001$), and the mean SBA ($r^2=0.40$, $P<0.0001$). When 120 pre-pubertal girls age 4–8 and 147 boys age 4–9, are analysed separately, the correlation is reduced to $r^2=0.215$, $P=0.019$ in girls but remains strong in boys, ($r^2=0.304$, $P<0.0001$). A child's BMI SDS is also positively correlated with the SBA deviation from chronological age in the wrist ($r^2=0.25$, $p<0.0001$), metacarpals ($r^2=0.17$, $p<0.0001$) phalanx ($r^2=0.13$, $P<0.001$), and the mean SBA ($r^2=0.22$, $P<0.0001$). In separate analysis of pre-pubertal children, the BMI correlations disappear. **Conclusions:** i) Shorter and thinner pubertal but not pre-pubertal children have delayed BA as compared to taller and heavier children. ii) The full-length phalanx maturation is affected by height more than the wrist and metacarpals' epiphyses. iii) The radius-ulna epiphyses are affected by BMI more than the metacarpals and phalanx. iv) These influences have now on to be accounted for in the assessment of a BA. **Conflict of interest:** SO is employed by SonicBone, NKM and ZH are independent consultant. **Funding:** The study was funded by SonicBone Ltd Rishon Lezion.

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The Association of Attention Deficit Hyperactivity Disorder and Autism Spectrum Disorders with the Mean Platelet Volume and Vitamin D

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Purpose: The purpose of this study was to assess the values of the mean platelet volume (MPV), a predictor of cardiovascular disease, in paediatric patients with attention deficit hyperactivity disorder (ADHD) and with autism spectrum disorders (ASD), in addition to healthy controls, to determine the risk of cardiovascular disease in these two disorder groups. **Material and method:** The study included a total of 79 patients aged 3–18 with ADHD (36 patients) and with ASD (18) and controls (25) in the Van Region of Turkey. The control group included subjects of matching age and gender with no ADHD, ASD, and chronic disease and taking no vitamins. After measuring the weight and height of the patients in the groups, blood samples were obtained. The haematological parameters of the patients including MPV, vitamin B12, and vitamin D were assessed. **Results:** The study included a total of 79 children and adolescents aged 2–18 (32 females and 47 males). Of the patients, 36 were in the ADHD group, 18 in the ASD group, and 25 in the control group. There was no statistically significant difference in haematological parameters between the groups, but there were significant differences in terms of vitamin D and vitamin B12. The patient groups showed lower levels of vitamin B12 and vitamin D when compared to the control group. In the ADHD group, there was a negative correlation between both vitamins and MPV ($P<0.05$). The partial correlation analysis of the ADHD group showed that in particular, MPV was negatively correlated to vitamin D, and not to vitamin B12 (P: 0.03). **Conclusion:** The difference in MPV between the patient groups and the control group may be due to the limited number of patients studied. The vitamin D deficit particularly in the ADHD group may contribute to the elevated MPV value found by Yoruk and coworkers.

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Dyslipidaemia in Children with Diabetes

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Background: Data on prevalence and phenotypic distribution of dyslipidaemia in children with type 1 diabetes (T1D) is scarce.

Studies have shown that lipid abnormality tracks from childhood to adulthood and contributes to atherosclerotic process, therefore initial assessment and follow-up is essential. **Aims:** To study the prevalence and phenotypic distribution of dyslipidaemia in children with T1D and compare with type 2 diabetes (T2D). **Methods:** A cross-sectional sample of diabetes patients, age 7 18 years on active follow-up between 1st January to 31st December 2014 were recruited. Fasting blood sample were analysed for glycated haemoglobin (HbA1C), total cholesterol (TC), high density lipoprotein (HDL), triglycerides (TG) and low density lipoprotein (LDL). Baseline demographic data and biochemical data was analysed using SPSS version 16. **Results:** Total 165 patients were recruited, (T1D: $n=115$; 69.7%, T2D: $n=50$; 30.3%). Prevalence of dyslipidemia was 73.3% ($n=121$) and almost similar in T1D & T2D (71.3% vs 78.0%). T1D had lower mean age at recruitment (13.61 years $\pm$ 2.58 vs 15.36 years $\pm$ 2.00; $P<0.001$) and longer mean duration of diabetes (5.85 $\pm$ 3.69 vs 2.82 $\pm$ 2.12; $P<0.001$) compared to T2D. Phenotypic distribution of dyslipidemia in T1D vs T2D, (LDL $\geqq$ 2.6 mmol/l: 66.1% vs 70.0%; $P=0.719$), (TG $\geqq$ 1.7 mmol/l: 11.3% vs 42.0%; $P<0.001$), (HDL $<$ 1 mmol/l:4.3% vs 12.0%; $P=0.091$). T1D & T2D had similar mean LDL (2.92 $\pm$ 0.86 vs 3.01 $\pm$ 1.06; $P=0.56$). Mean HbA1c was higher in T1D vs T2D (8.98% $\pm$ 1.96 vs 7.9% $\pm$ 2.27; $P=0.095$). There were 31 (18.8%) patients aged $\leq$10 years, mostly T1D ($n=28$; 24.3%), of which 67.7% had LDL $\geqq$ 2.6 mmol/l and 87.1% had no family history of lipid disorder. **Conclusions:** Patients with T1D in the present study showed higher LDL-C but not triglyceride. Significant proportion of T1D patients less than 10 years of age have elevated LDL-C levels without a family history of lipid disorder.

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Diabetes Mellitus and Hypoparathyroidism in a Girl with Mitochondrial Disease

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Background: Mitochondrial disease is an uncommon cause of diabetes mellitus and hypoparathyroidism in children. Coexistence of these two endocrinopathies in a child with mitochondrial disease is extremely rare. **Case report:** An 11-year-old girl was diagnosed with type 1 diabetes mellitus due to a blood glucose of 300 mg/dl. Simultaneous C-peptide and insulin were very low, however anti-GAD, anti-islet cell and anti-insulin antibodies were negative. HbA1c was 10.2% (N: 4.5–6.2%). Insulin was started, however repeated and frequent hypoglycemic episodes required replacing insulin with diabetic diet alone. HbA1c decreased to 5.4% on diabetic diet. At 12 years she developed paresthesias of the hands, and numbness around mouth during illness. Serum Ca level was 8.4 mg/dl (N: 9–11), P: 6.8 mg/dl (N: 3.7–5.4) ALP: 194 U/l (N: 105–420) and simultaneous PTH was 10.6 pg/mlml (N: 15–69) Low dose calcitriol treatment was started. At 13 years of age, she was referred to us for blood glucose regulation and insulin had to be reintroduced due to an increase in HbA1c to 8.4%. She was the second child of unrelated parents. Her grandmother had type 2 diabetes, and a maternal aunt had ptosis. On physical examination, height was 133.5 cm ($<$3 p) and BMI 12.2 kg/m^2 ($<$3 p).She had bilateral ptosis, external ophthalmoplegia, macular dystrophy, and sensorineural hearing loss at high frequencies. She had no weakness, and neurological examination was otherwise normal. Persistently high lactate combined with the clinical phenotype led to muscle biopsy showing ragged-blue fibers and cytochrome-c-oxidase negative fibers compatible with mitochondrial myopathy. **Conclusion:** Diabetes mellitus accompanying hypoparathyroidism, is an expected finding in autoimmune polyglandular syndrome. This patient reminds that it may also be seen in mitochondrial disease, however rare. Thus one should consider mitochondrial disease in differential diagnosis of patients with multiple endocrine abnormalities even when weakness or myopathy is absent. Also complete endocrine evaluation should be part of mitochondrial disease.

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Association of Ghrelin Levels and Insulin Resistance in Small for Gestational Age Rats

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Background: Because ghrelin is closely linked to insulin resistance and type 2 diabetes mellitus in adults, ghrelin might also participate in the development and progression of pathological changes in insulin resistance in SGA infants. **Objective and hypotheses:** This study aimed to determine insulin sensitivity index (ISI), variation in ghrelin levels, and their relationship in small for gestational age (SGA) rats. **Method:** The SGA animal model was established by the starvation method in pregnant rats. Experimental rats were grouped by body length and body weight 4 weeks after birth. Rats were divided into the following groups: i) SGA with growth catch-up (group S1, $n=26$); ii) SGA without growth catch-up (group S2, $n=31$); and iii) normal matched controls composed of male rats whose mothers ate and drank freely during pregnancy ($n=27$). Body weight and serum ghrelin levels were measured 4 weeks after birth. Body weight, and levels of serum ghrelin, blood glucose, and insulin on an empty stomach were measured when the rats were 12 weeks old, and then the ISI was calculated. Correlations of all indices were examined. **Results:** The ISI of 12-week-old SGA rats (group S1: 2.00 $\pm$ 0.58 and group S2: 2.23 $\pm$ 0.58) was significantly lower than that in controls (3.17 $\pm$ 0.54, both $P<0.05$). Serum ghrelin levels in SGA rats (group S1: 1.357 $\pm$ 0.548 ng/ml; group S2: 1.428 $\pm$ 0.714 ng/ml) were lower than those in controls (1.843 $\pm$ 0.459 ng/ml), but this difference was not significant ($P>0.05$). Ghrelin levels in 12-week-old SGA rats were negatively correlated with fasting insulin levels in blood ($r=-0.836$, $P<0.01$), and positively correlated with the ISI ($r=0.810$, $P<0.01$). **Conclusion:** A decrease in ghrelin levels is correlated with insulin resistance in adult rats that are born SGA. Low levels of ghrelin may result from insulin resistance.

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Protective Effects of Combined Intervention with Adenovirus Vector Mediated IL-10 and IGF1 Genes on Endogenous Islet β Cells in Nonobese Diabetes Mice with Onset of Type 1 Diabetes Mellitus

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Introduction: To investigate the protective effects of combined intervention with adenovirus vector mediated interleukin 10 (IL-10) and insulin-like growth factor 1 (IGF1) genes on islet β cells in nonobese diabetes (NOD) mice with type 1 diabetes mellitus (T1D) at early stage. **Methods:** Twenty-four female NOD mice at onset of diabetes and aged 17–20 weeks old were randomly divided into four groups. Mouse 1, 2 and 3 groups were intraperitoneally injected 0.1 ml of Ad-mIGFIGF11, Ad-mIL-10, and combined Ad-mIGF1 and Ad-mIL-10, respectively. Mouse 4 group were used as diabetes control. In addition, six age- and sex-matched non-diabetic NOD mice were intraperitoneally injected 0.1 ml of PBS and assigned five group as normal controls. All mice were weekly monitored for body weight, urine glucose and blood glycose, and sacrificed 3 weeks after injection. Their serum levels of IL-10, IGF1, IFN-γ, IL-4 and C-peptide were measured and the degree of insulitis and the local expression of IGF1 and IL-10 gene were observed. **Results:** 1) IL-10 and IGF1 levels in serum and pancreas were enhanced in 1, 2, and 3 groups; 2) serum INFγ level was decreased while serum IL-10 and IL-4 levels were increased in 1, 2 and 3 groups, and these alterations were more significant in three group than 1 and 2 groups ($P < 0.01$); 3) C-peptide level was not enhanced in 1 group, but significantly increased in 2 and 3 groups, and these increases were more significant in the latter ($P < 0.01$); 4) Three weeks later, the body mass of mice in 2 and 3 groups decreased significantly ($P < 0.05$). **Conclusion:** The administration of adenovirus vector mediated IL-10 and/or IGF1 gene showed limited immune regulatory and protective effects on islet β-cells in NOD mice with T1D at early stage, and no significant reduction in insulitis, blood glucose and body weight. **Funding information:** The project was sponsored by the National Natural Science Foundation of China (81170762) and Shandong Province Natural Science Foundation (Y2008C50).

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A Case of Donohue Syndrome: New Genetic Mutation and Added Phenotypic Characteristics

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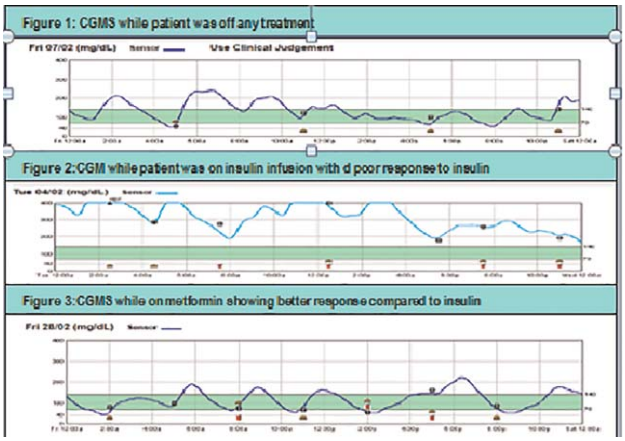
Background: Leprechaunism (Donohue syndrome) is an extremely rare AR disease that presents with special phenotypic features including severe type of insulin resistance with high mortality in infancy. **Case study:** R 3 ½ months old Syrian girl, born at 35 weeks of gestation with Asymmetrical IUGR. She



developed hyperglycemia from day1 of life > 150 mg/dl (350 +/− 60 mg/dl) and her serum insulin and c-peptide were very high (772 uU/ml and 29.9 ng/ml, respectively). Insulin infusion was started with requirement between 0.4–0.5 unit/kg/day to keep her BG < 200 mg/dl. After the first month, her insulin requirement decreased spontaneously and the insulin was stopped for 7–10 days three times (average BG = 130 +/− 55 mg/dl despite the presence of severe hyperinsulinemia (1900 and 2875 uU/ml). By the second month, facial dysmorphism became obvious in the form of prominent eyes and maxilla, upturned nose, large and low set ears, thick lips, gum hyperplasia, long narrow face, thick eye brows hypertrichosis of the forehead and the back, long feet and button-like nipples. CGMS recorded average BG = 350 +/− 100 mg/dl while off insulin with fluctuating levels (hypo- and hyperglycemia) and average BG = 300 +/− 50 mg/dl) while on insulin infusion. She was started on Metformin (50 mg PO aily), and her CGMS showed a reasonably good response to metformin with average BG of 150 mg/dl compared to BG on insulin. Continuous nasogastric feeding (NGT) with pancreatic enzyme replacement to prevent hypoglycemia was associated with weight gain. Genetic study revealed a peculiar autosomal recessive of INSR homozygous mutation (c.3583A > T p.Lys1195*). Both parents were carriers. **Discussion:** We report a case of Donohue syndrome with a peculiar mutation. Using CGMS showed clearly her glycemic abnormalities and response to different therapies. Metformin was successful therapy that maintained BG in the normal range most of the times. She had exocrine pancreatic insufficiency (not described before in DS) that responded well to pancreatic enzyme replacement. **Conclusion:** We described a cae of DS with peculiar genetic homozygous mutation of the INSR gene and some new phenotypic features (pancreatic insufficiency) and reasonable response to metformin therapy.

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Genetic Analysis and Follow-Up of 23 Neonatal Diabetes Mellitus Patients in China

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Objective: To study the clinical features and gene mutations of neonatal diabetes mellitus (NDM) in Chinese patients. **Methods:** Patients with clinically diagnosed NDM were subjected to genetic screening by targeted gene capture of the genes associated with glucose metabolism, and followed up. **Results:** Of the 23 cases of NDM studied, 16 (69.6%) were permanent neonatal diabetes mellitus (PNDM), 6 (26.1%) were transient neonatal diabetes mellitus (TNDM) and the remainder was unclassified and lost to follow-up. Symptoms at onset included fever, fainting, polydipsia and polyuria, glycosuria and seizure. All TNDM patients responded to insulin treatment. Three patients were successfully switched to glyburide; four cases were restarted on insulin due to glyburide resistance; one stopped oral glyburide because of serious gastrointestinal reactions and in other 8 cases glyburide was not tried until the last follow-up. The mean HbA1c of patients on insulin was 7.5% and in those switched to glyburide was 6.5%. Among 16 PNDM cases, 6 (38.5%) were found to have known KATP channel mutations, including one case of ABCC8 and five cases of KCNJ11 gene mutations. Novel non-KATP mutations including EIF2AK3, GLIS3 and SLC19A2 were found in three PNDM patients. One ABCC8/G296R mutation was found among six TNDM cases. **Conclusion:** Atypical symptoms such as seizure may be seen initially in NDM cases. Insulin therapy is effective in both TNDM and PNDM. About one-third of PNDM patients in the present study had KATP mutations and glyburide therapy was effective in three patients. **Funding information:** This work was supported by the Open Research Project of Shanghai Key Laboratory of Diabetes Mellitus(SHKLD-KF-1304).

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Level of Knowledge about Type I Diabetes Mellitus among Nurses Employed at Endocrinological Dispensaries

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Objective and hypotheses: The work was initiated to assess basic level of knowledge on essential concepts of type I diabetes mellitus among nurses employed at regional dispensaries of Uzbekistan. **Method:** We tested 194 nurses employed at the endocrinologist's offices and regional endocrinological dispensaries to assess level of knowledge on essential concepts of type I diabetes mellitus by means of a 20-question test made up under a 5-day training program in the School of Diabetes. **Results:** The testing demonstrated that initial basic level of knowledge among nurses in Uzbekistan as a whole was 65%, the highest one being registered in Tashkent (83%), the lowest one in Djizak (55%), Bukhara (58%) and Khorezm (58%) regions. Analyzing answers to each question we found that there were 91.8% of right answers to questions about distinguishing features of type I and type II diabetes mellitus, 89% of respondents gave right answers to question about changes in blood glucose upon insulin deficiency to indicate good level of knowledge on these concepts in Uzbekistan as a whole. 70% of nurses knew a thing or two about glucagon. 56% chose right answer to a question about macronutrients (proteins, fats or carbohydrates) facilitating increase of blood glucose. 82% of nurses knew normal values of glycemia. Only 57% of respondents had a good command of type I DM criteria of compensation in children and adolescents. 42% of respondents gave right answers to questions about value of measurement of glycated hemoglobin. Enquiry after training demonstrated the best results in Navoyi, Surkhandarya, Tashkent, Kashkadarya and Samarkand regions where right answers were given to 95-100% of questions. The lowest level of knowledge was found in Djizak, Bukhara and Khorezm regions indicating necessity of the repeated training and build-up of control over the regions. **Conclusion:** The tested nurses did not have adequate knowledge about clinical picture and pathogenesis of diabetes mellitus, misapprehending first-aid treatment upon acute complications and having a vague idea about insulin injection technique. Constant monitoring of a diabetic self-control should be performed by all health care professionals.

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Recombinant Human IGF1 Treatment in Patients with Insulin Receptor Mutations Resulting in Donohue Syndrome: A 10-Year Experience in a Tertiary Centre

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Background: Donohue syndrome (DS) is the most severe form of insulin-resistance due to autosomal recessive mutations in the insulin receptor gene. Previous reports demonstrate a role for recombinant human IGF1 (rhIGF1), however optimal treatment strategy remains unclear. **Case series:** Four males with DS have been treated with bolus rhIGF1 (see table below). They had no IGF1 response on an IGF1 generation test. No long-term side effects of rhIGF1 were reported. **Conclusion:** High dose rhIGF1 is safe and can mitigate metabolic abnormalities in patients with DS. We report survival into adolescence in a patient with no severe comorbidities, in whom the fast tolerance dramatically improved on rhIGF1 and long-term growth was relatively preserved. Although a twice daily regimen is the most frequently reported, 8 h administration may be required to optimise metabolic control, as demonstrated in Patient 2.

Table 1. (for abstract P2.250)

Patient	1	2	3	4
Current age (years)		11.5		0.8
Age death (years)/cause of death	14.7/unknown (recurrent sepsis and ketoacidosis)		1.3/liver dysfunction; respiratory infection	
Mutation	p.R1092Q (tyrosine kinase domain)	Paternal c.576C>G. p.I119M and maternal c.3334C>T, p.R1039X	p.G84Q (alpha subunit)	c.1924T>C, p.W642R
Age (years) commencement rhIGF1	1.9; restarted at 13.4	1.6 (IGF1+IGFBP3 until age 8)	0.1	0.1
Therapy duration (years)	3.3 (2 trials)	10	0.3	0.5
Height/weight SDS pre-rhlGF1	−7.1/−5.48	−1.96/−2.36	−2.1/−5	−7/−5.45
HbA1c (%) pre-rhlGF1	18.7	4.9	NA	5.9
Starting rhlGF1 dose (mcg/kg per day}	40	80	67	70
Frequency	Once daily	12 h	12 h	12 h
Latest rhlGF1 dose (mcg/kg per day}	590	325	116	150
Frequency	Once daily	8 h	12 h	12 h
Latest feeding	Oral	Oral/continuous enteral overnight	Continuous parenteral	Bolus/continuous enteral overnight
Fasting time pre IGF1/on rhlGF1	NA/12 h	2 h/8 h	1–2 h/1–2 h	2 h/2 h
Latest height/weight SDS	−7.1/−4.2	−2.89/−1.7	NA/−4.95	−7.19/−5.12
Latest HbA1c (%) on rhIGF1	11.5	6.7	NA	5.2
Latest daily mean glucose (mmol/l)	24.3	9.7	5.7	9.2

NA – not available.

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Sick Day Rule: Survey of Parents of Children with Type 1 Diabetes (Experience and Knowledge)

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Background: Inappropriate management of illness/stress, accidental or deliberate insulin omission are some of the causes of Diabetes ketoacidosis (DKA) in patients with established diabetes. During illness, patients with type 1 diabetes are advised to monitor for hyperglycaemia and ketosis, maintain fluid intake and if required, to administer supplemental insulin. Previous studies have confirmed that comprehensive diabetes self- management education (DSME) programs on management of sick days and availability of telephone support can lead to a reduction in the rates of DKA. **Objective and hypotheses:** The aim of the study is to establish parent's experience of self-management education programs and out of hours telephone support. In addition we evaluated their knowledge of sick day rules. **Method:** Parents of children with Type I diabetes completed an online questionnaire posted (October 2014-February 2015) on social media fora popular with parents of children with diabetes living in United Kingdom. The questionnaire was set up to allow only one response per internet protocol (IP) address. The questionnaire was validated for consistency by a panel of parents. It tested four domains of sick-day self-management; glucose monitoring, ketone monitoring, fluid intake and supplemental insulin administration. It also sought information on their experience of self- management education programs and telephone support. **Results:** completed the questionnaire. Median duration of their child's diabetes was three years. Median age of their children was ten years. 86% reported receiving training on managing sick days. Of these the majority (52.2%) received this as an informal session at diagnosis, with only 6.3% receiving annual updates. 32.7% reported that they received an information leaflet only with no formal or informal teaching session. The majority (52.1%) had access to their diabetes team out of hours, whilst 14.6% had access to ward staff/Paediatric Registrar for advice. Other popular sources of information when dealing with illness included other parents (49.2%), Facebook (63.3%) and Google (31.5%). Worryingly 40% either did not know what to do in the presence of raised blood glucose (BG) and high blood ketones (BK) or would have taken no action to prevent DKA **Conclusion:** Survey results highlight the need to improve quality of sick day rule education programs for parents of children with type 1 diabetes. **Funding information:** This work was supported by funding from ACDC (Association of children's diabetes clinicians) in United Kingdom who payed for the online survey.

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Brachial Flow Mediated Dilation and its Relation to Osteoprotegerin in Type 1 Diabetes Mellitus

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Background: Type 1 diabetes is a risk factor for cardiovascular disease. Osteoprotegerin is a predictor of cardiovascular disease.

Endothelial dysfunction is the earliest event in atherosclerosis and subsequent cardiovascular disease. Flow mediated dilation (FMD) of brachial artery can be used to detect endothelial dysfunction. **Objective and hypotheses:** To assess FMD of brachial artery in Type 1 diabetes and its relation to serum osteoprotegerin level. **Method:** Forty type 1 diabetic children were compared with 40 controls. All underwent anthropometric assessment, measurement of lipids, HbA1c, albumin: creatinine ratio, and serum osteoprotegerin. FMD of brachial artery was assessed by measuring brachial artery diameter at baseline (A) and at one minute after release of pressure (B). The absolute change in brachial artery diameter in mm (FMD (B – A)), and the delta change (Δ FMD) = (B – A)/A were estimated. **Results:** The mean (SD) age of patients was 12.1 (4.2) years, mean (SD) diabetes duration was 4.5 (3.7) years. No significant difference in age, gender, height SDS, weight SDS, BMI SDS, waist circumference SDS, and mean blood pressure existed between patients and controls. Serum osteoprotegerin, total cholesterol, and LDL-Cholesterol were significantly higher while HDL-Cholesterol was significantly lower among patients ($P < 0.05$). Brachial artery diameter at 1 minute after release of pressure (B), absolute difference FMD (B – A), and Delta change (Δ FMD) in brachial artery diameter were significantly lower in patients ($P < 0.001$). No significant correlation existed between osteoprotegerin and brachial artery FMD ($P > 0.05$). LDL-Cholesterol negatively correlated with FMD (B – A), and Δ FMD (B – A) while osteoprotegerin positively correlated with triglycerides. **Conclusion:** Endothelial dysfunction and risk of atherosclerosis exist early in children with type 1 diabetes. Early recognition of these events is important to prevent progression of atherosclerosis and cardiovascular disease at an early age.

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Value of the Intrarenal Arterial Resistivity Indices and Different Renal Biomarkers for Early Identification of Diabetic Nephropathy in Type 1 Diabetic Patients

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Objective: To compare resistivity index (RI) in type 1 diabetic patients and normal controls, secondly to evaluate whether high RI is associated with different biomarkers of diabetic nephropathy (DN) as early detection of DN offers the best chance of delaying or possibly preventing progression to end-stage renal disease. **Patients and methods:** The study included 62 type 1 diabetic patients and 30 healthy volunteer of the same age and sex. Blood sample was taken for assessment of glycosylated hemoglobin, lipid profile and urine sample was taken for assessment of albumin/creatinine ratio, Neutrophil gelatinase-associated lipocalin (NGAL), liver-type fatty acid binding protein (L-FABP) and kidney injury molecule-1(Kim-1). 45 diabetic patients & 30 control did renal Doppler. *t*-test or Mann Whitney – U test for independent variables, Pearson's or Spearman correlation analysis were used. **Results:** The mean age of diabetic patients was 16.3 ± 1.5 yrs, and mean duration of diabetes was 9.4 ± 2.9 years. RI, albumin/creatinine ratio, NGAL, Kim-1, L-FABP and uric acid were significantly higher in diabetics than controls and in microalbuminuric diabetics compared to normoalbuminuric diabetics. In normoalbuminuric diabetics, RI, NGAL, Kim-1 and L-FABP were significantly higher compared to controls. The study revealed significant ¬positive correlation between the RI in diabetics and both KIM-1 & albumin/creatinine ratio. **Conclusion:** Increased RI & renal biomarkers in diabetics are early sensitive specific markers of DN, even preceded the development of microalbuminuria, denoting that they can be used as an early and sensitive markers for early detection of DN.

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Can We Rely on Finger Stick Haemoglobin A1c? Comparison of Levels Assayed by DCA 2000 with IFCC Reference Method in a Paediatric Cohort

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Background: DCA 2000 is still a very popular device to determine HbA1c levels in diabetes practices through a finger stick. It allows clinicians to give immediate feedback to patients and to make changes in diabetes management during the three-monthly assessment. **Objective and hypotheses:** To compare HbA1c values measured with DCA 2000 with corresponding values measured with IFCC (considered as the reference method) in a single paediatric centre, to assess the reliability of DCA values. **Method:** 100 Caucasian paediatric patients (47 female; median age 13.2 years, IQR 9.5–15.9) with type 1 diabetes mellitus were enrolled during their annual review. HbA1c was measured for each patient using both the DCA 2000 and the laboratory IFCC assay. **Results:** The laboratory HbA1c values ranged 26–102 mmol/mol had a median of 62.4 mmol/mol (IQR 52.0 – 72.1). The DCA 2000 HbA1c values had a median of 8.1% (IQR 7.3 – 8.9) which corresponded to 64.5 mmol/mol (IQR 56.0 – 73.8). Values between the two methods were strongly correlated (Spearman, $r = 0.951$, $P < 0.001$) with a median of difference (DCA – IFCC) was 2.1 mmol/mol (IQR -0.2 – 5.1). Nevertheless DCA levels were tendentially higher than IFCC laboratory values; a U-shaped relationship has been found when comparing the IFCC values with the differences between the two methods, with major disagreements found at lower and higher HbA1c levels. **Conclusion:** DCA 2000 is a valid tool in everyday practice, with good agreement with IFCC reference method. However, it should be kept in mind that disagreements increase for extreme levels in a U-shaped fashion.

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Significant Impact of Nocturnal Melatonin Secretion on Obesity-Related Metabolic Disorders in Children and Adolescents

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Background: In addition to its function in circadian rhythm Melatonin plays an important role in energy metabolism and body weight regulation. In animals pinealectomy induces insulin resistance and administration of melatonin to diabetes prone rats ameliorates their glucose metabolism. Furthermore loss-of-function mutations of the melatonin receptor gene are associated with insulin resistance and DM II in humans. **Objective and hypotheses:** So far the effect of melatonin on energy metabolism in childhood remains unclear. As obese adolescents were found to have disturbed and shifted sleep rhythm a link between low melatonin secretion and impaired glucose metabolism was suggested. We therefore aimed to explore the effect of nocturnal melatonin secretion on glucose metabolism in obese children and adolescents. **Method:** We performed a cross sectional study of 148 obese (>97.percentile) children and adolescences (10–17 years). Based on fasting blood samples, insulin resistance was defined as age and sex adjusted R-HOMA >95. percentile (using Allard percentiles) and correlated with nocturnal Melatonin secretion. Melatonin secretion was measured as its main metabolite 6-sultatoxymelatonin normalized to urinary creatinine in the first morning urinary void. **Results:** Subjects with insulin resistance ($n=101$) showed significant lower nocturnal melatonin levels ($P=0{,}004$). The median ratio of 6-sulfatoxymelatonin to creatinine was 24.3 ng/mg (1st quartile = 15.7 ng/mg; 3rd quartile=33.0 ng/mg) among subjects with insulin resistance vs 32.8 ng/mg (1st quartile=23.1 ng/mg; 3rd quartile=42.7 ng/mg) among those with unimpaired insulin secretion. Adjusted for age, sex and Tanner status the effect remained significant. **Conclusion:** We found a strong association of lower nocturnal melatonin secretion and insulin resistance in obese children. To increase melatonin levels – either endogenously by prolonged nighttime darkness or exogenously by supplementation – might be one future strategy in management of obesity-induced morbidity.

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Exposure to Phthalates and Phenols in Relation to Gestational Blood Glucose Homeostasis

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Background: Endocrine disrupting chemicals (EDCs), such as phthalates and bisphenol A (BPA), have been associated with insulin resistance (IR) and type 2 diabetes (T2D) in non-pregnant adults. By contrast, recent pilot studies of pregnant women found negative associations between phthalates and blood glucose, and a lack of association with BPA. No studies have examined gestational IR or secretion in relation to EDC exposure. **Objective:** To confirm these results and explore associations with IR and secretion. **Methods:** 259 mothers without T1D/T2D with singleton male pregnancies were recruited as part of larger prospective study (Cambridge Baby Growth Study). Serum was collected at 10-12 weeks' gestation. 27 EDCs (16 phthalate monoesters, 9 phenols) were measured using liquid chromatography/tandem mass spectrometry. Summed levels were calculated for di(2-ethylhexyl)phthalate metabolites (ΣDEHPm) and all phthalate metabolites (Σall.phth.m). Gestational diabetes mellitus (GDM) was diagnosed from an oral glucose tolerance test at 28 weeks' gestation using WHO criteria. Homeostasis Model Assessment (HOMA)-IR and β-cell function were calculated. Regressions controlled for age, body mass index (BMI), deprivation index, ethnicity, smoking, and parity. **Results:** Six phthalates (MEP, MiBP, MnBP, MEHP, MECPP, MCiOP) and three phenols (BPA, TCS, BP-3) were detectable in >60% samples. Demographic variables and EDC levels did not differ between women with ($n=47$) and without GDM. Compared to quartile 1, Σall.phth.m quartile 3 alone was associated with decreased odds of GDM [adjusted-OR (95%CI) 0.13 (0.03-0.56), $P_{trend}=0.037$]; no other EDCs were associated with GDM in continuous or quartile analyses. ΣDEHPm (adjusted-β=0.241, $P=0.004$) and Σall.phth.m (adjusted-β=0.254, $P=0.001$) were positively associated with 2-h blood glucose. No EDCs were associated with HOMA-IR, HOMA-β-cell function, or disposition index. **Conclusion:** Serum phthalate levels were associated with stimulated blood glucose levels. Their association with GDM risk suggests a non-monotonic dose-response relationship. EDC exposure was not associated with perturbations of gestational IR or secretion. **Funding information:** This work was supported by a European Union Framework V programme, the World Cancer Research Fund International, the Medical Research Council (UK), the Newlife Foundation, the Evelyn Trust, and the NIHR (National Institute for Health Research) Cambridge Biomedical Research Centre.

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Developing a Targeted, Mobile-Health Technology (E-Book) to Promote Self-Care During Diabetes Transition

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Background: For young adults with type 1 diabetes, transition from a paediatric setting to an adult care setting is a vulnerable period with risks for gaps in care. These emerging adults need to develop skills for managing their diabetes yet it is often challenging to cover all anticipatory guidance topics related to type 1 diabetes. In the context of a structured transition clinic, we hypothesized that by leveraging teens' facility with technology and marketing/design we could develop a user-friendly mobile health application to facilitate diabetes self-care. **Objective and hypotheses:** The aim of this project was to develop a mobile health application (e-book) to promote self-care for emerging adults with type 1 diabetes and assess its acceptability. **Method:** Development of the e-book was loosely structured on McGuire's communication-persuasion matrix (1998) that posits 6 factors impact consumer behaviour in response to messages. Chapters (i.e. 1–2 page lay texts) were developed by a multidisciplinary team (both paediatric/adult) focusing on young adult topics and a design team helped develop e-book graphics and branding. Healthcare providers and transition patients were surveyed on acceptability. **Results:** We identified 28 topics (e-book chapters) spanning type 1 diabetes knowledge, self-management and anticipatory guidance for young adults. The six persuading factors include: source (expert stakeholders), message (diabetes education via stylized e-book), channel (private, tablet/smartphone), receiver (16–25 years, tech savvy), and destination (effective health promotion communication). Initial acceptability ratings from providers within a pluridisciplinary team were high and analysis of patient feedback is onging. **Conclusion:** We successfully developed a novel e-book specifically targeted to the needs of young adults with type 1 diabetes. Acceptability of this e-book underscores the utility of a mobile health intervention that can be used privately as a real-time health promotion resource for facilitating self-care.

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Cardiac Autonomic Neuropathy is Highly Predictive for Survival in Children with Mauriac Syndrome

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Background: Diabetic autonomic neuropathy (DAN) is predictive for subsequent mortality mainly due to terminal renal insufficiency. DAN is screened by cardiac tests based on heart rate variability (HRV). **Aim:** To assess cardiac autonomic neuropathy (CAN) and its predictive value for survival in children with Mauriac syndrome. **Material and methods:** The study included 12 patients with Mauriac syndrome (growth retardation, hepatomegaly and delayed puberty, seven boys, five girls). Ten were born 1980–1987 and two children 2005-2007. Time-domain and frequency-domain analyzes of R-R intervals of ECG at rest and during sympathetic and vagal stimuli were employed. Deviations out of referent 25–75 percentiles or ± 2 standard deviation scores (SDSs) were accepted as abnormal for heart rate (HR), HRV at rest, deep breathing (DB) and Valsalva maneuver and for total power (TP) and low/high frequency (LF/HF) of spectral analysis. The results were compared with 346 healthy controls and 202 diabetic children with normal growth. **Results:** The children with Mauriac syndrome had mean age at diagnosis 3.4 ± 2.5 year (eight months to 8.3 years), younger than other diabetic children ($P < 0.05$); mean age at the investigation 15.3 ± 2.7 (9.7 – 17.9 years); diabetes duration 12.1 ± 3 years (7.6 – 15.9); mean HbA1c $10.9 \pm 2.17\%$ (4.2–6). Growth retardation was $-3{,}27 \pm 0.92$ SDS. They had one or more late diabetic complications. The deviations below 25th percentile for TP, CV, DB, Valsalva and over 75th percentile for HR and LF/HF were 100% in the group. Mean SDSs for all HRV parameters were statistically different from healthy controls and diabetic children with normal growth/no late complications. ($P < 0.05$). At present, 8 out of 10 patients born before 1987 were not alive. Main reason for death was terminal renal insufficiency. **Conclusion:** Children with Mauriac syndrome developed CAN before age of 18 years together with other late complications. CAN predicted poor survival.

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Predictors of Cystic Fibrosis-Related Diabetes (CFRD) in Patients with cf and Pancreatic Insufficiency

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Background: Cystic fibrosis (CF) is the most common genetic sever disease in Caucasian populations. It is crucial to identify patients with CF who are at increased risk of acquiring CF-related diabetes (CFRD). **Objective:** To identify potential demographic, clinical, and laboratory predictors of CFRD in patients with CF. **Method:** The study group included patients more than 10 years of age with CF and pancreatic insufficiency who attended the CF clinic in 1999-2013. The following data were collected: demographics, anthropometric and laboratory data including annual oral glucose tolerance test (OGTT) values. Findings were compared between patients with CFRD and those with normal glucose tolerance (NGT) or impaired glucose tolerance (IGT). **Results:** Forty-four patients met the study criteria. The patients with CFRD ($N = 16$) had significantly higher glucose levels at 60 and 90 minutes after OGTT, area under the curve (AUC) of glucose, and HbA_1c concentrations one and two years before CFRD was diagnosed than the patients in whom CFRD did not develop ($n = 28$). On multiple regression analysis, the best predictor of CFRD was the AUC of glucose. Analysis of HOMA-IR at diagnosis in patients without CFRD as compared to those in whom CFRD developed, yielded a significant between-group difference (0.95 and 1.78, respectively, $P = 0.02$). No significant

differences were found in levels of insulin, C-peptide, and C-reactive peptide. The rate of liver disease was higher in the patients who acquired CFRD (62.5%) than in the patients with NGT or IGT (28.6%; $P=0.028$). There were no differences between the two groups in BMI SDS, FEV_1, or history of diabetes in the family. **Conclusion:** Glucose levels at 60 and 90 minutes after OGTT AUC, and HbA_1c values may predict an increased risk of CFRD. Insulin resistance appears to be the major cause of CRFD. CFRD is apparently not preceded by a significant decrease in insulin secretion.

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Adherence to Diabetes Care in Children and Adolescents with Type 1 Diabetes Mellitus in Spain: Results from the Chrystal Study

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Background: CHRYSTAL (Costs and Health Related qualitY of life Study for Type 1 diAbetes mellitus pediatric patients in Spain) is an observational study conducted in 2014 on a representative sample of 275 patients aged 1-17 years with Type 1 Diabetes Mellitus (T1DM) in Spain. **Objective and hypotheses:** One of the objectives of the study was to describe the adherence to diabetes care using the Self Care Inventory (SCI), and to compare results by HbA1c level for pediatric patients with T1DM in Spain. **Method:** Patients were asked to respond to the SCI, in a single visit, which is a 15-item self-report scale (each ranged from 1 to 5, 5 being the highest possible adherence level) to assess patients' perceptions of their adherence to diabetes self-care recommendations including the following dimensions: blood glucose testing and monitoring, insulin and food regulation, exercise, and emergency precautions. The overall and groups dimensions mean scores for CSI were calculated. Results by HbA1c level (HbA1c $<7.5\%$ vs HbA1c $\geqq 7.5\%$) were analyzed by Mann-Whitney U test. **Results:** Overall adherence scores were 4.03 (HbA1c $<7.5\%$, n=161) vs 3.87 (HbA1c $\geqq 7.5\%$, n=114), ($P=.047$). 'Blood glucose regulation', 'Insulin and food regulation', and 'Emergency precautions' are significantly different by HbA1c level (4.58 vs 4.43, $P=.035$; 4.08 vs 3.88, $P=.027$; and 4.72 vs 4.63, $P=.028$, respectively). 'Exercise' had the lowest adherence score but does not statistically differ by HbA1c level (3.11 vs 3.17, $P=.588$). **Conclusion:** Perception of adherence to diabetes care is an important factor to consider while managing diabetes. Overall adherence and some dimensions significantly differ by HbA1c levels. Consistently with the literature, the study concludes that children and adolescents' with higher levels of self-care were associated with better HbA1c levels than those with lower levels of self-care. **Funding information:** This work was supported by Eli Lilly and Company.

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Gaining from Patient Experience on a Local Level: The Introduction of Annual Questionnaires for Children and Teenagers with Diabetes

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Background: The children and teenage diabetes team currently care for 270 patients in the region and includes speciality doctors, specialist nurses, dieticians and psychologists. **Objective and null hypothesis:** To evaluate the strengths and weaknesses of the local care provided by the team, and learn from current patient experience. **Method:** An anonymous questionnaire was completed by diabetic patients aged 9–20 years when attending clinic appointments. It included tick box answers, rating scales and free text answers. **Results:** Feedback from 113 patients in 2013 was overwhelmingly positive, but allowed the team to identify key areas for development. Patients felt that the waiting room environment lacked educational information on diabetes, and reported inadequate emotional support and access to psychology appointments. Following the 2013 study, the team has relocated to a dedicated clinic for diabetic patients. Two psychologists also began working with the team and emotional wellbeing screening was introduced for all patients. The study was repeated in 2014 and completed by 114 patients, showing an encouraging response to interventions made. 22% more patients had been offered a psychology appointment, and 37% more patients found the appointment useful. 87% of patients felt emotionally well supported by the diabetes team compared to 79% prior to the changes. There was also an improvement in feedback for waiting times, appropriateness of environment and feeling welcome in clinic. The 2014 study also helped to identified areas for further improvement. Only 60% of patients were receiving written treatment plans, and only 47% of patients received care by team members designated to them. **Conclusion:** This patient questionnaire is an innovative method of obtaining honest and constructive local feedback on current strengths as well as identifying areas requiring improvement. We plan to repeat this questionnaire annually to encourage continued patient participation, optimising the quality of diabetes care provided.

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Factitious Administration of Analogue Insulin to a 2-Years-Old Child

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Background: Hypoglycaemia precipitated by factitious insulin administration presents in a very similar way to hypoglycaemia

caused by hyperinsulinism. It is difficult to ascertain clinically if the hypoglycaemia is secondary to exogenous administration or endogenous insulin secretion. Diagnosis is based on circumstantial evidence and biochemical tests which include insulin and C-peptide level. **Objective and hypotheses:** We would like to report a case of a 2-years-old girl, who soon after diagnosis of type 1 diabetes, presented with severe hypoglycaemia on multiple occasions, requiring intravenous dextrose infusion. Sustained hypoglycaemia despite adequate management prompted further investigations to look into the cause. **Method:** Insulin analysis was performed using the Mercodia Iso-insulin assay and C-peptide analysis was performed using the Mercodia C-peptide assay. To determine the type of insulin present in the blood sample, a combination of immunoaffinity purification, nano-liquid chromatography and high resolution/high accuracy (tandem) mass spectrometry (nanoLC-MS/MS) was employed. **Results:** Blood tests during a hypoglycaemic episode demonstrated a high blood insulin concentration of 270 pmol/l and low C-peptide levels of $<$94 pmol/l.The remainder of the hypoglycaemia screen including free fatty acid, 3-β hydroxybutyric acid, serum cortisol, free carnitine, serum aminoacids, lactate and ammonia were all within respective reference ranges. Mass Spectrometry demonstrated a positive result for the insulin derivative Aspart (Novorapid). However, pharmacokinetics were inconsistent with the last injected dose of Novorapid. Moreover, only Actrapid charted for the patient at that time, was being administered to the child in the hospital, and not Insulin Aspart (Novorapid). **Conclusion:** The presence of Novorapid insulin in the patient confirmed the cause of unexplained hypoglycaemia to be 3rd party administration of insulin. Following further investigations, the mother was established as having administered the insulin as Munchausen syndrome by proxy.

P2-263

Insulin Sensitivity in Adolescents with Gender Dysphoria During Puberty Suppressing Therapy with GnRH Agonists

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Background: In gender dysphoric adolescents GnRH agonists can be used to suppress pubertal development of the natal sex. The metabolic implications of the pubertal suppression have not yet been explored. Insulin sensitivity is known to be influenced by pubertal changes. During puberty a decrease in insulin sensitivity is normally observed. **Objective and hypotheses:** The effects of GnRH agonists on insulin sensitivity during 2 years of treatment in adolescents with gender dysphoria were examined. We hypothesized that withdrawal of sex steroids by centrally blocking the gonadotropic axis would cause insulin sensitivity to increase. **Method:** 91 adolescents with GD, 41 male-to-females (MtF) and 50 female-to-males (FtM) receiving 3.75 mg of the GnRH agonist triptorelin every 4 weeks, were studied by determining insulin sensitivity (QUICKI) using fasting glucose and insulin serum levels. **Results:** QUICKI (estimated marginal means + SE) at the start of treatment was 0.351 (0.005) in MtF, 0.354 (0.004) in FtM and after 2 years 0.354 (0.004) in MtF and 0.358 (0.006) in FtM. **Conclusion:** No significant change in insulin sensitivity occurred during 2 years of treatment with puberty suppressing therapy in genderdysphoric adolescents using GnRH agonists. **Funding:** An unrestricted educational grant from Ferring Pharmaceuticals BV, Hoofddorp, the Netherlands.

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Ethnic Variation in the Correlation of Waist Circumference to Daily Insulin Requirement in Children with Type 1 Diabetes

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Introduction: Daily insulin requirement in type 1 diabetes (T1D) depends on various factors. **Objectives:** To study the correlation of waist circumference (WC) and BMI to daily insulin requirements (TDD) and examine the ethnic variation in this correlation. Associations of estimated glucose disposal rate (eGDR) a surrogate marker of insulin resistance were also studied. **Methods:** Cross-sectional study of children with T1D attending a diabetes clinic in a multi-ethnic population was conducted. Ethical approval was obtained from Regional Ethics Committee. Data was collected from case notes and patients following written consent. Physical measurements were undertaken in the clinic setting. **Results:** patients were recruited. Mean age was 12.7 ($\pm$3.1) years, duration of diabetes 5.4 ($\pm$3.5) years and HbA1c 80 ($\pm$18) mmol/mol. The white (36 = Caucasians, 1 = white European) and non-white (29 = Asian Pakistani, 1 = Indian, 2 = mixed White Afro-Caribbean) groups had similar demographics and disease profile. Non-whites compared to whites had a higher prevalence of obesity (15% vs 5%), family history of type2 diabetes (T2D) (23% vs 18%) and deprivation (mean IMD score of 42 vs 30). WC and BMI were standardised to Waist-to-height ratios (WHtR) and BMIsds. WHtR and BMIsds were positively correlated to TDD in whites ($r = 0.61$, $P < 0.05$ and $r = 0.36$, $P = 0.29$ respectively) and negatively correlated in non-whites ($r = -0.39$, $P < 0.05$ and $r = -0.36$, $P < 0.05$ respectively). Negative correlation was most significant in non-whites with a first degree relative with T2D ($r = -0.93$, $N = 7$, $P < 0.001$). The eGDR in mg/kg per min was determined using a validated clinical formula utilising WC,

hypertension status and HbA1c. On linear regression analysis age adjusted eGDR was negatively associated to having a first degree relative with T2D ($P<0.05$) in Asians, BMIsds ($P<0.001$) in Caucasians and positively to disease duration ($P<0.05$) in both. **Conclusions:** Asian Pakistani population with a family history of T2D had a higher insulin requirement and low eGDR at lower WC indicating the presence of insulin resistance. Whereas in the Caucasians a high BMI was associated with increased insulin resistance. **Funding:** No funding received.

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Importance of Thrombocyte Volume Parameters in Type 1 Diabetes Mellitus Patients with and without Clinical Findings of Diabetic Ketoacidosis

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Background: Thrombocyte volume parameters such as mean thrombocyte volume (MPV) and PDW (thrombocyte distribution volume) are parameters used in evaluation of thrombocyte size which have hemostatic importance. The increased thrombocyte volume is a marker of thrombocyte activation. The thrombocyte activity is important in pathophysiology of diseases with a tendency of thrombosis and inflammation. In adult studies it has been reported that MPV increases in thrombotic diseases such as obesity, diabetes mellitus (DM), atherosclerosis, cerebrovascular diseases. **Objective and hypotheses:** The aim of the present study is to evaluate the risk of thrombosis by measurement of MPV and PDW values, in type 1 DM patients with and without the clinical findings of diabetic ketoacidosis (DKA). **Method:** The complete blood counts of 20 type 1 DM patients who has admitted with DKA and 26 type 1 DM patients without ketoacidosis and age and gender-matched 30 control cases were investigated at the time of admission, at least 1 week after improvement of clinical findings of ketoacidosis and at least 3 months after the admission and MPV and PDW values were recorded. pH and HCO3 values in blood gas analysis, HbA1c and blood glucose values were also recorded. **Results:** MPV and PDW values at the time of admission were found to be higher in cases with DKA when compared with the cases without DKA and also the values were found to be higher in cases without DKA when compared with the control group. A significant negative correlation was found between MPV values and pH and HCO3 values in patients admitted with DKA. In all type 1 DM patients, a decrease was observed in MPV values in parallel to the decrease in HbA1c and blood glucose levels 3 months after the diagnosis. **Conclusion:** It has been demonstrated that MPV and PDW values in cases admitted with DKA were higher when compared with the cases without ketoacidosis and the control group, and this increase in MPV values is related with the degree of acidosis and MPV values became normal after initiation of fluid and insulin treatment. The clinical manifestation of DKA is related with fluid-electrolyte loss, tendency to thrombosis and systemic inflammatory process. The measurement of thrombocyte volume parameters in cases with the clinical findings of DKA could be used in the diagnosis and progress of the disease. **Disclosures:** NZ-L, ZG, consultant (Novo Nordisk, Spring). MHR, MBO, employees Novo Nordisk. LS, consultant (Ferring, Novo Nordisk, Merck Serono, Pfizer, Sandoz); grants (Merck Serono, Novo Nordisk, Pfizer). TB, boardmember (Novo Nordisk, Sanofi, Eli Lilly, Medtronic, Bayer Health Care); institutional grant/expenses (Abbott, Medtronic, Novo Nordisk, GluSense, Sanofi, Sandoz, Diamyd); speaker bureaux (Eli Lilly, Bayer, Novo Nordisk, Medtronic, Sanofi, Roch); stocks (DreamMed).

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Increased Arterial Wall Stiffness in Children with Type 1 Diabetes and Poor Metabolic Control: An Early Marker of Vascular Complications?

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Background: The prevalence of macrovascular complications is probably underestimated in children with type 1 diabetes (T1D). Arterial stiffness (AS) represents a subclinical marker of CV risk. The most validated non-invasive method for AS measurement is pulse wave velocity (PWV). There are limited numbers of studies with PWV on children with T1D. **Aim:** Our aim was to assess the relationship between AS and parameters associated with metabolic control in children with T1D. **Patients and methods:** 59 children with T1D were examined (30 males, 51%) aged 9–19 years (median 16 years), with duration of T1D 2–17 years (median 9 years). 26 (44%) of them were treated with insulin pump (CSII). PWV was measured as the carotid-femoral pulse transmission time. The velocity adjusted for gender, age, heart rate and mean arterial pressure was expressed in normative percentiles using published paediatric references. The mean HbA1c from all patients assessed from last 24 months ranged from 50 to 119 mmol/mol IFCC (median 74 mmol/mol). 44 (75%) of all patients have evaluated ABPM using standard procedures, 16 from them (36%) children were hypertonic (included masked hypertension). Non-parametric test and a multiple regression analysis were used to compare the PWV percentiles and parameters associated with metabolic control. **Results:** Significant association between PWV percentiles and HbA1c levels ($P<0.01$) and both systolic and diastolic blood pressure ($P<0.05$) was found. Duration of diabetes, lipids profile and insulin treatment mode were not associated with PWV. In multivariable analysis the most significant variable associated with increased PWV was HbA1c ($P=0.0087$) followed by 24 h systolic blood pressure SDS ($P=0.0187$). **Conclusion:** The finding of increased PWV in poorly controlled T1D children is in accordance with the hypothesis of increased AS as an early predictor of CV risk. **Funding:** The work was supported by grant IGA No 5300.

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Glycaemic Dysregulation in Transfusion Dependent Thalassaemia Patient in a Children's Hospital

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Background: Thalassaemia patients are at risk of developing diabetes mellitus (DM) and pre-diabetes status predominantly due to iron overloading. The prevalence is 20–30% in adult patients. Age, serum ferritin, T2* magnetic resonance imaging (MRI) of the heart and pancreas volume has been found to be associated with DM. However, majority of the studies involved more adults than children. **Objective and hypotheses:** To establish the prevalence of glucose dysregulation in a group of Thalassaemia children, and to determine factors associated with development of this condition. **Method:** A cross-sectional study whereby all Thalassaemic children 12 years old and above by 31 January 2015 were enrolled. These children had annual blood screening for endocrinopathy, and also regular ferritin monitoring. Cardiac T2* MRI was done at least once in every 2 years. Their medical records were reviewed to extract the latest glucose levels, cardiac T2* MRI value, and calculate mean annual ferritin level. DM and pre-diabetes are diagnosed based on standard oral glucose tolerance test following WHO criteria. **Results:** There are total 55 children (41.8% female) fulfilled the criteria. The mean age was 14.0 years old. There are five DM and three pre-diabetes detected, making prevalence of glucose dysregulation in this cohort was 14.5%. Affected children were significantly older (mean 14.8 vs 13.9 years old, $P=0.022$), with higher ferritin level (median 11 224.5 vs 2 842.5 ng/ml, $P=0.049$) and lower cardiac T2* MRI (median 5.82 vs 21.20 ms, $P=0.009$). Puberty status was not significantly different between the groups ($P=0.592$). **Conclusion:** Prevalence of glycaemic dysregulation is high even in paediatric thalassaemia patients. Older age, higher ferritin and lower cardiac T2* MRI are associated with development of this condition.

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MODY-GCK and MODY-HNF1A in Children and Adolescents in Russian Population

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Background: The most common forms of maturity-onset diabetes of the young (MODY) are MODY-GCK and MODY-HNF1A. Prevalence of MODY in Russian population is unknown. **Aims and objectives:** To compare clinical laboratory characteristics of MODY-GCK and MODY-HNF1a in children and adolescents, to estimate prevalence of MODY. **Method:** 151 children and adolescents were screened for mutations in GCK and HNF1A. HbA1c, fasting and stimulated glucose, C-peptide, insulin levels (OGTT) were measured. The data is presented as medians (25; 75 percentile). Mann–Whitney U-test was used to compare medians. **Results:** We identified *GCK* mutations in 54 patients (35.7%), *HNF1A* mutations in 19 patients (12.5%). The prevalence MODY-GCK was 2.8 times higher than MODY-HNF1A. MODY-GCK patients were younger than MODY-HNF1A at the time of diagnosis with diabetes, (8.0 years (4.0; 11.3) vs 11.8 years (9.7; 13.5), $P<0.01$). HbA1c was lower in MODY-GCK (6.5% (6.1; 6.7) vs 6.8% (6.5; 7.8), $P<0.05$). MODY was confirmed by genetic analysis at 12.4 years (9.1; 15.4). Fasting glucose level was higher in MODY-GCK, 16.3% of patients MODY-GCK and 68.8% of patients MODY-HNF1A had normal fasting glycaemia. Stimulated glucose level was lower in MODY-GCK: 18.2% of patients had diabetes, 65.9% – impaired glucose tolerance, 15.9% – normal glucose tolerance. All MODY-HNF1A patients had diabetes. Fasting serum C-peptide and insulin didn't differ between MODY-GCK and MODY-HNF1A. Stimulated serum C-peptide and insulin were significantly higher in MODY-GCK than MODY-HNF1A (C-peptide: 1 h – 5.8 ng/ml (4.5; 7.6) vs 3.5 ng/ml (2.9; 5.1), $P<0.05$, 2 h – 5.9 ng/ml (4.6; 8.2) vs 4.7 ng/ml (3.8; 5.7), $P<0.05$. Insulin: 1 h – 49.1 U/l (32.6; 64.9) vs 21.9 U/l (19.4; 39.8), $P<0.05$, 2 h – 35.4 U/l (24.4; 54.7) vs 23.8 U/l (16.2; 37.9), $P<0.05$). **Conclusion:** The prevalence MODY-GCK was 2.8 times higher than MODY-HNF1A in Russian population. Patients with MODY-GCK were diagnosed earlier than MODY-HNF1A, and had milder presentation and higher stimulated C-peptide and insulin to compare to MODY-HNF1A.

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Clinical and Hormonal Profile in Mini-Puberty of Daughters Born after Pregnancies with Diabetes: Preliminary Report

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Background: Maternal diabetes is a pathologic state that increases the incidence of complications in both the mother and the foetus. Patients with diabetes mellitus (DM) may exhibit reproductive abnormalities, including PCOS and hypogonadotropic hypogonadism. Diabetes during pregnancy is an endocrine disruptor and studies performed in animal models have shown abnormalities in gonadal function in the offspring, but it is unknown whether pre-gestational (PGDM) and gestational diabetes (GDM) may affect ovarian function in the offspring of women with DM in the short or long term. **Objective and hypotheses:** To evaluate anthropometric profile and serum concentration of testosterone, SHBG and anti-müllerian hormone (AMH), in healthy infant girls born to women who had diabetes during pregnancy (PGDM or GDM) at the time of mini-puberty. **Method:** Healthy girls born product of a normal pregnancy in non-diabetic mothers (N=21)[§] and healthy daughters of mothers who had diabetes during pregnancy (DM, N=17) were estudied.

Anthropometry and blood sample was obtained. Circulating concentrations of testosterone, SHBG and AMH were determined by specific assays.[§] The control group is an historic group that was previously studied by Sir-Petermann T, Codner E, Maliqueo M, *et al.* (Increased Anti-Mullerian Hormone Serum Concentrations in Prepubertal Daughters of Women with Polycystic Ovary Syndrome. *J Clin Endocrinol Metab* 2006;**91**:3105–9). **Results:** Daughters of DM mothers had higher AMH (32.2 ± 32.8 vs 9.1 ± 8.6 pM/l, $P < 0.05$) and SHBG levels (251.1 ± 76 nM/l vs 95.8 ± 42.3 nM/l, $P < 0.05$) than daughters of healthy mothers, but similar testosterone levels (0.17 ± 0.3 vs 0.3 ± 0.2 ng/ml). **Conclusion:** AMH is produced by the granulosa cells and their serum levels are correlated with the development of preantral and small antral follicles. This preliminary report shows higher AMH levels measured in mini-puberty in a group of female infants born after a pregnancy with diabetes, suggesting that these girls may show evidence of an altered follicular development during early infancy. **Funding:** This work was supported by Proyecto Fondecyt N° 11121460, 2012.

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Growth and Endocrinopathy in Wolfram Syndrome: The Experience of a Nationally Commissioned Specialist Clinic

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Background: Wolfram syndrome (WS) is a monogenic disorder associated with diabetes mellitus (DM), optic atrophy, diabetes insipidus (DI), neurological deterioration and deafness. Growth has been poorly characterised in case series. **Objective and hypotheses:** To determine growth and prevalence of endocrine disorders, qualify therapies and metabolic outcome for DM, and relationship of cranial MRI findings to clinical findings in children and young people (CYP) with WS. **Method:** Examination of records of CYP attending a nationally commissioned specialist clinic for WS from 2012–2015, to determine height, weight, BMI, history, DM therapy, DI, thyroid and pubertal disorders. Results of gonadotrophin, sex steroid levels, TFTs, HbA1c, blood glucose, paired early morning plasma and urine osmolality. Height, weight and BMI were converted to standard deviation scores using UK 1990 growth data. Cranial MRI reports were examined for pituitary abnormalities (PA). **Results:** Mean height, weight and BMI SDS (SD) were −0.226 (0.98), 0.195 (0.74) and 0.427(0.88) respectively. No significant sex differences were present. DM was present in 89%. Median HbA1c was 8.0%, with 35.6% achieving target HbA1c <7.5% and 44% managed on intensive insulin therapy. Cranial MRI was successful in 68% of the cohort. DI was present in 39%. In patients with successful imaging posterior PA was present in 100% with DI, and 64% without DI. Two patients also had anterior PA without clinical evidence of anterior or posterior pituitary failure. Two CYP had hypergonadotrophic hypogonadism, requiring sex steroid replacement therapy. **Conclusion:** This data implies CYP with WS demonstrate normal growth. It is concerning to see that although outcomes are better than average for all forms of DM, the majority of CYP are treated more frequently with non-intensive insulin regimes, and have suboptimal diabetes control. This should be a focus for improving future outcomes. Further studies are required to study evolution of PA in WS.

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Evaluation of a Novel Tool to Adjust Insulin Boluses Based on Continuous Glucose Monitoring Trend Arrows and Insulin Sensitivity (Trend Arrow Adjustment Tool©) in Children and Youth with Type 1 Diabetes Using Insulin Pump Therapy

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Background: Continuous glucose monitoring (CGM) measures interstitial glucose and displays trend arrows, showing the direction and rate of change in glucose. Trend arrows allow the child/youth to take action to prevent hyper- and hypoglycaemia. Effective strategies for adjusting insulin for trend arrows are lacking. The JDRF CGM Study Group recommended a 10–20% increase/decrease in the insulin dose. However, the bolus dose is dependent on amount of food to be consumed and current blood glucose, which could potentially lead to overcorrection if preprandial glucose is elevated and/or if eating high carbohydrate meals. In addition, the formula requires the pump user to perform mathematical calculations with each arrow, limiting the tool's uptake in paediatrics. We developed an alternative tool, based on the patient's insulin sensitivity factor. **Objective and hypotheses:** To compare the effect of the Trend Arrow Adjustment Tool, the 10/20% adjustment, and no adjustment for arrows; on postprandial glucose. To evaluate patient satisfaction, ease and frequency of use of both adjustment methods. **Method:** A single-blinded, counterbalance, treatment assignment crossover study, of 20 subjects with type 1 diabetes. During a hospital assessment, trend arrows were induced through exercise or oral carbohydrate. Subjects consumed a meal with the insulin adjusted for trend arrows using the assigned method. Subjects used the assigned method during week 1; made no adjustment for arrows in week 2, and used the alternative method in week 3. CGM data was used to analyse postprandial glucose. **Results:** Time with postprandial glucose in target range was equivalent with Trend Arrow Adjustment Tool© and the 10/20% adjustment. There was a trend towards more time in target range and less hypoglycaemia, with use of either tool compared to ignoring arrows. Significantly more errors were made with the 10/20% adjustment. Satisfaction and ease of tool use was greatest with Trend Arrow Adjustment Tool©. **Conclusion:** The Trend Arrow Adjustment Tool© is a simple and well received method of adjusting insulin boluses for CGM trend arrows, which can be successfully used in the paediatric population. **Funding:** This work was supported by

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Circulating GLP-1 in Infants Born Small-for-Gestational-Age: Breast-Feeding Vs Formula-Feeding

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Background: Prenatal growth restraint associates with risk for later diabetes particularly if such restraint is followed by postnatal formula-feeding (FOF) rather than breast-feeding (BRF). Circulating incretins can influence the neonatal programming of hypothalamic setpoints for appetite and energy expenditure, and are thus candidate mediators of the long-term effects exerted by early nutrition. **Objective, hypotheses and method:** We have tested this concept by measuring (at birth and age 4 months) the circulating concentrations of glucagon-like peptide-1 (GLP-1) in BRF infants born appropriate-for-gestational-age (AGA; N = 63) and in small-for-gestational-age (SGA) infants receiving either BRF (N = 28) or FOF (N = 26). **Results:** At birth, concentrations of GLP-1 were similar in AGA and SGA infants. At 4 months, pre-feeding GLP-1 concentrations were higher than at birth; SGA-BRF infants had GLP-1 concentrations similar to those in AGA-BRF infants but SGA-FOF infants had higher concentrations. **Conclusion:** Nutrition appears to influence the circulating GLP-1 concentrations in SGA infants and may thereby modulate long-term diabetes risk.

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Utility of Estimated Glucose Disposal Rate and Fat Mass Percentage for Predicting Metabolic Syndrome in Children and Adolescents with Type 1 Diabetes

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Objective: To determine the prevalence of metabolic syndrome (MetS) and the clinical utility of fat mass percentage (%fat) and estimated glucose disposal rate (eGDR) for predicting MetS in children and adolescents with type 1 diabetes (T1D). **Method:** We conducted a descriptive, cross sectional study including T1D patients between 8–18 years of age. Modified criteria of IDF, WHO and NCEP were used to determine the prevalence of MetS. eGDR, a validated marker of insulin sensitivity, was calculated using A1C, hypertension status and waist-to-hip circumference ratio. %fat was determined by bioelectrical impedance analyses. ROC curve analysis was performed to ascertain cut-off levels of eGDR and %fat for predicting MetS. **Results:** The study included 200 patients with T1D (52% boys, 48% girls). Of these, 18% were overweight/obese (BMI $_{SDS} \geq 1.1$). MetS prevalence was found as 10.5, 9.5 and 10.5% according to IDF, WHO and NCEP criteria respectively. There were no statistically significant differences in age, gender, family history of T2D, pubertal stage, duration of diabetes, A1C levels and daily insulin doses between patients with or without MetS. LDL-cholesterol and triglyceride concentrations are higher in patients with than without MetS ($P < 0.001$). Lower eGDR levels, indicating greater insulin resistance, were found in MetS patients compared with those without (6.41 ± 1.86 vs 9.50 ± 1.34 mg/kg per min) ($P < 0.001$). An eGDR cut-off level < 8.24 mg/kg per min showed 81% sensitivity and 87% specificity for MetS diagnosis. Fat mass was significantly higher in MetS patients compared with those without (29.7 ± 7.8% vs 21.2 ± 7.9%) ($P < 0.001$). A %fat level of 27.9 had 76% sensitivity and 80% specificity for MetS diagnosis. **Conclusion:** Prevalence of MetS in our pediatric T1D cohort is not as high as reported in the other studies likely owing to relatively lower rate of overweight/obesity. Compared with other clinical variables, eGDR is a good indicator of diagnosing MetS. **Funding:** This work was supported by the Scientific Research Council of Ondokuz Mayis University (PYO.TIP.1904.15.017).

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Friedreich's Ataxia Presenting with Diabetes Mellitus in an Adolescent

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Background: Friedreich's ataxia (FA) is an autosomal recessive neurodegenerative disorder characterised by progressive ataxia with limb muscle weakness, absent lower limb reflexes, extensor plantar responses, dysarthria, decreased vibratory sense and proprioception. The most common molecular abnormality is a GAA trinucleotide repeat expansion in intron 1 of the *frataxin* (*FXN*) gene. Patients with FA are at risk of getting increased blood sugar levels, or glucose intolerance, and around 20% progress to overt diabetes mellitus (DM). The cause of diabetes in FA is poorly understood. Glucose intolerance and diabetes can result from a shortage in insulin secretion by the insulin-producing β cells in the pancreas, from insulin resistance, or from a combination of both. **Case:** A 15.5-year-old girl was admitted to the hospital with the complaints of weight loss, polyuria and polydipsia of 1-month duration. History revealed the presence of gait disturbance and pain in her soles for the last 3-years. Neurological examination demonstrated ataxic gait pattern, pes-cavus, intentional tremor, lower limb areflexia and fleksor plantar response. Thyroid gland was soft, and bilaterally 4 cm on palpation. Hyperglycaemia

(390 mg/dl) had been detected on laboratory and further tests showed ketonuria, insulinopenia (1.53 μIU/ml), c-peptide of 1.08 ng/ml (N: 1.1–5) and HbA1c of 13.4%. Basal and bolus insulin treatment had been initiated. Diabetes autoantibodies (anti-insulin, -GAD, and -islet cell antibodies) were negative. Echocardiography were normal. Hyperthyroidism was detected (TSH: 0.03 μIU/ml (0.34–5.6), fT_4: 1.79 ng/dl (0.61–1.12), fT_3: 4.57 pg/ml (2.5–3.9)) with negative thyroid autoantibodies. Thyromasole was added to treatment. *FTX* gene analysis revealed homozygous >66 GAA tri-nucleotide repeats in intron 1 (N: -), which is consistent with FA. **Conclusion:** FA should be considered in patients who presented with diabetes and ataxia. Non-autoimmune hyperthyroidism detected in this patient is a novel finding in FA.

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Do Pancreatic Functions Predict Cardiac and Liver Iron Loading in Transfusion-Dependent β-Thalassemia Major Patients Using Cardiovascular and Liver T2-Star (T2*)Magnetic Resonance?

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Background: Regular and frequent red blood cell transfusions have significantly increased the life expectancy of patients with β-thalassemia major (β-TM). However, when no appropriate chelation therapy is available, patients accumulate iron in the heart, liver, spleen, pancreas, and endocrine glands, leading to progressive organ dysfunction. **Objective and hypotheses:** To assess the correlation between cardiac and hepatic T2*MRI findings with the endocrine and exocrine pancreatic functions in known β-TM patients. **Method:** A total of 44 children and adolescents β-TM patients and 44 healthy controls were investigated via: serum amylase, lipase, triglyceride index, oral glucose tolerance test, and T2* MRI to assess iron content in the heart and liver. **Results:** Overt diabetes was found in 9.4% and 45.5% of patients had impaired fasting glucose. Median cardiac T2* was 22 ms (12–31 ms) and LIC was 6 ms (4–9 ms). Cardiac T2* was less than 10 ms in 21.4% indicating heavy load with iron in cardiac tissues. There is a significant decrease in serum amylase (87.5 vs 63.5 IU/l, $P=0.003$) and lipase (94 vs70 IU/l, $P=0.056$) among enrolled patients in comparison to control group. Thalassemic diabetic showed low serum amylase (32.5 vs 59.5, $P=0.0005$), serum lipase (39.5 vs 68, $P=0.0007$), low cardiac T2* was found (7 vs 22 ms, $P=0.0006$) and low LIC (2 vs 6 ms, $P=0.0006$) than other β-TM patients without diabetes. Inverse correlation was found between triglyceride index with cardiac T2* ($r=-0.376$, $P=0.014$) and low LIC ($r=-0.376$, $P=0.014$ respectively) but not with serum lipase ($r=-0.099$, $P=0.533$), ($r=-0.222$, $P=0.1570$) and serum amylase ($r=-0.191$, $P=0.225$), ($r=-0.053$, $P=0.738$) respectively. **Conclusion:** Follow up of thalassemic patients with impaired fasting glucose together with intensive chelation therapy may help to prevent the development of cardiac and hepatic siderosis.

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Determinants of Outcome of Children with Type 1 Diabetes in Cameroon

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Background: In Sub-Saharan Africa the prognosis of children with type 1 diabetes is poor. Many are not diagnosed and those diagnosed have a dramatically reduced life expectancy (<1 year). **Objective and hypotheses:** To identify the predictors of outcome in children and adolescents with type 1 diabetes. **Method:** A cross sectional study involving 76 children/adolescents (35 boys and 41 girls, mean age of 15.1 ± 3.1 years) with type 1 diabetes included in the 'changing diabetes in children' (CDiC) programme and attending the clinics for children living with type 1 diabetes in the North West Region of Cameroon. Data on glycosylated haemoglobin (HbA1c) was obtained from hospital records of participants. Socio-demographic characteristics and diabetes related practices were obtained from participants using a structured questionnaire. Odds ratios (OR) were calculated using logistic regression models to assess the association between determinants and good glycaemic control. **Results:** The study population had a mean HbA1c of $10.3 \pm 2.9\%$. Univariate analysis indicated that having a mother as the primary caregiver (OR: 0.07, 95% CI: 0.02–0.2), being on two daily injection (OR: 0.2, 95% CI; 0.1–0.5) and good blood glucose monitoring (BGM) adherence (OR: 0.1, 95% CI: 0.04–0.3) were significantly ($P<0.001$) associated to good outcome as indicated by HbA1c, while older age (OR: 1.1, 95% CI: 0.4–3.2) and longer diabetes duration (OR: 0.9, 95% CI: 0.3–2.9) were not ($P>0.05$). Minimal/moderate caregiver involvement in BGM (OR: 7.7, 95% CI: 2.7–22.0) and insulin injection (OR: 14.9, 95% CI: 4.8–46.5) were significantly ($P<0.001$) associated to poor outcome. Multivariate analysis showed that having a mother as the primary caregiver (OR: 0.02, 95% CI: 0.002–0.189) was an independent predictor of good outcome. **Conclusion:** This study confirms that mother's involvement in the diabetes management of their children is the most important determinant for treatment outcome.

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Psychosocial Screening in Children with Type 1 Diabetes in Ireland

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Background: Psychosocial factors may be fundamental explaining poor glycaemic control in children with type 1 diabetes

(T1DM). Anxiety, depression are well described in children with T1DM. According to Kauffman (2012), diabetes management can only be successful if psychosocial needs are assessed and addressed. **Objective and hypotheses:** To examine the association between glycaemic control and scores on two screening tools measuring psychosocial risk and emotional distress in an Irish cohort of children with T1DM. **Methods:** The risk index for poor glycaemic control (RI-PCG) is the screening tool to assess psychosocial risk. According to Schwartz *et al.* (2014) cut-off scores for low, moderate and high risk for poor glycaemic control are 0–2, 3 and >3 respectively. The paediatric index of emotional distress (PI-ED) was used for emotional distress assessment. **Results:** 34 children with T1DM (15 girls, 19 boys) aged 4–17 years (mean 12.24 ± 3.8) are was analysed. 78.1% had a low score (0–2) on the RI-PGC, 6.3% had a moderate score (3), 15.6% had high scores (<3). There was a significant association between higher RI-PGC scores and higher HbA1c ($r=0.33$, $P<0.05$). The mean total PI-ED score was 10.59 ± 6.2. Almost 10% of patients showed a high risk for emotional distress. Higher HbA1c values were not significantly correlated with higher PI-ED scores ($P>0.05$). There was a significant association between higher RI-PGC scores and higher levels of emotional distress (PI-ED scores) ($r=0.42$, $P<0.05$). **Conclusion:** High psychosocial risk is associated with poor glycaemic control and emotional distress. Preliminary analyses suggest that screening tools for psychosocial risk and emotional distress (RI-PGC and PI-ED) may have utility in clinical practice. The ability to predict higher risk of diabetes related complications and psychological distress would allow for early intervention by trained clinical Psychologist. However, further prospective assessment of the predictive power of these screening tools is warranted.

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Neonatal Diabetes – Experience from a Single Centre in Sri Lanka

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Background: Neonatal diabetes (NDM) is a rare form of monogenic diabetes which usually presents before 6 months of age. Both transient and permanent NDM have been described. **Objective:** To report the molecular genetics and clinical characteristics of patients with NDM from a single centre in Sri Lanka. **Method:** Retrospective analysis of clinical and molecular genetic data from patients referred to Lady Ridgeway Hospital Endocrinology unit from April 2014 to February 2015. **Results:** We identified ten patients (seven male) diagnosed with permanent diabetes before the age of 9 months. Consanguinity was reported in family. Sequence analysis identified mutations in nine of the ten patients (90%) screened. Testing is currently in progress for one patient. HomozygousEIF2AK3 mutations (p.S991Nand p.L863*) were identified in two patients confirming a diagnosis of Wolcott-Rallison syndrome. Both patients had skeletal dysplasia and one patient had glucose-6-phosphatase deficiency which was diagnosed following a presentation of episodic hemolytic anaemia. One male patient, who presented with nephrotic syndrome prior to the diagnosis of NDM, had a novel hemizygousFOXP3mutation (p.E412D). In two patients a heterozygous p.R89C INS mutation was identified. Four patients were heterozygous for a K-ATP channel mutation (p.R50Q, p.R50P, p.V59M in KCNJ11and-p.E208Kin ABCC8). Developmental delay was observed in two cases (p.V59M, p.R50P). Thereof these patients responded to sulphonylureas following the genetic diagnosis; the patient with the p.R50P mutation causing DEND syndrome showed no response. **Conclusions:** A genetic diagnosis was possible for 90% of patients diagnosed with NDM in our cohort. Identification of a K-ATP channel mutation resulted in improved treatment for three patients highlighting the importance of genetic testing in all patients diagnosed with NDM. This is the first report of molecular genetic screening in a cohort of patients with NDM from Sri Lanka.

P2-279

Dive: A Serious Game for Diabetes Therapeutic Education in Children

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Background: Implementation of type 1 diabetes (T1D) in children is constant from 20 years. In combination with insulin treatment, therapeutic patient education (TPE) is essential to improve care and prognostic. The use of video games as educational support appears suitable for learning in children, innovative, and interesting to respond to the increase in TPE needs in T1D and current economic constraints. **Objective and hypotheses:** To validate in a proof of concept (POC) the patients' interest for a serious game dedicated to TPE. **Method:** We designed the serious game diabetes virtual education (Dive). In a virtual environment reproducing patients life places (home, school, hospital) it provide patients theoretical (videos, animations and quiz in the game) and practical knowledge (role playing with an avatar to confront virtually to particular life situation). Each successful steps allows children to earn learning points and trophies and to access to the next level. Forums and tchat also allow children to interact with each other. In this POC, patients were given free access to the game and had to give their feedback through an auto questionnaire. **Results:** POC was conducted in

nine patients during 10 days. Number of connections confirmed patient's interest for this educative support and functionality of game interface. Majority of children have crossed 80% of stages and 31 280 points and 12 trophies were collected in 4 days. All report having learned about diabetes. Educational sequences were found interesting by children (100%) and tchat seems to be an asset of the game (83%), even if few children have used it. **Conclusion:** The POC confirm the interest of this serious game development for therapeutic child education in diabetes and allow to consider improvement in contents of educational sequences and game interface. To confirm these results, pilot study and multicentric controlled randomized study are planed.

P2-280

Glucose and Insulin Response at Standard Oral Glucose Load and Followed Submaximal Treadmill Test in Obese Adolescents

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Background: Exercise performance is dependent on glucose supply as fuel to working muscles. **Objective and hypotheses:** We hypothesised that postprandial insulin secretion impacts exercise induced glucose and insulin response. **Method:** 27 sedentary obese adolescent males aged 15.31 + 1.33 were examined. Standard 2 h oral glucose tolerance test (OGTT) with further calculation AUC for glucose and insulin for increments: 0–30 min ($AUCgl._{0\text{-}30}$; $AUCins._{0\text{-}30}$), 30–60 min ($AUCgl._{30\text{-}60}$; $AUCins._{30\text{-}60}$), 60–120 min ($AUCgl._{60\text{-}120}$; $AUCins._{60\text{-}120}$). Multi stage treadmill test (Bruce protocol) followed by measurement of insulin and glucose level at the moment test termination with calculation the relevant curves ($AUCgl._{ex}$, $AUCins._{ex}$). **Results:** Mean BMI *z*-score was 2.72 + 0.54. Impaired fasting glucose was established in 73%, impaired glucose tolerance in 26.6% participants. None of them was diabetic. Mean fasting glucose 5.29 + 0.79 mmol/l, mean fasting insulin 38.06 + 11.19 mIU/ml, mean Homa-IR 8.04 + 4.09. It was established progressive increasing of glycemic area $AUCgl._{0\text{-}30} < AUCgl._{30\text{-}60}$ ($P = 0.002$) $< AUCgl._{60\text{-}120}$ ($P = 0.004$) as well as insulin one $AUCins._{0\text{-}30} < AUCins._{30\text{-}60}$ ($P = 0.003$) $< AUCgl._{60\text{-}120}$ ($P = 0.03$). Glucose (4.49 + 0.55 mmol/l) and insulin levels (47.40 + 26.33 mIU/ml) were statistically decreased after the exercise test. $AUCgl._{60\text{-}120} > AUCgl._{ex}$ ($P < 0.0001$); $AUCins._{60\text{-}120} > AUCins._{ex}$ ($P < 0.0001$). We found two variants of insulin response at the exercise tolerance after the glucose load – with increased (29.6%) and decreased (70.4%) glucose and insulin secretion. AUCins. at all stages of OGTT lower at the first group ($P < 0.002$) as well as $Ins._{120}$ ($P < 0.001$). **Conclusion:** Metabolic response at the exercise is dependent on insulin secretion at the glucose load. Low postprandial AUCins. followed by Ins.120 < 30 mIU/ml are associated with plasma insulin levels rise to correct the glucose immediately after exercise exhaustion.

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Insulin Dynamics and Biochemical Markers for Predicting Impaired Glucose Tolerance in Thai Obese Youth

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Background: Subjects with impaired glucose tolerance (IGT) are at risk for type 2 diabetes mellitus (T2DM) and cardiovascular disease. The predictors of IGT in obese youth are not well described. **Objective and hypotheses:** We aim to evaluate insulin dynamics and biochemical markers for predicting IGT in Thai obese youth. **Method:** We studied 115 obese Thai children who underwent an oral glucose tolerance test (OGTT). Plasma glucose and insulin levels were calculated for assessment of β-cell function. Hemoglobin A1c (HbA1c), lipid profile, and clinical parameters were also used to determine predictors of IGT. **Results:** We found that three patients had T2DM and 30 subjects had IGT. IGT patients had significantly higher fasting glucose, 1 h postload glucose, 2 h postload insulin, and lower whole-body insulin sensitivity indices than in normal glucose tolerance subjects whereas other indices were comparable. By ROC curve analyses, 1 h postload glucose was the best predictor of IGT, but fasting glucose or HbA1c represented a poor diagnostic tool for prediabetes screening. Subjects with 1 h OGTT glucose > 155 mg/dl had significantly lower HDL levels, lower insulin sensitivity and more insulin resistance than those with 1-hr postload glucose of ≧155 mg/dl. **Conclusion:** Abnormal glucose tolerance is highly prevalent in obese Thai youth. Several fasting indices and HbA1c fail to predict IGT. A 1 h OGTT glucose of > 155 mg/dl appears to be more associated with adverse insulin dynamics and metabolic profile than 2 h postload glucose.

P2-282

Total-Body Irradiation is a Major Risk Factor for Young Adult Onset Diabetes Mellitus and Hyperlipidemia in Childhood Cancer Survivors after Hematopoietic Stem Cell Transplantation

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Background: Haematopoietic stem cell transplantation (HSCT) is a risk factor for young adult onset diabetes mellitus (DM) and hyperlipidaemia (HL) as late effects, especially the use of total-body irradiation (TBI). In order to investigate the clinical details, we retrospectively analysed the post-HSCT patients in our institution that required treatment for DM and/or HL. **Results:** From 1983 to 2012, 24 children received HSCT in our hospital

because of haematological malignancy and were followed up continuously to date. Among 24 patients, ten patients were conditioned with TBI; all the patients who developed DM and/or HL used TBI conditioning regimen. Four and five patients developed DM and HL, respectively, and four developed both. The prevalence of DM and HL in patients with TBI was 40 and 50% respectively, and Fisher's exact test revealed TBI significantly associated with DM ($P=0.035$) and HL ($P=0.012$). The mean age at TBI of DM and non-DM patients was 2.0 (1.8–2.8) and 11.0 years (7.5–13.0) respectively, suggesting that TBI for younger children is associated with risk of DM ($P=0.01$). We also examined other clinical backgrounds, including the type of disease (acute lymphoblastic leukaemia (ALL) or non-ALL), the cumulative dosage of prednisolone, BMI at the onset of DM or HL, and GVHD prophylaxis with tacrolimus. However, any of these were not relevant. The generalised linear model confirmed that TBI was an independent risk factor for DM and HL. **Conclusion:** Our data suggests that TBI is a risk factor for DM and HL, and younger age at TBI increases a risk for DM. The prevalence of DM and HL among patients received HSCT was higher than previously reported. This study showed that DM and HL is major late effects of TBI, and they should be taken into account for selecting the conditioning regimens for transplanting patients with haematological malignancies.

P2-283

Variables in Diabetic Children and Adolescents Associated with High, Acceptable and Low Range of Glycosylated Haemoglobin in a DGH Setting – An Analysis

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Background: Diabetes education empowers children and adolescents with diabetes to acquire practical skills in problem-solving and goal-setting to improve self sufficiency. Our aim was to identify variables that have an the impact on diabetes control in terms of psychosocial wellbeing and glycosylated haemoglobin (HbA1c). **Objectives and hypotheses:** To compare the level of understanding & knowledge of diabetes between three groups of diabetic children. To explore psychosocial variables that distinguish the three groups. **Method:** Retrospective analysis of HbA1c and the variables in the patient's diabetes education assessment questionnaire (adapted from the East of England Paediatric Diabetic Network guidelines) over a 1 year period from September 2013 and August 2014. 30 children were randomly chosen in each group. High HbA1c group (group A): range 9–14%, mean 9.6%. Acceptable HbA1c group (group B): range 5.7–8.8, mean 7.4%. HbA1c $<7.5\%$ (group C): range 5.7–7.4%, mean 7.2%. **Results:** General knowledge about diabetes, injection rotation, hypoglycaemia and hyperglycaemia was 10–15% greater in group C than other two groups. Group C's knowledge on exercise was at least two times $>$ the other groups. Group C also had good understanding of diabetes. Knowledge about HbA1c was greatest (73%) and blood glucose monitoring (66%) in group B. In spite of a good overall knowledge, group B topped group C in psycho social adjustment in terms of accepting the diagnosis better, involving friends in their care and being happy (40%). Knowledge about complications was similar in all age groups (13%). **Conclusion:** The children in group C appear to have good diabetes control secondary to being empowered by general knowledge about diabetes, hypo and hyperglycaemia. An important factor in good diabetes control is exercise. Group A contains children who are at the age where they are more likely to have knowledge about alcohol, a confounding variable. The role of psychosocial variables appear to be important in group B despite acceptable HbA1c levels.

P2-284

In-Patient Care for Children with Type 1 Diabetes – A Regional Audit in the Yorkshire and Humber Region in the North of England

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Introduction: An important part of diabetes management is maintaining high standards of in-patient care. A previous audit in the South of England demonstrated difficulties consistently achieving standards identified as good practice. **Objectives:** To identify variations in in-patient care provided to children with type 1 diabetes across the Yorkshire and Humber region. **Methods:** The audit was conducted against in-patient care standards identified by the Children and Young Person's Diabetes Implementation Support Group (CYPDISG). Questionnaires were sent to clinical leads of all paediatric diabetes units in the region, which serves 2599 children and young people with diabetes. **Results:** 63% of units, consisting of two tertiary and eight secondary care units, responded. Nine out of ten units had paediatric nurses in areas where children were cared for, but only tertiary centres always had trained paediatric nurses in the emergency department (ED). Paediatric wards and EDs in all units had protocols for management of new diagnosis of diabetes, diabetic ketoacidosis (DKA), hypoglycaemia and surgery. All units had regular education sessions for ward staff, although only 50% had education sessions for ED staff. A 24 h on-call service was only provided by 40% of the units. The diabetes team was usually contacted within 2 h of an admission in tertiary centres and within 24 h in secondary care units. Paediatric diabetes specialist nurses had an active role in in-patient management in all units. Only two units had insulin prescription charts and only tertiary centres routinely audited insulin prescription and administration errors. **Conclusions:** This audit demonstrates on-going difficulties achieving current standards of in-patient care for children and young people with diabetes. There is a lack of 24 h on-call service in majority of the paediatric diabetes units. There needs to be standardisation across the region and feasibility of implementation needs to be explored. **Funding:** No funding received.

P2-285

Implementation of Effective Transition from Paediatric to Adult Diabetes Care: Epidemiological and Clinical Characteristics – A Pioneering Experience in North Africa

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Background: Diabetes mellitus (DM) is a chronic metabolic disorder requiring daily care to prevent both acute and chronic complications. Healthcare providers are challenged to manage the transition of adolescents from paediatric to adult diabetes services. Until recent date, this change of the medical team was lived by teenagers as a tearing and a discontinuity of the medical care. **Objective and hypotheses:** While centres providing structured integrated paediatric and adult care seem optimal, diabetic teenagers suffered from an unsuitable care. These patients are in need of transition programs to prevent discontinuities in specialized care. **Method:** In collaboration with an adult endocrinology department, we developed a transition program for adolescents with DM. A meeting of transition is organised with the whole paediatric team and the adult one in which patients meet their new medical staff, ask their questions and express their fears. DM related issues are recorded in a specially developed 'diabetes health passport' used by the patient. This 'passport' accompanies the patient through the transition process, providing anticipatory guidance, ongoing assessment of psychosocial issues and promotes self-care in collaboration with both paediatric and adult healthcare providers. After this meeting, patients benefit from an outpatient transition in the endocrinology adult department. **Results:** 44 DM teenagers (23 females/21 males) have been successfully transitioned from paediatric to adult care after five meetings of transition from 2012 to 2014 in which 52% of them went accompanied by their mothers The mean age at the onset of their DT1 is 7.5 years with an average paediatric follow up time of 9 years (2–15 years). The mean age during transition is 14.9 years (14–23 years). 13% had a familial DM. 40% have switched to an intensive insulin therapy. Regarding their chronic complications, we noticed no diabetic retinopathy or cardiac disease, two cases of nephropathy and two cases of distal neuropathy. Associated autoimmune diseases are three cases of celiac disease and one case of hypothyroidism. All the teenagers developed a spontaneous puberty. Five teenagers have left their schooling. Those meetings of transition were determinant for 56.5% of the teenagers who attend them. **Conclusion:** We report on the successful implementation of a structured program for adolescents with DM transitioning from paediatric to adult care. Our systematic approach is pioneering in North Africa and appears to provide a structure for ensuring continuity of care and effective transition.

P2-286

Assessment of Ventricular Function by Tissue Doppler Echocardiography in Children and Adolescents with Type 1 Diabetes Mellitus

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Background: Tissue Doppler echocardiography can predict early stages and progression of diabetic cardiac changes; especially ventricular dysfunction, a complication that adversely affect the quality of life and prognosis of the disease. **Objective and hypotheses:** The aim of this study was to assess systolic and diastolic functions of both ventricles in type 1 diabetes (T1D) patients by conventional and Tissue Doppler echocardiography, and to correlate cardiac dysfunction with presence of hypertension, hyperlipidemia, and autonomic neuropathy. **Method:** A cross sectional study included 40 children and adolescents, 6–16 years old with T1D more than 5 years duration, following in the Diabetes, Endocrine Metabolic Pediatric unit, Children Hospital, Cairo University. 20 healthy age and sex matched children were included as controls. Anthropometric measurements, systolic and diastolic blood pressure measurement:supine, sitting and standing for detection of autonomic dysfunction, episodic hypertension and orthostatic hypertension. Laboratory assessment including glycosylated haemoglobin and lipid profile were done. 12 lead Electrocardiography, M mode echocardiography, conventional echocardiography and tissue Doppler assessment were performed. The latter was used to measure Myocardial peak systolic (Sm), early diastolic filling (Em) and late diastolic atrial filling (Am) velocities. **Results:** Among diabetic patients, 12.5% had right ventricular diastolic dysfunction and 12.5% had left ventricular diastolic dysfunction. No association was found between diastolic dysfunction on one hand and either duration of diabetes or HbA1c on the other hand. Isovolumic Relaxation time and Myocardial performance index of right ventricle were found significantly higher in diabetic patients (43.8 ± 6.37, 0.31 ± 0.07 respectively) compared to controls (35.76 ± 9.5, 0.27 ± 0.06 respectively) with a *P*-value of (0.001, 0.049 respectively). **Conclusion:** Assessment by tissue Doppler is warranted in patients with T1D to follow the progression from subclinical to symptomatic ventricular dysfunction. Further studies are needed to further explore the role of tissue Doppler in assessing cardiovascular complications of T1D. **Conflict of interest:** The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research project.

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Incidence of Type 1 Diabetes among Korean Children and Adolescents in 2012–2013: Analysis of Data from the Nationwide Registry of Korea

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Background: The incidence of type 1 diabetes mellitus (T1DM) in children and adolescents has increased worldwide. However, the epidemiology of T1DM among Korean children has not been reported since 2001. **Objective and hypotheses:** We therefore investigated the incidence of T1DM in Korean children and adolescents in 2012–2013 and compared it with data from 1995–2000. **Method:** Data were obtained from the National Health Insurance Service (NHIS) registry, and age- and sex-specific incidence rates were calculated per 100 000 population. **Results:** A total of 443 patients (204 boys and 239 girls, aged <15 years) with T1DM were registered in the NHIS in 2012–2013. The incidence rate per 100 000 population was 2.97 (95% confidence interval (CI) 2.70–3.26). We found incidence rates of 1.39 (95% CI: 1.07–1.77), 2.95 (95% CI: 2.47–3.49), and 4.25 (95% CI: 3.73–4.82) in children aged 0–4 years, 5–9, and 10–14 years respectively. The T1DM incidence was 2.64 (95% CI: 2.29–3.33) in boys and 3.33 (95% CI: 2.92–3.77) in girls. A higher T1DM incidence was seen in 2012–2013 than 1995–2000 (incidence rate ratio 2.17, 95% CI: 1.93–2.43; $P<0.001$). The annual increase in T1DM incidence was 5.3% (95% CI: 4.5–6.1%) between 1995 and 2013. **Conclusion:** We observed a significant increase in T1DM incidence in our study. This increase was higher in boys than girls and highest in youth aged 10–14 years. Studies to evaluate the long-term epidemiological trend of T1DM incidence should be performed.

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Functional Condition of the Kidneys (K/DOQI, 2002) by ACE Gene I/D Polymorphism in Children and Adolescents with Type 1 Diabetes Mellitus

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Aim: The work was initiated to assess functional condition of the kidneys and to study interrelation between ACE gene I/D polymorphism and stage of chronic kidney disease in children and adolescents with type 1 diabetes mellitus (DM) in compliance with K/DOQI recommendations (2002). **Materials and methods:** We examined 120 children and adolescents with type 1 DM, 53 (44.2%) males and 67 (55.8%) females among them (mean age 13.8 ± 0.24 years; 95% CI: 13.3–14.3). Glomerular filtration rate (GFR) was used to classify stages of chronic kidney disease in compliance with K/DOQI recommendations. DNA was isolated by Higuchi H.Erlich method (1989) with dry kit of Diatom DNAPrep 200. 49 (40.8%), 28 (23.4%) and 43 (35.8%) examinees with type 1 DM were carriers of II, I/D and DD genotype respectively. **Results:** Renal disorder with normal and high GFR (I stage) was found in 69 (57.5%) children and adolescents with type 1 DM, mean GFR being 168.9 ± 7.03/min/1.73 m^2 (95% CI: 155.1–18.7). Insignificant GFR reduction (CKD II stage) was found in 21 (17.5%) examinees, mean GFR being 77.8 ± 2.05 ml/min/1.73 m^2 (95% CI: 73.8–81/9). Moderate GFR reduction (III stage) was registered in 12 (10.0%) patients, mean value being 39.3 ± 2.05 ml/min/1.73 m^2 (95% CI: 35.3–43.3). CKD IV stage was observed in 18 (15.0%) examinees, mean GFR being 23.9 ± 0.90 ml/min/1.73 m^2 (95% CI: 22.1–25.6). No CKD V stage was registered in the group examined. II genotype was found prevalent in the examinees with CKD I stage ($n=46$, 66.7%), ID genotype being found in 23 (33.3%) and no DD genotype being found. With progression of CKD stage frequency of persons with II genotype was found decreasing, DD genotype cases being increased. ID genotype was found at III and IV stages CKD ($n=4$, 19%) and $n=1$, 8.3% respectively). No cases of II genotype was found at III and IV stages CKD, while DD genotype 1ncidence was very high ($n=11$, 91.7% and $n=18$, 100% respectively. DD genotype correlated with CKD severity ($r=0.66$; $P<0.05$) and presence of diabetic nephropathy (DN) ($r=0.32$; $P<0.05$). **Conclusions:** In compliance with (K/DOQI 2002) recommendations in most children and adolescents with type 1 DM (75.0%) CKD I and II stages were classified. With CKD progression upon DN in children and adolescents with type 1 DM DD genotype incidence was found increased, II genotype occurring more frequently with DN absent. The latter seems to be a protector from CKD progression, while DD genotype confers high risk of renal pathology in type 1 DM in children.

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Longitudinal Study of Irish Children and Adolescents on Continuous Subcutaneous Insulin Infusion

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Background: Early establishment of good metabolic control with intensive insulin therapy can reduce the incidence and delay the progression of complications in type 1 diabetes (T1D) mellitus. **Objective and hypotheses:** To investigate the long-term outcomes of all children and adolescents started on continuous subcutaneous insulin infusion or pump therapy in our tertiary centre. **Method:** All children with T1D who started on continuous subcutaneous insulin infusion (CSII) and had at least 12 months follow up data were included. Glycosylated haemoglobin (HbA1c) levels, insulin requirements, adverse events, and anthropometric data was collected pre CSII initiation, at 6 months follow up, and annually thereafter. Subgroup analysis was carried by age: ≤5 years old, 6–11.99 years old, and >12years old. Follow up data was obtained for 60% (38/63) of patients who had transitioned on to adult services. **Results:** 209 children underwent pump initiation of which 185 patients (96 female) met inclusion criteria. Mean (SD)

age at diagnosis was 6.0 (3.7) years; mean (SD) duration of diabetes was 8.1 (4.2) years; mean (SD) duration of CSII therapy was 4.86 (2.3) years (range 1.0–9.76 years). Mean (SD) HbA1c decreased from 8.75 (1.1) % pre-CSII, to 8.11 (0.84) % at year 1. HbA1c values at Years 2–7 post CSII were 8.08 (0.88) %, 8.12 (0.92) %, 8.12 (0.93) %, 8.32 (1.1) %, 8.28 (0.8) %, 8.2 (0.83) % respectively ($P<0.001$). Pre-schoolers and pre-adolescents had the greatest benefit in terms of HbA1c reduction. Mean BMI *z*-scores decreased during follow up (P = 0.03). Severe hypoglycaemia and diabetic ketoacidosis rates were extremely low in the cohort and reduced from 2.3 to 0.7 and 4.7 to 0.86 per 100 patient-years post-CSII respectively. **Conclusion:** CSII therapy is a safe and effective long-term treatment for management of T1D in children and adolescents. Use of sensor augmented CSII may offer additional benefits.

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C-Peptide Variation after the Diagnosis of Type 1 Diabetes in Paediatric Age

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Background: C-peptide secretion is the most accurate measurement of residual β-cell function in type 1 diabetes (T1D) and even residual levels seem to positively correlate with a lower probability of complications. **Objective and hypotheses:** Identify key determinants to the evolution of the β pancreatic cell function, measured by fasting C-peptide (FCP). **Method:** Prospective study of patients diagnosed with T1D, with evaluation of the FCP at diagnosis and after 12 months of follow-up. The FCP evolution was correlated with age at diagnosis (group 1: ≧5 years; group 2: 6–10 years and group 3: ≧11 years), autoimmunity, hemoglobin A1c (HbA1c) and presence of ketoacidosis at diagnosis. SPSS 22 was used for data analysis. **Results:** 20 patients were included, with equal gender distribution. At diagnosis, the median age was 8 years old and 25% had ketoacidosis. The mean value of FCP was 0.53 ng/ml at diagnosis and 0.51 ng/ml after 12 months of follow-up. Group 1 showed a FCP mean decrease of 0.31 ng/ml, while those in group 3 showed a mean increase of 0.49 ng/ml ($P<0.05$). Group 2 maintained a similar value with a decrease of 0.05 ng/ml. At 12 months of follow-up, the mean HbA1c in group 1 was 7.4%, 7.2% in group 2 and 6.7% in group 3. The patients with a HbA1c ≤7.5 showed a better residual β-cell function ($P<0.05$) and less insulin requirements ($P<0.05$). There was no association between FCP variation and autoimmunity, gender and ketoacidosis at diagnosis. **Conclusion:** The FCP level variation was positively correlated with age. The group of patients with ≤5 years had a worse metabolic control and a more pronounced loss of pancreatic reserve, translated by the declining value of C-Peptide.

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Metformin Utilisation Patterns in Paediatric Population Aged 10–19 Years in the US: 2009–2013

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Background: Metformin is the only oral antihyperglycaemic agent (AHA) approved for use in youths with type 2 diabetes mellitus (T2DM). It may also be used to treat other conditions such as hyperinsulinaemia, pre-diabetes, and polycystic ovarian syndrome (PCOS). Therefore, an assessment of the prevalence of T2DM in the paediatric population based on the utilisations for metformin may overestimate the burden of the disease. However, metformin utilisation patterns in youths remain unclear. **Objective and hypotheses:** To assess metformin utilization patterns in paediatric patients in the US from 2009 through 2013. **Method:** We used annual data from the National Disease and Therapeutic Index (NDTI), an ongoing office-based physician survey conducted by IMS Health (Plymouth Meeting, Pennsylvania) that provides national level estimates of disease and treatment patterns occurring in physician offices. Drug use frequency and therapeutic indications of single-ingredient metformin for paediatric patients 10–19 years of age between 2009 and 2013 were extracted and analysed. Descriptive statistical analysis was used to examine changes in the number of and reasons for metformin use over the 5-year period. **Results:** Metformin use by physicians for youths has decreased by 42.8% from 2009 to 2013 (from 217 716 in 2009 to 124 386 in 2013). The most common therapeutic indication metformin was used was diabetes (34.9%), followed by metabolic syndrome (25.5%), PCOS (17.2%), and obesity (6.5%). Metformin utilisation pattern remained stable between 2009 and 2013. **Conclusion:** Diabetes only accounted for approximately a third of the total metformin use in paediatric population aged 10–19 years. Other indications included metabolic syndrome, PCOS and obesity. Despite the NDTI's limitations arising from sampling and data collection methodologies, our study provides useful insights into metformin utilization patterns among paediatric population and suggests that caution should be exercised when utilising metformin prescription as a proxy to estimate the burden of T2DM in youths. **Conflict of interest:** All authors are employees of Merck & Co., Inc., Kenilworth, NJ. **Funding:** This study was funded by Merck & Co., Inc., Kenilworth, NJ.

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Incidence of Type 1 Diabetes in Children Under 15-Years-Old in Navarre (Spain) between 1980 and 2014

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Background: The incidence of childhood T1DM is rising worldwide. The incidence varies based upon geography, age, gender, genetic susceptibility, ethnicity, environmental risk factors or differences in features and quality registers, ranging from 0.1 to 65 per 100 000 children younger than the age of 15 years. In Spain, the incidence is high (20.6) but fluctuates among Autonomous Communities. **Objective and hypotheses:** Study the epidemiological data in patients younger than 15 years with childhood T1DM in a tertiary referral hospital in the community of Navarra, between January 1980 and December 2014. **Method:** Retrospective study of children under 15 years old diagnosed with type 1 diabetes between 1st January 1980 and 31st December 2014 in Navarre. Mark and recapture method was done after collecting information from Local Hospitals, Primary Care Centers and The Diabetes Association of Navarre. Incidence rates were calculated and a Poisson regression model was fitted to analyze changes in the incidence over time. **Results:** Between 1st January 1980 and 31st December 2014, a total of 505 new cases of T1DM aged under 15 were recorded (284 boys and 221 girls) with an average of 14.4 cases/year (a minimum of three cases in 1996 and a maximum of 27 in 2014). The highest incidence was found in the group aged 10–14 years (47.5%). Average incidence rate presented by 5-year periods: 9.0/100.000 between 1980–1984, 13.7/100.000 between 1985–1990, 12.8/100.000 between 1990–1995, 12.5/100.000 between 1995–1999, 19.9/100.000 between 2000–2004, 20.5/100.000 between 2005–2009 and 22.4/100.000 between 2010–2014. The results of the Poisson regression model showed a significant increasing trend in incidence rates ($P < 0.001$), being the annual average change factor 1.031 (IC 95% 1.022–1.040). **Conclusion:** The incidence of T1DM in children under 15-years old in Navarre has clearly increased over time from 1980 to 2014. The age group with the highest incidence was 10–14 years among all the study period.

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Quality of Life in Adolescent with Type 1 Diabetes and Its Relationship with Metabolic Control

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Background: Type 1 diabetes (T1D) has great psychological impact on adolescents and family's lifestyle. It influences their perception of their quality of life (QOL), their metabolic control, and it may lead to future complications. **Objectives:** Identify how QOL affects on T1D adolescents and its relation to metabolic control. **Methods:** This is a retrospective study of 55 adolescents with T1D. Diabetes impacts patients' concerns, life satisfaction, and their perceived health were assessed in the following manners: QOL was measured using QOL questionnaire 'Hvidore' for adolescents with T1D. The questionnaire contains 3 sections: parents, patients and caregivers. The results were measured related to sex, age, metabolic control, duration and type of treatment. **Results:** Patients included in this sample were 52.7% male and 47.3% female, with an average age of 16.15 years (13.3–19). 7.2 average years after diagnosis (1.1–14.57), mean HbA1c 7.9 ± 1.1%, insulin dose 0.96 U/kg per day and 4.1 ± 1.1 insulin/day injections. 85.5% multiple daily injections (MDI), 14.5% continuous subcutaneous insulin infusion (CSII). In regards to their QOL, teens who reported a high impact on their life because of diabetes presented more likely to have poor metabolic control; 21.4% of them needed psychological assessment. Patients with adequate metabolic control (measured by an HbA1c $< 7.5\%$) feel healthy than the worst controlled ($P = 0.017$). Life satisfaction improved in patients with good metabolic control. There was a lower reported life satisfaction in men, those older and in those with a longer duration of T1D. Adolescents with CSII had a greater life satisfaction report than those with MDI. Metabolic control was worse in monoparental families ($P =$ NS). Good metabolic control assumes greater family involvement from the parents' point of view ($P = 0.05$) and caregivers. **Conclusions:** Poorly controlled T1D interferes with QOL and perceived health status. Patients poorly controlled require more frequent psychological support. Greater family involvement is related to better metabolic control.

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The Prevalence of Different Subtypes of Maturity-onset Diabetes of the Young in Russian Federation as Defined by Targeted Next-generation Sequencing

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Background: Among the currently known variants of maturity-onset diabetes of the young (MODY) subtypes 1–3 are the most prevalent, while their relative frequencies vary in different populations. Other types of MODY are more rare, although the studies addressing their prevalences are limited. Recent implementation of next-generation sequencing (NGS) enables simultaneos analysis of multiple candidate genes making it an attracive approach in various monogenic disorders, including MODY. **Objective and hypotheses:** To evaluate the frequency of different subtypes of MODY in the Russian population using a targeted NGS. **Method:** 224 subjects (age range, 0.3–25 years; females, $n = 106$ males, $n = 118$) were included in the study. The patients fulfilled the following MODY criteria: diabetes or intermediate hyperglycemia, absence of β-cell autoimmunity (ICA, GAD, IA2, and IAA antibodies), preserved C-peptide secretion. 'Diabetes panel' genes were sequenced using a custom Ion Ampliseq gene panel and PGM semiconductor sequencer (Ion Torrent). Non-synonymous sequence variants were rated as 'probably pathogenic' if they had allele frequency $< 1\%$ and

pathogenic *ljb* database scores (ANNOVAR). **Results:** 129 pathogenic or probably pathogenic mutations were found in 65.6% of the patients ($n=147$). Mutations in *GCK* were found in 107 cases (47.8%); *HNF1A,* in 16 cases (7.1%); *HNF4A*, in four cases; (1.8%); *HNF1B*, in six cases (2.7%); *KLF11*, in two cases (0.9%); *CEL*, in four cases (1.8%); *PAX4*, in two cases (0.9%); *INS*, in one cases (0.4%); *BLK*, in three cases (1.3%); and *ABCC8*, in four cases (1.8%). Five patients had digenic mutations. **Conclusion:** MODY2 was shown to be the most prevalent in the studied population. The panel sequencing was useful in identifying rare subtypes of MODY as well as mutations in other genes with potentilally modifying effect on the phenotype.

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Sirolimus Therapy in Infants with Congenital Hyperinsulinism after Near Total Pancreatectomy

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Background: Congenital hyperinsulinism is the most common cause of persistent hypoglycaemia in neonates and children. It is important to minimize recurrence of episodes of hypoglycaemia. In some cases, Hypoglycemia was not controlled even after near total pancreatectomy. **Objective and hypotheses:** To study the glycemic response of sirolimus in patients with hyperinsulinemic hypoglycaemia that was not responsive to octreotide and calcium channel blocker after near total pancreatectomy. **Method:** A 35^{+4} weeks appropriate for gestational age neonate was presented with severe hypoglycemia on day 1 of life. Because of severe hyperinsulinemic hypoglycaemia that was unresponsive to maximal dose of diazoxide (20 mg/kg per day), octreotide (35 μg/kg per day) and amlodipine (1.5 mg per day), the patient was underwent near total pancreatectomy at 3 months of age. In genetic study, single heterozygous mutation in *KCNJ11* (C406C>7, p.Arg136Cys) was reported. After pancreatectomy, hypoglycaemia which was unresponsive to octreotide and amlodipine was recurred. Sirolimus was started at an initial dose of 0.5 mg per square meter of body-surface area (0.2 mg) per day in one dose to the patient. The dose was increased slowly to achieve serum trough level of 5–15 ng per ml. The serum trough level of sirolimus was measured 5–15 days interval. Regular monitoring of complete blood count, serum lipid levels, renal function and liver function test was performed. **Results:** A good glycemic control was achieved. Amlodipine and i.v. glucose infusion were discontinued and the dose of octreotide was gradually decreased. The patient was discharged with 0.6 mg per day of sirolimus and 12 μg/kg per day of octreotide 12 day after sirolimus use. After 3 months, the dose of sirolimus was increased up to 1.5 mg per day and sirolimus trough level was 6.2 ng/ml. Elevation of liver aminotransferase levels was observed (AST 50 IU/l). Except that, no other side effect of sirolimus was found. Blood glucose was maintained about 60–100 mg/dl. **Conclusion:** Severe hyperinsulinemic hypoglycemia due to single heterozygous mutation of *KCNJ11* was responded to therapy with sirolimus with mild side effect.

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Children Born from Mother with Gestational Diabetes Mellitus are at Higher Risk in Metabolic Syndrome

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Background: The metabolic outcome in adult life is known to be determined during fetal life. Prenatal poor nutrition also affects growth and maturation, formation of insulin resistance during childhood. Little is known about the effect of maternal gestational diabetes mellitus (GDM) on early metabolic and growth outcome of their children. **Objective and hypotheses:** To investigate growth, glucose metabolism, and blood pressure in children of mothers with GDM by comparing healthy controls from non GDM mothers. **Method:** Children of Seiiku birth cohort and GDM cohort are involved in this study ($n=1125$, 5 years old group: GDM 50 and non GDM 1 014, 9 years old group; GDM 14 and non GDM 97, male to female ratio $=1$). The auxological data (height, weight, BMI, waist circumference, blood pressure) and biochemical data (WBC, blood glucose, HbA1c, Glycoalbumin (GA), LCL-cholesterol, HDL-cholesterol, IGF1, insulin) were obtained at 5 and 9 years old. Statistical analysis was performed to determine significant difference among four groups (5GDM+, 5GDM−, 9GDM+, 9 GDM−). **Results:** Height and height velocity were within normal range in all subjects. Obesity rate did not differ significantly, however, 9GDM+ group showed higher rate than the other groups. Waist circumference was significantly bigger in 5GDM+ than 5GDM- (52.5 vs 49.8 cm (mean), $P<0.0001$). Waist of 9GDM+ was bigger than 9GDM- (57.9 vs 55.3 cm), but not significant. Systolic blood pressure was significantly higher in 5GDM+ than in 5GDM−. HbA1c level was significantly high in 9GDM+ than in 9GDM−, and 5GDM− (Mean 5.3, 5.14, and 5.06% respectively). 5GDM+ showed HbA1c level at 5.2%, which was not significantly different from the other groups. On the other hand, GA, LDL-C, HDL-C showed no significant difference among groups. IGF1 level was significantly higher in 5GDM+ than 5GDM− ($P<0.001$). **Conclusion:** Children born from GDM mothers had higher waist circumference and higher systolic blood pressure than controls at 5 years of age, and had higher HbA1c at 9 years old. Although there were no apparent diabetes, obesity, or hypertension, children from GDM mothers seem to be prone to metabolic derangement. Although there were no apparent diabetes, obesity, or hypertension, children from GDM mothers seems to be prone to metabolic derangement. **Funding:** This work was supported by Research grant from Ministry of Health, labor and welfare, Japan (grant numbers Seiiku Research grant 26–19).

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GH Promotes mRNA Expression and Secretion of Progranulin in 3T3-L1 Cells

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Background: Recently, progranulin (PGRN) was a novel adipokine which is a key adipokine insulin resistance in adipose tissue. While GH was closely related to glucose metabolism and insulin resistance. **Objective and hypotheses:** We suspected that there maybe some positive relationship between GH and PGRN. Our study was to detect expression and regulation of PGRN in mouse 3T3-L1 cells follow the treatment with GH. **Method:** The mRNA was measured by quantitative PCR and the protein was tested by Western blot in mouse 3T3-L1 cells follows a series of concentrations and treating time of GH. **Results:** We find that both Western blot analyses and quantitative PCR showed that 500 ng/ml GH increases the expression of PGRN in a quick reaction (0.5–2 h), and decreases since 4 h, while 5 ng/ml GH promotes the expression of PGRN but without change with time. **Conclusion:** Our results show that GH regulated the expression of PGRN in a time and concentration dependent manner.

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Early Diagnostics of Wolfram Syndrome

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Background and aims: Wolfram syndrome is rare, progressive autosomal recessive disease with characteristic neurological and endocrine features. Signs and symptoms appear with different combination during the lifespan in different patients. Here we report the family case of Wolfram syndrome with different phenotype variable. **Case presentation:** Patient 4 years and 4 months old girl with diabetes mellitus since the age of 2 years and 3 months. Born term, healthy, with no previous medical problems. Was hospitalised in clinic for diabetic ketoacidosis. Treatment with human insulin was started. Patient's parents are healthy, no consanguinity. Patient's two maternal aunts had Wolframs syndrome. The older of the two had DM, optic atrophy, deafness, mental retardation (psychiatric problems). The younger aunt had DM, Diabetes insipidus, optic atrophy, a large bladder. Both died at the age of 15 and 13 years with complications (hypoglycaemia, infection). It is significant that, in both cases diseases started at a young age (DM by the age of 6, optic nerve atrophy, diabetes insipidus, and deafness by the age of 10 years). Physical examination-no significant findings. Insulin daily requirement 0.21 U/kg. Fasting C-peptide 0.50 ng/ml, islet-cell-ab <5 JDF-U, islet-cell titer 1: <10 titer. GAD <5 IU/ml, TSH 1.00 mIU/l, cortisol 231.48 ng/ml. Mean HbA1c 5.9%. Genetic testing for *WFS1* gene mutation was performed, with both PCR as well as whole genome sequencing. c.1523-1524deLAT (p.Tyr508Cysfs*34) homozygous mutation in the eighth exon of *WFS1* gene was found. **Conclusion:** Characteristic features of Wolfram syndrome are variable even in the same family. Course of DM is quite mild in our patient with minimal insulin requirement, compared to other patients. Early identification of this syndrome gives us a chance to for early detection and proper management of associated conditions and its complication with maximal efficacy.

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Improving Glycaemic Control at Diagnosis of Type 1 Diabetes: Insulin Dosing Depending on Degree of Ketonaemia at Presentation

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Background: The effects of metabolic memory highlight the importance of good glycaemic control following diagnosis of type 1 diabetes (T1D). There is relative insulin resistance at diagnosis, particularly in the presence of ketonaemia. Local prescribing guidelines reflect this with higher insulin starting doses with ketonaemia. **Objective and hypotheses:** Current insulin dosing guidance for children with newly diagnosed T1D appeared insufficient to achieve optimal glycaemic control prior to discharge. Our objective was to audit initial doses and thus optimise prescribing guidance. **Method:** Medical records of children with newly diagnosed T1D presenting to our tertiary paediatric hospital over 6 months were reviewed for data on blood glucose (BG) and insulin dosing at presentation, hospital discharge, and clinic follow-up. This information was used to revise our care pathway dosing guidance. A repeat audit was carried out to determine if the insulin dose change improved glycaemic control. **Results:** Audit 1: results were analysed from 23 children in three cohorts: patients in DKA ($n=11$); those not in DKA with ketones ≥ 1.5 mmol/l ($n=5$); and patients with ketones <1.5 mmol/l ($n=7$). Starting dose of subcutaneous insulin was 0.5–0.7 units/kg per day depending on ketonaemia as per prescribing guidance. Total daily dose of insulin required to be increased prior to discharge in both cohorts with elevated ketones at presentation. Twenty-four hours mean BG pre-discharge was above target in all cohorts. Guidelines were adjusted to provide insulin starting doses of 0.55–1.1 units/kg per day depending on degree of ketonaemia. Audit 2: the initial ten patients using this new protocol showed improved mean blood glucose at hospital discharge and less requirement for escalation of insulin dose during admission. Episodes of hypoglycaemia were infrequent ($n=2$). **Conclusion:** Children with significant ketonaemia at diagnosis required more s.c. insulin at initiation of treatment than initially prescribed. Care pathways have been revised to provide 0.55–1.1 units/kg per day, which has shown improvement in glycaemic control in the early period following diagnosis.

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Non-Immune Diabetes Mellitus and Neurodegeneration: Two Distinct Cases of Wolfram Syndrome

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Background: Wolfram syndrome features diabetes insipidus, diabetes mellitus, optic nerve atrophy, and deafness (DIDMOAD). Especially the neurological degeneration usually leads to a very poor prognosis. We present two cases of Wolfram syndrome, an autosomal dominant and an autosomal recessive type, caused by heterozygous mutations in the *WFS1* gene. **Case report:** Case 1: a 13-year-old girl with a history of progressive sensorineuronal hearing loss and optic nerve atrophy presented with growth failure. GH deficiency was diagnosed and accordingly treated. Non-immune diabetes mellitus developed after the initiation of GH therapy, eventually leading to the diagnosis of Wolfram syndrome. Wolfram syndrome was confirmed by a pathogenic heterozygous mutation in the WFS1 gene: c.2051C > T(p.Ala684Val) variant in exon 8. Our patient responded well to GH therapy, reaching normal adult height. After discontinuation of GH treatment our patient remained fully insulin dependent. Case 2: a 13-year-old boy presented with bilateral loss of vision (50%) and diplopia since 4 months. Optic nerve atrophy was diagnosed. Hyperglycemia was observed during work-up and non-immune diabetes mellitus was revealed. In retrospect, the boy experienced polydipsia and polyuria since 2 years. Treatment with continuous subcutaneous insulin was started. The diagnosis of Wolfram syndrome was confirmed by two heterozygous mutations in the *WFS1* gene: c.631 + 2T > G(r.spl?) and c.1511C > G(p.(Pro504Arg). **Conclusion:** The clinical picture of Wolfram syndrome is highly variable. The combination of insulin-dependent non-immune diabetes mellitus and bilateral progressive optic nerve atrophy are the main diagnostic criteria. However, in our first patient diabetes mellitus only appeared after the occurrence of neurodegenerative disease and pituitary dysfunction, delaying the diagnosis of Wolfram syndrome. In the second patient vision loss was the main presenting symptom with hyperglycemia as an incidental finding. Therefore, the diagnosis of Wolfram syndrome should also be considered in patients without diabetes mellitus who have evidence of neurodegenerative disease.

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Evaluation of Continuous Glucose Monitoring in Cystic Fibrosis Patients

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Introduction: Use of continuous glucose monitoring (CGM) as a diagnostic tool for cystic fibrosis-related diabetes (CFRD) is receiving increasing attention. We aimed to: i) describe the glucose profile by CGM in CF patients > 10 years of age; ii) compare CGM and oral glucose tolerance test (OGTT) results; and iii) evaluate lung function and nutritional status changes over the previous year. **Methods:** Prospective study of CF patients aged ≥ 10 years. OGTT and CGM (Ipro2TM) were performed between November 2012 and May 2014. Changes in BMI–SDS and percent forced expiratory volume in 1s (%FEV1) in the year preceding both tests were assessed. Patients with exacerbations treated with steroids, GH, immunosuppression, or insulinised or transplanted were excluded. ROC curve (compared to the gold standard OGTT) was used to determine optimal glycaemic cut-offs for detecting clinical changes. Analysis using STATA Statistical Software. **Results:** Twenty-one patients: (43% males); mean age 16 years. Genotype: 38% homozygous F508del, 38% heterozygous F508del, and 24% other mutations. In CGM: average max glucose 191 mg/dl (178–201), average min glucose 59 mg/dl (47.5–66.5), average time > 140 mg/dl: 5%. Nine patients presented glucose values < 60 mg/dl and six > 200 mg/dl (three with greater than one peak). Two patients had fasting blood glucose (FBG) > 126 mg/dl. Abnormal tolerance glucose (ATG) was defined as postprandial CGM time > 140 mg/dl ≥ 4.5% or FBG CGM time > 30% between 100 and 126 mg/dl; and CFRD glucose was defined as > 200 mg/dl greater than one peak or FBG levels > 126 mg/dl. The ATG patients on CGM had a variation of BMI and FEV1 greater (−0.1 SDS and −4.5% respectively) than the normal CGM patients (+0.05 SDS and −1%). Four (36.3%) of the 11 patients with normal OGTT had normal CGM with a variation of +0.05 BMI–SDS vs 7 (63.7%) who had ATG CGM with a variation of −0.18 BMI–SDS. Nevertheless, in these patients, there were no differences in lung function. **Conclusions:** i) CGM is a useful tool for diagnosing and managing carbohydrate metabolism in patients with CF. ii) CGM reveals early glucose tolerance abnormalities that remain undiagnosed by OGTT screening and are correlated with clinical abnormalities.

P2-302

The Impact of Diurnal Glycaemic Variability on the Cardiovascular System in Children with Type 1 Diabetes Mellitus

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Background: Diurnal glycaemic variability has a direct impact on the formation of chronic complications of type 1 diabetes mellitus (T1DM) in children. **Aim:** To clinically assess the function of the cardiovascular system depending on the diurnal glycaemic variability in children with T1DM. **Material and methods:** The study involved 65 children (30 girls and 35 boys) aged 4–17 years (mean age – 11 + 0.4 years old) with T1DM

duration from 1 to 14 years (mean duration of the disease 4 + 0.3 years old) in the Endocrinology Centre of CPH No. 2 (Tver, Russia). The subjects underwent clinical examination: they had HbA1c testing, 24-h blood glucose monitoring and electrocardiography (ECG). Depending on the glycemic variability parameters, the subjects were assigned to one of the two groups: group 1 – glycemic variability <5 mmol/l per day (3.7 + 0.26 mmol/l, $n=15$) and group 2 – >5 mmol/l per day (7.8 + 0.30 mmol/l, $n=50$). **Results:** The study has revealed significant increase in HbA1c in group 2 (9.5 + 0.29%) compared to group 1 (8.4 + 0.54%, $P<0.05$). The ECG analysis showed a significant increase in the frequency of sinus arrhythmia in group 2 (35%) compared to group 1 (14%, $P<0.01$). There was no significant difference in the incidence of tachycardia between the two groups. In group 2 we found a significantly higher incidence of early repolarization syndrome compared to group 1 (25 and 7%, respectively, $P<0.05$), wandering atrial pacemaker (7 and 0%, respectively, $P<0.01$), second degree sinoatrial block (7 and 0%, respectively, $P<0.01$). **Conclusions:** Diurnal glycaemic variability affects the function of the cardiovascular system in children with T1DM, which requires a differentiated approach to monitoring and rehabilitation.

P2-303

Multiple Malformations Extending the Phenotypic Spectrum of Antley–Bixler Syndrome in a Patient with P450 Oxidoreductase Deficiency due to Two Novel Mutations of the *POR* Gene

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Background: P450 oxidoreductase deficiency (PORD) is characterised by glucocorticoid and sex steroid deficiency and skeletal malformations, resembling Antley–Bixler syndrome (ABS, MIM 124015), a skeletal malformaton phenotype also present in patients with fibroblast growth factor receptor 2 mutations (FGFR2, MIM 176943). While genetic testing confirms both conditions, establishing the exact diagnosis on clinical grounds can be challenging. **Objective and hypotheses:** To characterise cause of disease in a patient with 46,XY DSD and complex malformations. **Methods:** A now 2-year-old child of non-consanguineous parents was investigated immediately after birth for 46,XY DSD (female external genitalia, palpable labial testicles) and complex malformations, including ABS (craniosynostosis, midface hypoplasia, arachnodactily, rocker-bottom feet, and bilateral talipes), spinal dysraphism and right bronchial stenosis. We performed hormonal investigations, urinary steroid profiling by gas chromatography mass-spectrometry (GC/MS) and genetic analysis of the *POR* gene. **Results:** A short Synacthen test revealed adrenal insufficiency and the patient was started on hydrocortisone replacement. 17OHP was moderately elevated (20.6 nmol/l). Urinary steroid profiling at 2 months of age showed combined 21-hydroxylase and 17α-hydroxylase/17,20 lyase deficiency, indicative of PORD. *POR* gene analysis revealed compound heterozygosity for a novel missense mutation p.A200T and a novel intronic c.1248 + 1G > T mutation, predicted to cause aberrant mRNA splicing. The child was raised as a girl and gonadectomy was performed at 11 months of age. Shortly thereafter the mother fell pregnant again and GC/MS analysis of maternal urine confirmed that the foetus was unaffected; the mother subsequently delivered a healthy baby. **Conclusion:** This case of PORD presented with complex malformations rarely observed in PORD and more typical for *FGFR2* mutations while 46,XY DSD indicated PORD. GC/MS analysis reliably detects PORD in affected children and can help with prenatal diagnosis in further pregnancies. Assessment of adrenal function should be part of the early investigations in complex DSD.

P2-304

A Novel Homozygous Missense Mutation in *RSPO1* Associated with a Familial Case of 46,XX Testicular and Ovotesticular DSD

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Background: RSPO1 is an activator of the canonical Wnt signalling pathway by acting as a ligand for LGR4–6 receptors and an a 46,XX individual it represses testicular development. Only three families have been reported in the literature with recessive mutations in *RSPO1* and syndromic 46,XX sex-reversal. **Objective and hypotheses:** We identified a consanguineous family from Southern Morocco with two sibs presenting with 46,XX testicular and ovotesticular DSD, palmoplantar keratoderma, and hearing impairment. We hypothesised that the phenotype may be due to a recessive loss-of-function mutation involving *RSPO1*. **Method:** We performed exome sequencing with an average coverage of 60× using the Illumina HiSeq2000 Systems. All rare (MAF <0.01) and novel variants were identified and evaluated for there contribution to the phenotype. **Results:** Both sibs were *SRY*-negative. We identified a novel homozygous c.332G > A mutation that is predicted to result in a p.Cys111Tyr amino acid change (ENSP00000348944). Both parents were heterozygous for the mutation and the mutation was not observed in 200 normospermic controls from Morocco. The mutation disrupts an evolutionary conserved residue in the second furin-like repeat and the amino acid change is predicted to be highly deleterious by both SIFT and PolyPhen2. **Conclusion:** This is the forth family to be identified with syndromic ovotesticular/testicular DSD carrying a recessive mutation in *RSPO1*. This highlights the key role that RSPO1 signalling plays in repressing testicular development in XX individuals. **Funding:** This work was supported by the ACIP, Institut Pasteur.

P2-305

'www.steroidogenicfactor-1.info': An Online Database of Variants in Steroidogenic Factor 1 (SF-1, *NR5A1*) and Resource for Families and Professional Healthcare Providers

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Background: Steroidogenic factor 1 (SF1), encoded by the gene *NR5A1*, is a member of the orphan nuclear receptor superfamily and important regulator of gonadal and adrenal function. Variations in SF1 lead to a spectrum of conditions including 46,XY DSD, hypospadias, adrenal insufficiency, male factor infertility, and primary ovarian insufficiency. Inheritance patterns can be complicated (e.g. *de novo* dominant, sex-limited dominant, and autosomal recessive). Information currently available on SF1 is generally not easily accessible for patients and families or healthcare professionals not working in the field. **Objective and hypotheses:** To make available a database of the published variants of SF1 together with general information about SF1 through a website www.steroidogenicfactor-1.info. **Method:** A systematic review of published mutations in SF1 since 1999 was undertaken using a basic literature search. Information regarding the variant and phenotypic information was entered onto a database. General information about SF1, associated features, inheritance patterns, and key resources was developed as a web-based format. **Results:** To date there are 62 primary peer reviewed publications in the SF1 database and more than 100 potentially disease associated variants. These findings have been summarized in a schematic figure to illustrate the amino acid residue variants and conditions associated with them. Approximately two-thirds of SF1 variants are missense changes. There is an emerging clustering of DSD-related changes in the DNA-binding domain and key codons within the ligand-like binding domain, whereas male factor infertility-associated variants cluster within the hinge region. A website has been set up to host this database as well as useful information about SF1available for patients and the public. **Conclusion:** SF1/*NR5A1* is an ever important cause of endocrine disorders with diverse phenotypes and inheritance patterns. Development of 'www.sterodiogenicfactor-1.info' will assist researchers, clinicians, patients, and families with background knowledge, phenotypic and genetic information, and related resources for support. **Funding:** This work was supported by The Wellcome Trust (098513).

P2-306

Two Testes and 2X Chromosomes: Why?

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Background: A 60-day-old infant with genital ambiguity was assessed in the multidisciplinary urogenital clinic. The baby was born full term and weighed 3.4 kg at birth. The antenatal history was noncontributory. On physical examination, there was no obvious dysmorphic features. On genitourinary exam, there was a well developed scrotum that was bifid, with rugae and pigmentation. There was penoscrotal transposition. His phallus was of a normal breadth and length with ventral curvature. In addition there was hypospadias at the base of the phallus. Both testes were palpable in the scrotum. **Objective and hypotheses:** Given the mild to moderately undervirilised male, the clinical impression was idiopathic isolated severe hypospadias. **Method:** This is a case report of an interesting and rare case with genetic confirmation. **Results:** Laboratory workup included an LH of 1.3 IU/l (0.1–4.8 IU/l), FSH 2.0 IU/l (0–15 IU/l), and testosterone level was 3.7 nmol/l normal for age is $<$16.0 nmol/l. Surprisingly, further testing revealed a 46,XX karyotype and FISH for SRY was negative. Genomic microarray analysis showed a copy number gain in chromosome region Xq27.1. This region contains the SRY related HMG box-containing gene 3 (*SOX3*) gene. SOX3 is a single exon gene located in a highly conserved region of the X-chromosome. It is a transcription factor, encodes a protein that is most similar to SRY. **Conclusion:** The clinical significance of duplication of the SOX3 locus in 46,XX individual is currently unclear, however a recent report suggested that copy number changes within this genomic region may be associated with 46,XX sex reversal. Further investigation of this copy number gain is in progress.

P2-307

Diagnostic Approach to a Newborn with Suspected DSD: Results From an International Survey of Specialist Care for DSD

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Background: The approach to investigating a newborn with a suspected DSD is likely to vary between centres and may be

influenced by local availability. **Method:** To explore the current diagnostic practice and needs, an international survey of 124 paediatric endocrinologists, identified through DSDnet and the I-DSD Registry, was performed in 2014. **Results:** A total of 77/124 (62%) clinicians, in 74 centres, from 38/42 (91%) countries responded to the survey. In a suspected case of 46,XY DSD, the investigations that would be performed routinely within the first week of presentation included testosterone (97%), karyotype (96%), ultrasound (94%), 17-hydroxy-progesterone (83%), androstenedione (75%), dihydrotestosterone (DHT, 73%), X/Y probes by FISH/PCR (69%), cortisol (68%), and anti-Müllerian hormone (AMH, 58%). Second-line investigations included further imaging (86%), array CGH (69%), cortisol ACTH stimulation (69%), hCG stimulation test (62%), and urinary steroid profile (USP, 51%). The diagnostic tests reported to be not available locally but desirable included USP (43%), array CGH (31%), DHT (21%), and AMH (21%). Clinicians reported that, locally, they had access to the following genetic tests: *SRY* (75%), *AR* (66%), *SRD5A2* (53%), *NR5A1* (53%), exomic/genomic analysis (51%), *WT1* (51%), *DAX1* (49%), *SOX9* (44%), and a wider panel of genes (44%). The genetic tests the clinicians would perform routinely in a case of 46,XY DSD included: *SRY* (51%), *AR* (43%), *SRD5A2* (31%), and *NR5A1* (26%), while they would perform *DAX1* (73%), *WT1* (71%), *NR5A1* (65%), *SRD5A2* (62%), and *SOX9* (61%) only if family history or biochemistry were suggestive. For diagnosing 5a reductase deficiency, 49% of them reported genetic testing as the single most preferable test whilst 38 and 13% reported testosterone:DHT ratio and USP respectively. The corresponding figures for 17bHSD3 deficiency were 55, 32, and 13%. **Conclusion:** There is considerable variation in the diagnostic evaluation of a newborn with suspected DSD between centres and access to specialist tests may influence this factor. Molecular genetic testing is increasingly common in specialist centres. Clearer guidance in complex cases and collaboration through a network of centres could rationalise the need as well as access to diagnostic investigations.

P2-308

MAP3K1 Mutation in a Patient with Complete XY Gonadal Dysgenesis

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Background: 49,XY gonadal dysgenesis (GD) is a very rare disorder of testes development with an incidence of 1:50–100 000. MAP3K1 is a MAPK that mainly regulates the MAPK pathways. High Map3k1 expression was found in female and male mice gonads at 13.5 dpc. In 2010, MAP3K1 mutations were identified in two families with complete and partial XY GD and in two unrelated sporadic cases with complete XY GD (Pearlman 2010 AJMG). Recently, four additional mutations (four out of 40) in XY GD (Baxter 2015 J Clin Endocrinol Metab) were identified. **The patient:** Clinical signs: 16 years, primary amenorrhea, height 177 cm, weight 60 kg. B1, P3. Hormones: FSH 86 U/l, LH 36 U/l, estradiol <5.0 pg/ml, and testosterone 0.13 ng/ml. Ultrasound: infantile uterus, no gonads. Karyotype 46,XY. The diagnosis complete XY GD was made. The patient reported female gender identity and the wish for further female development. Estradiol-valerate therapy was started. Gonadectomy was performed at the age of 17 years of age. **Methods and results:** We have detected the same heterozygous mutation (exon 2, c.566T$>$C, p.Leu189Pro) as previously reported in a sporadic case with complete XY GD by exome sequencing. The mutation is located in the conserved focal adhesion kinase (FAK) binding site. The mutation was not found in the 1000 Genomes Project. In cultured primary lymphoblastoid cells, this mutation was previously found to increase phosphorylation of the downstream target p38, ERK1 (MAPK3)/ERK2 (MAPK1) compared to WT. **Conclusion:** MAP3K1 is a novel important regulator of testis development. Exome sequencing is an appropriate tool to reveal the genetic cause in the rare cases of XY GD. **Funding:** Institut Pasteur core funding.

P2-309

Alterations in Germ Cell Memory and Mini-Puberty Induce Infertility in Cryptorchidism

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Background: Spermatogonia contain processing bodies (P-bodies) that harbour P-element induced wimpy testis (Piwi) proteins associated specifically with Piwi-interacting RNAs to silence transposable DNA elements. In mice loss-of-function mutations in the Piwi pathway lead to de-repression of transposable elements, resulting in male-specific sterility. **Objective and hypotheses:** No previous studies have examined expression of transposons silencing gene microchidia 1 (*MORC1*) in cryptorchidism. **Method:** For microarray analysis we included 19 rice-grain-sized testicular biopsies. High infertility risk group (HIR, $n=7$) is defined as a lack of Ad spermatogonia due to impaired mini-puberty while low infertility risk group (LIR, $n=12$) is defined as ≥ 0.1 Ad spermatogonia per tubular cross section and intact mini-puberty. **Results:** Conserved epigenetic regulator gene *MORC1* an important repressor of transposons acting by facilitating DNA methylation of specific repetitive elements classes, was not expressed in HIR; 3.49 log2 in contrast to robust expression in LIR; 5.26 log2 ($P<0.004$).The HIR group showed stronger L1 staining in the cytoplasm of the germ cells. In contrast, *ASZ1* testis specific transposon silencing gene was not expressed in the high infertility risk group, and it was not detected in four out of seven LIR testes. Three boys in the LIR group showed *ASZ1* expression. Their testes had spermatocytes.

Therefore, *ASZ1* expression in prepubertal testes appeared to be correlated to the existence of spermatocytes. **Conclusions:** This observation further supports our very recent finding that seven members of the TDRD family, three members of DDX family and *GTSF1* gene had significantly lower RNA signals in high infertility risk group. Although both LIR and HIR groups contained GTSF1, L1, and PIWIL4 proteins in the germ cells, the HIR group showed weaker GTSF1 and PIWIL4 expression and stronger L1 staining. Furthermore, these new findings provide strong evidence that infertility in cryptorchidism is a consequence of alterations in the Piwi-pathway. MORC1 participates down-stream of the piRNA pathway with a separate silencing role. Moreover, this novel observation implies that the growth and formation of P-bodies are hormonally regulated during mini-puberty, and that, during that time, P-bodies contribute to the establishment of germ cell memory and male-specific DNA methylation pathways. Intact mini-puberty appears to be essential for the development of the endogenous defence system. mediated by transposon.

P2-310

Management of Gonads in Adults with Androgen Insensitivity: An International Survey

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Background: Individuals with androgen insensitivity syndrome (AIS) have an increased risk for developing a germ cell cancer (GCC). The risk is low during childhood; therefore, gonads are commonly preserved until after puberty. Little is known about GCC development in AIS during adulthood. This question is particularly relevant as many adult AIS women decline gonadectomy. **Objective and hypotheses:** To gain insight in attitudes towards gonadectomy in various DSD centers around the world and estimate the proportion of AIS adults who have retained gonads, reasons for declining gonadectomy and frequency of GCC occurrence. **Method:** International survey among health care professionals of DSD centers, retrieved through the I-DSD Registry. **Results:** Response rate (20/40 centers – 50%) was low despite regular email invitations; providing data on 200 patients (167 CAIS and 33 PAIS). In CAIS, 16/20 centers routinely propose gonadectomy before (4/20) or at the end (12/20) of puberty. 17/167 (10.1%) of CAIS patients have retained gonads, either because gonadectomy was not proposed, or because patients refused this procedure. Reasons for declining are being anxious about surgery and its complications and worries about long-term effects of HRT, timing of surgery and not having processed the diagnosis. Decision and timing of gonadectomy in PAIS is highly variable; overall, only 24.2% of PAIS males in this survey still have one or both gonads. (Invasive) GCC were not reported by any of the respondents. **Conclusion:** Differences in attitudes towards gonadectomy exist in centers caring for AIS patients. Patients are concerned about surgery and HRT, but generally accept gonadectomy at the end of puberty. The occurrence of an invasive GCC seems rare in AIS adults, questioning the necessity of routine gonadectomy in this population. Gaining further knowledge about eventual progression of (pre)neoplastic changes towards invasiveness in AIS specifically will help to improve counseling and patient-oriented management.

P2-311

The Localisation of Cells with XX and XY in Gonadal Tissues Associated with Ovotesticular Disorder of Sexual Development with a 46,XX/46,XY Karyotype

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Background: Individuals with a mixed 46,XX and XY karyotype, categorized as ovotesticular disorder of sexual development (ODSD), have gonads with either an ovary in one side and a testis in the other side or an ovotestis. **Objective and hypotheses:** This study aimed to investigate the relationship between sex chromosomes and testicular and ovarian cell types in gonadal tissues associated with ODSD patients with 46,XX/46,XY. **Method:** Gonadal tissues from three ODSD patients with a 46,XX/46,XY karyotype were examined for histopathological features, fluorescent *in situ* hybridization (FISH) for X and Y chromosomes, and immunohistochemistry for SOX9 as a Sertoli cell marker and FOXL2 as an ovarian follicular epithelial marker. **Results:** The histological features of the gonadal tissues of three patients showed an ovotestis, a testis and an ovary on each side, and a testicular tissue only, respectively. FISH analysis of the ovotestis demonstrated that cells with XX signals were involved within the Sertoli cells in seminiferous tubules, while cells having Y signals were observed within the epithelia of ovarian follicles. Likewise, the involvement of cells with opposite sex chromosomes was seen in the gonads of the other two patients. The expression of SOX9 was seen only in the seminiferous tubules and that of FOXL2 was observed only in the ovarian follicles, despite the involvement of opposite sex chromosomes. **Conclusion:** We suggest that the destiny of individual gonadal epithelial cells is influenced by local environmental factors rather than by the sex chromosome type. **Funding:** This work was supported by New Zealand and Japan Partnership Strategy, Japan Society for the Promotion of Science, and Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japan (25460427).

P2-312

Birth Weight in Different Aetiologies of Disorder of Sex Development

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Background: It is well known that boys are heavier than girls at birth. Causes of this difference are thought to originate from the Y chromosome and as a result of androgen action. Although some studies showed that sex dimorphism in size at birth is dependent of fetal androgens, one study reported that it is not generated by action of androgens. **Objective and hypotheses:** To determine birth weight (BW) of children in different aetiologies of disorder of sex development (DSD). **Method:** Data regarding diagnosis, BW, karyotype and associated anomalies were gathered from the International DSD Registry (www.I-DSD.org). Gestational ages of cases were not accessible in the registry. BW below 2500 g was defined as low BW (LBW). Cases were evaluated according to disorder classification in I-DSD as disorders of gonadal development, androgen synthesis, androgen excess, androgen action, nonspecific disorder of undermasculinisation, Leydig cell defect, persistent Müllerian duct and others. **Results:** Of 405 accessible cases with BW, 332 (82%) were 46,XY, 73 (18%) were 46,XX. LBW was detected in 98 cases (24.2%). Proportions of LBW were not statistically significant between 46,XX and 46,XY cases (9.6 and 15.6%, respectively, $P=0.21$). BWs were similar in each disorder group between 46,XX and 46,XY cases in both BW $\geq$2500 g and LBW groups. When BWs were compared between disorder subgroups, no statistically significant differences were detected. Among those children with known gestational age ($n=86$) BW was expressed as SDS according to national standards for each country. Analysis of these BWSDS in the different diagnostic groups did not reveal any significant differences between 46,XX and 46,XY cases. Other anomalies beyond the genitourinary system were more frequent in LBW cases (46.9 and 13.7%, respectively, $P=0.0001$) and in 46,XY group (27.2 and 6.8%, respectively, $P=0.0001$). **Conclusion:** Size at birth in both karyotypes seems unlikely to be dependent on fetal androgens. Syndromal forms of DSD with multi-system involvement are more likely to have a LBW.

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A Novel Human CYP19A1 Deletion-Insertion Mutation Reveals that the C-terminus of the Aromatase Protein is Crucial for its Activity

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Background: The steroidogenic enzyme aromatase is encoded by the *CYP19A1* gene. Aromatase activity is required for estrogen biosynthesis from androgen precursors in the ovary and several extragonadal tissues. The role of aromatase and thus estrogens for human biology is best illustrated by disease states, both deficiency and excess which might be caused by genetic disorders. **Aim:** A novel deletion-insertion mutation spanning from intron 10 to the 3′ UTR of the CYP19A1 gene was found in a 46,XX girl presenting with ambiguous genitalia at birth. The mother virilized during pregnancy and parents were first cousins. We investigated this novel mutation genetically and performed functional and structural studies to characterize the role of the C-terminus of the aromatase protein. **Methods and results:** Direct sequencing of the *CYP19A1* gene revealed a deletion of 2081 nt starting in intron 10 to the 3′ UTR corresponding to c.1263+354_*922del. Minigene experiments confirmed that this deletion prevented splicing leading to a shorter protein of 426 aa, namely p.P423_H503delinsRALP. Aromatase activity of WT and mutant CYP19A1 was assessed in transiently transfected HEK293 cells using radiolabeled androstenedione as substrate and the tritiated water release assay to measure conversion to estrone. Compared to WT, the mutant aromatase enzyme showed complete loss of activity. Structure analysis suggested that the C-terminal membrane anchor and heme binding cysteine residue were deleted in the mutated protein. The mutated protein was predicted not to bind heme and would therefore have no enzymatic activity. **Conclusion:** The c.1263+354_*922del *CYP19A1* mutation codes for a C-terminally truncated aromatase protein which causes a severe phenotype of aromatase deficiency in humans. In line with the phenotype, this aromatase mutation has no activity *in vitro* indicating that the C-terminus of the aromatase protein is crucial for its activity.

P2-314

Pubertal Virilization in Two Unrelated XY Teenagers with Female Phenotype due to *NR5A1/SF-1* Gene Mutation

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Background: Pubertal virilization in a 46,XY DSD patient is generally due to partial androgen insensitivity, 5-alpha-reductase deficiency, or 17-ketoreductase deficiency. Recently, reports have identified virilization signs associated with *NR5A1/SF-1* gene mutations. **Cases presentation and method:** We present two unrelated cases of pubertal virilization due to *NR5A1/SF-1* gene mutation. Both were suspected to be primarily affected by 5-alpha-reductase deficiency but no mutation was identified within the *SRD5A2* gene coding sequence. The first case was a young high-level female athlete with biological and clinical signs of hypervirilization. The second case was a girl first investigated in infancy for coalescence of the labia minora. At this time, the karyotype revealed a discordant 46,XY formula. Genetic investigation of the SRD5A2 gene identified no abnormality. When she was 15 years old, her physician observed striking signs of virilization: clitoromegaly, high plasma testosterone (8.2 ng/ml) and high FSH (45 UI/l) contrasting with normal LH (6 UI/l). **Results:** Genetic investigation of the first case revealed a *de novo* deletion, c.361delG, in exon 4 that led to a frameshift and premature stop codon. In the second case, we identified an 11-nucleotide deletion (c.630_640delGTACGGCTACC) in exon 4 that led to a frameshift and premature stop codon. **Conclusions:** We report two new *NR5A1/SF-1* deletions in 46,XY DSD girls with pubertal virilization. In both cases, the initial diagnosis was 5-alpha-reductase deficiency. In addition to 5-alpha-reductase and 17-ketoreductase deficiencies, these data suggest that *NR5A1/SF-1* should systematically be investigated in XY adolescent girls with virilization at puberty.

P2-315

Chimerism in a Teenager with Ovotesticular Disorder of Sexual Development

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Background: Chimerism is the phenomenon of two or more genetically distinct cell lines (originating from different zygotes) in the same individual. In situations when the sex of the fertilised eggs is disparate, it can lead to intersex phenotypes. **Objective and hypotheses:** We report a case of ovotesticular disorder of sexual development with chimerism resulting from a twin pregnancy (not involving assisted reproductive technologies). **Results:** A 17-year-old adolescent from Togo presented at birth with perineoscrotal hypospadias. He was raised as a male and underwent urethroplasty at age 10. His twin sister was phenotypically normal and healthy. At 12 years he developed severe gynecomastia. He expressed male gender identity and at 17 years he asked for mastectomy. At that time he exhibited Tanner stage $A_2P_4G_4$ with hypospadias (after Bracka's 1st stage hypospadias surgery), unilateral cryptorchidism (L), gynecomastia (B_5) and reported periodic hematuria. Hormonal assessment showed testosterone 4.4 nmol/l (9–32), estradiol 0.39 nmol/l (0.035–0.13), LH 12.6 U/l (2–9), FSH 7.7 U/l (2–12), AMH 10.9 pmol/l (male range 4.1–75.7) and inhibin B 35.1 pg/ml (male range 67–304). MRI revealed small yet morphologically normal right testis (3.2 ml), absent prostate, intraabdominal left ovary (2.8×2.7 cm) and presence of both an uterus (9.3 ml) and the proximal two thirds of a vagina. Karyotype indicated 46,XX[82]/46,XY[18] chimerism. Following consultation with a multidisciplinary DSD team, he underwent the 2nd stage of Bracka's hypospadias surgery, mastectomy and laparotomy including left ovariectomy, hysterectomy, and placement of a testicular prosthesis (L). After surgery he developed compensated hypergonadotropic hypogonadism with increase of serum testosterone levels up to 12.1 nmol/l (9–32) and he exhibited spontaneous, progressive virilization. **Conclusion:** Very few cases of chimeric ovotesticular DSD have been reported. Such situations raise important questions concerning sex of rearing, gender identity, fertility and risk of gonadoblastoma.

P2-316

Partial Androgen Insensitivity: Syndrome or Symptoms?

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Background: Partial androgen insensitivity syndrome (PAIS) covers a large spectrum of phenotypes, with the common denominator being insufficient virilisation of the external genitalia in an XY child with normal testosterone (T) production. Genetic diagnosis of PAIS is based on the identification of an androgen receptor (AR) gene mutation. **Aim:** The aim of this work was to determine whether the PAIS-like phenotype is associated with other gene mutations. **Methods:** During the last few years, we had the opportunity to perform molecular analyses of 200 children diagnosed with PAIS-like syndrome. **Results:** An AR gene mutation was identified in only 15% of the cases, confirming the PAIS. In five cases, 5-alpha reductase deficiency was responsible for the undervirilisation. An SF1 mutation was identified in three cases. Three patients presenting undervirilisation were found to have a WT1 gene mutation. In a group of 70 infants with a severe form of PAIS-like syndrome, we identified two MAMLD1 gene mutations and three polymorphisms. **Conclusions:** The diagnosis of PAIS as a syndrome requires the identification of an AR gene mutation. Undervirilisation of XY patients with normal plasma T should not be limited to analysis of the AR gene, as PAIS-like syndrome may be symptom of another clinical form of 46,XY DSD, such an 5-alpha reductase deficiency, or SF1, WT1, or MAMLD1 gene mutation.

P2-317

Next-Generation Sequencing as a Rapid Molecular Diagnosis in Patients with 46,XY Disorder of Sex Development

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Background: 46,XY DSD occurs as a result of testicular developmental disorders, defect in androgen synthesis or action. Nowadays, the diagnosis of DSD is quite costly and it takes a considerable amount of time due to lengthy hormonal and genetic analysis. **Objective and hypotheses:** The use of targeted next-generation sequencing of all known genes associated with 46 XY DSD for a fast molecular genetic diagnosis in patients in whom underlying defect of DSD was not previously diagnosed. **Method:** Twenty paediatric patients with 46,XY DSD were recruited from Ege University, School of Medicine, Department of Pediatric Endocrinology. Firstly, androgen receptor (AR) and 5-alpha reductase (SRD5A2) gene mutations which are the most common causes of 46,XY DSD were excluded. The 46 genes that have been shown to be related to 46,XYDSD were sequenced by Illumina MiSeq Next Generation Sequencing System and the Illumina TruSight Exome Kit. **Results:** The parents of 14 (66.7%) cases were consanguineous. A total of 9 (45%) mutations in four different genes were identified in 20 patients. Six mutations were novel. Mutations in the HSD17B3 gene were observed in six patients (30%). Two unrelated patients of these six patients carried p.Y287X mutation homozygously. Three other HSD17B3 gene mutations, p.T54A, p.R175T, p.R80Q, were detected in three unrelated patients in homozygous situation. One patient were compound heterozygous for the mutations p.R80Q/p.E93K in the HSD17B3gene. A heterozygous p.P396R mutation in WT-1gene in one of the patients with a suspicion of gonadal dysgenesis and in another case a hemizygous p.Q178X mutation in SRY gene were detected. One patient with a suspicion of testosterone production defect had a homozygous p.A483D mutation in LHCGR gene. All mutations were predicted to be pathogenic in in-silico analysis. **Conclusion:** Targeted next-generation sequencing is an efficient, rapid and cost-effective technique for the mutation detection in genetically heterogeneous diseases such as 46,XYDSD. HSD17B3 gene mutations may be one of the most common causes of 46,XY DSD in societies having high rate of consanguineous marriages. **Funding:** Ege University Research Committee 2014-BAP-0131.

P2-318

When, if Ever, Should the Müllerian Remnants be Removed from Subjects with Mixed Gonadal Dysgenesis Raised as Males?

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Background: Mixed gonadal dysgenesis (MGD) is the second most frequent cause of XY disorders of sex development (DSD). Genotype is either X/XY or XY, while the phenotype ranges from partial to complete gonadal dysgenesis, and from female to male external genitalia. Müllerian remnants are present in these patients because of insufficient or untimely foetal secretion of Müllerian inhibiting factor (MIF). **Aim:** To assess the therapeutic policy of physicians of patients with MGD regarding the removal of the Müllerian remnants. **Methods:** Physicians who entered data on gonadal dysgenesis into the I-DSD registry were e-mailed and asked, 'When, if ever, do you recommend the removal of the rudimentary uterus from boys with gonadal dysgenesis associated with a X/XY or XY karyotype?' **Results:** Thus far, 20 physicians have responded. Thirteen promote removal of the Müllerian remnants in childhood at the same time as the removal of the dysgenic gonads because of the risk of recurrent infections, uterine adenocarcinoma, or in order to prevent any ambiguity in gender identity. Two physicians advise delaying removal until adulthood for patient consent and understanding, four physicians do not recommend removal unless there is a medical reason, and two physicians assess their patients case by case. **Conclusion:** Even though there is a shift from the earlier 'optimal gender policy' (the paternalistic approach) to a 'full consent policy', most of the responding physicians contend that the Müllerian remnants should be removed as soon as the decision is made to raise the child as male.

P2-319

Gonadotropin Surge During the Early Postnatal Activation Period in 46,XX Testicular/Ovotesticular Disorder of Sex Development Patients

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Background: During the 1st months of postnatal life serum luteinizing hormone (LH) levels in girls are lower than in boys. The mechanism of this sex difference is not known. It has been proposed that foetal or perinatal androgenic steroids have an effect on the control of LH secretion. **Objective and hypotheses:** To study the possible influence of high levels of androgens on serum gonadotropins during the 1st months of life in a cohort of nine 46,XX testicular/ovotesticular DSD patients during the early postnatal activation period. **Method:** We analysed the hormonal profile of nine 46,XX testicular/ovotesticular DSD patients between 12 and 142 days of age. Inclusion criteria required lack of detection of SRY gene in peripheral genomic DNA and an adequate male testosterone response to hCG stimulation. **Results:** Gonad histological studies revealed bilateral ovotestes in three patients, one ovary and one testis in two, one ovotestis and one testis in one patient, while the remaining three patients presented bilateral disgenetic testes. In all patients, serum basal LH levels (mean $\pm$ S.D.: 5.23 $\pm$ 3.11, range 1–10.9 U/l) were significantly higher than in normal female ($P < 0.05$), and in three were even higher than reference values (RV) for males, while serum basal FSH levels (mean $\pm$ S.D.: 3.61 $\pm$ 1.89 UI/l, range 1.3–6.13 UI/l) were in all patients within female RVs and in six within male RVs. Basal serum FSH/LH ratio (mean $\pm$ S.D.: 0.99 $\pm$ 1.12, range 0.25–3.83) was within the normal range for the male sex and below the normal range for the female sex. **Conclusion:** In conclusion this study reinforces the concept that prenatal androgen exposure might be involved in programming of the hypothalamo–pituitary–gonadal axis independently of chromosomal sex.

P2-320

The Evaluation of AR and *SRD5A2* Gene Mutations in 87 Patients with 46, XY DSD Children in Turkey

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Background: Main diagnosis of 46,XY disorders of sex development (DSD) with normal testosterone secretion Androgen insensivity sydrome (AIS) or 5α-reductase deficiency (5α-RD). In prepubertal period, AIS and 5α-RD present indistinguishable phenotypes that necessitate the molecular analyses for the definitive diagnosis. **Objective and hypotheses:** Clinical, hormonal and genetic investigation of 46,XY DSD patients who considered as PAIS or 5α-RD, to understand the causes underlining the phenotype for suitable follow up, prognosis and management. **Method:** Eighty-seven patients, who diagnosed as AIS or 5α-RD according to clinic and hormonal evaluations, were investigated. Severity of ambiguous genitalia (AG), LH, FSH, T, dihydrotestosterone (DHT) levels were determined. Short-term hCG test was applied in proper cases and T/DHT ratios were evaluated. *SRD5A2* mutations were investigated in the cases that had T/DHT ratio of above 20, whereas *AR* mutations were investigated when the ratio under 20. Sanger DNA sequencing was used for molecular analysis. **Results:** The mean age of cases on application was 1.9 years ($\pm$3.5). Mutations that can lead to disease were detected in 21 (n=%24.1) patients (n=12 for *AR*, n=9 for *SRD5A2*). Eight of patients were found to have homozygous and one was found to have compound heterozygous mutations in *SRD5A2*. Three novel *SRD5A2* mutations in homozygous form were detected in four patients (c.269A>C, c.468-470delAAT, c.453delC). Furthermore, three novel mutations were detected in four patients with *AR* gene mutations (c.2585delAGCTCCTG, c.2676T>A, c.2084C>T). Three patients were found to have Klinefelter Syndrome (n=1*SRD5A2* mutation, n=2 *AR* mutation, n=1 undetermined genetic cause) .One patient had 47,XYY karyotype with *AR* mutation. Except one, all other cases with *AR* mutations had T/DHT ratio under 20. This ratio was below 20 in two of the *SRD5A2* cases. **Conclusion:** Novel *SRD5A2* and AR mutations were identified in study. T/DHT ratio in diagnosis of AIS and 5α-RD is an important hormonal criterion, but in some cases, T/DHT ratio may lead to diagnostic confusion. So, molecular diagnosis is important for the robust diagnosis of 46,XY DSD patients correctly.

P2-321

Familial Mutation of NR5A1/SF-1 Gene Associated with DSD and Spleen Agenesis: A New Syndrome?

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Background: A recent report (JCI, 2014) described a new homozygous NR5A1/SF-1 mutation in a patient with XY DSD and spleen agenesis. To date, no other data have confirmed this association, raising the hypothesis of fortuity. **Case presentation and method:** We had the opportunity to study an adolescent girl

referred for virilisation during puberty. She presented voice deepening and clitoral hypertrophy. Biological investigations showed high plasma testosterone (2 ng/ml) and gonadotropin levels and undetectable levels of AMH and inhibin B. The family history revealed that her father had had surgery for hypospadias in infancy. At 45 years, he was hospitalized for purpura fulminans, at which time asplenia was diagnosed. **Results:** Sonography and MRI showed three small residues which were evocated for spleen. Genetic investigation identified a new heterozygous NR5A1 gene mutation (c.1227C > A) within exon 7. This mutation creates a premature stop codon (p.Tyr409X) and results in a truncated protein. The father's genetic analysis revealed the same mutation. However, this mutation was absent from both paternal grandparents. In vitro assays of this mutation are in progress to investigate the mutant transactivation capabilities. **Conclusion:** As reported in mice, SF-1 gene invalidation leads to XY complete gonadal dysgenesis, adrenal agenesis and abnormal spleen development. In human, an SF-1 mutation may lead to both gonadal dysgenesis and spleen hypotrophy, raising the suggestion of a new syndrome. These data underline the usefulness of spleen function investigation in all patients with SF-1 gene mutation.

P2-322

Clinical Spectrum of 45,X/46,XY Mosaicism and Variants in Children

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Background: The phenotypic manifestations in the 45,X/46,XY karyotype is diverse and there are challenges in management due to this diversity. **Objective and hypotheses:** The aim of this study was to describe the clinical spectrum of 45,X/46,XY mosaicism and variants diagnosed in childhood. **Method:** A retrospective review of 20 patients with 45,X/46,XY ($n=7$) and its variants ((45,X/46,X,der(Y) ($n=12$)) and 46,X,der(X),t(X;Y) ($n=1$)) followed at a tertiary center between January 1997 and July 2014 was performed. **Results:** The mean age at diagnosis was 5.0 years (range 0.1–15.1) presenting with genital ambiguity, short stature and delayed puberty. Genital ambiguity was present in 86% of 45,X/46,XY patients and 33% of 45,X/46,X,der(Y) patients ($P=0.09$). All patients with 45,X/46,XY karyotype ($n=7$) and 75% of 45,X/46,X,der(Y) karyotype showing ambiguous genitalia ($n=4$) or signs of virilization ($n=1$) underwent gonadectomy. Gonadoblastoma was detected in intraabdominal gonads of three phenotypically female patients, of which two were diagnosed at later ages of 9.5 and 13.7 years respectively. Thirteen patients were reared as females while seven were reared as males. External masculinization scores were evaluated (males 9.2 vs females 1.2, $P<0.001$). Turner characteristics ($n=16$, 80%), cardiac anomalies ($n=3$, 20%) and kidney anomalies ($n=4$, 31%) were present. The percentage of patients with height z-scores less than the third percentile increased from 42% at diagnosis to 68% at growth hormone (GH) treatment initiation ($P=0.005$). Sixteen patients received GH and showed significant increases in height z-scores ($P<0.001$). Ten patients achieved final adult height with a median height z-score of -1.07 ± 0.89. **Conclusion:** The clinical spectrum of the 45,X/46,XY karyotype is diverse and patients require individualized care. There is a risk for gonadoblastoma even with the 45,X/46,X,der(Y) karyotype showing virilization. Although height progressively decreases from diagnosis, GH has a positive effect on growth and FAH.

P2-323

Chromosomal Variations in Children and Adolescents with Gender Dysphoria: Is Routine Karyotyping Indicated?

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Background: Chromosome analysis is always indicated in disorders of sex development (DSD), but the need for karyotyping in gender dysphoria (GD) is less clear. **Aims and objectives:** We therefore aimed to review the place of routine chromosome analysis in the management of GD in children and adolescents. **Patients and methods:** 490 children and adolescents with GD have been referred to the two endocrine clinics forming part of the joint National Gender Identity Development Service since 2009. Chromosome analysis and physical examination are performed routinely to exclude a DSD. **Results:** One *de novo* sex chromosome variation (47,XYY) was identified. The prenatal diagnosis of 47,XXX was confirmed in one other (total sex chromosome aneuploidy rate 1:245). Neither would have been suspected phenotypically nor did the finding have any bearing on the management of the GD. In addition, karyotyping revealed two individuals with balanced familial translocations and one with a small marker chromosome, none of which had any clinical consequences (total autosomal aneuploidy rate 1:163). The finding of these karyotype variations is within known population aneuploidy prevalence rates (1:250 sex chromosomes; 1:150 autosomes). **Conclusions:** No additional chromosome variations were identified in children and adolescents with GD over and above the frequency expected within the general population. This differs from the situation in a DSD. Chromosome analysis in children and adolescents with GD may not, therefore, be routinely indicated.

P2-324

DSD 46,XY and Serum Steroid Profile Ambiguity due to Combined 17-Beta Hydroxysteroid Dehydrogenase/21-Hydroxylase Deficiencies

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Background: An accurate and comprehensive assessment of steroid hormones is pivotal for differential diagnosis of disorders of sex development (DSD) 46,XY, a part of which may be due to defects of testosterone biosynthesis. **Objective and hypotheses:** To describe and characterise a case of DSD 46,XY presented with unusual serum steroid profile. **Method:** Serum steroid hormones were analysed by liquid chromatography-tandem mass spectrometry (LC-MS/MS). *HSD17B3* and *CYP21A2* genes were analysed by Sanger sequencing. **Results:** An 18-year-old professional female athlete presented with primary amenorrhea. Physical examination showed increased muscle mass, no breast development, male pattern of hair distribution, clitoris enlargement and blind-ending pseudo-vagina. Ultrasound examination revealed bilateral inguinal gonads and no uterus. Karyotype analysis showed 46,XY. Profile of serum steroid hormones assayed by LC-MS/MS was abnormal and not compatible with any known disorder of steroid hormone biosynthesis: 17OHP, 35.6 nmol/l (1.5–7.2); 21-deoxycortisol, 9.9 nmol/l (0.5–3.4); cortisol, 353 nmol/l (150–650); androstenedione, 29.5 nmol/l (1.4–7.9); testosterone, 12.9 nmol/l (12–33). Combination of HSD17B3 and CYP21A2 deficiencies was suspected. Sequencing of *HSD17B3* gene showed a known pathogenic homozygous splicing mutation c.277+4A>T, whereas analysis of *CYP21A2* gene revealed a homozygous p.V281L mutation, a frequent finding in non-classical congenital adrenal hyperplasia (NC CAH). **Conclusion:** To our knowledge, this is the first description of combined HSD17B3 and CYP21A2 deficiencies. Owing to the fact that NC CAH is frequent in certain populations, its contribution to observed peculiarities of phenotype and/or steroid profiles may be considered.

P2-325

Frequency of Cryptorchidism and Age at Operation in Helsinki Area between 2004 and 2014

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Background: Cryptorchidism is a risk factor for testicular cancer and poor semen quality. The incidence of cryptorchidism has been lower in Finland than in the other Nordic countries. **Objective and hypotheses:** We focused to investigate the recent trends in the incidence of undescended testes in the Helsinki area. In addition, we evaluated the age at orchidopexy before and after the release of the Nordic consensus in 2007 recommending operation between 6 and 12 months of age (Ritzén ME *et al.* 2007 Nordic consensus on treatment of undescended testes. *Acta Paediatr* 96 638–43). **Method:** The study material included referrals of boys with unilateral, bilateral or undefined cryptorchidism who were evaluated at Children's Hospital between 2004 and 2014 ($n=1214$). Medical records of patients with bilateral cryptorchidism ($n=136$), who were operated upon, were reviewed to obtain their ages at the time of orchidopexy. **Results:** The annual number of referrals for evaluation of cryptorchidism (110 ± 20) remained stable during the evaluation period. Between 2004 and 2007, all bilateral cases ($n=38$) were operated after the age of 1 year. After 2007, however, 26/98 boys (27%) were operated before the age of 1 year ($P<0.001$). **Conclusion:** The incidence of cryptorchidism, as estimated on the basis of referrals to a tertiary center, has not increased in Helsinki area between 2004 and 2014. The release of the Nordic consensus on treatment of cryptorchidism is associated with an earlier age at operation and conceivably better outcome.

P2-326

Prevalence of Partial Androgen Insensitivity Syndrome in 3 Cohorts of 46,XY Children Presenting with Isolated Hypospadias, Isolated Micropenis or Isolated Persistent Pubertal Gynecomastia

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Background: The clinical diagnosis of partial androgen insensitivity syndrome (PAIS) should be systematically considered for all 46,XY newborns/infants with undervirilisation contrasting with normal/elevated plasma testosterone levels. Confirmation of PAIS is based on the identification of an androgen receptor (AR) gene mutation. **Aim:** This work was undertaken to determine whether the minor forms of undervirilisation such as isolated hypospadias, isolated micropenis, or isolated persistent pubertal gynecomastia (PPG) should be considered as true cases of PAIS, i.e., the result of an AR gene mutation. **Methods:** AR gene sequencing was performed on the DNAs of 292 infants with isolated hypospadias, 52 infants with isolated micropenis, and 26 adolescents with isolated PPG. **Results:** In the cohort of 292 infants with isolated hypospadis, an AR gene mutation was observed in nine cases (3%). In the group of 52 infants with

isolated micropenis, AR gene sequencing revealed four mutations (7.7%). In the group of 26 adolescents with isolated PPG, we identified three AR gene mutations (11.5%). **Conclusions:** Isolated hypospadias, micropenis or PPG may be the only clinical manifestation of PAIS. The systematic search for an AR gene mutation in this common clinical situation may be criticised in today's difficult financial context. Yet identifying an AR gene mutation permits an aetiological diagnosis, fuller discussion of the prognosis, a foundation for choosing the therapeutic approach and – not least – the offer of genetic counselling for siblings.

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A Novel Mutation of Anti-Mullerian Hormone Receptor Gene in a Male with Persistent Mullerian Duct Syndrome

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Background: Persistent Mullerian duct syndrome (PMDS) is a rare genetic disorder of internal male sexual development defined as a lack of regression of Mullerian derivatives in an otherwise normally virilized XY male. Approximately 85% of the cases are caused by mutations of the Anti-Mullerian hormone (AMH) or its' receptor (AMHR-II) genes. In the current study, we report a novel homozygous mutation in the AMHR-II gene in a patient with PMDS and discuss the dilemma of the definitive treatment. **Case presentation:** A 3- months-old healthy male infant with normal penile length and bilateral cryptorchidism was found to have uterus and fallopian tubes in the inguinal sac during an elective inguinal hernia repair surgery. He had 46, XY karyotype and normal serum levels of testosterone and gonadotropins for his age. High serum levels of AMH raised the possible diagnosis of AMHR gene mutation. Sequencing of the AMHR-II revealed a novel homozygous missense mutation, c.928C>T in exon 7 of the AMHR-II gene which cause a stop codon p.Q310X. This mutation results in a lack of most part of the intracellular serine/threonine kinase domain of the receptor. Following the genetic results, orchiopexy and partial Mullerian remnants resection was performed. There is no consensus regarding the surgical approach in patients with PMDS. Reports of Mullerian remnants malignancy and the known risk of testicular cancer in undescended testes encourage removal of the Mullerian remnants and bilateral orchiopexy. However, the excision of the Mullerian structures risks the blood supply to the testes and vas deferens, which may cause infertility and impair testicular function. **Conclusion:** AMH serum levels can distinguish between AMH and AMHR gene mutations and may follow by molecular sequencing of either gene. The current report emphasise the clinical dilemma in the surgical approach in patients presented with PMDS.

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miR-122 and Non-Alcoholic Fatty Liver Disease in Prepubertal Obese Children

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Background: The incidence of non-alcoholic fatty liver disease (NAFLD) is dramatically increasing among children worldwide. The gold standard for diagnosis is the liver biopsy. Reliable serum markers are lacking. Recently, circulating miRNAs have been studied as biomarkers of disease progression. Specifically, miR-122 was proposed as predictive marker for liver disease in adults, while no data are available for children. **Objective and hypotheses:** To investigate the relationship between circulating miR-122 levels and liver steatosis severity and metabolic parameters in obese children. **Method:** Antropometry, biochemical and metabolic assessment were performed in 50 prepubertal obese children (15 female, age 9.78±2.17 yrs, BMI SDS 3.44±1.39). Serum cytokeratin-18 (CK18) fragment, a novel biomarker of NAFLD, was determined by ELISA. In 44 subjects liver ultrasound was performed revealing no ($n=19$, group 0), mild ($n=15$, group 1), moderate ($n=8$, group 2), or severe steatosis ($n=2$, group 3). Serum miR-122 was determined by qPCR. **Results:** CK18 did not display a gender dimorphism, while miR-122 was higher in male subjects (1.06±1.55 vs 0.28±0.29, P 0.045). CK18 positively correlated with serum triglycerides ($r=0.38$, $P=0.006$), AST ($r=0.54$, $P<0.0001$), ALT ($r=0.42$, $P=0.002$), and GGT ($r=0.26$, $P=0.07$). miR-122 positively correlated with age ($r=0.36$, $P=0.01$), CK18 levels ($r=0.40$, $P=0.006$), AST ($r=0.40$, $P=0.007$), ALT ($r=0.71$, $P<0.0001$) and GTT ($r=0.28$, $P=0.06$) levels. After adjustment for age and sex correlations persisted. Serum miR-122 levels were higher in severe steatosis group when compared to the other groups ($P<0.05$). CK-18 levels were higher in severe steatosis group when compared to subjects without steatosis ($P<0.05$). There was a positive correlation between miR-122 levels and HOMA-IR, whereas no correlation was found for CK18. **Conclusion:** Already in prepubertal children, miR-122 levels were associated with

measures of liver disease. Further studies will elucidate if miR-122 provides a useful biomarker for liver disease progression in children. **Funding:** This project was supported by an ESPE-RU collaborative project grant.

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Meteorin-Like (*METRNL*) Expression in Human Adipose Tissue is Associated with Adipocyte Hypertrophy and Inflammation and is Down-Regulated During Human Adipogenesis

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Background: The new adipokine/myokine meteorin-like (Metrnl) has been proposed to be of interest for obesity and metabolic disease through its potential role for brown/beige fat thermogenesis and macrophage activation in mice. METRNL was reported to be expressed in white adipose tissue (AT) and upregulated during adipogenesis and by exercise and. **Aims:** In this study we analysed the expression of *METRNL* during human adipogenesis and its regulation by metabolic regulators. Furthermore, we compared its expression in AT components from lean and obese children of our Leipzig Childhood Adipose Tissue cohort ($n=103$), and analysed associations with obesity and metabolic parameters. **Results:** Metrnl was down-regulated during human adipogenesis of SGBS preadipocytes on mRNA (to $22.7\pm13\%$) and protein level. Dexamethasone inhibited *METRNL* expression to $65\pm6\%$ in preadipocytes but not adipocytes, while insulin, IGF1 and isoproterenol had no effect. In human AT samples, *METRNL* expression was fivefold higher in SVFs compared to adipocytes. In adipocytes, but not in whole AT or SVF, obese children showed higher expression compared to lean children (7.1 ± 4.0 vs 5.0 ± 2.5; $P=0.003$) and in both, adipocyte and SVF *METRNL* expression correlated with BMI-SDS ($r=0.33$, $P=0.001$ and $r=0.24$, $P=0.002$) and adipocyte size ($r=0.26$, $P=0.005$ and $r=0.28$, $P=0.03$), but not with adipocyte number. *METRNL* expression in SVF was negatively related to experimental cell doubling time ($r=-0.40$, $P=0.008$). AT samples containing brown adipocytes, as indicated by histology and high *UCP1* expression, did not show higher *METRNL* expression compared to UCP1-negative samples. *METRNL* expression in adipocytes correlated with HOMA-IR as a marker of insulin resistance, macrophage number and CD68 expression, which was, however, not independent from BMI. **Conclusion:** In AT of children, *METRNL* is expressed in adipocytes and SVF in relation with BMI-SDS but shows a fivefold higher expression in SVF. The down-regulation of *METRNL* during adipocyte differentiation, the negative association in SFV with proliferation potential, and the positive association with adipocyte size may indicate that *METRNL* is associated with hypertrophic AT and may explain the association with markers of insulin resistance and AT inflammation. **Funding:** This work was supported by grants from the Federal Ministry of Education and Research (BMBF), Germany, FKZ: 01EO1001 (IFB AdiposityDiseases) and the German Research Council (DFG) for the Clinical Research Center 'Obesity Mechanisms' CRC1052/1 C05.

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Abdominal fat Distribution Measured by Magnetic Resonance Imaging in 197 Children Aged 10–15 Years – Correlation to Anthropometry and Dual X-Ray Absorptiometry

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Background: Obesity in childhood is defined by age- and sex-specific BMI cut-off values. However, BMI does not disclose the distribution of fat mass. Increased abdominal adipose tissue is associated with a higher risk of cardio-metabolic disease in adulthood. Thus, precise measurements of abdominal adipose tissue in children may enable early prevention of disease. **Objective and hypotheses:** To validate measurements of abdominal adipose tissue by anthropometry and Dual X-ray Absorptiometry (DXA) against Magnetic Resonance Imaging (MRI) in a cohort of healthy Danish children. **Method:** A population-based cohort study of 197 children (83 girls) aged 10–15 years. On the same day, a multi-slice MRI-abdomen (L1-L4), a DXA with determination of regional fat percentages and a clinical examination with measurement of height, weight, BMI, waist circumference (WC) and skinfolds and standard deviation scores (SDS) were calculated. Pubertal development was assessed. Subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) percentage of total abdominal volume was determined by MRI and android fat percentage by DXA. **Results:** SAT was significantly higher in girls compared to boys (mean 20.1% vs 15.0%, $B=4.3$ (95% CI 1.9–6.6), $P<0.001$). VAT was similar in girls and boys (mean 6.7% in both genders, $B=0.1$ (95% CI -0.4–0.6), $P=0.654$). Analyses were adjusted for puberty. DXA android fat percentage, suprailiac skinfold, BMI-SDS and WC-SDS correlated positively with SAT ($r=0.89$, $r=0.79$ $r=0.68$ and $r=0.57$, all $P<0.001$) and VAT ($r=0.39$, $r=0.32$, $r=0.22$ and $r=0.22$, all $P<0.005$). The best anthropometric predictor of both SAT and VAT was suprailiac skinfold, explaining 62.8 and 9.9% of the variance, respectively (both $P<0.001$). **Conclusion:**

Anthropometric measurements are good proxies for SAT determined by MRI in healthy non-obese children, reflecting that simple anthropometry can be used to determine obesity in childhood. However, prediction of VAT was less precise probably due to the sparse accumulation at this age.

P2-331

Autonomic Nervous System Function Assessed by Heart Rate Variability in Children and Adolescents with Long Term Follow up of Craniopharyngioma

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Background: Obesity is a well-recognized complication of craniopharyngioma. Increased hypothalamic involvement (HI) by the tumour and accordant treatment has been associated with greater obesity. Changes in hypothalamic control of the autonomic nervous system (ANS) have been implicated in the development of hypothalamic obesity however, long term changes in the ANS have not been assessed. **Objective and hypotheses:** We aimed to evaluate ANS activity using heart rate variability (HRV) in children and young adults with long term follow up for craniopharyngioma. Associations between HRV, degree of HI, obesity, physical activity and metabolic abnormalities were analysed. **Method:** HRV was assessed in 28 children and young adults (14 males) aged 10–30 years with more than 3 years of follow up after initial surgery. Anthropometrics, fasting metabolic sample, physical activity measures by questionnaire was obtained at the time of HRV testing. A retrospective review of the pre and postoperative clinical course and grading of HI on magnetic resonance imaging (MRI) was done. **Results:** The mean post-operative follow up was 11.6 (range 3.6–21.1) years. Patients with greater HI showed increased BMI *z*-score at the time of study. S.D. of the NN interval (SDNN) and total power (TP), indices of the overall variability, were decreased with greater HI. High frequency (HF), a parameter of parasympathetic activity, was decreased (195 ± 183 m^2 vs 409 ± 326 m^2) while the low frequency (LF) to HF ratio, a parameter of sympathetic activity was increased (1.76 ± 1.73 vs 0.80 ± 0.49). HF negatively correlated with fasting glucose ($P = 0.041$) and triglyceride ($P < 0.001$) and positively correlated with physical activity ($P = 0.047$). **Conclusion:** Greater HI in craniopharyngioma showed decreased overall HRV with increased sympathetic and decreased parasympathetic activity. Decreased parasympathetic activity was associated with metabolic abnormalities in glucose and triglyceride levels. These results provide a new perspective regarding autonomic dysfunction in long term follow up of craniopharyngioma.

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SIRT1 and SIRT2 Gene Expression in Peripheral Blood Mononuclear Cells of Obese Children and Adolescents and their Relationship with Metabolic Parameters and Insulin Resistance

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Background: Sirtuins are NAD^+-dependant protein deacetylases that target histones, transcription factors, co-regulators, as well as metabolic enzymes to adapt gene expression and metabolic activity in response to the cellular energy state. SIRT1 and SIRT2 are two important enzymes of sirtuin family. SIRT1 has an important role in glucose metabolism and improves glucose homeostasis. It can also regulate fatty acid oxidation and hepatic cholesterol and bile acid metabolism. SIRT2 has an antioxidant activity and negatively regulates insulin resistance. **Objective and hypotheses:** The aim of this study was to evaluate SIRT1 and SIRT2 gene expression in peripheral blood mononuclear cells (PBMCs) of children and adolescents with obesity and their association with metabolic parameters and insulin resistance. **Method:** children and adolescents (30 obese and 30 age and gender matched control subjects), (8–15 year old), were selected. PBMCs were separated and their total RNA was extracted. After cDNA synthesis, SIRT1 and SIRT2 gene expression were analysed by real-time PCR. Relative differences in gene expression were calculated by ΔCt method using β-actin as a normalizer. Serum insulin was measured using ELISA, and insulin resistance (IR) was calculated by the Homeostasis Model of Assessment of Insulin Resistance (HOMA-IR). Fasting plasma glucose, triglyceride, total cholesterol, LDL-C and HDL-C were also measured. **Results:** Expression of SIRT1 gene was significantly diminished in obese subjects compared to control ones (0.33 ± 0.02 vs 1.37 ± 0.25) ($P = 0.000$). It was also significantly lower in obese children with IR compared to obese children without IR (0.33 ± 0.079 vs 0.97 ± 0.17) ($P = 0.008$). There was a trend toward a lower SIRT2 expression in obese subjects but the difference was not significant (1.88 ± 0.19 vs 2.83 ± 0.36) ($P = 0.057$). SIRT1 expression was significantly correlated with BMI and waist circumference as well as insulin and MOMA-IR. SIRT2 was significantly correlated with SIRT1 and HDL-C. **Conclusion:** SIRT1 is decreased in obesity and is associated with insulin resistance in children and adolescents. Targeting SIRT1 can be valuable in treating obesity and insulin resistance in childhood and adolescence. **Funding:** This work was supported by Endocrinology and metabolism

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Leptin Replacement Improves Central Ventilation in a Patient with Congenital Leptin Deficiency: First Report in Childhood

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Background: Congenital leptin deficiency (CLD) is characterized by severe early-onset obesity due to hyperphagia and impaired satiety. The impact of obesity in obstructive sleep apnoea hypopnoea syndrome (OSAHS) was originally reported as mechanical, but recent data suggest that adipokines may influence central ventilation. We highlight that treatment with recombinant human leptin (RHL) in CLD with OSAHS improves ventilation before weight loss. **Case presentation:** A 10-month-old female of Pakistani origin was severely obese (weight: 17.9 kg (+5.6 SDS) and BMI: 29.4 kg/m^2 (+5.3 SDS)). Born at term to consanguineous parents. Mother reported rapid weight gain during first months of life, due to intense hyperphagia with food-seeking behaviour. Family history showed a first cousin with CLD: genetic analysis confirmed the same homozygous leptin mutation. RHL replacement was started with good reduction of appetite. Three months before starting treatment (weight: 26.1 kg (+7.6 SDS)) oxicapnography showed normal mean saturations and CO_2 but clusters of deep desaturations (desaturation index (DI) 19.8/h of >4%). After 50 days of treatment polysomnography was performed showing a significant improvement in clusters of desaturation (DI 9.3/h) and a mixed pattern of both obstructive and central events with an apnoea hypopnoea index (AHI) 13.7/h. At this stage the weight was stable at 26.9 kg (+6.7 SDS), BMI was 34.8 kg/m^2 (+6.6 SDS). After 5 months of treatment a significant loss of weight was seen (weight: 22.0 kg and BMI: 32.6 kg/m^2, both at +4.7 SDS). Repeat polysomnography showed marked improvement with an AHI 4/h and a DI 4.2/h. **Conclusion:** To the best of our knowledge, this is the first report showing an improvement in ventilation, in a patient with CLD following treatment with RHL before significant weight loss. In mice, leptin microinjections into specific brain areas, are associated with increased pulmonary ventilation and enhanced bioelectrical activity of inspiratory muscles, suggesting that leptin may influence ventilation through a direct effect on respiratory control centres. Leptin appears to have central effects on ventilatory regulation, which need to be explored further.

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Childhood Obesity Negatively Influences Adult Leydig Cell Function

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Background: Childhood obesity is a global health problem and co-morbidities develop already during childhood and adolescence. Male obesity impacts negatively on reproductive function. Testosterone is decreased, sperm quality reduced, and the physical and molecular structure of germ cells altered in obese males. However, less is known about the role of prepubertal obesity on future reproductive function. We therefore explored Leydig cell function and reproductive potential in a rat model with prepubertal onset of obesity. **Objective and hypotheses:** To explore the influence of prepubertal obesity on reproductive potential and Leydig cell capacity to produce testosterone in adult male rats. **Method:** Lewis male rats were exposed to high fat diet (HFD) and standard chow (SC) from day 21 until 3 (group 1) and 9 months (group 2). Various anthropometric data including fat mass and adipocyte diameter were analyzed. Mating studies and semen analyses were performed. Sex steroids and gonadotropin levels were determined by immunoassays. Testis morphology was evaluated by microscopy. Expression of Leydig cell specific genes was analyzed at the transcriptional (q-PCR) level. **Results:** HFD increased body fat by 3 and 10% ($P \leq 0.001$) in groups 1 and 2 respectively. The ratio testis:body weight was reduced by 6% in group 1 but significantly (by 22%, $P = 0.008$) in group 2 compared to SC control. Serum levels of testosterone were reduced in obese rats from group 2 (by 29%), while estradiol (E_2) was elevated in both groups of obese animals (by 44, $P = 0.018$ and 40%, $P = 0.005$ respectively). The decline in serum levels of testosterone in obese rats with the longest period of HFD exposure was associated with marked suppression of the expression of Leydig cell-specific genes (e.g. *StAR, Cyp11a1, Hsd3b1, Hsd17b3*, and *Insl3*). **Conclusion:** Long-term obesity developed in the prepubertal period significantly affected Leydig cell capacity to produce testosterone and altered the testosterone:E_2 ratio in obese rats. Furthermore steroidogenic enzymes were down regulated. The observed perturbations of sex hormone levels may disturb normal spermatogenesis and attenuate reproductive potential and fertility in obese males. **Funding:** ESPE Research Fellowship.

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Network Coordinated Primary Care Intervention in Obese Children and Adolescents: Almost a Decade of Experience

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Background: French health authorities have developed a national program to organize outpatient care networks for the prevention and management of obesity in children and adolescents (Réseau de Prise en Charge de l'Obésité Pédiatrique (REPOP)). To date, REPOP Ile-de-France has more than 250 primary care physicians with dietitians, nurses, educators, and psychologists trained in the management of childhood obesity as part of a standard care pathway, working in close collaboration with expert hospital staff. **Objective and hypotheses:** To describe the evolution of BMI in children and adolescents followed by REPOP Ile-de-France and to determine factors associated with the evolution of body size. **Method:** All children and adolescents prospectively included in the REPOP cohort from 09/2003 to 02/2012. Results are expressed as median (q_1;q_3). The primary endpoint was the evolution of BMI *Z*-score and improvement was defined as a decrease $>10\%$ at the last follow-up visit. Cox models were used to analyze the influence of clinical and familial characteristics. **Results:** Among 4174 patients, 59% were available for analysis beyond 3 months. Subjects lost to follow-up were more likely female (62.6% vs 58.8%, $P=0.01$), older (10.5 years (8.5; 12.7) vs 10.3 (8.2; 12.4), $P=0.02$) and more obese (BMI *Z*-score 3.4 (2.8; 4.2) vs 3.3 (2.7; 4.0), $P=0.00001$). The other 2468 subjects were used for analysis, with a median duration of follow-up of 11 months (5.7; 19.5). The median change in BMI *Z*-score was -0.26 (-0.56; -0.02). The primary endpoint was met in 1047 patients (42.4%) with significant associations with age (OR 0.93 (0.88; 0.99), $P=0.02$), BMI *Z*-score at baseline (OR 0.95 (0.92; 0.99), $P=0.02$), maternal BMI (OR 0.98 (0.97; 0.99), $P=0.01$), and time between consultations (OR 0.88 (0.84; 0.91), $P<0.0001$). The proportion of subjects with waist-to-height ratio ≥ 0.5 decreased from 89 to 80%, $P<0.0001$). **Conclusion:** Network coordinated primary care intervention is associated with clinical improvement in obese children and adolescents. These results suggest that early identification and referral is associated with improved outcome. They could help to improve the program by highlighting population at risk of loss of follow-up.

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Diagnosing the Metabolic Syndrome in Survivors of Childhood Haematopoietic Stem Cell Transplantation and Total Body Irradiation

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Background: The well-documented increased cardiometabolic risk in haematopoietic stem cell transplantation and total body irradiation (HSCT/TBI) survivors is under-recognised using standard (International Diabetes Federation (IDF)) metabolic syndrome (MetS) criteria. This is defined as the presence of central adiposity using increased waist circumference (WC) or BMI, (often not abnormal in HSCT/TBI survivors despite increased central adiposity), plus additional features including two of following: ↑ triglycerides (TGs) >1.7 mmol/l, ↓ HDL (M <1.03 mmol/l and F <1.29 mmol/l), BP $>130/85$, and ↑ fasting glucose >5.6 mmol/l or known diabetes. **Objective:** To identify alternative measures of central adiposity to define the MetS which are more representative of metabolic risk in HSCT/TBI survivors. **Method:** Childhood leukaemia survivors treated with HSCT/TBI (10–14.4 Gy; $n=21$, 10M) at mean aged 9.3 (1.0–10.8) years were compared with chemotherapy-only ($n=31$), and obese non-leukaemic controls ($n=30$). All subjects (16–26 years) had BP and auxological measurements (BMI, waist, and hip circumferences) and blood tests (HDL, TG, and oral glucose tolerance tests). The prevalence of the MetS defined by ↑ waist-to-height (WHtR; >0.5) or waist-to-hip ratios (WHR) (M >0.9 and F >0.8) rather than standard criteria of WC (M >94 cm and F >80 cm) or BMI >30 kg/m^2 were compared using odds ratios and ANOVA (5% significance). **Results:** The HSCT/TBI group had two patients with diabetes and a higher prevalence of low HDL (57%) vs chemotherapy-only (27%), $P=0.003$; raised TG (48%) vs both chemotherapy-only (10%), $P=0.005$ and obese (13%, $P=0.001$) groups but significantly lower mean BMI ($P<0.001$), WC ($P<0.001$), WHtR ($P<0.001$) than the obese, and lower WHR ($P=0.003$) than the chemotherapy-only groups. There was no difference in the prevalence of the MetS using standard IDF criteria: HSCT/TBI (19%), chemotherapy-only (10%, $P=0.4$), and obese (17%, $P=0.8$) groups. When WC was replaced by WHtR, the prevalence increased to 38% in HSCT/TB, significantly higher than chemotherapy-only (13%, $P=0.047$) patients. Using WHR, HSCT/TBI prevalence was 43%, significantly higher than both chemotherapy-only (10%, $P=0.011$) and obese (17%, $P=0.044$) groups. The prevalence in the obese group remained unchanged with all three definitions. **Conclusions:** The WHR is more representative of central adiposity allowing identification of metabolic syndrome and risk in HSCT/TBI survivors. **Funding:** This work was funded by the IPSEN clinical research fellowship, BSPED research Award, David Telling Research funds, and Peel Medical research award.

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Laparoscopic Sleeve Gastrectomy in Adolescents: Metabolic Consequences

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Background: Severe obesity (SO), defined as BMI $\geq$95th percentile, has increased worldwide among adolescents. American studies estimated that 1.3–2.8% of 12–19-year-old individuals have

a BMI >40 kg/m^2 or a BMI >35 kg/m^2 with at least one serious co-morbidity. The immediate and long-term risks associated with SO in adolescents include cardiovascular and metabolic diseases, obstructive sleep apnoea, and nonalcoholic fatty liver disease. However, the results of sleeve gastrectomy in adolescents are still uncertain. **Objective and hypotheses:** We aimed to assess the safety, efficacy, and metabolic changes of laparoscopic sleeve gastrectomy in adolescents with SO. **Method:** Longitudinal retrospective study of 23 adolescents with SO who underwent laparoscopic sleeve gastrectomy. Clinical and metabolic variables immediately before surgery and after 6, 12, 18, and 24 months were assessed. **Results:** Seventeen females and six males between 13 and 18 years old were followed-up for a mean of 2 years. At the initial evaluation, the mean BMI was 44 kg/m^2 and the mean weight was 120 kg. The 6-, 12-, 18-, and 24-month mean BMI and weight were respectively, 35.1, 34.9, 34.3, and 37.4 kg/m^2 ($P<0.0001$) and 97.1, 96.6, 95.2, and 102.3 kg ($P<0.0001$). Leptin, insulin, HDLc, triglycerides, and hepatic enzymes improved at 24 months of follow-up compared to prior surgery levels ($P<0.05$). One patient presented with unexplained iron deficiency anemia during the follow-up. No other complications were observed. **Conclusion:** Laparoscopic sleeve gastrectomy in adolescents with SO seems to be a safe and effective procedure associated to weight and BMI loss and significant metabolic improvement in the first two years.

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A Novel Melanocortin-4-Receptor Gene Mutation Associated with Early Onset Severe Obesity

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Background: The melanocortin-4-receptor gene (*MC4R*) is a key regulator for appetite and satiety. *MC4R* mutations account for 6–8% of severe obesity in children with variable expression and penetrance. **Case presentation:** A 3-year-old girl is presented with severe early onset and progressive obesity. She was born full-term with appropriate of gestational age weight by non-consanguineous parents. She had normal psychomotor milestones and no syndromic features but her red-brown hair was characteristic. Her BMI at presentation was 30 kg/m^2 ($+4.5$ SDS) and her waist circumference was 81 cm ($+6.1$ SDS). She exhibited a remarkably increased linear growth with bone age advancement by 2 years and no signs of pubarche. At the age of 5 years (BMI 29.6 kg/m^2, $+3.2$ SDS) despite her effort with a healthy lifestyle, she developed hyperinsulinaemia and was commenced on treatment with metformin. A novel heterozygous mutation *MC4R* p.M215del (c.643_645delATG) deletion was found on the patient and her father who was also obese (BMI 33 kg/m^2). 3D structural dynamic simulation studies have been used to investigate the conformational changes induced by this novel amino acid deletion. Additionally, the *in silico* software package 'Mutation Taster' was used to predict the pathogenicity of p.M215del deletion and identified it as a disease causing mutation. **Conclusion:** The deletion of methionine at position 215 causes global conformational and functional changes as it is localized at the alpha-helical transmembrane regions and the membrane spanning regions of the beta-barrel. This novel mutation produces a severe obesity phenotype especially with additional negative effect of environmental factors and unhealthy lifestyle habits even in heterozygote patients.

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Hypothalamic Obesity, Hyperphagia, and Hyperinsulinaemia: Time for a Paradigm Shift in Assumptions?

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Background: Hypothalamic obesity (HyOb) is a syndrome of inexorable, treatment-resistant obesity seen after congenital (e.g. septo-optic dysplasia (SOD)) or acquired (e.g. tumour-related) hypothalamic damage, often co-existing with hyperphagia, panhypopituitarism, autism, sleep, and temperature dysregulation. Its pathophysiology is poorly understood but hyperphagia and excess caloric intake may be less important than previously thought. **Objective and hypotheses:** To determine the frequency of hyperphagia and its association with hyperinsulinaemia in HyOb in comparison to common obesity. **Method:** Multiway case-control comparison of Dykens Hyperphagia Questionnaire Scores (DHQS), 2-h oral glucose tolerance test (OGTT)-stimulated plasma glucose and insulin indices in 49 obese (SOD 14, hypothalamic tumours 15, and common obesity 20) vs 29 lean (SOD 13, hypothalamic tumours 3, and controls 13) children. **Results:** Patients were of median age 12.0 years (range 2.5–19.6, 50% females), with a median BMI $+2.8$ ($+2.0$ to $+3.8$) and $+0.8$ (-2.9 to $+1.9$) SDS in obese and lean groups, respectively, with no significant differences between SOD, tumour or control subgroups. DHQS and insulin-related indices were similar between patients with HyOb and common obesity ($P>0.05$). Of the DHQS sub-scores, only hyperphagic drive was correlated with BMI SDS (Spearman's $\rho=0.292$, $P<0.05$), whilst Hyperphagic Drive, overall DHQS and BMI SDS correlated with fasting insulin, HOMA-IR, and the Matsuda index (all $P\leq0.01$). 5/38 obese patients (13.2%) fulfilled WHO criteria for impaired

glucose tolerance (IGT), whilst one tumour survivor (2.6%) had frank type 2 diabetes (T2DM). Autism ($P=0.001$), learning difficulties ($P<0.05$), and sleep disturbances ($P<0.001$) were frequent in SOD and tumour patients but were not significantly associated with DHQS or BMI SDS. **Conclusion:** Hyperphagia is not, as commonly perceived, unique to HyOb or the hypothalamic syndrome, but its presence increases BMI and insulin insensitivity. Hyperinsulinaemia *per se* does not explain the pathophysiology and treatment-resistance of HyOb. IGT and T2DM are becoming increasingly prevalent in children with obesity from any cause. **Funding:** This work was supported by the BUPA Cromwell Hospital (grant number 1DAAG), Great Ormond Street Hospital Children's Charity (grant number 1DAAJ), Great Ormond Street Hospital Biomedical Research Centre (grant number 1DAAN), and the British Society of Paediatric Endocrinology (grant number 1DAAP).

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Prevalence of Scoliosis in a Large Cohort of Paediatric and Adolescent Prader–Willi Syndrome: A Scottish–Italian study

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Background: A variable prevalence of scoliosis has been reported in Prader–Willi syndrome (PWS). Clinical detection can be challenging. The role of GH therapy (GHT) in the onset and progression of scoliosis remains controversial as does the modality of screening. **Objective and hypotheses:** To define the prevalence of scoliosis in our PWS patients and analyse the role of age, gender, genotype, BMI, and GHT on its onset and severity. **Method:** We analysed patients attending Italian ($n=74$) and Scottish ($n=28$) PWS dedicated clinics. 102 genetically confirmed (44del, 41UPD, and 17 unknown) PWS patients (50F) were seen during the study period (2011–2014), mean age 8.6 years (0.8–17.2). Auxological and GH data was collected, as well as the assessment of scoliosis including Cobb Angles (CA) measurements. 89 (87%) are or have been on GHT. Spinal X-ray was performed in 90/102 (88%) patients. **Results:** Scoliosis (CA $>10^{\circ}$) was present in 55/90 (61%) patients (31F and 24M) who had undergone X-ray. 13 (27%) patients had severe scoliosis (SS),with a CA $>25^{\circ}$ and required referral to spinal deformity service due to a high risk of progression. We did not find significant differences in age, gender, genotype, or age starting GH among scoliosis (SG) and non-scoliosis group (NSG). In SG, 81/89 (91%) patients were on GHT, previous or ongoing ($P<0.05$ vs NSG) (non-SS in 83%; $P\leq0.001$ vs SS). BMI *Z*-score was higher in SG ($+1.3\pm1.3$ vs -0.4 ± 6.1, $P<0,05$). No difference was found among age, BMI *Z*-score, age starting GH in SS vs non-SS patients. Univariate and multivariate analysis showed that only BMI *Z*-score seems to influence scoliosis development (β: 0.474; $P<0.001$), while age, gender, and GHT did not seem to play a role. No correlation was found for SS patients. **Conclusion:** In our patients scoliosis was frequent (61%), increasing with BMI *Z*-score. It is difficult to define the role of GH, given the high percentage of our patients treated. We suggest regular spinal X-rays, especially where clinical spinal examination is difficult due to underlying obesity. Regular radiological assessment for scoliosis is justified pre and post-GHT.

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Palmitic Acid Could Modify Cognitive and Behavioural Functions Through Sex Specific Activation of Hippocampal Astrocytes

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Background: Prolonged poor dietary habits can result in hypothalamic inflammation and gliosis with more recent studies suggest that other brain areas may also be affected. Western or high fat diet intake has been associated with increased cognitive impairment and aberrant feeding behavior, with males and females being differentially affected. The hippocampus participates in both of these functions. Saturated free fatty acids can induce astrocyte inflammation and this could potentially result in adverse neurologic processes. Undoubtedly, a delicate balance between pro- and anti-inflammatory signals will determine long-term cellular homeostasis. **Objective:** Our aim was to determine the effects of palmitic acid on hippocampal astrogliosis and whether these effects are sex-specific. **Method:** Primary hippocampal astrocyte cultures were established from male and female rats (P2) using standard procedures. After 10 days, cell cultures were shaken overnight to eliminate microglia and oligodendrocytes. Cells were plated at a density of 15 000 cells/cm^2. Twenty-four hours later, cells were treated in serum free media with palmitic acid (25 or 50 μM, 24 h). Levels of glial fibrillary acidic protein (GFAP) and pro- or anti-inflammatory factors were measured by western blotting. **Results:** Palmitic acid increased GFAP levels in males (170% of control; $P<0.01$), but induced a decrease in female (30% of control; $P<0.01$). Levels of the inflammatory cytokine interleukin 6 (IL6) were also increased in males (390% over

control; $P<0.05$) and decreased in females (70% of control; $P<0.05$). Levels of the pro-inflammatory intracellular signal p-IκB did not change in males or females. **Conclusion:** Glial cells of the hippocampus respond to palmitic acid in a sexually dimorphic manner. As these cells were derived from prepubertal animals, the differential response could be an inherent difference between the sexes and could partially underlie the sex differences in propensity to develop some cognitive or behavioral dysfunctions. **Funding:** This work was supported by Ministerio de Ciencia e Innovación (BFU2011–27492) co-funded by European FEDER Program, and Centro de Investigación Biomédica en Red Fisiopatología de Obesidad y Nutrición of the Instituto de Salud Carlos III, and Fundación de Endocrinología y Nutrición.

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Changes in Insulin Sensitivity in Adolescents Who Underwent Bariatric Surgery: Effects of Laparoscopic Sleeve Gastrectomy and Laparoscopic Gastric Banding

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Background: In adults, bariatric surgery has gradually emerged as a 'metabolic' surgery, able to rapidly improve metabolic disturbances linked to severe obesity. Even if type 2 diabetes is rare in european obese adolescents, alterations in insulin sensitivity are present in almost all. **Objective and hypotheses:** To evaluate the modification of insulin resistance (IR) and insulin sensitivity (IS) in severe obese adolescents who underwent bariatric surgery, comparing two methods: laparoscopic sleeve gastrectomy (LSG) and laparoscopic gastric banding (LGB). **Method:** Forty patients followed for 12 months were studied. 20 underwent LSG (mean age 17.14±1.46 years, BMI 44.73±9.37; *Z*-score 4.7±0.95) and 20 underwent LGB (mean age 15.55±1.9 years; BMI 37.86±4.12; *Z*-score +4.48±0.68). IR was estimated by homeostasis model of assessment (HOMA-IR). The IS was evaluated by quantitative insulin sensitivity check index (QUICKI). **Results:** Among patients who underwent LSG, improvement in IR was significant after 6 months (baseline HOMA-IR 4.7±0.95 vs 3.35±2.0 at T6, $P=0.036$) and 12 months (2.089±2.11). Normalisation of IS was observed in all patients after 6 months (baseline QUICKI 0.29±0.01; 0.34±0.03 at T6, $P=0.020$). The change in IS was not correlated with weight loss. In LGB patients, improvement of IS was slower, showing a trend without reaching significance (baseline HOMA-IR 4.87±2.62 vs 4.26±2.54 at T6, 3.95±3.20 at T12, baseline QUICKI 0.29±0.01, 0.31±0.02 at T6 and 0.32±0.03 at T12) and it was correlated to weight loss ($P<0.001$). **Conclusion:** Our observation confirms the metabolic benefits of LSG even in a cohort of very young patients. Unlike LGB, the improvement of insulin sensitivity is sharp and not correlated to weight loss.

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Chronodisruption in Obese Children

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Background: Altered circadian and ultradian blood pressure (BP) and heart rate (HR) rhythmicity has been described in many diseases with increased cardiovascular risk. **Objective and hypotheses:** We tested the hypothesis that rhythmicity in obese children is changed, compared to healthy subjects. **Method:** Circadian and ultradian BP and HR rhythmicity was assessed with Fourier analysis from 24-h ambulatory BP measurement (ABPM) in 75 obese children, 45% girls, BMI SDS median 2.79 (interquartile range (IQR) 2.54 to 3.41), median age 11.6 years (IQR 9.0 to 13.6) and compared with an age- and gender matched healthy control group of 150 subjects (45% girls) with BMI SDS median 0.32 (IQR −0.39 to −1.13), median age 11 years (IQR 8.0 to 13.0). Multivariate regression analysis was applied to identify significant independent factors explaining rhythmicity variability in this population. Subgroup analysis of non-hypertensive participants was performed. **Results:** Prevalence of 24- and 6-h BP as well as 12-h HR rhythmicity in obese group was lower ($P=0.03$, $P=0.02$, and $P<0.0001$). Prevalence of 8-h HR rhythmicity was higher in obese children ($P<0.0001$). Prevalence of BP rhythmicity excluding hypertensive participants showed comparable results with lower prevalence for 24- and 6-h BP rhythmicity in obese participants ($P=0.02$ and $P=0.03$). 24-h BP and HR acrophase was delayed in obese children ($P=0.004$ and $P<0.0001$), 24-h BP amplitude was comparable ($P=0.07$), 24-h HR amplitude was flattened ($P\leq0.0001$). BP Mesor in obese cohort was higher ($P=0.02$) and HR Mesor was comparable ($P=0.1$). Multivariate regression analysis failed to identify anthropometric or blood pressure parameters explaining the variability of BP and HR rhythmicity. **Conclusion:** We showed altered prevalence and parameters of circadian and ultradian BP and HR rhythmicity in obese children compared to healthy controls. This was independent of anthropometric and blood pressure values, suggesting other factors being involved in altered cardiovascular rhythmicity.

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Configuring a Better Estimation of Obese Children's Kidney Size

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Background: Obesity ignites numerous health and psychosocial problems and is associated with various comorbidities. BMI is also independently associated with improved risk for numerous kidney disorders. As renal length is considered a vital parameter in the clinical assessment of renal patients, normal renal length has to be defined in accordance to BMI. The aim of this study is to define normal kidney length in obese children, comparing ultrasound measurements of the kidney length in obese and non-obese children, in order to reduce unnecessary evaluations for nephromegaly. **Materials and methods:** Fifty obese children and 50 non-obese children, aged 1–19 years old, were selected from patients of paediatric clinic in two hospitals (Rasoul-e-Akram and Shahid Fahmideh) between June 2010 and 2012. After the nephrologist's and endocrinologist's approval, abdomino-pelvic ultrasonography was done for both groups, during which the largest longitudinal dimension was measured in the deep inspiration position. **Result:** It was revealed that both left and right kidney in obese group were significantly larger than control group ($P=0.044$ and $P=0.040$ respectively). Obesity status, height, and age were proven to be significant and independent predictors of both kidney lengths and left kidney length was significantly larger than right kidney length, separately in both obese and control groups ($P<0.001$). **Conclusion:** A specific standard cut-point limit or normogram has to be formulated solely for obese children, in order to facilitate the diagnosis of kidney diseases, including organomegaly, in obese children.

P2-345

Early Onset of Adiposity Rebound is Associated with Higher Leptin Concentrations in 12-Year-Old Children

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Background: We previously reported that children with an earlier adiposity rebound (AR), which is defined as the time at which the BMI starts to rise after infancy, have a higher BMI and a greater atherogenic metabolic status at age 12. In addition, it has been reported that higher levels of leptin at age 3 is associated with greater weight gain and adiposity by age 7. This finding suggests that leptin resistance may begin in early childhood, even before age 3. **Objective and hypotheses:** To investigate if early onset AR is related to the acquisition of leptin resistance at age 12. **Method:** A total of 296 children (157 boys and 139 girls) in one Japanese community were enrolled in the study. 271 children were able to define the age of AR and were divided into six groups according to AR age: $\leq$age 2, 3, 4, 5, 6, and $\geq$7. Leptin levels were measured at age 12. The association between age at AR and leptin levels were examined. **Results:** Geometric mean leptin levels in 12-year-old children were 3.3 ± 1.6 and 5.2 ± 1.5 ng/ml (boys and girls respectively) in non-obese children, 6.5 ± 1.5 and 6.8 ± 1.2 ng/ml in light obese subjects, 8.5 ± 1.6 and 13.2 ± 1.6 ng/ml in moderately obese subjects, and 20.1 ± 1.3 and 20.9 ± 1.3 ng/ml in severely obese subjects. An earlier AR was associated with higher level of leptin at age 12. **Conclusion:** An earlier AR was associated with higher leptin levels at age 12, regardless of gender, suggesting that the timing of AR is an important factor that can predict leptin resistance in the future. Therefore, we propose that age of AR should be considered in early childhood to identify children at high risk for leptin resistance.

P2-346

Metformin Treatment for Obese Children and Adolescents with Insulin Resistance

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Background: Obesity in children is already a global health problem. Obese children and adolescents with insulin resistance provide the pediatric healthcare professionals management challenge. Obesity with insulin resistance, dyslipidemia and elevated blood pressure constitute the metabolic syndrome and each of these is an independent risk factor for cardiovascular disease (CVD). Metformin is well-established oral hypoglycaemic agent in the treatment of adult and young patients with type 2 diabetes. **Objective and hypotheses:** To analyse the effect of metformin treatment of obese children and adolescents with insulin resistance on the BMI, fasting serum glucose and insulin (calculated as insulin resistance index – HOMA) and the ratio waist circumference:height (as a sign of abdominal adiposity and risk factor for metabolic syndrome, CVD, and type 2 DM). **Method:** Investigation and follow up of 57 children and adolescents (16 boys), aged 7 years and 6 months–16 years and 9 months. Patients received metformin for an average period of 14, 6 months (6–36 months) twice daily dosage of 1000–1700 mg. Anthropometry (height, weight, and waist circumference), clinical examination with regard to presence of acanthosis nigricans and oral glucose tolerance test were performed at baseline and end of treatment period. **Results:** Mean age of subjects at baseline was 13 years and 7 months with median BMI 30 and 95 kg/m^2 and waist circumference:height ratio 0:62. After the treatment period BMI was reduced with 1.91 kg/m^2 and waist circumference:height ratio became 0:51. Acnathosis nigricans was found in 51% of all patients and pretreatment HOMA IR was 5.52. Metformin therapy

had beneficial effect on HOMA which fall to 3.16. **Conclusion:** Date from pediatric randomized controlled trials have shown that metformin use for the treatment of obese children and adolescents with insulin resistance lead to improvement in BMI, fasting serum glucose, and insulin and lipid profile as well as waist circumference:height ratio according to the results of the presented data.

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A Double-Blind, Placebo-Controlled Comparison of Cinnamon Extract to Metformin Effects upon Insulin Resistance, Apolipoprotein B:Apolipoprotein A1 Ratio, and BMI of Obese Adolescent Girls with Polycystic Ovary Syndrome

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Background: Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies, affecting 5–10% of population. Insulin resistance, apolipoprotein B:apolipoprotein A1 ratio, and BMI commonly increases in obese PCOS patients and are among the indicators of the disease. On the other hand, metformin and cinnamon are generally believed to control these. **Objective and hypotheses:** To compare the effects of cinnamon with those of the metformin on insulin resistance, apolipoprotein B:apolipoprotein A1 ratio, and BMI of obese adolescent girls with PCOS. **Method:** In a prospective, double-blind, randomized, placebo-controlled clinical trial, 112 adolescent girls (12.6–17 years old) with PCOS were treated with cinnamon extract (500 mg twice daily), metformin (500 mg twice daily), or placebo, at the Outpatient Paediatric Endocrine Clinic of a University Children's Hospital in Tehran for 1 year. **Results:** Cinnamon and metformin differed from placebo in significantly decreasing insulin resistance: both homeostasis model insulin resistance index ($P<0.005$) and quantitative insulin sensitivity check index ($P<0.01$), and also apolipoprotein B:apolipoprotein A1 ratio. There was no significant difference between cinnamon and metformin effects on these indexes, however they both slightly but significantly decreased body mass index compared to placebo ($P<0.05$). **Conclusion:** This first randomised controlled clinical trial in obese teenage girls with PCOS shows that cinnamon does not differ from metformin in decreasing the insulin resistance but decrease the BMI less.

P2-348

Pantoprazole Treatment of Exogenous Obesity and Hyperinsulinism in Childhood

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Aim: The purpose of this study was to assess whether pantoprazole could be a new treatment option in the therapy of children with obesity and insulin resistance. **Methods:** This study was conducted on 46 children and adolescents with exogenous obesity and insulin resistance. The patients were randomly chosen and divided into therapeutic groups of metformin, pantoprazole, and metformin plus pantoprazole. **Results:** There was no difference between the groups in terms of age, gender, and anthropometric measurements made before therapy. In the pre-therapy OGTT, the glucose levels at 60 and 90 min were highest in the metformin group and lowest in the pantoprazole group. In the post-therapy OGTT, the glucose level at 60 and 90 min were lowest in the metformin group which had the highest level prior to therapy. Likewise, the metformin group showed the lowest insulin levels at 60, 90, and 120 min. When the post-therapy values of HOMA-IR, Quick index, and fasting insulin:glucose ratio were compared, there was a significant improvement in all three groups, however, when the groups were compared with each other, there was no statistically significant difference between the groups in terms of improvement. **Conclusion:** Pantoprazole may be a new treatment option for children and adolescents with obesity and insulin resistance.

P2-349

Subepicardial Adipose Tissue and Carotid Intima–Media Thickness in Obese Children and Their Relationship Between Metabolic and Clinical Parameters

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Introduction and objective: Atherosclerosis is one of the most important causes of obesity-related diseases. The clinical symptoms usually begin in adulthood, but the pathological changes in vascular structure could be observed in a much earlier period. Carotid intima–media thickness (cIMK) which is one of the noninvasive marker of early atherosclerotic changes, has been shown to be significantly increased in obese children. Subepicardial adipose tissue (SAT) is a component of visceral adipose tissue. Obesity is the most common predisposing factor leading to the increase of SAT. Transthoracic echocardiography is a valuable imaging modality to evaluate SAT. The determination of SATT could be important in grading the risk of obesity-related complications. We aimed to evaluate the relationship between SATT and cIMK with anthropometric and metabolic parameters in obese children with his study. **Materials and methods:** This study was conducted at Child Health and Disease Clinic of Turgut Ozal University Faculty of Medicine between January 2014 and September 2014. The children's age were between 7 and 17 years. 29 obese girls and 27 obese boys were included in the study a total of 56 pubertal children. 27 girls and 29 boys were included in the study a total of 56 pubertal children as control group. Pubertal examination was performed according to Tanner stages. Tanner stage II was considered as pubertal. SATT was measured on the right ventricle by transthoracic echocardiography and cIMK by

high-resolution B-mode Doppler ultrasonography (USG) in all children in the obese and control group. Serum fasting blood glucose, fasting insulin, HOMA-IR, LDL and HDL cholesterol, total cholesterol, and triglycerides were measured biochemically. Height, body weight, BMI, and waist circumference were measured as anthropometric parameters. All parameters were compared between groups and within groups in this study, and evaluated for statistical significance. **Results:** The mean age was 12.9 ± 2.4 years in obese group and 12.9 ± 2.2 years in the control group. There were no statistically significant differences between obese group and control group in terms of average age, average height, mean fasting blood glucose, and mean right cIMK ($P > 0.05$). There were statistically significant differences in the average weight, BMI, waist circumference, fasting blood level, HOMA-IR, total cholesterol level, LDL cholesterol level, TG level, SATT, and left cIMK between the obese and control group ($P < 0.05$). All these paramaters were higher in the obese group than the control group. HDL cholesterol level was statistically lower in the obese group than the control group. There was a strong positive relationship between weight, BMI, waist circumference, fasting insulin, HOMA-IR and SATT; and a moderate positive relationship between LDL cholesterol and SATT. There was a moderate negative relationship between HDL cholesterol and SATT. There was a moderate positive relationship between weight, waist circumference and right cIMK. There was a moderate positive relationship between weight and left cIMK. **Discussion:** The lipid profile is impaired in childhood obesity with increasing BMI. Insulin resistance is observed, and SATT and cIMK values are increased. SATT and cIMK show a significant relationship with some of the anthropometric and metabolic parameters. These results indicate that SATT and cIMK could show the cardiovascular risk factors associated with childhood obesity. Childhood SATT and cIMK predict the problems that may arise secondary to obesity in adulthood.

P2-350

The Switch in Eating Behaviour in Infants with Prader–Willi Syndrome is Associated with an Increase in the Acylated:Unacylated Ghrelin Ratio: Results of a Longitudinal Study

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Background: Prader–Willi syndrome (PWS) is characterized by a switch from failure to thrive to excessive weight gain and hyperphagia with impaired satiety in early childhood. An elevated, more unfavorable ratio between acylated:unacylated ghrelin (AG:UAG) may be involved in the underlying mechanisms of this switch. **Objective and hypotheses:** To assess the evolution of the appetite regulating hormones AG, UAG, and the AG:UAG ratio in infants with PWS and to investigate their association with the switch in eating behaviour. **Method:** Longitudinal study in 36 infants with genetically confirmed PWS (age at inclusion 3 months–4 years). Serum AG and UAG levels were assessed 6-monthly for at least four times. AEBSF was used to inhibit deacylation of AG. **Results:** Both AG and UAG levels were high in infants with PWS. AG levels decreased from the age of 3 months–2.5 years and subsequently increased. UAG levels slightly decreased in the first 2 years of life and subsequently sharply decreased. This resulted in a decreasing AG:UAG ratio in the first 2.5 years and an increase after this age. Infants in nutritional phase 1a, with hypotonia and difficult feeding, had an elevated AG:UAG ratio, which normalized in phase 1b, where the infants had an appropriate growth without difficult feeding. In phase 2a and above, when patients gained weight and became hyperphagic, the AG:UAG ratio increased again. **Conclusion:** The switch in eating behavior in PWS is associated with an increase in AG:UAG ratio.

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Domino Liver Transplantation for the Pre-Emptive Therapy of Compound Heterozygous Familial Hypercholesterolemia: A Case of 2-Year-Old Girl

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Background: Patients with homozygous and compound heterozygous familial hypercholesterolemia (FH) have markedly elevated plasma LDL cholesterol (LDL-C) from birth. If untreated, patients develop cardiovascular atherosclerosis resulting in death before the second decade of life. Medication and apheresis are only partially effective in reducing LDL-C levels, and do not significantly improve the prognosis. Liver transplantation (LT) can nearly normalize the cholesterol metabolism. We report a first case received domino LT in early infancy as a pre-emptive, rather than preventive therapy for compound heterozygous FH. **Case presentation:** A 1-year-old girl was referred to our institution with xanthoma and hypercholesterolemia. Her serum cholesterol levels were extremely elevated; total cholesterol 1007 mg/dl and LDL-C 867 mg/dl. She was diagnosed as having FH with apparent family history in both parents. She has been treated on low-fat diet and medication with ezetimibe, bile acid sequestrants, and statins, however, maximal medical treatment could not lower her cholesterol levels. Genetic analysis revealed compound heterozygote for *LDLR* gene (c.IVS12 + 2T > C/c.418G > A), and enzyme assay showed 0% in lymphocytic LDL receptor activity. When she was 2-year-old, a cardiac catheterization was performed and no

pathological changes were found in coronary arteries. We recommended LT to the family before vascular changes occur. Living donor LT from the family was not recommended because of the elevation of LDL-C. Eventually there was an opportunity to perform domino LT from the donor with maple syrup urine disease, which was accepted by the family. Her cholesterol levels dramatically normalized right after the donor liver was fixed in her. Postoperative course was uncomplicated, and her xanthomas are gradually fading in color and regressing. **Conclusion:** LT for severe FH performed in early infancy before onset/progression of atherosclerosis is pre-emptive treatment rather than prevention. Domino liver transplantation is currently a good option of treatment for severe FH.

P2-352

Metformin Prescriptions as a Proxy for Paediatric Type 2 Diabetes Burden

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Background: Since metformin (MET), approved for treatment of type 2 diabetes (T2D), is the most commonly used oral anti-hyperglycaemic agent in youths MET prescriptions (Rx) could be used as a proxy for T2D burden in these populations. However, the extent of off-label use of MET in paediatrics is not well studied. **Objective and hypotheses:** Estimate the annual prevalence of $\geq$1 MET Rx among youths and calculate proportions with concomitant diagnoses of T2D and others. **Method:** Patients, 10–20 years old, from a large US claims database, Truven Health MarketScan, with $\geq$1 metformin Rx during 2009–2013 with $\pm$6 months continuous enrollment from the index MET Rx date were eligible. Prevalence proportions and 95% CI were calculated using Poisson regression. Diagnosis and procedure codes within $\pm$6 months of the index MET Rx were used to identify T2D and other medical conditions. **Results:** During 2009–2013, 22 387 patients (80% females and 83% 15–20 years of age) had $\geq$1 MET Rx. Annual prevalence proportions were consistent across years and were 0.39 (0.36, 0.41) and 1.13 (1.27, 1.34) $P=1.000$ for 10–14 and 15–20 age groups, respectively, in 2013. Among MET Rx patients, mutually-exclusive proportions with concomitant diagnoses were PCOS alone (23%), obesity alone (12%), PCOS and obesity (7%), T2D alone (10%), T2D with PCOS/obesity, or both (8%), or other diagnoses (40%). Sensitivity analyses on the subset of patients with $\geq$2 MET Rx within a 6-month window showed similar results. **Conclusion:** Within a large US claims database, only a minority of patients (18%) with $\geq$1 or $\geq$2 MET Rx had a diagnosis of T2D; the vast majority ($\sim$80%) had diagnoses other than T2D, suggesting that off-label use of MET is very common in youth in the USA. Therefore, the use of metformin Rx as a proxy for T2D in youth may grossly overestimate the burden of the disease. **Declaration of interest:** All authors are employees of Merck & Co., Inc., Kenilworth, NJ, USA. **Funding:** The study was funded by Merck & Co., Inc., Kenilworth, NJ, USA.

P2-353

A New Mutation of *PCSK1* Revealed by Neonatal Malabsorptive Diarrhoea, Panhypopituitarism, and Major Obesity

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Background: Proprotein convertase subtilisin/kexin types 1 and 2 (PCSK1 and PCSK2) are expressed in neuroendocrine tissues where they cleave a subset of inactive prohormones into biologically active hormones, including pro-opiomelanocortin (POMC), proTRH, proinsulin, proglucagon, and proGnRH. Congenital deficiency of PCSK1 is a very rare syndrome causing malabsorptive diarrhea contrasting with severe early-onset obesity and hypopituitarism. We described here a new case of congenital PCSK1 deficiency. **Case presentation:** The male proband was born in 2008 at 41 weeks of amenorrhea from consanguineous parents of Turkish origin, after an uneventful pregnancy. He presented macrosomia at birth (weight 4580 g and height 55 cm). Moderate dysmorphic features were noticed: macroglossia, bilateral clinodactyly of fourth and fifth toes, frontal bossing, mid-facial hypoplasia, depressed nasal bridge, and micropenis. He developed severe malabsorptive diarrhea with pancreatic exocrine insufficiency and recurrent hypoglycaemia immediately after birth. Nocturnal parenteral nutrition was necessary during 3 years. Endocrine investigations confirmed isolated GH deficiency at 2 months. Multiple pituitary hormone deficiency was diagnosed by the age of 3, including diabetes insipidus, central hypothyroidism, and hypocortisolism. Pituitary MRI was normal. He developed severe early-onset obesity and eating disorders with a BMI of 28 kg/m^2 at 6½ years. In view of the combination of chronic diarrhoea, rapid weight gain, and hypopituitarism, the possibility of PCSK1 deficiency was entertained. Fasting plasma insulin was normal (2.7 μU/ml; *n* 5–25) but proinsulin was very increased (300 pmol/l; *n* 3.3–28). Exome sequencing found a variant in PSK1 corresponding to a homozygous stop codon. In hg19, coordinates of isoform NM_000439 were chr5: 95757609-95757609; exon 5; c.C595T p.R199X. Considering the precocity of the stop codon, we expect for a haploinsufficiency of PCSK1, as already described mutations. **Conclusion:** We described a rare case of neonatal malabsorptive diarrhoea associated with panhypopituitarism and severe obesity caused by a new homozygous mutation in *PCSK1*.

P2-354

Overweight and Obesity in Childhood Cancer Survivors

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Background: Obesity is a potential late-effect of therapies for childhood cancer. Reported prevalence rates of obesity in childhood cancer survivors are heterogenous and currently unavailable for children treated according to protocols of the German Society for Paediatric Oncology. Furthermore, risk factors for the development of obesity following childhood cancer remain largely unknown. **Methods:** From a cohort of $n=149$ patients followed in a late-effects clinic, $n=52$ patients who were either survivors of ALL ($n=23$), M. Hodgkin ($n=16$), or solid tumors not involving the CNS ($n=13$) fulfilled the following inclusion criteria: follow-up ≥ 3 years after completion of therapy, no relapse, no genetic disorders, and additionally in the group of patients with solid tumors: no exposition to glucocorticoids and no amputations of extremities. **Results:** Average BMI percentile at diagnosis of oncological disease was significantly higher in patients with ALL (perc. 57.6 ± 32.7) and M. Hodgkin (perc. 51.9 ± 302) compared to patients diagnosed with solid tumors (perc. 27.9 ± 18.5, $P<0.01$). Obesity prevalence (defined as BMI >97th) increased in ALL-patients from 8% before therapy to 27% after completion of therapy and 23% after 3 years follow-up respectively. In the M. Hodgkin group, 13% were obese before therapy, and obesity prevalence remained stable throughout therapy and follow-up. No patient in the solid tumor group was affected by obesity. Patients with ALL or M. Hodgkin receiving higher doses of glucocorticoids ($>15\,000$ or $<15\,000$ mg/m^2 BSA cortisol equivalent dose), showed a trend towards a larger increase in BMI *Z*-score after 3 years follow-up (Δ BMI *Z*-score $+0.95$ vs $+0.61$, *P* NS). **Conclusions:** Our study confirms, that obesity is significantly more prevalent in patients with paediatric ALL compared to patients with M. Hodgkin or solid tumors. Longitudinal data demonstrates a marked increase of BMI *Z*-score during intensive therapy in ALL patients, which persists during midterm follow-up.

P2-355
Berardinelli Seip Congenital Lipodystrophy: A Light of Hope

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Background: The lipodystrophy syndromes are a heterogeneous group of congenital or acquired disorders characterized by either complete or partial lack of adipose tissue (lipoatrophy). Berardinelli Seip congenital lipodystrophy (BSCL) is a rare metabolic disorder characterized by severe generalised lipodystrophy since birth, insulin resistance, and dyslipemia since early infancy. **Case presentation:** We report a 6-year-old girl who arrived from Pakistan with the diagnosis of diabetes mellitus. She was the third baby, parental consanguinity was described in father grandparents. Antenatal and neonatal period was uneventful, adequate somatometry at birth was report. Almost from birth she presented generalized absence of fat and a prominent abdomen. Since the year before polyuria and polydipsia appeared, starting at that time with subcutaneous insulin. Clinical features: weight and stature were $<$P10, absent of adipose tissue almost completely except on mouth, palms, soles, and scalp. Protuberant abdomen due to 7 cm hepatomegaly. Acanthosis nigricans was present and a systolic murmur in aortic focus was listened. Biochemical analyses: glucose 14.8 mmol/l, normal total cholesterol concentration with low serum HDL, triglyceride 4.96 mmol/l, HbA1c 12%, insulin 5.3 μU/ml, and leptin 1.7 ng/ml. Gene mutation: AGPAT2 c.755_763delTGAGGACCA. After a year serum triglyceride raised to 6.45 mmol/l, glucose 16.6 mmol/l, and HbA1c 13.6%. Human recombinant leptin replacement was initiated as compassionate use by our reference hospital in Spain. Initial dosage was 0.87 mg/24 h, maximum 1.8 mg/24 h. After a year of treatment glucose serum levels decreased to 7.55 mmol/l, HbA1c 6.3%, and triglyceride levels 1.13 mmol/l. Leptin levels raised to 26.5 ng/ml. Stature increased up to ten percentiles and abdominal circumference decreased 6.5 cm. Appetite reduction was de unique adverse effect objectived. **Conclusion:** Human recombinant leptin is effective for controlling diabetes, hypertriglyceridemia and hepatic steatosis. Positive effects are notorious since the beginning of the treatment. No remarkable adverse effects where observed.

P2-356
Physical and Metabolic Evolution of Obese Children and Adolescents after the Attainment of Intense Weight Reduction

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Background: Despite the lack of drugs, conservative management of childhood obesity allows for considerable weight reduction. **Objective and hypotheses:** i) To evaluate anthropometric and metabolic changes in obese children after intense weight loss. ii) To analyze the influence of the amount of weight loss and the time spent to attain it on the observed changes. iii) To investigate BMI evolution during the first 3 years after weight reduction. **Method:** Out of 1300 obese children/adolescents evaluated, a prospective study was conducted in 132 (11.28 ± 2.83 years; 3.99 ± 1.93 BMI–SDS; 62.1% males; and 47.7% prepubertal) who reduced their BMI more than 1.5 SDS (52.1%)

and/or their weight over 10% (47.9%). Studied variables: glycaemia, insulin, HOMA, HbA1c, uric acid, lipid profile, and nutritional markers (25-OH-vitamin-D, proteins, albumin, and ferritin); raw weight difference and time gap from baseline (B) to weight reduction; BMI–SDS at 6 months and yearly up to 3 years after weight reduction. **Results:** Mean time to weight reduction was 0.79±0.60 years (35%, <6 months and 80.2%, <1 year), resulting in an increase in HDL and a decrease in the remaining parameters of the lipid profile, glycemia, insulin, HOMA (all $P<0.01$), with no nutritional impairment. No correlations were found between the magnitude in metabolic changes, the amount of weight lost, nor the time from baseline to weight reduction. Mean BMI–SDS remained unchanged during the first year after weight reduction (at baseline: 3.99±1.93 and at weight reduction: 2.69±1.21; 6 months after weight reduction: 2.35±1.29 ($n=114$) and 1 year after weight reduction: 2.67±1.69 ($n=72$)), with a partial regain during the second year (3.11±1.74 BMI–SDS ($n=41$)) and sustained BMI in the third year (3.16±2.51 BMI–SDS ($n=31$)). **Conclusions:** i) Conservative treatment allows for considerable BMI reduction in around 10% obese children/adolescents, resulting in metabolic improvement without impairment of nutritional status, independently of the time spent to achieve weight loss. ii) Attained weight loss can be sustained up to 3 years after its achievement. **Funding:** This work was supported by the CIBER Fisiopatología de la Obesidad y Nutrición (CB06/03) and the Instituto de Salud Carlos III, Fondo de Investigación Sanitaria (FIS: grant numbers PI10/00747 and PI13/02195).

P2-357
TG:HDL Ratio as Best Predictor for IGT Screening in Overweight Children

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Background: The prevalence of dysglycaemia is high among overweight children and adolescents. Current screening criteria with fasting laboratory values have low sensitivity to detect IGT. Fasting triglycerides (TG) >1.17 mmol/l has been proposed as a criterion for screening obese children and adolescents at risk for IGT. **Aims and objectives:** We aimed to compare the performance of different screening criteria for detecting IGT in obese and overweight children and adolescents. **Methods:** We studied a cohort of 307 Caucasian obese and overweight children and adolescents (age 11.4±3.2, range 3–18; 46% males, BMI 27.9±4.7, and range 20.4–47.6) who consecutively underwent clinical evaluation, fasting blood analysis, and oral glucose tolerance test (OGTT) in our Pediatric Endocrinology Unit from July 2011 to March 2013. We compared the discriminative properties of fasting glycaemia, TG, HDL, insulinaemia, HOMA index, HbA1c, and triglycerides:HDL (TG:HDL) ratio for the detection of IGT. The association of these variables with IGT was assessed by logistic analysis and by receiving operating characteristics (ROC). **Results:** After OGTT, 23 children (6.9%) presented an IGT. The 1.17 mmol/l TG threshold showed a 45% sensitivity and 83% specificity in detecting IGT. In logistic analysis, HDL and TG:HDL were the only variables significantly associated with IGT (HDL, $P=0.034$ and TG:HDL, $P=0.043$). TG:HDL presented the best area under the ROC (TG 0.658, TG:HDL 0.668, glycaemia 0.522, insulinaemia 0.539, HOMA 0.524, HbA1c 0.566, and HDL 0.624). The 0.8 threshold for TG:HDL presented the highest sensitivity (70%) and specificity (59.5%) in detecting IGT. **Conclusions:** The TG:HDL ratio presented the best predictive value for IGT screening in our cohort of overweight paediatric patients, while other fasting laboratory values presented a poor performance.

P2-358
Elevated Serum Irisin Level is not Related to Metabolic and Anthropometric Parameters in Obese Children

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Background: Irisin is a newly discovered myokine which regulates energy metabolism and obesity (type 2 diabetes pathogenesis). However, results of the clinical studies investigating the relation of irisin with metabolic and anthropometric parameters remain controversial, and studies in obese children are limited. **Objective and hypotheses:** We aimed to investigate the relation of serum irisin level with metabolic and anthropometric parameters in obese children. **Method:** The study included obese children with a BMI >95th percentile and healthy children (3-85th percentile). Healthy and obese groups had similar age and gender distribution. Waist circumference (WC) measurement and bioimpedance analysis were performed to asses body fatness. Fasting serum glucose, insulin, lipid profile, leptin and irisin levels were measured. **Results:** The study included 36 obese and 30 healthy children. Obese group had significantly higher BMI, BMI-SDS, WC, fat mas (kg), free body fat ratio (%), serum lipid level, insulin, and insulin resistance index by the homeostasis model assessment, systolic and diastolic blood pressure values when compared with the control group ($P<0.05$). Serum leptin and irisin level of the obese group was significantly higher than that of the control group ($P<0.01$). No statistically significant difference was found when leptin and irisin levels were compared among obese patients regarding the presence of insulin resistance ($P=0.202$). In the obese and control groups, irisin level was not

significantly correlated with any of the anthropometric and metabolic parameters ($P > 0.05$). **Conclusion:** This is the first study to evaluate irisin level in relation with leptin and body fat parameters in obese children, who had significantly higher irisin levels. We did not find any relation between irisin and anthropometric or metabolic parameters. We suggest that reasons for higher irisin level in obese children could be clarified with expanded studies accompanying status of the physical activity and muscle mass.

P2-359

FTO rs9939609 Polymorphism is Associated with the Presence of Obstructive Sleep Apnoea in Obese Youth

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Background: Emerging evidence suggests FTO polymorphisms are associated with obesity-related comorbidities including type 2 diabetes (T2DM), hypertension and polycystic ovarian syndrome (PCOS). However association of FTO with other comorbidities such as obstructive sleep apnoea (OSA) in paediatric populations is less clear. **Objective and hypotheses:** To investigate the prevalence of obesity-related comorbidities according to FTO genotype in an obese paediatric cohort. **Method:** Data were collected from patients attending the weight management service at The Royal Children's Hospital (Melbourne). Comorbidities assessed were; impaired glucose tolerance/T2DM, hypertension, hyperlipidaemia, non-alcoholic fatty liver disease, OSA, PCOS, mental health and eating disorders, orthopaedic and neurological disorders. A binary comorbidity score was assigned (range: 1–9), to assess additive risk. Genotype (FTO rs9939609 SNP alleles; Sequenom MassARRAY MALDI-TOF MS), activity levels (Actical accelerometry) and dietary consumption(Australian Food Frequency Questionnaire), were measured and collected. Data were statistically analysed using χ^2, one-way ANOVA and logistic regression as appropriate. **Results:** Amongst the 197 patients genotyped (age; 10.8 ($\pm$3.5) years, BMI-Z score; 2.44 ($\pm$0.44), male/female ratio; 91/106), 45 were risk allele homozygous (AA), 100 heterozygous (AT), and 52 non-risk allele homozygous (TT). There were no significant differences in anthropometric, biochemical or physical activity measures. Dietary survey analysis revealed minor differences between FTO genotype groups (vitamin A; $P=0.01$, retinol; $P=0.02$). Using recessive modelling, patients with AA genotype were twice as likely to have OSA than those with AT or TT genotypes, after adjusting for total percentage body fat (OR 2.21 (CI: 1.01–4.89), $P=0.04$) but not BMI-Z. No further effects of FTO genotype on other obesity comorbidities were observed. **Conclusion:** Recessive genotype FTO risk allele was associated with increased presentation of clinical paediatric OSA, independent of body fat percentage. FTO genotype may independently or synergistically magnify the burden of obesity-related comorbidities.

P2-360

Increasing Waist/Height Ratio and BMI Z-Score are Associated with Increased Comorbidities in Obese Youth, although Neither Accurately Identifies those with Abnormal Glucose Metabolism

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Background: At a population level, increasing age/sex corrected BMI Z-score (BMI-Z) is associated with increased risk of complications. It is unclear whether severity of obesity is a good predictor of comorbidities within groups of obese children. This knowledge is required to inform clinical management and pathways of care. **Objective and hypotheses:** In obese youth, to identify whether 1 increasing BMI-Z+/− waist/height ratio(WHtR) is associated with more comorbidities, and two activity levels and/or dietary factors show associations with comorbidities. **Method:** Anthropometric and comorbidity data were collected from obese paediatric patients attending the weight management service at The Royal Children's Hospital (Melbourne). Activity level (Actical accelerometry) and dietary consumption (Australian Food Frequency Questionnaire) data were additionally collected. Statistical analysis was performed using χ^2, one-way ANOVA, Pearson's correlation tests and linear regression as appropriate. **Results:** There were no significant differences in cohort demographics ($n=349$, male; 169, age; 10.6($\pm$3.6) years, BMI-Z; 2.46($\pm$0.46). Comorbidities were common in the cohort: hypertension (50%), IGT (38%), non-alcoholic fatty liver disease (NAFLD, 32.9%), hyperlipidaemia (23.9%), obstructive sleep apnoea (OSA, 22.3%), polycystic ovarian syndrome (14.4%), mental health disorders (11.4%), type 2 diabetes (3.6%), eating disorders (1.4%) and neurological complications (0.3%). Both increased WHtR and BMI-Z were associated with comorbidities, with WHtR being the better predictor ($P<0.01$). Neither was associated with IGT, fasting glucose or 2-h glucose. Lower daily vitamin C and higher vitamin A and retinol consumption were also significantly associated with comorbidities, while reduced activity levels showed no association. **Conclusion:** WHtR better associates with comorbidities than BMI-Z in an obese paediatric population, but neither predicts the presence of abnormal glucose metabolism. Alterations in dietary micronutrient consumption may be an important association for the development of comorbidities in this group of patients.

P2-361

Early Determinant Factors of Childhood Obesity

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Background: Incidence of Obesity in infants is increasing with the risk to continue till adulthood with the entire health burden that can produce. **Objective and hypotheses:** To elucidate the early factors that can determine obesity we studied a group of obese children (group 1) compared with a control group regarding, mode of delivery, breast feed and its duration, age at start of solid food, and how take care of the child. **Method:** 230 children (100 boys, 130 girls) were included in-group 1, BMI was ⩾ percentile 97, age was 5.5±0.5 years (M±DS), without hormonal or genetic abnormality. 210 children (94 boys, 116 girls) were included in-group 2, with normal weight for age and length and age of 5.2±0.6 years. A questionnaire was given to parents to answer regarding the four determinants included in the study. **Results:** No difference by sex was found. *Mode of delivery*: In the group 1, 190 children were born via caesarean section, while in group 2 only 80. *Breast feed*: in group 1: 80 children were fed for 6 month, 120 for 3 month, 30 were not breast fed. IN group 2; 112 were Brest fed for 6 months, 86 for three months, ten were not breast fed. *Age of Solid food introduction*: in-group 1 it was started at three month in 150 children, the rest in 6 months, in-group 2; 96 started at 3 months the rest at 6 months. *Caregiver*: the grandmother or a nurse cared for 180 children In-group 1, only 50 were taken care for by their mother. In-group 2; 150 were cared for by their mother, 60 were cared for by other person. **Conclusion:** Mode of delivery, breast feed duration, age at start of solid food and how cares for the baby seem to be the early determinant factors in the incidence of childhood obesity.

P2-362

Nonalcoholic Fatty Liver Disease and Intestinal Inflammation in Obese Children

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Background: The prevelance of pediatric obesity is increasing in childhood. Nonalcoholic fatty liver disease (NAFLD) is frequently associated with obesity, insulin resistance (IR), diabetes, and hypertriglyceridemia. Gut microbiota was suggested to play a role in both etiology of NAFLD and also progression to steatohepatitis. Feacal calprotectin (FCP) is a noninvasive marker of intestinal inflammation. **Objective and hypotheses:** To evaluate FCP and its association with IR and NAFLD in obese children. **Method:** The study included 63 obese children (33F), with a mean age of 12.4±3.1 years (range 6.0–18.0). Anthropometric measurements were obtained, BMI SDS was calculated and BMI >95% was defined as obesity. IR was expressed as HOMA-IR index from fasting glucose and insulin concentrations. FCP was measured by an ELISA test. Values >50 μg/g indicate intestinal inflammation and this level was accepted as the cut-off for FCP. NAFLD diagnosis was made by ultrasound. The patients were divided into two groups according to liver echogenicity as normal or NAFLD. **Results:** Age, BMI SDS, HOMA-IR, and FCP levels of patients with normal liver echogenicity and NAFLD are seen in the Table. There was a positive correlation between BMI SDS and HOMA-IR ($r=0.274$, $P=0.045$) but there was no correlation between FCP and BMI SDS or FCP and HOMA-IR. In high FCP (>50 μg/g) patients, NAFLD was seen in 92.6% while in patients with normal FCP, NAFLD was seen in 66.6% ($\chi^2=6.000$, $P=0.014$). **Conclusion:** FCP could be a helpful method during the follow up of obese children with NAFLD.

	Normal ($n=14$)	**NAFLD** ($n=49$)
Age (years)	13.3±3.5	12.1±2.9
BMI SDS	2.6±0.5	2.6±0.7
HOMA-IR	4.5±2.4	4.4±2.0
FCP (μg/g)*	31.0±21.5	75.3±71.7

Mean±S.D. are given. *$P=0.020$, Mann–Whitney U test.

P2-363

Sleep and Weight Status at 4 Years in the Inma Asturias Cohort

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Background: Epidemiologic studies have documented that sleep duration is associated with obesity risk children's. **Objectives:** To investigate sleep duration of 4-year-old children (h/day) and to evaluate the association of sleep patterns with weight status at 4 years. **Methods:** 393 children from the INMA birth cohort of Asturias (Spain). We analysed sleep duration (h/day) during the night and afternoon nap, reported by their parents, and BMI was calculated. Children were categorized as normal weight, overweight (OW) or obese (OB) according to the IOTF. Definition of 'short sleep' for children is usually <10 h. **Results:** 89–393 children were overweight or obese at 4 years. Total sleep duration (night and afternoon nap) were 10.43 h/day (1.04 S.D.) and according BMI were normal weight 10.4 (1.04), OW 10.51 (1.07), and OB 10.55 (1.06). There are not association between BMI at 4 years and sleep duration during the night or including afternoon nap. The risk of OW or OB according sleep duration is (OR raw

1.16, 95% CI 0.92–1.46; not statistical significance). After adjusting by gender, social maternal class, educative maternal level, physical activity, frequency of fruit and vegetable intake adjusted by calories and total calories intake, there is not statistical significance neither (OR adjusted 1.12; 95% CI 0.89–1.40). **Conclusions:** Our children slept a mean of 10.43 h/day. No association between sleep duration and weight status in 4-year-old children were found. Children included in other studies were older and slept fewer hours.

P2-364

Evaluation of Acylated Ghrelin and Obestatin Levels and Ghrelin:Obestatin Ratio in Obesity

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Background: Ghrelin is 28-amino acid peptide predominantly produced by the stomach and have an orexigenic property as well as potent GH-releasing activity. Acylated ghrelin (AG) is the active form of this hormone. Obestatin is a 23-amino acid peptide, is produced by post-translational modification of a protein precursor that also produces ghrelin. Obestatin has the opposite effect of ghrelin on food intake. **Objective and hypotheses:** To evaluate acylated ghrelin and obestatin levels in obese and normal weight children and adolescents and their association with metabolic syndrome parameters. **Method:** A total of 73 children and adolescents (31 normal weight control and 42 obese), aged 7–16 years, were recruited into study. Serum AG, obestatin, leptin, insulin (ELISA), fasting plasma glucose (FPG), triglyceride (TG), total cholesterol (TC), LDL-C, and HDL-C were measured. Insulin resistance was calculated by homeostasis model assessment of insulin resistance (HOMA-IR). MetS was determined according to IDF criteria. Data for AG and obestatin were presented as median (25th–75th percentiles). **Results:** AG levels were significantly lower in obese subjects compared to control group (58.1 (18.95–70.0)) pg/ml vs (124.12 (56.28–193.11)) pg/ml respectively ($P<0.001$). AG level was lower in obese children with MetS than subjects without MetS, 22.65 (14.92–64.0) pg/ml vs 60.0 (22.04–70.0) pg/ml respectively ($P<0.01$). On the other hand, obestatin levels were significantly higher in obese subjects compared to control group, 267.9 (193.6–450.3) pg/ml vs 180.8 (123.2–214.8) pg/ml respectively ($P<0.001$). Obestatin level was higher in obese children with MetS compared to those without MetS, 307.4 (160.7–497.4) pg/ml vs 227.9 (193.6–300.7) pg/ml respectively ($P<0.05$). AG:obestatin ratio was significantly lower in obese subjects compared to normal subjects 0.13 (0.07–0.26) vs 0.68 (0.36–1.3) respectively ($P<0.001$). AG had significant negative and obestatin positive correlation with BMI *Z*-score as well as TG, LDL-C, leptin, and HOMA-IR. **Conclusion:** Ghrelin is decreased and obestatin is elevated in obesity. So these are not the cause but are effect of it. Obestatin is a valuable marker to investigate MetS. **Funding:** This work was supported by Tehran University of Medical Sciences Research Council (grant number, 91-04-30-20238).

P2-365

A Novel *MC4R* Mutation Associated with Infancy-Onset Obesity

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Background: The melanocortin-4-receptor gene (*MC4R*) is a key regulator of energy homeostasis, food intake, and body weight which has intensively been analysed in molecular genetic obesity research. MC4R dysfunction in humans causes hyperphagia, impaired satiety and obesity. Most patients are heterozygotes, with some reports of homozygotes and compound heterozygotes. **Objective and hypotheses:** A 2-year-old boy with progressive weight gain from infancy admitted to the hospital with hyperphagia and increased linear growth. His parents were nonconsanguineous and his birth weight was 3650 g (0.50 S.D.). His height and BMI SDS was −1.86; 7.3 S.D. respectively. There was no phenotype of morbid obesity in the parents or sibling. In his laboratory analyses lipids, fasting glucose, and insulin levels were normal. Coding region of the *MC4R* gene was sequenced by Illumina MiSeq Next Generation Sequencing System. A novel c.870delG (p.I291SfsX10) homozygous mutation in *MC4R* gene was detected. By *in-silico* analysis softwares this novel mutation predicted to be disease causing and it is expected to have a 32 aminoacids shorter MC4R protein. Mother was shown to be a heterozygous carrier for the mutation. **Conclusion:** We present the molecular findings and clinical features associated with a novel *MC4R* mutation. This rare homozygous mutation in *MC4R* gene markedly impairs its function and is associated with early-onset obesity and hyperphagia. Investigating the mutations in *MC4R* gene in patients with severe childhood-onset obesity is useful for better patient management and is also important to detect the other family members with same condition. Preimplantation genetic diagnosis might be offered to the families who have mutations in *MC4R* gene in order to have healthy offsprings.

P2-366

Homozygous Mutation in *FBN1* Gene In-Patient with Prader–Willi Syndrome: Variant Marfan Syndrome?

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Background: Prader–Willi syndrome (PWS) is caused by absence of expression of imprinted genes on the paternal chromosome 15 (15q11.2–q13) due to a paternal deletion, maternal uniparental disomy 15 and rarely an imprinting defect. The clinical signs of PWS are hypotonia, muscle weakness, excessive eating, morbid obesity, delayed global development, hypogonadism, and short stature. Marfan syndrome is caused by mutations in the *FBN1* gene, located on chromosome 15 (15q21.1) , inherited in an autosomal dominant manner. It is a connective tissue disorder with cardinal features in the ocular, skeletal, and cardiovascular system. **Case presentation:** A 16-year-old boy with PWS, based on maternal uniparental disomy, showed more severe hypotonia, and muscle weakness compared to other children with PWS. He had myopia (−2.5) and a striking stature with a relatively low BMI (16.8 kg/m^2; −1 S.D.), a flat thorax, scoliosis, and increased joint laxity (a picture of the patient will be included in the presentation). The arm/height ratio was normal (1.02). DNA investigation showed a homozygous mutation (c.4075A>G, p.Ile1359Val) in the FBN1 gene. Opthalmological and cardiological screening revealed no abnormalities. His systemic score (Ghent criteria for Marfan syndrome) was 3, based on positive thumb sign, scoliosis, and pes plani. His mother carried the same *FBN1* mutation, in heterozygous state. She had no marfanoid features. The pathogenicity of this variant is yet unknown. Considering the presentation of our patient we suspect that in the homozygous state it may lead to a marfanoid phenotype. Both mother and son will be investigated regularly in our Marfan clinic. **Conclusion:** Uniparental disomy increases the likelihood of diseases due to recessive or mild dominant mutations. An abnormal presentation of a known disease could be a trigger for the search of a second genetic disorder.

P2-367

Residual Excess Weight Difference Between BMI 35–40 and Over 40 After Laparoscopic Sleeve Gastrectomy in Severely Obese Adolescents: Midterm Outcomes

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Background: Severe obesity among adolescents is increasing worldwide. Bariatric surgery is a controversial subject in this group of age, surgical timing is even more controversial. Patterns of surgical weight loss could be different between patients with greater excess weight, perhaps with less promising results. **Objective and hypotheses:** To compare anthropometric outcomes among adolescents with BMI 35–40 and over 40, underwent laparoscopic sleeve gastrectomy (LSG). **Method:** Descriptive, non-randomized, retrospective study, adolescent patients (15–19 years) with BMI >35 kg/mt^2, and comorbidities with 1 year of multidisciplinary medical treatment and failure in weight loss, underwent LSG between September 2009 and September 2014. **Results:** 59 patients, 37 females (63%), mean age 17.3 years±1.4 (15–19), mean weight 111.4 kg±20.6 (80.7–185), mean BMI 40±4.4 (35–54), and residual BMI 15±4.4 (9.9–29). Group BMI 35–40: 36 subjects, 23 females (64%), mean age 17.4±1.4 (15–19), mean weight 103.6 kg±12.7 (80.7–124.6), mean BMI 37.3±1.4 (35–39.7), and residual BMI 12.3±1.4 (9.9–14.8). Follow-up 6, 12, and 24 months: residual BMI of 2.09; 0.13; and 3.07 respectively. Group BMI >40: 23 subjects, 14 females (60%), mean age 17±1.3 (15–19), mean weight 123.7 kg±24.7 (92–185), mean BMI 44.3±3.9 (40–54), and residual BMI 19.3±3.9 (15.1–19). Follow-up 6, 12, and 24 months: residual BMI of 9.35; 3.9; and 7.4 respectively. The differences between the groups are statistically significant: 6 months $P=0.012$, 12 months $P=0.0053$, and 24 months $P<0.001$. **Conclusion:** Residual excess weight in the group with BMI >40 is significantly higher than the group with lower BMI, which keeps their comorbidities. This makes us reconsider the timing of the surgical indication. However, it is imperative to continue to follow these patients to agree on the controversy of this intervention in this age group.

P2-368

Effect of Visfatin on Gene Expression of Insulin Signaling Molecules in SW872 Adipocytes

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Background: To evaluate potential function of visfatin in SW872 adipocytes under the conditions which produce insulin resistance by free fatty acids (FFAs). Then to explore the mechanism of visfatin on the level of signal molecules. **Objective and hypotheses:** To evaluate the effects of visfatin on the mRNA expressions of the insulin signal molecules including insulin receptor substrate 1 (IRS1), IRS2, and phosphatidylinositol 3 kinase (PI3K) on the states of insulin resistant in SW872 adipocytes. We hypotheses that visfatin may promote the glucose transport and play a physiological role in the insulin resistance in SW872 adipocytes by modulating the signalling molecules of IRS1, IRS2, and PI3K. **Method:** Preadipocytes of the line SW872 were cultured and induced to differentiate to be mature SW872 adipocytes. Then the cells were treated with oleate at concentration of 1.0 mmol/l for 24 h to induce insulin resistance. And the cells were cultured with visfatin at concentration of 100 nmol/l for 1 h, then the mRNA was extracted. RT-PCR method was used to detect the mRNA levels of IRS1, IRS2, and PI3K. **Results:** The mRNA expression levels of IRS1, IRS2, and PI3K in SW872 adipocytes were significantly increased stimulated by 100 nmol/l visfatin.

Compared with control group, the mRNA levels of IRS1, IRS2, and PI3K were increased respectively by 36.54% ($P<0.01$), 12.81% ($P<0.05$), and 55.69% ($P<0.01$). In the insulin resistant states, after the stimulating of visfatin, the mRNA expression levels of IRS1, IRS2, and PI3K were increased by 26.98% ($P<0.05$), 35.59% ($P<0.05$), and 27.61% ($P<0.01$). In the insulin resistant states, compared with the control group (0 ng/ml visfatin group), the mRNA expression levels of IRS1, IRS2, and PI3K were decreased by 16.52% ($P<0.05$), 37.60% ($P<0.05$), and 31.68% ($P<0.01$); moreover their mRNA levels were decreased by 18.22% ($P<0.01$), 22.16% ($P<0.05$), and 33.47% ($P<0.01$) after the stimulating of visfatin. **Conclusion:** Taken together these data suggest that visfatin may promote the glucose transport and play a physiological role in the insulin resistance in SW872 adipocytes by modulating the signalling molecules of IRS1, IRS2, and PI3K.

P2-369

Childhood Obesity and Normocalcaemia with a *GNAS* Mutation also Present in Mother

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Background: Assessment in childhood obesity includes looking for obesity syndromes. Dysmorphic features should guide investigations. When clinical signs are subtle, genetic investigations aide diagnosis. A case (S) of progressive childhood obesity is described. He was found to have a pathogenic *GNAS* mutation which was also present in his mother. Both mother and son had a similar phenotype and did not have hypocalcaemia or PTH resistance described in pseudohypoparathyroidism type 1a (PHP1a). **Case:** S was referred at 6 years old for a growth assessment because of escalating weight from the age of 1 year. Birth weight at full term was normal at 3.66 kg. His height tracked along the 75th centile in his growth records and weight was above the 99.8th centile. S was well behaved and did not appear to have learning difficulties. On examination, S had mild rhizomelic limb shortening, brachyphalangy and no obvious shortening of the third or fourth metacarpals, no subcutaneous calcifications were palpable. His phenotype and digits were similar to his mother's. Mother's BMI was 35.5 kg/m^2. **Investigations:** Skeletal survey, oral glucose tolerance test, thyroid function, bone biochemistry, and PTH levels were requested. DNA was sent for the Genetics of Obesity Study and saved for further analysis. **Results:** Skeletal survey showed generalised brachydactyly and brachymetacarpia, especially the fourth and fifth. Fasting glucose 4.5 mmo/l paired with insulin 153 pmol/l, glucose at 120 min 6.1 mmol/l. Calcium 2.36 mmol/l (2.12–2.55) and PTH 6.1 pmol/l (1.2–9.3). Leptin concentration was normal for his percentage of body fat. Plasma insulin was raised but proinsulin and split proinsulin were normal. *GNAS* mutation analysis showed that he was heterozygous for R342Q, also present in his mother but not father and sister. **Conclusion:** PHP1a is usually caused by maternally inherited G(s) α loss of function mutations in the *GNAS* gene. This condition includes Albright's hereditary osteodystrophy (AHO) and hypocalcaemia with PTH resistance. Maternal, but not paternal, G(s)α mutations lead to obesity, as in S. However bone biochemistry and PTH was normal in S, suggesting variable renal tubular expression of this imprinted gene. Mutation in exon 12 of *GNAS* appears to be associated with normocalcaemia and obesity.

P2-370

Information Technology Supported Treatment of Obese Children and Their Families: A Pilot Study

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Background: Multiprofessional therapy programs for obese children and their families, including physical activity, nutritional, and behavioral interventions, have been shown to be effective, in group (MGP) as well as in individual (MIT) settings. However, due to limited personal and financial resources, <1% of children affected participate in such programs. **Objective and hypotheses:** Health IT systems (HIS) have the potential to improve therapy assisting families in different settings. A novel mobile application that accompanies obese children and their parents during everyday situations was developed. **Method:** A HIS offering physical activity, mood, photo documentation and eating speed services on a tablet PC was designed by specialists and children, with a secured direct transfer of usage data between home and centre. In a pilot observational study, usage as well as physical and psychological outcomes were explored for 7 months in each six children with HIS and group therapy (HIS-MGP) or individual therapy with HIS (HIS-MIT) or without HIS (C-MIT). Physical and mental health, motivation, eating disorders, well-being and parenting were assessed as previously described with nationally validated questionnaires. **Results:** In all groups likewise, children were extremely obese (total mean $\pm$ S.D.: BMI–SDS 2.9 $\pm$ 0.5, age 13.2 $\pm$ 3.4 years). Both in HIS-MGP and C-MIT, BMI–SDS decreased by 0.3 and 0.2 S.D., respectively, but not in HIS-MIT. Before and after therapy, there were no major group differences in the main outcome parameters. The trend ($P=0.07$) to reduce obesity under higher emotional strain was not reflected by HIS usage. Despite contracts with children and parents, HIS, mainly activity and mood services, were only used by those patients who were closely supervised by therapists or parents. Therapists found HIS to be helpful in coaching the patients. **Conclusion:** MGP and MIT are effective therapies. This pilot study cannot demonstrate that mobile Apps alone improve obesity therapy. Only under close supervision, HIS did simplify communication between therapist and patients. Further randomized controlled studies in less severely obese patients will prove whether a HIS with an automatic SMS reminder system in addition to a closely supervised therapy program can support lifestyle changes. **Funding:** This work was supported by the Swiss National Foundation (SNF grant number CR10I1_135552).

P2-371

Prevalence and Phenotypic Characterization of *MC4R* Mutations in a Large Paediatric Cohort

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Background: The melanocortin-4-receptor (MC4R) plays a key role in body weight regulation. Hypothalamic activation of MC4R reduces food intake and increases energy expenditure. Mutations in the *MC4R* gene lead to the most common cause of monogenetic obesity. More than 150 different mutations are currently known. Their prevalence in obese subjects differs between 0.2 and 5.8%, depending on ethnicity, age and grade of obesity of the analysed cohort. Impact on phenotype and metabolic characteristics is still debated; a MC4R syndrome with early onset obesity, increased linear growth and hyperinsulinaemia is claimed. **Objective and hypotheses:** In a large German cohort of obese paediatric outclinic patients we aim to determine the prevalence and whether there is a specific phenotype as mentioned. **Method:** 899 individuals were screened for coding *MC4R* mutations by DNA sequencing after PCR amplification. Further on statistical analysis of metabolic features and metrics traits was performed in the whole cohort and in a matched case–control setting. Individuals were matched for age, sex, and BMI–SDS. **Results:** In total we found 22 carriers of heterozygous mutations (2.45%), of these 14 (1.56%) carriers had a mutation with impaired receptor function. One new nonsynonymous and one new frameshift mutation were detected. Regarding the whole cohort, mean height-SDS of MC4R deficient subjects was greater than of WT subjects at all ages. In matched individuals this trend persisted (eight of 11 pairs). No differences were found in glucose and insulin levels of matched pairs performing an oral glucose tolerance test. **Conclusion:** Prevalence of mutations with impaired receptor function is comparable to other paediatric cohorts. MC4R deficiency tends to a taller stature, confirming previous clinical reports. This finding might be explained by decreased somatostatin mRNA expression like it is found in Agouti-related protein overexpressing mice. Hence GH secretion is possibly not as suppressed as normally seen in obesity.

P2-372

The Effect of *ABCA1* Gene C69T Single Nucleotide Polymorphism on Dyslipidemia and Insulin Resistance in Obese Children

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Background: ATP-binding cassette transporter A1 (ABCA1) mediates the transport of cholesterol and phospholipids from cells to lipid-poor apolipoproteins. It has been demonstrated that the *ABCA1* gene C69T single nucleotide polymorphism (SNP; TT genotype) is associated with lower HDL cholesterol and higher triglycerides (TG) levels. The relation of this polymorphism with type 2 diabetes mellitus has also been shown. **Objective and hypotheses:** As dyslipidemia and insulin resistance are important characteristics of the metabolic syndrome (MS), we aimed to investigate the role of the C69T SNP of the *ABCA1* gene on MS parameters in obese children. **Method:** A total of 284 obese children were enrolled to the study. Children were diagnosed as MS according to International Diabetes Federation definition. The frequencies of different genotype of the *ABCA1* gene C69T SNP in simple obese and MS groups were investigated. The parameters of the dyslipidemia, insulin resistance, and hypertension were compared according to different genotype of the *ABCA1* gene. **Results:** The 105 of the 284 obese children had MS (36.9%). There was no statistical difference between simple obese and MS groups regarding the frequencies of investigated SNP (P 0.829). However, children with TT genotype had lower HDL levels (40.51 ± 9.11 vs 45.35 ± 9.50, P 0.031) and higher HOMA-IR levels (7.67 ± 5.29 vs 5.63 ± 3.79, P 0.037) than CC genotype carriers. **Conclusion:** Although the direct relation of *ABCA1* gene C69T SNP with MS could not be demonstrated, it has been shown that the TT genotype worsens dyslipidemia and insulin resistance parameters in obese children. **Funding:** This work was supported by the Bezmialem Vakif University Research Council.

P2-373

Obese 5 Years Old Remain Obese at Age 12

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Background: Childhood obesity starts in early childhood. The natural history of childhood obesity has not been reported and it is unknown how obese children in early childhood improve to become non-obese adolescents. **Objective and hypotheses:** To investigate the natural history of obese children from early childhood to puberty and identify patterns and trends in this process. **Method:** 1207 children (614 boys and 593 girls) born in Fujioka town and Otawara city in Tochigi prefecture, Japan, were enrolled in this study. Height and weight were measured at 5, 6, 8, and 12 years of age. Obesity was characterized by an excess of $\geq +15$ and $\geq +20\%$ standard body weight at 5 and ≥ 6 years of age respectively. We calculated the percentage of children who remained obese at 12 years of age. **Results:** At the beginning of the study, 133 (11.0%), 152 (12.6%), 244 (20.2%), and 235 (19.5%) children were obese at age 5, 6, 8, and 12 respectively. 85 (63.9%) of 133, 110 (72.4%) of 152, and 166 (68.0%) of 244 children were still obese at age 12. 50% of the children who showed light obesity ($\geq +20$ and $< +30\%$ excess body weight) at 5 years of age were not obese at 12 years of age, whereas only 10% of the children who

were severely obese ($\geq +50\%$ excess body weight) at age 5 were not obese at age 12. Interestingly, among children who were obese at 5 years of age, boys remained obese at 12 years in high prevalence compared to girls. **Conclusion:** Greater than 60% of the obese children in early childhood remained obese at 12 years of age. This endorses the importance of prevention and intervention of obesity before age 5.

P2-374

Lifestyle Habits and Arterial Hypertension in Children and Adolescents

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Background: Elevated blood pressure (BP) may occur from childhood, increasing the risk for hypertension in adulthood. **Aim:** To investigate the effect of anthropometric characteristics and lifestyle habits in children's and adolescents' BP. **Methods:** 949 children (<12 years old) from Lakonia, 178 teenagers (12–18 years old) from Athens and 372 from Kalamata, Greece, had participated during 2011–2014. A specially designed questionnaire was used and anthropometric and biochemical analyses were performed. **Results:** Elevated BP was found in 39% boys and 29% girls. In the teenagers' population: 23% of boys and 12.1% of girls in Kalamata, and 35% of boys and 59% of girls living in Athens had high BP. With statistical importance ($P \leq 0.05$) we observed a positive correlation between BP, BMI%, and waist circumference (WC%) in children. Regarding their eating habits, the consumption of cereals, olive oil, and fast-food increased BP while vegetables decreased it. Regarding children's sleep habits, sleeping late (after 2200 h) was positively correlated with BP, while night sleep duration and siesta was negatively correlated with BP. In adolescents living in Athens and Kalamata, a positive correlation between BP, BMI% and WC% was found. Lack of breakfast consumption was positively correlated with BP, in both populations. Legumes and fruits seemed to decrease BP while rice, cereals and sweets seemed to increase it. In the adolescents of Athens, dairy products increased BP while in Kalamata fish consumption decreased BP. In Athens, the hour when adolescents go to bed was positively correlated with BP. 57.86% of them, watch television during meals, which is positively correlated with WC% and BP. In the total population of children and adolescents in all areas we found that a family history of cardiovascular diseases and diabetes was associated with high BP. **Conclusions:** In an effort to prevent complications like heart or renal failure it is necessary to preserve appropriate lifestyle habits.

P2-375

The Relation of Serum Nesfatin-1 Level with Anthropometric and Metabolic Parameters in Korean Children and Young Adolescents

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Background: Nesfatin-1, a recently discovered anorexigenic neuropeptide, seems to play an important role in hypothalamic pathways regulating food intake and energy homeostasis. **Objective and hypotheses:** The aim of this study is to evaluate the relation of serum nesfatin-1 level with anthropometric and metabolic parameters in children and adolescents. **Method:** This study included 78 Korean children and adolescents (42 obese/overweight group and 36 healthy control group). Fasting serum nesfatin-1 was quantitatively assayed by ELISA. Lipid profile, fasting blood glucose, fasting insulin, and the homeostasis model assessment of insulin resistance (HOMA-IR) were measured as metabolic parameters. **Results:** Serum nesfatin-1 was significantly lower in obese/overweight group than in control group (median 1.4 ng/ml vs 2.0 ng/ml; $P=0.003$). Pubertal subjects had the lower serum nesfatin-1 level than pre-pubertal subjects (median 1.5 ng/ml vs 2.6 ng/ml; $P=0.02$). Nesfatin-1 level was negatively correlated with BMI SDS ($r=-0.26$; $P=0.02$) and chronological age (CA; $r=-0.37$; $P=0.001$). The association of BMI SDS with serum nesfatin-1 level was evident among prepubertal subjects ($r=-0.38$; $P=0.04$), but it was not evident among pubertal subjects. The negative correlation between CA and serum nesfatin-1 was not evident among prepubertal subjects, but it was evident among pubertal subjects ($r=-0.30$; $P=0.04$). Serum nesfatin-1 was not correlated with fasting insulin, HOMA-IR, or lipid profiles. **Conclusion:** Our results suggest that serum nesfatin-1 is negatively associated with adiposity and pubertal development during childhood and adolescence.

P2-376

Metabolic Syndrome Components of Normal Weight Central Obese Adolescents in Korea Stratified by Waist-To-Height Ratio: Results from K-NHANES 2008–2010

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Background: A subset of central obese but normal weight individuals has been identified, who harbor potentially increased risks for development of MS despite a normal BMI. **Objective and hypotheses:** We try to evaluate metabolic syndrome (MS)

components of normal weight central obese adolescents in Korea stratified by waist-to-height ratio (WHR). **Method:** This is a cross-sectional study. Data were obtained from the Korean National Health and Nutrition Examination Survey conducted during 2008–2010. The subjects were grouped as normal (5th–85th percentiles) or overweight (≥85th percentile) by BMI and central obesity was defined as those in the upper highest quartile of age and sex specific WHR. Body composition groups were classified into no central obesity normal weight (NW), central obesity normal weight (CONW), no central obesity overweight (OW), and central obesity overweight (COOW). **Results:** The prevalence of NW was 72.7% (604/832), CONW was 9.6% (83/832), OW was 2.5% (20/832), and COOW was 15.1% (125/832) in females. The prevalence of NW was 72.3% (662/909), CONW was 7.0% (61/909), OW was 2.2% (21/909), and COOW was 18.5% (165/909) in males. In females, CONW showed higher levels of insulin ($P<0.006$), HOMA-IR ($P<0.006$), and ALT ($P<0.001$) than NW. In males, CONW had higher levels of insulin ($P<0.0001$), HOMA-IR ($P<.0001$), and WBC count ($P<0.021$) and lower level of HDL ($P<.0001$) than NW. However, there was no significant difference in MS components between CONW and OW in both females and males. WHR had significant positive correlations with BMI, insulin, HOMA-IR, and ALT in females. WHR also had significant positive correlations with BMI, insulin, HOMA-IR, TG/HDL ratio, and ALT, WBC and a negative correlation with HDL in males. In males, CONW showed 2.5 times (95% CI, 1.21–5.00) more likely to having high insulin resistance than NW after adjusting for age, weight, and ALT. **Conclusion:** The use of WHR has discovered CONW. The CONW has higher insulin resistance than NW in male Korean adolescents.

P2-377

The Effect of Exenatide on Weight and Appetite in Overweight Adolescents and Young Adults with Prader–Willi Syndrome

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Background: Prader–Willi Syndrome (PWS) is a genetic disorder associated with hyperphagia and hyperghrelinemia with major morbidity due to obesity. The aetiology of hyperphagia is unknown, but presumed to be multifactorial, and, as ghrelin is orexigenic, high levels may contribute to weight issues in PWS. Currently, there is no effective medical treatment for hyperphagia in PWS, but targeting appetite could be beneficial. Exenatide (Byetta (synthetic exendin-4); AstraZeneca) is a GLP1 receptor agonist which reduces appetite and weight. In rodent studies, exendin-4 decreased ghrelin levels. Thus, exenatide may be an effective treatment in PWS. **Objective and hypotheses:** The objective of this pilot study was to determine the effect of a 6-month trial of exenatide on appetite, weight, and gut hormones in youth with PWS. **Method:** Ten overweight or obese subjects with PWS (13–25 years) were recruited for an open-label, non-randomized, 6-month longitudinal study using standard exenatide dosing. Primary outcomes were weight, BMI, truncal fat, appetite, and acylated (active) ghrelin at 0,1, 3, and 6 months and during mixed meal tolerance tests (MMTT) at 0 and 6 months. A syndrome-validated appetite questionnaire, DXAs, anthropometrics, and metabolic markers were assessed. Consistent caregivers completed questionnaires with possible scores between 11 and 55 (higher values = higher appetites). No dietary modifications were made. Data are presented as mean ± S.D. and within-subject changes between visits were analysed by mixed model repeated measures. **Results:** Total appetite scores significantly decreased from baseline (32.2 ± 8.7) after 1, 3, and 6 months of treatment (27.5 ± 8.8, 25.4 ± 9.3, and 25.4 ± 7.2, respectively; $P=0.004$). However, there were no significant changes in weight, BMI Z-score, or truncal fat. There was no significant change in fasting or ghrelin excursion during MMTT based on area under the curve data. There were no significant adverse events. **Conclusion:** Exenatide was safe and effective in decreasing appetite in youth with PWS, without decreases in weight or BMI in the short term. Larger, controlled, longer-term trials are needed to confirm the safety and efficacy of exenatide, and to evaluate whether its use might induce weight loss when given in conjunction with behavioral modification. **Funding:** Department of Endocrinology, Children's Hosptial Los Angeles (CHLA) Merit Fund (8030-RR1000019-00, $30,000, 2011), NIH NCRR CTSI grant (1UL1RR031986, $10,000, 2011), and Amylin Pharmaceuticals (now AstraZeneca) (2011-E-0389, drug only, 2011).

P2-378

Early-Onset Obesity and Adrenal Insufficiency Associated with a Homozygous *POMC* Mutation

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Background: Isolated hypocortisolism due to ACTH deficiency is a rare condition that can be caused by mutations in the gene encoding pro-opiomelanocortin (POMC). POMC is the precursor to bioactive peptides (ACTH, β-endorphin, and

α-β-γ-MSH). Mutations that inactive POMC typically result in secondary adrenal insufficiency, severe obesity and red hair; fewer than 50 affected individuals have been reported in the literature. **Case presentation:** A 10-month-old female was referred to our clinic for macrosomia and delayed psyco-motor development. She was the only child to consanguineous Pakistani parents (first cousins), whose family history was not relevant. She was born full-term through spontaneous vaginal delivery (weight 3170 g, length 52 cm, and head circumference 35.8 cm) and neonatal hypoglicemia was reported; since 3 months of age she showed hyperphagia with marked weight and length gain. At the first clinical evaluation, her weight was 15 kg, length was 82.5 cm (both $\gg$97th percentile), and head circumference 50 cm (97th percentile). Neurological examination showed axial hypotonia and delayed motor milestones. Facial dismorphysms (telecanthus, strabismus, wide nasal bridge), pale skin, and dark-brown hair were noted. Laboratory work-up (routine, α-fetoprotein, CEA, β-HCG, metabolic studies, and karyotype) was normal. Thyroid hormones, prolactin, GH, IGF1, and insulin levels were normal, while ACTH and cortisol were very low ($<$5 pg/ml and $<$10 μg/l respectively). Brain MRI showed pituitary hypoplasia and partial hypotrophia of corpus callosum. Congenital ACTH deficiency was diagnosed and substitutive therapy with hydrocortisone was started. Due to severe obesity and adrenal insufficiency, although the patient did not have red hair, POMC deficiency was suspected. Gene sequencing of POMC revealed an homozygous c256C$>$T change causing a stop codon (R86stop), inherited from the heterozygous parents. **Conclusion:** *POMC* gene mutation should be considered in patient with early-onset severe obesity and secondary adrenal insufficiency, even without red hair. Adrenal insufficiency should be treated as usual, while the management of obesity in POMC deficiency remains challenging.

P2-379

Clinical and Laboratory Differences between Metabolically Healthy and Unhealthy Obese Children

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Background: Some obese children are metabolically healthy obese (MHO), while some are metabolically unhealthy obese (MUO) having dyslipidemia and/or insulin resistance which increase mortality and morbidity related to cardiovascular diseases during adulthood. **Objective and hypotheses:** This study is designed to assess factors affecting metabolic condition in obesity and compare clinical and laboratory findings between MHO and MUO children. **Method:** In total 1085 obese individuals aged 6–18 years (mean 11.1$\pm$2.9 years, 57.6% females, and 59.7% pubertal) with age- and sex-matched BMI above 95th percentile were included in the study. Cases without dyslipidemia, insulin resistance, hepatosteatosis, and hypertension were considered as MHO. Dyslipidemia was defined as total cholesterol $>$200 mg/dl, triglycerides $>$150 mg/dl, LDL $>$130 mg/dl, or HDL $>$40 mg/dl. Insulin resistance was evaluated using HOMA-IR index. Obesity duration, physical activity, eating habits, screen time, parental obesity, serum levels of TSH, free T_4, ALT, AST, and hepatosteatosis in ultrasonography were also assessed retrospectively. **Results:** Six hundred forty-two (59.2%) cases were MHO. Older age, sedentary life style, male gender, and higher BMI SDS was associated with being MHO. Rare/non consumption of junk food was predictive for good metabolic condition only in prepubertal obese cases. In MUO group serum free T_4 levels were lower; TSH was higher. **Conclusion:** Active life style and restriction of junk-food consumption are the major parameters to prevent metabolic disorders in obesity.

P2-380

Insulin Resistance and Abnormal Glucose Tolerance After Paediatric Hematopoietic Stem Cell Transplantation in Blood Cancer Survivors

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Background: Patients who had undergone hematopoietic stem cell transplantation (HSCT) during childhood have been reported to have a higher risk of early metabolic syndrome (MS) and diabetes mellitus (DM) with a consequent increased risk of cardiovascular disease. Previous studies reported a cumulative incidence of abnormal glucose tolerance of 11.6% at 5 years from HSCT and of 69.3% at 10 years and a prevalence of MS of 32% at 4 years from HSCT. **Objective and hypotheses:** Assess the prevalence and potential risk factors for MS and abnormal glucose tolerance in young patients who underwent pediatric HSCT. **Method:** This is a single-centre, prospective, descriptive, and cross-sectional study. Clinical and laboratory data including oral glucose tolerance test (OGTT) of 45 blood cancer survivors treated with HSCT (mean age: 13.9$\pm$4.8 years) and 95 matched healthy controls (mean age: 13.8$\pm$4.9 years) were analysed. **Results:** *7/45 patients (15.5%) showed impaired glucose tolerance (IGT) or DM, 1/45 (2.2%) was obese and none fulfilled the criteria for MS. Abdominal adiposity (waist-to-height ratio $>$0.5) was more common in IGT/DM patients, in comparison with both normal glucose tolerance patients (NGT) and controls. Analysis of insulin resistance/sensitivity indexes suggested an insulin-resistant state in HSCT survivors (both NGT and IGT/DM patients) compared to controls. In IGT/DM patients, the use of total body irradiation (TBI) during the conditioning regimen was significantly more common, and the time elapsed from HSCT was significantly longer than in NGT patients. **Conclusion:** Blood cancer survivors treated with HSCT may develop insulin resistance early after

transplantation, showing redistribution of fat tissue with central fat accumulation despite a normal BMI. The main factors associated with increased metabolic risk are TBI and time from HSCT. Evaluation of MS and glucose tolerance should be part of hormonal follow up, which should be routinely proposed to these patients in order to prevent cardiovascular disorders.

P2-381

Metformin in Combination with Lifestyle Changes Effectively Reduces BMI and Waist Circumference in Overweight/Obese Children and Adolescents

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Background: Overweight (OW) and obesity in paediatric population has been shown to be associated with an increase in prevalence of insulin resistance and type 2 diabetes (T2D) in youth. **Objective and hypotheses:** The aim of this study was to assess the efficiency and safety of metformin use in combination with lifestyle changes or alone for weight management in OW and obese (OB) children and adolescents. **Methods:** Study included 145 10–17 years old OW (BMI 1.0–2.0 S.D.) and OB (BMI $\geq$2.0 S.D.) children and adolescents of age. Study participants were randomised into four groups: group 1 – controls ($n=33$), group 2 – lifestyle changes with two-times weekly swimming pool exercise and monthly dietologist consultations ($n=26$), group 3 – metformin treatment ($n=21$), and group 4 – metformin treatment in combination with lifestyle changes ($n=32$). Anthropometric parameters were evaluated in all study subjects at baseline and after 12 months of intervention. **Results:** Mean age of study participants was 13.4$\pm$2.0 years; 44.1% were boys; 32.6% were OW, others – OB. Reduce in BMI, waist circumference (WC), and WC–SDS adjusted by gender and puberty stages was significantly greater in the group 4 compared to the group 1 (Δ $-1.07\pm$ 2.8 kg/m^2 vs Δ 0.18$\pm$2.1 kg/m^2, $P=0.029$; Δ -4.5 ± 5.7 cm vs Δ -1.8 ± 5.2 cm, $P=0.04$, and Δ -0.85 ± 0.8 vs Δ -0.38 ± 0.7, $P=0.009$ respectively). Changes in these parameters in other groups compared to group 1 were not significant. Initially, mild side effects of metformin (nausea and diarrhoea) were observed in 21.6% of subjects from groups 3 to 4, which disappeared within 1 week of metformin administration. **Conclusion:** Twelve months metformin treatment with lifestyle modification was effective and safe method reducing BMI and waist circumference in OW/OB children and adolescents, superior to that of lifestyle changes alone. **Funding:** Lithuanian Research Council (grant number MIP-039/2013), grant from Research Foundation of Lithuanian University of Health Sciences (2013).

P2-382

Insulin-Like Factor 5 –A Novel Orexigenic Hormone in Humans is Dysregulated in Obesity

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Background: Insulin-like factor 5 (INSL5), a member of the insulin superfamily, is expressed in the colorectum and hypothalamus. INSL5 levels are elevated by prolonged calorie restriction and declined with feeding, suggesting that it might be an orexigenic hormone. **Objectives and hypotheses:** Our aim was to explore the relationship between INSL5 and different metabolic parameters in lean and obese subjects and to identify possible links between INSL5 and the development of metabolic disorders such as obesity and diabetes. **Methods:** INSL5 was measured in serum samples by ELISA. 20 lean and 20 obese females and males were included. 15 morbidly obese patients were tested before and 6 months after they underwent bariatric surgery. We measured INSL5 levels in ten lean and obese individuals after an overnight fasting, after a meal and during an oral glucose tolerance test (OGTT). For all groups, correlations between INSL5 concentrations and anthropometric, metabolic and hormonal measures were investigated. **Results:** Serum levels of INSL5 were significantly higher (by 25.5%, $P<0.05$) in lean females compared to lean males. This gender specific difference was not observed in obese subjects. Basal INSL5 was significantly lower in the obese group (by 28.6%, $P<0.05$). Levels of INSL5 were negatively correlated to testosterone in lean and obese males and positively to insulin and glucose in both genders. After bariatric surgery males lost 25% of their body weight, increased their testosterone levels (by 97%) and reduced INSL5 levels (by 17.4%). Obese subjects with type 2 diabetes (T2DM) had lower INSL5 before and after surgery compared to obese persons without T2DM. Food consumption decreased INSL5 levels in lean females (by 21.8%) and males (by 20.8%), while interestingly this effect was not observed in obese individuals of both genders. **Conclusion:** The fact that the gender-related difference in INSL5 was observed only in lean individuals suggests that INSL5 regulation is dependent on the metabolic state. Negative influence of insulin resistance and T2DM on INSL5 in obese individuals may indicate a link between beta cell function and INSL5 regulation. Therefore, INSL5 may become an interesting target for the development of new therapeutic agents to treat metabolic disorders. **Funding:** ESPE Research Fellowship.

P2-383

Tryptophan Supplementation as Conjunctive Therapy to Life Style Changes in Obese Adolescents

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Background: The correlation between obesity and depression is well established. Tryptophan (Trp) is an essential amino acid that acts as substrate for serotonin and melatonin biosynthesis, both know to play a role in satiety, anxiety, and depression. Furthermore, low plasma Trp levels have been associated with obesity. **Objective:** To investigate the effects of Trp supplementation as a conjunctive therapy to conventional life-style intervention on weight loss and psychological wellbeing. **Methods:** Randomised double-blind placebo-controlled clinical trial with parallel groups. Obese children (BMI 2–4 SDS) ages 12–17 were assigned to either Trp supplementation (3.5 mg/kg per day) or placebo as a conjunctive therapy to the conventional life-style intervention. Both groups received nutritional education, behavioral counseling and exercise recommendations of equal intensity throughout the 6 months intervention. The study was conducted at a university hospital and was approved by the Institutional Review Board. **Results:** 43 patients were enrolled and 40 completed the study (19 assigned to Trp group and 21 to placebo). There were no significant differences on the baseline characteristics between study groups. After a 6 months intervention both groups showed a significant reduction in BMI *z*-score and total caloric intake ($P<0.01$). BMI reduction tended to be greater in the tryptophan group (ΔBMI *z*-score -0.33 ± 0.05 in Trp *vs* -0.20 ± 0.05 in placebo, $P=0.078$). Trp supplementation improved depression and anxiety scores, based on IDER and CMAS-R scale ($P<0.05$), suggesting an impact on psychological wellbeing. No significant differences between groups were found for other variables. **Conclusion:** In our study Trp supplementation in obese adolescents in conjunction with life-style intervention improved some aspects of psychological wellbeing and showed a tendency to greater weight loss with no significant effect on caloric intake. Given our results and the lack of successful treatments, further studies are needed. **Funding:** Fondo Investigaciones Sanitarias del Instituto de Salud Carlos III (EC10-148).

P2-384

Obesity in ROHHADNET Syndrome: Does Cortisol Play a Role?

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Background: ROHHADNET syndrome is characterised by rapid onset childhood obesity, hypoventilation, variable hypothalamic-pituitary and autonomic dysfunction, and neuroendocrine tumors in 30–40%. Autoimmunity and paraneoplastic syndrome have been proposed as possible pathophysiological mechanisms, but the exact aetiology remains unclear. **Objective and hypotheses:** We present the clinical course of ROHHADNET syndrome in a 17-year-old girl, with consecutive symptoms indicated in her growth chart. **Method:** Case report. **Results:** At the age of 4 years, the girl presented with rapid weight gain and a decline in linear growth. IGF1 was low, but low GH concentrations in stim tests were judged as false positive, secondary to obesity. In subsequent years, she was diagnosed with central hypothyroidism and diabetes insipidus, initially with normal adrenal axis functioning. Because of persisting low IGF1, GH treatment was started at the age of 10 years, after which impressive weight loss occurred. Shortly thereafter, low dose hydrocortisone treatment was started because of presumed ACTH deficiency, after which she regained 15 kg of weight. Discontinuation of hydrocortisone resulted in weight loss, but an Addisonian crisis at the age of 15 years necessitated restarting low dose hydrocortisone treatment with concurrent weight gain. 3 years after the accidental finding of a chest ganglioneuroma, ROHHADNET was suspected and severe central hypoventilation was discovered. **Conclusion:** Because of the still unknown aetiology of this orphan disorder, detailed case descriptions can be helpful in unravelling the pathophysiology and maybe the aetiology of ROHHADNET syndrome. This case report learns that low IGF1 concentrations should trigger towards the diagnosis of growth hormone deficiency in obese patients. Furthermore, neuroendocrine tumors in combination with hypothalamic-pituitary dysfunction should lead directly towards the syndrome diagnosis. Lastly, this girl seemed to exhibit greatly increased cortisol sensitivity, resulting in extreme weight changes. This new observation may be a clue to the cause of obesity in ROHHADNET syndrome.

P2-385

TNFα Downregulates CIDEC *Via* MEK/ERK-dependent PPARγ Phosphorylation and Nuclear Exportation in Human Adipocytes

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Background: Cell death-inducing DFF45-like effector C (CIDEC) is a novel lipid droplet-coating protein that promotes triglyceride accumulation and inhibits lipolysis. TNFα downregulates CIDEC levels to enhance basal lipolysis, while CIDEC overexpression could block this effect. However, the signalling mechanism by which TNFα regulates CIDEC expression in human is still unknown. **Objective and hypotheses:** The aim of this study was to investigate the signalling pathway of TNFα-mediated CIDEC downregulation in human adipocytes. **Method:** We first

detected CIDEC expression by RT-PCR in human adipose tissue of lean and obese subjects. Next, using fully differentiated human adipocytes, we investigated the temporal and dose-dependent effects of TNFα on CIDEC levels. Both MAPK inhibitors and siRNA were used to suppress ERK cascade activated by TNFα. Furthermore, we resorted to subcellular fractionation technique and immunostaining to study PPARγ localisation after TNFα treatment. Reporter assay was performed to confirm the direct effects of TNFα on CIDEC promoter. **Results:** CIDEC expression was markedly decreased in obese subjects and negatively correlated with adipose TNFα levels as well as systemic lipolysis. TNFα reduced CIDEC expression in both time and dose-dependent manner. However, suppression of MEK, either by selective inhibitors or siRNA, prevented TNFα-mediated CIDEC downregulation. Further results showed that PPARγ, the transcription factor of CIDEC, was phosphorylated and redistributed by TNFα in a MEK-dependent manner. Reporter assay confirmed that TNFα downregulated CIDEC expression by inhibiting its promoter activity. **Conclusion:** TNFα downregulates CIDEC protein levels through phosphorylation and nuclear export of PPARγ by MEK/ERK cascade and this adds new aspects of TNFα-induced lipolysis in human. **Funding:** This work was supported by National Natural Science Foundation of China No. 81172689.

P2-386

The Sequence of Prenatal Growth Restraint and Postnatal Catch-Up Growth Leads to a Thicker Intima Media and More Pre-Peritoneal and Hepatic Fat by Age 3-6 Years

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Background: Infants born small-for-gestational age (SGA) who develop postnatal weight catch-up are at risk for insulin resistance, central adiposity and cardiovascular disease in later life, even in the absence of overweight. **Objective and hypotheses:** In young (age 3–6 years) non-obese SGA children, we assessed arterial health by intima-media thickness (IMT) and abdominal fat distribution (subcutaneous, visceral, pre-peritoneal and hepatic components by magnetic resonance imaging (MRI) and/or ultrasound (US)) besides a selection of endocrine markers. **Method:** Comparisons of measures in SGA ($n=27$) *vs* appropriate-for-GA (AGA) children ($n=19$) of similar height, weight and BMI. Longitudinal outcomes (age 3–6 years) were carotid IMT (cIMT); fasting glucose, circulating insulin, IGF1 and high-molecular-weight (HMW) adiponectin; abdominal fat partitioning by US. Cross-sectional outcomes (age 6 years) were aortic IMT (aIMT) and abdominal fat partitioning by MRI. **Results:** At 3 and 6 years, cIMT and IGF1 results were higher and HMW adiponectin lower in SGA than AGA children; at 6 years, SGA subjects had also a thicker aIMT and more pre-peritoneal and hepatic fat, and were less insulin sensitive (all P between <0.05 and <0.0001). cIMT correlated positively with pre-peritoneal fat, particularly at 6 years. Post-SGA status and weight gain in early childhood (between 3 and 6 years) were independent predictors of cIMT at 6 years, explaining 48% of its variance. **Conclusion:** SGA children aged 3–6 years were found to have a thicker intima-media and more pre-peritoneal and hepatic fat than AGA children of comparable size.

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Biovascular Markers in Children with Kabuki Syndrome

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Background: Asymmetric dimethylarginine (ADMA) is an endogenous competitive inhibitor of endothelial nitric oxide synthase (NOS), which prevents synthesis of nitric oxide (NO). Low levels of NO are associated with endothelial dysfunction and an increased risk of cardiovascular disease. Diseases associated with high levels of ADMA include metabolic syndrome, chronic kidney disease, diabetes mellitus, insulin resistance, hyperthyroidism and multiple organ failure. Notable, GH treatment is associated with a significant decrease of ADMA. A rare example of individuals resembling several features matching metabolic syndrome are patients with Kabuki syndrome (KS). KS is a multiple anomaly syndrome mainly characterized by specific facial features, short stature, hypotonia and mental retardation. **Objective and hypotheses:** Earlier research showed a positive effect of GH treatment to metabolic parameters. Therefore, a GH treatment study has been started in Maastricht to assess the effect of GH to metabolic parameters in KS children. **Method:** 15 prepubertal children with a genetically confirmed diagnose of KS (*KMT2D* or *KDM6A* mutation) were included. The KS children received daily GH treatment. Plasma ADMA levels and lipid profiles were measured at baseline and after six months of GH treatment. ADMA levels were assessed using the LC-MS/MS tandem mass spectrometer. **Results:** After 6 months of GH treatment, plasma ADMA levels were similar or reduced compared to baseline levels. In addition, total cholesterol was even more decreased compared to baseline levels. **Conclusion:** Children with KS receiving GH treatment showed improved biovascular parameters after 6 months compared to baseline levels. Concluding, GH treatment in KS patients seems to be favourable concerning biovascular markers and their associated risk to cardiovascular disease. **Funding:** This study is sponsored by Pfizer.

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Phthalate Exposure and Metabolic Parameters in Korean Girls

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Background: Phthalates are synthetic chemicals produced in extremely large volumes for a wide variety of uses in personal care and consumer products, including building materials, food packaging, medical devices, toys and cosmetics. Though a few studies have shown that concentrations of phthalate metabolites are associated with obesity and insulin resistance in adults, studies in children are limited. **Objectives:** We studied to examine the associations of urine levels of phthalate metabolites with obesity and metabolic parameters in Korean girls. **Methods:** A total of 139 girls (67 overweight cases and 72 controls, aged 6 to 13 years) were recruited. Anthropometric indices and body composition analysis were measured, and fasting glucose, insulin, AST, ALT, and lipid profiles were determined. Spot urine samples were collected and phthalate monoesters were analysed using gas chromatography-mass spectrometry (GC-MS). Associations between phthalate exposure and anthropometric indices/metabolic parameters and their trends were examined by multiple linear regression and Logistic regression analyses respectively. **Results:** Di-2-ethylhexyl phthalate (DEHP) metabolites showed the highest detected concentration (82.5 μg/g creatinine, 100%), and mono-benzyl phthalate (MBzP) showed the lowest detected concentration (6.3 μg/g creatinine, 87.8%). There was no significant difference in the concentrations of all phthalate monoesters between overweight and control girls, however, percentage fraction of MEOHP among DEHP metabolites (MEOHP%) were significantly lower in overweight girls than in controls. After adjusting for age, pubertal stages, and height percentile, MEHHP% was positively associated with waist circumference and MEOHP% was negatively associated with body mass index (BMI) percentile. Concentrations of MiBP, MnBP, MEHP, MEHHP, sum of DEHP metabolites, and sum of high molecular weight phthalates (HMP) were positively associated with serum ALT. Concentrations of MiBP were also positively associated with total cholesterol/LDL-cholesterol levels. After controlling for age and pubertal stages, MEHHP% was positively associated with fasting insulin and HOMA-IR, whereas MEOHP% was negatively associated with fasting insulin and HOMA-IR. However, after further adjustment for BMI percentile, the significant associations were remained only for MEOHP%. **Conclusions:** Urinary concentrations of several phthalate metabolites were positively associated with serum ALT levels, and MEOHP% was negatively associated with insulin resistance. Prospective studies are needed to determine potential causal links between phthalate exposure and metabolic derangement in children.

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Childhood Craniopharyngioma with Hypothalamic Obesity – No Long-term Weight Reduction due to Rehabilitation Programs

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Background: Severe obesity due to hypothalamic involvement has major impact on prognosis in long-term survivors of childhood-onset craniopharyngioma. The long-term effects of rehabilitation efforts on weight development and obesity in these patients are not analysed up to now. **Method:** 108 patients with childhood-onset craniopharyngioma recruited in HIT Endo before 2001 were included in the study. Long-term weight development (BMI SDS after >10 years follow-up) was analysed in regard to rehabilitation, which was performed in 31 of 108 (29%) patients (one rehabilitation in four patients (13%), more than one in 21 patients (68%), six patients unknown) in 13 German rehabilitation clinics. **Results:** 84% of patients underwent rehabilitation in order to reduce hypothalamic obesity (BMI > +2 SD), whereas 12% of patients were normal weight. Childhood-onset craniopharyngioma patients with rehabilitation presented with higher BMI at diagnosis (median BMI: +1.32 SD; range: −1.08 to +7.00 SD) and at last evaluation (median BMI: +4.93 SD; range: −0.20 to +13.13 SD) when compared with patients without rehabilitation (median BMI at diagnosis: +0.24 SD; range: −2.67 to +6.98 SD; BMI at evaluation: +2.09 SD; range: −1.48 to +10.23 SD). A long-term weight reducing effect of rehabilitation was no detectable regardless of degree of obesity, frequency of rehabilitation, and hospital of rehabilitation. **Conclusion:** Treatment options for hypothalamic obesity in terms of rehabilitation are limited. Accordingly, strategies for prevention of hypothalamic lesions and psychosocial effects of rehabilitation are currently in focus for improvement of prognosis in childhood craniopharyngioma patients. **Funding:** German Childhood Cancer Foundation, Bonn, Germany.

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Programming of Rat Behaviours and the Stress Response by Duration of the Infancy Stage

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Background: The age at weaning programs life history adaptively. Shorter infancy resulted in longer/thinner animals with a reproductive-strategic shift to earlier physical and sexual

development (BMC Med, 2013). **Hypotheses:** The length of infancy impacts also the stress-response and has behavioural consequences. **Method:** Sprague-Dawley pups (generation F1), which usually are weaned at age 21 days, were weaned by cross-fostering at age day (d) 16, 21 or 26, and separated from their foster mothers at d30. At d60 females (F) and males (M) were mated within the weaning groups and generation F1, F2 and F3 animals were tested weekly in an open field maze from age 22–60 days for motor activity, anxiety/curiosity, short-term memory and stress-related corticosterone (CS) levels. **Results:** Motor activity in an open field was similar in the three groups at generation F1, but increase in d16 vs d26 animals by a mean 19% in F and 27% in M rats at F2 ($P<0.05$) and 16% (F and M) in F3 ($P<0.02$). Anxiety, measured as time spent next to the maze walls, was similar at F1, but smaller by 58% and 68% in d16 vs d26 young animals at F2 ($P<0.05$) and F3 ($P<0.05$). Anxiety was associated with greater CS levels in d16-weaned (25.3 ± 4.6 μg%) as compared to d26-weaned animals (11.6 ± 0.8 μg%, $P<0.01$). Curiosity, measured as time spent in the maze centre was greater in d16 F2 and F3 rats vs d26-weaned rats ($P<0.05$). Short-term memory, measured as object recognition, was similar between groups in F1 but greater in d16 as compared to d26-weaned rats by a mean 25% in M and 19% in F ($P<0.05$) at F2 and 10% in both F and M at F3. **Conclusion:** The age at weaning programs the stress-response and behaviours adaptively. In line with a faster reproductive strategy, shorter infancy resulted in a shift to greater motor activity, short-term memory and curiosity, and smaller anxiety but greater associated CS response. M were affected more than F animals and these traits built up trans-generations.

P2-391

POMC DNA Hypermethylation Variant is Highly Associated with Obesity in Adults

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Background: POMC plays a major role in central body weight regulation. Recently we have shown that a *POMC* hypermethylation variant is significantly associated with obesity in children and adolescents (Kuehnen *et al. PLoS Genetics* 2012). **Objective and hypotheses:** Here we report about our extended studies to elucidate the mechanism behind the occurrence of the *POMC* hypermethylation variant in obese individuals. **Method:** We tested the *POMC* DNA methylation in obese adults ($n=144$), normal weight individuals ($n=101$), 20 obese monozygotic and 19 obese dizygotic twin pairs and 49 trio families. The DNA methylation was analysed in DNA extracted from peripheral blood cells with a sodium-bisulfite based protocol and pyrosequencing. **Results:** We could now reproduce our initial findings in children also in adults and observed a highly significant enrichment of the *POMC* hypermethylation variant in obese compared to age-and sex matched normal weight individuals. In children-parent-trio families we could found no correlation with maternal but a significant correlation with the paternal DNA methylation level. We excluded a potential impact of genetic variations in *cis* by sequencing analysis of the complete *POMC* locus in all individuals. Moreover we identified in monozygotic twins a high grade of DNA methylation concordance, which was completely missing in dizygotic twins. The similarities of the *POMC* DNA methylation pattern in monozygotic twins -in the light of excluded genetic influence- argue for potential parental effects or rather oocyte specific pre-splitting random re-methylation events. **Conclusion:** Taken together the *POMC* hypermethylation variant represent the strongest factor that is associated with the individual risk for obesity so far since all described genetic variants have shown to have a much lesser impact on the individual BMI compared to the here described *POMC* locus hypermethylation. In addition the hypermethylation variant seems not to result from primary genetic variation but rather seems to originate from sporadic early embryonic random remethylation difference.

P2-392

Unaltered Ratio of Circulating Levels of GH Isoforms after Administration of Different GH Provocative Tests in a Population of Short Stature Children

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Background: Human GH is a heterogeneous protein hormone consisting of several isoforms, the most abundant being 22 kDa- and 20 kDa-GH. The availability of analytical methods to measure these GH isoforms might represent a valuable diagnostic tool to investigate GH secretion in short stature. **Objective and hypotheses:** Aim of the present study was to measure circulating levels of 22 kDa- and 20 kDa-GH in children with different diagnosis of short stature such as idiopathic short stature (ISS), isolated GH deficiency (GHD), short stature by bioinactive GH (BIO-SS) or GHD subjects at time of retesting at the end of GH therapy (Re-GHD), using different GH provocative tests (insulin, arginine, GHRH + arginine or glucagon). **Method:** A total of 118 short-statured children (males/females: 72/46; age range 1.1–15.6 years) after administration of insulin, arginine, GHRH + arginine or glucagon was consecutively recruited from January 2010 to December 2014. The results were analysed subdividing the study population on the basis of the administered GH provocative test or the diagnosis of short stature (ISS, GHD, BIO-SS or Re-GHD). The data are expressed as mean ± standard

deviation. **Results:** When considering GH provocative test, there were no statistically significant differences in the ratio of GH peak 22/20 kDa (insulin: 7.0±2.7; arginine: 9.2±7.2; GHRH+arginine; 7.0±2.9; glucagon: 7.7±3.3). Similarly, when considering diagnosis of short stature, there were no statistically significant differences in the ratio of GH peak 22 kDa/20 kDa (ISS: 7.0±8.2; GHD: 5.4±3.9; Re-GHD: 5.4±3.0; BIO-SS: 7.1±1.8). **Conclusion:** The main GH provocative tests currently used in paediatric endocrinological practice, which are based on different neuroendocrine mechanisms, stimulate a similar secretion of GH isoforms. Moreover, different causes of short stature are not associated with an unbalance in GH isoforms.

P2-393

Study of IGF1 Receptor Gene in Small for Gestational Age Patients with Short Stature Treated with RHGH

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Background: IGF1 is essential for pre and postnatal growth. Mutations in IGF1 receptor (IGF1R) gene have been described in patients with intrauterine growth retardation and other anomalies. **Objective and hypotheses:** To study IGF1R gene in small for gestational age (SGA) patients with short stature and correlate the results with clinical presentation and response to rhGH treatment. **Method:** Longitudinal retrospective study of 69 SGA patients with short stature registering weight, height, IGF1 levels, adult height, target height, height at start of rhGH and height gain after treatment. Genetic analysis consisted in DNA amplification, sequencing and electrophoresis. Statistics SPSS V20.0 ($P<0.05$). **Results:** From the total cohort (79.7% female) 10.1% showed mutation in IGF1R (Y487F,pL81Fexon2C>T and (IVS (+30) delGT), 81.4% polymorphisms(E1013E, IVS (+72) A/G, V532V and N608N) and 13% were normal. Patients with mutations were significantly smaller at birth (length: −3.96 SDS, Weight: −2.48 SDS, Cephalic circumference: −2.8 SDS) and presented with familiar short stature. Patients with polymorphisms showed lower length and weight at birth, target height and adult height compared with those with normal IGF1R analysis (NS). Within patients with polymorphisms, those with IVS (+72) A/G initiated before rhGH (6.4±2.6 vs 8.9±2.9 years; $P=0.03$), with more affected height (−3.32±0.6 vs −2.54±0.6 SDS; $P=0.04$), lower levels of IGF1 (117±71 vs 264±130 mg/d; $P=0.03$) l and showed a better response in the first year of treatment (Δ0.94±0.8 vs Δ0.38±0.3 SDS; $P=0.01$). **Conclusion:** IGF1R gene mutations cause severe prenatal growth failure and are usually associated with familiar short stature. Polymorphisms in this gene (E1013E and IVS (+72) A/G) have been found in SGA patients with short stature. The presence of different polymorphisms can influence the response to rhGH treatment in these patients.

P2-394

Gene Expression Profiles in GH Deficient Children Relate Peak GH Levels to Circadian Clock, Chromatin Remodelling, and WNT Signalling Pathways

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Background: GH deficiency (GHD) is classically defined on the basis of a cut-off applied to the peak GH level during stimulation tests; a process with recognised limitations. Identifying the functional role of genes whose expression is associated with pGH may help with our understanding and classification of GHD. **Objective and hypotheses:** Identify patterns of gene expression (GE) related to pGH and to describe the function, and regulation of these genes. **Method:** Pre-pubertal children with GHD ($n=98$) were enrolled from the PREDICT study (NCT00256126). All children enrolled had two GH stimulation tests both with pGH levels <10 μg/l. Whole blood GE was determined prior to GH treatment using Affymetrix U133v2 microarrays. GE was correlated with pGH using rank regression (gender, ethnicity, age, and BMI as co-variates). Network models were generated (Biogrid/Cytoscape) and the hierarchy of gene modules determined (Moduland); upstream activity in the network model was assessed using causal network analysis (Ingenuity Pathway Analysis). **Results:** Rank regression identified 347 genes that were correlated with pGH: 188 positively and 159 negatively ($R>\pm 0.28$, $P<0.01$). Hierarchical clustering identified five distinct clusters of GE (two clusters positively correlated with pGH and three negatively correlated). For the positively correlated GE clusters one cluster associated with network modules related to cell cycle and the second with chromatin remodelling and circadian clock ($P<0.01$). For the negatively correlated GE clusters two associated with network modules related to circadian clock, DNA replication and WNT signalling while the third associated with apoptosis ($P<0.01$). Upstream regulators of these modules were PIK3R3 (circadian clock), *SIRT2* (growth factor signalling), and *APC2* (WNT signalling) ($P<7.7\times10^{-3}$). **Conclusion:** GE profiling identified a genomic signature related to pGH levels functionally linked to circadian clock and growth factor signalling and regulated by PIK3R3, SIRT2, and APC2.

P2-395

Growth and GH in Kabuki Syndrome

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Background: Kabuki syndrome (KS; OMIM 147920) is a congenital anomaly/intellectual disability syndrome caused by a mutation in the *KMT2D* or *KDM6A* gene. Children with KS have a spectrum of clinical features, but one of the key features in KS patients is postnatal growth retardation. GH deficiency has been reported in some children with KS, but no structural research is done in this field. **Objective and hypotheses:** We studied the growth hormone and IGF1 pattern in order to learn more about a possible mechanism involved in this postnatal growth retardation. **Method:** Currently, we have assessed 15 KS children (age 3–10 years old, 6.44 ± 2.29) with a known *KMT2D* or *KDM6A* mutation. Both clonidine (CLO) and arginine (ARG) tests were used to stimulate GH release. GH and IGF1 were measured according to international standard. **Results:** Height was variable, with a mean height SDS of −2.38 ± 1.41. GH deficiency was present in four of the 15 (26.67%) children. In addition, in two children the GH tests showed a tendency to GH resistance, although no one actually met the defined criteria. **Conclusion:** Apparently GH deficiency is not the only cause for small height in KS patients. Further research is necessary to determine the underlying cause of growth retardation. Currently we are performing a clinical study with GH treatment in children with KS; the results are pending but promising. **Funding:** This study is sponsored by Pfizer.

P2-396

IGF2 and Lipid Profile in Paediatric Obesity: A Marker of Cardio-Metabolic Risk?

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Background: IGF2 polymorphisms have been associated with BMI, lipid profile and blood pressure. IGF2 methylation status has been linked with lipid profile in obese children. No data are available on blood IGF2 concentrations in obese children. **Objective and hypotheses:** To evaluate serum concentrations of IGF2 and determine their relationships with anthropometric, metabolic and body composition parameters in a cohort of obese children. **Method:** 82 obese children (44 females/38 males, aged 12.08 ± 2.35 years) were studied. Anthropometric, biochemical and metabolic parameters and IGF2 (expressed as SDS) were assessed. Body composition was evaluated by dual x-ray absorptiometry (DXA) in 58 subjects. Results were compared with those obtained in 15 lean children (ten females/five males, 10.95 ± 2.58 years). **Results:** Obese children showed significantly higher IGF2 levels (−0.46 ± 0.78 vs −1.17 ± 0.58 SDS) than lean controls. IGF2 levels correlated with total cholesterol ($r = 0.27$; $P = 0.016$), LDL-cholesterol ($r = 0.25$; $P = 0.025$), and triglyceride levels ($r = 0.28$; $P = 0.011$), triglyceride/HDL ratio ($r = 0.25$; $P = 0.028$), and both AST ($r = 0.29$; $P = 0.009$) and ALT ($r = 0.30$; $P = 0.006$). No association between IGF2 levels and body composition parameters was found. **Conclusion:** IGF2 serum concentrations are significantly higher in obese children and are associated with a worse lipid profile. IGF2 could be a biomarker of cardio-metabolic risk.

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Silver Russell syndrome: A Cause of Partial IGF1 Resistance?

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Background: Silver-Russell syndrome (SRS) is characterized by intrauterine and postnatal growth retardation, relative macrocephaly at birth, prominent forehead, severe feeding difficulties and body asymmetry. In around 50%, it is secondary to hypomethylation at the IGF2/H19 imprinted locus on 11p15 (11p15 LOM), and in 10% to a maternal disomy of chromosome 7 (mUPD7). Mechanisms of postnatal growth failure in SRS are not well understood. **Objective and hypotheses:** Document IGF1 and IGFBP3 serum levels in SRS without and with GH therapy. **Method:** IGF1 and IGFBP-3 serum levels were measured by IRMA and RIA respectively in SRS children without ($n = 45$) and after one year of GH treatment ($n = 22$). **Results:** In the 45 children (median age: 3.9 years, median height: −3 SDS, 39 patients with 11p15 LOM and six patients with mUPD7) no IGF1 < −2 SDS level was documented, despite severe feeding difficulties. Basal levels of IGF1 and IGFBP-3 were increased > +2 SDS in respectively 24 and 11% of the SRS children before GH treatment and in 64 and 54% after 1 year of GH, only in the SRS group of patients with 11p15 LOM. The median 1 year growth response to GH (median dose 31 μg/kg per day), expressed as the change in height SDS score, was +0.8 (range 0 to +1.4). **Conclusion:** Basal levels of both IGF1 and IGFBP-3 are increased for some SRS with 11p15 LOM even before GH treatment and very frequently during GH treatment. IGF1 levels are more often elevated than IGFBP-3 levels. During the first year of GH, growth velocity increased but only modestly, however GH augmentation was limited by elevated IGF1 levels in most patients. This suggests that SRS patients with 11p15 LOM have a partial IGF1 insensitivity of unknown mechanism complicating thereby the management of GH therapy in this group of patients.

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The *In vitro* Functional Analysis of Gene Promoter Region Single Nucleotide Polymorphisms Associated with GH Response in Children with GH Deficiency

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Background: Response to GH treatment has been associated with single nucleotide polymorphisms (SNPs) within the promoter region of growth-related genes including GRB10 (rs1024531 (A/G, allele A increased response)), IGFBP3 (rs3110697 (G/A, G increased response)), CYP19A1 (rs10459592 (T/C, T increased response)) and SOS1 (rs2888586 (G/C, C increased response)). SOS1 is a positive regulator of GH signalling (MAPK pathway); the aromatase CYP19A1 promotes oestrogen synthesis to impact on GH secretion and growth, while IGFBP-3 is the main carrier of IGF1. Conversely, GRB10 has a negative impact on growth, inhibiting GH and IGF1 signalling. **Objectives:** To test the impact of promoter SNPs in *IGFBP3, GRB10, CYP19A1* and *SOS1* on transcriptional activity (TA) in an *in vitro* cell system. **Methods:** Each allele within a 500 bp fragment of the promoter sequence was cloned into a secreted alkaline phosphatase (ALP) reporter gene plasmid (pSEAP, Clontech) and transfected into human MCF-7 cells, known to be GH responsive. TA of each construct was evaluated by ALP induction after 24 h of GH stimulation with a dose-dependent titration (range: 0, 2, 20 and 200 ng/ml). **Results:** When the cells were stimulated with GH, the alleles associated clinically with better GH response had higher TA at all GH concentrations for *IGFBP3* (allele G), *CYP19A1* (allele T) and *SOS1* (allele C) (all $P<0.05$). Conversely for *GRB10*, the allele associated with better GH response (allele A) had a significantly lower TA at all GH stimulations ($P<0.05$). **Conclusions:** We have shown that SNPs associated with response to GH therapy can alter TA after GH stimulation. The differential TA of the SNPs after GH stimulation relates directly to the effect of the gene on growth promotion or inhibition. The observation of induction over a range of GH concentrations supports the *in vivo* relevance of these findings. **Funding:** This work was supported by ESPE Research Fellowship, sponsored by Novo Nordisk A/S.

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Is Retesting in GH Deficient Children Really Useful?

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Background: Patients with childhood-onset GH deficiency (GHD) are usually retested in late adolescence or young adulthood, after achievement of final height, to verify whether they need to continue GH treatment. Most of the patients found to have idiopathic GHD when tested as children have normal GH responses when retested in the early or late adolescence. Indeed, the 2007 Consensus guidelines for the diagnosis and treatment of GHD adults recommended that idiopathic GHD patients should be re-evaluated. **Objective and hypotheses:** The aim of the present study was to investigate if GH stimulation test is really necessary to confirm a permanent status of GHD or if IGF1 measurement alone at the same time could be used. **Method:** We studied 163 children with idiopathic GHD (54 females and 109 males), age 16.2 ± 1.4 years retested when they reached final height using GHRH (1 μg/kg i.v.) + arginine (0.5 g/kg i.v.) test or arginine alone (0.5 g/kg i.v.). GH and IGF1 levels were measured by a chemiluminescent assay (Immulite 2000). **Results:** 39 (23.9%) patients showed severe GHD (GH peak at diagnosis <5 ng/ml) and 124 patients (76.1%) showed partial GHD (GH peak <10 ng/ml). By taking a peak GH value of <10 ng/ml in the arginine test and <19 ng/ml in the GHRH + arginine test, 28 patients (17.2%) were found to have persistent GHD and 135 (82.8%) to be transiently GH deficient. Among patients with severe GHD, 32 patients (82.1%) showed transient GHD, while among patients with partial GHD 103 (83.1%) children showed transient GHD. IGF1 levels were comparable between total GHD (0.13 ± 1.04 SDS) and partial GHD subjects (0.18 ± 0.84 SDS). Furthermore, among persistent total GHD patients only two showed very reduced levels of IGF1 (< -2.0 SDS), while in transient total GHD group no patients showed pathologically reduced IGF1 levels. **Conclusion:** Most of the cases of idiopathic childhood-onset GHD is transient. The reasons for such findings are not clear but may include the variability of GH responses to stimulation. After the end of GH substitutive treatment, a re-evaluation of GH secretion is mandatory for reconfirming the diagnosis of GHD. IGF1 levels alone are not useful for discriminate persistent from transient GHD subjects.

P2-400

Regulation of IGF1R mRNA Expression by GnRH Agonist may be Involved in the Decrease of Height Velocity During Central Precocious Puberty Therapy

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Background: Growth spurt is a major event in central precocious puberty (CPP). GnRH analogue (GnRHa) therapy inhibits gonadal axis and decreases height velocity. However, serum IGF1 and IGFBP-3 remain high as before therapy. Reports on IGF type 1 receptor (IGF1R) in CPP are yet unavailable. **Aim:** To study IGF1R mRNA expression in girls with CPP before and during GnRHa therapy. **Methods:** 34 girls with CPP were studied. Sixteen of them (8.0 ± 0.7 years) were evaluated before (group A)

and 18 (9.4±0.8 years) during GnRHa therapy (group B). Age-matched prepubertal girls were studied as controls ($n=18$). Fasting blood samples were collected for IGF1R mRNA expression in peripheral lymphocytes (RT-PCR) and serum IGF1, IGFBP-3, IGFBP-1 and insulin analysis. **Results:** IGF1R mRNA expression was higher in group B than in group A ($P=0.04$) and control ($P=0.03$). No significant difference was observed between group A and control. IGF1, IGFBP-3 and IGF1/IGFBP3 molar ratios were similar in groups A and B but lower in control ($P<0.0001$). IGFBP-1 was higher ($P<0.0001$) in control than in groups A and B. IGBPB-1 was also higher in group A than in group B. Insulin levels were lower in control than in group A ($P=0.01$), but no significant difference was observed between groups B and A. Six girls were studied at two moments, before and during GnRHa therapy. In this group, IGF1R mRNA expression was also higher during GnRHa therapy ($P<0.01$) while IGF1, IGFBP3 and IGF1/IGFBP3 molar ratios were similar in both evaluations. **Conclusion:** The decrease in height velocity during CPP therapy with GnRHa cannot be explained by changes in IGF1 availability. However, the increase in IGF1R mRNA expression suggests impairment of IGF1 signalling with compensatory up regulation of IGF1R. Increased GH concentrations due to reduction of IGF1 feedback could explain the IGF1, IGFBP-3 and IGFBP-1 findings.

P2-401

GRB10 Knockdown in Zebrafish is Associated with Decreased Weight-to-length Ratio without Alterations in AKT and ERK Activity: A Model to Study Human Growth Regulation

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Background: In humans *GRB10* negatively regulates GH and IGF1 signaling predominantly *via* altering phosphorylation of PI3K/mTOR/AKT and MEK/ERK pathways which relate to both growth and metabolic function. We have previously shown that *Grb10* knockdown in Zebrafish results in overgrowth with an increase in length and head size. However the impact on weight in relation to length has not been assessed. **Objective:** To develop a model to study weight-to-length ratio in Zebrafish and to examine the mechanisms through which *Grb10* knockdown mediates overgrowth. **Methods:** *Grb10* knockdown was obtained by injecting splice-blocking morpholino (MO) into one-cell stage embryos alongside control-injected (CT) Zebrafish. Weight-to-length ratio (mg/mm^2) was assessed at 54, 72 and 120 h post-fertilization (hpf); these developmental periods were chosen to model early through late childhood growth. Chemical inhibition of the PI3K/mTOR/AKT (NVPBEZ235) and the MEK/ERK pathways (PD184352) was performed from 30 to 72 hpf. Total and phosphorylated AKT and ERK were evaluated on Western-Blot to assess the activity of phosphorylation on these molecules with and without pathway inhibition. **Results:** In the MO Zebrafish (*Grb10* knockdown), the weight-to-length ratio significantly decreased over time and the reduction was most significant at 120 hpf ($n=8$, $P<0.001$). At all times, weight-to-length ratio was significantly increased in CT vs MO ($P<0.05$). The comparison by Western-Blot with and without pathway inhibition in MO vs CT samples indicated that global AKT and ERK activities were not affected by *Grb10* knockdown. **Conclusions:** We now demonstrate in Zebrafish *Grb10* knockdown that not only is length increased but weight-to-length ratio is decreased, implying a 'leaner' phenotype. However this is not related to the PI3K/mTOR/AKT and MEK/ERK pathways. We have developed a method to study both length and weight changes in genetically modified Zebrafish which may be useful in modelling human disorders of growth and metabolism.

P2-402

The Involvement of the Epidermal Growth Factor Receptor in the Successful GH Signalling and the Role of p21 in the Negative Regulation of the GH/GHR and EGF/EGFR Pathways, in GH Transduction Defect

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Background: GH transduction defect (GHTD) is characterised by severe short stature and impaired STAT3 phosphorylation, which is overcome by simultaneous induction of GHTD fibroblasts with 200 ng/ml GH and short interference mRNA CIS (GH200/siRNA) or with 1 000 ng/ml GH (GH1000) and is clinically expressed with 'catch-up' growth after rhGH treatment. **Objective and hypotheses:** The involvement of epidermal growth factor receptor (EGFR) in the successful GH signaling and the role of p21 in the regulation of the GH/GHR and EGF/EGFR pathways were studied in one control and one GHTD patient. **Method:** Fibroblast cultures were developed from gingival biopsies of one GHTD patient (PF) and one control (CF).The protein expression and cellular localization of EGFR, pEGFR and p21 were studied by Western Immunoblotting and Immunofluorescence respectively, i)At the basal state and after induction with GH200,either with or without siRNA CIS and ii)At the basal state and after inductions with GH200,GH1000 or 50 ng/ml EGF. **Results:** After GH200/siCIS: i) The protein expression and the membrane localisation of EGFR and pEGFR were increased, especially in PF, ii) The protein expression and the nuclear localisation of p21 was reduced in CF and PF. In the inductions of successful GH signalling (GH200 in CF and GH1000 in PF): i) The

protein expression and the membrane localization of EGFR and pEGFR were increased, ii) The protein expression and nuclear localization of p21 were reduced. After induction with EGF: i) The protein and membrane expression of EGFR and pEGFR were increased similarly in CF and PF, ii) The protein expression of p21 was increased in CF and PF. **Conclusion:** The EGFR participates in the successful GH signalling, but induction with a higher dose of hGH is needed in the PF. The EGF/EGFR pathway, which is more primed in P than in C, is possibly involved when exogenous rhGH is administered. Also, p21 is a negative regulator of the EGF/EGFR pathway, which unlike the GH/GHR pathway, is not impaired in the PF.

P2-403

Homozygous Carriers of a Novel IGFALS Mutation are 1.5 SD Shorter than Heterozygous Relatives and Tend to have Lower Bone Mineral Density

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Background: There are limited data on differences in height, bone mineral density (BMD) and pubertal delay between homozygous and heterozygous carriers of IGFALS defects. **Objective and hypotheses:** To describe clinical and laboratory features and BMD of homozygous and heterozygous carriers of a novel IGFALS mutation in a large Kurdish family. **Method:** Index cases were two first degree cousins presenting with short stature, low IGF1, very low IGFBP-3 and normal baseline GH, caused by a homozygous (c.1462G > A, p.Asp488Asn) mutation in IGFALS. This novel IGFALS mutation introduces a new N-glycosylation site, which may lead to misfolding of the protein leading to its relatively rapid intracellular degradation. All family members consented to genetic, clinical and laboratory assessment. Age at menarche (females) and age at accelerating growth, testicular growth and shaving (males) were recorded. Height and biochemical findings were expressed as SDS, and BMD (Horizon DXA, Hologic) as *z*-score (NHANES). Ternary complex formation was investigated by size-exclusion chromatography. **Results:** Eight homozygous carriers (6 < 18.0 years), 11 heterozygotes (7 < 18 years) and one non-affected (height −0.9 SDS) were studied. Homozygotes were 1.5 SD shorter than heterozygous carriers, who were 1.7 SD shorter than the population's mean. Delayed puberty could be evaluated in two homozygotes (both delayed) and six heterozygotes (4/6 delayed). Serum IGF1, IGFBP-3 and ALS showed the expected pattern for complete and partial ALS deficiency, respectively. BMD tended to be lower in homozygous carriers (NS), possibly partially caused by height differences. Ternary complex formation was markedly diminished in sera from homozygous patients, and heterozygotes showed an intermediate pattern. **Conclusion:** Homozygous carriers of the IGFALS mutation were 1.5 SD shorter than heterozygous carriers, BMD *z*-score tended to be lower and pubertal delay appeared frequent in both groups.

Table 1.

Mean (SD)	Homozygotes ($n=8$)	Heterozygotes ($n=11$)	*P*-value
Age (years)	11.7 ± 5.2	21.5 ± 16.1	0.283
Height SDS	−3.3 (0.6)	−1.7 (1.0)	0.003
Height SDS range	−4.2 to −2.7	−3.2 to −0.1	
IGF1 SDS (age < 18)	−2.2 (0.3) ($n=6$)	−0.7 (0.7) ($n=5$)	0.006
IGFBP-3 SDS (age < 18)	−4.0 (0.7) ($n=6$)	0.1 (0.7) ($n=5$)	0.006
IGFBP-2 SDS	−1.04 (0.9)	−0.5 (1.4)	0.237
ALS SDS	−4.6 (1.5)	−1.5 (0.8)	< 0.001
BMD *z*-score	−1.3 (1.2)	−0.6 (0.4)	0.110

P2-404

The Role of β-TrCP, an E3 Ubiquitin Ligase, in the Signalling of the GH and Epidermal Growth Factor Pathways in Growth Hormone Transduction Defect

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Background: epidermal growth factor (EGF) stimulates cell growth and differentiation through its receptor EGFR. Cross-talking between the GH and EGF signaling pathways is important for normal cellular development. GH transduction defect (GHTD), a clinical disorder characterized by impaired STAT3 phosphorylation due to excessive GHR degradation, is caused by over-expression of the E3 ubiquitin ligase, CIS.Induction of GHTD fibroblasts with 200 ng/ml hGH (GH200) and silencing mRNA CIS (siCIS) or high dose hGH, 1 000 ng/ml (GH1000), suppresses excess CIS and restores normal GH signalling. After rhGH treatment,GHTD children show significant 'catch-up' growth and normal adult height. β-transducin repeat-containing protein β-TrCP (β-TrCP), another E3 ubiquitin ligase, also plays a role in GHR endocytosis. **Objective and hypotheses:** To study the role of β-TrCP in the regulation of the GH/GHR and EGF/EGFR pathways were studied in normal and GHTD cells. **Method:** Fibroblast cultures were developed from gingival biopsies of a GHTD patient (P) and control (C) child. Protein expression and cellular localization of β-TrCP were studied by Western Immunoblotting and Immunofluorescence respectively, at i) the

basal state and after GH200 induction, either with or without siCIS and ii) the basal state and after GH200, GH1000 or 50 ng/ml EGF inductions. **Results:** i) After GH200/siCIS, the protein expression and cytoplasmic and membrane localization of β-TrCP were increased in the P. ii) After induction with GH200 in the C and GH1000 in the P (inductions of successful GH signaling), the protein expression and cytoplasmic localization of β-TrCP were increased. iii) After induction with EGF, the protein expression and cytoplasmic localization of β-TrCP were also increased in both the C and P. **Conclusion:** In GHTD, β-TrCP increases, possibly as a compensatory negative regulator of the GH/GHR pathway when the excessive CIS is suppressed. β-TrCP also seems to be part of the negative regulatory mechanism of the EGF/EGFR pathway under normal conditions and in the clinical disorder, GH transduction defect.

P2-405

SGA Short Stature Bearing with a Novel Nonsense Mutation (p.W1249X) in the IGF1R Gene

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Background: The type I IGF1R plays a role in intrauterine and postnatal growth. Heterozygous *IGF1R* mutations have been identified in over 20 families. Some of them are linked to the etiology of short stature in previous studies. In addition, we previously reported that a heterozygous nonsense mutation (p.Q1250X) of the *IGF1R* gene led to decrease IGF1R protein expression through endoplasmic reticulum-associated protein degradation (ERAD) mechanism, resulted in growth failure. **Objective:** We aimed to describe the clinical features of the patient with a novel mutation in the *IGF1R* gene and to evaluate the molecular characteristics of it. **Case presentation and method:** A 3-year-old Japanese girl, with a birth weight of 2.110 g (−3.0 SDS) and height of 44.3 cm (−2.8 SDS), had a short stature (−3.1 SDS). At the age of 2.4 years, her basal serum GH level was high (10.5 ng/ml), but serum IGF1 level showed upper limit of normal (185 ng/ml). We analyzed *IGF1R gene* in the patient, determined the protein expression of mutated *IGF1R* and performed quantitative RT-PCR of IGF1R mRNA on whole blood cells. The analysis of *IGF1R, ALS and IGFBP3* gene by multiplex ligation-dependent probe amplification (MLPA) was performed. **Results:** A novel heterozygous nonsense mutations (p.W1249X) was identified in the *IGF1R* gene. The mutation site of p.W1249X is located next to p.1250X which causes the decrease of IGF1R protein through ERAD. Although this mutation did not affect blood IGF1R mRNA level, the expression of IGF1R protein was significantly decreased in transiently transfected cells. The copy number of *IGF1R, ALS and IGFBP3* gene was normal. **Conclusion:** It is suggested that the p.W1249X mutation of the *IGF1R* gene result in short stature through ERAD due to the location of the mutation.

P2-406

Metabolic Health in Short Children Born Small for Gestational Age Treated with GH and GnRHa: Results of a Randomised, Dose-response Trial

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Background: Previously we showed that pubertal children born small for gestational age (SGA) with a poor adult height (AH) expectation can benefit from treatment with GH 1 mg/m^2 per day (∼0.033 mg/kg per day) in combination with 2 years of GnRH analogue (GnRHa) and even more so with a double GH dose. GnRHa treatment is thought to have negative effects on body composition and blood pressure. Long-term effects and GH-dose effects on metabolic health in children treated with combined GH/GnRHa treatment are unknown. **Objective and hypotheses:** To investigate body composition, blood pressure and lipid profile during GH treatment, either with or without 2 years of additional GnRHa. To assess whether GH 2 mg/m^2 per day (∼0.067 mg/kg per day) results in a similar or even more favorable metabolic health at AH than GH 1 mg/m^2 per day. **Method:** Longitudinal, randomized, dose-response GH trial involving 107 short SGA children (58 girls) treated with GH until AH (GH randomized 1 or 2 mg/m^2 per day during puberty). 64 children received additional GnRHa. At AH, metabolic parameters were compared between children treated with combined GH/GnRHa and those with only GH. The GH-dose effect on metabolic health was evaluated in a subgroup of 47 children who started GH treatment in early puberty (randomized 1 or 2 mg/m^2 per day) with 2 years of GnRHa. **Results:** At AH, fat mass percentage (FM%) SDS, lean body mass (LBM) SDS, blood pressure SDS and lipid profile were similar between children treated with combined GH/GnRHa and those with only GH. In the pubertal subgroup, FM% SDS was lower during treatment with 2 mg GH/m^2 per day. There was no GH dose-dependent effect on LBM SDS, blood pressure and lipid profile. **Conclusion:** Combined GH/GnRHa treatment has no long-term negative effects on metabolic health compared to only GH. Started in early puberty, a GH dose of 2 mg/m^2 per day results in a similar metabolic health at AH and a more favorable FM% than the standard 1 mg/m^2 per day. **Funding:** This study was an investigator initiated study, supported by an independent research grant from Pfizer B.V. the Netherlands.

P2-407

A Phase 2, 6-Month, Randomised, Active-Controlled, Safety and Efficacy Study of TransCon hGH Compared to Daily Human GH in Children with GH Deficiency

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Background: TransCon human GH (hGH) is a long-acting prodrug of recombinant hGH that releases fully active unmodified hGH. TransCon hGH was shown in phase 1 studies in healthy volunteers and a phase 2 study in adults with hGH deficiency to: i) be safe and well tolerated, ii) provide dose-dependent hGH levels, with same peak level and exposure compared to daily GH, iii) be suitable for a once-weekly dosing regimen, and iv) induce an IGF1 response within the normal range. This ongoing pediatric phase 2 clinical study was designed to investigate safety, efficacy, pharmacokinetics and pharmacodynamics of TransCon hGH compared to daily hGH over a treatment period of 6 months. **Objective and hypotheses:** The objective of this study is to investigate i) safety and tolerability, ii) pharmacokinetics and pharmacodynamics, and iii) efficacy of TransCon hGH in children with GH Deficiency (GHD). **Method:** Pre-pubertal, treatment naïve GHD children received s.c. injections of one of three once-weekly TransCon hGH doses (0.14, 0.21 and 0.30 mg hGH/kg per week) or daily hGH (Genotropin 0.03 mg hGH/kg per day = 0.21 mg/kg per week) over a 6-month treatment period, in a randomized phase 2 study. GHD diagnoses were established in accordance with international consensus guidelines. **Results:** In an interim analysis of 25 patients, mean annualized height velocities among the three once-weekly TransCon hGH doses ranged from 11.9 cm for the 0.14 mg/kg per week dose to 14.5 cm for the 0.30 mg/kg per week dose. No safety concerns were observed. Maximum hGH blood concentration was comparable to an equivalent dose of daily hGH, and a dose-proportional increase in IGF1 levels into the normal range was observed. **Conclusion:** To date, this phase 2 pediatric study with TransCon hGH in GHD confirms the safety and efficacy profile observed in previous clinical trials. Final data from this pediatric phase 2 study will be presented. **Funding:** This study was sponsored by Ascendis Pharma A/S.

P2-408

Does Skeletal Disproportion in Children with Idiopathic Short Stature Influence Response to GH Therapy?

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Background: Children with ISS have an array of causes that lead to short stature and/or poor growth velocity. Genetic causes of short stature, notably SHOX mutations, can be associated with subtle skeletal disproportion with shorter limbs, manifesting as increased sitting-to-standing height ratios or SDS. **Objective and hypothesis:** Children with ISS and skeletal disproportions have a diminished growth response to GH treatment compared to children with proportionate short stature after 1 year (short-term) and at near-adult height (NAH; long-term). **Method:** ISS patients registered in Pfizer international growth database with a stimulated peak GH >10 μg/l and treated with GH were included. Short- and long-term growth responses were analyzed. Sitting height % SDS was grouped as: normal (SDS $-1.0-<1.1$), mild (SDS $1.1-<2.1$), and moderate (SDS >2.1) disproportionate short stature. Wilcoxon rank sum test was used for univariate statistical comparisons. ANOVA was used for group comparisons. *P*-value <0.05 was considered significant. **Results:** Prior to GH treatment, the ISS group displayed Gaussian distribution for skeletal proportion. For short-term analyses, the number of patients in each group was: normal ($n=193$), mild ($n=191$), and moderate ($n=140$). The corresponding number of patients in each group attaining NAH was: normal (57), mild (52), and moderate (28). Short-term growth responses, expressed as Studentized Residuals using the KIGS ISS 1st-year prediction model (Ranke MB et al. Horm Res 2007; 68:53–62), showed a trend toward poorer growth response with greater severity of disproportion (mean values; normal $=-0.04$, mild $=-0.16$, and moderate $=-0.25$, $P=0.07$). Long-term growth showed a larger difference, expressed as delta height SDS from GH start to NAH (median values; normal/mild = 1.75 vs moderate $=1.39$, $P<0.05$) **Conclusion:** Children with ISS and skeletal disproportion (shorter limbs) have reduced long-term height responsiveness to GH compared to those without disproportion suggesting subtle GH resistance in the former. **Conflict of interest:** C Camacho-Hubner and A Lindberg are employees of Pfizer Inc. W Cutfield is a member of the KIGS Steering Committee. **Funding:** Pfizer International Growth Database (KIGS) currently is a static database sponsor by Pfizer Inc. No authors were paid to conduct the research study submitted in this abstract.

P2-409

The Influence of GH Therapy on Chemerin Concentration, Body Mass and Selected Parameters of Carbohydrate Metabolism in Prepubertal Non-Obese Children with GH Deficiency

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Background: Chemerin is an adipocytokine which plays a great role in metabolism of carbohydrates. Chemerin concentration correlates positively with body mass (BM). GH deficiency (GHD) is associated with excess of abdominal fat tissue also in patients with normal BMI. **Objective and hypotheses:** To estimate the chemerin concentration and its correlation with BM and carbohydrate metabolism in non-obese, prepubertal children with isolated GHD before (GHD untreated group) and after 6 months of GH therapy (GHD after 6 months group). **Method:** 32 (22 boys, ten girls) children with GHD (mean height 117.9 cm, −2.77 SD, mean BMI −0.75 SD), mean age 8.87 years. Control group (CG): 18 (11 boys, nine girls) age matched healthy children (mean height 125.8 cm, −0.93 SD, mean BMI −0.28 SD). Serum fasting chemerin was measured in all. In GHD untreated and GHD after 6 months the following exams were done: body composition (bioimpedancy), fasting serum glucose and insulin. Fasting glucose/insulin ratio was calculated. **Results:** The mean serum concentrations of chemerin did not differ significantly between CG, GHD untreated and GHD after 6 months. FGIR was significantly higher in GHD after 6 months comparing to FGIR in GHD untreated (0.076 vs 0.090, $P<0.01$). In GHD untreated chemerin concentration correlates positively with BM (both with lean and fat mass) and FGIR ($r=0.35$ and $r=0.40$ respectively). Δ chemerin (chemerin level GHD after 6 months – chemerin level GHD untreated) correlates negatively with FGIR and negatively with chemerin level in GHD untreated ($r=-0.57$ and $r=-0.59$). Δ chemerin correlates positively with Δ SD BM ($r=0.44$). **Conclusion:** Chemerin concentration correlates positively with BM and FGIR in prepubertal non-obese children with GH deficiency before start of GH therapy whereas Δ chemerin correlates negatively with FGIR and Δ SD BM. It seems that Δ chemerin levels may influence carbohydrate metabolism during GH therapy in GHD children. **Funding:** This work was supported by Department od Health Sciences, University od Jan Kochanowski, Kielce, Poland (internal grant).

P2-410

Response to GH Treatment in the Very Young with GH Deficiency

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Aim: Data on response to GH treatment in the very young children with GH deficiency is scarce. The aim of this study was to evaluate the growth response in such children in a national multicentre study and to analyse the factors affecting the growth response. **Materials and methods:** In this study, we retrospectively evaluated the files of GH deficiency patients who had started GH treatment between 0–3 years of age who were being followed in 14 different centres from different regions of Turkey between 19 February 2014 and 23 October 2014. The study was approved by the Clinical Studies Ethics Committee. All collected data were obtained from patient hospital records. An electronic case recording form (CRF) was created. The CRF covered demographic features, as well as clinical and laboratory findings of the patients. The CRF was uploaded to the website of FAVOR Web Registry System (www.favorsci.org). Data entered in the registry were also checked for consistency by one of the authors (SÇ). The time given for patient enrolment was eight months. By the end of the deadline the collected patient record data were entered to Microsoft Excel database and subsequently transferred to SPSS for Windows statistical software for statistical analysis. The duration of GH treatment was accepted to be at least 12 mo. The patients were further subdivided according to isolated vs multiple pituitary hormone deficiency (MPHD) and age at onset of therapy: 0–12 months vs 12–36 months. Patients with MPHD received appropriate replacement therapy. **Results:** There were 42 patients with GH deficiency (23 males, 19 females) with a peak GH response (after GH stimulation test or at hypoglycaemia) of 0.69 ± 0.14 ng/ml. 30 had MPHD and 12 had isolated GH deficiency. The mean age at onset of GH therapy was 11.2 ± 1.03 mo. Mean GH dose used was 31.7 ± 1.4 μg/kg per day. Results of GH therapy over 1 year are shown on the Table. There was a significant increase in length SDS ($P=0.000$), weight SDS ($P=0.000$) and BMI SDS ($P=0.02$) over 1-year of therapy. Height velocity over one year showed positive correlation with weight increment ($r=0.38$), but did not show correlation with birth weight, peak GH level, GH dose and BMI. In MPHD Group 1st year response was significantly higher (16.5 ± 4.2 cm) than in the isolated GH deficiency group (12.8 ± 3.3 cm) ($P=0.014$). In the group started GH between 0–12 months the response (18.0 ± 4.2 cm) was higher than in the ones started between 12–36 months (13.3 ± 3.1 cm) ($P=0.013$). There was no difference between girls and boys with respect to the growth response. Neither was a difference in growth response between those with minipuberty or not. Multiple regression analysis did not reveal a significant parameter to explain the differences in growth response. **Conclusion:** Among children with GH deficiency, young children with MPHD respond better than isolated GH deficiency and those children aged between 0–12 months at onset of therapy respond better than 12–36 months children. The most significant factor in growth response was weight gain.

P2-411

Estimation of Adipsin, Omentin and Vaspin Concentration in Prepubertal Children with GH Deficiency before and after 6 Months of GH Treatment

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Background: GH deficiency (GHD) is usually associated with excess of abdominal fat tissue and increased risk of developing cardiovascular diseases. Adipose tissue produces different adipocytokines that could explain the relationship between excess of fat tissue and increased metabolic risk. Adipsin, omentin and vaspin are adipocytokines which are still not well examined. **Objective and hypotheses:** To estimate the effect of 6 months GH therapy on serum concentrations of adipsin, omentin and vaspin in prepubertal children with isolated GHD. **Method:** The 32 (22 boys, ten girls) non-obese, short children with GHD (mean height 117.9 cm, −2.77 SD, mean BMI −0.75 SD), mean age 8.87 years. Control group (CG) consisted of 18 (11 boys, nine girls) age matched healthy children (mean height 125.8 cm, −0.93 SD, mean BMI −0.28 SD). Serum fasting adipsin, omentin and vaspin were measured in all children: in CD group and in GHD children before and after 6 months of GH therapy. In statistical analysis *t*-student and U Mann–Whitney tests were applied. **Results:** The mean serum concentrations of adipsin, omentin and vaspin did not differ significantly between children with GHD before start of GH treatment and control group. Mean adipsin concentration in GHD untreated patients and in CG children was 890.4 and 826.8 ng/ml respectively. Mean omentin concentration in GHD untreated patients and in CG children was 352.3 and 316.0 ng/ml respectively. Mean vaspin concentration in GHD untreated patients and in CG children was 0.126 and 0.123 ng/ml respectively. Adipsin and omentin concentrations were significantly lower after 6 months of therapy comparing to results before commencing GH therapy (890.4 vs 777.9 ng/ml, $P<0.01$ and 352.3 vs 314.5 ng/ml, $P<0.05$ respectively). Vaspin concentration was significantly higher after 6 months of therapy comparing to results before starting GH therapy (0.164 vs 0.106 ng/ml, $P<0.05$). **Conclusion:** GH therapy causes lowering of adipsin and omentin and increasing of vaspin in non-obese children with GHD. **Funding:** This work was supported the Department of Health Sciences University of Jan Kochanowski in Kielce (internal grant).

P2-412

Final Height and Safety Outcomes in GH-Treated Children Born Small for Gestational Age: Experience from the Prospective GeNeSIS Observational Study

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Background: GH treatment in children born small for gestational age (SGA) has both short- and long-term growth-promoting effects and is approved in Europe and the USA (recommended dosages 0.25–0.47 mg/kg per week). **Objective and hypotheses:** To assess final height (FH) and safety outcomes in SGA patients receiving GH treatment in routine clinical practice using data from GeNeSIS. **Method:** 1208 GH-treated SGA patients were enrolled (114 Russell-Silver syndrome, 111 other known cause, 932 unknown cause). FH (defined by ≧1 of: closed epiphyses, height velocity <2 cm/year, bone age >14 years (girls)/ >16 years (boys)) was available for 203 patients (FHPop1). Subanalyses were performed for patients with baseline age ≧4/ <11 years and ≧5 years GH treatment (FHPop2, N=62) and another subset with initial GH dose ≧0.2/<0.3 mg/kg pe week (FHPop3, N=26). **Results:** Mean±SD baseline ages for FHPop1, FHPop2, and FHPop3 were 10.9±3.1, 8.3±1.7, and 8.9±1.9 years respectively; height SD scores (SDS) were −2.6±0.9, ∓2.8± 0.9, and −2.6±0.8. Initial GH dose was 0.28±0.10 mg/kg per week, increasing by ≤12% (all FHPops). FH SDS for FHPop1, FHPop2, and FHPop3 were −1.5±0.9, −1.3±0.8, and −1.1± 0.8 respectively, at 16.1±1.5, 16.0±1.2, and 16.0±1.2 years of age, and after 5.0±2.9, 7.5±1.8, and 6.8±1.5 years of GH treatment; height gains were 1.1±1.0, 1.5±0.8, and 1.4±0.9 SDS respectively. ≧1 adverse event was reported for 283/1111 (25%) SGA patients vs 5 552/20 060 (28%) for all patient diagnoses in the database. Adverse events reported at ≧2.0% were precocious puberty (3%), headache, hypothyroidism, arthralgia, and ADHD (all 2%). Notable events included two deaths (displaced ventriculoperitoneal shunt; MELAS syndrome), one malignancy (lymphoma), and four diabetes cases (two type 2, one type 1, and one associated with MELAS). **Conclusion:** Height gains for SGA patients in GeNeSIS were similar to those in previous studies with dosage similar to that approved in Europe; younger age at treatment start was associated with greater height gain. No new safety concerns were identified. **Conflict of interest:** Author is an employee and stockholder of Eli Lilly and Company. **Funding:** Sponsored by Eli Lilly and Company.

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Results up to January 2015 from PATRO Children, a Multi-Centre, Non-Interventional Study of the Long-Term Safety and Efficacy of Omnitrope® in Children Requiring GH Treatment

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Background: PATRO Children is an international, open, longitudinal, non-interventional study designed to evaluate the long-term safety and efficacy of Omnitrope®, a biosimilar recombinant human GH (rhGH). **Objective and hypotheses:** Long-term safety of Omnitrope® is the primary objective of PATRO Children (particularly the diabetogenic potential of GH in short children born small for gestational age, the risk of malignancies, and other safety signals associated with GH therapy in Prader-Willi syndrome). Long-term efficacy of Omnitrope® is a secondary objective. **Method:** The study population includes infants, children and adolescents receiving treatment with Omnitrope® according to local prescribing information. To evaluate safety, all adverse events (AEs) are monitored and recorded. Laboratory values (including glucose metabolism and anti-hGH antibodies) are requested at least once a year. To evaluate efficacy, height SD score (HSDS), height velocity (HV) and HVSDS are calculated using height measurements and country-specific reference tables. **Results:** As of January 2015, 3928 patients have been recruited from 270 sites across 14 countries. The mean (SD) treatment duration is 27.0 (19.9) months. One case of new-onset diabetes has been reported. There have been no clinically relevant positive anti-hGH antibody titres in the patients tested so far. A total of 156 patients (4.0%) have experienced treatment-related AEs and 139 (3.5%) have experienced a serious AE (SAE). SAEs were considered treatment-related in eight (0.2%) patients. There have been no reports of GH-related malignancies and no additional safety concerns. Efficacy data indicate that Omnitrope® has a positive effect on growth parameters in prepubertal children across indications, irrespective of gender and pre-treatment status. **Conclusion:** Results to date show that Omnitrope® is safe and well tolerated across paediatric indications, and is effective in the majority of children. PATRO Children will continue to extend the evidence base for Omnitrope®, and GH use in general, in the paediatric population. **Conflict of interest:** ES and MZ are employees of Sandoz. **Funding:** This work was supported by Sandoz International GmbH.

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GH Treatment Prevents Hypoxia-Induced Decrease of GH and IGF1 Plasma Concentrations in Neonatal Mice

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Background: Hypoxia represents a main risk factor for acquired brain injuries and neurological disabilities in premature and full-term infants. Stabilization of hypoxia-inducible transcription factors (HIF) is one of the most important adaptive mechanism modulating the degree of hypoxic-ischemic brain lesions due to cellular adaptation to reduced oxygen concentrations. Additionally, neuro-protective effects of GH and GH-induced neurotrophic factors are evident as shown by previous *in vitro* studies. **Hypothesis:** GH treatment prevents hypoxia-induced disturbances of the GH/IGF1 axis mediating protective effects under global hypoxia during early brain development. **Methods:** At postnatal day 7 (P7) 180 mice were randomized into treatment groups of eight animals and exposed to normoxia or hypoxia (8% O_2) for 6 h using an INVIVO$_2$400 hypoxia workstation (Baker Ruskinn). Within 30 min after re-oxygenation and once daily for three consecutive days, mice were injected (i.p.) with 10–4 000 µg/kg hGH (Genotropin, Pfizer). Body weight and length as well as mGH and IGF1 plasma concentrations were monitored. **Results:** Mice treated with 10–250 µg/kg hGH gained 72% less weight ($P<0.0001$) until P10 and were significantly shorter than non- or sham-treated mice. Growth retardation persisted until P21 in mice dosed with 10 and 50 µg/kg hGH and were correlated to significantly decreased mGH and IGF1 plasma concentrations. Hypoxia-exposed non- and sham-treated animals gained significantly less weight ($P<0.0001$) between P7 and P10 than normoxic litter mates. Simultaneously, exposure to hypoxia significantly decreased plasma mGH ($P<0.05$) and IGF1 levels ($P<0.05$) for at least 1 week. Notably, treatment with 1 000 and 4 000 µg/kg hGH restored hypoxia-induced disturbances of the GH/IGF1 axis compensating hypoxia-associated growth deficiency in neonatal mice. **Conclusions:** Our data clearly indicate that GH treatment stabilizes the somatotropic axis after perinatal systemic hypoxia preventing hypoxia-induced disturbances of the GH-/IGF1 system. Furthermore, demonstrating GH-dose-dependent and hypoxia-induced effects on GH regulation, our present study extends present knowledge on GH regulation during early development serving as a promising basis for further research on neuro-protective mechanisms of the immature rodent brain. **Funding:** This study was supported by an unrestricted grant from Pfizer (WI178424).

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The Pharmacokinetics and Pharmacodynamics of TV-1106, a Once Weekly GH Supplement: Results from a Phase 2 Study of TV-1106 in Adults with GH Deficiency

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Background: TV-1106 (Teva Pharmaceuticals Ltd) is a genetically fused recombinant GH (rhGH) and human serum albumin in development as a once weekly treatment of GH deficiency (GHD) in children and adults. TV-1106 has an extended duration of action compared to daily rhGH treatment, reducing the frequency of injections. **Objective and hypotheses:** The pharmacokinetics and pharmacodynamics of TV-1106 were evaluated in phase 2 study using non-compartmental analysis (NCA) performed on serum concentrations of adults with GHD during week 12 of TV-1106 treatment. **Method:** Patients with GHD (N=93) on stable rhGH treatment and having a normal IGF1 level (−1.5 to +2.0 SDS) participated in screening; to be eligible for randomization, they had to demonstrate reduction of at least 1 IGF1 SDS from screening during a 4 weeks washout period and IGF1 SDS <0 post washout. Of 41 patients randomized to TV-1106, 31 were included in pharmacokinetic analyses and were divided into one of four TV-1106 dose quartiles (3.36–<8.96 mg, ≧8.96–<12.32 mg, ≧12.32–<15.12 mg and ≧15.12–≤31.92 mg). 11 patients received daily injections of Genotropin as an active control. **Results:** There was a wide variability in plasma concentrations of TV-1106 with the highest overall exposure based on C_{max} and $AUC_{0\text{-}t}$ observed for highest dose quartile and substantially less exposure for three lower dose quartiles. Overall pharmacodynamic effect of TV-1106 on IGF1 levels followed a similar pattern with mean IGF1 C_{max} values highest for highest dose quartile and lowest for lowest dose quartile. Mean C_{max}, the maximum levels of C_{max} in SD score (SDS) units, and median T_{max} IGF1 values were similar between the TV-1106 and Genotropin groups. **Conclusion:** Adult patients with GHD, previously stable with daily rhGH treatment, when given weekly TV-1106 administration show IGF1 levels comparable to Genotropin. **Funding:** This work is supported by the Research and Development Division of Teva Pharmaceuticals Ltd. Israel.

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Effects of GH Treatment on the Heart in Children with GH Deficiency

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Introduction: GH deficiency (GHD) in adults is associated with impaired cardiac function, contributing to increased mortality due to cardiovascular disease. Research has shown that adults with GHD have high levels of brain natriuretic peptide as a measure of cardiac function. GH replacement therapy can improve cardiac function and lower BNP levels. The scarce research carried out in children appears to show that GHD is linked to decreased left-ventricle size and reduced left-ventricle mass, although heart function is unimpaired. Therapeutic action from childhood onwards could contribute to lowering mortality due to cardiovascular disease in GHD patients. **Aim:** To evaluate the effects of GHD on cardiac function and left-ventricle mass, and the effects of GH replacement therapy on these. **Material and methods:** This observational, prospective, case-control study examined 41 prepubertal children aged under 12 with diagnosed GHD before and 6 months after GH replacement therapy, and 41 age-matched healthy controls. The following were recorded: age, body surface area, blood pressure and heart rate; ecocardiographic morphological data (ventricular mass, left-ventricle systolic and diastolic diameter), cardiac function (LV systolic and diastolic function, E/A ratio, E/E' ratio, isovolumic relaxation time); RV function (TAPSE); and BNP elevels. For statistical analysis, data were subjected to Student's t test, with a significance level of $P<0.05$. **Results:** Indexed left ventricular mass was lower in GHD patients than in controls; systolic and diastolic function were similarly normal, and no inter-group difference was found for heart-rate, blood-pressure or BN levels. After 6 months' replacement therapy, indexed left ventricular mass had increased in GHD patients, while systolic and diastolic cardiac function remained normal. **Conclusions:** GHD in children is associated with lower left ventricular mass, though cardiac function is unimpaired. GH replacement therapy prompts an increase in left ventricular mass without affecting normal systolic and diastolic function. Acting on risk factors from childhood onwards may help to reduce mortality due to cardiovascular disease in adults.

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GH Therapy in Skeletal Dysplasias: Final Height Data

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Background: Skeletal dysplasias are characterised by bone-cartilage involvement and impairment of growth and body proportions. Reports of the benefits of GH treatment are difficult to evaluate for the small number of subjects, short period of treatment, few final height (FH) data in groups with and without GH deficiency (GHD). **Objective and hypotheses:** The aim of our study was to assess FH and body proportions in pts with skeletal dysplasia and GHD. **Method:** We studied 24 patients treated with GH (25–30 μg/kg per day) for 6.5±3 years: six patients with achondroplasia (ACH), four with hypochondroplasia (HCH), four with pseudoachondroplasia (PSACH), three with spondylo-epiphyseal dysplasia congenital (SEDC), four with spondylo-epi-metaphyseal dysplasia (SEMD) and three

with Leri-Weill dyschondrosteosis (LWD). **Results:** At the beginning of therapy mean age was 7.3±3 years and at FH was 16.3±1.6 years. At FH, mean SDS height gain (HG) was positive only in HCH (0.2±1.1 SD) and LWD (0.5±0.75 SD). At multiple regression analysis SDS-HG was related to treatment duration ($P<0.0001$) and growth velocity at the 1st yr of therapy ($P<0.009$) . At FH mean SDS sitting height (SH) was significant lower than baseline in ACH (−1±1.3 SD) and in HCH (−0.3±1.4 SD), while mean SDS subischial leg lenght (SLL) was significantly higher than pre-therapy in ACH (0.9±1.8 SD), HCH (0.5±1.4 SD) and LWD (0.7±1.9 SD). Pre-therapy mean IGFI was −0.3±1.2 SD, at the 1st year of treatment 1±0.9 SD and at FH 0.7±1 SD. **Conclusion:** In HCH GH therapy mildly impoved FH and body proportions, in LW enhanced FH, in ACH only body proportions were improved. SEMD, SEDC and PSACH pts had no HG and should not be treated. Waiting for new pharmacological treatments for FGFR3 related conditions, GH therapy, in presence of GHD, should be considered in HCH and in ACH associated with surgical lengthening of limbs, to improve FH and body proportions.

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Random Forest Classification Predicts Response to Recombinant GH in GH Deficient Children Using Baseline Clinical Parameters and Genetic Markers

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Background: Prediction of response to recombinant GH (r-GH) is currently based on regression modelling. This approach generates a prediction equation which can be applied to data from an individual child. However this method can underestimate the effect of inter-dependent variables. Random forest classification (RFC) is an alternative prediction method based on decision trees that is not sensitive to the relationships between variables. **Objective and hypotheses:** To assess the predictive value of RFC in GH deficient (GHD) children. **Method:** We used pre-pubertal GHD children (peak GH (GH) <10 µg/l) from the PREDICT long-term follow-up study (NCT00699855, $n=113$) and the PREDICT validation study (NCT01419249, $n=293$). Single nucleotide polymorphisms (SNP) associated with 1st year growth response to r-GH ($n=22$) were genotyped. RFC was undertaken to identify variables associated with growth response (change in height (cm)) using the baseline clinical variables of gender, age, GH peak, GH dose, distance to target height SDS and mid-parental height SDS. Accuracy ((true positives+true negatives)/total population) of the RFC models was assessed and a variable importance score (VIS) calculated by permutation. **Results:** RFC demonstrated that basal clinical variables could predict growth response with high accuracy (80.6%, $P<1.1\times10^{-39}$). The variables were ranked by VIS as follows: 1/GH peak 2/gender 3/age 4/mid-parental height SDS and 5/distance to target height SDS. The addition of genetic data could not improve prediction (accuracy 80.7%, $P<2.8\times10^{-38}$); however SNPs alone could act as weak but distinct predictors of growth response, accuracy (accuracy 65.4%, $P<1.9\times10^{-13}$). The SNPs with predictive value were rs1024531 (*GRB10*) and rs7101 (*FOS*). **Conclusion:** The Ranke regression model[1] predicts 65% of the variability in first year response in GHD with GH peak as the most significant variable. RFC also predicts response and identifies GH peak as the most important variable. Interestingly, two genetic markers alone can provide a level of prediction. **Conflict of interest:** Dr Adam Stevens has received honoraria as an investigator from Merck Serono. **Funding:** The PREDICT study was supported by Merck Serono S.A - Geneva, Switzerland.

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Safety Evaluation of Long-Term Recombinant GH Treatment in Childhood: Interim Analysis of the NordiNet® International Outcome Study (IOS)

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Background: Long-term safety data are reported for paediatric patients treated with recombinant GH (GH; Norditropin®, Novo Nordisk A/S) at the treating physician's discretion and enrolled in the observational NordiNet® International Outcome Study (IOS) (NCT00960128). **Objective and hypotheses:** To evaluate incidence rates (IR) (events/1 000 patient-years) of adverse drug reactions (ADR), serious adverse events (SAE), and serious ADR (SADR). **Method:** Events were classified by MedDRA Preferred Term/System Organ Class. Patients were categorised by long-term mortality risk (sub-groups): low (idiopathic GH deficiency (IGHD)/idiopathic short stature (ISS), 62.4%; small for gestational age (SGA), 37.6%), intermediate (multiple pituitary hormone deficiency, clinically defined syndromes), or high risk (patients treated for malignancy, craniopharyngioma, chronic renal failure). IR during GH treatment were calculated by risk group and mean GH dose up to the event (µg/kg per day; % patients): 0–20 (4.6%), 20–30 (27.2%), 30–40 (46.5%), >40 (21.6%). **Results:** Data for 15,067 patients (male 57%, mean (SD), baseline age 8.70 (3.89) years; treatment duration, 3.99 (2.90) years) treated during 1998–2014 were analysed. 342 events were reported in 297 patients. IR for

ADR, SAE and SADR were greater in the high- than low-risk group (Table 1), but were similar between the IGHD/ISS and SGA subgroups (3.13, 1.73, 0.61 vs 2.38, 1.77, 0.61 respectively). Five neoplasms/malignancies/cardiovascular events/nervous system disorders were reported in five patients in the low-risk group (benign oral neoplasm, brain neoplasm, T-cell lymphoma, hypotension and benign intracranial hypertension). For all event types, no association between IR and GH dose up to the event was found in any of the risk groups. **Conclusion:** NordiNet® IOS data show a good safety profile for paediatric GH therapy. **Conflict of interest:** LS: member Nordinet® IOS ISC, consult. (Ferring, Novo Nordisk [NN], Merck Serono, Pfizer, Sandoz); grants (Merck-Serono, NN, Pfizer). TRR: Nordinet IOS ISC; consultation and speaker fees (Ferring, NN, Merck Serono, Pfizer). OB: Nordinet IOS ISC. EP, BTP: NN employees. M-TS: none **Funding:** This study was sponsored by Novo Nordisk Health Care AG.

Table 1.

	Incidence rate, events/1 000 patient-years (P vs low-risk)		
	Low risk ($n=9269$)	Intermediate risk ($n=4992$)	High risk ($n=806$)
ADR	2.85	3.78 ($P=0.0544$)	8.66 ($P<0.0001$)
SAE	1.74	4.35 ($P<0.0001$)	12.82 ($P<0.0001$)
SADR	0.61	1.28 ($P=0.0101$)	4.50 ($P<0.0001$)

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Hypoglycaemic Adverse Events Reported in Children Enrolled in the European Increlex® Growth Forum Database in Europe (5-Year Interim Data)

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Background: The post-authorisation registry, European Increlex® (mecasermin (rDNA origin) injection) Growth European Increlex Growth Forum Database (EU-IGFD), initiated in December 2008, collects safety and efficacy data in children receiving Increlex® for growth failure. Hypoglycaemia has been reported as a common adverse event (AE) during any IGF1 replacement therapy in randomised clinical trials, and is therefore of interest in real-life settings captured in registries. **Objective and hypotheses:** To investigate hypoglycaemic AEs reported in the EU-IGFD registry and identify predictive factors. **Method:** Multicentre, open-label observational study, multivariate analysis. **Results:** As of 2 October 2014, 61 hypoglycaemic events (27 suspected, 26 verified, eight not specified) were reported in 34/200 patients of the safety population (17.0%), making them the most frequently reported targeted AE. Eight serious AEs of hypoglycaemia were reported in five patients. In three patients, episode(s) occurred following fasting or exercise without food intake. In patients with hypoglycaemia, diagnosis of Laron syndrome (LS) was more common (35.3% vs 10.2%, $P<0.001$) and they tended to be younger at first Increlex® intake (median age: 8.9 vs 10.8 years, $P=0.165$) and to have more often prior history of hypoglycaemia (11.8% vs 4.8%, $P=0.133$). In the multivariate analysis, only LS was identified as predictive factor for hypoglycaemia (OR (CI 95%): 0.21; (0.09; 0.50)). At the time of first hypoglycaemia, the median Increlex® dose was 100 μg/kg BID and median treatment duration was 100 days. Increlex® dose at 1 year ($\leq$100 μg/kg vs $>$100 μg/kg) was not clearly associated with the occurrence of hypoglycaemia (Gehan test $P=0.16$). **Conclusion:** Rates of hypoglycaemic AE reported in Increlex®-treated patients in the EU-IGFD registry were similar or lower than rates reported previously (14–86%). LS was identified as an independent predictive factor for occurrence of hypoglycaemic AE while age and dose were not. **Conflict of interest:** AH and CS: employees of Ipsen. MP and JW: advisory boards for Ipsen and Novo Nordisk. **Funding:** This work and the study on which it is based were supported by Ipsen.

P2-421

Application of Neural Networks for Final Height Prediction Based on Pre-Treatment Data in Children with GH Deficiency Treated with GH

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Background: Prediction of the effectiveness of GH therapy in children with short stature is an important issue. Artificial neural networks (ANN) seem to be promising tool for this purpose, not requiring any assumption on functions linking independent and dependent variables. **Objective and hypotheses:** The aim of the study was to compare ANN models of GH therapy effectiveness, based on the data available at therapy onset with multiple linear regression (MLR) model. **Method:** Retrospective analysis comprised the data of 150 short children (101 boys), diagnosed with isolated GH deficiency, treated with GH up to the attainment of final height (FH). The following parameters (input variables) were assessed before treatment for each patient: gender, chronological age, bone age, mothers' and father's height, pubertal status, height velocity, GH peak after falling asleep and in two stimulation tests, IGF1 and IGFBP-3 concentrations, birth weight and gestational age. The output variable was FH or FH SDS. **Results:** The best MLR model included height SDS of the patient and of parents, pre-treatment height velocity and IGF1 SDS as

significant variables and explained 44% of variability of FH SDS in learning group and 36% in testing group, with the mean error (RMSE) of predicted FH 3.5 and 3.8 cm respectively. The best ANN model for the same input variables explained 43% of variability of FH SDS for learning group and 40% for testing group with RMSE 3.6 and 3.7 cm respectively. The best ANN model eliminated GH peak after falling asleep and father's height and explained 86% of variability of FH SDS for both learning and testing group with RMSE 3.2 and 3.4 cm respectively. **Conclusion:** Neural networks are more accurate in FH prediction and explain more variability of FH in children with isolated GH deficiency than linear regression.

P2-422

Physical Performance and Right Ventricular Function in Children with GH Deficiency before and after 12 Months-GH Replacement Therapy

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Background: Several metabolic abnormalities, including unfavourable lipid profile, impaired cardiac performance, muscle strength and endurance capacity have been documented in GH Deficiency (GHD) adults. Alterations in cardiac morphology and left ventricular function and early markers of cardiovascular risk have been also detected in GHD children; however, no studies have so far investigated the effects of GHD on physical performance and right ventricular (RV) function in childhood. **Objective and hypotheses:** To evaluate the effect of GHD and GH therapy on physical performance and RV function in children. **Method:** 18 GHD children (13.0±2.2 years) and 18 age-, sex- and BMI-matched controls performed cardiopulmonary exercise testing (CPX) and echocardiography before and after 12 months of GH therapy. CPX was performed according to a multistage treadmill protocol. Children were asked to perform the test until they were unable to continue it because of dyspnea or fatigue. Measurements of oxygen consumption (VO2) were taken at rest and during exercise. The maximum VO2 (VO2max) and maximum power output (Wpeak) were defined as the highest VO2 and power output values measured during the exercise. RV function was assessed recording the following measurements: RV fractional area change (RVFAC) and Tricuspid annular plane systolic excursion (TAPSE). **Results:** GHD children compared to controls showed significantly reduced values of VO2max (22.8±4.8 vs 26.4±4.93 ml/Kg per min, $P=0.03$) and Wpeak (80.0±30 vs 101.0±31 watts, $P=0.04$) at baseline. No difference was found in RVFAC (51.39±7.16 vs 49.31±12.1%) and TAPSE (2.18±0.26 vs 2.06±0.3 mm). GH therapy was associated with a significant increase in VO2max (26.32±5.04; $P=0.04$) and a slight improvement in Wpeak (94.06±27.37). RVFAC and TAPSE did not significantly change during GH treatment. **Conclusion:** Our results suggest that aerobic and anaerobic capacity are impaired in children with untreated GHD and are restored by few months of GH replacement therapy. No significant alterations were found in RV cardiac function.

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The Accuracy of Bioelectrical Impedance Analysis to Detect the Body Composition Changes in Adolescents with Severe GHD During Transition

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Background: Male adolescents with severe GH deficiency show both loss of lean body mass (LBM) and gain of fat free mass (FFM) when off GH treatment. We recently showed that determining gain of FFM and loss of LBM by dual-energy x-ray absorption (DXA) is helpful in the diagnosis of severe GHD during transition as these body composition changes are correlated to the GH-peak of the arginine-GHRH-re-test. **Objective and hypotheses:** We wanted to explore if the measurement of body composition by multi-frequency arm-to-leg bioelectrical impedance analysis (mf-BIA) can substitute DXA during transition. **Method:** In total 40 male adolescents with childhood-onset GDH (age 14.7–19.6 years; mean 16.5±1.1 years)) underwent an examination of their body composition at time 0 and +6 month after stop of GH-treatment. At +3 month an arginine-GHRH-test was performed. A GH-peak less than 16 ng/ml indicated severe GHD. LBM and FFM were measured by DXA and mf-BIA at the same day under fasting conditions. The body composition changes score (BCC score) was calculated as the sum of gain of FFM and loss of LBM between time 0 and time +6 month. **Results:** BIA failed at eight patients due to technical problems. Six patients were diagnosed with sGHD. All had a BIA-BCC larger than 4.5 kg and a DXA-BCC larger than 7.0 kg. Using these BCC scores as cut-offs, false positive BCC scores were found in eight of 28 patients (29%) with normal GH response using BIA and in two of 34 patients (6%) using DXA. The correlation of the GH-peak to BIA BCC score was lower ($r=0.33$) than to DXA BCC score ($r=0.55$). **Conclusion:** BIA is comparably sensitive, but less specific than the gold-standard DXA in detecting body composition changes in male adolescents with severe GHD during transition.

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Timing of GH Peak in Provocation Tests is Important in Predicting the Effectiveness of Treatment with rhGH in Prepubertal Children with GHD

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Background: Peak GH level during stimulation tests (STs) stands as an important parameter in growth prediction models and recently it was shown that timing of the peak value in glucagon stimulation test (GST) may be an important indicator of growth hormone deficiency (GHD). **Objective and hypotheses:** To detect a possible relationship between timing of the peak value of GH during STs and the effectiveness of treatment with rhGH in children with idiopathic GH deficiency (iGHD). **Method:** We retrospectively studied 92 patients with iGHD (57 boys, mean age at diagnosis: 9.93 years). Diagnosis was confirmed with two different STs, GST and clonidine stimulation test (CST). Auxological parameters were recorded and SD scores were calculated according to sex- and age- matched population. Observed and predicted (according to KIGS Prediction Model) height velocity (HV) during the first year of treatment and the index of responsiveness IoR were calculated for the prepuberdal children ($n=65$). Atypical GST was defined as that with peak GH value at time 0', 30', 60' and 180' whereas atypical CST that with peak timing at 0', 30' and 120'. **Results:** Atypical GST was recorded in 18 patients (19.6%). IoR was lower in the prepubertal children with atypical GST (-1.81 ± 0.67 vs -1.34 ± 0.85 $P=0.051$). In the CST the 19 children who had atypical timing had significantly lower height SDS (-2.35 ± 0.51 vs -2.07 ± 0.51 $P=0.032$), lower target height SDS (-0.52 ± 0.58 vs -0.5 ± 0.72 $P=0.02$), and a significant lower IoR (-1.86 ± 0.66 vs -1.35 ± 0.84 $P=0.047$). When the patients were categorized according to the number of atypical tests, significant differences in the IoR were found (-2.09 ± 0.68 with two atypical STs ($n=6$), -1.64 ± 0.61 with one atypical ST ($n=16$) and -1.29 ± 0.87 with no atypical ST ($n=43$), $P=0.048$). **Conclusion:** The presence of atypical ST correlates with lower response in the rhGH treatment of prepubertal children with iGHD.

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Comparison of Baseline Parameters and Response to GH Treatment in 125 Children with Short Stature with Eight Different Diagnosis

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Background: Response to rhGH treatment is variable among GH deficiency (GHD), GH insensitivity and several intermediate conditions. **Aims and objectives:** To compare baseline parameters and response to rhGH treatment in eight diagnostic categories of patients with short stature. **Methods:** We selected 125 prepubertal children presenting at least 2 years of rhGH treatment (mean 5.29 years, range 2–15.6 years), hormonal and clinic parameters alterations ($0<$IGF1 <-2 SDS and/or GH stimulated peak secretion <8 μg/l and $H<-3$ SDS or HV <-2 SDS or $H<-2$ SDS + $HV<-1.5$ SDS). We divided patients in eight groups: 19 organic-GHD (GHD-O), 19 isolated idiopathic-GHD (GHD-II), 16 neuroscretory dysfunction (NSD), 14 radio-treated-GHD patients (rt-GHD), 15 ISS, 11 SGA, 11 SHOX-Deficiency, 20 Turner syndrome (TS). Changes in height and in height velocity SDS at 1 year and at the last visit were evaluated in relation to years of treatment and average doses of rhGH. **Results:** At the 1st year all groups gained >1 height SDS. At the last visit, GHD-O gain 1.78 ± 1.58 SDS, SGA 1.07 ± 0.4 SDS, NSD 0.90 ± 0.65 SDS, ISS 0.84 ± 0.66 SDS, GHD-II 0.72 ± 0.55 SDS, SHOX-D 0.72 ± 0.49 SDS, TS 0.23 ± 0.61 SDS, rt-GHD 0.05 ± 1.84 SDS. Statistical significant differences in height gain SDS at the last visit were found between: GHD-O vs rt-GHD (P 0.0014); GHD-O vs GHD-II (P 0.0246); rt-GHD vs GHD-II (P 0.0154); rt-GHD vs NSD (P 0.0112); SHOX-D vs TS (P 0.0318), while was not found between GHD-II vs BSI (P 0.3228). **Conclusions:** rhGH treatment improves the short-term response in all groups and the long-term response in most patients: GHDO has the better response, radio-treated patients have the lowest, GHDII and ISS intermediate comparable response. Our data indicate that it is better review periodically the selection criteria and response to treatment.

P2-426

The Acid-Labile Subunit Dose Matters? Response to Human GH Treatment in Patients with Acid-Labile Subunit Deficiency

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Background: In patients with acid-labile subunit (ALS) deficiency, the inability to build ternary complexes results in a marked reduction of circulating total IGF1. Height reduction by heterozygosity is about 1 SD in comparison to wild type. In homozygosity or compound heterozygosity a height loss of -2 to -2.5 SD occurs. This is suggestive of a gene-dose effect. How does treatment with human GH influence height development in relation to the underlying genetic defect and the ALS concentration? **Patients:** We report on two growth retarded boys with documented ALS deficiency. Patient 1 has a homozygous mutation and undetectable ALS and IGF1 concentrations, and patient 2 has a heterozygous mutation and low levels of ALS and IGF1. Patient 1 had an age of 6.7 years and a height of -3.03 SD and patient 2 an

age of 15.8 years and a height of – 1.9 SD when GH treatment was started. After GHD exclusion the patients were treated with GH in escalating doses up to 0.05 mg/kg bw/day. **Results:** Patient 1 did not profit from treatment with GH and showed no increase in height-SD. We also used recombinant IGF1 to improve his height development, without any success. There was no change in IGF1 levels throughout treatment. His near final height is −3.0 SD. Patient 2 with low, but detectable IGF1 and ALS levels improved his height during GH treatment and his final height is at −0.4 SD. During GH treatment his IGF1 levels increased. **Discussion:** In patients with an absolute deficiency of ALS, treatment with either GH or IGF1 might be without use. However, those patients with low but detectable IGF1 and ALS levels, and a heterozygous mutation, might profit from GH treatment. We speculate that the ALS dose could matter when weighing treatment options in height reduction in ALS deficiency.

P2-427

rhGH Replacement Therapy Ameliorates Body Composition Substantially but has No Effect in the Quality of Life in Adolescents with GH deficiency – A Cross-Sectional Study

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Background: GH is fundamental in skeletal growth during puberty, however detailed studies of body composition analyses in adolescents with GH deficiency on GH therapy are scarce. Moreover, there are few studies on the psychologic aspects of hrGH therapy in this population. **Objective and hypotheses:** In this case-control study, we investigated differences in body composition based on bio-impedance measurements between adolescents with idiopathic GH deficiency (GHD) who were treated with recombinant human GH (rhGH) for at least 6 months (treatment group) and adolescents with idiopathic short stature who had not received rhGH as yet (control group). **Method:** Participants were evaluated for short stature and underwent dual frequency bio-impedance assessment with the use of the BIA-ACC, BIOTEKNA© device. The questionnaires QUALISSY-C and CODI for short stature coping were distributed in both groups. **Results:** Over a period of 1.5 years, 13 adolescents (ten males, three females; mean age ± SD: 12.66 ± 2.46 years) on rhGH treatment and 12 controls (seven males, five females; mean age ± SD: 13.38 ± 2.02 years) matched for age, height, BMI and bone age, were enrolled. Total ($P=0.047$) and extracellular ($P=0.038$) water volumes were significantly increased in the treatment group. Body cell mass protein ($P=0.023$), extracellular fluid protein ($P=0.022$), bone mass ($P=0.038$), soft tissue mineral content ($P=0.016$) and body calcium ($P=0.017$) were increased, along with increased metabolism of the bones ($P=0.016$) and skeletal muscles ($P=0.022$). Interestingly, no statistically significant differences in fat mass and in the QUALISSY-C and CODI questionnaires were found between the two groups. **Conclusion:** Bio-impedance analysis is a potent, non-invasive tool for assaying body composition, confirming the expected beneficial changes of rhGH treatment. The lack of differences in the psychometric questionnaires may reflect the negative effects of short stature in both groups. **Conflict of interest:** Dario Boschiero is the main investigator of BIOTEKNA srl, Venice, Italy, who provided the devices.

P2-428

Evaluation of the Effect of GH Treatment on Insulin Resistance and Cardiovascular Tissue

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Background: GH treatment may cause insulin resistance, which is associated with metabolic syndrome and co-morbidities. **Objective and hypotheses:** The aim of our study was to evaluate GH deficiency (GHD) patients on GH treatment for

Table 1. (for abstract P2-428)

	GHD ($n=71$)	Control ($n=47$)	P
Age	13.7 ± 2.6 (14;6.8-18.8)	13.3 ± 2.9 (13.2;6.5-18.3)	0.45
Height SDS	−1.7 ± 0.9 (−1.6;−4.0–0.5)	−0.1 ± 0.9 (−0.2;−1.9–2.2)	0.00
Weight SDS	−0.9 ± 1.3 (−1.2;−2.5–6.5)	−0.4 ± 0.8 (−0.4;−2.0–1.6)	0.01
BMI SDS	−0.2 ± 1.9 (−0.6;−1.9–13.4)	−0.4 ± 0.8 (−0.4;−1.9–1.9)	0.62
GLS-SDS	1.35 ± 0.481	1.42 ± 0.5	0.66
CIMT	0.47 ± 0.12	0.41 ± 0.09	0.01
CIMT-SDS	0.018 ± 0.051	−0.003 ± 0.06	0.03

hyperlipidemia, insulin resistance and carotid intima media thickness (CIMT) and left ventricular global longitudinal strain (GLS) and assess cardiovascular tissue level effects of insulin sensitivity. **Method:** 71 GHD patients on GH treatment (54 males, 17 females) and 43 (25 males, 17 females) healthy subjects, matched for sex and age as the control group, were recruited in this study. We performed OGTT in all GHD patients. Insulin sensitivity was evaluated with HOMA-IR and Matsuda index, derived from OGTT. Atherogenic index (AI) and serum lipid levels were evaluated. CIMT and GLS were measured by Doppler and two-dimensional ultrasound techniques. SPSS 15 used for statistical analyses. **Results:** As shown in the Table, there was no difference in BMI SDS between the groups. HOMA-IR, lipid levels and AI showed no statistical difference either. 31 GHD patients showed insulin resistance after OGTT, but there was no patient with glucose intolerance. CIMT and CIMT-SDS values were higher in GHD group ($P=0.01$; $P=0.03$) but there were no differences in GLS-SDS. GLS-SDS and CIMT-SDS values showed no correlation with Matsuda index and HOMA-IR. **Conclusion:** GH treatment in GHD children leads to insulin resistance. CIMT and GLS as feasible techniques may serve as descriptors of possible effects of GH on cardiovascular tissue. **Funding:** This work was supported by Scientific Research Projects Coordination Unit of Istanbul University (Project Number : 46983).

P2-429

Effectiveness of Recombinant IGF1 Treatment in a Patient with Isolated GH IA Deficit Producer of Anti-GH Antibodies

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Background: GH deficiency type IA represents the most serious form of isolated deficit GH (IDGH). It's transmitted as an autosomal recessive pattern and in most cases there is a homozygous deletion of the GH1 gene. Good initial response to treatment is characteristic, although often could appear antibodies against recombinant GH. **Case presentation:** We report a case of a 5-year-old Pakistanist boy evaluated for severe growth failure (heigh <8.07 SDS). No records of the patient's height before the visit were available. No relevant neonatal history and normal psychomotor development. Parents were first cousins with normal height. He presented with low IGF1 levels and GH deficit was confirmed after clonidine test. The karyotype was 46 XY and MRI showed pituitary hypoplasia. There weren't other abnormal hormonal results in blood test. Clinical phenotype consisting on truncal obesity, prominent forehead, and craniofacial disproportion. It was suspected IDGH type IA, and genetic study showed absence of GH1 gene in homozygous. He started on r-hGH therapy. Heigh velocity increased to 12 cm/year with normal IGF1 levels initially, but it dropped to 3.3 cm/year (-3.5 SD) 6 months later, with undetectable IGF1 levels. Presence of anti-hGH antibodies was suspected and confirmed on laboratory analysis. Recombinant IGF1 treatment was started, increasing growth velocity to 10 cm/year without complications in his evolution. **Conclusion:** Development of anti-GH antibodies is an inconstant finding despite identical molecular defects. Response to r-hGH treatment could be different. In our reported case, rIGF1 treatment has been shown as the only possible alternative therapy, resulting highly effective with no side effects. We consider the importance of reporting clinical experience and response to new treatments available for an uncommon pathology.

P2-430

Analysis of CD133+CD45+ Hematopoietic Progenitor/Stem Cells and CD133+/CD45- Very Small Embryonic-Like Stem Cells in Children with GH Deficiency Subjected to GH Therapy

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Background: GH deficiency (GHD) is an endocrine condition, caused by problems arising in the pituitary gland that does not produce sufficient quantities of GH. GHD is treated by replacing GH with one daily injections. Recent studies suggested that GH could be involved in regulation of certain stem cell subset potential and function. However, the exact effects of GH therapy on biology of stem cells in paediatric patients were not studied in detail. **Methods:** Here we aimed to evaluate the levels of very small embryonic-like cells (VSELs) delineated by Lin-CD133+ CD45- phenotype and hematopoietic stem/progenitor cells characterized by Lin-CD133+CD45+ phenotype in relation to treatment with GH. Study groups consisted of children with GH deficiency that were diagnosed with GHD but did not start GH therapy yet; children diagnosed with GHD and treated with GH and healthy controls (HC). Peripheral blood samples were subjected to extracellular staining using fluorochrome-conjugated monoclonal antibodies: anti-CD235 FITC, anti-CD45 PE, anti-CD133 APC, and Lin 1 FITC mixture. Following incubation immunostained blood samples were incubated for with BD FACS Lysing Solution and washed twice to get rid of erythrocytes. **Results:** We demonstrated that children with GHD who were treated with GH presented with higher VSEL, and to a lesser extent, HSC levels than untreated GHD patients. Notably, VSEL and HSC levels were significantly higher in GHD patients treated with GH than in HC. **Conclusion:** Altogether, we propose that GH therapy in GHD paediatric patients can be associated with

expansion of peripheral blood stem and progenitor cells. Further studies assessing the longevity of such phenomenon are still warranted.

P2-431

Effectiveness of rhIGF1 Treatment in a Girl with Leprechaunism

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Background: Infants with severe insulin resistance syndrome show failure to thrive. **Objective and hypotheses:** Effect of rhIGF1 treatment on growth in a patient with severe insulin resistance syndrome. **Method:** Case report. **Results:** The patient is a 4-years-old Caucasian girl of unrelated healthy parents. She was born after a 40 weeks gestation as a small for gestational age infant with a birth weight of 1970 g. After birth she developed high blood glucose levels of >400 mg/dl with high levels of insulin (>2000 mU/ml) and c-peptide (>60 ng/ml), fasting hypoglycaemias and high blood pressure. The molecular analysis revealed two mutations in the insulin receptor gene. At the age of 35 month she was admitted to our hospital. She had decreased subcutaneous fat, hirsutism and acanthosis nigricans. Her body length and weight were 80.4 cm (−3.7 SDS) and 8.8 kg respectively. Levels of IGF1 and IGFBP-3 were extremely low (1 μg/l (−8.0 SDS) and 0.18 mg/l (−9.4 SDS) respectively). We started treatment with rhIGF1 (Increlex©, Ipsen, Ettlingen, Germany) with a dose of twice a day 0.6 mg/s.c. After 1 year at the age of 48 month, her length was 89.6 cm (−3.0 SDS), leading to an increase in length of +0.7 SDS during the 1st year. Levels of IGF1 were 91 μg/l (−0.08 SDS) bevor and 274 μg/l (+2.2 SDS) 2 h after s.c. injection. Levels of IGFBP3 remained low (0.94 mg/l (−3.6 SDS) and 0.82 mg/l (−4.28 SDS) respectively). Treatment was well tolerated, blood glucose levels remained stable and haemoglobin A_{1c} level was within the normal range (5.7%). **Conclusion:** This leprechaun patient has an IGF1 deficient state and rhIGF1 treatment induced catch-up growth.

P2-432

A Perioperative Change of Anti-Mullerian Hormone and E2 in a Patient with Sex Cord Tumour with Annular Tubules

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Background: Sex Cord Tumour with Annular tubules (SCTAT) is a rare ovarian benign tumour accounted approximately for 5% of ovarian tumour. SCTAT is an oestrogen producing ovarian tumour and can cause precocious puberty. For SCTAT, oophorectomy is recommended as the first-line therapy. Since SCTAT has a high rate of recurrence, it is clinically important to find a monitor method that can detect cancer recurrence in an early stage. In the previous reports, E2 and anti-mullerian hormone (AMH) were reported as useful tumour markers. Here, we firstly describe perioperative change of these markers in a pediatric patient. **Case presentation:** 6 years-old girl. She presented with GnRH independent precocious puberty (LH, FSH undetectable, E2 131 pg/ml). Ultrasonography showed a multiple cystic tumour sized in 5 cm in diameter arising from left ovary. Left oophorectomy was performed. The tumour was pathologically diagnosed as SCTAT. We examined AMH and E2 of cystic fluid of the tumour and perioperative blood sample. Cystic fluid and preoperative blood sample showed elevated AMH and E2 (Cystic fluid: AMH 1 830 ng/ml, E2 38 499 pg/ml, Blood sample: AMH 75.7 ng/ml, E2 153 pg/ml). Other ovarian tumour markers such as CEA,CA19-9, CA125 and hCG were all negative. Serum E2 became undetectable after 24 h from operation. AMH was also normalised after 1 month from operation. After 2 years from operation, no signs of relapse has been noted so far. **Conclusion:** AMH and E2 may be used as useful tumour markers in a paediatric patient with SCTAT as it had been reported with adult patient. AMH can be a more useful marker in a paediatric patient since AMH level remains relatively stable from 4 to 8 years of age regardless of patients' pubertal stage.

P2-433

Oral Contraception Vs Low-Dose Pioglitazone-Spironolactone-Metformin for Adolescent Girls with Hyperinsulinaemic Androgen Excess: On-Treatment Divergences

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Background: Hyperinsulinemic androgen excess is the most common cause of hirsutism, acne, seborrhea and menstrual irregularity in adolescent girls. The ovarian androgen excess originates most often from an absolute or relative excess of fat (in adipose tissue and in organs such as the liver) and from the ensuing elevations in insulinaemia and gonadotropin secretion. There is no approved therapy for androgen excess in adolescent girls. The prime recommendation is to reduce body adiposity with lifestyle measures. The addition of an oral estro-progestagen contraceptive (OC) is a standard approach. An alternative is to add an insulin-sensitizing medication for those hyperandrogenic girls who are not sexually active. **Objective and hypotheses:** Here we report a first randomized study comparing the effects of a widely prescribed OC (20 μg ethinylestradiol plus 100 μg levonorgestrel) to those of a low-dose insulin-sensitizing combination with pioglitazone (Pio, only 7.5 mg/d), spironolactone (Spi, 50 mg/d)

and metformin (Met, 850 mg/d) in adolescent girls with hyperinsulinemic androgen excess and without need for contraception ($n=30$). **Method:** Endocrine-metabolic markers, carotid intima-media thickness (US), visceral and hepatic adiposity (MRI). **Results:** Over 1 year, both treatments attenuated the clinical and endocrine measures of androgen excess. However, pioglitazone-spironolactone-metformin (PioSpiMet) had more normalizing effects than OC, particularly on fasting and post-oGTT insulinemia, and on circulating GGT and C-reactive protein (all P between 0.01 and 0.001). OC and PioSpiMet had opposing effects on hepatic adiposity so that, after 1 year, the OC girls had about twice as much liver fat as the PioSpiMet girls ($P<0.0001$). There were no noteworthy side-effects in either subgroup. **Conclusion:** PioSpiMet conferred more broadly normalizing effects than OC over 1 year. Given that adolescence is a potential time window of developmental plasticity (including for the liver), it will be of interest to study whether on-treatment divergences between OC and PioSpiMet girls do persist in the post-treatment phase.

P2-434

Confirmation of Exogenous Serum Estrogenic Activity in a Girl with Premature Thelarche

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Background: The oestrogenic activity of endocrine-disrupting compounds (EDCs) has been reported to be associated with premature thelarche (PT) and precocious puberty. Some years ago, we developed a recombinant cell bioassay to determine serum estrogenic bioactivity (EBA) that is useful in physiology, as well as in the field of the environmental-related endocrine diseases. We recently improved the assay with an evaluation of EBA before and after incubation with estrogen receptor-α (ER-α) ligand-binding domain. Since ER-α is used in limited amounts, it preferentially captures compounds with high affinity, like endogenous oestrogens, with residual EBA being related low-affinity estrogenic compounds like EDCs. **Aims and objectives:** To better characterise the high EBA in a 5-year-old girl with PT. This girl had a low radioimmunological plasma estradiol level (<9 pg/ml) contrasting with high EBA (S1) (Figure 1). Her EBA was 86% of the reference value measured in the presence of 10nM E2, which was taken as 100%, i.e., at a pubertal level. **Methods:** We reevaluated EBA after incubation of the serum sample with ER-α ligand-binding domain. **Results:** EBA remained at 64% of the basal value (S1 ER-α), suggesting that the remaining EBA was potentially due to xenoestrogens (Figure 1). Questioning of the patient's family revealed that hydrating cream was being applied to her skin for eczema lesions. This cream contained parabens. We hypothesized that the cream might be increasing the EBA, and the basal EBA indeed fell to prepubertal levels, i.e., below 20% (S2) (Figure 1), when her mother switched to a cream without parabens or staining, confirming our hypothesis. **Conclusions:** We confirmed the usefulness of our new EBA assay for evaluating environmental endocrine diseases. This should be studied in a higher number of girls with PT.

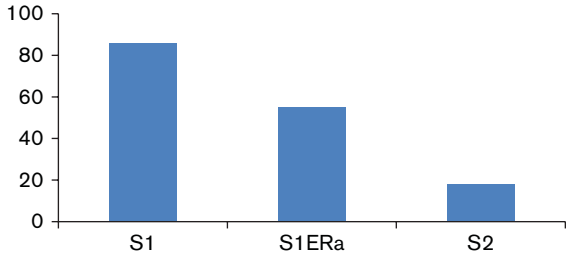

Figure 1 EBA is expressed as the percentage of luciferase activity; the value measured in the presence of 10 nM E2 was taken as 100%.

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Clinical Criteria Remain Paramount for the Diagnosis of Polycystic Ovary Syndrome in the Adolescent Age Group

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Background: Adolescent polycystic ovary syndrome (PCOS) may be difficult to distinguish from pubertal changes and diagnosis remains a challenge. **Objective and hypotheses:** To investigate the value of different biochemical parameters for the diagnosis of PCOS and also to assess the prevalence of non-classical congenital adrenal hyperplasia (NCCAH) among adolescent girls referred for clinical symptoms suggesting PCOS. **Method:** Retrospective data of 114 girls aged 13–18 with a clinical presentation suggesting PCOS were analysed, including results of basal androgens, prolactin, GnRH and ACTH stimulation tests, and pelvic ultrasound. Clinical and laboratory characteristics of girls diagnosed with PCOS (based on Rotterdam criteria) were compared to those of girls having 'Isolated' hyperandrogenism or menstrual irregularities ('non-PCOS'). **Results:** Of the 114 girls, 9 (7.9%) were diagnosed with NCCAH and 87 with PCOS; 18 were non-PCOS. Compared to non-PCOS girls, those with PCOS had a significantly higher prevalence of hirsutism ($P<0.002$), PCO morphology by ultrasonography ($P<0.001$), menstrual irregularities ($P<0.001$) and acne ($P<0.001$). Androstenedione, ($P<0.01$), basal LH ($P<0.02$) and basal LH/FSH ratio ($P<0.002$) were significantly higher in girls with PCOS, but overlap between groups was observed. Peak LH/FSH ratio was similar in both groups. There were no significant differences between the subgroups in any other biochemical or anthropometric parameters. Using stepwise logistic regression, the only predictive factor for PCOS was the basal

LH/FSH ratio, with insufficient sensitivity and specificity. **Conclusion:** While an increased basal LH and basal LH/FSH ratio may support the diagnosis of PCOS in adolescents, the GnRH stimulation test is not contributory. Given the significant prevalence of NCCAH among adolescents presenting as PCOS, an ACTH test should be included in the work-up, at least in populations with higher prevalence. Since no one parameter is diagnostic for PCOS, clinical criteria remain paramount.

P2-436

Gonadal and Sexual Dysfunction in Childhood Cancer Survivors

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Background: Gonadal or sexual dysfunctions are common and important complications of childhood cancer survivors. But few studies have been conducted on these areas, and if any, they are only about gonadal dysfunctions. Semen quality or sexual functions were rarely investigated. **Objective and hypotheses:** We purposed to evaluate prevalence of gonadal failure, semen abnormality, and sexual dysfunction of adolescent/young adult childhood cancer survivors. Risk factors for gonadal failure and semen abnormality were also evaluated. We also hypothesized that a romantic relationship will be affected by gonadal and sexual dysfunction. **Method:** Demographic and medical characteristics were obtained from the patients' medical records. Hormonal evaluation and semen analysis were performed. Sexual function and romantic relationship were evaluated *via* questionnaire. **Results:** Included were childhood cancer survivors aged 15–30 years. More than 2 years should have passed after completion of therapy. Among the 88 participants, 45 (51.1%) were male. Median age at diagnosis and at study was 14.0 and 19.8 years respectively. 12 females (27.9%) needed sex hormone replacement, for which peripheral blood stem cell transplantation was a significant risk factor ($P=0.004$). Among the males, three had testis volume <15 cc, but none were on sex hormone replacement. On semen analysis, 12 among 24 subjects (50%) showed azo/oligospermia. Older age at diagnosis or cyclophosphamide equivalent dose more than 8 000 mg/m^2 was observed to increase risks for azo/oligospermia. 37 (18 males and 19 females) responded to the questions on sexual function. Erectile dysfunction was found in 13 among 18 males. Only six males and six females were in romantic relationship at the time of study. Only one among 13 males with erectile dysfunction and one among 12 females on sex hormone replacement had a lover. **Conclusion:** A significant proportion of childhood cancer survivors have gonadal and sexual dysfunction, which is then thought to affect their romantic relationship. Thus, proper strategies for managing these complications are needed to improve their quality of life.

P2-437

Implementation of a High Sensitive LC-MS/MS Method for Measurement of Oestradiol, Oestrone and Oestriol

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Background: Specific measurement of low serum/plasma concentrations of 17β-oestradiol (E2) is important in pre-pubertal and pubertal children in routine paediatric endocrinology. The role of oestrone (E1) and oestriol (E3) is not as comprehensively well understood in different pediatric endocrine disease states. We describe a method for high sensitivity analysis of estradiol (E2), oestrone (E1) and oestriol (E3) using LC-MS/MS. **Objective and hypotheses:** Determination of E2, E1 and E3 in serum/plasma derived from prepubertal and pubertal children. Implementation of a high sensitive LCMSMS method in daily routine and establish reference ranges of E2, E1 and E3 for children. **Method:** 0.1 ml serum and plasma samples respectively, were combined with stable isotope-labeled internal standard and subsequently, estrogens were extracted by SPE (solid phase extraction). The solvent was evaporated, estrogens were derivatized to form dansyl derivatives, the samples were analyzed using UPLC-MS/MS in positive MRM mode. **Results:** The method was linear from 0.01 nmol/l (3 pg/ml) up to 50 nmol/l (13 600 pg/ml) for E1, E2 and E3. The lowest limit of quantification was 0.018 nmol/l (4.8 pg/ml). Preliminary method-specific reference ranges for children, age, sex and pubertal stage were established. Also preliminarily but expectedly, LC-MS/MS-determined E2 in girls with untreated precocious puberty was significantly higher compared with age-matched controls in contrast to E1 and E3. Obese girls and obese boys (BMI $>$ 97th centile respectively, did not show significantly higher E1, E2, and E3 levels than controls. **Conclusion:** We developed a robust, fast and reliable method for analyzing the major estrogens in the daily pediatric endocrine routine. Our LC-MS/MS-triple-assay will help to get more insights into the differential roles of these three oestrogens in paediatric endocrine development and disease.

P2-438

Gonadal Function in the Prader-Willi Syndrome from Infancy to Adulthood

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Background: Prader-Willi syndrome (PWS), caused by loss of paternally imprinted genes in the 15q11-13 region, results in

Table 1. Serum indices of fertility were (for abstract P2-439).

	AMH (ng/ml) (♀:1.3–7.0 ♂:2–4)	Inhibin B (ng/l) (♀:10–200 ♂:100–400)	Estradiol (pg/ml) (♀:40–250)	Testosterone (ng/dl) (♂:250–1000)	Testes (ml)
HHH	0.94 ± 0.62	8.67 ± 2.88	94.35 ± 40.29	–	–
Female ($n=4$)					
Male ($n=5$)	23.07 ± 21.63	67.0 ± 35.10	–	737.40 ± 312.02	li10.4 ± 8.4 re10.2 ± 8.6
HP	2.76 ± 1.30	60.82 ± 42.29	77.04 ± 101.89	–	–
Female ($n=14$)					
Male ($n=20$)	6.40 ± 3.53	272 ± 170.19	–	629.15 ± 258.24	li19.3 ± 4.3 re19.8 ± 4.3
CAH	3.15 ± 3.77	46.66 ± 49.51	132.81 ± 193.13	–	–
Female ($n=12$)					
Male ($n=9$)	6.03 ± 3.02	180.71 ± 92.10	–	482.78 ± 186.75	li18.6 ± 6.0 re18.9 ± 5.6
TS ($n=23$)	0.31 ± 0.80	114.67 ± 9.07	58.59 ± 30.24	–	–

hypogonadism which is more severe in males. **Objective:** To review the gonadal status of patients seen in a dedicated PWS clinic from 1990–2013 inclusive so as to establish the clinical patterns and hence to optimise future management. **Method:** Retrospective case note review over a 23-year period. **Results:** 80 patients (50 males: 30 females) with PWS due to paternal deletion (51), maternal disomy (20), imprinting centre mutation (2), translocation (1) and unknown (6) were seen, median (range) current age 23 (5–65) years. Females: known age at B2 and menarche was highly variable: range (median) 7.3–14.8 (11.5) ($n=15$) and 11–18.3 (15.3) years ($n=6$) with oligo-amenorrhea in all postpubertal patients. Basal/peak LH and FSH at B4-5 were also variable:0.5–5.3/4.1–35.4 u/l; and 0.8–14.1/6.2–21.3 u/l indicating both central and peripheral hypogonadism. Norethisterone was used to regulate menstrual bleeding in four patients and the combined pill in three girls. Males: Only one boy had normally descended testes. Bilateral/unilateral orchidopexy was recorded in 24/18 patients. Surgery was unsuccessful in nine patients but hCG injections avoided surgery in two boys and brought the testis to the external inguinal ring in five. Age at G2 was 11.7–15.6 (13.1) with maximum genital stage/testicular volume G3/8–10 ml ($n=8$). In boys aged >11 years basal/peak LH&FSH at G1 was 0.5–3.7/0.5–23.1 u/l & 0.8–6.8/0.5–12.4 u/l ($n=8$); and at G3 0.7–7.4/12–80.5 & 0.4–27.7/11.4–53.9 u/l ($n=4$). Testosterone replacement was started in 15 subjects aged 13.9–29.2 years, usually as 100 mg i.m. every 6 weeks. **Conclusion:** Hypogonadism is almost constant in PWS, manifesting as pubertal delay with oligoamenorrhea in girls; cryporchidism and pubertal delay with arrest at G3 in boys; and biochemical features of mixed central and peripheral gonadal impairment in both sexes. Preoperative hCG rarely avoids but may facilitate surgery. Boys require testosterone treatment from around 13 years in order to complete puberty. The case for treating postpubertal girls with oestrogen remains uncertain.

P2-439

Markers of Fertility and Quality of Life in Adolescents with Chronic Endocrine Diseases at the Time of Transition from Paediatric to Adult Care

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Background: 25–50% of paediatric patients with chronic endocrine diseases are lost for follow-up in adult care. **Aims and objectives:** A standardised medical and psychological work-up to identify disease specific morbidity and to comprehend quality of life in adolescents with chronic endocrine diseases at the time of transition from paediatric to adult care. **Methods:** The quality of life (DISABKIDS[1] and KIDSCREEN[2]) and serum markers of fertility (anti-mullerian hormone (AMH), Inhibin B, oestradiol, testosterone) were examined in adolescence after near final height was reached. Results are presented as mean ± S.D. Patients and parents gave informed consent and approval by the local ethics committee was obtained. **Results:** 120 patients aged 14–30.6 years (70 females, 50 males) were recruited: Turner Syndrome (TS) ($n=23$), congenital adrenal hyperplasia ($n=21$), hypopituitarism with hypogonadotrophic hypogonadism (HH) and T/E_2 replacement (HHH; $n=9$), hypopituitarism without HH (HP; $n=34$), SGA short stature ($n=18$) and others ($n=15$). DISABKIDS TRS was 82.3 ± 14.0 (reference 76.9 ± 18.3[1]; n.s.). KIDSCREEN TRS (ten sub-scales) ranged between 64.7 ± 24.9 and 92.9 ± 11.6 (reference 66.8 ± 19.3 and 90.3 ± 15.5[2]; n.s.). **Conclusion:** The quality of life in these patients is normal. HH in girls is associated with lower serum AMH and Inhibin B as in TS. HH in boys is related to higher serum AMH and lower Inhibin B. This may reflect gonadal immaturity in females and males with HH but the relevance for gonadal reserve remains unclear. **Funding:** This study was supported with an unrestricted research grant to Janna Mittnacht from Pfizer.

P2-440

A Novel Androgen Receptor Gene Mutation in Two Patients with a 46, XY Disorder of Sex Development

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Background: Androgen insensitivity syndrome in its complete form (CAIS) is a disorder of hormone resistance

characterised by a female phenotype in an individual with an XY karyotype and testes producing age-appropriated normal concentrations of androgens. Pathogenesis is the result of mutations in the x-linked androgen receptor (AR) gene, which encodes for the ligand-activated AR. We report the clinical, biochemical and molecular features of two affected sisters in whom a novel mutation has been detected. **Cases:** Two sisters were referred presenting primary amenorrhea. A 17-year-old woman (patient 1) and her 15-year-old sister (patient 2) presented with normal breast development (Tanner V) and absent axillary and pubic hair. The phenotype and external genitalia were female. The endocrine profile revealed elevated testosterone and abnormally high LH. Patient 1: Testosterone:5.1 μg/l (2.7–8.3), LH:30 UI/l (2–9), FSH:8 UI/l (2–10), Oestradiol:14 ng/l (20–45); Patient 2: Testosterone:2.7 μg/l (2.7–8.3), LH:36 UI/l (2–9), FSH:7 UI/l (2–10), Oestradiol:12 ng/l (20–45). Transabdominal pelvic ultrasonography showed internal gonads and absence of uterus. Karyotype was 46, XY. Analysis of AR showed a point mutation in intron 5, two nucleotides preceding exon 6: c.2319-2A>G in both. This nucleotide is located in the splice site regulatory transcription region (AG/GT). It can, therefore, be predicted that this mutation gives rise to an anomalous and inactive protein. At present, gonadectomy has been deferred to complete puberal development and optimize bone density, although it will be recommended from the second decade of age to prevent the risk of gonadal tumours. **Conclusions:** This mutation had not been previously reported. AR gene mutation is the most frequent cause of 46, XY disorder of sex development, with a clearly higher frequency in the complete phenotype. Loss of function mutations can be found in most women with suspected CAIS, but only in about 15-20% of subjects with suspected partial androgen insensitivity syndrome (PAIS).

P2-441

The Effect and Pharmacokinetics of Percutaneous Administration of Dihydrotestosterone Gel in Chinese Children with Microphallus

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Background: Percutaneous administration of dihydrotestosterone (DHT) gel has been successful used in promoting phallic growth in children with micropenis. We investigated whether percutaneous administration of DHT gel is similarly effective in Chinese children with microphallus due to various etiologies. **Objective and hypotheses:** To study the pharmacokinetics and effect of percutaneous administration DHT gel in the Chinese microphallus patients. **Method:** 14 patients (age range 1.45–8.47 years) with microphallus of miscellaneous etiologies were studied prospectively. 2.5% DHT gel was applied to the phallus once daily at a dose of 0.3–0.4 mg/kg body weight. Serum DHT concentrations were measured at 0, 2, 4, 8, 12 and 24 h following application of DHT gel. **Results:** Peak DHT concentrations were attained within 2–12 h after application of the gel and subsequently remained within the pre-adolescence range in all but one patient, who remains consistently high level. An increase in phallic growth, ranging from 0.2–1.7 cm in lehgth, 0.1–2 cm in width, and 0.3–1 cm in circumstance was achieved after 3–4 months of treatment in all patients whose DHT concentrations were maintained within pre-adolescence range. **Conclusion:** Percutaneous administration of DHT in a dose of 0.3–0.4 mg/kg once daily for a period of 3–4 months may be useful in the management of patients with testosterone biosynthetic defects in Chinese patients with micropenis prior to reconstructive surgery.

P2-442

Differential Regulation of Serum Sex Hormone Binding Globuling in Polycystic Ovarian Syndrome Girls in Relation to Weight

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Introduction: It is thought that sex hormone binding protein (SHBG) is involved in glucose homeostasis in addition to regulate the levels of sex hormones. Clinical studies associate reduced SHBG concentrations with insulin resistance (IR). **Objective:** To evaluate the relationship of SHBG with IR and hyperandrogenism markers in a group of adolescents affected with polycystic ovarian syndrome (PCOS), and how weight could affect these markers. **Patients and methods:** 35 women aged 12–19 years, who fulfilled Rotterdam diagnostic criteria for PCOS were evaluated. Glucose, insulin, SHBG, testosterone, LH and FSH were determined among other biochemical variables. Homeostasis model assessment-estimated IR (HOMA-IR) and free androgen index (FAI) were calculated. Patients were divided into: normal weight (BMI <25 kg/m^2 ($n=17$) and overweight/obesity (BMI >25 kg/m^2 ($n=19$)). **Results:** SHBG was significantly lower (22.1 ± 11.8 nmol/l vs 35 ± 16.9 nmol/l, $P=0.015$) and HOMA-IR and insulin were significantly higher (5.4 ± 2.8 vs 2.3 ± 0.63 $P=0.001$; 25.6 ± 13.7 mUI/ml vs 12.8 ± 5.3 mUI/ml $P=0.003$) in girls with overweight/obesity respected to the normal weight group. In overweight girls SHBG levels inversely correlated with BMI ($r=-0.521$, $P=0.001$), insulin ($r=-0.476$, $P=0.011$), HOMA-IR ($r=-0.438$, $P=0.025$) and FAI ($r=-0.651$, $P<0.001$), whereas in the normal-weight group SHBG inversely correlated with FAI ($r=-0.736$, $P=<0.001$), testosterone ($r=-0.476$, $P=0.039$) and hirsutism ($r=-0.491$, $P=0.033$) and positively with FSH ($r=0.589$, $P=0.021$). Stepwise regression analysis showed HOMA-IR as the only independent variable explaining 43% of SHBG variability ($P=0.011$) in overweight/obesity girls, whereas in the normal weight group, FSH was the only independent predictor explaining 34.7% of changes in SHBG ($P=0.021$). **Conclusions:** In girls affected with PCOS, serum SHBG is subjected to different regulation according to the weight. In overweight/obese group, HOMA-IR is an independent factor

which explains SHBG variability, so this supports the hypothesis that could be an early marker of IR in this group. However, in the normal weight group SHBG variability is explained by FSH.

P2-443

Usefulness of 3D Ultrasonography for Assessment of the Morphology of the Ovary in Adolescents with Hyperandrogenism

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Background: Polycystic ovary morphology (PCOM) in USG should not be identified with polycystic ovary syndrome (PCOS) and it is not a criterion for diagnosis of this syndrome in adolescents. **Objective and hypotheses:** Assessment of the usability of 3D ultrasonography in diagnostics of androgen excess disorders. **Method:** 40 girls aged 14–18 with hyperandrogenism were subjected to endocrinological examinations and transrectal USG of the reproductive organ. The patients were divided into two groups: I – girls with PCOS and II – girls that did not meet the criteria for the diagnosis of PCOS (regularly menstruating girls). **Results:** In both groups, there was a correlation between the size of both ovaries and hyperinsulinaemia defined by the level of insulinaemia >100 mU/l in 75 g oral glucose load test. No correlation was found between the HOMA IR ($P=0.045$ vs 0.968) and the ovary volume; comparison of the groups showed that the value was significantly higher only in group II ($P=0.005$ vs $P=0.218$). There was no significant correlation between the number of ovary follicles and insulinaemia (for OGGT; $P=0.740$and HOMA IR; $P=0.699$). The mean level of androgenemia in groups I and II (FAI $=12.44$ vs 5.97 respectively) and the mean number of follicles in the right ovary (26.81 vs 17.89) were significantly higher in the group of adolescents with PCOS. **Conclusion:** Our observations indicate that, in adolescents with hyperandrogenism, the size of the ovary rather than the number of follicles correlates considerably better with endocrine disorders, since androgens are produced in the interstitial ovary cells. It seems that hyperinsulinaemia is one of the most important factors determining the ovary size in adolescents. Evaluation of ovaries by the 3D ultrasound technique facilitates accurate measurement of the volume of the ovary and can be a useful tool for examination of girls with hyperandrogenism.

P2-444

An Unusual Cause of Primary Amenorrhoea Suggested by the Urine Steroid Profile

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Background: The optimal timing and appropriate first-line investigations for delayed menarche in an otherwise well teenager with fully developed secondary sexual characteristics is debatable. **Case presentation:** A 15 year-old female presented with parental concerns of cliteromegaly. Facial acne and primary amenorrhoea were also noted. Pubic hair development started at age 10 years and breast development age 12 years. Family history revealed delayed menarche in her mother (age 17 years). On examination, she was Tanner stage 4 (B4, P4) with normal height (SDS 1.55), weight (SDS0.41) and BMI (SDS -0.26). On examination, the clitoris was normal and there was no hepatosplenomegaly or masses on abdominal palpation. Investigations to exclude adrenal causes associated with primary amenorrhoea demonstrated normal LH (6.2 UI/l), FSH (8.7 UI/l), androstendione (5.4 nmol/l), DHEAS (1 umol/l) and 17OH-Progesterone (1.8 nmol/l), but elevated testosterone (5.3 nmol/l). Transabdominal pelvic ultrasound (US) scan was normal. The 24-h urinary steroid profile (USP) revealed high a-cortolone (1592 μg/24 h (N: 738 ± 183)) compatible with portal hypertension; androstenetriol (2646 μg/24 h (N: 107 ± 62)) was significantly elevated and tetrahydrocortisol (1237 μg/24 h (N: 1683 ± 355)) low. Repeat analysis post Dexamethasone suppression showed a similar profile and excluded exogenous sources of steroid. Further investigations confirmed autoimmune hepatitis. Referral was made to a paediatric liver unit. **Conclusion:** Initial investigations were guided by the patient's clinical features. The diagnosis was suggested by the urine steroid profile requested to exclude adrenal pathology. Clinical stigmata of chronic liver disease were absent. The relative increase of a-cortolone in the USP has previously been demonstrated in cirrhosis, but raised androstenetriol has not been previously reported. There was also a low ratio of cortisone (11-oxy) relative to cortisol (11-hydroxy) metabolites, which is not an invariant feature, but is likely to reflect impairment of 11-hyroxysteriod dehydrogenase-1 in hepatocytes. Although primary amenorrhoea is often physiological in teenage girls, it may also be the first presenting sign of an underlying chronic disease. Careful evaluation is always needed. o avoid missing an alternative diagnosis.

P2-445

The Late Effects after the Haematopoietic Stem Cells Transplantation for Patients with Non-Neoplastic Disease

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Background: As a curative therapy, haematopoietic stem cells transplantation (HSCT) has been also used for patients with non-neoplastic diseases such as aplastic anemia, primary immunodeficiency, and some congenital metabolic diseases. For these diseases, the intensity of the conditioning has been reduced comparing to that of malignancy diseases. Therefore, late effects of HSCT for non-neoplastic diseases has been expected to be milder than that for neoplastic diseases, however few studies have been

reported and clinical details are not elucidated yet. **Objective and method:** Since 1983–2013, 73 of non-neoplastic disease patients of our institute were received HSCT, and 19 patients were followed up to date (three: severe combined immunodeficiency disease (SCID), two: severe congenital neutropenia, four: Wiskott-Aldrich syndrome (WAS), four: CD40L deficiency, three: aplastic anemia (AA), one each: Chronic Mucocutaneous Candidasis, Ectodermal dysplasia with immunodeficiency, EB virus associated hemophagocytic syndrome). We retrospectively analysed the clinical courses of post-HSCT patients with non-neoplastic diseases. **Results:** Because x-linked diseases (SCID, WAS and CD40LD) are main causes of immunodeficiency, the number of males was larger than that of females (16:3). The median age of the patients was 14.0 ± 10.7 (range: 2–41, median: 12.2), and the mean age at HSCT was 5.9 ± 6.4 (range: 0–21, median: 3.0). We observed two patients with growth failure whose heights were < -3 S.D., three with hypogonadism and one with subclinical hypothyroidism. Steroid therapy for GVHD could be a risk for short stature. (Fisher's exact test, $P = 0.036$), however, other risks for these endocrinological abnormalities, especially gonadal failure were not identified. **Conclusion:** Our study revealed HSCT causes late effects even in patients with non-neoplastic disease. In order to clarify the clinical details, further large scaled studies are necessary, and our study suggests the clinical importance of late effects of post HSCT patients with non-neoplastic disease.

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BMI Negatively Correlates with GH Response to GH Provocation Testing

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Background: In adults it has been shown, that GHmax values after provocation testing are negatively correlated to BMI. Preliminary studies in children have found a similar correlation. Consequently children with elevated BMI would be overdiagnosed with GHD. However, studies so far were too small to define this correlation exactly. This would be a condition to judge whether and to what extend adjustments of GH cut-off levels should be considered also in children with elevated BMIs. **Objective and hypotheses:** To establish a more precise correlation between BMI and GH peak levels in GH provocation tests in a larger cohort of children with short stature. **Method:** Using the local CrescNet database we retrospectively investigated data from 804 children with short stature who were tested between 2004 and 2014. A total of 1109 GH stimulation tests were performed (812 arginine initially, and 297 glucagon as confirmatory test). Children with known syndromes (i.e. UTS), severe chronic illness, or under antipsychotic or sex steroid medication were excluded from study. A linear model was used to assess the correlation between BMI-(SDS) and GHmax. We divided the GH stimulation tests in two groups (prepubertal: 905 and pubertal: 204) to account for possible effects of puberty on GH secretion. Also the correlations of GHmax to BMI-SDS was compared in respect to whether the fixed cut-off level for GHD (7.09 ng/ml) was reached or not. **Results:** There was a significant (negative) correlation of BMI-SDS and the GH max levels reached during stimulation tests. This correlation was neither altered when studied according to gender of the probands nor by the substance used for testing. Also, this (negative) correlation was not found to be significantly changed by puberty, although GHmax levels in average were significantly higher in pubertal children. Finally, in prepubertal children no significant difference of this correlations (r^2: 0.458, P-value: $<$2.2e-16) was observed between children with and without GHD (cut-off GH max $>$7.09 ng/ml). **Conclusion:** We found that increasing BMI significantly and negatively influences GH max values in both arginine and glucagon GH stimulation tests. As this effect is similarly observed on 'both sides' of established cut-off levels for GHD, BMI should be taken into account when interpreting GH stimulation tests by development of a correction factor. BMI must be taken into account when interpreting GH stimulation tests and the development of a correction factor, could be very helpful in order not to overdiagnose GHD.

P2-447

SHOX Mutation Spectrum in an Unbiased Cohort of 585 Patients Referred for Leri-Weill Dyschondrosteosis or Idiopathic Short Stature

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Background: *SHOX* encodes a transcription factor implicated in skeletal development. Approximately 70% and ~2.5% of Leri-Weill dyschondrosteosis (LWD) and idiopathic short stature (ISS) patients, respectively, have a defect in *SHOX* or its regulatory regions. **Objective and hypotheses:** i) To perform *SHOX* mutation screening in a cohort of 585 patients referred with a clinical suspicion of LWD or ISS. ii) To determine which is the *SHOX* mutation spectrum in an unbiased cohort. **Method:** A total of 585 patients were referred for *SHOX* analysis during the last 16 months. Mutation screening of *SHOX* and its regulatory regions was performed by MLPA, HRM and Sanger sequencing. *In silico* pathogenicity analysis was undertaken using Alamut V2.6. Family analysis was undertaken when possible. **Results:** Molecular defects in *SHOX* or its enhancers were identified in 75 probands (14%), 65 referred for LWD and 10 for ISS. All mutations were observed in heterozygosity except for one LWD individual who was homozygous for the common 47.5 kb PAR1 deletion. The mutation spectrum encompassed: 18 (24%) *SHOX* encompassing

deletions, 27 (36%) PAR1 enhancer deletions (18 were the common ~47.5 kb deletion), 25 (33%) *SHOX* missense or splicing mutations (9 were p.A170P), 1 (1%) *SHOX* duplication and 4 (6%) enhancer duplications. Five of the mutations are novel: four missense and one exon 6a deletion. **Conclusion:** *SHOX* mutations were identified in 14% of an unselected cohort of LWD and ISS referrals. *SHOX* mutations accounted for 59% of the mutations whilst the remaining 41% were PAR1 deletions encompassing enhancer sequences. The frequent ~47.5 kb deletion is the most common mutation (24%) in our cohort. Interesting cases include: i) The identification of the first deletion of a unique *SHOX* exon; and, ii) The identification of a homozygous *SHOX* downstream enhancer deletion in a patient with LWD, showing the variable expressivity of some *SHOX* alterations. **Funding:** This work was supported by a MINECO grant (SAF2012-30871) and the EndoScreen project (IdiPaz and UAM).

P2-448

Determination of the Pathogenicity of *SHOX* P_2 Promoter Variants, Identified in Patients with Léri-Weill Dyschondrosteosis or Idiopathic Short Stature

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Background: Expression of SHOX, a transcription factor implicated in skeletal development, is regulated by the interaction of two promoters, weak, P_1 (exon 1) and strong, P_2 (exon 2), with at least, seven enhancers. SHOX haploinsufficiency, due to mutations in SHOX or its enhancers, explains ~70% of Leri-Weill dyschondrosteosis (LWD) and ~2.5% idiopathic short stature (ISS) cases whilst the underlying molecular mechanism in the remaining is unknown. **Objective and hypotheses:** Several *SHOX* promoter variants have been reported but their pathogenicity is unknown. We set out: i) To determine the pathogenicity of the *SHOX* P_2 promoter variants detected in LWD/ISS patients (LOVD SHOX database); ii) To screen the *SHOX* P_2 promoter in our LWD/ISS cohorts with no known *SHOX* defect. **Method:** i) Functional characterization of six *SHOX* P_2 promoter variants reported in LWD/ISS patients, by dual-promoter-luciferase experiments in U2OS cells. ii) Mutation screening of P_2 in two LWD/ISS cohorts: Cohort-A: 124 patients with suspected LWD without a known *SHOX* defect; Cohort-B: 1031 LWD/IISS referrals for *SHOX* testing. **Results:** Functional assays showed a significant decrease in luciferase expression for variant, c.-243G>A, compared to wild-type. No P_2 variants were observed in cohort A, whilst in cohort B, 10 c.-65C>A and six c.-55C>T variants were detected. **Conclusion:** The observation that the c.-243G>A variant reduced promoter activity and that it cosegregates with the LWD phenotype in a family, suggests that it is a pathogenic mutation. The two variants observed in cohort-B, have been shown by us and others to also cosegregate with LWD in two/three generations, but as with the other three variants, did not reduce promoter activity. Despite this, they still may affect *SHOX* expression by an alternative mechanism, such as affecting the interaction with *SHOX* enhancers. In conclusion we have confirmed the pathogenicity of one variant but further experiments are required for the remaining five variants. **Funding:** This work was supported by a MINECO grant (SAF2012-30871) and the EndoScreen project (IdiPaz and UAM).

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Risk for Non-Alcoholic Fatty Liver Disease in Young Adults Born Preterm

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Background: Non-alcoholic fatty liver disease (NAFLD) is considered the hepatic manifestation of metabolic syndrome. Accelerated catch-up in weight during infancy in subjects born term has been associated with increased risk for NAFLD in adulthood, but this association has not been studied in subjects born preterm. **Objective and hypotheses:** To investigate the associations of birth weight, gain in weight for length and accelerated catch-up in weight in the first year after term age with the fatty liver index (FLI) in young adults born preterm. **Method:** In 162 adults aged 18–24 years with a gestational age <36 weeks, we determined BMI, waist circumference, serum triglyceride, gamma-glutamyltransferase (γ-GT), alkaline phosphatase (ALP), alanine aminotranserase (ALT), and aspartate aminotransferase (AS) levels. FLI (0–100) was calculated. Associations between birth weight SDS, first year gain in weight- and length SDS after term age and FLI were assessed. In addition, we performed comparisons between subjects with and without accelerated catch-up in weight in the first year after term age. A FLI-score (low, intermediate, high risk for NAFLD) was assigned to each participant to determine clinical relevance, and ordinal regression analyses were performed. **Results:** Accelerated gain in weight in the first three months after term age was associated with FLI as a continuous variable, whereas gestational age and low birth weight were not. Of the subjects with accelerated catch-up in weight for length after term age, 7.3% had a high FLI at the age of 21 years, whereas none of the subjects without accelerated catch-up in weight had a high FLI. **Conclusion:** Our study shows that accelerated infant weight gain after term age is associated with increased risk for developing NAFLD in young adults born preterm. **Funding:** The study was financially supported by Netherlands Organisation for Scientific Research (A C S H-K. received the ASPASIA award, Grant 015 000 088), and by grants from Revolving Fund 2001, Trustfonds, Erasmus University Rotterdam, the Jan Dekker-stichting/Dr Ludgardine Bouwmanstichting, Stichting De Drie Lichten and an investigator-initiated research grant provided by Pfizer Inc., USA.

P2-450

Pharmacokinetics and Efficacy of a Long-Acting Human GH with Fc Fusion Protein

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Background: Recombinant human GH (rhGH) therapy requires daily s.c. injections, this inconvenient treatment regimen results to poor compliance of the patient. Thus, to improve patient compliance, long-acting rhGH products including various protein fusion techniques have been in development during past 15 years. **Objective and hypotheses:** In this study, we describe the pharmacokinetics and efficacy of a novel long-acting GH using Fc fusion protein (rhGH-Fc) in animal study. **Method:** The pharmacokinetics and pharmacodynamics of rhGH-Fc were assessed in male SD rats and hypophysectomized rats. **Results:** A single s.c. injection dose of 1.0 mg/kg of rhGH-Fc had a slower absorption phase, greater C_{max}, and remained significantly elevated for at least 7–10 days compared with daily s.c. injection dose of 0.2 mg/kg of rhGH in S.D. rats. In efficacy study, there were no significant differences between rhGH (daily dose of 15 μg/animal for 14 days and rhGH-Fc (weekly dose of 240 μg/animal for 14 days with a dosing interval of a week) in hypophysectomized rats, as assessed by changes in body weight and the width of the tibial growth plate. **Conclusion:** rhGH-Fc may provide the potentiality that one of the novel long-acting rhGH products will be administered up to weekly form. Further evaluation including measurements of anti-rhGH-Fc antibody titer in animal and human, and study for other safety problems such as injection-site lipoatrophpy should be needed.

P2-451

SHOX Deficiency: Clinical, Radiological Signs and Value of Screening Scores

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Objective and hypotheses: We studied the prevalence of deficiency in the short stature homeobox containing gene (SHOX) in short-statured children and analysed clinical and radiological signs. **Method:** A total of 162 children aged 1–17 years (53% females, 67% prepubertal, median age 6.6 years, median height SDS −1.7) presenting with short stature between 2008 and 2014, were analysed for SHOX mutations by direct sequencing and multiplex ligation probe-dependent amplification analysis. Children with SHOX deficiency (SHOX-D) were compared to 1:2 age- and gender- matched children without SHOX deficiency with respect to radiological findings and anthropometrics. **Results:** We identified 8 (4.9%) patients with SHOX-D and functionally relevant SHOX variations: one (12.5%) subject had a deletion, two children (25%) demonstrated a deletion in the enhancer domain, and five (62.5%) patients showed a point mutation in the coding region. The two groups did not differ with respect to height SDS, BMI SDS, or target height SDS. Subjects with SHOX mutations demonstrated significantly more frequently micrognathia. While none of the controls showed radiological signs, 25% of SHOX-D patients demonstrated Madelung deformity ($P<0.05$). The ratio of arm span to height did not significantly differ between the two groups while sitting height-to-height ratio was increased in SHOX-D children ($P<0.05$). The arm span to height ratio and the Rappold score showed the highest sensitivity to detect SHOX deficiency, while sitting height-to-height ratio demonstrated the best positive predictive value. The negative predictive values did not differ between the various scores. However, screening criteria would not identify some SHOX-D patients. **Conclusion:** The phenotype of children with SHOX deficiency is highly variable. Moreover, clinical and radiological features are nonspecific or difficult to highlight, limiting their diagnostic value thus many subjects may be missed.

P2-452

Skeletal Dysplasia with Short Stature and a Larsen-Like Phenotype due to a Homozygous Mutation in B3GAT3

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Background: Proteoglycans are abundant and structurally complex bio macromolecules. They reside on the cell surface and are a major component of the extracellular matrix including bone. Defective formation of proteoglycans may case pleiotropic connective tissue syndromes including EDS-like and Larsen syndrome–like phenotypes. **Objective and hypotheses:** We report on a girl with disproportionate short stature and joint laxity with pes planus and radial head dislocation. She was previously assigned to Spondyloepimetaphyseal dysplasia with joint laxity type 1 (SEMDJL1) which is characterised by vertebral abnormalities and ligamentous laxity that result in spinal misalignment and progressive severe kyphoscoliosis and respiratory compromise resulting in early death. The phenotype was similar, but except atlantoaxial hypermobility she did not develop scoliosis. This prompted us to Whole-Exom-Sequencing for a recessive mutation. Nonaxial skeletal involvement included elbow deformities with radial head dislocation, genu valgum, flat feet, and tapered fingers with spatulate distal phalanges. The girl had a round face, flat midface, prominent eyes with blue sclerae, and a long philtrum. Decreased bone density was confirmed in the patient (*z*-score at

the hip −3.3). Final height was 130 cm (−5.3 SDS), weight 37 kg (<3rd centile), normal cognitive function. **Results:** We add an additional patient to a group of patients with short stature and joint laxity caused by mutations in the linker region of glycosaminoglycans (GAG) including syndromes with mutation in B3GAT3, B3GALT6 (Ehlers-Danlos- like), B4GALT6 (Ehlers-Danlos-like syndrome with kyphoskoliosis), and B4GALT7 (Larsen of Reunion Island syndrome). **Conclusion:** Whole Exome Sequencing by SOLID 5500 (ThermoFIsher) revealed a homozygous missense mutation in B3GAT3-gene coding for Glucoronyl-transferase I (enzymatic step in the Golgi apparatus for a linkage region synthesis of proteoglycans i.e heparan sulfate): c.416C>T, p.Thr139Met.

P2-453

Cross-Sectional and Longitudinal Follow-Up of Changes in Glucose Metabolism in Prepubertal GH-Treated SGA-Patients: Results of an Unicentric Study

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Background: Several studies show impaired glucose tolerance at a certain number of years after start of growth hormone in SGA-children. **Objective and hypotheses:** To perform a longitudinal and cross-sectional evaluation of the oGTTs (glucose-insulin-pairs) in prepubertal GH-treated SGA-children and to evaluate if ISI and HOMA are effective surrogates for glucose tolerance and of prognostic value (0–1 year data). **Method:** In 81 prepubertal SGA-children oGTT, HOMA and ISI were determined before start and yearly under GH-treatment until puberty (maximum 4 years of treatment). **Results:** In oGTT, highest values for glucose and insulin were seen at 30 min in all years: maximum values for glucose at 0–2 years, for insulin between 1 and 3 years of treatment. Mean glucose/insulin-ratio continuously decreased. HOMA increased until 3 years (0.8±0.5 to 1.6±1.2). ISI continuously decreased from 0 to 4 years (14.9±9.8–6.4±1.2). 3/81 children showed 0-min-glucose values >100 mg/dl indicating impaired fasting glucose (IFG) even before GH-treatment, 7/81 120-min-values >140 mg/dl (IGT) and three elevated fasting insulin (>10 µU/ml). None of them had pathologic oGTTs later. Only 4/81 had pathologic HOMA (>2.5) and/or ISI (<5) at baseline. After 1 year of treatment 7/72 showed IFG, 2/72 IGT, five fasting insulin >10 µU/ml. 5/72 showed elevated HOMA and 8/72 decreased ISI (mostly not the same as at 0 years). 9 of 59 followed for >1 year who had any abnormal value before changed to normal. 16/59 who had completely normal tests at 0 and 1 year showed at least one pathologic value later. **Conclusion:** We found continuously raising insulin resistance until at least 4 years of GH-treatment. 30-min-values always were the highest (not represented in ISI-index!). As HOMA and ISI can deteriorate independently of each other, if surveillance of glucose homeostasis shall be performed, determining only the fasting values is not sufficient and in oGTT also the 30-min-results should be considered. Neither baseline nor 1-year-data for HOMA, ISI and/or oGTT are of prognostic value for the further development of glucose tolerance during GH-therapy. In our collective temporarily pathologic values had no therapeutic consequence and none of the patients developed diabetes.

P2-454

Growth Pattern in Children Affected of Lowe Syndrome – Descriptive Multicentre International Study: Preliminary Data

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Background: Lowe syndrome or oculocerebrorenal syndrome is a very rare condition (1:50 000) caused by mutations in the OCRL1 gene. It is an x-linked disorder characterized by congenital cataracts, renal tubular dysfunction, neurological defects (generalized hypotonia and mental retardation) and growth disorders. Growth pattern in Lowe syndrome has not been described in population-based studies so far. **Objective:** Descriptive multicenter international study aimed to describe growth pattern in Lowe syndrome affected subjects. **Method:** 47 subjects have been identified around the world. Auxologic data of 14 subjects (age 3–24 years) with Lowe syndrome from Spain ($n=8$), Italy ($n=5$) and Argentina ($n=1$) were reported through a web-based questionnaire. **Results:** Length/height is expressed as followed in media±S.D. 3 month: 61.2±2.75; 6 month: 65.8±1.94; 9 month: 69.7±2.39; 12 month: 71.3 cm±4.97; 18 month: 75.4 cm±3.37; 2 years: 78.9±7.13; 3 years: 84.6±7.43; 4 years: 86.8±6.38; 5 years: 90.4±7.82; 6 years: 96.8±5.19; 7 years: 102±5.29; 8 years: 106.2±4.54; 9 years: 111.3±4.92; 10 years: 118.3±1.53; 12 years: 124.3±0.35. Only one subject older than 13 years was identified with the following height measurements: height at the age of 13, 15, 16 and 23 were 130, 135, 149 and 158 cm respectively. **Conclusion:** Data regarding growth patterns of children affected of Lowe-syndrome would enhance to design specific growth charts for children with this condition. Lowe syndrome as well as other rare conditions requires joint efforts and advocacy of both healthcare members and patient's families to go further in the knowledge of the disease. 'Rare Commons' online platform is a collaborative project network (including families and doctors) to gain knowledge in rare diseases.

P2-455

Effect of Aromatase Inhibitor Treatment During Adolescence on the Final Adult Height in Males with Idiopathic Short Stature

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Background: Aromatase inhibitors (AIS) can block the conversion of androgens to estrogens, thus can be used to delay bone maturation in males, however, the effect on improvement of final adult height (FAH) is still controversial. **Objective and hypotheses:** A prospective study was performed to evaluate the effect of letrozole used on the FAH in males with idiopathic short stature (ISS). **Method:** 55 boys with ISS and had entered puberty were separated into three groups: group 1 (N = 22), received letrozole 1.5 ~ 2 mg/m^2 per day, for (2.11 ± 0.66) years. Group 2 (N = 20), GnRHa for (2.00 ± 0.54) years. Group 3 (N = 15), without interventions. **Results:** i) Height velocity (HV) in the first 6 months, second 6 months, third 6 months separately during therapy were (8.35 ± 1.70) cm/year, (7.42 ± 1.92) cm/year, (6.23 ± 2.08) cm/year respectively in group1, significantly more than that in group2: (7.20 ± 1.77) cm/year, (4.75 ± 1.42) cm/year, (4.37 ± 1.01) cm/year, ($P = 0.04$,$P < 0.01$,$P < 0.01$). ii) △BA/△CA during the first year and the second year were (0.67 ± 0.09) and (0.50 ± 0.15) in group 1 respectively, more than that in group 2: (0.61 ± 0.16) and (0.44 ± 0.33) respectively, ($P = 0.04$, $P = 0.05$). But no significant differences of △HtSDSBA were found between group 1 and group2, (0.96 ± 0.48) vs (0.62 ± 0.61) ($P > 0.05$). iii) FAH in groups 1 and 2 had no differences: (170.27 ± 4.28) cm vs (168.55 ± 5.60) cm ($P > 0.05$), but higher than predicted AH before treatment (161.25 ± 2.50 cm, 162.33 ± 3.33 cm) and FAH in group 3 (161.96 ± 3.57)cm ($P < 0.01$). iv) During letrozole therapy, LDL decreased slightly: (1.49 ± 0.23) mmol/l vs (1.71 ± 0.40) mmol/l ($P < 0.01$), however, no significant changes of TG, LDL, HOMA-IR were found. **Conclusion:** Long term letrozole therapy during puberty in male with ISS can delay bone maturation without obviously decrease of linear growth, and thus can improve the FAH.

P2-456

The Effect of Inhaled Glucocorticoid Therapy on Growth Patterns in Pre-Pubertal Children with Asthma Compared to Controls

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Background: Controversial data exist on the possibility that inhaled glucocorticoids (IGs) affect growth in children with mild-to-moderate asthma. The majority of these studies are short-term reports lacking long-term assessment until the achievement of final height (FH). **Objectives:** To assess whether IGs affect growth and FH in asthmatic children compared to controls. **Methods:** 113 asthmatic (57/56 (males/females)) were compared to 66 control children (29/37 (males/females)). Asthmatic children presented mild-to-moderate asthma and had exclusive IGs (budesonide ($n = 36$) *vs* fluticasone ($n = 43$) vs mometasone ($n = 34$)) for a mean-period of 6.56 ± 1.20 years and a mean-cumulative dose of 560.07 ± 76.02 mg. Height and weight were retrospectively collected at four study-visits (pre-puberty, onset and late puberty, FH) and converted to S.D. scores (SDS). Growth trajectories were assessed: i) in puberty, using peak height velocity (PHV) and pubertal height gain-SDS (PHG-SDS); ii) until FH achievement, using FH-SDS and FH gain-SDS (FHG-SDS). Repeated measurement analysis was performed across longitudinal study-visits. A general linear model (GLM) was performed in asthmatic group evaluating the effect of glucocorticoid type, treatment duration and cumulative dose on FH-SDS corrected for age, gender, weight-SDS and asthma severity. **Results:** At pre-puberty age, height and weight-SDS were similar between the groups ($P > 0.05$). Height-SDS progressively declined over the study period in asthmatic patients from pre-puberty to FH (P-trend = 0.002), whereas it did not change over time in controls (P-trend > 0.05). Asthmatic children showed decreased PHG-SDS compared to controls (−0.30 ± 0.93 vs 0.02 ± 0.46, $P = 0.016$) and lower PHV (5.77 ± 3.13 vs 7.49 ± 2.04, $P = 0.001$). FH-SDS was significantly reduced in asthmatic group compared to controls (−0.24 ± 0.39 vs 0.20 ± 0.60, $P = 0.004$), as well as FHG-SDS (−0.56 ± 0.76 vs 0.04 ± 0.42, $P < 0.001$). The GLM showed a significant effect of glucocorticoid type, duration and cumulative dose on FH-SDS ($P < 0.05$). **Conclusions:** IGs affect pubertal growth determining reduced FH in children with asthma compared to controls, in a dose and duration-dependent manner.

P2-457

Low Plasma Ghrelin Levels in Children with Severe Protein Energy Malnutrition

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Background: Protein energy malnutrition (PEM) is a catabolic state with altered energy balance and anorexia. Ghrelin is a peptide hormone, produced by neuro-endocrine cells in the stomach, which stimulates appetite, increases food intake and growth hormone release. Although many trials have shown short term efficacy of ghrelin to increase appetite in anorexic and cachectic patients, data on the children with PEM is scarce. **Objective and hypotheses:** The study was conducted to ascertain difference in plasma ghrelin levels among children with varying grades of PEM and healthy controls. **Method:** A cross-sectional observational study was conducted over 1 year period in

hospital setting. A total of 78 children (mean age: 26.71 ± 16.47 months, 49 males and 29 females) including 59 with PEM and 19 healthy controls were enrolled in the study. Children with PEM were classified as mild, moderate and severe as per WHO criteria for malnutrition. Children with concomitant chronic systemic illnesses causing malnutrition were excluded from the study. The study population was divided into three groups: 36 children with severe PEM, 23 children with mild to moderate PEM and 19 children as controls. Plasma fasting ghrelin levels were measured using radioimmunoassay. Median with inter-quartile ranges (IQR) values of plasma ghrelin levels in three groups were compared. **Results:** Median serum ghrelin level in severe PEM group was 1.942 ng/ml (IQR: 0.064, 9.506), in mild to moderate PEM was 17.662 ng/ml (IQR: 1.658, 40.129) and in control group was 17.525 ng/ml (IQR: 0.626, 27.361). The median ghrelin levels were significantly low (*P*-value, 0.027) in severe PEM group when compared to mild to moderate PEM group. **Conclusion:** The plasma ghrelin levels are significantly reduced in children with severe PEM when compared to mild to moderate PEM. **Funding:** This work was supported by Indian Council of Medical Research in form of Rs 15000/- thesis grant.

P2-458

Sleep Apneas in Silver Russell Syndrome: A Constant Finding

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Background: Imprinting disease such as Prader-Willi syndrome (PWS) are associated with pathological sleep due to central and obstructive apneas. No data are available concerning Silver Russell syndrome (SRS) but most patients describe day asthenia and snoring. These patients also often present with maxillo-facial malformations. **Aims and objectives:** We wanted to characterise sleep in SRS and evaluate GH therapy possible effect on it. **Methods:** We analysed 54 sleep polygraphies and polysomnographies in 40 patients with genetically proven SRS (i.e 31 with 11p15 epimutation and nine with mUPD7), 19 prior to GH therapy, 34 during GH therapy and one after GH therapy. Five patients had sleep evaluation prior and after GH therapy initiation. **Results:** Sleep showed pathological patterns in all but one children before GH therapy ($n = 19$). Obstructive apneas were mainly implicated with a mean obstructive respiratory events index (REI) of 4.5 (1.2–16.4). Large tonsils were identified in eight patients by ear-nose-throat (ENT) examination, half were removed. Sleep abnormalities were severe in two patients, moderate in 11 and mild in five before GH therapy. We performed five polysomnographies with a sleep efficiency of 80.3% and microwakennings index of 14.2 per h. The mean REI was 5.6 (0–18.5) in all recordings. Preliminary results showed no worsening of the REI after GH initiation. **Conclusion:** Patients with SRS present sleep obstructive apneas syndrome that should be evaluated before GH therapy onset. Maxillo-facial abnormalities and tonsil hypertrophy could be implicated in such sleep pattern and we recommend systematic evaluation in SRS patients, preferably before GH therapy initiation, even if it seems to have no worsening effect on sleep features. High microwakennings index could contribute to day asthenia often describe in SRS patients. Caution should be given to central apnea presence even if not predominant they could testify of hypothalamic involvement as in PWS patients.

P2-459

Heterozygous NPR2 Mutations Cause Disproportionate Short Stature, Similar to Léri-Weill Dyschondrosteosis

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Background: Mutations in SHOX or its regulatory regions have been detected in ~70% of Léri-Weill dyschondrosteosis (LWD) and ~2.5% of idiopathic short stature (ISS) cases, suggesting the implication of other genes or loci. Recent studies have identified NPR2 defects in ISS patients. **Objective and hypotheses:** To investigate if NPR2 mutations can account for a proportion of the cases referred for LWD and ISS in whom no SHOX/PAR1 mutation was detected. **Method:** We undertook NPR2 mutation screening in 173 individuals referred for suspected LWD and 95 for ISS, with no known SHOX/PAR1 defect. In silico pathogenicity analysis was undertaken using Alamut V2.6. Intracellular localization and CNP-dependent guanylate cyclase activity were determined to characterize the pathogenicity of the identified NPR2 variants. Cosegregation analysis was undertaken when possible. **Results:** Eight NPR2 variants, four novel, were identified in nine individuals, seven referred for LWD and two for ISS. Seven of the eight variants were predicted to be pathogenic whilst only one was predicted to be a non-pathogenic variant. Functional analysis confirmed the pathogenicity of six of the variants, all of which were detected in the LWD referral group (~3%). The variants observed in ISS patients did not affect NPRB function. **Conclusion:** NPR2 mutations account for ~3% of

patients with disproportionate short stature and/or clinical or radiographic indicators of SHOX deficiency and in whom no SHOX defect has been identified. However, no patient has yet presented with Madelung deformity. Thus, NPR2 should be screened in the SHOX negative LWD referrals. Functional analyses are required as several NPR2 variants, predicted to be pathogenic, and were demonstrated to be non-pathogenic. Interestingly, one of the NPR2 mutation carriers is currently being treated with rhGH, and in contrast to previous reports is showing a positive response to the treatment. **Funding:** This work was supported in part by a MINECO grant (SAF2012-30871), the Jose Igea Award by the Foundation of the Spanish Society of Pediatric Endocrinology (F-SEEP) and the EndoScreen project (IdiPAZ and UAM).

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Individuals with Cow's Milk Allergy are at Risk for not Reaching their Growth Potential

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Background: Poor growth and inadequate nutrient intake by food allergic children have been suggested, particularly for children avoiding milk. **Objective and hypotheses:** To investigate the impact of a dairy-free diet on the final stature of IgE-mediated Cow Milk Allergy (IgE-CMA) young adults. **Method:** Anthropometric data was measured in 60 IgE-CMA patients (20.4 ± 3.4 years old, 26 males (43%)) and 36 volunteers without IgE-CMA (control group, 22.5 ± 4.2 years old, 15 males (42%)). All of them were at least 2 years post pubertal, as classified by Tanner's Stage 5. Age- and gender-specific SDSs and percentiles were determined according to Centers for Disease Control and Prevention growth charts. Nutrient intake assessment was based on 24 h dietary recall and presented as percent of dietary reference values (DRI's). Individuals with conditions or treatments affecting bone metabolism or growth, were excluded. **Results:** Height (cm) and height-SDS were significantly reduced in CMA subjects when compared to controls (164.8 ± 8.4 vs 168.5 ± 7.8, $P=0.03$; -0.56 ± 0.9 vs -0.04 ± 0.7, $P=0.004$). An abnormal distribution of height-for-age was noted in the CMA group, as compared to the controls (49% vs 17% were categorized as less than the 25th percentile, 18% vs 3% were categorized as $<$ the 10th percentile, and 10% vs 0% were categorized as $<$ the 5th percentile). In addition, height-SDS in CMA patients was significantly lower than their predicted height (mid-parental target height, MPH) ($P<0.0001$). Δheight-MPH in CMA patients and controls were -3.6 ± 5.2 and -0.60 ± 5.2 cm respectively, $P=0.01$. The incidence of subjects consuming less than 67% of the DRI was greater in the CMA group, as compared to controls. **Conclusion:** Individuals with CMA are at risk for not reaching their growth potential. Growth monitoring and appropriate dietary intervention may avoid nutritional deficiencies and growth retardation in these patients.

P2-461

French Growth Reference Charts should be Updated

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Background: Growth charts constitute an important tool to monitor a child's growth and development, and thus detect growth anomalies. Growth assessment allows early referral and management of treatable disorders. In France, the currently used growth reference charts were derived at the end of 1970s, based on children born on 1950s in Paris area. Questions are raised about their use for growth monitoring of more recently born children. **Objectives:** To evaluate actual data about growth and obesity in a large group of schoolchildren and compare these data with the widely used French reference charts. **Method:** Prospective analysis of anonymized growth (height, weight) and BMI data retrieved from regular school medical visits. 2736 children attending the third grade of elementary school in Paris during 2008–2009 have been included, after stratification of 75/345 schools. Growth and BMI data were computed according to French reference charts (Sempé 1979, 1991 respectively). BMI data were also compared to international standards (International Obesity Task Force, IOTF). **Results:** Our population of children was on average almost 1 S.D. taller and heavier than the reference. Height and weight were above the French values ($+0.9 \pm 1.2$ S.D. and $+1 \pm 1.7$ S.D. respectively). BMI was also higher, computed according to reference values ($+0.4 \pm 1.4$ S.D.). At 8–9 years of age, 15.3% of boys and 20% of girls had a BMI $>$ IOTF25 and were overweight or obese. **Conclusion:** The reference values currently used in France are no longer appropriate and new charts need to be established. A study published by Heude et al in 2015 underlines the need for actualisation of French growth charts, as the growth patterns of a large population of French children are closer to WHO standards than to Sempé. Finally, the high prevalence of obesity in schoolchildren remains a public health challenge. **Funding:** Supported in part by NovoNordisk (educational grant).

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Advanced Bone Age and Accelerated Dental Development Associated with Elevated Retinoic Acid Levels and Haploinsufficiency of CYP26A1 and CYP26C1

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Background: Nutritional excess of vitamin A, a precursor for retinoic acid (RA), causes premature epiphyseal fusion, craniosynostosis, as well as light-dependent retinopathy. Similarly, homozygous loss-of-function mutations in one of the major RA-metabolizing enzymes CYP26B1 causes advanced bone age, premature epiphyseal fusion, and craniosynostosis. We studied a patient with markedly accelerated skeletal and dental development, retinal scarring, and autism-spectrum disease. **Objective and hypotheses:** To characterise and identify the cause of this novel syndrome. **Method:** Genetic studies using comparative Genomic Hybridization (CGH) array, and whole exome sequencing. RA metabolites were assessed in patient, family members as well as in ten age-matched boys and ten girls using high-performance liquid chromatography (HPLC) coupled to tandem mass spectrometry (MS/MS). **Results:** The proband is a 10-years-old prepubertal male with bone age advanced 3.5 years over chronologic age. Anterior fontanel was largely closed at age 2 months. Dental age was also markedly advanced with 16 primary teeth present at age 12 months and shedding beginning at age 3 years. Linear growth has been normal along the 50th percentile since age 3 years. He also has photophobia, chorioretinal scarring, and developmental delay. CGH array identified a novel 8.3 megabase microdeletion on chromosome 10Q23.2-23.33. The 79 deleted genes include CYP26A1 and C1, both major RA metabolizing enzymes. Whole exome sequencing did not detect any variants that are predicted to be deleterious in the remaining copies of these genes, in CYP26B1, or other known RA-metabolizing enzymes. The patient exhibited elevated serum levels of total RA (16.5 nM vs 12.6 $\pm$ 2.9; patient vs controls (mean $\pm$ 2 S.D.)) and 13-Cis RA (10.7 nM vs 6.1 $\pm$ 2.2; patient vs controls (mean $\pm$ 2 S.D.)). **Conclusion:** The findings of elevated total RA and 13Cis RA support the hypothesis that elevated RA levels accelerate bone and dental maturation in humans. CYP26A1 and C1 haploinsufficiency may contribute to the elevated RA levels, although this phenotype has not been reported in other patients with similar heterozygous deletions, suggesting that other unknown genetic or environmental factors may also contribute. **Funding:** The work was supported by the Intramural Research Program of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), National Institutes of Health. AD received funding from NICHD, project number 5K23HD073351. ON is supported by the Swedish Research Council (project 2012-99X-221998–01-3 and K2015-54X-22736-01-4) and Karolinska Institutet.

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Recurrent IGFALS Gene Mutations p.E35Gfs*17 and p.(L409F; A475V): Hot Spot or Founder Effect?

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Background: Some *IGFALS* variants have been reported in more than one ALS-deficient family raising the question whether they originated from a single common ancestor allele (founder effect) or alternatively, as independent mutational events (hot spot). Since c.103dupG (p.E35Gfs*17) is located in a stretch of five consecutive guanine residues, where both G-duplication and deletion have been described in several families, we speculate that this region could be a hot spot. In contrast, c.(1225C>T;1424C>T) (p.(L409F;A475V)) variants, both present in the same allele in two unrelated families, could result from a founder effect. **Objective and hypotheses:** To test the hypothesis of a founder effect vs. hot spot by studying polymorphic variants surrounding *IGFALS* gene and uniparental lineage markers in families harboring the c.103dupG and c.(1225C>T;1424C>T) variants. **Method:** We sequenced the whole *IGFALS* gene and characterized two STRs flanking *IGFALS* gene locus in 30 individuals from six unrelated families, two harboring the c.(1225C>T;1424C>T) variants and four carriers of c.103dupG. Nine informative SNPs and two STRs were used to define the specific haplotype associated to the mutation (D16S3435/9 SNPs/D16S3024). In addition, patri- and matrilineal lineages were analyzed by means of 23 Y-STRs typing and mtDNA-D-Loop sequencing. **Results:** Four families carrying the c.103dupG variant presented the same STRs and SNPs microhaplotype (CA)12/gtcggtgcc/(CA)21 while all the c.(1225C>T;1424C>T) carriers of the other two families presented a different microhaplotype (CA)15/acgaaccgt/(CA)22 or (CA)23. Phylogenetic analysis revealed that all male lineages can be attributed to European or Eurasian haplogroups (50% E1b1b; 33% R1b and 17% Q) while mtDNA lineage belonged to Native American (56%), African (22%) and European (22%) haplogroups. **Conclusion:** Based on this number of families studied, the finding of two particular microhaplotypes support the hypothesis of a founder effect for both variants, c.103dupG (p.E35Gfs*17) and c.(1225C>T;1424C>T) (p.(L409F;A475V)); each originating from two independent ancestor alleles. **Funding:** This work was supported by grants from the Agencia Nacional de Promoción Científica y Tecnológica (PICT-2010 Nro.1916), and SANDOZ International GmbH, Business Unit Biopharmaceuticals.

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Infant with Phenotype Suggestive of Silver-Russell Syndrome and Study of Normal Methylation: Consider 12q14.3q15 Microdeletion Syndrome

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Background: The 12q14.3q15 microdeletion syndrome is a rare entity of which only 16 new cases have been described to date. The syndrome consists of the association of severe pre- and postnatal growth retardation, proportional short stature, psychomotor retardation and osteopoikilosis. The phenotypic appearance of these patients poses a differential diagnosis with Silver-Russell syndrome, among other entities. **Clinical description:** A 10-month-old boy was referred for study of growth retardation. Product of the first full-term gestation of non-consanguineous parents of normal stature. BW: 1.800 g (−2.5 S.D.), length: 40 cm (−4.5 S.D.). Triangular facies with prominent forehead and retrognatia. Mild clinodactyly of the little finger. No asymmetries or areas of hyperpigmentation. Mild psychomotor retardation. Weight: 5.0 kg (−3.8 S.D.), length: 61 cm (−4.8 S.D.), CP: 43.5 cm (−2.0 S.D.); normal genitals with testes of 1-cc. Complementary examinations: normal biochemical profile with normal coeliac disease markers. Hormone study: thyroid hormones normal, IGF1 59.0 ng/ml, IGFBP3 2.40 ng/ml. Glucagon test: peak of 4.6 ng/ml. Bone age: 7 months. Skeletal survey: osteopoikilosis in proximal metaphysis of the right ulna. MR of the sellar region normal. Methylation study of H19DMR and KvDMR domains, region 11p15 by sMPLA (ME030, MRC Holland) normal. Array-CGH study (ISCA v2, 8×60 K, Agilent) detected a deletion in the 12q14.3q15 region, involving 11 genes: HMGA2, LEMD3, GRIP1, MSRB3, RPSAP52, LLPH, TMBIM4, IRAK3, HELB, CAND1 and DYRK2 (Fig. 1). FISH study confirmed the 12q14.3q15 deletion in the patient and was normal in the parents. **Conclusion:** Compared genetic hybridisation techniques are useful to orient the diagnosis of patients with severe growth retardation and dysmorphic phenotype. Growth retardation and other clinical characteristics of the patient are considered to be related to the chromosomal abnormality detected and described as 12q14.3q15 microdeletion syndrome in other patients. Haploinsufficiency of the HMGA2 gene has been implicated as a cause of short stature in these patients.

P2-465

Making Adult Height Prediction Complete: Forecasting the Age of the Growth Spurt and the Height and Velocity Trajectories Until Adulthood

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Background: Adult height prediction (AHP) based on bone age appears as an incomplete procedure – it does not reveal the path from the present to the end-point. Growth charts offer little help in this respect because they average over children with different age of growth spurt (AGS). **Objective and hypotheses:** To extend AHP by also forecasting AGS and the entire height and velocity trajectories until adulthood and displaying this in a growth chart made from the same data as the AHP model. **Method:** The First Zurich Longitudinal study of 231 normal children born in 1955 was previously used to derive the AHP model (JCEM 2009). We used the same data to derive a model to predict AGS, and we derive height velocity curves corresponding to different AGS values. We also estimate a standard growth chart, which like the AHP model can be scaled to any mean population height. For a new child, the method predicts AGS, which is used to select the most likely height velocity trajectory. This is normalised and integrated to form the most likely height trajectory that ends up in the most likely value predicted by the previously developed AHP model. **Results:** The method is implemented as a freely available, interactive tool available on www.BoneXpert.com/adult-height-predictor. One enters gender, age, bone age and current height (and optionally parental height or height at menarche), and the tool displays a growth chart with the most likely height trajectory, and the most likely velocity curve. The AHP and AGS are also shown with their 1 SD uncertainties. **Conclusion:** The tool can provide a useful illustration in clinical practice and in the dialogue with the patients. It conveys the important message that the shape of an individual's growth curve is quite different from the shape of the growth chart. At the same time the illustration is anchored in the well-validated AHP model. **Conflict of interest:** HHT is the owner of Visiana which develops and markets the BoneXpert product for automated determination of bone age. **Funding:** D Martin is supported by Tübingen University.

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Whole Exome Sequencing Identifies *De Novo* HRAS Mutation Underlying Primary IGF1 Deficiency (PIGFD)

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Background: Primary IGF1 deficiency (PIGFD) is a rare condition defined by low IGF1 levels, GH sufficiency and absence of secondary causes of growth failure. PIGFD is an approved indication for treatment with recombinant IGF1 (rIGF1). Its genetic causes remain largely unknown. **Objective and hypotheses:** To elucidate genetic causes of PIGFD. **Method:** Clinical phenotyping followed by trio-based whole-exome sequencing (WES) in 11 complete case-parent-trios. **Results:** By WES we identified a HRAS mutation (G13C) in a boy with

syndromic PIGFD. His phenotype included a history of infantile feeding problems, short stature, mild psychomotor delay, sparse hair and long eyelashes. Biochemically, at age 4 years serum IGF1 was 9 ng/ml (−4.1 SDS), IGFBP3 0.5 µg/l (−4.9 SDS) with sufficient stimulated GH secretion and slightly elevated prolactin concentration. Probatory GH treatment moderately improved his growth, but did not lead to a significant increase of circulating IGF1 concentration. **Conclusion:** Our report of a patient with HRAS mutation enlarges the spectrum of genetic causes underlying syndromic PIGFD. With regard to rasopathies, GH insensitivity has been reported only in subjects with Noonan syndrome and PTPN11 mutations. Considering the increased risk for benign and malignant neoplasm in subjects with HRAS mutations, close clinical monitoring and a thoroughful discussion on the risk/benefit ratio of potential treatment with GH or rIGF1 is mandatory. **Conflict of interest:** JW served as an advisor for Ipsen and Novo Nordisk. **Funding:** This work was supported by the BONFOR reseach program of the University of Bonn, Germany and by an unrestricted research grant by Ipsen.

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Clinical and Biochemical Characteristics of a Female Patient with a Novel Homozygous STAT5B Mutation but Lack of Pulmonary Disease

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Background: STAT5B deficiency is characterized by severe postnatal growth failure, low IGF1, elevated levels of GH and prolactin, and immunodeficiency. To date, only ten patients with seven different mutations have been described. **Objective and hypotheses:** Describe clinical characteristics of a novel homozygous frameshift mutation in *STAT5B*. **Results:** A 17-year-old female was referred for proportionate short stature and primary amenorrhea. She was born at term with a normal birth weight; her short stature became evident after 2 years. She had no history of severe or recurrent infections, or pulmonary disease. Parents were first cousins and target height was 152.2 cm (−1.3 SDS). At first evaluation (15.2 years) height SDS was −6.2, weight SDS −4.1, delayed pubertal development (Tanner stage B2P2), and bone age was retarded by 4 years. She had midface hypoplasia, frontal bossing, high-pitched voice, and normal intelligence. Examination of the skin revealed generalized ichthyosis and, erythema and papules on hands. A biopsy of the lesions led to a diagnosis of chronic dermatitis. Serum IGF1 was undetectable and IGFBP3 was 0.5 mg/l, with persistently elevated prolactin (97–139 ng/ml). Results of two GH provocation tests showed GH peaks of 0.7 and 3.8 ng/ml. Cranial and pituitary MRI were normal. hGH treatment, however, did not significantly improve serum IGF1 levels or increase growth rate. Targeted gene analysis identified a novel homozygous frameshift mutation in the *STAT5B* gene, exon 12: c.1453del, p.Asp485Thrfs*29, which segregated appropriately. Absolute lymphocyte counts were in normal ranges. However, she had low $CD3^+$ T cell, elevated $CD19^+$ B cell and normal NK cell counts. $FOXP3^+$ expression on $CD4^+CD25^+$ cells was normal. *In vitro* T lymphocyte proliferative blastogenesis in response to stimulation with CD3 were also normal. **Conclusion:** Severe immunodeficiency and chronic pulmonary fibrosis, present in all but two previously reported patients, are not obligatory features in patients with STAT5B deficiency.

P2-468

Novel Heterozygous ACAN Mutations in Short Stature: Expanding the Clinical Spectrum

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Background: Homozygous aggrecan (ACAN) mutations have been described in a few skeletal dysplasias whilst more recently, heterozygous *ACAN* mutations have been reported in few families presenting with idiopathic short stature with advanced bone maturation and premature growth cessation. **Case presentation:** We describe two novel heterozygous *ACAN* stop mutations, detected using a skeletal dysplasia NGS panel and confirmed by Sanger sequencing, in two Spanish families with unknown aetiology of autosomal dominant short stature. Case 1: an 18-year old male with disproportionate short stature (height 149 cm, −4.3 S.D.), limb shortening, frontal bosing and macrocephaly. Poor pubertal growth spurt. No evidence of endocrine disorders or advanced bone age during childhood. Short stature and a similar phenotype was present in four generations (heights −4.3/−5.3 S.D.). A heterozygous *ACAN* mutation in exon 16, c.7276G>T (p.Glu2426*), was identified in the proband and cosegregated with the short stature in the family. Case 2: a 2.5-year-old girl with proportionate short stature (height 85 cm, −0.14 S.D.), relative macrocephaly, midfacial hypoplasia, flat nasal bridge, frontal bosing and acromicria. Normal laboratory results. Skeletal survey revealed advanced bone maturation (BA 4 years, CA 2y) and cone-shaped phalanges. Familial history included short stature in four generations (heights −2.9/−5.8 S.D.). A heterozgyous *ACAN* mutation, c.61G>T in exon 1 (p.Glu21*) was detected in both child and affected mother. **Conclusions:** Two novel *ACAN* mutations have been identified in

two families with short stature, mild dysmorphic features and no or mild skeletal abnormalities. Whilst case 2 showed advanced bone maturation, as previously reported, case 1 did not. Thus, *ACAN* should be considered a candidate gene in cases with short stature and accelerated skeletal maturation but further studies are required to determine the frequency of *ACAN* mutations in other short stature phenotypes. In summary, our findings broaden the spectrum of disorders caused by mutations in *ACAN*.

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Major Improvement in Parental Perception of their Children's Height-Specific Quality of Life after 1 Year of GH Treatment: Our Experience with the QoLiSSY Questionnaire

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Background: Short stature may be a source of social and affective stress in children and their parents, and thus impact negatively on their quality of life (QoL). Treatment by GH may improve QoL through normalisation of height. **Objective:** To evaluate height-specific QoL in short stature children after 1 year of GH treatment. **Methods:** Prospective study. Inclusion criteria were: having started GH treatment at Hôpital Necker-Enfants Malades between April 2012 and December 2014, age $\geq$ 4 y.o and short stature (≤ -2 SDS). Exclusion criteria were the presence of a serious chronic disease (e.g. brain tumour, idiopathic juvenile arthritis), syndromic cause (e.g. Turner syndrome, Prader–Willi syndrome), or developmental delay. Two questionnaires (general PedsQoL 4.0 and height-specific QoLISSY) were completed on the day of first GH injection (T0) and one year later (T12), both in parents and in children. Paired *t*-test was used to evaluate changes in QoL. **Results:** Of 66 patients who filled in the T0 questionnaires, 30 have completed the T12 evaluation, 12 girls and 18 boys. Median age: 10.3 y.o. (4.2–13.7). In PedsQoL questionnaires, parents reported a significant improvement of their child's emotional QoL ($P=0.009$). In QoLISSY scores, a very statistically significant improvement was noted in parental perception of their child's physical ($P=0.006$), emotional ($P=0.002$) and social ($P=0.006$) QoL. Children's questionnaires showed a significant improvement in their beliefs concerning importance of height ($P=0.015$), and a trend towards improvement of their emotional ($P=0.051$) and social ($P=0.058$) QoL. There was no correlation between height gain in SDS (mean: $+0.8$ SDS) and improvement in QoL. **Conclusions:** Our preliminary results show that after one year of treatment, children's height-specific QoL (physical, emotional, social) is significantly improved, according to parental perception. Results obtained after completion of the study will further clarify if there exists a change in children's QoL. **Funding:** This study was supported partially by Pfizer.

P2-470

Hypomethylation within the Imprinted *Dlk1 - Dio3* Domain: a Potential Regulatory Mechanism of Pre and Postnatal Growth

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Background: Genomic imprinting causes genes to be expressed or repressed depending on their parental origin. The 1-Mb *DLK1-DIO3* imprinted domain is located on human chromosome 14. Gene expression along this cluster is regulated by an intergenic differentially methylated imprinting control region ('IG-DMR'). In mice, altered gene dosage within this cluster is associated with alterations in embryonic and placental growth. **Objective and hypotheses:** To study the association between *DLK1-DIO3* IG-DMR methylation and placental, foetal and postnatal growth in humans. **Method:** We studied by means of pyrosequencing the DNA methylation of 18 CpG dinucleotides across the IG-DMR in placentae from 80 healthy mothers who delivered healthy infants. The studied chromosomal locations within the cluster were: Region 1: chr14:101270990-101271064; Region 2: chr14:101278037-101278081 and Region 3: chr14:101292465-101292596. At birth, placentas and infants were weighed (gestational age 39 ± 1 weeks; birth weight *Z*-score 0.31 ± 0.89) and placenta samples were collected. Infants' weights were measured monthly during the first year of life. **Results:** Children with hypomethylation within region 3 showed lower birth weight-to-placental weight ratios ($r=0.316$; $P=0.014$) and higher increases in weight during the first year of life ($r=-0.380$; $P=0.004$). We also performed analyses of individual CpG sites within region 1 and 2. In region 1, lower levels of methylation were related to lower birth weight ($r=0.270$; 0.017) while two different CpGs in region 2 showed significant associations, respectively, with placental weight (position 1: $r=-0.306$; $P=0.011$) and weight increase during the first year of life (position 5; $r=-0.301$; 0.044). All these associations remained significant after adjusting for confounding variables. **Conclusion:** For the first time, we show that placental hypomethylation at the *DLK1-DIO3* IG-DMR is associated with decreased foetal growth and increased placental weight and postnatal growth. We suggest that hypomethylation in the *DLK1-DIO3* imprinted domain may be a new mechanism regulating pre and postnatal growth in humans. **Funding:** This study was supported by a grant from the Ministerio de Ciencia e Innovación, Instituto de Salud Carlos III (ISCIII), Madrid, Spain (PI13/01257), project co-financed by FEDER.

P2-471

Growth and Metabolic Phenotypes in Patients with SRS: a Multi-Centre Cross-Sectional Observational Study

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Background: Silver–Russell syndrome (SRS; OMIM 180860) is a genetically and clinically heterogeneous low birthweight syndrome characterised by poor postnatal growth and a number of variable dysmorphic features. Small-for-gestational age infants in general have an increased risk of metabolic complications, some initially occurring in late childhood and adolescence. **Objective and hypotheses:** To identify i) response to GH based on genotype and ii) development of metabolic complications whilst on GH treatment or as young adults. **Method:** A cross-sectional, observational multi-centre study across England, investigating patients >5 years with clinical or genetically confirmed SRS for response to GH and evidence of insulin resistance and hypertension on baseline screening. **Results:** 37 patients (18 H19; nine mUPD7 and ten clinical; 22M: 15F, mean age at assessment 11.74 years, range 5.0–39.1). GH treatment increased height SDS by 0.99 (0.56 S.D.) SDS after 1 year and 1.97 (1.16) SDS after 3 years; $P<0.001$). A significantly better response to GH treatment was seen in mUPD7 patients compared to H19 after 3 years (P0.002). BMI increased by 0.41 SDS (1.0; P0.046) on GH treatment after 3 years. No significant difference between genetic subtypes seen. Mean % fat mass (assessed by Tanita scales) was 16.3% (5.26) with no significance between pubertal and pre-pubertal individuals. Baseline fasting lipid, insulin, glucose, leptin and adiponectin levels showed no evidence of insulin resistance or impaired fasting glycaemia ($n=30$) and OGTT data ($n=7$) showed no insulin resistance. Basal blood pressure measurements showed no evidence of hypertension (diastolic and systolic measurements <90 centile). Adrenarche was seen in seven patients and central precocious puberty requiring treatment in four patients. **Conclusion:** GH treatment improves height SDS and BMI SDS in SRS patients with significant difference in height SDS increase between mUPD7 and H19 after 3 years of treatment. No evidence of insulin resistance or hypertension was seen on baseline screening. **Funding:** This work was supported by Child Growth Foundation and Newlife Foundation.

P2-472

Characterisation of Partial *SHOX* Deletions/ Duplications Reveals Intron 3 to be a Hotspot Region

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Background: SHOX, located on the pseudoautosomal region 1 (PAR1), encodes a transcriptional factor implicated in human skeletal growth. Alterations in SHOX or its regulatory elements are observed in ~70% of patients with Leri–Weill dyschondrosteosis (LWD), in ~90% with Langer mesomelic dysplasia (LMD) and ~2.5% of patients with idiopathic short stature (ISS). SHOX deletions/duplications are a frequent alteration, with the majority encompassing the entire gene. **Objective and hypotheses:** During routine *SHOX* diagnostics, a total of 15 partial *SHOX* deletions (14 LWD, one LMD), and 12 partial duplications (nine LWD, three ISS) were detected. We set out to characterise these 27 partial *SHOX* alterations and to determine if certain regions were more susceptible to breakages. **Method:** A total of 15 partial *SHOX* deletions and 12 partial duplications were characterised using chromosome Y specific array-CGH (Nimblegen), two custom-designed MLPA assays and breakpoint junction PCR sequencing. **Results:** Nine intragenic deletions and seven duplications were characterised, with the smallest involving a single exon. Six deletions and five duplications extended upstream (five and four, respectively) and downstream (one in each case) of *SHOX*. No reciprocal partial deletions and duplications were observed. To date, deletion breakpoints have been determined in four patients, three of which were located in intron 3. Although not all breakpoints have been finely characterised, we have observed that 13/27 (48%) alterations have a distal or proximal breakpoint in intron 3 (5994 bp, 28.6% repetitive elements). **Conclusion:** We have characterised 15 partial deletions and 12 partial duplications of *SHOX* in patients with LWD, LMD, and ISS. Approximately half of the breakpoints are located in intron 3 which is rich in repetitive elements. Together with other reported cases, we propose that the highly repetitive intron 3 has a high predisposition to breakage and represents a hotspot region for deletions and duplications. **Funding:** This work was supported by the MINECO (SAF2012-30871).

P2-473

The Pubertal Gain in Height is Inversely Related to BMI in Childhood

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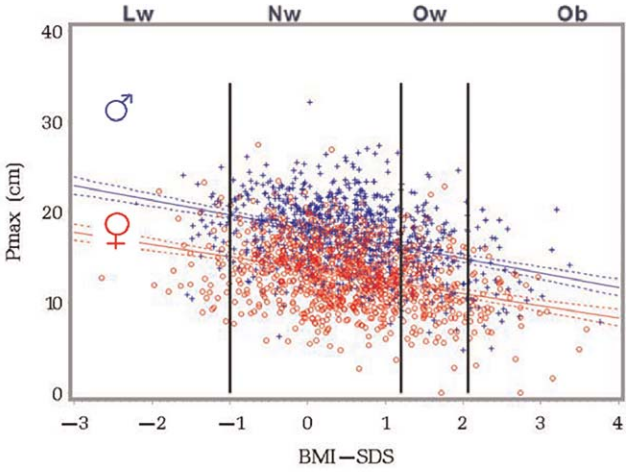
Background: Weight in childhood may influence the pubertal timing and pattern of growth. **Objective:** To investigate the impact of BMI in childhood on further growth, especially the specific pubertal pattern of growth. **Method:** The longitudinally followed *GrowUpGothenburg1990* birth cohort, was analyzed using the QEPS growth model (Nierop *et al. Horm Res in Ped.* 2013; **80**(suppl 1):152–153) (describing total height as a combination of four mathematical functions; Quadratic – Q, Exponential – E, Pubertal – P and Stop – S). Individual BMI_{SDS} values, from 3.5–8 years of age were calculated for linear and subgroup analyses (low/normal – Lw/Nw, overweight/obese – Ow/Ob), based on the IOTF 2012 reference (Cole TJ, Lobstein T. Pediatric obesity. 2012; **7**(4):284–94.). **Results:** Across the whole BMI range a negative dose-response effect of childhood BMI on pubertal gain (Pmax) was found. Already at birth Owob children were heavier, and they grew faster in height in the prepubertal period compared to Lw/Nw, as evidenced by an increased Q function. Owob children of both genders had earlier puberty (91–117 days), $P=0.0004$, reduced growth during puberty, boys/girls 3.13/2.26 cm less pubertal gain $P=0.0001$, from the specific pubertal growth function (Pmax). The adult height was not related to BMI in childhood. **Conclusion:** The higher BMI in childhood, the faster the prepubertal growth, the earlier onset of puberty, the less pubertal gain. This was evident across the whole BMI-range, making weight status an important modifier of growth. **Funding information:** This work was supported by the Swedish Research Council (VR no 7509 and VR 2006-7777), VR/FORMAS/FORTE/VINNOVA (259-2012-38 and 2006-1624); EpiLife-TEENS research program, Pfizer AB, the Governmental Grants for University Hospital Research (ALF), the R&D Department, County of Halland, and the Foundation Växthuset for children.



For girls; P_{max} = 13.66 - 1.35 x BMI SDS, adjusted r^2 = 0.1074.

For boys; P_{max} = 18.05 - 1.61 x BMI, adjusted r^2 = 0.1312.

P2-474

Growth Curves for Height, Weight, BMI and Head Circumference in Children with Achondroplasia

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Background: Close monitoring of growth is vital when following children with achondroplasia yet existing growth curves suffer from a simple chart format and their clinical use is therefore limited. Also, references for body proportions; i.e. sitting height, relative sitting height and arm span, are lacking. **Objective and hypotheses:** The aim of this study was to construct age-specific growth curves for height, weight, body mass index, head circumference and body proportions in children with achondroplasia. **Method:** A combination of longitudinal and cross-sectional measurements were collected from about 550 children and adolescents with achondroplasia aged 0 to 20 years. Standard deviation curves were estimated using the Generalized Additive Models for Location, Scale and Shape (GAMLSS). **Results:** Retrieved averages for these four variables were similar to the existing growth references by Horton et al. and Hoover-Fong et al. To better capture growth development during the first 4 years of life, the curves for head circumference, height and weight were combined on the same page by using logarithms for all axes. Similar approaches were used for the design of a separate BMI and a separate head circumference chart, both covering 0–20 years of age. **Conclusion:** Sex- and age-specific curves for height, weight, body mass index and head circumference were constructed and designed in a format that makes it easy to follow growth development of the individual. The body proportion references are under construction. **Funding information:** This work was supported by Stiftelsen Promobilia.

P2-475

Growth Hormone Deficiency and Pituitary Dysgenesis in a Girl with Microdeletion 2q31.1

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Background: Microdeletions of the chromosomal region 2q31.1 are rare. Growth retardation is reported in the majority of these patients, but information about growth hormone status is not given in the literature. Other typical features in 2q31.1 deletion syndrome are developmental delay, limb abnormalities, short palpebral fissures, heart defects, among others. **Objective and hypotheses:** A 12 year old girl presented at the age of 7 years with severe growth deficiency: height was 104.2 cm (−4.4SDS), growth velocity was 1.3 cm per year (−7.0SDS). Bone age was retarded

(5;6 years). IGF1 and IGFBP3 were measured below the 3rd percentile. She has small palpebral fissures, but no limb anomalies and no heart defect. Motor and mental development is severely retarded. **Method:** Karyotyping was performed according to standard procedures. Array-CGH was carried out with an average resolution of 0.15 Mb. **Results:** Chromosomal analysis showed a normal Karyotype 46,XX. Array-CGH revealed a heterozygous deletion of 4.3 Mb in the chromosomal region 2q31.1. Subsequent analysis of the parents showed that the deletion occurred *de novo*. Growth hormone (GH) deficiency was diagnosed (maximum GH peak 1.2 ng/ml). Cerebral MRI scan demonstrated dissociation of anterior and posterior pituitary. No other hormone deficiencies were detected. Treatment with recombinant growth hormone resulted in significant catch up growth. At the age of 12 years the girls height is 142.4 cm (−1.6SDS), growth velocity is 9.5 cm per year (+1.9 SDS). Puberty has started (Tanner stage B2). **Conclusion:** This is the first report of a pituitary malformation with the consequence of growth hormone deficiency in a patient with microdeletion 2q31.1. Because these patients frequently have limb abnormalities and also because syndromic short stature may be assumed, growth hormone deficiency may be missed.

P2-476

One Year Screening Program for Stature Deviations – Strategy and Outcome

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Background: Many children still miss the early recognition of their stature problems due to inefficient screening strategies. **Objective and hypotheses:** To assess stature deviations referral through recruiting general practitioners (GPs) and providing them with tools for easier anthropometric data assessment and enhanced access to the Paediatric Endocrinologist. **Method:** Thirty-one general practitioners with a total of 23 058 patients between 2–18 years were recruited to the Screening program for one year. They were supplied with computer software alerts if patients' height, weight or waist circumference (WC) were ≧/± 2/SDS. CDC standards for height and weight and WC local data were used as reference. The GPs' teams were trained twice on proper anthropometry and on the Screening program protocol. Compliance was checked monthly. Deviating patients were to be referred to a weekly University Screening clinic. At final evaluation GPs were divided into two groups, based on their compliance with the study protocol. **Results:** A total of 81 short children (0.35% of all participants and 11.7% of the expected about 3%) were found within 24 478 health check visits with anthropometric measurements. The compliant doctors' group found 0.65% short children vs. 0.09% in the non-compliant group. Only 2552 children (11.1%), all from the compliant GPs group', were fully assessed. Among them 1.15% were short and 7.99% were tall (4.78% non-obese). Of all 81 short children 39.5% showed up for further assessment and only 9 agreed to further work-up (4 with constitutional delay in growth and puberty, 3 with syndromic short stature, 2 with GH deficiency). At the same time, 2 GH deficient children from the studied group came to the Clinic through Internet self-found information. **Conclusion:** This screening strategy proved as inefficient. The large share of non-attendance and assessment refusal shows that future strategies with media advertising might prove more beneficial.

P2-477

BASIC: Bone Age Study in Children

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Background: Bone age studies require X-ray of the left hand and wrist to assess skeletal maturity. The Tanner-Whitehouse 3 (TW3) scoring method provides an objective framework for calculating bone age and specifies exact placement of the hand. In our service we have noted a number of poor quality films, caused by difficulty with hand placement, e.g. scrunching of the fingers. This compromises the ability to score accurately and in a proportion necessitates re-X-ray, with time, financial and radiation exposure consequences. **Aim:** To assess X-ray quality and need for re-X-ray in patients having TW3 bone ages. **Method:** We performed a prospective study of all bone age X-rays conducted at Sheffield Children's Hospital from May 2013 to February 2014. The quality of bone age X-rays was rated by a single specialist auxology nurse. The position of the thumb, fingers and the overall clarity of the X-ray were scored on a simple 1–3 scale (poor, adequate, good), generating a score out of 9. The need for re-X-ray was noted. **Results:** Of the 259 bone ages studied, from patients aged 1.92 to 18.48 years, 123 were females. There were 12 X-rays scoring 1 (4.6%) (poor quality) for both the finger and thumb positions and 9 for X-ray clarity (3.5%). The number of studies scoring less than 3 for position of fingers, thumb and overall clarity was 38 (14.7%), 26 (10.0%) and 77 (29.7%) respectively. The number of re-X-rays required was 28 (10.8%). **Discussion:** We have shown that achieving good quality films on which to assess bone age may be more difficult than presumed. We believe the re-X-ray rate to be unnecessarily high and have devised a simple hand outline template, placed on the X-ray plate, to encourage the correct positioning of the hand. We are currently evaluating its efficacy using the same scoring system.

P2-478

Comparison of the Turkish Growth Standards with the Who Standards

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Background: Growth standards are important tools in the monitoring of growth. In 2006 the World Health Organization (WHO) published new growth charts based on infants and young children living in optimal conditions in six countries and proposed that these and the NCHS data on North American children be accepted as standards for children in all countries throughout the world. Studies comparing country specific standards with WHO growth charts are therefore necessary. **Objective and hypotheses:** To compare the WHO growth charts from birth to 18 years of age with the Turkish reference curves. **Method:** The national growth data on infants and young children were based on 36330 anthropometric measurements (19523 boys, 16807 girls) of 2391 boys and 2102 girls attending a Well-Child Clinic. For children 6 to 18 years, height and weight measurements (6007 boys, 5657 girls) of 1100 boys and 1020 girls were obtained from healthy school children. The LMS method was used for the analyses. The studies were longitudinal, but the data were analysed cross-sectionally. Mean z scores for height and BMI by age and sex were calculated and graphically compared with the WHO curves. **Results:** From birth to 3 years of age, the national group of children was on average 0.5 standard deviations (SD) taller compared to the WHO data. This difference continued to show a similar pattern during childhood and the local children were 0.3 SD taller during puberty up to 18 years of age compared with the WHO growth standards. Mean z score values for BMI were similar to the WHO standards during childhood except for puberty at which time our group had higher values. **Conclusion:** Our charts showed that population differences in growth may exist and become more apparent during the pubertal years. Differences from the WHO growth charts beyond a certain magnitude would favour the use of country-specific standards.

P2-479

Moya Moya Syndrome in a Patient with Growth Hormone Deficiency and Hypergonadotropic Hypogonadism: to Treat or not to Treat with Growth Hormone Therapy?

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Background: Moya Moya disease is a chronic cerebrovascular angiopathy characterized by progressive stenosis of terminal part of internal carotid vessels and the compensatory development of collateral vessels. We present here the case of a young boy with growth hormone deficiency (GHD) and testicular insufficiency that was diagnosed with Moya Moya syndrome. **Case presentation:** A 12.9 year-old boy of Serbian origin was referred to the Endocrinology Department of Necker university Children's Hospital because of growth failure (height:-3SD). Tanner puberty stage was two. Hormonal work-up revealed isolated GHD (low GH peak after two stimulation tests, low IGF1 levels), normal for pubertal stage testosterone level (1.2 ng/ml) and normal pituitary assessed by MRI. Response to GH treatment was moderate with a final height of 1.62 m (target height: 1.80 m) with rather slow pubertal evolution. At age of 17, endocrine evaluation showed low testosterone (3.8 ng/ml), high LH (13 U/L) and FSH (38 U/L) levels, low inhibin B (7 pg/ml). Spermogram revealed azoospermia. Blood karyotype was normal (46XY). GHD was confirmed at re-evaluation and GH therapy (low dose) was prescribed. The association of GHD and primary gonadal dysfunction suggested the possibility of Moya Moya syndrome, which was confirmed by molecular analysis: deletion of BRCC3 and MTCP1 genes. Therefore a brain angio-MRI was performed which showed Moya Moya characteristic vessels anomalies. After discovery of these vascular anomalies GH therapy was stopped. But the patient complained about asthenia and GH therapy was again prescribed with regular control of IGF1 levels. **Conclusion:** Moya Moya syndrome must be suspected when GHD and testicular insufficiency are associated. This case promotes discussion concerning the use of GH treatment in patients with GHD and cerebral vascular anomalies in whom the risk of ischemic and hemorragic brain damage may be increased by the background disease.

P2-480

In Vitro Functional Characterization Of *IGFALS* Gene Variants Found In ALS Deficient or Idiopathic Short Stature (ISS) Children

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Background: ALS deficient (ALS-D) patients present severe IGFI and IGFBP3 deficiencies and variable degree of growth retardation. Heterozygous carriers for *IGFALS* variants, ALS-D relatives or a subset of ISS children, have levels of IGFI, IGFBP3 and ALS intermediate between ALS-D and wildtype (WT) subjects. This supports that *IGFALS* gene variants may affect ALS synthesis, secretion and/or function and could be responsible for the observed phenotype. **Objective and hypotheses:** We aim to study the impact of ten *IGFALS* gene variants identified in ALS-D or ISS children (p.E35Kfs*87, p.E35Gfs*17, p.L213F, p.N276S, p.P287L, p.A330D, p.L409F, p.A475V, p.C540R, and p.R548W) on ALS protein synthesis and secretion and to characterize whether the secreted protein variants retain functional capacity for ternary

complex formation *in vitro* (iv-TCF). **Method:** *IGFALS* gene variants were introduced by site-directed mutagenesis into a commercial vector containing the entire human *IGFALS* cDNA. CHO cells were transiently transfected with WT-*IGFALS* or each of the ten variants. Both lysates and conditioned media (CM) were analyzed by WIB. Iv-TCF was performed for WT and mutant ALS variants by Superdex 200 exclusion column chromatography. **Results:** WIB showed that WT-ALS was found mostly secreted into the CM at 24 hours. For variants p.E35Kfs*87, p.E35Gfs*17, p.N276S, p.L409F and p.C540R, we found absence of protein in both lysates and CM; for variant p.L213F, presence of protein in lysates but absence in CM; and for variants p.P287L, p.A330D, p.A457V, and p.R548W, presence of protein in lysates and CM. All the normally synthesized and secreted variants retained their ability for iv-TCF. **Conclusion:** Six of the *IGFALS* gene variants analyzed impaired the biosynthesis, secretion and/or stability of the protein. All secreted variants retained the ability to form iv-TCF. It remains to be explored how these variants affect the IGF system in the context of a whole organism. **Funding information:** This work was supported by grants from the Agencia Nacional de Promoción Científica y Tecnológica (PICT-2010 Nro.1916), and SANDOZ International GmbH, Business Unit Biopharmaceuticals.

P2-481

Klinefelter Syndrome with Short Stature and Microcephaly: An Unusual Combination

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Background: Patients with Klinefelter syndrome (SK) have a 47, XXY karyotype and tall stature as a result of overexpression of the SHOX gene. The case of a patient with peculiar phenotype, microcephaly, proportional short stature and 47, XXY karyotype with a deletion in band p11.3 of one X chromosome is presented. **Clinical description:** A 2-year, 4 month-old boy was referred for study of growth retardation. The product of a first gestation of 39 weeks of healthy non-consanguineous parents of normal stature. BW: 2.850 g (−1.3 SD), length: 47.5 cm (−1.7 SD), PC: 33 cm (−1.0 SD). Physical exam: weight: 8.6 kg (−3.0 SD), length: 78 cm (−3.6 SD), CP: 40 cm (−2.0 SD). Phenotype: peculiar facies with narrow forehead and hypoplasia of nostrils. Microcephaly. Hypoplastic external genitalia. Testes in 1-cc sacs. Mild psychomotor retardation and axial hypotonia. Bone age: 2 years. Normal biochemical profile with normal coeliac disease markers. Hormone study: thyroid hormones: normal, LH <0.07 U/L, FSH 0.61 U/L, inhibin-B 113.0 pg/ml, ACTH 25.9 pg/ml, cortisol 18.6 mcg/dl, prolactin 6.1 ng/ml, IGF-1: 51.4 ng/ml, IGFBP-3: 3.6 ng/ml. Glucagon test: basal GH 4.4 ng/dl and maximum peak: 7.6 ng/dl. MR: pituitary hypoplasia, ectasia of the optic nerve sheath, ponto-cerebellar hypoplasia, mild demyelination of white matter. Array-CGH (ISCA v2, 8x60K, Agilent): presence of two X chromosomes and a deletion in Xp11.3 involving the CASK, NDP, KDM6A, GPR34, GPR82, MAOA, MAOB, EFHC2, FUNDC1 and DUSP21 genes (Default 1). 47, XXY Karyotype. FISH study with BAC RP11-24p8 confirmed the Xp11.3 deletion in the patient and was normal for the parents. Fundus: retinitis pigmentosa. **Conclusion:** Array-CGH techniques are useful to orient the diagnosis of patients with severe growth retardation and dysmorphic phenotype. The combined effect of haploinsufficiency of the CASK gene and pituitary hypoplasia may be responsible for the short stature in our patient.

P2-482

Childhood Growth of Boys with Congenital Hypogonadotropic Hypogonadism

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Background: Congenital hypogonadotropic hypogonadism (CHH) provides a model to study the impact of sex steroid deficiency on childhood growth. **Aims and objectives:** We characterised growth patterns in male CHH patients with special emphasis on growth during the minipuberty of infancy. **Methods:** Growth charts of 38 men with CHH (28 from Finland and 10 from Denmark) were evaluated. Fifteen (39%) patients had representative length measurements during the 1st year of life; 8 of them had signs of profound GnRH deficiency (history of micropenis and/or cryptorchidism). Sixteen men (42%) had molecular genetic diagnosis of CHH (mutations in KAL1 in 7, FGFR1 in 5, GNRHR in 2, CDH7 in 1, and PROK2 in 1 patient). **Results:** The mean ($\pm$ SD) length standard deviation score (SDS) at birth (0.2 ± 1.6 SDS) decreased significantly during the first 3 (to -0.9 ± 1.2 SDS, $P<0.01$) and 6 months of life (to -0.7 ± 1.3 SDS, $P<0.05$). The respective mean length SDSs were lower than the mean mid-parental target height (MPH) ($P<0.05$). Importantly, the length SDS deflected strongly in those with signs of profound GnRH deficiency from 0.8 ± 1.8 SDS at birth to -1.0 ± 1.4 SDS at 3 months of age ($P<0.01$); and to -0.5 ± 1.2 SDS at 6 months of age ($P<0.05$). During the first 6 months of life, CHH patients grew thinner (mean change in weight-for-length, $-6.7\pm11\%$, $P<0.05$). Between 6 and 8 years or age, height SDSs were, on average, -0.8 ± 1.3 below the mean MPH ($P<0.05$), and the boys were shorter than the general population ($P<0.01$). At an average age of 15.8 ± 0.8 years, height SDS reached its nadir (-1.8 ± 1.4 SDS), reflecting pubertal failure. Final heights, however, did not differ from MPH ($P=$NS). **Conclusions:** Sex steroids modulate human growth during the first few months of life. Moderate length deflection in infancy is a novel non-reproductive feature of CHH. **Funding information:** The Finnish Foundation of Pediatric Research, the Academy of Finland, the Helsinki University Central

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P2-483

Hypermethylation at the Imprinted *C19mc* Microrna Cluster: A New Link between Maternal Metabolism and Infant's Growth

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Background: Maternal obesity can have long-term consequences for the offspring's health, including increased risk of type-2 diabetes and cardiovascular disease. The *C19MC* imprinted locus on chromosome 19q13.4 comprises a cluster of 46 microRNAs, which are usually expressed only in the placenta and from the paternal allele exclusively. Besides its role favouring trophoblast migration, the *C19MC* locus is deregulated in several human cancers. It is unknown whether the degree of DNA methylation at the *C19MC* locus could be linked to maternal metabolism and infant's growth. **Objective and hypotheses:** To determine the association between DNA methylation at *C19MC* and maternal weight, blood pressure and post-load glucose, and with the infant's weight and length. **Method:** The degree of DNA methylation at 3 CpG dinucleotides in the *C19MC* promoter was studied by means of pyrosequencing in placentas from 79 healthy pregnancies. The studied chromosomal location within the cluster was chr19:54,151,133-54,151,183. A glucose-challenge test was performed between 24 and 28 weeks of gestation. Maternal weight and blood pressure data were also collected prior to birth. At delivery, placentas were collected and weighed, and the weight and length of the newborns were measured (gestational age 39 ± 1 weeks; birth weight z-score 0.31 ± 0.89). **Results:** Increased placental methylation of the *C19MC* locus was associated with maternal obesity ($P = 0.016$). Furthermore, higher levels of methylation were also associated with higher maternal systolic blood pressure ($r = 0.430$; $P = 0.001$) and post-load glucose levels ($r = 0.264$; $P = 0.035$). Higher placental levels of methylation were also associated with increased infant's growth, showing positive associations with weight z-score ($P = 0.267$; $r = 0.026$) and height z-score ($r = 0.272$; $P = 0.024$) at birth. All these associations remained significant after adjusting for confounding variables. **Conclusion:** This study shows for the first time that aberrant hypermethylation at the *C19MC* locus provides a link between a poorer maternal metabolic phenotype and increased growth of the offspring. **Funding information:** This study was supported by a grant from the Ministerio de Ciencia e Innovación, Instituto de Salud Carlos III (ISCIII), Madrid, Spain (PI13/01257), project co-financed by FEDER.

P2-484

Challenged Diagnosis on Hypoglycaemia: Hirata Disease X Factitious Hypoglycaemia

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Introduction: The Insulin Autoimmune Syndrome (IAS or Hirata Disease) is rare among children. Non-ketotic hyperinsulinaemic hypoglycemia and the presence of insulin auto-antibody (IAA) are the conditions to diagnose the syndrome. The occurrence of hypoglycemia is due to the binding of the antibody to the insulin molecule at the immediate postprandial, followed by this binomial dissociation, which releases free insulin on serum and triggers symptomatic hypoglycaemia. **Case report:** A 6-year-old boy was followed by symptomatic hypoglycemia. Seizures since 7 months old were treated and controlled with anticonvulsants until the age of five, when raised hypoglycemia symptoms. Several hospitalizations, some highlighted exams: random glycemia 21 mg/dL (1.16 mmol/L), insulin 34.7 μU/mL, other critical sample exams were negative, abdominal MRI was normal. No improvement after taken diazoxide, somatostatin, hydrochlorothiazide and glucagon. As he did not improve, and there was still a suspect of exogenous insulin, new exams and a new hospitalization occurred: glycemia 26 mg/dL (1.44 mmol/L), insulin 686.7 μu/ml. Even though his mother was kept away from him, the insulin level increased to $>$ 1000 μU/ml, c-peptide was 5.1 ng/ml (1.1 – 4.4), sulphonylurea dosage was negative, and two extended OGTT were performed, ranging insulin 407–1000–μU/ml, C-peptide 1.5–5.2 ng/ml and glycaemia 21–112 mg/dl (1.16–6.2 mmol/l). Insulin antibody was found, associated to the insulin molecule, which resumes the syndrome. As soon as dietary and physical activities recommendations were followed, there had been less hypoglycemic episodes. **Conclusion:** To exclude factitious hypoglycemia, four hospitalisations and judicial separation of mother and child were necessary to prove the mother was not giving inadvertently insulin to his child. Only when IAA was performed, which set the presence of autoantibodies bound to native human insulin, the diagnosis was elucidated. As IAS is usually related to previous exposure to drugs, this case is considered a novel insight into clinical practice.

P2-485

Is Bedside Monitoring of Blood Beta-Hydroxybutyrate Levels Reliable in the Management of Hypoglycaemia in Children?

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Background: Bedside blood ketone measurement has often been used in the management of diabetic ketoacidosis. However

there is no available data on its reliability in the evaluation of hypoglycaemia in children. We aimed to assess the reliability of bedside ketones (β-hydroxybutyrate, BHB) in the evaluation of hypoglycaemia in children. **Objective and hypotheses:** To assess reliability of bedside ketone measurement in a clinical setting of hypoglycaemia in children. **Method:** We collected data on 20 children who had paired measurements of bedside and lab BHB at the end of a controlled fast. Bedside BHB was measured by finger prick at end of the controlled fast or at the time of hypoglycemia (blood glucose <3 mmol/l) using Precision Xceed Pro blood glucose & β–ketone monitoring system (Abbott Diabetes Care, Alameda, USA). Venous sample was sent simultaneously for measurement of BHB concentration using an enzymatic method (Randox laboratories, Crumlin, UK). Bland-Altman analysis & Regression analysis were used to compare bedside BHB measurement with the established lab BHB assay. **Results:** The mean age was 3.8 years (M:F = 14:6). Out of 20 children, 6 with CHI (congenital hyperinsulinism) underwent fast to assess fast tolerance on treatment, 6 underwent fast when they came off diazoxide therapy for CHI and 8 underwent diagnostic fast for recurrent hypoglycaemia, which was subsequently confirmed as ketotic hypoglycaemia. Both bedside and measurements showed good correlation on regression analysis [$r=0.98$ ($P<0.01$)]. Using Bland-Altman analysis, mean difference between the two assays was noted to be minimal [0.11 (SEM $\pm$ 0.107)]. **Conclusion:** In this study, we have demonstrated that assessment of bedside ketones using Precision Xceed Pro system is a reliable way of evaluating ketotic response during hypoglycaemia in children. Bedside ketone measurement is a simple tool that would provide valuable insight into the aetiology of hypoglycaemia.

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Transient Hyperinsulinaemic Hypoglycaemia in Association with a Novel ABCC8 Mutation: Expanding the Clinical Phenotypes

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Background: Hyperinsulinaemic hypoglycaemia (HH) can be transient or permanent. Transient HH (spontaneous resolution of HH within few weeks) is associated with intrauterine growth restriction, maternal diabetes, erythroblastosis fetalis etc. Transient HH has not been reported with ABCC8/KCNJ11 mutations, which are the commonest cause of HH. **Aim:** Molecular characterisation of a novel ABCC8 mutation associated with a transient HH phenotype seen in a family with two affected cousins. **Patients and methods:** Two cousins developed transient HH in the neonatal period, which lasted 8–12 weeks. Molecular genetic analysis identified a novel maternally inherited heterozygous ABCC8 mutation (c.4547C>T; p.T1516M). Point mutation was introduced in the hamster SUR1 cDNA in the pcDNA3.1 plasmid by site-directed mutagenesis. HEK293 cells were transfected with mutant hamster SUR1 cDNA and WT human Kir6.2 cDNA using FuGENE. Functional properties of reconstituted KATP channels were studied using whole-cell patch-clamp recordings. Both homogenous and heterozygous expressions of the mutants were studied. **Results:** Negligible KATP currents (current equivalent to endogenous HEK293 current) were noticed when p.T1516M SUR1 subunit was expressed with WT Kir6.2 subunit (44 ± 13pA/pF vs. 48 ± 13pA/pF; $P=$ns). This clearly established the pathogenicity of T1516M mutation, which is located in the nucleotide-binding domain 2 (NBD2) region of SUR1. With heterozygous expression as seen in the proband, KATP currents equivalent to WT KATP currents were observed (325 ± 54pA/pF vs. 229 ± 56pA/pF; $P=$ns). The WT SUR1 subunit was able to rescue the function of the mutant SUR1 subunit. **Conclusion:** This study extends the clinical phenotypes reported with ABCC8 mutations to transient HH. Molecular characterisation was consistent with the observed clinical phenotype. **Funding information:** The work was supported by MRC UK.

P2-487

Congenital Hyperinsulinism in Ukraine

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Background: Congenital hyperinsulinism (CHI) has not been studied in the Ukraine. **Objective and hypotheses:** We investigated the genetic aetiology and treatment of patients with CHI. **Method:** Routine clinical and laboratory investigations were performed in children with hypoglycaemia. Genetic testing was undertaken for seven patients with CHI from 9 families. *KCNJ11, ABCC8, HNF4A* genes were sequenced in all patients. For those who were negative in the initial screening, were also tested for *GLUD1* gene, as well as tNGS of all known CHI genes was performed. ^{18}F-DOPA PET-CT (and ^{68}Ga-DOTA PET-CT) scans were performed in selected cases. **Results:** In seven patients hypoglycaemia (glucose 0,8 [0,5; 1,2] mmol/l) with detectable insulin (43,1 [1,2; 45,9] mIU/l) and/or C-peptide (6,9 [1,1; 9,9] ng/ml) confirmed CHI. The median age at diagnosis was 55,4 [1,0; 330] days and the median birth weight was 4078 [2850; 5200] g. The incidence of CHI in the Ukraine was calculated at 1 in 258,650 births. Mutations were detected in 6/7 patients. In one patient without a mutation, ^{18}F-DOPA and ^{68}Ga-DOTA PET-CT scanning revealed diffuse disease. All patients showed a poor response to medication and had varying degrees of developmental delay and seizures. 5/7 were surgically treated. Postoperative complications included transient fasting hyperglycaemia (1), cicatricial hernia development after convulsions (1) and persistent subclinical exocrine insufficiency (1). **Conclusion:** Children with

Table 1. Genetic causes of CHI (for abstract P2-487).

Patient	Gene	Protein change	Inheritance		Treatment	Histological form
			Mother	Father		
1	*ABCC8*	p.Q444H		p.Q444H	Surgical	Focal
2	*ABCC8*	p.?		c.4415-13G > A	Surgical	Focal
3	*ABCC8*	p.Q444H p.Q923X	p.Q923X	p.Q444H	Medication	
4	*ABCC8*	p.R1437X		p.R1437X	Surgical	Focal
5	Not found				Surgical	Atypical
6	*KCNJ11*	p.F333S		p.F333S	Surgical	Focal
7	*ABCC8*	p.R1251X p.Y1287X	p.Y1287X	p.R1251X	Medication	

hypoglycaemia and unsuppressed insulin and C-peptide levels should undergo genetic and eventual PET CT scan for characterization of the type of CHI. Further studies to identify novel CHI genes are required. **Funding information:** This work was supported by the Medical Research Council (grant number 98144).

P2-488

Unexplained Altered States of Consciousness in a Girl

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Background: In children, congenital hyperinsulinism is the most common cause for endogenous hyperinsulinaemic hypoglycaemia (HH). Beyond infancy other diagnoses may be considered, such as insulinoma, an insulin-secreting neuroendocrine tumour (NET) arising mostly from the pancreas. The latter is a rare cause of HH in children. The estimated incidence of insulinoma is 1:250'000 person-years of all age groups with a median age at diagnosis of 47 years. Herein, we report an adolescent girl with malignant insulinoma, which is extremely rare in children. **Case presentation:** A previously healthy 15-year-old girl presented at the emergency department with a history of vertigo, fatigue, recurrent feeling of faintness, intermittent inadequate behaviour and amnesia for the event for the last 6 months. Physical and neurological examinations were normal. No evidence for organic brain disease was present and symptoms were interpreted to be functional. The patient was hospitalised for further evaluation. At the first night, the patient fell unconscious and hypoglycaemia was diagnosed. She rapidly recovered under intravenous glucose supply. Further evaluation revealed increased serum insulin and C-peptide levels. An MRI scan of the abdomen demonstrated a solid mass in the pancreatic tail as well as two liver lesions, suspicious for metastases. Surgical resection of the tumour and the pancreatic tail was performed. The intrahepatic lesions were identified by ultrasound and resected as well. Histological examination confirmed the diagnosis of a NET with liver metastases. MEN-Typ1 was excluded. A follow-up 8 months later revealed no evidence of hypoglycaemia, but a new suspicious liver lesion on MRI scan. **Conclusion:** Unclear behavioural changes should prompt blood glucose measurement. Malignant insulinoma is an extremely rare finding in children and its management in case of progression or relapse remains mainly experimental.

P2-489

The Effectiveness of Sirolimus in a Newborn with Hyperinsulinaemic Hypoglycaemia

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Background: Hyperinsulinaemic Hypoglycaemia (HH) is a rare genetic disease and the treatment of HH in cases with unresponsiveness to medical therapy is subtotal pancreatectomy. In a recent study, the authors showed that sirolimus could be an alternative treatment in these patients. We aimed to evaluate the effectiveness of sirolimus in a newborn with HH. **Case:** A 10 day-old neonate presented with hyperinsulinaemic hypoglycaemia (glucose: 26 mg/dl, insulin: 55 mIU/ml). She was born at term with a birth weight of 3300 gr. Hypoglycaemia had persisted despite the administration of high intravenous (IV) glucose (perfusion rate up to 20 mg/kg/min) and diazoxide (15 mg/kg/d). Octreotide was added on postnatal 14th day and increased to 40 mcg/kg/d. Due to the unresponsiveness to octreotide, glucagon infusion (0.01 mg/kg/h) and sirolimus (0.5 mg/m^2/d) were started on postnatal 21st day and sirolimus doses were titrated according to plasma sirolimus levels. Diazoxide and glucagon therapies were discontinued after 2 weeks of sirolimus treatment (table 1). IV hydration was stopped on 34th day of sirolimus and she was discharged with octreotide and sirolimus on 44th day. She is currently 5 months old

Table 1. The follow-up of the patient after sirolimus treatment.

	5. day	11. day	16. day	19. day	24. day	30. day	34. day	44. day	77. day
Sirolimus level (4.5–28 μg/l)	3.1	20	10	4,6	10.9	8	7.7	9.9	11.9
Sirolimus dose (mg/m^2/d)	0.5	1	1	1	1.6	1.6	2.3	3	2.4
Octreotide dose (μg/kg/d)	40	40	40	40	stop	40	40	40	25
Glucagon (μg/kg/h)	10	5	stop						
GPR (mg/kg/min)	18	10	6	12.5	5	10	stop		
Diazoxide dose (mg/kg/d)	15	5	stop						

and still uses sirolimus with no side effects and octreotide (10 mcg/kg/d). A novel homozygous ABBC8 mutation (p.H59P) was detected. **Conclusion:** Sirolimus could be beneficial in patients with unresponsiveness to diazoxide and octreotide treatment.

P2-490

Congenital Hyperinsulinism Caused by a Combination of Novel Heterozygous *ABCC8* and *KCNJ11* Mutations

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Background: Congenital Hyperinsulinism (CHI) is a common cause of persistent hypoglycaemia in the neonatal and infant period. It is most commonly caused by mutations in one of the K_{ATP} channel subunits, either SUR1 encoded by the gene ABCC8 or Kir6.2 encoded by the gene KCNJ11. Patients carrying mutations in the ABCC8 and KCNJ11 genes simultaneously have not been reported yet. **Objective and hypotheses:** Our aim was to describe the clinical phenotype and to perform in-vitro functional analysis of a combination of novel heterozygous *ABCC8* (Y1293D) and *KCNJ11* (R50W) mutations found in one Czech patient with CHI in order to clarify the pathogenic effect on the pancreatic β-cell function. **Method:** Novel heterozygous *ABCC8* (Y1293D) and *KCNJ11* (R50W) mutations were created *in vitro* using site-directed mutagenesis. The functional analysis using radioactive Rubidium ($^{86+}$Rb) was performed in HEK293 cell cultures transfected with a combination of these novel heterozygous *ABCC8* and *KCNJ11* genes mutations. Mutant and wild type (WT) channels were exposed to different drug conditions: control (DMSO), 100 μM diazoxide, 100 μM diazoxide and 10 μM glibenclamide, 2.5 mM NaCN and 20 mM 2-deoxy-D-glucose and 2.5 mM NaCN, 20 mM 2-deoxy-D-glucose and 10 μM glibenclamide. $^{86+}$Rb efflux was measured in a liquid scintillation counter using Cherenkov radiation. **Results:** The functional study of this heterozygous combination of *ABCC8* (Y1293D) and *KCNJ11* (R50W) mutations revealed that the activation by diazoxide in mutated K_{ATP} channels was decreased by 60.1% when compared to WT channels. **Conclusion:** We report for the first time a patient with CHI caused by a combination of novel heterozygous mutations in both of the genes (*ABCC8* and *KCNJ11*) encoding the K_{ATP} channel subunits. We have proved a pathogenic effect on the pancreatic β-cell function of this combination of mutations by an *in vitro* functional study. **Funding:** This work was supported by the ESPE Short-term Research Fellowship for Dr Klára Roženková and the Grant Agency of Charles University, Prague, Czech Republic (GAUK 248 213).

P2-491

Functional Analysis of Novel *ABCC8* Mutations Found in Czech Patients with Congenital Hyperinsulinism

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Background: Congenital Hyperinsulinism (CHI) is a heterogeneous genetically determined condition that is characterised by unregulated secretion of insulin from pancreatic β-cells. The most common and severe cases are caused by mutations in the *ABCC8* gene encoding the SUR1 subunit of the K_{ATP} channel subunit. To assess the pathogenic effect of novel *ABCC8* mutations we performed in-vitro functional studies. **Objective and hypotheses:** The aim of our study was to identify Czech patients with CHI caused by *ABCC8* mutations and to perform in-vitro functional study of novel *ABCC8* mutations found in our cohort. **Method:** The molecular genetic analysis of *ABCC8* gene was performed on DNA samples of 42 Czech patients with CHI. Novel mutations were created by site directed mutagenesis and

transfected into HEK293 cells for functional studies using radioactive Rubidium ($^{86+}$Rb). Mutant and wild type (WT) channels were exposed to different drug conditions: control (DMSO), 100 μM diazoxide, 100 μM diazoxide and 10 μM glibenclamide, 2.5 mM NaCN and 20 mM 2-deoxy-D-glucose and 2.5 mM NaCN, 20 mM 2-deoxy-D-glucose and 10 μM glibenclamide. $^{86+}$Rb efflux was measured in a liquid scintillation counter using Cherenkov radiation. **Results:** Mutations in *ABCC8* were identified in 12 out of 42 patients (28.6%) – one homozygous and 11 heterozygous (five novel: F48del, G389R, A478del, R657Q, and K1373del). The $^{86+}$Rb efflux assay showed that in mutant channels the activation by diazoxide was decreased by 41–91.4% (median 82.2%) when compared to WT channels. The most severe effect on K_{ATP} channel function was observed in case of A478del (activity decreased by 91.4%). On the other hand in case of R657Q there was a residual activation by diazoxide in correspondence with the patient's phenotype (activity decreased by 41%). **Conclusion:** We report the biggest cohort of Czech patients with CHI published so far. The proportion of heterozygous mutations is much higher when compared to other published cohorts, most probably due to lack of consanguinity in the Czech population. Moreover, using in-vitro functional study, we have proved the pathogenic effect of 5 novel heterozygous *ABCC8* mutations on the pancreatic K_{ATP} channel function. **Funding:** This work was supported by the ESPE Short-term Research Fellowship for Dr Klára Roženková and the Grant Agency of Charles University, Prague, Czech Republic (GAUK 248 213).

P2-492

Syndromic Hypoketotic, Hypoinsulinemic Hypoglycaemia due to a Mosaic Activating Phosphatidylinositol 3-Kinase Mutation

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Background: In contrast to hypoglycaemia due to congenital hyperinsulinism, there are patients with a similar metabolic profile of hypoketotic hypoglycaemia, but low insulin levels and relatively low glucose requirements to maintain euglycaemia. So far, four patients with activating mutations in the insulin signal-transducing kinase AKT2 have been described, each also showing a syndromic phenotype including hemihypertrophy. **Objective and hypotheses:** We present a 3.5 year-old girl with similar metabolic and syndromic features, but no AKT2 mutation, suggesting a possible mutation in another gene of the same pathway. **Method:** Exome sequencing was undertaken in the proband and parents and analysed to look for either de novo or compound heterozygous pathogenic mutations. **Results:** A mosaic mutation (p.Glu726Lys) in PIK3CA, encoding the p110 catalytic subunit of phosphatidylinositol 3-kinase, was detected in lymphocyte, hair bulb, fibroblast, and cheek swab DNA from the patient but neither parent. Mosaic mutations in this gene are known to cause segmental overgrowth disorders such as the Megalencephaly-Capillary malformation (MCAP) syndrome, which have not been described to be associated with hypoglycaemia so far. Typical features of this syndrome (e.g. Macrocephaly, Epilepsy, Capillary malformations, Focal or segmental body overgrowth) were found in our patient on review. Although glucose requirements to maintain euglycaemia in our patient is relatively low (2.4mg/kg/min), fasting tolerance is very short (~2.5–3 h, aged 3 years). Increased basal levels of signalling downstream from phosphatidylinositol 3-kinase (PI3K) were detected in serum starved dermal fibroblasts from the patient. We suggest that liver affection in somatic mosaicism of PIK3CA mutation leads to suppressed hepatic gluconeogenesis, driven by constitutive, ligand-independent activation of the insulin receptor pathway explaining the hypoglycaemic phenotype in this patient. **Conclusion:** Here, we present a patient that extends the spectrum of MCAP syndrome to include markedly reduced fasting tolerance and recurrent hypoketotic hypoglycaemia with low insulin levels. **Funding:** RKS is supported by The Wellcome Trust (Senior Research Fellowship in Clinical Science 098498/Z/12/Z.

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Long Acting Somatostatin Analogue (Lanreotide) Therapy in Congenital Hyperinsulinism – Pharmacokinetics and Long-Term Follow-Up Study

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Background: Congenital hyperinsulinism (CHI) causes severe hypoglycaemia in children. Diazoxide and daily octreotide injections are first and second-line of treatment for CHI respectively. Diazoxide can cause severe hypertrichosis resulting in parental anxiety and compliance issues. **Objective and hypotheses:** To evaluate the efficacy, safety and pharmacokinetics of Lanreotide therapy in CHI patients. **Method:** Patients >6 months of age either on high dose diazoxide (causing side effects), or daily octreotide were started on 30 mg Lanreotide every 4-weeks. Children >3 years of age had Paediatric Quality of Life (PedsQL) with Strengths and Difficulties questionnaires (SDQ) pre- and 1-year post-Lanreotide. Plasma Lanreotide concentrations measured by radioimmunoassay were collected at times

0, +1, +2, +4, +24 and +96 hours post 1st dose and subsequently prior to each dose for 6 months. **Results:** 29 children were commenced on Lanreotide and three had to stop treatment. 18/26 were on daily octreotide and eight on diazoxide. Five children have stopped overnight continuous feeds. Out of 26 children, 22 children had diffuse hyperinsulinism, three were protein sensitive and one had focal lesion (had three surgeries). Pharmacokinetic data on 21 children showed highest median value (25^{th}–75^{th} interquartile range) of Lanreotide concentration was 14.93 ng/ml (4.39–31.6) at +4 h of 1st dose. The median values (25^{th}–75^{th} interquartile range) prior to 2nd, 3rd, 4th, 5th, 6th and 12th doses were 0.88 ng/ml (0.66–1.32), 1.09 ng/ml (0.89–1.35), 1.21 ng/ml (0.87–1.49), 0.79 ng/ml (0.67–1.55), 1.35 ng/ml (1.19–1.86) and 1.44 ng/ml (1.08–2.18) respectively. PedsQL showed significant change in total health and psychosocial score and significant reduction in overall stress in the SDQ after 1-year post-Lanreotide ($P < 0.05$). **Conclusion:** This study demonstrates lanreotide is safe and effective alternative to diazoxide and octreotide therapy in CHI patients with a significant improvement in blood glucose control and quality of life. There is cumulative effect in lanreotide concentration after each dose. Our 2.5 years follow-up data shows no adverse effects on growth.

P2-494

Congenital Hyperinsulinism in Association with Poland Syndrome and Chromosome 10p11-p13 Duplication

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Background: Poland syndrome (PS) is characterized by unilateral absence or hypoplasia of the pectoralis muscle, most frequently involving the sternocostal portion of the pectoralis major muscle, and a variable degree of ipsilateral hand and digit anomalies, including symbrachydactyly. Congenital Hyperinsulinism (CHI) is the result of unregulated insulin secretion from the pancreatic β-cells leading to severe hypoglycaemia. We report a baby with Poland's syndrome and 10p11-p13 duplication in association with CHI. This association has not been previously described in the literature. **Case:** The baby girl was born at term by emergency C-section due to abnormal CTG to non-consanguineous parents with a birth weight of 2kg (−3.3 SDS). She was born in good condition. She was noted to have recurrent hypoglycaemic episodes since birth. Further investigations revealed an inappropriately high plasma insulin (77 pmol/l) and low plasma free fatty acids (447 μmol/l) and β-hydroxy butyrate (<29 μmol/l) during hypoglycaemia (blood glucose 1.0 mmol/l) confirming a diagnosis of CHI. The patient was commenced on diazoxide (5 mg/kg per day) to which she was responsive. She had absence of pectoralis major on the left side of the chest. The x-ray and MRI imaging of the spine revealed the absence of left upper thoracic ribs, sprengel deformity of the left scapula and myelomeningocele at the cervico-thoracic junction of the spine. Microarray revealed duplication in the 10p11-p13 region. The MRI scan of brain did not reveal any abnormality. The parents' microarray results are awaited. **Conclusion:** CHI can be an associated feature of several genetic and developmental syndromes. This is the first reported case of CHI in association with PS and 10p11-p13 duplication. The genetic mechanism(s) in this syndrome that leads to dysregulated insulin secretion is unclear.

P2-495

Rapid Biochemical Evaluation Aids Timely Management of Congenital Hyperinsulinism

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Background: Congenital Hyperinsulinism (CHI) is the commonest cause of persistent neonatal hypoglycaemia and is characterised by inappropriately detectable plasma insulin during hypoglycaemia. Management depends on the timely analysis of biochemical parameters, which would help initiate appropriate management and avoid potential neurological compromise. The technical difficulties in sending the appropriate sample and the delay in processing the sample in the lab sometimes contribute to the delay in diagnosis of CHI. **Objective and hypotheses:** To identify the benefit of rapid biochemical evaluation of plasma insulin and ketones in establishing a diagnosis of CHI. **Method:** The hospital database of 50 CHI patients who were managed over the last 12 months in the quaternary centre of CHI was analysed. Blood samples were obtained during controlled hypoglycaemia (blood glucose <3 mmol/l) for evaluation of plasma insulin, 3-β hydroxy butyrate, free fatty acids, cortisol and lab glucose. The time interval between blood sampling and diagnosis of CHI was determined. **Results:** 17 patients were diagnosed outside the unit and were excluded. The 33 remaining patients (20 males) were studied. The hypoglycaemia was initially stabilized using high concentration dextrose fluids in all patients. The median age was 7 days at the time of controlled hypoglycaemia screen. The median time interval between controlled hypoglycaemia screen and the diagnosis of CHI was 1 day (range 0–5). 70% (23 patients) had a diagnosis of CHI confirmed within 2 days and 90.9% (30 patients) within 4 days of the hypoglycaemia screen. **Conclusion:** The diagnosis of CHI was confirmed within 2 days in majority of the patients who underwent hypoglycaemia screen. It is important to analyse the lab samples for plasma insulin and ketones as an urgent facility in infants where there is a strong suspicion of CHI. This would aid prompt initiation of treatment for CHI.

P2-496

Serial 3-Dimensional Ultrasonographic Evaluation of Foetal Adrenal Volumes in the 2nd and 3rd Trimester of Pregnancy Characterises Human Adrenal Development *in utero*

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Background: The human foetal adrenal (FA) undergoes vast physiological changes as pregnancy progresses. Original descriptions of FA development emerged following morphometric studies from spontaneous/medical terminations. These revealed the greatest increase in FA size was during the first trimester. Recently, sonographic evaluation of human FA volume and length has led to the creation of normal FA growth centiles and correlations between FA size and estimated foetal weight (EFW). These studies are limited by single time-point observations or single-plane measurements. **Aim:** To characterise normal human FA growth by performing the first serial 3-dimensional ultrasonographic studies of FA volume during the 2nd and 3rd trimesters of pregnancy. **Methods:** A prospective longitudinal study of 33 foetuses was undertaken. Serial 3-dimensional transabdominal ultrasound measurements (Voluson-730 and -E8 systems; 4–8 MHz array transducer) of FA volume and foetal biometry were performed at gestational age (GA) ~20/40 weeks, 28/40 weeks, 34/40 weeks and 38/40 weeks. FA volume was calculated using Virtual Organ Computer-aided Analysis software. Women were followed until the outcome of pregnancy was known. **Results:** A linear correlation between FA volume and EFW was observed ($r=0.6290$, $P<0.0001$). The mean adrenal growth velocity was 0.097 cm^3/week between GA 20–28/40, 0.034 cm^3/week between GA 28–34/40 weeks, and 0.447 cm^3/week between GA 34–38/40 weeks. An increase in 3rd trimester FA growth velocity has not previously been reported. **Conclusion:** Serial 3-dimensional ultrasonography of FA volumes during the 2nd–3rd trimesters of pregnancy provides detailed normative data. The observed increase in FA growth velocity as pregnancy nears completion is interesting, and suggests novel functional implications in terms of steroid production, and a potential role for the FA in the onset of parturition. **Funding:** This work was supported by the Joan Adams Fellowship (grant number NDM9050B) and Rosetrees Charity (grant number M296).

Table 1. Foetal biometry and adrenal volume vs GA.

GA (weeks) (mean ± S.D.)	FA volume (cm) (mean ± S.D.)	EFW (g) (mean ± S.D.)
20.35 ± 0.68	0.3701 ± 0.06925	347 ± 40.36
28.07 ± 0.75	1.168 ± 1.234	1095 ± 152
34.42 ± 0.75	2.336 ± 2.367	2197 ± 301.2
38.09 ± 0.62	3.899 ± 3.681	2990 ± 365

P2-497

Genetic Variation in the FSH Signalling Pathway Affects Female Reproductive Hormones During Infancy

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Background: Studies have shown that genetic variations in the FSH pathway (SNPs: FSHB −211G>T, FSHR −29G>A, and FSHR 2039A>G) affect peripubertal levels of serum FSH and age at pubertal onset in girls. **Objective and hypotheses:** Genetic variations in the FSH pathway reflect circulating levels of female reproductive hormones during the postnatal gonadotropin surge. **Method:** Blood samples were taken in girls of the Copenhagen Mother-Child Cohort at the age of 3 months and reproductive hormones measured by immunoassays. 235 girls were genotyped for FSH SNPs using KASP assays. Differences in hormone levels between genotypes were analysed with Kruskal-Wallis test. **Results:** Girls homozygous for the minor allele *FSHR* -29AA showed a significantly lower level of serum FSH (median 3.1 IU/l) compared to the more common variants GG and GA (medians 4.1 and 3.5 respectively), $P=0.016$. Lower circulating oestradiol was observed in homozygous carriers of the minor allele *FSHR* 2039GG (median 23.5 pmol/l) compared to carriers of AA and AG (medians 31.0 and 33.0 respectively), $P=0.052$. No significant associations were found with LH, SHBG, inhibin A, and inhibin B. **Conclusion:** As expected, reduced FSHR transduction (*FSHR* 2039GG) was associated with lower oestradiol levels. We were puzzled to find a negative association of *FSHR* −29 minor allele with FSH levels. Whether this reflects immature regulation of the HPG axis during the neonatal gonadotropin surge remains to be elucidated.

P2-498

Longitudinal Comparison of Inhibin B and AMH Levels and Testicular Volumes between Preterm and Full-Term Infant Boys

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Background: Decreased reproductive rates have been reported in men born prematurely. This potentially relates to an impaired Sertoli cell proliferation during the postnatal

hypothalamic-pituitary-gonadal activity, which has been suggested to have a role in later reproductive capacity. **Objective and hypotheses:** To compare the levels of Sertoli cell markers in premature (PT) and full-term (FT) boys in infancy. **Method:** Serum AMH and inhibin B (inhB) levels and testicular volumes (TV) were measured at one week (D7) and three months (M3) of calendar age and at 14 months of corrected age (cM14) in 33 PT (gestational age, GA 24.7-36.6 weeks) and 29 FT (GA 37.1–42.1 weeks) boys. **Results:** At D7, both AMH and inhB levels were higher in PT than in FT boys ($P=0.048$ and $P=0.001$ respectively). From D7 to M3, AMH and inhB levels increased in both groups ($P<0.001$). AMH levels did not change significantly from M3 to cM14 in either group, but inhB levels decreased in both ($P<0.001$). At M3 and cM14, AMH levels were lower in PT than in FT boys ($P=0.057$ and 0.026 respectively). InhB levels were not significantly different between groups after D7. TV was significantly smaller in PT than in FT boys at D7, but not after that (at M3 $P=0.055$ and at cM14 $P=0.4$). AMH and inhB levels correlated only at D7 (rho = 0.45, $P=0.001$). AMH correlated with TV at cM14 (rho = 0.4, $P=0.015$). InhB and TV correlated positively at M3 and cM14, but at D7 their association was negative in PT (rho = −0.49, $P=0.009$) and positive in FT infants (rho = 0.45, $P=0.022$). **Conclusion:** Postnatal increase in AMH and inhB levels was observed not only in FT but also in PT boys indicating a robust Sertoli cell activity that is also reflected in testicular growth. High AMH and inhB levels in PT boys at D7 probably reflect decrease in fetal Sertoli cell activity towards term. After minipuberty at cM14, lower AMH levels in PT than in FT boys may indicate altered Sertoli cell function in PT boys. **Funding:** This work was supported by grants from the Kuopio University Hospital, Pediatric Research Foundation, National Graduate School of Clinical Investigation, Emil Aaltonen Foundation, Jalmari and Rauha Ahokas Foundation, Sigrid Jusélius Foundation and Academy of Finland.

P2-499

Postnatal Catch-Down Growth is not Associated with Disturbances in Metabolic Parameters in Large-for-Gestational-Age Infants at the Age of 8 Years

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Background: Children born small-for-gestational-age (SGA) especially when they experience rapid catch-up growth have an increased risk for obesity and metabolic disturbances later in life. **Aims and objectives:** Little is known about the effect of catch-down (c-d) growth and its effect on metabolic parameters in children born large-for-gestational-age (LGA). **Patients and methods:** 101 pre-pubertal children with a birth-weight and/or length >95. *P* were examined at a median age of 8.0 years (range, 4.3 12.1). C-d was defined as postnatal change of SDS >0.67 during the first year of life. Fasting insulin, HbA1c, HOMA, lipoproteins, IGF-BP1, Leptin, Visfatin, Amylin, Ghrelin, IGF1, IGF-BP-3 were analysed. **Results:** C-d for weight, length, and BMI was observed for the vast majority of the group (88%) during the first year beginning mostly at three months of age and lasting until one year and remained unchanged thereafter. However, actual mean height-SDS was still significant different from target height (0.67 SDS vs 0.22 SDS; $P<0.001$). Individuals who did not c-d were significantly taller ($+1.57$ SDS ± 0.85 vs 0.54 SDS ± 1.0; $P=0.001$) and heavier than those who c-d (weight-SDS ($+0.99 \pm 0.59$ vs 0.45 ± 1.0; $P=0.013$). However, there was no significant difference for BMI-SDS ($+0.34 \pm 0.67$ vs 0.24 ± 0.96; $P=0.069$) or other anthropometric parameters such as waist-, hip-, skinfold-thickness-SDS. No significant differences between the two groups were found for all measured metabolic and hormonal parameters. **Conclusion:** The vast majority of infants born with LGA show a pronounced c-d growth, which lead to a rapid normalisation of length/height and weight. However, height-SDS remained significant different from target height. Although height and weight-SDS remained different between those LGA with vs. no c-d growth during the first year of life we could not find significant differences in parameters of body composition or the measured endocrine and metabolic parameters. Therefore, no signs of disturbance of carbohydrate or lipid metabolism was found in association to c-d growth.

P2-500

Birth Incidence of Prader-Willi Syndrome in France

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Background: Prader-Willi syndrome (PWS) is a rare and complex genetic disorder characterised in neonates by hypotonia and feeding problems. French birth incidence has never been reported. **Objective and hypotheses:** To evaluate incidence of PWS at birth in France. **Method:** Identification of patients with a molecular diagnosis of PWS born between January 1st, 2013 and December 31st, 2013 was obtained by combining various approaches in order to try to reach exhaustive results: e-mailing to members of the Pediatric Endocrinology French Society and Neonatology French Society, to genetics laboratory involved in the molecular prenatal and neonatal molecular diagnosis of PWS and to the French PWS patients association. In addition, number of live births with PWS was obtained from the annual report of the National Statistic Institute. **Results:** 37 newborns with molecular diagnosis of PWS were identified in France in 2013. Three prenatal diagnoses were made during this period whose outcome was a pregnancy interruption, giving the number of 40 diagnoses per

year. There were 781621 live births in 2013, birth incidence of SPW was therefore 1/19540. Molecular mechanism was known for 35 patients (95%). We found 54% of neonates having deletions and 40% maternal uniparental disomy (mUPD) with 6% of cases yet unknown. **Conclusion:** Birth incidence of Prader-Willi syndrome in France in 2013 was close to 1/20 000 live births. We confirmed the increasing proportion of mUDP.

P2-501

Variation of Environmental Chemicals Measured in Serum During Pregnancy

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Background: Significant changes in metabolism and water equilibrium are registered during pregnancy. However, very limited previous investigations have been carried out on variations of exposure levels and metabolism of non-persistent environmental chemicals during pregnancy. **Objective and hypotheses:** The objective of this longitudinal study is to describe variation in exposure of pregnant women to environmental chemicals. We hypothesise that variation in exposure levels between trimesters are observed, and that individuals maintain an either low or high exposure level with limited intra-subject variation. **Method:** Serum samples ($n=534$) from 128 women (average 4.2 per woman) collected 2000–2002 were analysed for: Phenols: bisphenol A (BPA), triclosan (TCS), triclocarban (TCCB), benzophenone-3 (BP-3), 2,4-dichlorophenol (2,4-DCP), 2,5-dichlorophenol (2,5-DCP), 2,4,5-trichlorophenol (2,4,5-TCP), 2-phenylphenol (2-PP), 4-phenylphenol (4-PP); Parabens: methyl- (MeP), ethyl- (EtP), iso-propyl- (i-PrP), n-propyl- (n-PrP), iso-butyl- (i-BuP), n-butyl (n-BuP) and benzyl paraben (BzP). Exposure to phthalates will be measured. The samples were selected to correspond to first ($n=77$), second ($n=250$) and third trimester ($n=207$). Chemicals were analysed with TurboFlow-LC-MS/MS. P-values calculated with Krustall-Wallis non parametric test. Intraclass correlation coefficients (ICC) were calculated using reliability analyses in SPSS. **Results:** BPA, BP-3, 2-PP, MeP and n-PrP were detectable in more than half of the tested population, TCS and EtP were detectable in 25% (P-values ranging 0.08–0.62). There does not seem to be a change in median exposure levels between the three trimesters. Single measures ICCs for the within-person variance of repeated measures for BPA = 0.007, BP-3 = 0.153, 2-PP = 0.149, MeP = 0.027 and n-PrP = 0.586. **Conclusion:** Exposure of pregnant women assessed by serum concentrations of phenols and parabens does not appear to vary between trimesters. In accordance with other study populations, individual exposure levels tend to stay within the same quartile over time. **Funding:** CEHOS – The Danish National Center of Endocrine Disruption.

P2-502

Auxological Parameters, Endocrine Growth Factors and Insulin Resistance from Birth to 12 Months of Life in Children Born Small for Gestational Age

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Background: At present, literature regarding postnatal growth in small for gestational age (SGA) subjects and its' correlation with growth factor levels is still controversial. A relation between IGF1 and IGFBP3 levels at birth and weight and length catch up growth has been demonstrated. In the first months of life a rapid weight catch-up growth has also been associated to an increase of leptin, basal insulin and insulin resistance. **Objective and hypotheses:** To evaluate the correlation between weight and length growth, growth factor levels and insulin resistance index (HOMA-IR) in the first year of life of 30 subjects born SGA. **Method:** A total of 30 subjects born at term were studied: 15 with a birthweight < -2 S.D. and a normal length; 15 with both length and weight < -2 S.D. for gestational age. Anthropometrical parameters and blood sampling for the evaluation of glucose, insulin, IGF1, IGFBP3 and leptin were obtained at birth (T0), 1st (T_1), 3rd (T_2), 6th (T_3) and 12th (T_4) month of life. Insulin resistance was calculated by Homa-IR. **Results:** Length and weight catch-up growth was observed in all infants within the 6th month of life. A significant increase ($P<0.05$) in the growth factors evaluated and Homa-IR values was found at 12 months when compared with values at birth. IGF1, insulin and HOMA-IR values correlated positively with the increase in weight at 1st month ($P< 0.05$), while leptin values were significantly correlated only at 6th month of life ($P<0.05$). IGF1 and IGFBP3 values correlated positively with length catch up growth only at 1st month of life ($P<0.05$). **Conclusion:** Our data confirm the important role of IGF1, insulin and leptin in rapid weight catch-up growth in the first months of life; the significant increase of early insulin resistance may explain later metabolic abnormalities that characterize SGA subjects. Less clear remains the role of IGF1 and IGFBP3 on length catch-up growth.

P2-503

Serum Fetuin-a Level for Diagnosis Hepatic Steatosis in Children with Type 1 Diabetes Mellitus

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Backgound: Type 1 diabetes mellitus (T1DM) is one of the chronic disease frequently encountered in childhood and the non-alcoholic fatty liver disease is one of the uncommon complications in the management of these patients. **Objective and hypotheses:** In this study, we aimed to investigate the relationship between serum fetuin-A levels which a negative acute phase reactant and the non-alcoholic fatty liver disease in T1 diabetic patients. **Methods:** Serum fetuin-A levels were measured and liver ultrasonography were performed in addition to the routine tests to 80 patients (Male/Famele: 1/1) which had T1DM at least 5 years. Patients were divided in to two groups, with/without hepatic steatosis (HS+/HS−) according to ultrasonography. Two groups were compared for age, gender, anthropometric parameters (waist/neck circumference, BMI, lean body mass (LBM), body fat ratio), serum lipid profile, liver function tests, DM duration, daily insulin requirements, glycemic controls and serum fetuin-A levels. **Results:** Eight (10%) patients presented hepatic steatosis (grade 1). The BMI, body fat ratio, waist circumference, HbA1c, ALT, GGT and total cholesterol levels were significantly higher in HS+ group than HS−. There was no difference between two groups for age, DM duration, neck circumference, LBM, BMI at the time of diagnosis and insulin requirements. The median level of fetuin-A HS+ cases was 619.84 μg/ml, HS− cases was 378.36 μg/ml and the levels difference was statistically significant ($P<0.001$). Hyperlipidemia, poor glycemic control, BMI, waist circumference and body fat ratio was positive correlated with serum fetuin-A levels. **Conclusion:** We conclude that hepatosteatosis is more common with T1DM cases who had poor glycemic and metabolic control, in addition fetuin-A is a reliable parameter for diagnosis and follow up T1DM patients with hepatic steatosis.

P2-504

Association of Dll4 Levels and VEGFR-1, VEGFR-2 in Mice Model of Oxygen-Induced Retinopathy

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Background: Notch1 – Delta-like ligand 4 (Dll4) signaling pathway has a biological effect of negative feedback regulation to VEGF in retinal vascular development process. There are few studies on the inhibition of Notch1-Dll4 signaling pathway in ROP and the regulatory pathway of VEGF. **Objective and hypotheses:** 67-day-old mice were divided into oxygen-induced retinopathy group and control group. We took ten mice from each group at postnatal day 7 (p7), p12 and p17 respectively, and then enucleated the eyeballs to detect the DLL4, VEGFR-1 and VEGFR-2 by immunohistochemistry. **Method:** 67-day-old mice were divided into oxygen-induced retinopathy group and control group. We took ten mice from each group at postnatal day 7 (p7), p12 and p17 respectively, and then used the retinas to extract RNA. We detected mRNA expression of DLL4, VEGFR-1 and VEGFR-2 by RT-PCR. **Results:** The positive rate of VEGFR-1 was of no difference between these two groups in p7 and p12 ($P<0.05$). While in p17, the rate in retinopathy group was lower than that in control group ($P=0.048$). The positive rate of VEGFR-2 was of no difference between these two groups in p7, p12, p17 ($P<0.05$). The positive rate of DLL4 was of no difference between these two groups in p7 ($P<0.05$), and in p12 and p17, the rate in retinopathy group was lower than that in control group ($P>0.001$). In retinopathy group, the positive rate of VEGFR-1 and DLL4 decreased from p7 to p17 ($P>0.001$), and that of VEGFR-2 increased from p7 to p17 ($P=0.013$). **Conclusion:** Notch1 – DLL4 signalling pathway may be involved in the regulation of VEGF in the process of retinal angiogenesis. The expression of DLL4 was inhibited in oxygen-induced retinopathy mice during the formation of neovascularization, so it failed to show negative feedback regulation to VEGF.

P2-505

Evaluation of Thyroid Function in Preterm Newborns of 24–30 Weeks of Gestation

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Background: Preterm newborns due to their immaturity, a higher incidence of mortality and increased susceptibility to iodine, are at risk of decreased thyroid function. Low levels of thyroid hormones during a critical period for the development of the central nervous system may negatively affect their psychomotor development. Screening for congenital hypothyroidism with capillary TSH is invalid for preterm babies and would require an specific thyroid function control. **Objective and hypotheses:** To assess the protocol applied in our hospital during 2011–2014. To find out the prevalence of hypothyroxinaemia and hyperthyrotropinemia of prematurity. To review how many premature are treated and its clinical evolution. **Method:** Longitudinal descriptive and prospective study of thyroid function in preterm infants admitted to NICU during 2011 2014. Determination of FT4 and TSH (venous sample blood test) in the 2nd week of life, depending on the results:• If TSH 5–15 mU/L and: fT_4 <0.8 ng/dl repeat in 24–48 h *;- fT_4 >0.8 ng/dl repeat in 10–15 days; – fT_4 >1 ng/dl repeat in 4 weeks or before discharge. • If TSH>12–15 mU/L, in two determinations initiate levothyroxine. • * If fT_4 <0.8 ng/dl in two determinations: initiate levothyroxine (4–6 μg/kg per day). **Results:** N=337 (126 <27 WG). Exitus: 47 (12.4%). 38 (11%): No blood test was obtained. Patients with *hypothyroxinaemia* (normal TSH with fT_4 <0.8 ng/dl) $n=11$ (3%): 8 in the 1st blood test (range 0.41–0.79), three in the 2nd blood test (range 0.66–0.77 ng/dl), only one of 11 was treated with levothyroxine. • Patients treated: $n=12$ (3.5%): 8 for hyperthyrotropinemia (TSH mean 27.03, range 12.5–46.6 mU/l), three for hypothyroidism (TSH mean 41.3 mU/L, fT_4 mean 0.59 ng/dl) and one for hypothyroxinaemia (TSH 1.27 mU/l, fT_4 0.41 ng/dl). Screening for congenital hypothyroidism (capillary TSH) was negative for all

the patients. Seven patients are still on treatment. **Conclusion:** Thyroid function of the preterm infants <30 WG should be evaluated, apart from universal screening for congenital hypothyroidism. The second week of life is an appropriate time to assess the thyroid function in preterm babies. The implementation of our protocol does not involve an excessive number of additional extractions. This protocol is able to detect which patients should be treated and wouldn't be detected by capillary TSH.

P2-506

Mini-Puberty in Boys with Cryptorchidism

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Background: The period of transitory postnatal activation of the hypothalamo-pitutary-gonadal axis (mini-puberty) plays an important role in the testicular maturation. **Objective and hypotheses:** To evaluate the functional condition of the gonads in 1–3 months boys with cryptorchidism. **Method:** 40 boys ages 1–3 months with cryptorchidism were examined: group 1–30 boys with unilateral inguinal retention testis and group 2–10 boys with unilateral abdominal testis. Control group consist of 40 healthy boys ages 2–3 month. Methods: orchiometriya and hormonal tests – gonadotropins, testosterone and inhibin B serum levels by immunoenzyme assays. **Results::** In group 1 scrotal testicular 2.3 ± 0.46 cm^3 was like as control group ($P=0.8$). Hormonal tests results showed the increase of the LH serum level in 24% and the increase of FSH in 40%. The testosterone – 4.0 (3.0; 5.4) nmol/l and inhibin B – 380 (344; 422) pg/ml remained normal. In group 2 scrotal testicular volume – 1.6 ± 0.5 cm^3 was reduced ($P=0{,}02$). Hormonal tests revealed increase the LH level – 7.8 (3.5; 11.1) IU/l ($P=0{,}0007$) and decrease testosterone – 3.1 (0.9; 4.5) nmol/l ($P=0.023$) in 50% boys; high FSH serum level – 11.2 (5.4; 19.7) IU/l ($P=0.003$) and low inhibin B level – 193 (174; 236) pg/ml ($p=0{,}001$) in 80% boys. **Conclusion:** subclinical testicular disorders was diagnosed in 40% patients with unilateral inguinal cryptorchidism and the primary gonadal dysfunction – in 80% boys with unilateral abdominal cryptorchidism.

P2-507

Fanconi Anemia Endocrine Abnormalities – Case Report

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Background: Fanconi anemia (FA) is a rare, genetically and phenotypically heterogeneous, autosomal or x-linked recessive chromosome instability disorder characterized by multiple congenital anomalies, bone marrow failure, and increased susceptibility to specific malignancies. Other findings, including short stature, skin pigmentation, and endocrine abnormalities have been recognized, most notably GH deficiency (GHD), hypothyroidism, and hypogonadism. **Case presentation:** This report includes three patients with FA referred to paediatric endocrinology consultation at our Hospital. Patient 1 and 2 are siblings. Patient 1, 21 years old female, referred to us at 11 years old, due to dyslipidemia and abnormal glucose metabolism. No need for medication up to 18 years old, when she started metformin with improvement in glucose metabolism and triglycerides, while maintaining hypercholesterolemia. Therefore simvastatin was initiated, with normalization of lipid profile. Patient 2, 11 years old male, referred to us at 7 years old, for short stature. Endocrine testing including evaluation of GH axis, and GH stimulation tests revealed GHD. Magnetic resonance imaging (MRI) showed a small pituitary gland. GH was initiated at 9 years old, with favorable response (height velocity of 6–9 cm/year). Patient 3, 5 years old male, premature of 35 weeks, fetal growth restriction, referred to us at 3.5 years, for short stature. Endocrine testing including evaluation of GH axis, thyroid function and lipidic profile were normal. Brain MRI showed normal pituitary gland, despite the absence of the corpus callosum. Bone age determination revealed a delay <2 S.D. Seriated height velocity were normal (6.3–6.9 cm/year) and he remains without treatment. **Conclusion:** We pretend to emphasize the importance of periodic endocrine evaluation for patients with FA, looking for precocious diagnosis and treatment. In the particular case of GH treatment in FA patients, long-term risk is unknown, therefore, continued surveillance is needed, considering the increased risk for solid tumours in FA patients.

P2-508

The IGSF1 Deficiency Syndrome: An Unusual Case

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Background: IGSF1 deficiency has been recently found to be a novel cause of x-linked central hypothyroidism, macroorchidism and delayed puberty. **Case presentation:** We present a family, in which the proband was diagnosed with congenital central hypothyroidism by neonatal screening and treated accordingly. Further pituitary examination revealed an unmeasurable prolactin level, normal IGF1, normal cortisol and no abnormalities of the pituitary on MRI. The patient exhibited normal growth and bone age. However, the patient had excessive weight gain and remarkable testicular enlargement (5–6 cc). The enlargement was noticed first at 3.6 years of age and the macroorchidism was present at least until his last evaluation at age 12 years. At 6.3 years old, the patient still had a prepubertal LHRH stimulation and a

pubertal LHRH was first observed at 10.3 years old, when his testicular size was 10–12 cc. The proband's brother was referred for short stature at age 13 years and he was found to have congenital central hypothyroidism with a normal prolactin, normal GH secretion and low testosterone level for a testicular size of 25–28 cc (disharmonious pubertal development). His BMI was normal and besides poor growth, he did not have any of the manifestations of long standing untreated hypothyroidism. The family was referred for genetic evaluation, which revealed that the index patient, his brother, mother and maternal grandfather carry a nonsense mutation in the IGSF1 gene, specifically c.3411_3412del, p.Tyr1137*. **Conclusions:** We present here a unique case of a family with IGSF1 deficiency. The proband presented with macroorchidism at an early age, which has not been previously documented. Also, other family members had congenital central hypothyroidism and did not present with classical manifestations of long standing hypothyroidism. Identification of this constellation of manifestations leading to mutational analysis of the IGSF1 gene is key. Further investigations into this family are still ongoing.

P2-509

Survival, Hypothalamic Obesity, and Neuropsychological/Psychosocial Status after Childhood-Onset Craniopharyngioma: Newly Reported Long-Term Outcomes

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Background: Quality of life and long-term prognosis are frequently, often severely impaired in craniopharyngioma (CP) patients. **Objective and hypotheses:** Knowledge of risk factors for long-term outcome is important for optimisation of treatment. **Method:** Overall survival (OS) and progression-free survival (PFS), BMI, neuropsychological status (EORTCQLQ-C30, MFI-20), and psychosocial status were analysed in 261 patients with childhood-onset CP diagnosed before 2000 and longitudinally observed in HIT-Endo. **Results:** 20-years OS was lower ($P=0.006$) in CP with hypothalamic involvement (HI) ($n=132$, 0.84 ± 0.04) when compared to CP without HI ($n=82$, 0.95 ± 0.04). OS was not related to degree of resection, gender, or diagnosis age or year (before/after 1990). PFS ($n=168$, 0.58 ± 0.05) was lower in younger (age <5 years at diagnosis) ($n=30$, 0.39 ± 0.10) compared with patients 5–10 years ($n=66$, 0.52 ± 0.08) and >10 years ($n=72$, 0.77 ± 0.06). PFS was not associated with HI, degree of resection, nor gender. HI led to severe weight gain during the first 8–12 years of follow-up (median BMI increase: $+4.59$ S.D.) compared to no HI (median increase: $+1.20$ S.D.) ($P=0.00$). During >12 years follow-up, patients with HI presented no further increase in BMI. QoL in CP patients with HI was impaired by obesity, physical fatigue, reduced motivation, dyspnoea, diarrhoea, and non-optimal psychosocial development. **Conclusion:** OS and QoL are impaired by HI in long-term survivors of CP. HI is associated with severe obesity, plateauing after 12 years. OS/PFS are not related to degree of resection, but gross-total resection should be avoided in cases of HI to prevent further hypothalamic damage, exacerbating sequelae. **Funding:** German Childhood Cancer Foundation, Bonn, Germany.

P2-510

Chronic Inappropriate Antidiuresis in Childhood: Experience with Tolvaptan

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Background: The syndrome of inappropriate antidiuresis (SIAD) is one of the most common causes of hyponatremia: it's a disorder of sodium and water balance, characterized by urinary dilution impairment and hypotonic hyponatremia, in the absence of renal disease or any non-osmotic stimulus, able to induce antidiuretic hormone (ADH) release. SIAD can be manifestation of a wide range of diseases, including cancer, head trauma, hydrocephalus and epilepsy. Usually transient and self-limited, is easily controlled in the short term with fluid's restriction and sodium supplementation. More difficult is the management of the chronic SIAD, especially in children. We report our experience with tolvaptan, an orally active vasopressin V2-receptor antagonist that promotes aquaresis. **Method:** The efficacy of tolvaptan was evaluated in a 4 years old child with chronic hyponatremia after surgery for suprasellar arachnoid cyst. Patient was assigned to oral tolvaptan at a dose of 3.75 mg daily (0.46 mg/Kg per die). Serum sodium concentrations achieved to 131–134 mEq/l and the drug was well tolerated, without any side effects. Therefore, the dose of tolvaptan was increased to 7.5 mg daily, based on serum sodium concentrations and kidney function. **Results:** Aquaretic drugs induce an increase in urinary volume and urinary free water, associated with a decreased urinary osmolarity with a consequent increase in plasma sodium. This belong to a family of vasopressin receptor antagonist, V2 in particular, that regulate tubular water reabsorption. Tolvaptan has increased serum sodium concentration, allowing liberalization of the water's introit and suspension of oral supplementation of NaCl. **Conclusion:** In this patient with euvolemic hyponatremia, tolvaptan was effective in increasing and maintaining serum sodium concentrations, with values greater than 130 mEq/l, without side effects and allowing the child a free fluid intake and diet.

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Pituitary Hormone Secretion Profiles in IGSF1 Deficiency Syndrome

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Background: Loss-of-function of immunoglobulin superfamily, member 1 (*IGSF1*) causes an x-linked syndrome of central hypothyroidism, macroorchidism, delayed pubertal testosterone rise, variable prolactin deficiency, and variable partial growth hormone deficiency in childhood. The clinical features and gene expression pattern suggest a pivotal role for IGSF1 in the pituitary, but detailed knowledge on pituitary hormone secretion in this syndrome is lacking. **Objective and hypotheses:** To study in detail the 24 h pituitary hormone secretion in male patients with IGSF1 deficiency. **Method:** We collected blood samples every 10 min for 24 h in eight adult male IGSF1 deficient patients and measured circulating TSH, prolactin, gonadotropins, and GH. Deconvolution, modified cosinor, and approximate entropy analyses were applied to quantify secretion rates, diurnal rhythmicity, and regularity of hormone release. Results were compared to matched healthy controls and, for TSH, to patients with untreated mild (subclinical) primary hypothyroidism. **Results:** Compared to both healthy controls and patients with mild primary hypothyroidism, IGSF1 deficient patients showed decreased pulsatile secretion of TSH with decreased disorderliness and reduced diurnal variation. Basal and pulsatile secretion of GH and FSH were increased by over 200%, while LH secretion did not differ from healthy controls. We observed a bimodal distribution of prolactin secretion, i.e. severe deficiency in three and increased basal and total secretion in the other five patients. **Conclusion:** The altered TSH secretion pattern is consistent with the previously hypothesized defect in TRH signalling in IGSF1 deficiency. However, the phenotype is more extensive and includes increased GH and FSH secretion without altered LH secretion, and either undetectable or increased prolactin secretion. **Funding:** The work was supported by an unrestricted research grant from Ipsen Farmaceutica BV, and one of the authors was supported by a CIHR operating grant MOP-133557.

P2-512

Pituitary Function after Mild to Severe Traumatic Brain Injury in Children 2–18-Years-Old: A Prospective Study

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Background: In recent years, traumatic brain injury (TBI) has been identified as a significant cause of pituitary dysfunction in children. Paediatric prospective studies are rare especially for mild TBI. **Objective and hypotheses:** The aim of this present study was to evaluate the frequency of hypopituitarism after mild, moderate and severe TBI in hospitalized children, and determining factors of this deficiency. **Method:** A prospective study was conducted for children from 2 to 18 years old, hospitalised after TBI between September 2009 and June 2013. Clinical parameters, basal pituitary hormone concentration at 0, 6 and 12 months and a dynamic test at 12 months after TBI were performed (insulin tolerance test or glucagon test if contra indicates for assessment of somatotropic and corticotropic axes), confirm by a second test in case of GH insufficiency. **Results:** 117 patients, sex ratio H/F 79/38, median age 7.6 years (range 2 to 17.8 years). Distribution plot shows 109 mild, four moderate and four severe TBI, according to Glasgow Coma Scale. Pituitary insufficiencies (PI) were present in 43 (37%) children at 12 months after TBI. Six of them have two or more hormonal deficits. 30 and 50 children have a secondary adrenal insufficiency (SAI) and GH deficiency (GHD) respectively, after insulin tolerance test. Confirmed GHD was present in 15 cases. GHD were severe in two children but only one have low velocity rate. One gonadotropin, five prolactin, and no TSH insufficiency nor central precocious puberty were observed at 12 months after TBI. **Conclusion:** Biological PI is present in 37% of TBI even if majority of patient have mild TBI. Interrogation persists in clinical relevance of biological GHD because velocity rate is often conserved. However, practitioner should keep in watch children growth, tiredness and puberty after TBI whatever its severity. **Conflict of interest:** This study received a financial support from IPSEN. **Funding:** This study received a financial helps from IPSEN.

P2-513

A Novel Mutation within the *AVP* Gene in an 18-Year-Old Male Patient with Kallmann Syndrome and Combined Pituitary Hormone Deficiency

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Background: Kallmann syndrome is the most common form of hypogonadotropic hypogonadism and is associated with genes such as *KAL1, KAL2, CHD7, NELF, PROK2*, and *PROKR2*. Genetic factors in hypopituitarism are involved with the gene mutation of *PROP1, POU1F1, HESX1, LHX3, LHX4*, and *PTX2*. We found a

novel mutation of the *AVP* gene in a Kallmann syndrome patient with hypopituitarism. **Case presentation:** The patient, who was 18 years old, showed general weakness, short stature, and no puberty signs. His height and weight were 156 cm (<1 percentile) and 47 kg (<1 percentile). His testicular sizes were each 4 cc. Peak levels of GH, cortisol, LH, and FSH were found to be 0.4 ng/ml, 0.38 ug/dl, 1.31 mIU/ml, and 0.87 mIU/ml on a cocktail test. Therefore, he was diagnosed with GH deficiency, secondary adrenal insufficiency, and hypogonadotropic hypogonadism. In addition, the water deprivation test showed central diabetes insipidus. The sella MRI showed an absent olfactory bulb and pituitary stalk, a small anterior pituitary gland, and an ectopic posterior pituitary bright spot at the base of the hypothalamus. He also had anosmia. Thus, he was diagnosed with Kallmann syndrome. We performed whole exome sequencing and found a c.127C>G (p.Pro43Ala) mutation of the *AVP* gene. This mutation was not found in 100 normal control case, and it has not been reported yet. Although the relation between this mutation and the patient's diseases is not clear, his father did not have this mutation. **Conclusion:** We report a novel mutation of the *AVP* gene in a Kallmann syndrome patient with hypopituitarism through whole exome sequencing.

P2-514

Hydrocephalus and Hypothalamic Involvement in Paediatric Patients with Craniopharyngioma or Cysts of Rathke's Pouch: Impact on Long-term Prognosis

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Background: Paediatric patients with sellar masses such as craniopharyngioma (CP) or cyst of Rathke's pouch (CRP) frequently suffer disease- and treatment-related sequelae. **Objective and hypotheses:** We analysed the impact and prognostic relevance of initial hydrocephalus (HY) and hypothalamic involvement (HI) on long-term survival and functional capacity (FC) in children with CP or CRP. **Method:** Using retrospective analysis of patient records, presence of initial HY or HI was assessed in 177 pediatric patients (163 CP, 14 CRP). 20-years overall survival (OS) and progression-free survival (PFS), FC, and BMI were analysed with regard to initial HY, degree of resection, or HI. **Results:** 105 patients (103/163 CP, 2/14 CRP) presented with initial HY and 96 presented with HI. HY at diagnosis was associated ($P=0.000$) with papilledema, neurological deficits, and higher BMI at diagnosis and during follow-up. OS, PFS, and FC were not affected by HY at initial diagnosis. HI at diagnosis (96/177) had major negative impact on long-term prognosis. Sellar masses with HI were associated with lower OS (0.84 ± 0.04; $P=0.021$), lower FC ($P=0.003$), and higher BMI at diagnosis and last follow-up ($P=0.000$) when compared with sellar masses without HI (OS: 0.94 ± 0.05). PFS was not affected by HI or degree of resection. **Conclusion:** Initial HY has no impact on outcome in patients with sellar masses. OS and FC are impaired in survivors presenting with initial HI. PFS is not affected by HY, HI, or degree of resection. Accordingly, gross-total resection is not recommended in sellar masses with initial HI to prevent further hypothalamic damage. **Funding:** German Childhood Cancer Foundation, Bonn, Germany.

P2-515

Contrasting Central Diabetes Insipidus due to preproAVP Mutations: Earlier Onset of Symptoms in Recessive than in Dominant Forms

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Background: Central diabetes insipidus may result from mutations in the preproAVP gene, most often heterozygous and occurring de novo or inherited in an autosomal dominant mode; in these cases, intracellular accumulation of the misfolded product of the mutated allele slowly destroys the AVP-producing neurons, so that the onset of symptoms may be delayed for up to 28 years by which time the posterior pituitary hyperintense signal is no longer visible on magnetic resonance imaging (MRI). Very few cases of autosomal recessive inheritance have been described. **Case presentation:** A 4-year-old boy was referred for longstanding polyuria and polydipsia. The mother is French-Canadian and the father Lebanese. When seen for failure to thrive at 7 months, a serum sodium had been recorded at 145 mmol/l with a urine specific gravity <1005. At age 4 years, after 4 h of water deprivation, serum sodium was 144 mmol/l, serum osmolality 314 mmol/kg and urinary osmolality 111 mmol/kg. 2 h after 2.5 µg of DDAVP intranasally, urinary osmolarity was 442 mOsm/kg. Chronic treatment with DDAVP resulted in the disappearance of polyuria/polydipsia and in catch-up growth to target. MRI showed a normal posterior pituitary hyperintense signal. *preproAVP* was sequenced in the proband and in his asymptomatic parents. The patient was a compound heterozygote, having inherited a novel A to G transition in the splice acceptor site of intron 1 (IVS1-2A>G) from his mother and the known P26L mutation from his father; the latter has been reported in the homozygous state in two inbred Middle-Eastern pedigrees. **Conclusion:** Consistent with bi-allelic inactivation of preproAVP, our patient had onset of symptoms in the first year of life. The presence of the posterior pituitary hyperintense signal suggests preservation of the AVP neurons. Making a genetic diagnosis avoided repeated MRI studies and allowed for family counseling.

P2-516

Endocrine Disorders in Children with Optic Chiasm Glioma

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Background: Pituitary function in children with optic chiasm glioma may be impaired. **Objective and hypotheses:** We aim to describe the frequency of endocrine abnormalities at diagnosis of the tumor and over the follow-up period in a group of children with chiasmatic glioma and its relation with different variables. **Method:** Retrospective study using the records of patients under 14 years old followed for optic chiasm glioma. Sex, age at diagnosis, personal history of type 1 neurofibromatosis (NF), clinical signs and symptoms at presentation, primary treatment of the tumor, endocrine abnormalities at diagnosis and over the follow-up period were recorded. Quantitative variables are expressed as mean $\pm$ S.D. and compared using Wilcoxon test. Qualitative variables are expressed as proportions and compared using Fisher test. **Results:** 14 patients (six women) were included. The range of age at diagnosis was 6 months to 7 years (2.97 ± 2.32 years) and follow-up time was 8.64 ± 3.30 years (range 4.0–14.0 years). Six patients suffered NF. Reasons of consultation were neuro-ophthalmic signs/symptoms in eight cases and endocrine in three (precocious puberty in all three). Other three were diagnosed subclinically (neuroimaging). Primary treatment for the glioma was needed in eight children, predominating in patients without NF ($P = 0.02$). The proportion of cases with any endocrine disorder increased to 12/14 at the end of the follow-up period: seven children with precocious puberty and five pituitary deficiencies. Hormonal deficiencies were related to history of neuro-ophthalmic signs before age of five ($P = 0.02$) and to primary treatment requirement ($P = 0.03$). On the other hand, precocious puberty was not related to any other variable. **Conclusions:** Children with optic chiasm glioma may present endocrine disorders from the time of diagnosis of the tumor and, mainly, along its evolution. Precocious puberty is the most frequent abnormality. Pituitary deficiencies are related to more aggressive tumors (those presenting with neuro-ophthalmic signs before the age of 5 years or requiring primary treatment).

P2-517

Be Aware of Congenital Panhypopituitarism in Children with a Family History of Polydactyly

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Background: Congenital panhypopituitarism is associated with a variety of gene mutations. Abnormalities in the Gli2 gene were only recently described to be associated with congenital panhypopituitarism (Franca et al. 2010). Gli2 is a gene that encodes a transcription factor downstream of the Sonic Hedgehog pathway – known to play an important role in morphogenesis during embryology. **Objective and hypotheses:** Although Gli2 mutations were described to be related to holoprosencephaly, we like to present a family with pituitary hormone dysfunction and polydactyly. **Method:** The index case was a girl admitted with extreme failure to thrive at the age of 6 weeks. The heel prick screening for congenital hypothyroidism was normal. She experienced hypoglycaemia and hyperbilirubinemia in the neonatal period. Hormonal testing and MRI investigations showed panhypopituitarism and an ectopic neurohypophysis. Her mother had isolated polydactyly. Family history showed that out of 26 family members of three generations, six persons had either panhypopituitarism, polydactyly or both. One person had cryptorchidism, choanal atresia and a single median incisor, besides panhypopituitarism and polydactyly. **Results:** In all six affected family members the pathogenic frameshift mutation c.3676C>T (p.Arg1226X) in the Gli2 gene was found. This mutation leads to truncation of the Gli2 protein. Two family members also had a 80 kb deletion of chromosome 18q22.1 encompassing the CDH7-gene which is probably not related to the phenotype. **Conclusion:** In this family the same Gli2 mutation is related either to a relatively mild phenotype of isolated polydactyly, or to a more severe phenotype consisting of pituitary dysfunction, in the absence of holoprosencephaly. Knowledge of the co-occurrence of polydactyly and panhypopituitarism with the same gene defect is important for clinicians because i) it provides a tool for early recognition of congenital panhypopituitarism and ii) it enables targeted genetic testing. Furthermore, these data confirm the role of Gli2 in the embryogenesis of both the extremities and the pituitary gland.

P2-518

A Novel Single Nucleotide Variation Contributing to the Expression of Isolated Hypogonadotropic Hypogonadism

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Background: The molecular genetics of isolated hypogonadotropic hypogonadism (IHH) has been a subject of interest and recent discoveries. Multiple genetic variants with x-linked and autosomal inheritance are involved in the regulation of the hypothalamic pituitary gonadal axis. **Objective and hypotheses:** We undertook an extensive genetic evaluation to elucidate a possible genetic aetiology in two brothers with clinical and biochemical evidence of IHH. We hypothesize that polymorphic genetic variation is responsible for the phenotypic expression of IHH in our patients. **Method:** Whole exon sequencing of genomic DNA followed by SNV of interest validation using PCR was performed. Seven genes derived from sequencing results were selected for further validation. The selected genes contained

coding region SNV(s) and were associated with the hypothalamic-pituitary axis and the patient's clinical phenotype. **Results:** More than 600 SNPs were observed in >70 different genes; No SNPs were found in the GnRH receptor gene; nine SNPs in seven x-linked genes were validated by PCR; Of the nine valid polymorphisms, eight produced an amino acid change; All selected SNVs were known in the NCBI database. **Conclusion:** Patients both have IHH, while they only have the same SNV in one gene (MAMLD1 exon 3).

P2-519

Eating Behaviour, Weight Problems and Eating Disorders in 101 Long-Term Survivors of Childhood-Onset Craniopharyngioma

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Background: As a result of hypothalamic involvement and/or treatment-related hypothalamic damage, up to 75% of childhood craniopharyngioma patients develop hypothalamic obesity.outcome is important for optimization of treatment. **Method:** Eating behaviour was analysed in 101 survivors of childhood craniopharyngioma, recruited from 1980 to 2001 in the HIT-Endo multicentre study, and in 85 BMI-matched healthy controls using the Inventory for eating behavior and weight problems (IEG) and the inventory for eating disorders (ESI). **Results:** Severely obese patients (BMI >8 S.D.; $n=9$) presented with pathological eating behavior, more weight problems, and eating disorders, as compared to obese (BMI 3–8 S.D.; $n=44$) and normal or overweight patients (BMI <3 S.D.; $n=48$). Craniopharyngioma patients with different degrees of obesity showed similar or even less pathological findings as compared to BMI-matched normal controls. **Conclusion:** Severe obesity is associated with pathological eating behaviour/disorders in craniopharyngioma patients. As these disorders are not disease-specific, risk factors for hypothalamic obesity should be the focus of further craniopharyngioma research. **Funding:** German Childhood Cancer Foundation, Bonn, Germany.

P2-520

Two Novel LHX3 Mutations in Patients with Combined Pituitary Hormone Deficiency and Sensorineural Hearing Loss

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Background: Pituitary hormone deficiency combined type 3 (CPHD3; MIM# 221750) is an autosomal recessive combined pituitary hormone deficiency caused by mutations in LHX3, a LIM-homeodomain transcription factor gene which is necessary for the normal pituitary and motorneuron development. **Aims:** Clinical manifestations of CPHD3 are pituitary dwarfism and might be accompanied by rigid cervical spine leading to limited neck rotation or sensorineural deafness. In this study, three patients from two unrelated consanguineous families of Saudi origin with combined pituitary hormone deficiency were examined. **Results:** Clinical evaluation revealed that all the three patients had severe combined pituitary hormone deficiency, short neck and sensorineural hearing loss. The patient displayed a severe pituitary hypoplasia, whereas one patient also presented secondarily with an enlarged anterior pituitary. We identified one novel missense LHX3 mutation (p.C146F) in the LIM2 domain at a phylogenetically conserved residue, and a novel nonsense mutation (p.R156*) predicting a severely truncated protein, both in the homozygous form. **Conclusion:** This report describes the first LHX3 mutations from Saudi patients and also expands the allelic spectrum for this gene and helps in the differential diagnosis.

P2-521

A Novel Entity Characterised by GH Deficiency and Central Precocious Puberty in Two Siblings and their Father, in the Absence of Central Nervous System Defect

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Background: The association of GH deficiency (GHD) with central precocious puberty (CPP) has been reported in individuals with central nervous system (CNS) abnormalities, congenital or acquired. Co-existence of GHD and CPP has been rarely reported, always as an isolated, sporadic disorder. **Objective and hypotheses:** To present the familial occurrence of combined GHD and CPP. **Method:** GH was measured post L DOPA, glucagon and GHRH and gonadotropins were determined post GnRH administration, using established methodology. CNS was evaluated using brain magnetic resonance imaging (MRI). **Results:** Two siblings were examined for short stature; a female at age 11 years and her brother at age 8.2 years. The girl, reportedly, had puberty initiation at 6 years and menarche at 7.8 years. Peak GH on two provocative tests was <1 ng/ml with no response to GHRH, while results of GnRH test disclosed CPP. The girl's pathology wasn't recognized promptly and received no therapy, reaching a final height of 122 cm (−8 SDS). The boy's height at age 8.2 years was 107 cm (−4.6 SDS). He entered puberty at age 10 years. He received rhGH and GnRHan and reached a final height of 170 cm (−1.1 SDS), the target height

being 161.5±4.5 cm. On provocative testing, the mother had normal GH peak (26 ng/ml), while the father (Ht SDS −3) had low GH (2 ng/ml). There was no evidence of optic nerve atrophy or CNS defect. **Conclusion:** The combined familial defect of GHD and CPP most likely represents a novel entity, possibly inherited as an autosomal dominant trait. It should be attributed to a mutated transcription factor affecting both GHRHR and GnRHR or the somatotrophs and gonadotrophs acting in a diverse manner; loss and gain of function respectively. The existence of such complex natural prototypes can act as the key to understand pituitary development and function.

P2-522

Effect of Specimen Repeated Freeze-Thaw Cycles on Urinary Gonadotropin Determined by Immunochemiluminometric Assays

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Background: It remains unclear whether specimen repeated freeze-thaw cycles can influence urinary lutenising hormone (LH) and follicular stimulating hormone (FSH) assayed by immunochemiluminometric assays (ICMA). **Objective and hypotheses:** To investigate the effect of specimen repeated freeze-thaw cycles on urinary LH and FSH determined by ICMA. **Method:** The first morning-voided urine was collected and divided two parts. One part was stored at −20 °C (Frozen Sample), and the other was stored at 4 °C. Urinary LH and FSH were assayed by ICMA between 0 and 13 freeze-thaw cycles (between 0 and 14 days). **Results:** Compared with the original specimen, urinary LH for all specimen were unaffected from the first to the second days, and urinary FSH within 14 days for all specimen, too. The correlation between urinary LH in Frozen Sample as a percentage of original LH and freeze-thaw cycles was −0.879, for urinary FSH as a percentage of original FSH was 0.102. **Conclusion:** When urinary specimen are stored at −20 °C, ICMA can measure urinary LH within two freeze-thaw cycles, and FSH up to 13 freeze-thaw cycles. **Funding:** This work was supported by Scientific Research Projects of regular institutions of higher education for postgraduates in Jiangsu province (grant numbers:CXLX13_828), and Scientific Research Projects of Wuxi city in Jiangsu province (grant numbers:Q201204).

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Copy Number Variants in Patients with Congenital Hypopituitarism Associated with Complex Phenotypes

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Background: The aetiology of congenital hypopituitarism (CH) is unknown in the majority of patients. In our cohort of 200 cases, it was possible to establish the genetic cause in only 13 patients (6.5%). Copy number variants (CNVs) have been implicated as the cause of genetic syndromes with previously unknown aetiology. **Objective:** To study the presence of CNVs and its relevance in patients with CH of unknown cause associated with complex phenotypes. **Patients and methods:** 35 patients were selected for whole-genome array-CGH screening in a customised platform of 180 K (Oxford Gene Technologies). **Results:** Among the 35 selected patients, ten had septo-optic dysplasia (SOD); six had developmental delay/intellectual disability (DD/ID) and four had midline craniofacial malformations. In this cohort 15 patients (43%) presented CNVs: 13 were considered as variants of uncertain clinical significance (VOUS) and two were considered pathogenic. Among the patients with CNVs, four of them had well-defined genetic syndromes: trichorhinophalangeal syndrome, Rubinstein-Taybi syndrome, Joubert syndrome and PHACE syndrome. Among the CNVs, seven were heterozygous deletions with sizes ranging from 27 Kb to 10.5 Mb, seven were duplications ranging from 55 KB to 1.3 Mb and in one patient two CNVs were found. The pathogenic CNVs were identified in two patients: one patient with the trichorhinophalangeal syndrome, a deletion of 10.5 Mb in chromosome eitht (8q23.1–q24.11) and one patient with Rubinstein-Taybi syndrome with a terminal duplication of 14.7 Mb in chromosome two and a terminal deletion of 4 Mb in chromosome four (two CNVs). **Conclusion:** CNVs could explain the genetic aetiology of two patients with syndromic CH. Variants of uncertain clinical significance may also be implicated in the aetiology of CH but further studies are necessary to establish the role of each CNV. **Funding:** This work was supported by the National Council for Scientific and Technological Development (CNPq) (grant numbers 305743/2011-2 to B.B.M. and 304678/2012-0 to A.A.L.J.) and Sao Paulo Research Foundation (FAPESP) (grant number 2013/03236-5 to A.A.L.J.).

P2-524

Pulsatile GnRH is Superior to hCG in Therapeutic Efficacy in Adolescent Boys with Hypogonadotropic Hypogonadodism

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Background: We investigate the efficacy and safety of two different treatments which have not been evaluated in peri-puberty boys with HH. **Objective and hypotheses:** To assess the effectiveness and safety of pulsatile GnRH or hCG treatment in adolescent boys with hypogonadotropic hypogonadodism. **Method:** 12 patients received 8–10 μg of GnRH, subcutaneously injected every 90 min using a pump. Another 22 patients received hCG, which was injected intramuscularly as follows: for the first three months, 1000 IU of hCG was injected two times per week, then once every other day for the next 3 months. The dose of hCG was increased to 2000 IU after 6 month treatment and the above cycle was repeated for another 6 months. All patients were treated for 12–14 months and followed up every 3 months. **Results:** Patients treated with GnRH showed larger testes than those treated with hCG. Patients in both groups showed increased length of penis, however the differences were not statistically significant, compared to the pretreatment groups. Testosterone levels were significantly increased in both groups, compared to the pretreatment group, but the difference of two groups was not statistically significant. There was no significant difference in side effects associated with the two treatments. **Conclusion:** Adolescent boys with HH may be effectively treated with pulsatile GnRH. We suggested that GnRH exhibits higher efficacy in treating adolescent boys with HH than hCG.

P2-525

The Lack of *MKRN3* Gene Mutations in Patients with Idiopathic Sporadic GnRH-Dependent Precocious Puberty

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Background: Central precocious puberty (CPP) results from activation of the hypothalamic-pituitary-gonadal axis before the age of 8 years in girls and 9 years in boys. The molecular basis of the maturation of this axis is still poorly understood. The *MRKN3* gene located in the Prader-Willi syndrome critical region (chromosome 15q11–q13), inhibit factors stimulating pulsative. GnRH secretion. In 2013 inactivating mutations in the *MRKN3* gene were discovered to cause some of the cases of familial precocious puberty. Subsequently, there have been few reports of apparently *de novo* mutations causing sporadic CPP. **Objective and hypotheses:** The objective of the study was to investigate mutations in *MKRN3* gene in patients with apparently sporadic idiopathic CPP. **Method:** Blood samples were collected from 25 unrelated patients (24 girls and one boy), from two university medical centres. All patients were clinically diagnosed with precocious puberty of central origin. DNA was isolated from lymphocytes using standard procedures. The whole coding region of the *MRKN3* gene was divided between five sets of primers. Each fragment was amplified with PCR, routinely cleaned and then sequenced with the classical Sanger's method. **Results:** No pathogenic variants of the *MRKN3* gene were found among the studied group. **Conclusion:** Although deficiency of MKRN3 causes CPP in humans, mutations in *MRKN3* gene are a very rare genetic cause of isolated CPP.

P2-526

Serum AMH Levels are Lower in Healthy Boys Who Develop Pubertal Gynaecomastia

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Background: Pubertal gynaecomastia is thought to be a clinical sign of an oestrogen-androgen imbalance, affecting up to 60% of boys. In most cases no underlying endocrinopathy can be identified. In boys, Anti-müllerian hormone (AMH) is produced by immature Sertoli cells and circulating level decreases as testosterone increases during pubertal maturation. In a previous cross sectional study we found significant lower levels of AMH in boys with pubertal gynaecomastia (Mieritz *et al.*, *Clin Endocrinol*, 2013). **Objective and hypotheses:** To investigate serum AMH levels and genetic polymorphisms in boys with or without gynaecomastia. **Method:** 99 healthy Danish boys (aged 5.8–16.4 years) were followed in a prospective cohort over 8 years with semi-annual examinations (total examinations, $n=951$), including breast palpations and blood samples. Serum AMH concentrations were analysed by immunoassay (Beckman Coulter). Furthermore, we analysed two single nucleotide polymorphisms (SNPs) located in exon 1 of the gene encoding AMH (*AMH* rs10407022 T>G) and in a putative enhancer of the AMH-receptor (*AMHR2* rs11170547 C>T) respectively. **Results:** Pubertal gynaecomastia was observed in 47/95 (49%) of the boys during follow-up. Circulating levels of AMH were significantly lower in boys with pubertal gynaecomastia compared to boys without – even after controlling for pubertal stage ($P<0.001$). Presence of the minor allele (T) of the AMH-receptor SNP was associated with lower serum levels of AMH after onset of puberty (age 13–15 years, median 359.0 vs 305.0 pmol/l, $P=0.008$); no association between AMH SNPs and serum AMH was found. Pubertal gynaecomastia was not associated with AMH SNPs (GG+GT vs TT, $P=0.324$,

Chi^2) or AMH-receptor SNPs (CC vs CT, $P=0.963$). **Conclusion:** This is to our knowledge the first longitudinal study to find an association between low serum levels of AMH and the development of pubertal gynaecomastia. We speculate that this might be due to impaired testicular function in these boys.

P2-527

Evaluation of Final Height in Girls Taking GnRH Analogue: Should the Age Limit for Precocious Puberty be Changed?

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Background: The age limit for precocious puberty (PP) in girls is a topic that continues to be debated, and there is a new trend that supports the idea that the beginning of breast development in girls between ages 6 and 8 should not be accepted as true PP and it is necessary to label this clinical condition as accelerated puberty or early normal puberty. **Objective and hypotheses:** The aim of the current study is to determine the diagnostic criteria for girls between the ages of 6 and 8, in which puberty has begun as a result of secular trend to early puberty, to decide for which patients treatment initiation is appropriate and rational. **Method:** The patients who were diagnosed with idiopathic central PP (CPP) were investigated in four groups as: patients who were treated before age 6, patients who were treated between ages 6 and 7, patients who were treated between ages 7 and 8, and the patients who were treated after age 8. Their final heights were evaluated. A fifth group was formed from patients who were diagnosed after age 7; however, they were not given treatment and were monitored for puberty progress, and the final heights of the group in which treatment was initiated and in which treatment was not initiated were compared. **Results:** All of the patients who underwent treatment reached a final height that was close to the target height, and while the final heights were taller than the predicted adult height (PAH) before treatment, the heights were shorter than the PAH at the end of treatment. While the height gain was 11.5 ± 1.6 cm in cases in which treatment began before age 7, it was 6.2 ± 1.8 cm in the group in which treatment began after age 7. The cases who were diagnosed and treated after age 7 and the cases in the same age group who were followed-up without treatment all reached a final height close to the target height and the final heights of both groups were similarly taller than the PAH at the time of diagnosis. The height gain of both groups were also similar. (6.2 ± 1.8 cm vs 5.7 ± 2.0 cm). **Conclusion:** Of the cases who were diagnosed with CPP according to the classical definition, the number of cases diagnosed after age 7 was high and the height gain and final heights with or without treatment were similar in this age group. Thus, this suggested that, in fact, the puberty of these cases could be normal and although the age of onset of puberty was earlier due to the secular trend, we might have unnecessarily investigated and treated these cases as we still used the classic age limit of 8 for the definition of PP.

P2-528

Correlation of Clinical Phenotype and Genotype of Prader-Willi Syndrome and the Deletion of Paternal MKRN3 Allele in PWS Patients with Central Precocious Puberty

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Background: Prader-Willi syndrome (PWS) is caused by the deletion of the paternally-derived 15q11-13 region or the maternal uniparental disomy of chromosome 15 (mUPD(15)). Puberty is usually delayed and central precocious puberty (CPP) is very rare in PWS. **Objective and hypotheses:** This study was undertaken to correlate clinical features focusing on pubertal progression with genotype with or without *MKRN3* deletion to understand the mechanism of CPP in patients with PWS. **Method:** A total of 114 patients were enrolled. Genetic study was done utilizing routine chromosome, fluorescent *in situ* hybridization, and methylation-specific PCR analyses. The presence of *MKRN3* deletion was determined by multiple ligation-dependent probe amplification analysis in patients with microdeletion of 15q11-q13 region. **Results:** Microdeletion of paternally-derived chromosome 15q11-q13 was observed in 81 patients (71.1%), while the other 33 (28.9%) had mUPD(15). *MKRN3* was deleted in 29 of 81 patients (35.8%) with microdeletion, while 11 of them (13.6%) did not have deletion of *MKRN3*. Patients with microdeletion presented with hypopigmentation and feeding difficulty in the neonatal period more frequently than those with mUPD(15). HbA1c levels were significantly higher in microdeletion group. There were no significant differences in height-, weight-SDS, height velocity, and BMI between the two groups. Notably, 10 of 33 patients (30.3%) with mUPD(15) showed advanced bone age than those with microdeletion. Two females manifested CPP and one girl had early puberty in mUPD(15) group, while one male was diagnosed with CPP among *MKRN3* deletion group. **Conclusion:** Patients with microdeletion of chromosome 15q11-q13 region displayed feeding difficulty in infancy and severe hyperglycemia more frequently than those with mUPD(15). CPP in PWS is presumed to be caused by a deletion of active paternal *MKRN3* allele. Further study should be needed to elucidate functional impact of *MKRN3* and interaction with other adjacent genes deleted in PWS patients with CPP.

P2-529

Doppler Evaluation of the Uterine Artery for the Diagnosis and Follow-Up of Patients with Precocious Puberty

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Background: Pelvic ultrasound is used for the diagnosis and follow-up of girls with precocious puberty (PP). This tool may be somewhat misleading, because during treatment some patients may persist with pubertal uterine and ovarian anatomy. Oestrogens decrease the resistance of the uterine arteries, so Doppler evaluation of these vessels might be a useful complementary exam to determine the effects of treatment in these patients. **Objective and hypotheses:** To evaluate the usefulness of uterine artery Doppler analysis in the diagnosis and follow-up of girls with PP. **Method:** 14 girls with central PP (breast Tanner stage II-V, <8 years, LH >6.0 IU/L after leuprolide stimulation, >3,5 cm uterus length) were treated with long acting triptorelin pamoate 22.5 mg, which lasts 6 months. A single operator performed a pelvic ultrasound at the time of diagnosis, and after 6 and 12 months of analogue therapy, by measuring uterine size, ovarian volume and a Doppler analysis of the uterine arteries was performed. The blood flow velocity waveform was characterized as either high resistance, which represents lack of pubertal development, or low and/or intermediate resistance, which indicates active puberty. These parameters were correlated with the LH levels observed in these patients at the time of diagnosis and during treatment with triptorelin pamoate 22.5 mg. **Results:** All patients received 1 dose of triptorelin at times 0 and 6 months, and completed 1 year of treatment. Mean age at the beginning of treatment was 7.9 years +1.3(4–8), and LH peak before treatment was 34.0 IU/L+23.0(8.6–91.0). At baseline, ten out of 12 patients (83%) had low or intermediate resistance with Doppler analysis, whereas two patients (17%) had high resistance. Mean peak LH at 6 months of treatment was 2.2 IU/L+0.8(0.7–3.7), and 13 patients (93%) showed high resistance, whereas 1 patient showed an intermediate pattern. All 14 patients (100%) showed high resistance blood flow velocity waveform at 12 months, which was associated with a mean peak LH of 1.8 IU/L+1.0(0.3–4.0). **Conclusion:** Uterine artery Doppler colour analysis is a valuable complementary tool for the diagnosis and management of girls with central PP. This technique shows a good correlation with LH levels, and may be useful for patients with this condition during LHRH analogue treatment. Supported by Debiopharm, Switzerland. **Conflict of interest:** This study was supported by Debiopharm, Switzerland. **Funding information:** This study was supported by Debiopharm, Switzerland.

P2-530

Nephrogenic Diabetes Insipidus with Partial Response to Ddavp Caused by a Novel AVPR2 Splice Site Mutation

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Background: Congenital diabetes insipidus (DI) can be due to mutations in the arginine vasopressin (AVP) gene (familial neurohypophyseal DI), the AVP receptor type 2 (AVPR2) or aquaporin 2 (AQP2) genes (congenital nephrogenic DI, NDI). The clinical manifestation of congenital NDI, especially the response to AVP, can vary greatly depending on the functional effect of the AVPR2 mutation. Here we present two male siblings with NDI and partial response to ddAVP. **Objective and hypotheses:** To identify the genetic cause of the condition. **Method:** Whole exome sequencing was performed in selected family members. A minigene splicing assay was used to evaluate the effect of two splice site variants in AVPR2. **Results:** Two male siblings presented with failure to thrive, polyuria, and polydipsia. Laboratory evaluation showed hypernatremia, elevated serum osmolality, and low urine osmolality. During water deprivation urine osmolality remained low. Subcutaneous ddAVP administration (1 mcg) increased urine osmolality modestly to 250–350 mOsm/kg, consistent with partial NDI. The two parents, a sister, and a brother were unaffected. Initial Sanger Sequencing reported no pathogenic variants in *AVPR2* or *AQP2*, with mention of a possible splice site variant of unknown significance. We performed exome sequencing and found the same variant. In fact, we confirmed that both the patient and brother were hemizygous for two *AVPR2* variants with *in silico* predicted effects on mRNA splicing. A minigene assay revealed that only one, the novel *AVPR2* c.276 A>G mutation created a cryptic splice acceptor site that led to 5' truncation of *AVPR2* exon 2 when tested in HEK293 cells. This truncation leads to a frameshift and premature stop codon, which is likely to be the cause for these familial cases of NDI with partial responsiveness to AVP. Both patients were treated with high dose ddAVP and showed improvement of DI symptoms as well as improved growth and weight gain. **Conclusions:** A novel *AVPR2* splice site mutation as a cause of X-linked NDI was identified. Patients with DI of unknown etiology can harbor splice site mutations whose pathogenicity may be underestimated on routine sequence analysis. In NDI with partial response to ddAVP, high dose ddAVP treatment may be considered. **Funding information:** "The work was supported by the Intramural Research Program of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and National Human Genome Research Institute, National Institutes of Health."

P2-531

Regional Brain Volume and Luteinising Hormone in Girls with Idiopathic Central Precocious Puberty

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Background: During puberty, gray matter (GM) volume decreases and white matter (WM) volume increases in brain. It has

been suggested that pubertal hormones may induce some neuroanatomical changes during puberty. Central precocious puberty (CPP) is caused by premature activation of the hypothalamus-pituitary-gonadal axis in inappropriately early age. However, little is known about the differences of brain structure (especially brain volume) in idiopathic CPP. Also the relation between luteinizing hormone (LH) and brain morphology in CPP remains unclear. **Objective and hypotheses:** This study aimed to evaluate the difference of brain structure in idiopathic CPP, age-matched healthy control, and the normal puberty girls, and the association between LH and brain structure. **Method:** The study enrolled fifteen girls with idiopathic CPP, 15 age-matched healthy girls and 15 normal puberty girls as controls. The subjects underwent on a 1.5 Tesla Avanto MR Scanner. Anatomical T1-weighted images were acquired with a T1 spin echo sequence. MR image data were processed by using SPM8 with DARTEL algorithm. **Results:** The mean age of CPP, age-matched group and puberty group were 8.0 ± 0.9 year, 7.8 ± 0.9 year and 11.9 ± 0.9 year. Compared with controls, CPP showed a significant increase in GM volume of the left cerebellar cortex, and in WM volume; the left superior temporal lobule (STL), right middle temporal pole (MTP) and left lingual gyrus (LiG) ($P < 0.001$). Especially, the WM volume of the STL ($r = 0.56$), MTP ($r = 0.56$) and LiG ($r = 0.57$) was positively correlated with LH concentrations ($P < 0.05$). **Conclusion:** Regional GM and WM volumes were increased in girls with idiopathic CPP compared with age-matched and pubertal controls. The growth of white matter might be directly or indirectly mediated by LH production in idiopathic CPP. These data suggest that the presence of early sexual maturation-related variations in structure of developing brain of girls with idiopathic CPP.

P2-532

Determination of Final Height in Girls with Precocious Puberty. Which is the Most Accurate Method?

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Background: Central precocious puberty (CPP) is a common condition in girls and has been associated with deterioration of final height (FH). Height prognosis (HP) is critical for the decision of treatment in CPP. There are several methods for predicting FH in CPP but none is completely reliable. Most methods consider bone age (BA), which is very imprecise, but there is no consensus on which method is the best to estimate FH. **Objective:** To compare the accuracy of three methods in the prediction of FH in girls with untreated CPP. **Patients and methods:** 143 girls consulted for CPP between 1993 – 2000, 93 had reached their FH without being treated with LHRH analogues and they came to measure their current height. FH was considered with BA > 15 years. Parent's heights were registered. BA was reported by the same four observers. We compared the initial HP, by three methods: Bayley-Pinneau (BP), Roche-Wainer-Thissen (RWT) and midparental height; with their FH. Statistical correlation between HP and FH was evaluated with Bland and Altman method. **Results:** The age at diagnosis of the 93 girls was 8.3 ± 1.2 years (6.4–10.5); their BA was 9.9 ± 1.7 years and their current age was 19.1 ± 3.3 years. The BP method vs. FH showed x: −1.01 cm difference, but with great interindividual variation (+8.87 cm: and −10.89 cm, ±2DS respectively). Similarly RWT method showed x: +0.96 cm difference (+9.65 and −7.72 ± 2DS respectively). In contrast, midparental height showed less dispersion and variation: (x: +0.05 cm difference with +6.19 and −6.10 cm, ±2DS respectively). **Conclusions:** All methods for predicting FH showed good results in average, but they have a considerable individual variation which may be explained by the subjectivity of the radiological interpretation of BA. Midparental height, which does not consider BA, demonstrated superior ability to predict FH.

P2-533

The Relationship between Steriod Receptors and Aromatase in the Mouse Brain

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Background: Local oestrogen production in the brain regulates critical functions including neuronal development, gonadotropin secretion and sexual behaviour. In the mouse brain, a 36 kb distal promoter (l.f) regulates the *Cyp19a1* gene that encodes aromatase, the key enzyme for oestrogen biosynthesis. *In vitro*, promoter l.f interacts with oestrogen receptor alpha (*Esr1)* and Progesterone receptor (*Pgr*) to mediate *Cyp19a1* mRNA expression and enzyme activity in mouse hypothalamic neuronal cell lines. The *in vivo* mechanisms that control mammalian brain aromatase expression during fetal and adult development, however, are not thoroughly understood. **Objective and hypotheses:** Our aim was to elucidate the basis of the in vivo connection between *Esr1, Pgr and Cyp19a1.* **Method:** Pregnant mice were sacrificed at gestational days 9, 11, 13, 15, 16, 19, 21 and the brain tissues of the foetuses were harvested along with five newborns at the age of postnatal day 2. *Esr1*KO (female) were also sacrificed and their hypothalamus were excised out. Then both foetuses and adults RNA were isolated, reverse transcribed and amplified employing primers specific for *Esr1, Pgr and Cyp19a1 with Real time PCR.* **Results:** In the foetal mouse brain, *Cyp19a1* mRNA levels are inversely correlated with both *Esr1* and Pgr mRNA levels in a temporal manner. Moreover, *Cyp19a1* mRNA levels increased in the hypothalamus of oestrogen receptor-alpha knockout female mice (*Esr1*KO). **Conclusion:** Taken together, our findings might indicate that *Esr1* and *Pgr* have crucial roles in the *in vivo* regulation of aromatase expression in the brain during foetal and adult life. **Funding information:** Northwestern University start up funds.

P2-534

Evaluation of Body Proportions in Children with Precocious or Delayed Puberty

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Background: Over the past 20 years there is growing evidence that onset of puberty and changes in body proportions occur at an earlier age, especially in girls. Several studies have suggested this trend is linked to increasing rates of overweight and obese children. However, data on delayed pubertal trends are scant. **Objective and hypotheses:** To characterize body proportions of children evaluated for pubertal disorders. **Method:** Retrospective study of a large cohort of patients followed at a single tertiary center during a 17 year period (1996–2013). Clinical data including height, weight, the upper to lower segment (U/LS) ratio, body mass index (BMI) and clinical outcomes were reviewed and analysed. **Results:** The cohort comprised 647 patients. In total, 304 were evaluated for precocious puberty (86% girls, of whom 72% were diagnosed with idiopathic central precocious puberty) and 347 presented with delayed puberty (67% boys, of whom 92% had constitutional delay of growth and puberty). There was a trend (not significant) towards earlier puberty in recent years with more referrals for early puberty and fewer related to delayed puberty. BMI z-score was significantly greater in the patients referred for early puberty compared to delayed puberty counterparts (girls mean +1.6 vs. -0.57 SDS, boys mean +2.2 vs. −0.78 SDS, $P<0.001$). Significant U/LS ratio differences ($P<0.015$) between these groups were equally found. Height, BMI, and basal LH values were associated with having initiated treatment in early puberty, but not in late puberty. **Conclusion:** BMI z-scores and U/LS ratio differ significantly in children referred for precocious or delayed puberty. Lower height- and BMI z-scores and higher basal LH values were predictors of those children starting treatment for early puberty. Clinical follow-up over time seems mandatory.

P2-535

GH Deficiency with Advanced Bone Age: GHRH Receptor Mutation Detected by Exome Sequencing Associated to Non-Classical Congenital Adrenal Hyperplasia (CAH)

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Background: Isolated Growth Hormone Deficiency (IGHD) is usually associated with a delayed bone age. A genetic cause for IGHD is more frequently found in patients with familial cases and/or consanguineous parents. **Objective and hypotheses:** To diagnose the genetic cause of IGHD and clarify the unusual clinical presentation of advanced bone age in one patient born to consanguineous parents. **Method:** Sanger sequencing of *GH1*, *GHRH*, *GHRH receptor* and *CYP21A2* followed by whole-exome sequencing. **Results:** A Caucasian boy presented at 7.5 years with severe short stature (102.5 cm, SD-3.7), high-pitched voice, blue sclera and prominent forehead. Genital examination revealed Tanner stage I, normal penile length (4 cm) and normal topic testis (length 1.5 cm). He was born at term by vaginal delivery with a length of 50 cm and weight of 3.400 g. Parents were second-degree cousins. Bone age was 6 years. Clonidine and combined pituitary stimulation tests, resulted in a peak of GH = 0.6 ng/ml indicating GH deficiency and a peak cortisol of 16.1 mcg/dl initially interpreted as partial ACTH deficiency. Pituitary MRI was normal. The patient was successfully treated with rGH (33 mcg/kg/day) with a first year growth velocity of 11.7 cm. Surprisingly at 10.8 years of age he presented with advanced bone age (13 years) without signs of puberty and with prepubertal serum LH and testosterone levels. An ACTH test showed respectively, basal and peak, cortisol 6.1 and 18.8 mcg/dl, 17 hydroxyprogesterone 9.4 and 52.0 ng/ml and androstenedione 1.2 and 2.0 ng/ml indicating nonclassical 21-hydroxylase deficiency. CYP21A2 sequencing revealed homozygous p.Val281Leu mutation and cortisone acetate was added to his treatment. Sanger sequencing of *GH1*, *GHRH* and *GHRH receptor* were performed and no mutations were found. In order to establish the genetic cause of IGHD, whole-exome sequencing was performed revealing a homozygous c.431C > T, p.Leu144His mutation in GHRH receptor. This mutation had been previously described in unrelated Caucasian patients with IGHD from Sergipe/Brazil, Spain and United States. **Conclusion:** Whole-exome sequencing was able to establish the genetic cause of IGHD not previously identified by Sanger sequencing. Clinicians should be aware that patients born to consanguineous parents might have more than one genetic disease. **Funding information:** This work was supported by the National Council for Scientific and Technological Development (CNPq) (Grants: 305743/2011-2 to B.B.M. and 304678/2012–0 to A.A.L.J.) and the Sao Paulo Research Foundation (FAPESP) (grant 2013/03236–5 to A.A.L.J.).

P2-536

Ultra-Deep Next-Generation Sequencing: A reliable Method for the Molecular Diagnosis of McCune Albright Syndrome

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Background: The molecular diagnosis of McCune Albright syndrome (MAS) is difficult because the detection of somatic *GNAS1* mutations is usually performed in blood, in which the fraction of mutated allele could be barely detectable. To improve the usual techniques (selective enrichment, either with nested PCR and enzymatic digestion or with use of peptide nucleic acid probes), and to avoid technical problems like contamination, a new approach using next generation sequencing was tested. **Objective and hypotheses:** We tested the ability of ultra-deep sequencing on an Ion Torrent PGM™ System to detect and to quantify *GNAS1* mutations in MAS. **Method:** Using primer fusion technique, we designed an amplicon targeting the two prevalent mutations, p.R201C and p.R201H. In each run, 11 samples were multiplexed on a 314 chip: eight patients, one control sample with the p.R201C mutation, one control sample with the p.R201H mutation and one negative control without mutation. Detection of mutations was performed with the Variant Caller developed in the Torrent Suite™ software, **Results:** We tested 23 samples, for which we previously studied *GNAS1* with the selective enrichment method. 15 of them were known to be mutation carriers, whereas for the eight other, no mutation was detected in the previous study. Due to the high depth of sequencing we were able to quantify the fraction of mutated allele. The presence of the mutation was confirmed in the 15 patients, whereas no additional mutation was detected in the eight negative samples. The mutant allele frequency of the most abundant mutation was about 30%, and the rarest mutated allele had a frequency of about 0.3% **Conclusion:** Ultra-deep sequencing on PGM™ is a reliable technique to detect *GNAS1* somatic mutations, allowing mutant allele quantification. The previous techniques could be used to confirm the identification of a mutation.

P2-537

Increased Ambulatory Blood Pressure in Adolescents with Gender Dysphoria Treated with Gonadotropin- Releasing Hormone Analogues

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Background: Adolescents with gender dysphoria (GD) are treated with gonadotropin-releasing hormone analogues (GnRHa) to prevent the development of characteristics of the undesired sex. Subsequently, sex steroids of the desired sex, cross sex hormones (CSH) are added. GnRHa treatment is generally considered to be safe in the treatment of precocious puberty in children. However, we observed that some adolescents with GD developed hypertension during GnRHa monotherapy (Klink D *et al. Endocrinol Metab Int J* 2015 **2**(1): 00008). **Objective and hypotheses:** To prospectively study blood pressure (BP) development during gonadal suppression with GnRHa in adolescents with GD. **Method:** In 34 natal girls (median age 14.5 years) and 16 natal boys (median age 12.8 years) with GD BP was measured using 24 h ambulatory BP monitoring prior to start of GnRHa and throughout gonadal suppression. Mean diurnal, nocturnal and 24 h systolic (SBP) and diastolic BP (DBP) were converted to SDS according to natal sex and height. **Results:** Median duration of gonadal suppression in natal girls and natal boys was 11 and 12 months, respectively. Nocturnal SBP (median SDS 0.00 vs. 0.30; $P=0.008$) and DBP (median SDS -0.55 vs. 0.35; $P=0.019$) increased in natal girls but not in natal boys. **Conclusion:** A sex difference for BP elevation during gonadal suppression in adolescents with GD was observed. This has previously been described in adults (Bonfirraro G *et al. Minerva Ginecol* 1995 **47**(10): 467–70) and may be due to loss of the BP lowering properties of estrogens (Hinojosa-Laborde C *et al. Hypertension* 2000 **35** (1 Pt 2):484–9). Furthermore, CSH in natal girls with GD in a later stage includes testosterone which may also increase BP. Natal girls with GD that are treated with GnRHa and CSH may be at risk for hypertension.

P2-538

Plasma Humanin Levels During Normal Childhood and Puberty. Study of Possible Correlations with Sex, Age, and Insulin Levels

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Background: Humanin is a novel signaling peptide which has been showed, by *in vitro* and in vivo studies, to improve insulin sensitivity. As plasma humanin levels decrease during adulthood, particularly during aging, it has been proposed that the increment of insulin resistance in aging might be associated with lesser humanin plasma values. **Objective and hypotheses:** The physiological insulin resistance observed during puberty in normal children might be related to a physiological decrement of plasma humanin levels. Since there are no data available in normal children and adolescents of both sexes our aim was to evaluate the developmental changes of plasma humanin levels in normal children of both sexes as a function of chronological age (CA), pubertal stage and insulin levels. **Method:** Plasma humanin and serum insulin levels were determined in 69 girls (33 pre-pubertal)

and 94 boys (69 pre-pubertal). **Results:** Plasma humanin levels did not change as a function of CA, sex and Tanner stage of pubertal development (mean ± SD (pg/ml); boys 1852±367, and girls 1856±314). However, in boys, linear correlation analysis between plasma humanin levels and CA showed a tendency to decrease ($P=0.05$). In the whole group ($P<0.02$), in all males ($P<0.03$) as well as in pubertal males ($P<0.02$), but not in normal pubertal girls, a significant negative correlation between plasma humanin and serum insulin levels was found. In a Multiple Regression Model including BMI, CA, serum insulin and sex steroids (testosterone, androstenedione, and DHEAS) no significant correlation was found. **Conclusion:** As non dynamic changes of plasma humanin levels in normal pre-pubertal and pubertal children of both sexes was observed, it seems that humanin might not be involved directly in the mechanism of physiological insulin resistance described in puberty. However, the relevancy of the sexual dimorphism in insulin/humanin negative correlation during puberty should be elucidated.

P2-539

GnRH Infusion in Females with Hypogonadotropic Hypogonadism

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Background: Hypogonadotropic hypogonadism (HH) in females is an uncommon and heterogeneous condition. There is little data regarding biochemical profile of gonadotropins to further substantiate the diagnosis. **Objective:** To evaluate the gonadotropaic secretion profile after GnRH infusion in a female cohort diagnosed with HH. **Patients and methods:** GnRH iv infusion test (0–120 min) were performed in 17 patients (17.5±2.3 years) with suspicious of HH for pubertal delay or primary amenorrhea associated with: Group1 (G1)- acquired or congenital pituitary pathology ($n=7$) or G2- hypo/anosmia ($n=6$) or G3- lack of spontaneous pubertal progression after a brief estrogenic therapy or lack of pubertal clinical and biochemical progression for one year ($n=4$). LH, FSH at 0, 15, 30, 45, 60 and 120 min (IFMA) and basal Estradiol (ECLIA) were determined. Basal pubertal cutoffs were defined as FSH > 1.5 IU/L and basal LH > 0.3 IU/L. **Results:** Basal FSH <1.5 IU/L and LH <0.3 IU/L were found in 88% and 82% of patients, respectively. All patients had basal E_2 < 15 pg/ml. FSH peak occurred in all the patients at 120 minutes (maximum 8 IU/L), whereas the occurrence of the LH surge was variable (maximum 8.9 IU/L). Areas under the curve of both gonadotropins were compared among three groups and they did not show any significant difference. Peaks LH were: G1: 3.4±2.5 IU/L, G2: 1.8±0.42 IU/L and G3: 5.2±3 IU/L. FSH peaks were: G1: 3.9±2.4 IU/L, G2: 3±1 IU/L, and G3: 4.9±2.9 IU/L. **Conclusion:** The occurrence of simultaneous basal FSH <1.5 IU/L, basal LH < 0.3 IU/L and E_2 <15 pg/ml, or peak values LH < 8.9 or FSH < 9 IU/L after the infusion of GnRH support the diagnosis of HH in females suspected of this condition. Patients with hypo/anosmia showed the lower gonadotropin profile variability.

P2-540

A Case of Familial Central Precocious Puberty Caused by a Novel Mutation in the Makorin RING Finger Protein 3 Gene

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Background: Central precocious puberty (CPP) is often familial but its genetic cause is largely unknown. Very recently, the makorin RING finger protein 3 (MKRN3) gene, located on chromosome 15 in the Prader-Willi syndrome (PWS)-associated region (15q11-q13), has been found mutated for the first time in five families with familial precocious puberty, with a peculiar kind of transmission. In fact, it is an imprinted gene which is expressed only if transmitted from the father. The function of this gene is not completely known and the phenotype of patients with mutations in MKRN3 gene is not yet completely elucidated. We report a new mutation (Pro160Cysfs*14) in the paternally imprinted MKRN3 gene causing familial CPP. **Case presentation:** When the index case, a 7 years old girl, came to our observation, showed Tanner stage 3 and pubic hair stage 1. Her bone age evaluated by TW2 method was 10.3 years. Her laboratory data confirmed diagnosis of central precocious puberty. Familial medical history revealed precocious puberty in a cousin on paternal side and in her paternal grandmother. Genetic analysis revealed a new mutation (Pro160-Cysfs*14) in the paternally imprinted MKRN3. Puberty onset was at about 6 years in all affected female family members and the grandmother presented also premature menopause. Precocious puberty was well controlled by pharmacological therapy. **Conclusion:** We highlight the importance of an accurate family medical history to disclose the peculiar pattern of inheritance of this gene and add new data to knowledge of the phenotype of MKRN3 mutations. We expand the phenotypic knowledge of mutations of this gene reporting an affected family member with both early menarche and premature menopause.

P2-541

Distribution of Mutations in Genes Known to be Associated with Familial Idiopathic Hypogonadotropic Hypogonadism in a Large Cohort

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Background: Idiopathic hypogonadotropic hypogonadism (IHH) is characterised by failure of initiation or maintenance of puberty due to insufficient gonadotropin release, which is not associated with anosmia/hyposmia. **Objective and hypotheses:** The objective of this study was to determine the distribution of causative mutations in an hereditary form of IHH. **Method:** In this prospective collaborative study, families with more than one affected individual (i.e. multiplex families) with IHH were recruited and screened with Sanger sequencing as a first step of the larger study for genes known to be associated with IHH. **Results:** Mutations were identified in seven genes in 35 families. Number of occurrence per gene is given in parenthesis in decreasing order: *GNRHR* (12), *TACR3* (11), *KISS1R* (5), *FGFR1* (3), *GNRH1* (2), *TAC3* (1), and *KISS1* (1). **Conclusion:** Mutations in two genes (*i.e. GNRHR* and *TACR3*) occurred in two third of the families, thus these two genes should be prioritized for diagnostic studies in familial IHH. **Funding information:** This work was supported by the TUBITAK (grant number 113S962).

P2-542

Gonadotropin-Releasing Hormone Agonist Analog (Tripotorelin) Stimulation Test in Evaluation of Pituitary -Testicular Function in Boys

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Background: The hypothalamus-pituitary-gonad (HPG) axis is crutial to the development and function of reproductive system. Gonadotropin-releasing hormone (GnRH) has been the standard test for the assessment of activation of HPG axis. Because GnRH is no longer available, GnRH analogues (GnRHa) are now used. In previous studies, GnRHa stimulation tests have been the mainstay for establishing the diagnosis of precocious puberty in female and distinguishing constitutional delay of growth and puberty from isolated hypogonadotropic hypogonadism in male patients. Neither the clinical values of GnRHa tests in evaluating the activation of HPGA across the pubertal transition, nor the optimal sampling times for luteinzing hormone (LH) have not yet to be established. **Objective and hypotheses:** To investigate the clinical values of GnRHa (Triptorelin) stimulation test in the evaluation of the activation of the HPGA in boys and to provide a scientific method in the early diagnosis of puberty onset in boys. And to determine the appropriate sampling time for LH post triptorelin challenge. **Method:** A prospective study of multi-sample GnRHa stimulation tests were performed in 68 boys. Based on the testicular volume (≧4 ml) and serum testosterone (≧0.2 ng/ml), they were divided into two groups, in which 30 boys with prepuberty and 38 boys with puberty. After 3 mcg/kg of Q7 Triptorelin, samples were obtained at 0, 1, 3, 6 hours. The 68 stimulation tests were reviewed and analysed. For each parameter, the sensitivities and specificities were estimated and ROC curves were constructed. **Results:** Both serum Follicle-Stimulating Hormone (FSH) and LH concentrations were different at 0, 1, 3, 6 hour after GnRHa tests in prepubertal group and pubertal group. In prepubertal group, ΔFSH was much higher than ΔLH. In pubertal group, ΔLH was much higher than ΔFSH. No differences were found among the serum ΔFSH or peak FSH between two groups. There are differences among either peak LH or peak LH/FSH in prepubertal and pubertal groups. The measurement of peak LH≧13.98 IU/L and peak LH/FSH≧0.92 had rather high sensitivity (81.5%) and specificity (86.7%) for distinguishing pubertal boys from those in prepubertal stage. Percentages of peak LH after GnRHa tests appeared at 1, 3, 6 h in a total of 68 cases were 10%, 68% and 22%, respectively. **Conclusion:** Triptorelin stimulation test appears to have a great value in the assessment of the activation of HPGA in boys. The measurement of both peak LH and LH/FSH has rather high sensitivity and specificity in diagnosing puberty onset. A single serum LH sample collected 3 hours post GnRHa challenge is the optimal sample to establish the diagnosis of puberty onset.

P2-543

The Endocrine Response to a Gonadotropin Releasing Hormone (GnRH) Test: Establishing a Reference Interval in Healthy Girls below 6 Years of Age

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Background: Premature thelarche and precocious puberty are frequently diagnosed even in girls below 6 years of age. A GnRH test is often included in the diagnostic work up. Interpretation of the GnRH test in girls below 6 years of age is, however, difficult, because the reference interval has not been established in this age group. **Objective and hypotheses:** To establish the normal endocrine response to a GnRH test in healthy girls below 6 years of

age. **Method:** Thirty-six healthy girls aged 3.77 (range 0.85–5.99) years were included. Anthropometrics, Tanner stage, bone age, and baseline serum levels of estradiol and sex hormone binding globulin (SHBG) were determined. Each girl participated in a GnRH test: Blood samples for serum values of luteinizing hormone (LH) and follicle stimulating hormone (FSH) were drawn before and 30 minutes after an i.v. injection of gonadorelin 0.1 mg/m^2 (max 0.1 mg). LH, FSH, estradiol, and SHBG were measured by chemiluminescence immune-assay (Roche Cobas E601, module immunology analyzer). **Results:** The 30 minute LH response (median and 95% CI) was 3.18 (2.55–3.62) Iu/l and the FSH response was 16.17 (13.59–17.91) Iu/l. Stimulated LH and FSH concentrations correlated inversely with age, $r = -0.59$ ($P < 0.001$) and $r = -0.42$ ($P = 0.01$), respectively. The stimulated LH/FSH ratio was 0.21 (95% CI 0.18–0.25, range 0.06–0.39) and did not correlate with age. **Conclusion:** This clinical investigation reports the largest series of GnRH tests in healthy girls below 6 years of age. We provide a normal reference interval for the GnRH test in girls in this age group. Our data are of major clinical relevance when evaluating girls below 6 years of age with premature sexual characteristics. **Funding Information:** This work was supported by Aarhus University, Institute of Clinical Medicine, The A.P. Møller Foundation, Søster og Verner Lipperts Fond, and Grosserer L. F. Foghts Fond.

P2-544

Increasing BMI is Associated with Lower Luteinising Hormone Levels in Girls with Central Precocious Puberty at the Early Pubertal Stage

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Background: Girls with precocious puberty have high LH levels and bone age was advanced over chronological age by 1 year. Obese children start puberty at an earlier age than non obese children. The mechanisms that cause obese children to grow faster starting from early childhood are not well defined. **Objective and hypotheses:** We analysed the effects of obesity on luteinising hormone (LH) secretion by using gonadotropin-releasing hormone (GnRH) tests in girls with precocious puberty. **Method:** A total of 621 subjects with idiopathic precocious puberty who completed gonadotropin-releasing hormone stimulation testing between 2007 and 2012 were included in the study. Subjects were divided into two groups based on BMI; the normal weight group (BMI between the 5th and 85th percentile) and the obese group (BMI greater than 85th percentile). **Results:** In Tanner 2 girls, peak stimulated LH levels were 10.9 ± 9.2 and 9.2 ± 5.6 IU/L between normal weight and obese subjects, respectively ($P = 0.047$). In Tanner 3 girls, peak stimulated LH levels were 15.5 ± 11.7 and 11.1 ± 7.5 IU/L, respectively ($P = 0.026$). However, in Tanner 4 girls, peak stimulated LH levels were not significantly different between normal, overweight, and obese subjects. On multivariate analysis, BMI was significantly and negatively associated with peak LH in Tanner 2 and 3 girls. **Conclusion:** In girls with CPP, increased BMI affects peak stimulated LH levels during the early pubertal stage (Tanner stages 2 and 3). However, BMI was not associated with LH secretion in Tanner stage 4 girls with CPP.

P2-545

Change of Growth Pattern and Bone Mineral Density in Ovariectomised Female Rats According to Oestrogen Dosage

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Objective and hypotheses: The purpose was to get the basic data of optimum serum concentration of oestrogen in pubertal growth spurt, minimising the decrease of bone mineral density or acceleration of epiphyseal closure of long bones. **Method:** i). Fifteen female S.D. rats (4-week aged) were ovariectomised to inhibit their endogenous oestrogen effect and randomly divided into three groups. After 1 week, the group 1 were injected subcutaneously with sesame oil, as a control, group 2 were with 100 μg/kg/week of oestradiol depo as a high-dose, and group 3 were with 200 μg/kg/week of it as a super-high-dose for 10 weeks on their posterior neck area. ii) Their crown-lump length, body weight, and bone mineral density of spine and long bones were checked weekly from 1 week before through 10 weeks after injections. iii) Serum levels of GH and oestradiol were checked with ELISA before and after injections. iv) After 10 weeks of injections, they were euthanized, pituitary glands were dissected and their pituitary Gh_1 mRNA levels were checked with quantitative RT-PCR. v) Their proximal tibia were dissected and stained with hematoxylin-eosin. vi) The thicknesses of epiphyseal plate including proliferative and hypertrophic zone of the proximal tibias were measured in 20 evenly divided sites with microscope. vii) Statistical analyses were done among the 3 groups before and after injections using ANOVA with multiple comparisons for auxological data, and Kruskall Wallis test for serum levels of GH, oestradiol, and pituitary Gh_1 mRNA levels with SPSS ver.13.0. **Results:** i) There were no significant differences in body lengths among 3 groups. ii) The body weights were decreased, and the bone mineral densities were increased in group 3 but there were no significant differences. iii) Serum GH levels and pituitary Gh_1 expressions were significantly increased in group 3. iv) There was no significant difference in the thickness of total epiphyseal plate, proliferative zone, but that of hypertrophic zone of the epiphyses was significantly increased in group 3. **Conclusion:** i) GH secretion and Gh_1 gene expression were increased after super-high dose oestrogen treatment. ii) There were tendencies that body weight is negative and bone mineral density is positive relation with oestrogen dosage, but with no significant differences. iii) The thickness of hypertrophic zone in

epiphyseal plate was relatively increased after super-high-dose oestrogen treatment, maybe because of increased transdifferentiation of osteoblast to osteocyte. iv) The effects of oestrogen on epiphyseal plate in rodents may be different with human.

P2-546

Gynecomastia with Precocious Onset in Peutz-Jeghers Syndrome: Managing the Aromatase Overexpression

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Background: Testicular tumours are an unusual cause of prepubertal gynecomastia. However, in boys with Peutz-Jeghers Syndrome (PJS), a rare autosomal dominant disorder caused by mutation in LKB1/STK11 gene, is mandatory to exclude this etiology, given the well-known association between PJS and Large-Cell Calcyfing Sertoli-Cell Tumor (LCCSCT). This mutation promotes aromatase overexpression in neoplastic Sertoli-cells, leading to gynecomastia. **Case presention:** We report the case of a 4-year-old boy, with genetic diagnosis of PJS, who had been presenting gynecomastia since the age of 2 and a marked height velocity (HV). He exhibited hyperpigmented lesions of the lower-lip, bilateral breast enlargement (female Tanner-B4), absent pubic/axillary hair, infantile penis and testicular volume of 4 mL. His height was 110.5 cm(+1.88SDS) and HV was 8.64 cm/year(+2.65SDS). Bone and chronological age were coincident. LHRH test was performed, excluding GnRH-dependent precocious puberty, as well as abdominal MRI, that excluded adrenals' oestrogen-producing tumour. Testicular ultrasound evidenced bilateral size of 22×10 mm and multifocal microcalcifications. Blood tests revealed: LH<0.20 mUI/mL, FSH <0.20 mUI/mL, oestradiol<20.0 pg/mL, testosterone <3.00 ng/dL, prolactin 5.4 ng/mL, androstenedione <0.30 ng/mL and inhibin-A 4.6 pg/mL(0.9–1.7). The diagnosis of LCCSCT was made given the patient's syndrome and the ultrasound's description. Considering the frequent benign nature of LCCSCT, we've chosen to perform conservative treatment with anastrozol. One year after the start of this drug the patient evidenced a less tense Tanner-B3 and a HV of 5.68 cm/year (−0.71SDS); serum inhibin-A had become negative (<0.4 pg/mL). **Conclusion:** We describe the case of a boy with one of the most precocious PJS-related gynecomastia reported in the literature associated to a marked increase in HV. It has been described that, although oestrogen level may be under the detection limit, it can be sufficient to stimulate breast tissue and growth plates, probably due to increased tissular sensitivity/bioavailability/local biosynthesis. In this patient, the aromatase inhibitor has promoted reduction of breast volume, HV and serum inhibin-A.

P2-547

The Impact of Growth Hormone (GH) Therapy Combined with Estrogens on Blood Pressure (BP), Cardiac Left Ventricular (LV) Dimensions and Lipid Metabolism in Pubertal Girls with Turner's Syndrome (TS)

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Background: The risk of hypertension is estimated to occur in 7–17% of children and adolescents with TS. Even girls with TS who are normotensive have been shown an abnormal circadian BP rhythm, increasing the risk of end-organ hypertensive damage. **Objective and hypotheses:** We performed this study to assess the effects of GH treatment combined with estrogens for short stature on LV dimensions, systemic BP and lipid metabolism in girls with TS without clinically relevant cardiac abnormalities. **Method:** 20 girls with TS 12.4±1.09 years old, not treated before, were recruited in the study and treated with GH (0.05 mg/kg/daily) and estrogens (applicated 100 mg/daily) during 2 years. Anthropometry, systemic BP assessed every 3 months. Total cholesterol (TH), low density lipoproteins (LDL), high density lipoproteins (HDL), triglycerides (TG) levels were measured every 6 months, LV systolic function (LVSF) was estimated by echocardiography every 12 months. The measurement parameters were: LV end diastolic (LVED), LV end systolic (LVES), LV ejection fraction (LVEF). Stroke volume index (SVI) was calculated. **Results:** Over a period of treatment height gain was 16.18±2.98 sm. Before the start of GH- treatment, mean BP was within the age-related normal range. After 2 years of treatment systolic BP and diastolic BP levels were not significantly different from baseline. I TH, TG, LDL, LDL levels were not changed related to baseline. At baseline the LV dimensions of all the girls were within normal range, and the mean SD scores were close to zero. During 2 years of GH-therapy LVED was significally increased from 45.23±9.77 to 55.91±9.37(P=0.012), SVI was increased accordingly from 25.30±2.67 to 29.86±2.25 (P=0.019). There were not significant changes in LVES and LVEF between baseline and 2-years timepoint. These data give evidence that myocardial contractility was improved. **Conclusion:** i) GH treatment does not result in LV hypertrophy or hypertension in girls with TS during 2-years therapy, despite the dramatic body height gain. ii) GH-therapy combined with estrogens in girls with TS was not induced 9 change in lipids levels probably because of its levels were in normal ranges at baseline.

P2-548

Sensitivity of Measured Parental Height and Target Range in the Diagnosis of Turner Syndrome

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Background: Girls with Turner syndrome (TS) are inappropriately short for their parents' heights; measured parental height is therefore useful in diagnosis. **Objective and hypotheses:** To examine the sensitivity of measured parental height in the diagnosis of TS; and to audit the frequency of parental height measurement in our clinic. **Method:** Case note review of all girls with TS attending our dedicated Turner clinic between 1989–2013, recording the first accurate height measurement after the 1st year of life as well as karyotype, birth weight, gestational age and associated disorders. Each parent's height was noted as measured, reported or not known/recorded. Midparental height (MPH) and lower end of parental target range (LTR) were calculated using a correction factor of 12.5 cm, with 8.5 cm as 2 standard deviation (SD). Heights and BW were converted to SD score (SDS) using LMS software. Girls' height (Ht) SDS was compared with LTR SDS. **Results:** 176 girls were seen during the study period, 4 of whom were excluded (inadequate data). 142/172 girls were frankly short (Ht SDS $<$-2) giving a sensitivity of 82.6% for short stature screening. BW, available in 136 girls, was <0 SDS in 102 (76%). Both parents had been measured in 94 girls (54.6%) 2 of whom were excluded. Mean $\pm$ age at 1st accurate measurement in the 92 girls was 6.93 ± 3.9 years with Ht SDS -2.63 ± 0.94 versus LTR SDS of -1.77 ± 0.81 ($P < 0.001$). 78/92 girls had Ht SDS $<$LTR giving an overall sensitivity of 85%. All but 3 of the 14 girls with Ht SDS $\geqq$ LTR were aged <5 years while karyotype was mild in 5 (45,X/46,XX in 2 and 45,X/47,XXX in 3). **Conclusion:** Measured parental height, available in only about half of our cohort, is highly sensitive in the diagnosis of TS in girls aged >5 years and more specific than crude short stature screening. BW, although below average in $>75\%$, is not a sensitive marker. Height status may be normal in younger girls and also those with milder karyotypes.

P2-549

Balance Control in Children and Adolescent Girls with Turner Syndrome

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Background: Turner syndrome (TS), affects approximately 1/2500 live female births. The clinical features range from a severe phenotypic character to reduction of final height and premature ovarian failure. **Objective and hypotheses:** Processing of sensory information from visual, vestibular and somatokinesthetic systems is required to organize an adequate motor response aiming at gaze and posture stabilization according to the expected task and to the environmental contexts, each element of the sensory-motor chain being possibly affected in TS. This study aimed to analyze balance control specifities in TS children and adolescent girls. **Method:** Twenty four patients underwent visual and otological evaluation and posturography tests. A sensory organisation tests (EquiTest, Neurocom, Clackamas, Oregon) allows to calculate a composite equilibrium score (CES) to evaluate global balance performances. In a second test, the patients were submitted to slow rotational oscillations of the support in EO and EC conditions (Maastricht Instruments, The Netherlands), and partitioned in two groups according to the stability (type 1) or instability (type 2) of balance control. **Results:** TS patients were partitioned according to central nervous system (CNS) or peripheral balance disorders. Six of them were considered as CNS troubles, five as peripheral, six as mixed, and seven as without vertigo or dizziness. In five patients, a second evaluation was performed 6 months later, in order to strengthen out the evolutive characteristics of balance control impairment (more stabilized in CNS disorders and more variable in peripheral disorders). CES was low in TS, with falls in certain conditions, and type 2 recordings were recorded in 17 patients in slow rotational oscillations. Posturography performances were lower and more fixed in CNS troubles and in mixed troubles than peripheral troubles. **Conclusion:** Balance control is altered in Turner patients and this has to been taken in account for prevention of the adult fracture increased risk.

P2-550

Short Stature with Neurodevelopmental Delay in Familial Variant Turner Syndrome

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Background: Turner syndrome (TS) is classically a sporadic cause of short stature and gonadal dysgenesis in girls. We report familial variant TS affecting twelve individuals of both sexes over three generations. Affected children manifest short stature and varying degrees of neurodevelopmental disorder but no visceral abnormalities. **Case presentation:** A 27-year-old female in her 12th pregnancy presented for 20-week ultrasound. Fetal cardiac and renal anomalies led to amniocentesis, revealing terminal deletion of the short arm of one X chromosome at band 22.3, consistent with variant TS. This baby girl had pedal and hand oedema at birth. Echocardiogram was normal but kidneys remained echogenic. Speech and language delay became evident by preschool. Now 3-years-old, her height is on the 25th centile. Seven other females (proband's mother, half-sister, two half-aunts, three cousins and grandmother) and three males (proband's half-brother and two cousins) carry the Xp22.3 deletion. They are short (height $<2^{nd}$ centile). Five out of eight affected females also displayed disordered neurodevelopment. Two girls have speech and language delay. Three adult women have learning disability.

All three affected boys manifest a more severe phenotype. Two have global developmental delay and autism. The third, now 12-weeks-old, was born premature, needed ventilatory support and is being investigated for Hirschsprung disease. **Conclusion:** This is variant TS affecting both sexes in three generations of a family due to Xp22.3 deletion. Of the 42 known contiguous genes in Xp22.3, deletion of NLGN4, ARSE and SHOX may explain the phenotypes in this family (Online Mendelian Inheritance in Man, OMIM). NLGN4 deletion is linked to developmental delay and autism. ARSE deletion is associated with x-linked chondrodysplasia punctate (short stature with short distal phalanges). SHOX haploinsufficiency is considered solely responsible for short stature in TS. Familial variant TS should be considered in short boys with the relevant family history.

P2-551

Diagnostic Significance of Serum Concentrations of Osteoprotegerin and Proinflammatory Cytokine IL-1β in Children with Autoimmune Thyroid Disease

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Background: Chronic autoimmune thyroiditis (cAIT) leads to hypothyroidism due to T cell-mediated cytotoxicity in most cases. By contrast, Graves' disease (GD) with thyrotropin receptor stimulatory autoantibodies cause hyperthyroidism. OPG a cytokine receptor which mediates suppressive effect on osteoclastogenesis is a key regulator of inflammation and may be a link between bone, autoimmune disease and vasculature. **Objective and hypotheses:** Cytokines OPG and IL-1β play a crucial role in modulating immune response in these two opposite clinical and hormonal thyroid diseases. **Method:** The study group consisted of 64 children: 44 newly diagnosed, untreated children with cAIT ($n=22$), GD ($n=22$) and 20 healthy children. Cytokine concentrations were evaluated using ELISA. **Results:** We observed significantly higher concentrations of OPG in children with GD ($P<0.01$) (mean $\pm$ S.D.; 4.48 $\pm$ 2.01 pmol/l) compared to control (3.02 $\pm$ 1.17 pmol/l); whereas no significant difference between children with cAIT (3.79 $\pm$ 1.28 pmol/l) vs control ($P>0.05$) and cAIT vs GD ($P>0.05$) was observed. IL-1β concentration were significantly higher in children with cAIT (median 2.16 pg/ml, IQR 0.87) compared to control (median 1.88 pg/ml, IQR 1.04, $P<0.05$) and GD (median 1.39 pg/ml, IQR 1.27, $P<0.01$). In children with hypothyroidism IL-1β correlated positively with OPG ($r=0.44$; $P<0.05$). ROC curve indicates good efficacy of OPG to discriminate hyperthyroid and healthy children (AUC = 0.716; $P=0.017$) at cut-off point of 4.54 pmol/l with low sensitivity 54.5% but high specificity 95%. In contrast IL-1β may be a marker of hypothyroidism and effectively differentiates the group of hypothyroid children from GD children (AUC = 0.773; $P=0.002$) with good sensitivity 72.7% and high specificity 86.4% as well as the group of healthy children with cAIT children (AUC = 0.77; $P=0.003$) with sensitivity of 59.1% and high specificity 95%. **Conclusion:** We suggest, that OPG may be considered as a marker of hyperthyroidism (GD) and IL-1β as marker of hypothyroidism (cAIT) in children with autoimmune thyroid disease.

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Even in the Era of Congenital Hypothyroidism Screening Mild and Subclinical Sensorineural Hearing Loss Remains a Relatively Common Complication of Severe Congenital Hypothyroidism

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Background: Only few studies have focused on neurosensory hearing function of patients with congenital hypothyroidism (CH) identified by CH screening programs and treated early and, therefore, this issue remains still controversial. **Objective and hypotheses:** The aim of this study was to ascertain whether an early and adequate replacement treatment may be able to prevent sensorineural hearing loss in 32 screened children with CH and no associated risk factors for neuro-otologic alterations. **Method:** These patients were recruited according to highly selective criteria aiming to preliminarily exclude the negative interference of both treatment variables and other underlying risk factors. All the selected patients underwent, at a median age of 15.4 years, an audiologic investigation. **Results:** Eight patients (25%) exhibited, at audiometry, a mild sensorineural hearing impairment (between 25 and 40 dB HL), which was bilateral in five cases and unilateral in the remaining three cases. The poorest hearing scores were recorded in the individuals with athyreosis and in those with absence of distal femur bony nucleus at CH diagnosis. The prevalence of hearing impairment was significantly higher in CH patients than in 32 age-matched control subjects with no thyroid problems and no clinical suspect of hearing impairment (25 vs 3.1%; $\chi 2=6.3$, $P<0.025$). Also the prevalence of hearing impaired ears was significantly higher in CH group (20.3 vs 3.1%; $\chi 2=9.1$, $P<0.0025$). **Conclusion:** i) 25% of CH patients detected by CH screening may show, at a median age of 15.4 years, a mild and subclinical hearing impairment, despite early and adequate replacement treatment; ii) the risk of hearing loss is higher in CH young patients than in age-matched control subjects without thyroid problems; iii) the risk of hearing loss is closely associated with the severity of CH; iv) this risk is particularly relevant in the children with pre-natal onset of hypothyroidism.

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Efficacy of Supplemental Liothyronine for Patients with Congenital Hypothyroidism and Pituitary Resistance to Thyroid Hormone

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Background: Recent guidelines recommend levothyroxine (LT_4) monotherapy for all infants with congenital hypothyroidism (CH). However, up to one-third of patients have pituitary resistance to thyroid hormone and, to normalize their TSH, require supranormal circulating levels of T_4. Liothyronine (T_3) has been proposed as a supplemental therapy for such patients, but data demonstrating its use and efficacy are limited. **Objective and hypotheses:** Through a retrospective chart review we sought to test the hypothesis that supplemental T_3 treatment will decrease both TSH and T_4 in patients with CH and pituitary resistance to thyroid hormone. **Method:** We studied all CH patients seen at Boston Children's Hospital from '99-present who were treated with T_3 for pituitary resistance and who were compliant with therapy.All patients were treated with LT_4, and T_3 was added because of failure to normalize TSH'. We used paired *t*-tests to compare serum TSH, free T_4 or total T_4 and T_3 during the 2 years before vs 2 years after starting T_3 treatment. **Results:** We identified six patients (four males, two females) treated with combined LT_4 and T_3. Patients started T_3 therapy at a median initial dose of 0.29 μg/kg per day divided once or twice daily, with a median decrease in LT_4 dose by 11%. T_3 treatment was associated with lower average TSH (9.2 vs 4.5 mIU/l) and a decrease of TSH values $>$ 10 mIU/l. Area under the curve of fT_4 or total T_4 decreased by 23 ± 9% after T_3 treatment. The proportion of serum T_3 values above normal tended to increase during T_3 treatment. **Conclusion:** Addition of T_3 to LT_4 monotherapy is associated with lower serum TSH and T_4 in CH patients with pituitary resistance to thyroid hormone. Larger prospective studies are needed to validate these findings and to investigate whether the addition of T_3 improves cognitive development.

P2-554

Hypoceruloplasminemia as a Marker of Severe Hypothyroidism

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Background: Hypothyroidism may be also a rare cause of acquired hypoceruloplasminemia. It has recently been underlined a role for thyroid hormone in the normal developmental regulation of ceruloplasmin (cp). **Case presentation:** A 3-year-old Caucasian girl was admitted to our clinic for recurrent pericarditis, fatigue and muscle weakness. Her family history was remarkable for Hashimoto's thyroiditis and Graves disease. Her recent personal history was significant for weight gain, swelling of the face and chronic constipation. On physical examination she had pale and round face with a normal thyroid size. Cardiovascular and abdominal examination were normal. Echocardiogram showed minimal dissection of pericardium. On laboratory evaluations an increase of transaminases about twice upper limit of normal was highlighted with low levels of cp equal to 12 mg/dl (normal range 20–60 mg/dl) and low serum copper 59 ug/dl (normal range 70–140 ug/dl). In order to exclude a Wilson disease, patient underwent to ophthalmologic evaluation and abdominal ultrasound that resulted normal. Thyroid study showed high levels of thyroid stimulating hormone (338.000 mIU/ml), low levels of free thyroxine (3.2 pmol/l) and positivity of anti-thyroid peroxidase antibodies (2373.00 UI/ml). Ultrasonography showed a mild enlargement of gland volume and a three grade ultrasound pattern according Sostre classification. Levo-thyroxine replacement was started and blood tests performed 4 weeks after starting therapy pointed out a normalization of thyroid function and cp levels. **Conclusions:** Thyroid hormones regulate positively serum copper levels inducing the hepatic expression of the two Cu-transport protein ATP7A and ATP7B as well as the major Cu-transport protein cp. To the best of our knowledge the association of Hashimoto's thyroiditis and hypoceruloplasminemia has not been reported to date. Our case confirms the role of thyroid hormones in the normal developmental regulation of cp and underlines that clinicians could suspect hypothyroidism in patients with hypoceruloplasminemia without Wilson's disease signs.

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Pituitary Resistance to Exogenous Levothyroxine in Humans

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Background: The pituitary set-point for TSH synthesis and secretion is known to be an individual parameter with a strong genetic influence. Type II iodothyronine deiodinase is a pituitary enzyme involved in local deiodination of T_4 and negative feedback loop for TSH secretion. Defects in DIO2 have not been reported in humans; however, Dio2 knockout mouse has pituitary resistance to T_4 with elevated TSH, T_4 and TSH/T_4 ratio, with normal T_3. **Objective:** To identify human phenotypes consistent with deiodination defects in DIO2. **Subjects and methods:** From a pediatric cohort of patients with suspected TH resistance without

THRB mutations (13/25 patients, 52%), we investigated those with elevated TSH (>5 mU/ml), fT_4 (>1.7 ng/dl) and TSH/fT_4 ratio (>0.15) with normal T_3 under high dose levo-thyroxine which was unable to decrease TSH, or decreased it at the cost of clinical hyperthyroidism. PCR and Sanger sequencing of DIO2 and TSHR genes. **Results:** Five patients (three males) compatible with such phenotype were identified (38.5%). 4/5 showed severe thyroid hypoplasia on ultrasound and/or scintigraphy detected at neonatal screening and one had euplastic hypothyroidism. From 2 years of age, all patients showed persistent elevation of TSH (12 ± 5.1 mU/ml) concomitant to elevated fT_4 (1.87 ± 0.1 ng/dl; 4/5), normal T_3 (4/5). and high TSH/fT_4 (0.51 ± 0.2, N: <0.13; 5/5) and fT_4/fT_3 ratios (4.16 ± 0.5; N <3.7; 3/5), suggesting pituitary resistance to exogenous T_4. Maximum dose of levothyroxine was 5.9 ± 1.4 μg/kg per day, which caused clinical hyperthyroidism in 3/5. No mutations were identified in the coding regions of the genes studied. **Conclusion:** We describe a pediatric phenotype of pituitary resistance to exogenous LT_4 heralded by persistently elevated TSH which only normalized under biochemical or clinical hyperthyroidism. The phenotype is recognizable by high TSH/fT_4 ratio and represents an aberrant set-point for TSH secretion and feedback whose genetic determinants need to be investigated.

P2-556
Novel *PAX8* Mutations in Zhuang Chinese with Congenital Hypothyroidism

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Background: Congenital hypothyroidism (CH) is a condition that characterize by the deficiency in thyroid hormone. CH has a proximate prevalence of one in 4 000 newborns. Major CH cases were reported to be linked with mutations in TSHR, PAX8, NKX2.1, NKX2.5 and FOXE1 genes. **Objective and hypotheses:** The clinical presentation of CH patients caused by *PAX8* mutations are variable and *PAX8* mutation rates differ significantly among different populations. This study was set to examine the *PAX8* mutation spectrum and prevalence among Zhuang Chinese CH patients. **Method:** Peripheral venous blood samples were collected from the patients. Genomic DNA was extracted from peripheral blood leukocytes. The *PAX8* gene were PCR-amplified with intronic primers covering all the exons and intron-exon boundaries. **Results:** Sequence analysis of *PAX8* in 378 CH patients revealed five different mutations in nine individuals (two are siblings). The mutations included two known missense variants, namely c.92G>A (p.R31H) and c.91C>T (p.R31C), and one novel missense variant c.68G>T (p.G23V), as well as two novel nonsense variants c.1090C>T (p. R364X) and c.658C>T (p.R220X). The p. R31H mutation is highly recurrent in our patient population but the clinical phenotypes vary a lot among those carried this mutation. *PAX8* mutations were mainly associated with permanent CH. **Conclusion:** The prevalence of PAX8 mutations was 2.38% among Zhuang Chinese. Our study expanded the PAX8 mutation spectrum and provided the best estimation of mutation rate for Zhuang Chinese CH patients. **Funding:** This study was supported by the National Natural Science Foundation of China (81260126), Key Projects of Guangxi Health Department (2012025) and Guangxi Natural Science Foundation Program (2012GXNSFAA053174).

P2-557
Potentially Excessive Levothyroxine Doses in Cases of Congenital Hypothyroidism with Eutopic Thyroid Gland

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Background: The intelligence prognosis of congenital hypothyroidism (CH) is remarkably improved by early detection and optimal levothyroxine (LT_4) treatment. Some groups have reported that initial LT_4 overtreatment results in a subsequent decrease of cognitive function. In universal guidelines, an initial dose of 10–15 μg/kg per day of LT_4 is recommended. However, there are cases of LT_4 overdosing. **Objective and hypotheses:** The purpose of this study is to investigate the influence of the initial LT_4 dosage on the frequency of LT_4 overdosing during infancy. **Method:** Of 95 patients, there were 54 cases of mild CH (thyroid stimulating hormone (TSH) 15–30 μIU/ml) and 45 cases of moderate-severe CH (TSH ≧30 μIU/ml), treated by either a high initial dose of levothyroxine (≧9 μg/kg per day) or a low initial dose (<9 μg/kg per day). Serum free thyroxine (fT_4) and TSH levels were measured before treatment (initial visit) and after initial treatment. We defined CH cases with <0.5 μIU/ml TSH and with >2.5 ng/dL fT_4 after initial treatment as cases of LT_4 overdosing. We investigated the LT_4 overtreatment ratio in each group by calculating the odds ratio. **Results:** The LT_4 overtreatment ratios after initial treatment for the mild/low-dose, moderate-severe/low-dose, mild/high-dose, and moderate-severe/high-dose group were 2.5% (1/40), 15.0% (3/20), 37.5% (5/14), and 48.0% (12/25) respectively. The odds ratio between mild/low-dose and mild/high-dose were 14.29 ($P<0.05$) and between moderate-severe/low-dose and moderate-severe/high-dose were 3.20 ($P<0.05$), while the LT_4 overtreatment ratio was significantly higher in each high-dose groups. **Conclusion:** Cases of CH with eutopic thyroid gland often do not eventually show significant clinical manifestations and lasting hypothyroidism as compared with thyroid dysgenesis cases. Even if these cases show remarkably high TSH value and are considered severe case, these clinical conditions may be often transient such as excess of iodine or DUOX2 mutation. Thus, discursive long-term high-dose administration may result in LT_4 overtreatment. The initial dosage of LT_4 of 10–15 μg/kg per day for neonatal-screening-positive CH cases with eutopic thyroid gland may raise the risk of LT_4 overtreatment.

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Objective vs Subjective Measurement of Thyroid Volume by Ultrasound in Infants Referred with TSH Elevation on Newborn Screening

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Background: Establishing thyroid size as large, normal or small in newborn infants with TSH elevation and *in situ* thyroid is important for diagnosis and informing molecular genetic studies. **Objective and hypotheses:** To compare intra-observer variation in the objective (Ox) measurement of thyroid volume (vol) by ultrasound (US); and the correlation between subjective (Sx) and Ox assessment. **Method:** Joint blinded retrospective review of static images by two observers on two separate occasions in infants referred 2007–2013 with TSH elevation and eutopic thyroid. Combined vol was derived from the sum of each lobe using the formula length × depth × breadth × π/6. Images were then blindly reviewed subjectively as five categories: small, small-normal, normal, large-normal and large. Equivalent Ox size was determined using population-specific mean ± S.D. of 2.4 ± 0.4 ml to give corresponding vols < 0.7, 0.7–< 0.9, 0.9–< 2.1, 2.1–2.3 and > 2.3 ml. Correlation between Ox and Sx was defined as concordant, partial or discordant if categories were equivalent, 1 apart or 2 apart. **Results:** Of 48 infants images were available in 42 (25 males: 17 females) comprising 17 with definite congenital hypothyroidism (CH), 18 status uncertain and seven transient TSH elevation. Causes of definite CH were dyshormonogenesis (DHG) in 13 – defined by proven mutation ± thyroglobulin elevation ± increased uptake on radioisotope scan; and thyroid hypoplasia in four (all with proven mutations). Length could not be measured in the images of five patients while assessment was not possible in a patient with allo-immune thyroiditis due to surrounding oedema. Mean ± S.D. intraobserver difference in vol was 0.1248 ± 0.23 ml, reducing to 0.06 ± 0.05 ml after excluding three infants in whom extrapolation was needed because of enlarged glands. Ox vs Sx was concordant in 15 and partial in nine but discordant in 11 – including two infants with 'bulky' glands on Sx but vol 0.7–0.9 ml on Ox (PAX8 mutation in one, suspected NKX.2 disorder in the other) and in five DHG infants with enlargement on Sx but normal size on Ox. **Conclusion:** Intra-observer error for newborn thyroid US volume assessment is small. Sx assessment may be markedly misleading. However, our method of Ox measurement ignores the isthmus, which may be enlarged in DHG. This may explain the discordance in some of infants with DHG and underlines the place of both objective and subjective thyroid US assessment in newborn infants.

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Central or Primary Hypothyroidism? How to Differentiate in Patients with Low T_4 but Mildly Elevated TSH Levels

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Background: Central hypothyroidism (CH) is caused by TSH and/or TRH deficiency leading to hypothyroxinemia with low, normal or mildly elevated TSH levels. Differentiation of CH with mildly elevated TSH levels from primary hypothyroidism (PH) can be difficult. However, this differentiation has important clinical implications (i.e. cortisol replacement before L-thyroxine). **Objective and hypotheses:** In this study, we constructed a nomogram allowing us evaluating TSH levels relative to fT_4 levels in CH and PH, thus providing more objective criteria for the diagnosis. **Method:** 63 patients with congenital PH (24 thyroid dysgenesis, 39 with eutopic thyroid) and 55 patients with CH having multiple pituitary hormone deficiencies (33 congenital hypopituitarism, 22 hypopituitarism secondary to hypothalamo-pituitary tumor and/or cranial radiation) and 63 healthy controls included in the study. TSH and fT_4 levels before initiation of L-thyroxine treatment were evaluated in the patients. **Results:** In CH, he mean TSH was 3.6 ± 3.5 uIU/ml (median: 2.8, range: 0.006–20.3) with a mean fT_4 of 0.61 ± 0.2 ng/dl (median: 0.66, range: 0.009–0.91). In PH group, mean TSH was 148 ± 205 uIU/ml (median: 40, range: 8.65–867) with a mean fT_4 of 0.78 ± 0.3 ng/dl (median: 0.89, range: 0.12–1.34). TSH versus fT_4 nomogram is shown in Figure. Analyses revealed that in a patient with hypothyroxinemia, a TSH cut off of < 10 uIU/ml is discriminatory for CH with a sensitivity and specificity of 96% (95% CI:

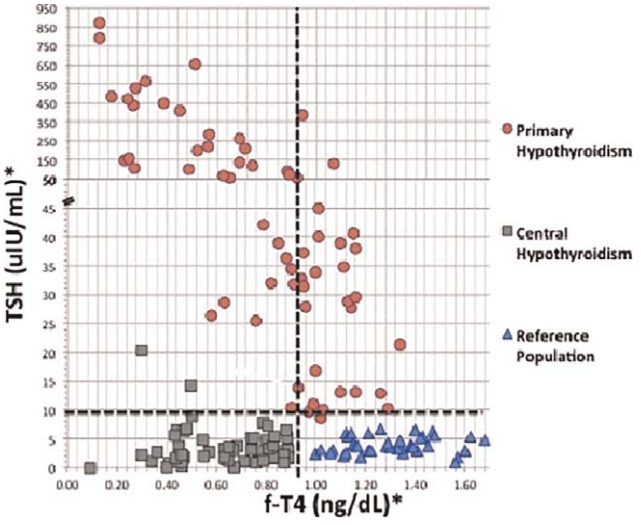

Figure 1 TSH and fT_4 levels in reference population, patients with primary and central hypothyroidism. *fT_4 and TSH were studied with ECLIA method with reference ranges of 0.93–1.7 ng/dl and 0.27–4.2 uIU/ml respectively

86%–99%) and 100% (95% CI: 88%–100%) respectively. Similarly, a TSH cut off of >25 uIU/ml is discriminatory for PH with a sensitivity and specificity of 97% (95% CI: 84%–99%) and 100% (95% CI: 91%–100%) respectively.There were two patients in CH group with TSH levels 20.3 and 14.3 uIU/ml who also had ACTH and GH deficiencies and, pituitary hypoplasia and pituitary hypoplasia with ectopic neurohypophysis on MRI, respectively. There was one patient with PH with TSH<25 uIU/ml. **Conclusion:** When fT_4 is low, TSH cut-off <10 uIU/ml is highly sensitive for diagnosis of CH, however TSH levels could be up to 20 uIU/mL in proven CH cases. Nomogram provided in this study could be useful for discrimination in uncertain cases.

P2-560

A Rare Adverse Effect of Methimazole: Serum Sickness

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Background: Serum sickness should be considered for the symptoms such as fever, arthralgia and urticaria existing 2–3 weeks after drug administration. Serum sickness is prototype of type 3 hypersensitivity reactions. Nephropathy and vasculitis may occur and main finding is hypocomplementemia. Several drugs such as antibiotics were reported as the reason of serum sickness disease. **Objective and hypotheses:** According to our knowledge, herein we report the first case who encountered serum sickness disease due to methimazole. **Method:** A 15-year-old boy was admitted to our hospital suffering from swelling, heat and pain in ankles and knees. We learned that he applied to another hospital due to fatigue and tachicardia 3 weeks ago. He was diagnosed with hyperthyroidism. Methimazole was initiated (25 mg/day). We are informed that symptoms occured on the 15th day of treatment. Physical examination revealed rash spreading all over the body. His body temperature was 38.7 C, heart rate was 100/min, he had no tension abnormality (90/60 mm/Hg). Laboratory tests revealed hyperthyroidism. fT_4 level was 2.25 ng/dl (0.93–1.7), fT_3 level was 5.87 pg/ml (2.3–5.0) and TSH level was 0.007 uIU/ml (0.51–4.3). Anti thyroglobulin antibody and anti thyroid peroxidase antibody levels were in normal range whereas anti thyroid receptor antibody level was high. Thyroid ultrasound revealed findings of thyroiditis. Hypocomplementemia was detected. Total C3 level was 41 mg/dl (88–201) and total C4 level was 8 mg/dl (16–47). **Results:** He was diagnosed with serum sickness disease. Methimazole treatment was stopped and he was hospitalized. Symptomatic therapy (steroid, non-steroid antiinflammatory drugs, propranolol) was initiated. His symptoms improved and he was discharged after a week. **Conclusion:** Serum sickness is a rare but life threatening condition. Along with agranulocytosis and hepatic failure, serum sickness should be anticipated after administration of methimazole and we should abstain from unneccessary uses of this drug.

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Analysis of Chosen Polymorphisms rs5742909 C/T – CTLA4, rs7522061 C/T – FCRL3, rs7138803 A/G – FAIM2 in Pathogenesis of Autoimmune Thyroid Diseases in Children

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Background: Autoimmune thyroid diseases are multifactorial diseases with a genetic susceptibility and environmental factors. A potential role of cytotoxic T-lymphocyte-associated protein 4 (CTLA4) gene, Fc receptor-like 3 (FCRL3) gene, Fas apoptotic inhibitory molecule 2 (FAIM2) gene polymorphisms on autoimmune thyroid diseases (AITDs) in children has not been established equivocally yet. **Objective and hypotheses:** To estimate the association of polymorphisms of CTLA4, FCRL3 and FAIM2 genes with the predisposition to Graves' disease (GD) and Hashimoto's thyroiditis (HT) in children. **Method:** The study was performed in 142 patients with GD, 57 with HT and 160 healthy volunteers. The three single nucleotide polymorphisms (SNPs): rs5742909 – CTLA4, rs7522061 – FCRL3 and rs7138803 – FAIM2 were genotyped by TaqMan SNP genotyping assay using the real-time PCR. **Results:** Rs5742909 C alleles were more frequent in GD patients in comparison to healthy subjects ($P=0.029$ with OR=1.8). It means that risk for development of GD is exactly 1.8 higher for C allele in comparison to T allele. Rs7522061 C alleles were more frequent in GB patients in comparison to healthy subjects ($P=0.007$, OR=1.76). Rs7138803 A alleles were more frequent in HT patients in comparison to healthy subjects ($P=0.025$, OR=3.57). Rs7522061 C alleles were also more frequent in GD female patients in comparison to healthy subjects ($P=0.021$, OR=1.87). In case of HT patients rs7138803 A alleles were also more frequent in females compared to healthy subjects ($P=0.069$, OR=1.87). **Conclusion:** Rs5742909 C/T, Rs7522061 C/T and Rs7138803 A/G polymorphisms could contribute to development of AITDs in children. The main risk factor for rs5742909 and also rs7522061 is allele C. In case of rs7138803 the main risk factor is allele A.

P2-562

Thyroid Dysfunction is Associated with Biochemical Markers of Non Alcoholic Fatty Liver Disease in Paediatric Population

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Background: Thyroid dysfunction is a common condition in children and has been associated with metabolic syndrome, hypertension, cardiovascular disease and mortality. Due to the obesity epidemic in paediatric population exists a higher prevalence of nonalcoholic fatty liver disease (NAFLD), a condition associated with insulin resistance and metabolic syndrome. In adults it has been observed that elevated TSH, even within the normal range, are positively correlated with increased biochemical markers of NAFLD. In pediatric population there is no evidence of this association. **Objective and hypotheses:** To determine association between thyroid function and biochemical markers of NAFLD in paediatric population. **Method:** 82 children 57% (female), 13.5 years old (6.1–18.9 year) were studied. Anthropometry, Sistolic and Diastolic blood pression, and TSH, fT_4, AST, ALT, GGT, glucose and lipid profile were deternined. Variables were transformed to log10 prior Pearson correlation. To perform statistical analysis we used STATA SE 12.0 for windows. **Results:** TSH and fT_4 average was 3.16 ± 2.06 uU/ml and 1.26 ± 0.19. A positive association between ALT (r: 0.35; $P < 0.01$) and GGT (r: 0.24; $P < 0.05$) with TSH, but not with AST were seen. The relationship persists after adjusting for BMI. There were no associations between liver enzymes with fT_4 levels. A positive association between triglycerides and TSH (r: 0.42; $P < 0.001$) and a negative association between HDL and TSH (r: -0.33; $P < 0.001$) were seen. **Conclusion:** TSH elevated levels are associated with markers of NAFLD in the paediatric population. The relationship persists after adjusting for BMI, suggesting that the thyroid dysfunction could have a direct effect on liver parenchyma independent of nutritional stage. More studies are needed to assess the causality of this association and the effect of treatment of thyroid dysfunction in the development of liver disease. **Funding:** This work was supported by Fondecyt 1130427 and 1150437, CORFO 13CTI-21526-P1, IMII P09/016-F(ICM) Chilean Grants.

P2-563

Nonautoimmune Neonatal Hyperthyroidism due to A633G Mutation in the Thyrotropin Receptor Gene

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Background: Congenital hyperthyroidism is a rare disease. In most patients with congenital hyperthyroidism are autoimmune forms caused by maternal thyroid-stimulating antibodies. In contrast to autoimmune hyperthyroidism that is transient, nonautoimmune form of congenital hyperthyroidism is persistent and results from activating germline mutations in the thyrotropin receptor (TSHR) gene. **Case presentation:** We report the case of a Korean male infant with severe nonautoimmune neonatal hyperthyroidism due to germline TSHR mutation (A633G). He was delivered by emergency Caesarian section from a mother without thyroid disease at 33 weeks of gestational age because of foetal tachycardia and premature rupture of membranes. He had persistent tachycardia at 24 days of life. Brain MRI revealed mild hydrocephalus with craniosynostosis. Echocardiography and electrocariography showed sinus tachycardia. Thyroid function tests was confirmed hyperthyroidism with T_3 10.52 ng/ml (0.78–1.82), fT_4 3.98 ng/dl (0.85–1.86), and TSH 0.05 mIU/l (0.17–4.05). Antibodies to TSHR, thyroid peroxidase (TPO) and thyroglobulin (TG) were negative. Thyroid ultrasonography showed increased vascularity and 2 mm sized hypoechoic nodule in right thyroid. Thyroid scan revealed diffusely increased uptake and goitre. He was started on propylthiouracil (PTU) and propranolol, but it was difficult to control hyperthyroidism. At the age of 3 months, craniosynostosis and hydrocephalus were aggravated. He underwent ventriculoperitoneal shunt operation. After 5 months of PTU treatment, thyroid function tests showed euthyroid state and tachycardia was resolved. PTU was changed to methimazole and after reducing the dose of methimazole, hyperthyroidism was relapsed. We increased the dose of methimazole again. In direct sequencing for whole exons including intron-exon boundaries of TSHR gene, a cytosine to adenine transition in exon 10 was identified. He was heterozygous for substitution of aspartate by glutamine at codon 633. **Conclusion:** This is the first report of a nonautoimmune neonatal hyperthyroidism due to A633G mutation in the TSHR gene. Now, the molecular analysis of his parents TSHR gene are processing. If the patient has *de novo* heterozygous mutation of TSHR gene, it can be difficult to control hyperthyroidism using antithyroid drugs only rather than familial form. We should also consider the thyroidectomy or radioiodine treatment to prevent comorbidity of hyperthyroidism.

P2-564

Are Children with Congenital Primary Hypothyroidism Overtreated?

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Background: Treatment of congenital primary hypothyroidism (CPHT) fluctuates between two opposite risks for the neuro-cognitive development in a critical window during the neonatal period, under- and over-treatment. **Objective:** To investigate the relevance of current international recommendations of 10–15 μg/kg per day for L-thyroxine (lT_4) doses in CPHT. **Method:** fT_4 and TSH were measured in a plasma sample after 15 days and one month of lT_4 treatment in 90 healthy full term newborns diagnosed with congenital hypothyroidism from routine screening on the 3rd day of life over a period of 9 years 3 months who were treated with doses of a liquid preparation of lT_4, ranging from 6.3 (2.5th percentile) to 11.6 (97.5th percentile) (median: 8.0) μg/kg per day. fT_4 and TSH levels at the 15th day of treatment served to adjust lT_4 doses. **Results:** At the 15th day of treatment, only 4.8% of the newborns had a plasma fT_4 level below the lower value of 12 pmoles/l, while 46.7% and 32.2% had a plasma fT_4 level above the upper values of 25 or 30 pmoles/l respectively. A significant independent positive correlation ($r^2 = 0.2$, $P = 0.0027$) was observed between fT_4 plasma levels at the 15th day of life and the initial lT_4 dose. The relationship between 15 day lT_4 dose and fT_4 at 1 month of treatment was weaker. **Conclusions:** Although significant enough, the correlation between initial lT_4 doses and fT_4 level at the 15th day is characterised by a dispersion inducing a frequent overtreatment by liquid lT_4 administration, when following recommended 10–15 μg/kg per day dosages in newborns with CPHT, whose neuro-cognitive consequences are to evaluate. **Funding:** French National Insurance Organization (Fund for Neonatal Screening).

P2-565

Metamorphic Thyroid Autoimmunity in Down Syndrome: From Hashimoto's Thyroiditis to Graves' Disease and Beyond

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Background: During the last years, it has been sporadically reported that Graves' disease (GD) and Hashimoto's thyroiditis (HT) may follow one another in the same individuals, due to a sequential phenotypic conversion from GD to HT or vice versa. **Objective and hypotheses:** To shed further light on the specific relationships between Down syndrome (DS) and metamorphic thyroid autoimmunity. **Method:** We have reconstructed the conversion process from HT to GD in a selected population consisting of 12 DS individuals aged between 3.0 and 13.5 years at HT diagnosis and between 4.1 and 19.9 years at GD diagnosis. All the patients underwent a treatment with methimazole (MMI), at a dose that was periodically adjusted on the basis of clinical findings and thyroid function tests. **Results:** After MMI treatment onset all patients exhibited, at varying time intervals, a prolonged clinical and biochemical remission of hyperthyroidism. In eight/12 patients this treatment is still being continued 2–7 years after its initiation. The mean MMI dosage needed to maintain euthyroidism in these eight patients was 0.12 ± 0.02 mg/kg per day. In the remaining four patients MMI was withdrawn from 1.9 to 7 years after its initiation and no relapses were recorded 2.0–2.1 years after its withdrawal. All these four patients developed, from 0.1–0.3 years after MMI withdrawal, a biochemical picture of overt hypothyroidism and needed treatment with LT_4, that is now being continued since 2.0–2.1 years. No patients needed non-pharmacological therapies, such as surgery or radioiodine ablation. **Conclusion:** i) DS children may be incline to manifest over time a phenotypic metamorphosis from HT to GD; ii) A share of GD children with DS may subsequently fluctuate from hyperthyroidism to hypothyroidism; iii) In DS HT presentation is absolutely peculiar; iv) in DS GD is characterized by a mild biochemical and clinical course.

P2-566

Analysis of B Regulatory Cells with Phenotype $CD19^+CD24^{hi}CD27^+IL\text{-}10^+$ and $CD19+IL\text{-}10^+$ in the Peripheral Blood of Children with Graves' Disease and Hashimoto's Thyroiditis

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Background: Autoimmune thyroid disease (AITD) is the most common organ-specific autoimmune disorder. Genetic background, environmental and endogenous factors are play important roles in determining the activation of immune cells or the efficacy of the immunoregulatory pathways. Recently emphasizes the immunosuppressive role of B regulatory cells (phenotype $CD19^+CD24^{hi}CD27^+IL\text{-}10^+$, $CD19+IL\text{-}10^+$) in regulation of immune response. **Objective and hypotheses:** The aim of the study was to estimate the expression of

$CD19^+CD24^{hi}CD27^+IL\text{-}10^+$ and $CD19+IL\text{-}10^+$(B10) B cells in patients with Graves' disease (GD) ($n=24$, mean age 14.9 years old), in patients with Hashimoto's thyroiditis (HT) ($n=22$, mean age 15.2 years old) in comparison with sex- and age-matched healthy control subjects ($n=20$, mean age 15.4 years old). **Method:** The expression of the immune cells populations were analysed by the four-color flow cytometry using a FACSCanto II cytometer (BD Biosciences). **Results:** In untreated patients with Graves' disease and HT we observed a significant decrease of $CD19^+CD24^{hi}CD27^+IL\text{-}10^+$ ($P<0.033$ for GB and $P>0.05$ for HT) and $CD19+IL\text{-}10^+$ ($P<0.0431$ for GD and $P<0.033$ for HT) B lymphocytes in comparison to the healthy controls. The analysis of $CD1d^+CD5^+CD19^+CD24^+CD27^+IL\text{-}10^+$B cells in the peripheral blood revealed comparable percentages of these cells in patients with thyroid autoimmune diseases to the healthy controls. In untreated Graves' patients negative correlation between percentage of $CD19^+IL\text{-}10^+$B cells and serum level of TSI ($P<0.01$) antibodies was found, while no such correlation were detected in relation to $CD19^+CD24^{hi}CD27^+IL\text{-}10^+$B cells. **Conclusion:** We conclude that the reduction number of Breg cells with expression of $CD19^+CD24^{hi}CD27^+IL\text{-}10^+$ and $CD19^+IL\text{-}10^+$(B10) could be responsible for loses immune tolerance and development of autoimmune process in thyroid disorders.

P2-567

Case Report: Resistance of Thyroid Hormone due to a Novel Thyroid Hormone Receptor β-Gene Mutation

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Background: Thyroid hormone resistance (THR) is an autosomal dominant, rare syndrome and result of the reduction sensitivity of target tissues to thyroid hormone. There is usually normal or slightly elevated TSH concentration with increase in serum fT_3 and fT_4 concentrations. The most common cause of resistance to thyroid hormone (RTH) is heterozygous thyroid hormone β (THR β) gene mutations. THR is defined by Refetoff et al. at 1967. THR mutations have been identified in more than 1 000 individuals in 362 families. In the present report, we describe the clinical, laboratory finding and genetic analysis of patients with a novel THR β gene mutation. **Case presentation:** Index case 11 years 6 month-old girl was admitted to our hospital because of sweating and palpitation. Her physical examination had revealed tachycardia and goitre. The elevated serum levels of fT_4 and fT_3 coexisted with unsuppressed TSH. The index cases' father, two uncles, grandmother and four cousin had findings consistent with the THR, Her father, two uncles and grandmother had a history of total thyroidectomy cause of goitre. In scanning the whole family, four adults and five children were identified a novel heterozygot missense mutation, A234D (c.701c>A) located in exon 8 of THR β-gene. **Conclusion:** Our study revealed that THR β gene mutations can be seen in diffferent clinical manifestations. Many cases do not need treatment. The TRβ-gene mutation confirms the diagnosis and prevent unnecessary and improper treatment.

P2-568

Levothyroxine Replacement in Primary Congenital Hypothyroidism: The Higher the Initial Dose the Higher the Rate of Overtreatment

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Background: Congenital hypothyroidism (CH) is the most frequent endocrine disorder during neonatal period and delay in diagnosis and treatment leads to irreversible complications. A high L-thyroxine (LT_4) dose is recommended for treatment, while the optimal starting dose is still a matter of debate. **Objective and hypotheses:** The objective of this study was to determine the effects of various starting doses of LT_4 on serum thyroid stimulating hormone (TSH) and thyroxine (fT_4) at the end of the first month of treatment. **Method:** A total of 71 patients (37 males) with CH were included in the study. The patients were divided into three groups according to the initial LT_4 doses: group 1 ($n=24$, 6–9.9 μg/kg per day), group 2 ($n=21$, 10–11.9 μg/kg per day), and group 3 ($n=26$, 12–15 μg/kg per day). A fT_4 level >2.3 ng/dl $\pm$a TSH level <0.5 μIU/ml were considered as overtreatment. **Results:** The mean age of the study population was 22.3 ± 13.2 days at diagnosis. At diagnosis, the mean fT_4 was 0.84 ± 0.32 ng/dl, and TSH was 39.3 ± 30 μIU/ml. The mean initial dose of LT_4 was 10.9 ± 2.9 μg/kg per day. Overtreatment rates were significantly different between the groups (group 1=25%, group 2=42.9%, group 3=61.5%, $P=0.034$) and significantly higher in group 3 compared to group 1 ($P<0.0167$). **Conclusion:** None of the patients was undertreated. In this study, we found that the rate of overtreatment was significantly higher in patients who were given 12–15 μg/kg per day LT_4. Thus, monitoring thyroid functions earlier than one month of treatment is necessary.

P2-569

Parenting Stress Profile and Children Behaviour in Patients with Congenital Hypothyroidism

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Background: Hypothyroidism has been associated with cognitive and motor impairments, the degree to which mild

hypothyroidism, or subclinical hypothyroidism impacts mood and cognitive functions and whether these symptoms respond to treatment, remains controversial. Furthermore, hypothyroidism is associated with an increased susceptibility to depression and reductions in health-related quality of life. **Objective and hypotheses:** Recent longitudinal studies stressed that the follow-up of children with treated congenital hypothyroidism (CHT) should not be limited to the cognitive domain. This study attempted to evaluate the emotional–behavioural profiles in children with CHT and the parenting stress profiles. **Method:** Data for children and families characteristics were collected from 33 families with a CHT child (13 males, 20 females; age: 6 months–6 years) diagnosed and treated since the newborn period. We analyzed the children by the Denver intelligence test and the child behaviour checklist (CBCL). Furthermore we proposed the parenting stress index (PSI) to their parents. **Results:** Denver intelligence test results demonstrated that nine/33 patients were normal, 20/33 were dubious, four/33 were not estimable. However the specific neuropsychiatric evaluation and QI confirmed a reduced performance only in three. The CBCL was normal in 18/33 patients (ten females; eight males), borderline in 8/33 (five females; three males), pathological in 7/33 (five females; two males). The children younger than 2 years showed a pathological or borderline score, with the exception of two. Between these, the more frequently pathological items were somatic complaints (five pathological; four borderline), anxious/depressed (two pathological; four borderline), attention problems (one pathological; four borderline). The PSI revealed a pathological test in six/33 patients. All the items were pathological in two; however in all the six pathological patients the PSI identified a 'difficult child'. No correlations were found between starting day of treatment and developmental outcome. Initial T_4 concentration and initial T_4 dose were weak predictors for developmental outcome. **Conclusion:** The diagnosis of a chronic disease of the son could interfere with the emotional relationship in the family.

P2-570

Goitrous Hypothyroidism of Pubertal Onset Caused by a Novel Mutation in DEHAL1 Gene

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Background: Iodotyrosine deiodinase (DEHAL1) is a thyroidal enzyme that deiodinates mono- and diiodtyrosines (MIT, DIT) and recycles iodine, essential for synthesis of thyroid hormone. Iodotyrosine deiodinase deficiency leads to hypothyroidism, goiter and variable mental retardation. The age for clinical onset was reportedly very diverse, allegedly related to individual iodine nutrition. **Clinical case:** We report on a boy, offspring of consanguineous parents from Lebanon, who presented at the age of 11 years with a very large goiter, rapidly developed within the previous 3 weeks, without other clinical signs. Hormonal investigations revealed severe primary hypothyroidism (TSH > 150 mU/l, fT_4 0.2 ng/dl, fT_3 2.4 ng/l, Thyroglobulin 8828 ng/ml, no anti-thyroid autoantibodies). Two weeks after 75 μg/day levothyroxine treatment, goiter volume shrank to a volume of 30 ml ($n < 5.4$ ml), as measured by ultrasonography (US). In further course, adherence to therapy was poor, and goiter re-increased to a volume 150 ml in the setting of relapsed biochemical hypothyroidism. US showed high perfusion of the gland and irregular structure of the thyroid parenchyma. After improved adherence to treatment, the goiter reduced to 110 ml in 4 months. Genetic investigations identified a novel homozygous mutation in *DEHAL* consisting in the insertion of one nucleotide in exon 1 (c.168-169insA), present in heterozygosity in apparently asymptomatic parents. This pathogenic deletion causes a frame-shift leading to a early stop-codon at amino acid 62 (p.A57SfsX62) of the protein. **Conclusion:** Full *DEHAL1* defects may remain asymptomatic for many years after birth in iodine-sufficient environments, and clinically present at puberty with dramatic severity. Goiter size is very sensitive to correction of hypothyroidism. The novel mutation is the most amino-terminally located so far in DEHAL1, and completely deletes the functional nitroreductase domain of the enzyme. Early urine MIT/DIT determinations in deserve investigation as possible biomarkers for pre-clinical diagnosis of *DEHAL1* defects.

P2-571

Mutation Screening of the TSH Receptor Gene in a Cohort of 192 China Patients with Congenital Hypothyroidism

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Background: Congenital hypothyroidism (CH) is a common endocrine disorder with a prevalence ranging from 1:2000 to 1:4000 newborns. The majority of CH cases were reported to be associated with mutations in several genes, which including the TSH receptor gene (TSHR). **Objective and hypotheses:** The aim of this study is to examine the frequency of TSHR gene mutations among CH patients in the Guangxi Zhuang Autonomous Region of China and to discover correlation between TSHR genotypes and clinical CH phenotypes. **Method:** We sampled blood from 192 CH patients in Guangxi Zhuang Autonomous Region, China; and extracted genomic DNA from peripheral blood leukocytes. All exons and exon-intron boundaries of the TSHR gene were screened by next-generation sequencing (NGS). **Results:** The NGS analysis of TSHR in 192 CH patients revealed four different mutations in five individuals. The mutations included one known missense variant, namely c.154C > A (p.P52T) and three novel missense variants c.1576G > A (p.A526T), c.1838A > G (p. Y613C) and c.2087T > G (p.F696C). **Conclusion:** The prevalence of TSHR mutations was 2.6% among Zhuang Chinese. Our study expands the knowledge of TSHR mutation spectrum and provides with an accurate estimation of mutation rate in Zhuang Chinese CH population. **Funding:** We thank the National Natural Science Foundation of China

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P2-572

Mutational Analysis of TSH Receptor and the Clinical Characteristics of Congenital Hypothyroidism

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Purpose: Aetiologies of congenital hypothyroidism (CH) in newborn period are various, and TSH receptor (TSHR) mutation is known as one of them. We evaluated mutational analysis of the gene TSHR and clinical characteristics in the patients with CH or neonatal hyperthyrotropinemia. **Method:** Mutation analysis was done in 96 children with CH or transient hyperthyrotropinemia who has been managed at the Department of Pediatrics in Dankook University Hospital. Clinical findings including gestational ages, birth weights, total T_3, fT_4, TSH, thyroglobulin as well as thyroid sonography were analysed by the review of their medical records. A P value of <0.05 was considered statistically significant using SPSS software program (version 20.0) and Mann–Whitney *U*-test, Chi-Square test were used in the study. **Result:** A total of 96 subjects were included in the study. 89 were diagnosed as having CH and seven were as having transient hyperthyrotropinemia. TSHR gene mutation was detected in 12 subjects (12.5%). R450H was the most common ($n=4$), followed by R519C ($n=2$), C390F ($n=2$), R531W, G245S, I81N, S305R. C390F, I81N, and S305R were the novel mutations. One subject with S305R mutation showed ectopic thyroid. There were no statistically significant differences in age at TSH elevation, gender, birth weights, findings of thyroid sonography, and the levels of total T_3, fT_4, TSH, thyroglobulin between a group with TSHR mutation and a group without TSHR mutation. Thyroid hormone replacement was continuously required in four children (44.4%) among nine subjects with TSHR mutation who were followed over 3 years of age. **Conclusion:** This study showed that the mutation of TSHR gene is the common cause of CH. Although there were no statistically significant differences of clinical characteristics between patients with TSHR mutation and those without mutation, more than half of patients with TSHR mutation could discontinue the replacement of thyroid hormone after 3 years of age.

P2-573

Characteristics of Delayed TSH Elevation in Neonatal Intensive Care Unit Newborns

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Background: Delayed TSH elevation (dTSH) is defined by normal TSH on the initial neonatal screening followed by elevated TSH on the second screen. Several studies concluded that dTSH is associated with low birth weight (BW) and is mostly transient. **Objective and hypotheses:** To elucidate clinical characteristics of dTSH in a large cohort of neonatal intensive care unit (NICU) newborns. **Method:** Clinical data were gathered from a cohort of 13 201 NICU newborns born between 1st January 2008 and 31st October 2014 that underwent TSH measurements due to low T_4 levels on the second screen. The clinical data included gestational age (GA), BW, timing of second test, T_4 levels and short-term follow-up. **Results:** 333 out of 13 201 (1:40) newborns presented with dTSH (TSH >15 IU/l), 129 (39%) of them had TSH levels >40 IU/l. dTSH had a peak incidence at GA of 37–39 weeks and 66% of the patients had BW >1500 g. There was no optimal timing to detect the disorder, as test timing was equally distributed after the third week of life. T_4 values in the 333 patients were negatively correlated with TSH levels ($r=-0.505$; $P<0.0001$) and were significantly lower than T_4 levels in 12 868 newborns with normal TSH: 5.9 ± 2.8 vs 7.6 ± 1.7 μg/dl; $P<0.001$. TSH levels were already elevated among patients with dTSH on the initial screening compared with the other newborns (8.3 ± 5.2 vs 4.2 ± 3.7 IU/l; $P<0.001$). A short-term follow-up in 193 of the dTSH patients demonstrated a persistence of TSH elevation and a need for levothyroxine treatment in 58% of them. Thyroid scans obtained in twelve patients in this subgroup were normal. **Conclusion:** Unlike previous reports, we found that dTSH is most prevalent in full-term newborns with BW >1500 g. Low T_4 is the best predictor for this disorder and apparently TSH elevation is already initiated within the 1st days of life.

P2-574

Years Follow-Up of Children with Abnormal Newborn Screening Results for Congenital Hypothyroidism: Who Needs Treatment and Who Needs Permanent Treatment?

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Background: As newborn screening test (NST) became popular, the incidence of congenital hypothyroidism (CH) was raised. But not all CH children require lifelong levothyroxine (LT_4) replacement therapy. **Objective and hypotheses:** We aimed to analyse predicting factors suggesting transient CH (TCH) compared to permanent CH (PCH) or transient thyroid function test (TFT) abnormality who had a positive screening results in our centers for the past decade. **Method:** 105 subjects (50 boys) who had an elevated TSH levels detected by NST were enrolled. Biochemical and imaging results, and treatment histories were reviewed retrospectively. TCH was defined when trial-off therapy was successful and kept their TFT within tolerable range at least 6 months of follow-up. PCH was defined when trial-off therapy

was failed or kept on medication over 3 years of age. Transient TFT abnormality was defined when the subjects did not require LT_4 replacement therapy and their follow-up TFTs were normalised. **Results:** CH was diagnosed in 75.2% (TCH 35.2% and PCH 40.0%) and the rest (24.8%) of the newborns showed transient TFT abnormality. Thyroid sonography or scintigraphy was performed in 78 subjects with CH and results were abnormal in 56.4% ($n=44/78$). Initial NST-TSH level (cutoff, 31.0 μIU/ml), LT_4 dose at 2 years of age (4.1 μg/kg per day), and maximal LT_4 dose (50 μg/day) revealed as significant predictive factors discriminating between TCH and PCH. While, initial serum level of fT_4 (1.06 ng/dl), not TSH levels, was the only factor to discriminate between transient TFT abnormality and TCH. **Conclusion:** As both NST-TSH level and treatment histories are important to predict a successful trial-off therapy in CH patients, the earlier re-evaluation might be possible when their initial NST-TSH level, maximal or 2-year-age LT_4 doses are low. And when initial serum level of fT_4 is above the average values in a neonate with mild elevation of TSH level, follow-up without LT_4 medication could be considered. Lastly, NST-TSH cutoff values might be readjusted to prevent unnecessary or over-treatment of TCH with normal thyroid gland.

P2-575

Attention Deficit and Sluggish Cognitive Tempo Symptoms in Congenital Hypothyroidism: Results from a Case-Control Study

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Background: Despite neonatal screening, children with congenital hypothyroidism (CH) may still display behavioural problems such as inattention, distractibility, hyperactivity and restlessness. **Objective and hypotheses:** The aim of present study was to evaluate attention and sluggish cognitive tempo (SCT) symptoms in 32 children with CH compared to 32 matched healthy controls. **Method:** The study population consisted of 32 CH children aged 9–14 years. CH children were diagnosed by neonatal screening and treated at a mean age of 19.34 ± 4.5 days with mean starting Levothyroxine (LT_4) dose of 11.8 ± 1.4 μg/kg per die (range 10–15 μg/kg per die). 32 healthy subjects, comparable for age, sex and socioeconomic status were enrolled as control. CH patients and controls underwent Child and Adolescent Disruptive Behaviour Inventory-Plus (CADBI-plus) to evaluate attention and SCT symptoms. Cooperation from both parents and from teacher of enrolled subject was required to enter the study. SCT is a newly defined childhood disorder associated with a slow cognitive processing, sluggishness, daydreaming, drowsiness, lethargy and under-activeness. **Results:** CH children scored significantly higher than controls in: attention problems referred by both mothers (M) (5.29 ± 5.01 vs 3.17 ± 2.54; P 0.04), and teachers (T) (7.2 ± 8.49 vs 2.69 ± 3.28, $P<0.01$) and SCT symptoms referred by both parents (F 9.61 ± 7.04 vs 5.41 ± 4.77, $P<0.01$; M 10.63 ± 9.57 vs 4.9 ± 4.68, $P<0.01$) and teachers (T 13.2 ± 13.01 vs 4.28 ± 5.63, $P<0.01$). No significant differences were found in hyperactivity or oppositional behaviors. Concerning academic performance, teachers report lower scores in mathematics in CH children compared to controls (6.25 ± 2.13 vs 7.1 ± 1.13, P 0.05). **Conclusion:** The results of our study suggest that CH children may have ADs, SCT symptoms and impaired mathematical abilities, despite early replacement therapy and high starting LT_4 doses.

P2-576

Relationship between Cord Blood Phthalates and Maternal and Neonatal Thyroid Functions

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Background: Phthalates are industrial chemicals extensively used as plasticizers in a variety of commercial products. Di-(2-ethylhexyl) phthalate (DEHP) is one of the most frequently used phthalates. DEHP is readily metabolized to mono-(2-ethylhexyl) phthalate (MEHP), which is more toxic than its parent compound. There are some animal and *in vitro* studies suggesting that phthalates can disrupt hypothalamus-pituitary-thyroid axis. **Objective and hypotheses:** Our aim was to investigate whether cord blood MEHP/DEHP concentrations were related with maternal or neonatal serum thyroid hormone levels. **Method:** A total of 100 newborns and their healthy mothers without any gestational complications were enrolled in the study. Cord blood MEHP and DEHP concentrations at delivery were measured by high pressure liquid chromatography method. Maternal and neonatal serum fT_4, fT_3 and TSH levels were measured at postnatal 3-7 days. **Results:** Mean cord blood MEHP and DEHP concentrations were 0.21 ± 0.8 ng/ml and 2.8 ± 0.9 ng/ml respectively. There was a negative correlation between cord blood MEHP concentrations and both maternal and neonatal serum TSH levels ($r=-0.23$, $P=0.02$ and $r=-0.29$, $P=0.006$ respectively). When adjusted for gestational age, cord blood MEHP levels were correlated with maternal fT_3 ($r=0.33$, $P=0.002$). **Conclusion:** These results suggest that prenatal MEHP exposure may potentially disrupt thyroid functions both in mothers and newborns.

P2-577

Osteoprotegerin and fT_4 Levels in Subclinical Hypothyroidism of Childhood

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Background: Osteoprotegerin (OPG) is a cytokine of the tumour necrosis factor receptor family, expressed in various cells types of the body including osteoblasts and endothelial cells. It acts as a soluble decoy receptor of RANK ligand preventing stimulation of osteoclastogenesis. In adults, subclinical hypothyroidism (SH) has been associated with cardiovascular complications. Furthermore several studies have linked OPG levels to increased cardiovascular risk. **Objective and hypotheses:** In the present study we investigated the levels of OPG and other indices of bone metabolism such as tartrate-resistant acid phosphatase (TRAP) and bone alkaline phosphatase (BAP) in children and adolescents with SH. **Method:** The present study included 129 children and adolescents with SH (TSH between 5 μIU/l and 10 μIU/l with fT_4 levels within normal range) and 346 healthy controls. In all subjects, age, gender and BMI were recorded and TSH, fT_4, OPG, TRAP and BAP were measured. Regression analysis adjusted for age and BMI after appropriate log transformations was used and statistical significance was indicated with p value <0.05. **Results:** All 475 subjects (215 males) had mean age 8.4 ± 3.62 years old. Age and BMI *z*-score were no statistically different between SH and control group. In children with SH OPG and TRAP levels were negatively correlated to the serum fT_4 levels with $r=-0.22$ ($P=0.015$) and $r=-0.16$ ($P=0.002$) respectively. No correlation was found between BAP and fT_4. The above associations were not observed in the control group. **Conclusion:** OPG and bone TRAP levels in children and adolescents with SH are negatively correlated with fT_4. Considering the probable effects of increased OPG in the vascular homeostasis, further research is needed to establish the role of childhood SH in the long-term cardiovascular risk.

P2-578

Cryptorchidism is Commonly Observed in Allan Herndon Dudley Syndrome

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Background: Allan-Herndon-Dudley syndrome (AHDS) is an x-linked mental retardation syndrome characterized by severe psychomotor retardation and pathognomonic thyroid parameters. Defects in monocarboxylate transporter 8 (MCT8), which facilitates thyroid hormone (TH) uptake and efflux across plasma membranes, have been linked to this disease. The incidence of undescended testes was reported to be 8% by Schwartz et al. On the other hand, we had the impression that cryptorchidism may be more frequent in patients with a severer phenotype. **Objective and hypotheses:** To determine whether the prevalence of cryptorchidism is higher in severely affected AHDS patients than previously reported. **Method:** A retrospective chart review of six AHDS patients seen at an academic medical center was performed. All patients demonstrated the severe phenotype; neither one could speak nor walk. Evaluation of the hypothalamic–pituitary–gonadal (HPG) axis was performed when possible. **Results:** The ages of the patients ranged from 3 years 3 months to 12 years 2 months (median: 6 years 8 months, mean: 7 years 0 months) on their last visit. Four were prepubertal, two were at the early stages of puberty. Due to undescended testes, unilateral or bilateral orchidopexy had been performed in one and three patients respectively. The contralateral testis was retractile in the patient who underwent unilateral orchidopexy. The remaining two also had retractile testes. Testis volume was 1–2 ml in all patients. **Conclusion:** Two thirds of the patients with severe AHDS manifested cryptorchidism, suggesting that sufficient TH transport may be necessary for testicular descent. The lower incidence in the initial study may be due to the large fraction of mildly affected patients in the cohort. Early detection is essential to avoid various complications that stem from this condition.

P2-579

Co-Existence of Thyroid Nodule and Thyroid Cancer in Children and Adolescents with Hashimoto Thyroiditis; A Single-Centre Study

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Background: There is currently an inadequate number of studies on nodule and malignancy development in children and adolescents with Hashimoto thyroiditis (HT).The aim of our study was to determine the rate of thyroid nodules and the nodule malignancy rate in our pediatric HT patients. **Material and methods:** Patients who were diagnosed with HT between 2004 and 2013 were included in the study. The HT diagnosis was made with the elevation of anti-TPO and anti-TG antibodies and a heterogenous appearance on thyroid ultrasonography. Fine needle aspiration biopsy (FNAB) was performed in cases with a nodule size over 1 cm or who had ultrasonography findings indicating malignancy (solid appearance, hypoechogenicity, subcapsular localisation, peripheral halo presence, microcalcification, co-existence of suspicious lymphadenopathy). **Results:** The mean age of the cases at the time of diagnosis was 12.1 ± 3.1 (5–18) years, and the mean follow-up duration was 3.1 ± 1.8 (1–9) years. A total of 39 (%13) thyroid nodules were detected in 300 patients with diagnosis of HT. FNAB was performed in five cases whose nodule size was over 1 cm and seven cases who had ultrasonography findings indicating malignancy although the nodule was ≤ 1 cm. Multiple noduler were present in five of the patients who underwent FNAB. Malignancy was not found in any patient with multiple thyroid nodules. Papillary thyroid carcinoma was diagnosed in two of the 12 cases in whom FNAB performed.

No difference was found between TSH levels in the follow-up of the patients with or without a thyroid nodule. **Conclusion:** Thyroid nodule frequency on at HT background was not found to be 13% and the thyroid malignancy frequency 0.67% in our study. A diagnosis of thyroid cancer was made in %5.1 of the patient.

P2-580

The Diagnostic, Treatment and Follow-Up Features of Childhood Thyroid Malignancies – A Preliminary Report

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Background: Thyroid cancer is a very rare malignancy of childhood. Approximately they account for 1.5% of all cancers before 15 years of age. In our country, this rate is %0.4 before 20 years of age. **Aims and objectives:** To analyses the clinical features and treatment results of children with thyroid malignancy in Turkey. **Methods:** In this multicentric and retrospective study the demographic and clinical characteristics of 124 children being followed-up for thyroid malignancies from 18 centers between 1991 and 2015 were recorded and analysed. **Results:** The age at diagnosis was 12.9 ± 4.3 years and female/male ratio was $84/40 = 2.1$. There was a family history of thyroid disease in 41 cases and thyroid cancer in nine cases. In the first application, cervical mass in 63 cases, thyroid nodule in 34 cases, and both nodule and mass in 14 cases were found. The results of cases that underwent to fine needle aspiration biopsy were benign in seven cases, suspected follicular neoplasm in 17 cases, suspected malignancy in 32 cases, and certain malignancy in 36 cases. Fourteen (11.3%) cases with disease had distant organ metastasis (13 with lung metastasis). Total thyroidectomy in 110 cases, near total in five cases, central compartment dissection in 20 cases, lobectomy in eight cases and total neck dissection in 18 cases were performed. Pathological examination revealed papillary carcinoma in 94 cases, follicular carcinoma in 14 cases, poorly differentiated carcinoma in two cases, medullary carcinoma in nine cases. Radioactive iodine ablation therapy was applied as low dose in 31% and high dose in 63% of the patients. Recurrence was observed in 14 patients. Recurrence was observed in 14 patients and mean event-free and survival times were 3.3 ± 2.3 and 4.07 ± 3.5 years respectively. **Conclusions:** The diagnostic, treatment and follow-up features of Turkish childhood thyroid malignancies were presented in a large multicenter cohort. These results are expected to contribute to evaluation, follow-up and treatment of these patients.

P3-581

New Mutation Causing Systemic Pseudohypoaldosteronism

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Background: Pseudohypoaldosteronism (PHA) is a rare heterogeneous syndrome of mineralocorticoid resistance. PHA type 1 (PHA1) is characterized by neonatal salt loss, failure to thrive, dehydration and circulatory shock. It includes two forms: renal (autosomal dominant), due to mutations in mineralocorticoid receptor coding gene NR3C2, and systemic (autosomal recessive), due to mutations in subunit genes of the epithelial sodium channel (ENaC). ENaC is constituted of three subunits, coded by SCNN1A gene located on chromosome 12p13.31 (alpha subunit), SCNN1B and SCNN1G genes on chromosome 16p12.1 (β and γ subunits respectively). Due to the rarity of the disease, no genotype-phenotype correlations have been established. The systemic form usually presents in the neonatal period with salt loss from kidney, colon, sweat and salivary glands and can show pulmonary symptoms, similar to cystic fibrosis. It is a life-long disease without improvement over time, characterized by life-threatening salt-losing crises that require extensive sodium supplementation and potassium-lowering agents. **Case presentation:** We report the case of a 6-months-old girl with systemic form of PHA1, presented in the neonatal period with dehydration, weight loss, feeding difficulties, hyperkalemia, hyponatremia, metabolic acidosis and elevated plasma aldosterone levels. Clinical conditions improved after elevated sodium and bicarbonathes supplementation, administration of ion exchange resins and nutrition with milk formula low in protein and electrolytes.

Nevertheless, frequent salt-losing crises occurred, requiring electrolytes and fluids intravenously. She also presented conjunctivitis and an altered sweat test with disventilation pulmonary area secondary to thick secretion. **Conclusions:** Genetic analysis showed a double heterozygosity in intron 8 of the SCNN1G gene: c.1294+5G>A (inherited from the father) and c.1295-10T>A (transmitted by the mother). The first mutation puts down the splicing site in 5' and is probably pathogenetic; the second one abolishes the splicing site in 3' and determines a cryptic splicing of unknown significance.

P3-582

Rapid Molecular Diagnosis of CAH by Strip Hybridisation Assay in DEMPU

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Background: Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder in which more than 90% of CAH cases are caused by mutations of the 21-hydroxylase (CYP21A2) gene. **Objective and hypotheses:** To determine the mutational spectrum in Egyptian CAH patients attending Diabetes Endocrine and Metabolism Pediatric Unit (DEMPU) including family members of CAH patients. **Method:** The use of reverse hybridization assay for the molecular diagnosis of common mutations in CYP21A2 gene in Egyptian patients with 21-OH deficiency CAH. **Results:** 98 CAH cases, diagnosed based on the clinical phenotype and elevated 17 OHP, along with 15 controls were tested by strip hybridization assay, 16 of them were further confirmed by real time PCR. Patients were 70 females and 28 males, with ages 6.2±5.3 and 4.3±4.9 years, respectively. 76 cases presented with salt wasting, 19 presented with simple virilizing form, late onset CAH was seen in only three cases. The most common mutations encountered were homozygous mutations for I2 splice, accounting for 14.2% of the analyzed cases. The most common combination seen is the combined homozygousity of three mutations namely the p.P30L, I2 splice and the 8 bp deletion present in 12% of the cases. The third most frequent genotype interestingly, was the 'normal' genotype (negative to all listed mutations) accounting for 11% of cases; meanwhile these cases expressed the typical phenotype of the disease, therefore mutations in these patients will be detected by another method (DNA sequencing) and if still found normal by DNA sequencing they will screened for other enzyme deficiencies causing CAH (3β-hydroxysteroid dehydrogenase and 11β-hydroxylase deficiencies). Furthermore, 5% of the cases showed a single heterozygous mutation, which is not sufficient to explain the observed phenotypes either. **Conclusion:** Strip hybridisation assay is an easy, rapid and cost effective testing for CAH patients and their families. **Funding:** This work was supported by the STDF; project ID (4671).

P3-583

Insufficient Mineralocorticoid Replacement as a Predictor Factor for the TART in Boys with Congenital Adrenal Hyperplasia

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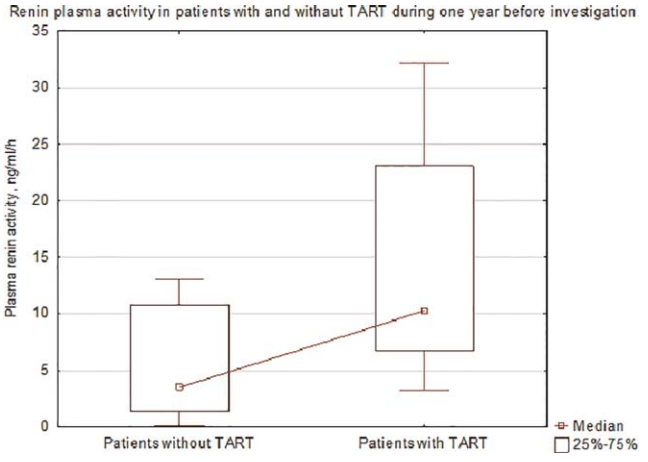
Background: Testicular adrenal rest tumor (TART) is one of the main causes of decreased fertility in men with congenital adrenal hyperplasia (CAH). TART may occurs in childhood but there is no currently identified factors influencing the development of this condition. **Objective and hypotheses:** To study the role of glucocorticoid and mineralocorticoid undertreatment in the TART development in children and adolescents with CAH, 21-hydroxylase deficiency. **Method:** We have studied 41 patients with salt-wasting (SW) form of CAH, median age 9.9 yrs (5.7; 13.4). All the patients were divided into two groups according to testis ultrasound: group 1 included patients with TARTs (30% patients (9/41)), median age 13.2 yrs (10.2; 15.9), group 2 included patients without TARTs, median age 9.9 years (5.7; 13.4). The levels of serum 17-OHP, ACTH and plasma renin activity were retrospectively evaluated during the three year period before the study and the average levels were calculated for three 1-year intervals (0–1 years, −1–2 years, −2–3 years). **Results:** We have found higher levels of plasma renin activity (10.3 (6.8; 23.1) vs 3.5 (1.4; 10.8) ng/ml per h, $P=0.039$) in the period 0–1 in roup 1, while the level 17 OHP, ACTH didn't differ between two groups. Plasma renin activity measurements in period 0–1 were less frequent in group 1 (1.0 (0.0; 1.0) vs 2.0 (2.0; 3.0) measurement per year; $P=0{,}022$). The levels of 17 OHP, ACTH, plasma %renin activity did not significantly differ in time periods −1–2 and −2–3 between two groups. **Conclusion:** TART occurs in children with poorly controlled treatment frequently:



mineralocorticoids undertreatment could be important for TARTs development.

P3-584

CYP11B1 Gene Mutations in Patients with Congenital Adrenal Hyperplasia in Turkey

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Background: Congenital adrenal hyperplasia (CAH) due to 11β-hydroxylase deficiency (11OHD), a rare autosomal recessive disorder, is the second most common form of CAH, resulting in glucocorticoid deficiency, hyperandrogenism and hypertension. **Objective and hypotheses:** To investigate the specific CAH mutations in *CYP11B1* gene and to examine for genotype-phenotype correlations. **Method:** 21 patients ($n=9$, 46, XX; $n=12$, 46, XY) with the classical 11OHD from 20 unrelated Turkish families were included in this study. Diagnosis of 11OHD was based on both clinical and hormonal criteria. Mutation screening of *CYP11B1* gene was performed using direct Sanger sequencing analysis. Known mutations were confirmed by database and literature search. Novel mutations were analyzed by in silico prediction tools (PolyPhen-2, SIFT and Mutation Taster). **Results:** The age of diagnosis at onset ranged from 6 days to 12.5 years. The rate of consanguinity was very high (75%). Four out of nine 46, XX patients received a late diagnosis (age 2–8.7 years) and were raised as males due to severe masculinization (Prader genital stages IV and V). Mutation analyses in 20 index patients revealed 12 different mutations in *CYP11B1* gene. These mutations were homozygous (HM) p.L299P (30%, 6/20), HM p.R141X (10%, 2/20), HM c.954G>A (silence, cryptic splicing; 10%, 2/20), HM IVS8+2T>C (novel splice-donor mutation, 5%, 1/20), compound heterozygous (CHT)((p.L299P)+(IVS8+2T>C); 5%, 1/20), HM p.W116C (5%, 1/20), HM p.R384Q (5%, 1/20), HM p.R448C (5%, 1/20), HM c.1449_1451delGGT (5%, 1/20), CHT ((G393+AG)+(p.L299P)); 5%, 1/20), HM c.1179_1180dupGA (novel; 5%, 1/20) and HM p.R143P (novel missense; 5%, 1/20). One patient had mutation in only one allele (p.T318M). There was no definitive correlation between genotype and phenotype. **Conclusion:** In this study, three different novel mutations were detected and the p.L299P was found to be the most common mutation. The results of the study might contribute to the establishment of molecular screening strategies. Identification of the disease causing mutations provides reliable information for genetic counseling for the families.

P3-585

Living with Adrenal Hyperplasia for Children in Primary School between 6 and 11 Years; Educational Innovation and Design of a Learning Tool for Therapeutic Education

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Background: Congenital adrenal hyperplasia (CAH) is a rare chronic disease diagnosed and treated from birth. Hormone replacement therapy is essential to lead a normal life and must be adapted to stress. Poor compliance to treatment or inefficacy is life threatening leading to high risk of by dehydration and hypoglycaemia. **Objective:** The objective of therapeutic education sessions is based on the skills needed for regular intake of pills and recognition of stress for children between 6 and 11 years in primary school. **Patients:** 21 patients aged 6–11 years were followed for CAH in our unit; ten girls and 11 boys were treated with 12–15 mg/m_2 hydrocortisone three times daily and Fludrocortisone 25–50 mg twice daily. **Method:** The therapeutic education session is conducted by a physician, a student and a nurse. It lasts 2 h and ends with a snack, one of two parents may attend. It includes an educational diagnosis (20 mn), an interactive slideshow is presented in four patients (20 mins), a 5 min break with drink and free discussion and interactive games to test their learning with gluing and cutting the personal notebook to the child (20 mn). The session concludes with an evaluation form completed by the child and his/her parents. **Results:** All parents wish to participate and they were very satisfied, the session was well suited to their child, they have recognized the need to explain the treatment. The vast majority of the children were happy, they learned about their disease and thought that that it would help them to take their treatment and to recognize stressful situations. **Conclusion:** Therapeutic education programs are essential in chronic disease management such CAH and must be developed.

P3-586

Longitudinal Changes During Prepubertal Years in Visceral Fat and Steroid Hormones – SGA vs AGA Children

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Background: Small for gestational age (SGA) children have reportedly increased DHEAS levels during prepubertal years. However, steroid hormones have not been followed longitudinally in a healthy population compared to body composition. **Aims and objectives:** To evaluate steroid hormone patterns in prepubertal children correlated to visceral fat measures. **Methods:** Body

composition was investigated with magnetic resonance (MR) of truncal fat (subcutaneous and visceral adipose tissue). Serum steroids were analyzed by mass spectrometry (LC-MS/MS) in samples taken at 8–9 in the morning. 33 (16 SGA) slightly preterm boys (gestational age 33–37 weeks) were recruited at birth and followed with MR and steroid measurements at 5, 7 and 10 years of age. Three SGA had pubic hair at 10 years of age but none testes >2 ml. **Results:** With exception to testosterone, there was a wide range of individual steroid levels during all years, and this increased over time. At 5 years cortisol ranged 157–388 nmol/l, cortison 50–96 nmol/l, 17-hydroxyprogesterone (17OH) 0.12–1.7 nmol/l, androstenedione 0.02–0.51 nmol/l and DHEAS 0.02–1.6 µmol/l. At 7 years, the mean levels of cortisol and cortisone were unchanged, but the range increased for cortisol (96–607). Contrary to this, there was no increase in range but a doubling of mean serum levels for 17OH, androstenedione and testosterone (all $P<0.05$) and almost three times for DHEAS ($P<0.01$). At ten years of age, the levels of 17OH did not increase further, but androstenedione, DHEAS and testosterone doubled in all boys ($P<0.01$ for all). Visceral fat did not correlate to cortisol, cortisone, 17OH or DHEAS. Mean DHEAS levels at 10 years were higher in SGA (2.17) compared to AGA (1.77) ($P<0.05$). **Conclusion:** Longitudinal steroid patterns differ between boys born AGA and SGA, with signs of an earlier adrenarche in SGA boys. Prepuberty, no substantial correlations were found between visceral fat and steroid hormones.

P3-587

Adrenal Atrophy Secondary to Inappropriate Oral Administration of Exogenous Steroid Presenting with Hypercalcaemia

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Background: Glucocorticoids are one of the most widely used drugs in clinical practice. Inappropriate use can result in secondary adrenal insufficiency. Adrenal insufficiency can be an occult cause of hypercalcaemia. **Case presentation:** A 3-months-old boy admitted for puffiness of the face, increase in weight. It was revealed that the patient was admitted to a hospital 2 months ago and was diagnosed to have congenital cataract and operated. The patient was then put on 5 mg prednisolone per daily. On examination, patient has symptoms of Cushing syndrome in the form of moon face and obesity. In laboratory, ACTH was <5 pg/ml and with low dose stimulation test peak cortisol response was 2.1 g/dl. Additionally, he was found to have calcium of 13.5 mg/dl (N: 9–10.6). Parathyroid hormone was appropriately suppressed, vitamin D level was normal and urinary calcium-to-creatinine ratio was increased. An ultrasound scan of the abdomen and chest radiograph showed no detectable abnormalities that could cause hypercalcemia except for bilateral adrenocortical atrophy. No underlying neoplastic or inflammatory process was identified. We excluded all causes of hypercalcaemia including CYP24A1 deficiency. ACTH stimulation test was indicative of adrenocortical insufficiency. The hypercalcaemia resolved with glucocorticoid supplementation. Now he is 9-months-old and treated with replacement hydrocortisone. He is being carefully monitoring for recovery of the hypothalamic-pituitary-adrenal axis and followed up in outpatient clinic with aim to try to gradually decrease his oral hydrocortisone replacement and restore normal adrenal function. **Conclusion:** This case illustrates the importance of considering adrenal insufficiency as a possible cause of unexplained hypercalcaemia in a patient with following withdrawal of long-term potent glucocorticoid. Although hypercalcemia is an infrequent presenting sign of adrenal insufficiency, it should be kept in mind.

P3-588

Case Report: Hypothyroidism and Acth-Deficiency Caused by TBX 19 Mutation Coincidence or Pathogenetic Correlation?

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Background: Congenital isolated ACTH-deficiency is a rare disorder characterized by low plasma ACTH and cortisol levels and normal secretion of other pituitary hormones. TBX19 is a t-box transcription factor with a specific role in the differentiation of corticotroph cells. TPIT gene mutations can be found in early onset isolated ACTH deficiency. **Case report:** We report on a 2; 6 year old girl, offspring from consanguineous parents from Turkey, born at 40 weeks gestational age by caesarian section because of placental insufficiency. The girl developed severe hypoglycaemia in the 1st day of life and cholestasis in the first weeks. Muscular hypotonia made tube feeding necessary, no further hypoglycaemias occurred. Metabolic and infectious diagnostic work-up was performed without pathological findings. Psychomotor development was delayed, at the age of 8 months central hypothyroidism was diagnosed and levothyroxine substitution was started. At the age of 15 months severe hypoglycaemia with status epilepticus occurred, anticonvulsive treatment was begun. Although neonatal hypoglycaemia, prolonged jaundice due to cholestasis and muscular hypotonia are characteristic symptoms of congenital hypoadrenalism, the diagnosis hypocortisolism was delayed and made at the age of 2 years. Further diagnostic evaluation showed isolated ACTH deficiency. Growth was normal, IGF1 and IGFBP3 were in the upper normal range. The molecular genetic testing rendered a mutation in the TBX 19 gene: Homozygous for c.856C$>$T (p.Arg286*), exon 6. The mutation has been previously

reported and is responsible for the isolated ACTH deficiency. **Conclusion:** Isolated ACTH deficiency is a rare disease and is a possible cause of congenital hypoadrenalism. To our knowledge the TBX19 Mutation is not related to central hypothyroidism.

P3-589

Deletion Mapping in Xp21 for a Family with Complex Glycerol Kinase Deficiency Using Array-Based Comparative Genomic Hybridisation

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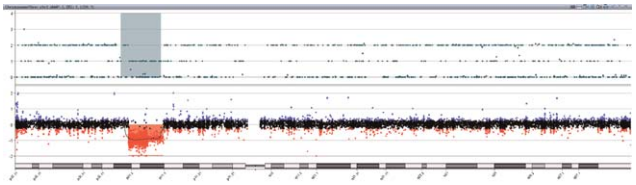
Aims: Complex glycerol kinase deficiency is caused by partial deletion of Xp21, which includes the genes responsible for glycerol kinase deficiency, adrenal hypoplasia congenita, Duchenne muscular dystrophy and intellectual disability. There are no definite dysmorphic features for this syndrome. The diagnosis is based on clinical and laboratory findings. Usually the first and most severe are the signs of adrenal hypoplasia, which, if not cured, may lead to death in a short time. The symptoms of glycerol kinase deficiency occur also early in life, but they may be masked by the deficiency of mineralocorticoids. Duchenne muscular dystrophy appears in childhood and is always accompanied by certain symptoms. **Methods:** Genomic DNA from the proband and his parents were extracted from peripheral blood leukocyte. Array-based comparative genomic hybridization of DNA from the family's peripheral blood lymphocytes was performed. **Results:** The proband, a male neonate, is the first child of healthy nonconsanguineous Chinese parents. He was born by uterine-incision delivery after 41 weeks of gestation. His birth weight was 4.0 kg. After 22 days of born, he was admitted with hyperbilirubinemia. He was diagnosed of temporary hypothyroidism, congenital adrenal hypoplasia, pneumonia and liver function damage. Treated with antibiotics and rehydration, he recovered. One month later, he presented with feeding problem and lethargy and was admitted again. He was suffered with adrenal hormone insufficiency, hypertriglyceridemia and highly increased creatine kinase. We performed array CGH and confirmed the deletion region of Xp21. Then we checked his parents and found his mother was the carrier and his father was normal. Proband's aCGH result: chrX: 28,612,178-37,392,685. The same deletion in Chromsome X was found in mother. **Conclusion:** A deletion of the Xp21 chromosomal region is found in both mother and the child. Before decades, complex glycerol kinase deficiency was usually diagnosed by clinical manifestation and Many of these patient deletions had been mapped by PCR and their breakpoints confirmed by sequencing. We confirmed that array CGH analysis can be performed to confirmed the diagnosis of patients along with the biochemical exams.



P3-590

Characterisation of Ovarian Adrenal Rest Tumours in Children and Adolescent Females with Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency

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Background: Ovarian adrenal rest tumours (OARTs) are rare in contrast to testicular adrenal rest tumours (TARTs). **Objective and hypotheses:** To summarise the characterization of OART in children and adolescent females with congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (21-OHD). **Method:** We have diagnosed four cases of CAH 21-OHD with OART in the recent 5 years and summarised the characterisations. **Results:** The four cases of CAH 21-OHD included three salt wasters and one simple virilizers. OART were diagnosed at the age of 8.9 years, 15.8 years, 21.4 years and 9.3 years respectively. There were histories of CAH poor control before the diagnosis of OART. The diagnosis could be confirmed before the operation in only one case. The diagnosis could not be made until the exploratory surgery in the other three cases. The follow-up periods of OART were 4.8 years, 4.7 years, 3.8 years and 2.7 years respectively. Removal of OART resulted in symptoms relieved at least partly. **Conclusion:** The diagnosis of OART is much more difficult than TART. Doctors should think about OART in CAH 21-OHD patients with poor control. In difficult cases of CAH with negative imaging finding may need further exploratory surgery. Removal of the OART resulted in symptoms relieved at least partly.

P3-591

Pseudohypoaldosteronism – Subtle Presentations with Critical Electrolyte Imbalances Experiences from One Hospital

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Background: Secondary pseudohypoaldosteronism presents with hyponatremia and hyperkalemia due to a transient aldosterone resistance. **Objective and hypotheses:** We recommend a check of urea and electrolytes in all infants with urinary tract infection, dehydration and failure to thrive. **Method:** A 5 month old presented with a day's history of poor feeding and two episodes of vomiting. He was afebrile with normal observations. His urine examination showed UTI and he was to be sent home on oral antibiotics. Before discharge he vomited and hence started on IV antibiotics. An incidental gas showed a sodium of 124 mEq/l and potassium of 8.6 mEq/l. ECG showed tall tented T waves. His aldosterone level was 2500 pmol/l, renin was 19 nmol/l per h, cortisol was1500 nmol/l and 17OHP was normal. His electrolytes normalised with saline, calcium and salbutamol. Investigations revealed bilateral hydronephrosis and posterior urethral valves. All electrolyte abnormalities resolved after surgery. An 8 week old presented with a 2 week history of vomiting and diarrhoea. He was clinically dehydrated with a sodium of110 mEq/l and a potassium of 8 mEq/l. Electrolytes normalised after 40 h of rehydration. He received IV antibiotics. His aldosterone was markedly raised at 47000 pmol/l (normal $<$ 850) and renin 102 nmol/l per h. His 17OHP was within the normal range and his cortisol was raised. Investigations showed UTI and bilateral hydronephrosis. His electrolyte abnormalities resolved with resolution of the infection. **Results and conclusion:** In both cases secondary pseudohypoaldosteronism was discovered by chance. In the first case, the presentation was subtle and could have been missed whilst the infant was showing cardiac manifestations of hyperkalemia. We recommend that all children presenting with hyperkalemia and hyponatremia be evaluated by renal ultrasound and urine culture. Finally these are good examples that hormonal change is transient and can be corrected when the obstruction is relieved and infection is controlled.

P3-592

Atypical Prednisone-Metabolism: Pharmacological Studies in a Boy with Classical Adrenal Hyperplasia and Suspected Malcompliance

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Background: We present a boy with classical adrenal hyperplasia (CAH) and constantly increased 17-OH-progesterone (17-OH-P) values despite multiple dose adjustments of hydrocortisone up to 18 mg/m^2 body surface and addition of fludrocortisone. After puberty, therapy was changed from hydrocortisone to prednisone without improvement of the 17-OH-P values. Non-compliance was suspected as cause of the inadequately controlled CAH. Alternatively, an atypical steroid metabolism was considered. **Objective and hypotheses:** To distinguish between non-compliance with insufficient intake of prednisone and an atypical metabolism of prednisone/prednisolone pharmacological studies were initiated. **Method:** A 24 h pharmacokinetic study of prednisone and prednisolone metabolism was performed with concomitant monitoring of 17-OH-P, ACTH, and androstendione. A second pharmacokinetic study was performed after changing from prednisone to prednisolone with individually adapted dosing intervals during the day and introduction of a modulated release prednisone formulation at night time. **Results:** The first pharmacokinetic study revealed an impaired conversion of prednisone to prednisolone with an increased clearance of prednisolone. Due to the atypically decreased half-life of prednisolone, inadequate suppression of 17-OH-P was observed in our patient. Based on these results the therapy was changed from prednisone to prednisolone with dosing intervals of only 4 h during daytime and a modulated release formulation of prednisone at night time. Due to this individually tailored therapy, 17-OH-P values were markedly improved in a second pharmacokinetic study during follow-up. **Conclusion:** Before blaming a patient with CAH on non-compliance due to raised 17-OH-P a pharmacokinetic study might be helpful to detect patients with atypical steroid metabolism. Modulated release prednisone formulation is a helpful tool to cover the longer period at night time and avoid the raise of 17-OH-P and ACTH in the early morning.

P3-593

CYP21A2 Gene Mutations Analysis in 21 Chinese Patients with Salt-Wasting form of Congenital Adrenal Hyperplasia

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Background: Studies about the genetics of congenital adrenal hyperplasia caused by 21-hydroxylase deficiency congenital adrenal hyperplasia (CAH) in Chinese children are less. **Objective and hypotheses:** Study the genotypes of Chinese probands with salt-wasting form of congenital adrenal hyperplasia caused by 21-hydroxylase deficiency (CAH) and performed pedigree-based linkage analysis. **Method:** We have performed genetic-testing (Method: qPCR and Sanger sequencing) in 21 probands with salt-wasting form of congenital adrenal hyperplasia caused by 21-hydroxylase deficiency (CAH), among which 19 patients were associated with pedigree-based linkage analysis. **Results:** Through pedigree-based conditional linkage analysis, there are two families occurred de novo mutation. The frequency of the pathogenic allele respectively, were c. 293-13C$>$G 38.78%, EX1-10DEL 20.41%, c.1069C$>$T 10.2%, c. 955C$>$T 10.2%, c. 518T$>$A 8.16%, EX3DEL 6.12%, c. 1279C$>$T 2.04%, c. 1451_1452delGGinsC 2.04%, c.740delA 2.04% in probands. The detected mutation c. 293-13C$>$ G, EX1-10DEL, c. 1069C$>$ T, c.

955C> T, c. 518T> A, EX3DEL in this study were the hot spots MariaI's research paper. Because we only involve salt-wasting type, the frequency of mutation are different. In particular, the mutation c.740delA was found for the first time that can result in premature termination of protein synthesis, leading to loss of protein function. In addition, we also carried out statistical analysis in mutation frequency among pedigree parents that higher frequency mutation were still c. 293-13C> G and EX1-10DEL. **Conclusion:** We found the new mutation point c.740delA, Others are hot spots. We found that pathogenic allel were homogenous due to partial or whole exon deletion which could lead to misjudgement in disease loci. To avoid diagnostic errors, it is recommended that large-scale deletion need to be tested first using qPCR and then detect point mutations.

P3-594

X-Linked Adrenoleucodystrophy Presenting as Addison's Disease in Childhood: A Case Report

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Background: X-Linked Adrenoleucodystrophy (X-ALD) is a rare neurodegenerative disorder characterised by impaired peroxisomal beta-oxidation of very long chain fatty acids (VLCFA; ≧C22) which is reduced to about 30% of control levels. Consequently, there is an accumulation of VLCFA in plasma and tissues, including the white matter of the brain, the spinal cord and adrenal cortex. It is caused by mutation in the ABCD1 gene encoding a peroxisomal transmembrane protein (ALDP) with the structure of an half ATP-binding cassette transporter. The clinical spectrum in males ranges from isolated adrenal insufficiency and slowly progressive mieloneuropathy to devastating cerebral demielination. **Case presentation:** An 4.8 year-old boy born to non-consanguineous parents was referred to our clinic because of oral melanosis (Peutz-Jeghers syndrome suspicion). Family history was unremarkable. Past medical history was positive for febrile seizures at age 2 and 3. On physical/neurological examination, only cutaneous-mucosal hyperpigmentation was noted. Growth was normal (height 112 cm, weight 18 kg, head circumference 50 cm). Serum cortisol (F< 10 μg/l) and ACTH concentrations (ACTH> 1250 pg/ml) were compatible with Addison's disease. Adrenal autoantibodies were negative, as well as molecular analyses of AIRE, DAX1, AAAS, MC2R and MRAP genes. The elevated plasma concentrations of VLCFA (C26:0 = 4.260 umol/, range 0.460–0.980; C26:0/C22:0 = 0.094, range < 0.096; C24:0/C22:0 = 1.66, range < 1.01) and the following molecular analysis with sequencing of ABCD1 gene established the diagnosis of X-ALD. Brain MRI and neurophysiological studies were normal. In addition to glucocorticoid therapy, the patient initiated restriction of VLCFA by reducing the intake of fatty foods. **Conclusion:** Addison's disease can be the presenting symptom of X-ALD, years before the onset of neurological symptoms. Because of the prognostic implications, the need for genetic counselling and the potential benefit of therapeutic intervention, such patients need to be identified promptly. Accordingly, we suggest that any boy with Addison's disease (in particular when circulating adrenal autoantibodies are absent) should be tested for X-ALD.

P3-595

Three Siblings with Corticosterone Methyloxidase Deficiency Type 2 due to c.1175T>C Mutation + a Novel c.788T>A Mutation in *CYP11B2* Gene

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Background: Corticosterone methyloxidase deficiency (CMOD) type 2 is an autosomal recessive disorder which presents with salt loss and failure to thrive in early childhood. We present three siblings with CMOD type 2 whose genetic analyses revealed a known c.1175T>C mutation (homozygous) and a novel c.788T>A mutation (homozygous) in *CYP11B2* gene. **Case 1:** The patient was admitted with salt loss and failure to thrive at the age of 6 months; had hyponatremia and hyperkalemia despite elevated renin and normal aldosterone levels. He was diagnosed as isolated aldosterone deficiency; salt and fludrocortisone treatment was started. At the age of 3 years, he had normal growth. He had high corticosterone, 18-OHcorticosterone and 18-OH corticosterone/aldosterone ratio (78). Genetic analysis revealed c.1175T>C mutation(homozygous) and a novel c.788T>A mutation (homozygous) in *CYP11B2* gene confirming the diagnosis of CMOD type 2. Parents with consanguineous marriage were heterozygous for both mutations. **Case 2:** At the age of 2 years, brother of case 1 admitted with failure to thrive. According to medical records, he had suffered from salt loss at the age of 3 months. Although his electrolytes were normal his height and weight SDS's were −1.99 and −2.14 respectively. With fludrocortisone treatment his growth normalized. Genetic analysis revealed the same mutation his brother had. **Case 3:** At the age of 3 months are admitted with poor weight gain, hyponatremia, mild hyperkalemia, increased renin and normal aldosterone levels. Fludrocortisone treatment resulted in adequate weight gain and normalized laboratory findings. Genetic analysis revealed the same mutation her brothers had. **Conclusion:** Genetic analyses are beneficial for diagnosis of the patients and other relatives at the risk of salt loss and failure to thrive. The mutation c.1175T>C is

known as responsible for reduction of enzyme activity; although novel mutation of c.788T > A probably affects the enzyme structure or function. Functional analyses will confirm loss of gene production.

secondary to pyeloric stenosis. With this case series, we highlight the importance of early appropriate investigations including USS in these children to avoid significant morbidity associated with delayed diagnosis of obstructive uropathy undetected by antenatal scans.

P3-596

Transient Pseudohypoaldosteronism as a Complication of Infected Obstructive Uropathy in Infancy, a Case Series

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Background: Pseudohypoaldosteronism is a rare condition of renal or systemic resistance to aldosterone, divisible into separate clinical presentations, each with a distinct physiological and genetic basis. Transient pseudohypoaldosteronism is a secondary form, characterised by reduced glomerulofiltration rate. It has been described in infants with obstructive uropathy and urinary tract infections. **Method:** We present five cases, presenting in infancy with sepsis and significant hyponatraemia, where underlying obstructive uropathy was subsequently discovered. **Results:** One female and four males presented unwell with vomiting and dehydration, between 26 days and 6 months old. All had normal antenatal scans. All were recognised as a 'sick child' before initiating investigations. Serum sodium at presentation ranged between 113 and 120 mmol/l, with potassium above 6 mmol/l. Serum osmolality was normal in presence of reduced urine osmolality. In all cases, random serum cortisol was > 1000 nmol/l. Unfortunately, aldosterone was not measured in our patients. Urinary tract infection was confirmed by pyuria. Organisms cultured included coliforms. One case was complicated by infective urinary ascites which grew Citrobacter koseri. Significant obstructive uropathy was demonstrated by ultrasound scan (USS), and further characterised by micturating cysto-urethrogram after the acute period. Management involved fluid resuscitation and intravenous antibiotics. One case, with an initial delay in the diagnosis of obstructive uropathy, was complicated by renal parenchymal abscesses and infective urinary ascites secondary to renal tract rupture. This required drainage and urostomy formation. The others made good recoveries, without further biochemical abnormalities. **Conclusion:** In infants presenting unwell with unexplained hyponatraemia and hyperkalaemia, differentials to be considered include congenital adrenal hyperplasia, pseudohypoaldosteronism secondary to obstructive uropathy or pyelonephritis, and biochemical disturbances

P3-597

Generalised Glucocorticoid Resistance in an Adolescent Girl with Severe Hyperandrogenia without Mutations in *NR3C1* Gene

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Background: Generalised glucocorticoid resistance (Chrousos syndrome) is a rare inherited disease characterized by tissue insensitivity to glucocorticoids and associated with defects in human glucocorticoid receptor (hGR) gene (NR3C1, 138040). Despite of elevated serum and urine cortisol the patients do not develop clinical picture of Cushing syndrome but present with hyperandrogenia and hypertension. **Case presentation:** We present a case in which clinical features and laboratory results correspond to the Chrousos syndrome, but no mutations were identified in the GR gene. A 15-year-old girl was investigated because of hirsutism, acne and secondary amenorrhea. Physical examination revealed significant growth of hair on the lower abdomen and acne all over the body. She had normal blood pressure. Clinical signs of Cushing syndrome were not observed. Laboratory evaluation showed altered circadian plasma cortisol and ACTH rhytm (08:00 23.3 μg/dl and 71.5 pg/ml, 23:00 16.7 μg/dl and 62.8 pg/ml respectively), increased 24-h urinary free cortisol excretion (757 μg/day; n.r. 4.0–56 μg/day) and serum testosterone (144 ng/dl n.r. < 7–75 ng/dl) and DHEA-S (368 μg/dl n.r. 44–332) concentrations. A 1-mg overnight dexamethasone suppression test (DST) showed insufficient cortisol suppression (24 μg/dl), whereas high-dose DST (8 mg) revealed an appropriate suppression (6 μg/dl). According to this data, we suspected glucocorticoid resistance. Dexamethasone therapy was started in dose 0.5 mg per day with partial effect. 5 days after the initiation of treatment testosterone and DHEA-S level decreased (72 ng/dl and 184 μg/dl respectively). Three month later her menstrual cycle restored. Sequencing of the coding region of the NR3C1 gene did not reveal any mutations. **Conclusion:** Severe hyperandrogenia in adolescents can caused by GC resistance. Other mechanisms of glucocorticoid resistance, than hGR gene mutations, remain to be elucidated.

P3-598

Remission with Cabergolin with Recurrent Hypercortisolism after Pituitary Surgery in Cushing's Disease

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Background: Diagnosis and treatment of Cushing's disease in children are challenging. **Objective and hypotheses:** Cabergolin is a long acting dopamine receptor agonist used for the treatment of patients with recurrent Cushing's disease. **Method:** year-old female patient admitted to the hospital because of short stature, amenorrhea, facial and body hair growth, rapid weight gain, hair loss and excessive acne. **Results:** Her birth weight was 3650 g, neuromotor development was normal. At the time of diagnosis her weight was 50 kg (−0.7 SDS), height 138 cm (−4.0 SDS), BMI 26.2 kg/m^2 (+1.7 SDS) and she was hypertensive. She was Tanner stage 5 with Cushingoid appearance. She was diagnosed as Cushing's disease with laboratory and clinical findings. MRI detected no pituitary adenoma. ACTH hypersecretion and lateralization to the left was found by petrosal sinus sampling. Endoscopic transnasal left hemi-hypophysectomy was performed. The operation was considered to have failed due to excessive bleeding in the pituitary. Although postoperatively hypercortisolemia persisted clinical findings for the first three months after surgery did not progress and the patient lost weight, markers of insulin resistance regressed. On the 6th month of her operation her following, clinical and laboratory evidences showed to relapse and a second transnasal left hemi-hypophysectomy was performed. Although diurnal cortisol rhythm was damaged after the second operation 24-hour urinary free cortisol was 70 μg/day (normal). 15 months after second surgery Cushing's disease relapsed clinically and biochemically. Because of the mortality and morbidity risk of the third operation. Cabergoline 1 mg/week was initiated. The patient responded to cabergoline treatment with normal urinary free cortisol and improve clinical findings on the 9th month of treatment. **Conclusion:** Cabergoline is effective in the control of cortisol secretion in the treatment of recurrent Cushing's disease.

P3-599

Phaeochromocytoma in Placental Mesenchymal Dysplasia: Who Should We Screen and for How Long?

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Background: Beckwith-Wiedemann syndrome (BWS) characterised by a group of clinical abnormalities (macrosomia, macroglossia, neonatal hypoglycaemia, omphalocoele and umbilical hernia) results from dysregulation of imprinted genes due to mosaic paternal uniparental isodisomy (patUPD) of 11p15.5. Its association with tumours of embryonic origin is well documented and screening guidelines largely aim to detect hepatoblastoma and Wilm's tumours during the first decade of life. BWS features have been noted in 25–30% of infants with placental mesenchymal dysplasia (PMD), a distinct condition with cystic placental histology and mosaicism for genome-wide patUPD. One previous case of bilateral phaeochromocytoma has been reported in PMD. **Case presentation:** We describe the case of a 12 year old female diagnosed with PMD in infancy on the basis of cystic placental histology, BWS-like clinical features and confirmatory genetic analyses. Her early years were complicated by severe congenital hyperinsulinism requiring subtotal pancreatectomy and hepatoblastoma. Antenatal sonography at 18, 22, and 28 weeks gestation documented bilateral cystic adrenomegaly which had regressed on postnatal imaging by 5 months of age. During prolonged screening a unilateral asymptomatic right sided adrenal cystic lesion was noted at age 11 which demonstrated no appreciable uptake on targeted imaging but which had increased in size over 12 months of surveillance to 3.7×3.1×3.6 cm and was secretory of noradrenaline and dopamine; this was confirmed as a phaeochromocytoma after an uneventful surgical removal of the lesion. Regular surveillance for a recurrent or left sided lesion is ongoing. **Conclusion:** BWS and PMD share clinical and genetic features and an increased risk of malignancy. Their association with phaeochromocytoma, while rare, may not be co-incidental given that there is a known association between these tumours and maternal loss of 11p15 genes. Due consideration of continued screening for phaeochromocytomas beyond the first decade of life may be appropriate for individuals with PMD.

P3-600

A Double Dose of Triples

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Background: 14½ year old girl presented with increased skin pigmentation, weakness of limbs and walking difficulty and delayed puberty. **Objective and hypotheses:** To evaluate the girl for the aetiology of hyperpigmentation, neuromuscular weakness and delayed development of secondary sexual characters. **Method:** The girl was evaluated by neurologist and found to have development delay, sensory and motor neuropathy, ataxia, amyotrophy and dysautonomia. Referred to endocrinologist for skin and mucosal hyperpigmentation. On evaluation, Serum cortisol was 125.9 nmol/l and Adreno-CorticoTrophic Hormone – 1250 pg/ml. Primary adrenal insufficiency was diagnosed and she was started on hydrocortisone and fludrocortisone replacement. Subsequent Follicle Stimulating Hormone was 38.58mu/ml and

Leutinizing Hormone 17 mu/ml, with an Estradiol value of 34 pg/ml. Ultrasound revealed infantile uterus and ovaries were not visualized. A possible diagnosis of Autoimmune Polyglandular Syndrome type 2 was entertained. **Results:** CT ordered by neurophysician revealed achalasia cardia and another MRI revealed alacrimia, thus leading to a diagnosis of Allgrove's syndrome. However, this could not explain sensory motor neuropathy and delayed puberty. MRI abdomen revealed small ovaries. Karyotype was 47XXX. **Conclusion:** A combination of *Triple A* (Allgrove's) syndrome and *Triple X* syndrome, resulted in the complex clinical findings of this disorder with development delay, sensory and motor neuropathy and delayed puberty due to 47XXX syndrome and adrenal insufficiency, achalasia, alacrimia and dysautonomia resulting from Allgrove's syndrome. She has also been started on estrogen replacement in addition to adrenal steroid replacement.

P3-601

Central Cortisol Deficiency (Isolated ACTH Deficiency) in a Child

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Background: Isolated ACTH deficiency is a very rare condition, there is only seven cases in the literature reported after infancy and the cause is still unknown. **Case study:** We are reporting 11.5 years old Qatari boy who was known to have G6PD deficiency only and who presented with generalised tonic colonic seizure at the day of admission with history of fever, ear pain and discharge fatigue and excessive sleep, and vomiting for 4 days. He had fever (39C) and hypotensive 90/50 mmHg, heart rate = 200 b/min, with progressive reduction of blood pressure. Exam revealed post- auricular tenderness suggestive of Mastoditis, no evidence of skin hyperpigmentation. His height SDS = 1.5 and BMI = 15 kg/m^2. He had pubertal hair and testicular size corresponding to Tanner II. **Results:** Investigations revealed recurrent hypoglycemia (BG = 0.9, 1.7, 1.8 mmol/l) with normal renal and hepatic functions, and normal electrolytes (Na, K, Ca, PO4 and HCO3).). Random cortisol level was taken and was 3 nmol/l during hypoglycemia. Cortisol response to ACTH was assessed using back-to-back low dose- standard dose ACTH test (table 1) IGF1 = 117 ng/ml, TSH = 4.9 mIU/l, fT_4 = 13.5 pmol/l, renin = 45.7 (NL 3-66 mU/l), aldosterone = 213 (NL (111–859) pmol/l). MRI of the brain with gadolinium enhancement revealed a small ill-defined hypo-intense focus within the right side of pituitary gland with no enhancement (small space occupying lesion). **Discussion:** We are reporting a new case of this condition at with typical presentation of sever life threating hypoglycaemia, no hyperpigmentation or electrolytes abnormalities, and the evidence of low plasma ACTH and cortisol of 0 mcg/dl before and after ACTH stimulation test who will responded to hydrocortisone with total resolution of hypoglycemia. The child was started on PO hydrocortisone of 10 mg/m^2 per day.The glucocorticoid replacement therapy resulted in total resolution of hypoglycaemia. **Summary:** This is a rare case of isolated ACTH deficiency presented sever life threating hypoglycaemia well responded to hydrocortisone with finding of MRI pituitary changes.

P3-602

The First Case of Primary Generalized Glucocorticoid Resistance in Serbia in an 8-Year-Old Boy with G679S Mutation of the *NR3C1* Gene

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Background: Primary generalized glucocorticoid resistance (PGGR) is a rare genetic condition characterised by generalised, partial target-tissue insensitivity to glucocorticoids owing to inactivating mutations of the *NR3C1* gene. **Case presentation:** An 8.5-year-old boy was hospitalized because of precocious puberty and arterial hypertension. Over the last year, the appearance of pubic hair and gynecomastia were noted. At the local centre, high levels of ACTH, cortisol, testosterone and 24-h urinary free cortisol excretion were noted, as well as hypokalemia, alkalosis and pubertal response during LHRH test. Abdominal CT scan was normal, while head MRI showed pituitary microadenoma of 3 mm in diameter. Patient was started on dexamethason and GnRH agonist therapy. Hypertension was treated by spironolactone, propranolol and captopril therapy. On admission to our hospital he was tall (90th percentile) and obese (BMI 22.2 kg/m^2 at 97th percentile) with arterial hypertension. No striae were noted and obesity was not centripetal in pattern. Serum cortisol levels were high with preserved diurnal variation. Morning serum cortisol was suppressed only after high-dose dexamethason test. Highly elevated ACTH level was noted, as well as elevated levels of 17-hydroxyprogesterone, DHEA, DHEAS, 11-deoxycorticosterone and testosterone. Urinary catecholamines, metanephrines and normetanephrines were normal. A boy and his

Table 1. ACTH (normal: 10 and 60 pg/ml), basal Cortisol (normal: 185–624 nmol/l), peak cortisol after ACTH (> 550 nmol/l). (for abstract P3-601)

Low dose ACTH			Standard dose ACTH		
Time/min	0 min (basal)	30 min	60 min	90 min	120 min
ACTH					
Pg/ml	8 (low)	-----	-----	-----	----
Cortisol (nmol/l)	<12	23	23	25	29

parents undergo genetic investigation. The entire coding region, of the human glucocorticoid receptor gene (*hGR*, *NR3C1*) and the intron/exon junctions, were amplified by PCR and bi-directionally sequenced. Boy was found to be homozygote for the mutation G679S in exon 8 of the *NR3C1* gene. **Conclusion:** We are presenting a first case of PGGR diagnosed in Serbia. Despite the fact that PGGR is a very rare disease, it is associated with severe and refractory hypertension and must be considered in a child with precocious pubarche.

P3-603

A Case of Phaeochromocytoma Diagnosed as Adrenal Incidentaloma

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Background: There are two main problems that should be solved when encountering adrenal incidentaloma. The first of these is to decide whether the adrenal mass is benign or malignant and the second is to determine whether the mass is hormonally active or not. **Objective and hypotheses:** We aimed to focus on the approach to adrenal masses in childhood. **Method:** A case of phaeochromocytoma, which was diagnosed as incidentaloma is presented. **Results:** A 17-year-old male patient was admitted with complaint of weight gain. Liver function tests were high and an abdominal ultrasonography was requested. In the ultrasonography, a uniform 60×51 mm hypoechoic mass was detected, localized in the left adrenal gland, in addition to Grade 2 steatosis and hepatomegaly. The abdominal tomography revealed the mass that consisted of areas of cystic necrosis and had dense heterogeneous contrast-enhancement. Plasma ACTH levels, serum cortisol levels, and 24-h urine free cortisol levels, which were examined for subclinical Cushing's syndrome were within normal ranges. Serum potassium, renin, and aldosterone levels, which were examined for primary hyperaldosteronism, and DHEA-S, testosterone, 17-OH progesterone levels, which were examined for androgen-secreting tumour, were all normal. A two- to three-fold increase was detected in fractionated catecholamine and metanephrine levels in 24-h urine, and the patient was diagnosed with phaeochromocytoma. As the patient's blood pressure values were accepted as hypertensive in 24-h blood pressure monitorization, selective α1 antagonist was initiated. After the preoperative preparation period, a left adrenelectomy was performed, and the pathology results were consistent with phaeochromocytoma. The patient was screened in terms of accompanying syndromes (MEN type 2, Von Hippel-Lindau Disease, Neurofibromatosis type 1, familial phaeochromocytoma/paraganglioma syndromes) and no positive findings were detected. **Conclusion:** The present case is a rare case of phaeochromocytoma that was diagnosed as adrenal incidentaloma in childhood. Phaeochromocytoma and Cushing's syndrome should be excluded in all cases with adrenal incidentaloma. Primary aldosteronism should be excluded in patients with hypertensive and/or hypokalemic episodes. A mutation analysis should be conducted on all cases with phaeochromocytoma that are diagnosed below age 20, without considering the presence of syndromic or familial characteristics.

P3-604

Severe High Blood Pressure with Renal Failure in a Neglected Case of 11β-Hydroxylase Deficient Congenital Adrenal Hyperplasia

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Background: Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders characterised by impaired cortisol synthesis. An enzymatic defect in 11-beta-hydroxylase is the second most common variant of CAH and accounts for approximately 5–8% of cases. Patients present with features of androgen excess and approximately two thirds of patients also have high blood pressure (HBP), which is initially responsive to glucocorticoid replacement, but may become a chronic condition subsequently requiring standard antihypertensive therapy. **Case presentation:** We present the case of a 16 years old girl, the child of a consanguineous couple, diagnosed with CAH in the neonatal period (ambiguous genitalia, female genetic sex. Daily treatment with glucocorticoids was initiated, but the medical follow-up and self-administered therapies were extremely irregular. There were several hospital admissions due to acute adrenal insufficiency until April 2014, when she presented severe hypertension, hyperkalemia and renal failure, precipitated by an infectious disease. Complete baseline endocrine evaluation (before restarting steroid replacement) was typical for CAH. Short stature (−3 S.D.), closed bone cartilages, amenorrhea were part of the clinical picture. Irregular medical compliance, poor medical fallow-up and inadequate stress adjustment of glucocorticoid dosage during acute infection resulted in irreversible consequences: severe hypertension, left ventricular hypertrophy, stage IV renal failure. **Conclusion:** Generally, HBP in CAH is mild to moderate, but it has the great potential for long-term morbidity and ultimately associated with left ventricular hypertrophy, retinopathy, and macrovascular events. As illustrated by our patient, while early treatment to prevent hypertension is mandatory in patients with CAH, once renal failure occurs, renal transplantation may the best choice of treatment. Early recognition and adherence to treatment can prevent morbidity and mortality.

P3-605

Delayed Diagnosis of Salt Wasting Congenital Adrenal Hyperplasia, without Complications of Cortisol Deficiency: A Case Report

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Background: In salt wasting congenital adrenal hyperplasia (SW-CAH) patients suffer from a deficiency of both cortisol and

aldosterone and develop life-threatening salt wasting crises neonatally. Treatment consists of glucocorticoids, mineralocorticoids and salt supplementation. We present a case with a two years delayed diagnosis of SW-CAH. **Case presentation:** The patient was admitted to the hospital at the age of two weeks because of poor feeding, irritability and weight loss. Laboratory analysis showed a hyperkalemia (7.5 mmol/l; normal values 3.5–4.7 mmol/l) and hyponatremia (132 mmol/l; normal values 135–145 mmol/l) with inadequately high urinary sodium excretion (46 mmol/l). Based on an abdominal ultrasound and a voiding cystourethrogram the diagnosis of posterior urethral valves was made. Consequently, the electrolyte abnormalities were attributed to secondary pseudohypoaldosteronism (PHA). The posterior urethral valves were surgically resected and the hyponatremia was treated with sodiumchloride. No glucocorticoids were prescribed. At the age of 2 years he still required high doses of oral sodiumchloride to prevent hyponatremia. Additional laboratory studies showed an increased 17-hydroxyprogesterone (309.80 nmol/l, normal values 0.2–7.4 nmol/l) and androstenedione (4.7 nmol/l, normal values 0.03–1.05 nmol/l). The diagnosis SW-CAH was made and confirmed with mutation analysis (homozygous R356W mutation, no residual enzyme activity). After initiation of treatment with hydrocortisone and fludrocortisone, he no longer needed extra sodiumchloride. **Conclusion:** We describe a SW-CAH patient who was not treated with glucocorticoids and mineralocorticoids during the first two years of life. Despite his severe enzymatic defect he had no clinically significant signs of cortisol deficiency despite undergoing surgery and suffering several illnesses. Based on the clinical observations in this patient and on *in vitro* studies showing that steroid precursors such as 17-hydroxyprogesterone and 21-deoxycortisol have an agonistic effect on the human glucocorticoid receptor, we hypothesize that in untreated CAH patients elevated levels of steroid precursors may (partially) compensate cortisol deficiency.

P3-606

Familial Hyperaldosteronism Type 1 in an Infant without Hypertension: How Important Could be the Early Treatment with Hydrocortisone?

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Background: Familial hyperaldosteronism type 1 (FH-1), is caused by the presence of a chimeric *CYP11B1/CYP11B2* gene that produces high amounts of aldosterone in response to ACTH and severe hypertension. An early diagnosis and treatment are important, not only to manage hypertension but also to avoid possible deleterious effects of aldosterone on the endothelium and cardiovascular diseases. **Clinical case:** A 3 months old boy was referred for evaluation because his mother, grandfather and uncle have FH-1 confirmed by presence of chimeric *CYP11B1/CYP11B2* gene. He was a pre-term newborn (36 weeks) and cesarean delivery due to IUGR (birth weight 2365 g.$<$p10th). He was admitted to hospital during his first week of life due to transient tachypnea, with normal electrolytes and blood pressure (75/54 mmHg, reference $<$106/62 mmHg) and unremarkable physical exam. Laboratory tests were consistent with hyperaldosteronism: serum aldosterone (SA)$>$ 120 ng/dl (reference: 5–90 ng/dl), PRA$=$ 0.39 ng/ml*h^{-1}, (reference: 2.35–37 ng/ml*h^{-1}), elevated aldosterone/renin ratio (ARR$=$307, no reference value for new-born), genetic study was performed by XL-PCR and confirmed chimeric *CYP11B1/CYP11B2* gene. The patient began treatment with cortisol (10 mg/m^2 per day) despite he had normal blood pressure. At the age of 8 months, his laboratory tests have normalized: SA (77.8 ng/dl, *n*: 5–90 ng/dl), PRA (5.2 ng/ml*h^{-1}), ARR (14.9), normal echocardiography, normal fundoscopic exam. He has remained normotensive and has shown catch up growth without Cushing signs. **Conclusion:** The early treatment with hydrocortisone (10 mg/m^2 per dau) resolves the biochemical hyperaldosteronism in a normotensive infant with FH-1; which has been associated with adverse cardiovascular, cerebrovascular, metabolic and renal sequels independently of its effects on blood pressure. We suggest genetic counsel and early diagnosis in high risk patient to have FH-1. **Funding:** Supported by Fondecyt 1130427 and 1150437, CORFO 13CTI-21526-P1 and IMII P09/016-F(ICM) Chilean Grants.

P3-607

Homozygosity for a Mutation in the CYP11B2 Gene and GH Deficiency in a Child with Severe Growth Delay

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Background: Isolated hypoaldosteronism is an autosomal recessive inherited disorder of terminal aldosterone synthesis, leading to selective aldosterone deficiency. Two different biochemical forms of this disease have been described, called aldosterone synthase deficiency or corticosterone methyl oxydase, types 1 and 2. In type 1, there is no aldosterone synthase activity and the 18 hydroxycorticosterone (18 OHB) level is low, whereas in type 2, a residual activity of aldosterone synthase persists and 18 OHB is overproduced. **Objective and hypotheses:** Isolated aldosterone synthase deficiency should be considered in neonates and infants with failure to thrive and salt wasting. Normal levels of plasma aldosterone compared with highly elevated levels of plasma

renin indicate an impaired aldosterone biosynthesis and suggest the disorder. **Case presentation:** We report the case of an infant with severe neonatal hyponatremia, hyperpotassemia and growth failure. She was born at 38 weeks of gestational age, weight: 3650 g. At the age of 1 month she was admitted to a paediatric unit for severe dehydratation, vomiting and growth failure. She showed normal values of plasma aldosterone (85 pg/ml) associated with hyperreninemia (88.2 ng/ml per h), hyponatremia and hyperkalemia. Molecular genetic analysis supported the diagnosis revealing a homozygous mutation for a pathogenic c.554C>T (p.T185I) mutation in exon 3 of the CYP11B2 Aldosterone synthase gene (8q22). Treatment with fludrocortisone and oral supplementation with sodium, resulted in correction of hyponatremia and hyperkalemia, and a transient catch-up growth. The unaffected mother was a heterozygous carrier of the T185I mutation as the sister, while the father was a heterozygous carrier of the same mutation with a severe clinical course at the neonatal period and a normal sodium balance without no further drug supplementation in adult age. However actually the girl is 1.7 years old and shows a severe failure to thrive (height: 70.3 cm; weight: 7.300 kg) with a low growth velocity (< −2 SDS). She shows a bone age delay (1 year) and low IGF1 levels (< −2 SDS for age). She underwent GH stimulation testing witch documented a GH deficiency after pharmacological induction (peak: 5.2 ng/ml). **Conclusion:** At our knowledge this is the first case report of a child with a CYP11B2 gene mutation associated with GH deficiency, a further support to growth failure.

P3-608

A Prospective Evaluation of Anthropometric and Metabolic Profile Premature Adrenarche Patients

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Background: Premature adrenarche (PA) is defined as the appearance of pubic and/or axillary hair before 8 years in girls and 9 years in boys. **Objective and hypotheses:** We aimed to evaluate the anthropometric measures, hormonal values of children with PA at time of diagnosis, distinguishing the patients with late onset congenital adrenal hyperplasia and to analyse the components of insulin resistance, obesity, hyperlipidemia, metabolic syndrome, menstrual irregularity, hirsutism and polycystic ovary syndrome (PCOS) in PA patients older than 10 years of age. **Method:** The study included 101 girls seen with PA, in Kocaeli University Pediatric Endocrinology Clinic, until May 2014. Retrospective data of the patients was recorded from department database. The 47 patients older than 10 years of age were invited to hospital for re-evaluation. Routine physical examination, height, weight, blood pressure, waist circumference, 12-h fasting serum lipid levels, fasting glucose and insulin levels, oral glucose tolerance test, serum FSH,LH, DHEAS, total testosterone, 17-OH progesterone and pelvic ultrasonography were performed. **Results:** Mean age at diagnosis was 7.82±1.1 years and mean age ot onset of symptoms was 6.73±0.91 years. Small for gestational age (SGA) birth was detected in 9.4% and late onset congenital adrenal hyperplasia in % 4. BMI was >1 SDS in 25% and bone age was advanced 35,6% of patients at time of diagnosis. Idiopathic PA (DHEAS <40 μg/dl) was 15%, typical PA (40–130 μg/dl) was 68% and exaggerated PA (130–180 mcg/dl) was 17% of patients. In children older than 10 years (prospective analysis), body mass index was >1 SDS in 19% and PCOS 27%. Hirsutism and PCOS were detected in 66% and biochemical hyperandrogenemia in all patients with history of SGA. Insulin resistance was detected in % 48.9 of patients and there was no significant difference between exaggerated adrenarche and isolated adrenarche groups due obesity, insulin resistance and PCOS. **Conclusion:** PA seems to be a benign condition but leads to insulin resistance, hirsutism and PCOS, especially in patients with history of SGA.

P3-609

The Prevalence of Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency among Children 0–18-Years-Old in Ukraine

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Background: The prevalence of congenital adrenal hyperplasia (CAH) in European countries is reported as 1:10–15 000. It depends on the quality of its diagnostics and efficacy of neonatal screening (NS). In Ukraine the NS was started in 2012. **Objective and hypotheses:** This is the first study of CAH epidemiology in children 0–18-year-old in Ukraine. **Method:** In 2013 it was created a database (DB) of Ukrainian children with CAH due to 21-hydroxylase deficiency on the basis of reports of regional paediatric endocrinologists and medical genetic centres. **Results:** The DB included 332 children: 161 (48.5%) boys and 171 (51.5%) girls. 130 patients (39.2%) had simple-virilising form (SVF) (among them 56 boys (43%)) and 192 (57.8%) children had salt-wasting form (SWF) (among them 105 boys (54.7%)), non classical form (NCF) was diagnosed in 10 (3%) girls. The ratio SWF: SVF = 1:0.7. Due to the DB 18 families had two children with CAH. During 2013 y. it had been identified 76 new cases of CAH: 47 (61.8%) infants and 29 (38.2%) children older than 1 year. Among them the SWF had 34 children (23 boys and 11 girls), SVF had 35 children (15 boys and 20 girls). NCF was diagnosed only in seven girls. In infants 30 cases (63.8%) of CAH were diagnosed by NS. According to the DB the prevalence of the CAH in Ukraine is 1:24 000, the incidence was calculated at one in 6 632 births (in 2013 it was born 503657 children in the ratio of boys and girls as 1:1). We calculated that the mean cost of diagnostic of one

confirmed case of CAH by NS was 17 542 USD. **Conclusion:** The use of NS only in boys and infants with ambiguous external genitalia will reduce the cost of screening by a half.

P3-610

Development of a Patient with Severe Pseudohypoaldosteronism due to Mutation in the α Subunit of ENaC

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Background: Pseudohypoaldosteronism type 1 (PHA1) is a rare disease which is characterised by hyponatremia, hyperkalemia, metabolic acidosis and elevated levels of aldosterone and renin. Aldosterone resistance is caused either by a mutation of the mineralocorticoid receptor gene or the epithelial sodium channel (ENaC). First causes autosomal dominant PHA1, also called renal form, second is responsible for the more severe and systemic form of PHA1 and is inherited in an autosomal recessive pattern. **Case presentation:** We present a 6 year old arabic boy, born preterm (33+1GW). The parents are related. At day 9 the boy was presented with failure to thrive, vomiting and fever. Hyponatremia (126 mmol/l) and hyperkalemia (8.9 mmol/l) but no metabolic acidosis was documented. The diagnostic work-up showed elevated levels of aldosterone 3 000 ng/l (normal: 70–830 ng/l) and renin 1 000 ng/l (normal: 5.9–132 ng/l) while 17-Hydroxyprogesterone, ACTH and cortisol were normal. Recurrent problems of the lower respiratory tract made the hypothesis systemic form of PHA1 very likely and we found an until then not described alteration in the SCNNA-Gene. Now the boy still needs sodium supplementation, but the amount could be reduced from ∼40 to ∼15 mmol/kg/d. Also he needs resonium and sodium bicarbonate, all is given by percutaneous gastrostomy. The boy develops well both somatic (height −0.14 SDS, MPH 1SDS, BMI −0.4 SDS) and mental, nevertheless we observed some life-threatening events which resulted from common infections and very frequent respiratory infections with the need for hospitalisation. **Conclusion:** PHA 1 has to be included in the differential diagnoses of severe hyponatremia. A secure access way is very important for the outcome of patients. Consequent immunisation should be performed to avoid common infections. The development with adequate therapy seems to be normal.

P3-611

Methodological Considerations into the Approach for Genetic Diagnostics of Congenital Adrenal Hyperplasia in a Girl with SW Form and Relatively Higher Needs of Mineral Corticoids

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Background: 80–95% of congenital adrenal hyperplasia (CAH) cases are due to mutations in the CYP21A2 gene encoding 21 hydroxylase**.** The residual activity of the gene defines the clinical form. Routine mutational screening of CYP21A2 defects is shown to effectively support the complex diagnostic and treatment procedure of newborns with CAH. **Objective:** We aimed to characterise the phenotype of a girl with compound heterozygosity of *CYP21A2* in order to derive a methodological approach for molecular diagnostics for patients with severe CAH. **Methods:** Clinical evaluation, Newborn screening by 17-OHP (Delfia), Biochemistry, G-banding (46XX) and MLPA (multiplex ligation-dependent probe amplification). Additional, direct sequencing of *CYP21A2* were conducted. **Clinical case:** We report a girl born at term, BW 3340 g, BL 50 cm, after first pregnancy, with severe asphyxia (Apgar 3), ambiguous genitalia (Prader 3–4), who developed aspiration pneumonia, gastroesophageal reflux. At first 17OHP screening -d7, extreme high levels were evident – 675.7 mnol/l (ISNS <20 nmol/l), the clinical diagnosis classical CAH – SW form was established and treatment introduced at d11. Genetic tests confirmed classical type of CAH due to 21-hydroxylase deficiency with compound heterozygosity (c.113G>A, Pro31Leu, Del8 E3-inherited from the mother; Q118X inherited from the father). SW phenotype is determined by Del8 E3 (frameshift) and Q118X, both of them affecting the hem binding site and leading to <1% enzyme activity. Persistent abnormal electrolytes were present until hydrocortisone and fludrocortisone dosages were several times adjusted to the high initial needs. **Conclusions:** The patient underlines once more the importance of complex screening, contemporary diagnostic and treatment procedures in the sense of personalized medicine for a most favourable outcome. Such multiple CYP21A2 mutations represent a unique opportunity for genotype-phenotype correlations. Further methodological approaches for revealing the underlying cause of patients who require higher doses of mineralocorticosteroids could be set up. **Funding:** Financial support by Medical University Sofia 30/2013, 42Д/2013.

P3-612

11β-Hydroxylase Deficiency: 20 Years Follow-Up

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Background: We presented 20-year follow-up of two patients with 11β- hydroxylase deficiency, one of them has novel mutation. **Case 1:** The male patient was diagnosed at the age of 9-months. He presented with penil growth and pubic hair. At diagnosis blood pressure was normal, his hormonal profile was distinctive of 11β-OHD, with elevated serum levels of 11-deoxycortisol

(DOC 134 ng/ml, N: 0–1.18). Hydrocortisone was introduced immediately after diagnosis. Analysis of the CYP11B1 gene revealed a novel missense mutations (R374G). At the age of 6, his testes were 4–5 cc, bone age was 12 years. Precocious puberty was diagnosed also. He was treated with GnRH analogue and ciproteron acetat for the following 5 years. At age of 11 yr, he was hypertensive (140/100 mmHg), antihypertensive therapy was started. At 19-years-old scrotal ultrasonography was consisted with adrenal rest tumour. His final height was not well within the normal range (162 cm). Currently, he is mildly overweight (body mass index, 26.2 kg/m^2) and normotensive (100/70 mmHg), and he receives glucocorticoid and antihypertensive therapy. **Case 2:** The girl presented at age 2-months with external virilisation. Growth acceleration was remarkable during childhood. Blood pressure was within the normal range. Basal DOC was elevated (8.5 ng/ml). Analysis of the CYP11B1 gene revealed two previously known missense mutations (R43Q, A386V). Her height was 141.8 cm (+2.83 SDS) with an advanced BA of 16 yr when she was 8 years She had her menarche at 12 years Now she is 20-years old, her height is 142.1 cm (−3.5 SDS) and menstrual periods are irregular. **Conclusion:** 11β-hydroxylase deficiency though rare, to understanding the clinical symptoms as well as genetic analysis for early diagnosis and management of complications are important. We want to emphasise the complications of 11β-OHD during long-term follow-up.

P3-613

Near-Final Height Outcome of Congenital Adrenal Hyperplasia due to Classic 21-Hydroxylase Deficiency in 55 Chinese Patients

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Background: Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (21-OHD) is reported inadequate growth and impairment of the final height (FH). **Objective:** We present the results of near FH in 55 patients with classic 21-OHD followed up for approximately 11.6 years(the longest 25.3 years)in a single institution, and the variables related to NFH. **Method:** Patients with classic 21-OHD followed up at our clinic, who had achieved the FH by 2014 were evaluated. FH was characterized by growth velocity less than 0.5 cm/year, and bone age greater than 15 for girls and 17 years for boys. The diagnosis was based on the clinical history, clinical status, and hormonal criteria. We compare the *z*-score for FH (FHZ) with the standard height for the population, the target height and the hydrocortisone treatment schedule. **Results:** 55 patients studied: 43 (78.2%) were female, 18 (32.7%) were salt-wasters, 14 (25.5%) were untreated. Median age at the beginning of follow-up was 4.67 years (ranging from newborn to 28.3 years). Mean follow-up until the FH was 11.6 years. Mean FH (FHZ) of the whole group was (151.88±7.41) cm (−2.0±1.2). Of the 55 patients, 27of them reached FH within the normal population range (≧ −2 S.D.). The treated patients were significantly taller than those untreated (FH (FHZ): (153.62± 7.35) cm) (−1.9±1.2) vs (146.74±4.91) cm (−2.6±0.9)).When corrected for the genetic potential, 48 of the 54 patients had NFH below their target height, and 15 patients had NFH even below −2 S.D. of the target range. A better height outcome was observed in patients with 'good' compliance, salt-wasters and non-overdose hydrocortisone administration. **Conclusion:** We conclude that growth in classic 21-OHD children is below expectation, as compared with both the reference population and the target height. Careful treatment adjustments and good compliance have a major influence on growth of children with classic 21-OHD.

P3-614

Late Diagnosis of Childhood Adrenal Insufficiency and Hypogonadotropic Hypogonadism due to DAX 1 Gene Mutation

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Background: DAX-1 mutation is a rare genetic cause of adrenal insufficiency also causing hypogonadotropic hypogonadism. **Case presentation:** The patient was born to a G1P1 mother. At the age of 1 month he developed acidosis, hyponatremia, hyperkalemia, diagnosed with congenital adrenal hyperplasia and started on hydrocortisone and fludrocortisone. No CYP 21 mutation was identified, fludrocortisone was continued for presumed hypoaldosteronism, hydrocortisone discontinued. At the age of 3 years he was rehospitalized. Labs were: BG: 40 mg/dl, Na: 128 mEq/l, K: 6.5 mEq/l, cortisol: 0.6 μg/dl, ACTH: 5102 pg/ml, aldosterone: 2.48 ng/dl. Scrotal ultrasound revealed cryptorchidism and underdeveloped right testis. He was started on hydrocortisone, continued on fludrocortisone and underwent unilateral left orchiopexy with right orchiectomy. Due to the combination of adrenal insufficiency- dysgenetic testes the possibility of DAX1 gene mutation was entertained. He was found to be hemizygote for the insertion c.1289_1290insTTAA, p.S431X exon 2 of DAX gene. **Conclusions:** DAX 1 gene mutation should be considered in the diagnosis of adrenal insufficiency in boys exhibiting signs of hypogonadism.

P3-615

Paraaortical Paragangliomas as Incidental Findings in a Female Adolescent

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Background: Paragangliomas are exceptionally rare neuroendocrine tumours for children and adolescents, located in an extraadrenal position and usually producing catecholamine. **Case presentation:** A 13.5-year-old girl with a known history of multiple exostosis disease was presented for investigation of two large nodal oval para-aortic lesions, which were incidentally found during abdominal ultrasonography. Medical history of the girl included non-autoimmune hypothyroidism since 12 year-old, under thyroxin medication and dyslipidemia during the last 4 months. Family history revealed mother, maternal grandfather and brother with multiple exostosis disease, dyslipidemia in father and hypertension, dyslipidemia and diabetes mellitus type 2 in maternal grandmother. Physical examination was normal, with symmetrical anthropometrics in the lower percentiles (10^{th}), pubertal Tanner stage IV and normal vital signs, revealing multiple exostotic lesions in upper and lower extremities and thorax, along with a café-au-lait spot in left iliac fossa. Biochemical, haematological and hormonal diagnostic laboratory evaluation was normal. However, 24-hour urine vanillylmandelic acid levels were found marginally elevated in one time-point evaluation but normal in re-screening. Abdomen magnetic resonance imaging revealed two paraaortic lesions (level of renal arteries) and biopsy under computed tomography control was performed. Pathology established the diagnosis of benign paraaortical paraganglioma. Functional imaging with 123I-MIBG single-positron emission computed tomography confirmed the presence of two metabolically active paravertebral neoplasms, consistent with paragangliomas without secondary lesions found. Additional In-111-Octreotide-Tc-99m-Tektrotyd scintigraphy did not reveale other MIBG-negative lesions. Pending patient's genetic tests are going to clarify the endogenous cause and classify the paraganglioma. **Conclusion:** Paraganglioma although rare in childhood, is important to be differentially diagnosed from more common childhood neoplasms such as neuroblastoma. Genetic investigation can offer on the final management of each individual case. After identification, surgical consultation is essential.

P3-616

Nephrotic Syndrome Developing in a Girl with Classic 21-Hydroxylase Deficiency – First Report

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Background: Nephrotic syndrome is the most common cause of kidney disease in children, but its pathogenesis remains unclear. Nephrotic syndrome in patients with congenital adrenal hyperplasia has not been reported. **Case presentation:** A 38-month-old female child was admitted with eyelid edema. She was the first child (birth weight, 3.0 kg, full term) of non-consanguineous parents of Chinese Han ethnicit. She had been diagnosed with congenital adrenal hyperplasia due to classic 21-hydroxylase deficiency, salt-wasting type in the neonatal period. Mutation analysis demonstrated that the patient was a compound heterozygote with mutations of paternal c.293-13C>G and maternal c.60G>A(p.Trp20X) in *CYP 21A2* gene. With good adherence to steroid replacement treatment with hydrocortisone and fludrocortisone, she was evaluated to be in 'Good Control'based on clinical criteria including signs of androgen excess, growth velocity and bone age increment. Laboratory examination showed that ALB was 17.4 g/l. Urinalysis showed the presence of proteinuria (+++) without hematuria. In addition, the 24-h urine protein was 1.52 g/day (95 mg/kg per day), serum creatinine was normal, triglyceride was 3.5 mmol/l, cholesterol was 9.6 mmol/l. Hepatitis B/C serology were negative. Complement C3 and C4 level were normal. The patient was diagnosed with idiopathic nephrotic syndrome, and treated with oral prednisone instead of hydrocortisone. Remission of proteinuria was attained after 5 days. Regular hydrocortisone and fludrocortisones for 21OHD were given after 5-month prednisone treatment. To this day, the patient has been followed up for 18 months with remisson of proteinuria. **Conclusion:** We first report a steroid-responsive idiopathic nephrotic syndrome occurring in 38-month girl with classic 21-hydroxylase deficiency. The relationship between nephrotic syndrome and congenital adrenal hyperplasia could contribute to the pathogenesis of nephrotic syndrome.

P3-617

Conservative Treatment Allows Substantial Improvement of Neonatal Cushing Syndrome in McCune Albright Syndrome, a 2 Year Follow-up

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Background: McCune Albright syndrome (MAS) is defined by the classic triad of precocious puberty, fibrous dysplasia of bone and café au lait skin pigmentation. However, the clinical spectrum is often more variable due to mosaic distribution of the postzygotic GNAS-mutation. Hypercortisolism occurs in a minority (5%) of patients. It is most frequently caused by nodular adrenal hyperplasia and can be life-threatening. Decisions on whether clinical management should be conservative or should involve active intervention are challenging. **Case presentation:** We report a male neonate (birth weight 2 560 g; −2.5 S.D.) with café au lait skin pigmentation as described in MAS and neonatal

cholestatic liver disease of unknown origin. At the age of 4 months he developed a Cushingoid appearance, failure to thrive (height 54.4 cm −3.2 S.D. and weight for height 3800 g −1.0 S.D.) and hypertension. Blood and saliva GNAS mutational analysis were both negative, but a mutation could be identified in tissue obtained during previous liver biopsy. Diagnostic work-up showed elevated evening saliva cortisol levels (22 nmol/l; ref1-6 nmol/l), normal urinary 24 h free cortisol excretion and variable serum cortisol levels. Cortisol levels were unsuppressed after a high-dose dexamethason suppression test. MRI showed unilateral enlargement of the adrenal gland. Therefore metyrapone treatment was initiated at the age of 6 months. A questionable clinical response and raising concerns towards the effect on cerebral white matter led to the decision to stop treatment after six months. Subsequently, growth and biochemistry were regularly assessed. At the age of 1.5 years the clinical condition of the toddler gradually improved. Currently, at age 2.5 years, failure to thrive has resolved and height growth is improving (−2 S.D. target height −0.8 S.D.). Cholestasic liver disease persists without deterioration. There are no signs of other hormonal involvement and clinical features of hypercortisolism have ameliorated. **Conclusion:** Conservative treatment of neonatal Cushing syndrome in MAS allows partial or complete recovery of Cushing syndrome, although close monitoring is required.

P3-618

A *CYP21A2* Gene Mutation in Patients with Congenital Adrenal Hyperplasia: Molecular Genetics Report from Saudi Arabia

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Background: Although the clinical presentations of congenital adrenal hyperplasia (CAH) have been studied in Saudi children, the literature review revealed no molecular report of 21-hydroxylase was published. **Objective and hypotheses:** The aim of this study was to determine the pattern of CYP21A2 gene-mutations of CAH in Saudi children. **Method:** Between January 2011 and March 2014 at King Fahad Military Complex, Dhahran, Saudi Arabia, we thoroughly examined 11 patients with CAH and two asymptomatic individuals with a history of affected siblings. Additionally, we sequenced the full coding regions of the CYP21A2 gene and screened the gene for deletion(s)/duplication(s) using the multiplex ligation-dependent probe amplification (MLPA) technique. **Results:** Nine patients had classic CAH and presented with ambiguous genitalia and/or salt-losing crisis. Two patients had the non-classic form of CAH and presented with precocious puberty. The remaining two subjects were asymptomatic. Screening the CYP21A2 gene, we detected p.Gln318X mutation in four patients, c.290-13 C>G (IVS2-13C>G) in another four, and a common deletion, involving exons 6 and 8 in three patients. **Conclusion:** Our strategy of Sanger sequencing followed by MLPA was very successful in detecting CYP21A2 mutations in all patients with CAH. **Funding:** This work was supported by King Fahad Military Complex, Dahran and College of Medicine Research Center, Deanship of Scientific Research, King Saud University, Saudi Arabia.

P3-619

Adrenal Cortex Dysfunction as a Consequence of Chronic Therapies other than Oral Steroid Therapy – Cases Presentation

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Background: An iatrogenic adrenal insufficiency as the consequence of chronic oral high doses steroid therapy is well known to developmental age medicine, other iatrogenic causes of this condition being rare. **Objective and hypotheses:** The primary objective of this study is to describe cases of adrenal dysfunction – hypofunction as well as hyperfunction - being caused by factors other than oral steroid therapy. **Method:** This is an observational and diagnostic study based on two cases admitted to endocrinology clinics. **Results:** Patient 1. at the age of 14 years, with Netherton syndrome (severe erythrodermia with ichtyosis, immunological disorders), was being diagnosed in our clinic because of short stature. During a standard examination, a morning hypocortisolism was identified. Hypoglycemia was not found. Steroid profile confirmed complete supression of adrenal cortex, and Synacthen test was typical for secondary hypoadrenalism. According to the patient's history, the most probable cause of adrenal cortex suppression was prolonged use of steroid unguents on a large skin surface. Patient 2. at the age of 5.5, with spinal muscular atrophy, was admitted to the clinic because of the appearance of pubic hair. Urine steroid profile showed significantly increased excretion of glucocorticoids and androgens. Analysis of all data and the lack of symptoms of adrenal dysfunction in the follow-up observation, suggested that a prolonged stress due to the necessity of constant use of a mechanical ventilation was responsible for the adrenal hyperfunction. **Conclusion:** Analysis of both cases led to diagnosis of rare iatrogenic causes of adrenal dysfunctions, other than a chronic oral steroid therapy: in case of patient 1 the adrenal cortex suppression was caused by steroid unguents applied externally, in case of patient 2 adrenal hyperfunction was most probably a result of prolonged stress.

P3-620

A Rare Cause of Hypertensıon: Pseudophaeochromocytoma

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Background: Although phaeochromocytoma is commonly considered in the differential diagnosis paroxysmal hypertension, only a small percentage of patients are actually diagnosed with this disorder. After exclusion of phaeochromocytoma, panic attack and pseudophaeochromocytoma should be considered in the differential diagnosis in patients with these symptoms. Here we report a rare case of pseudophaeochromocytoma presented with severe symptomatic hypertension attacks. **Case:** A 16-year-old boy was referred due to attacks of hypertension associated with palpitation with a suspected diagnosis of phaeochromocytoma. He had symptoms of sudden-onset headache, palpitation, chest pain and dyspnoea attacks which could occur even at rest for the past 6 months. Occasionally, these symptoms associated with severe hypertension (>99 p+5 mmHg) and flushing. Medical history revealed antidepressant and antipsychotic drug usage for his symptoms. On physical examination; his height was 182 cm (>97 p), weight 113 kg (>97 p), BMI 34 k/m^2 (>97 p) blood pressure 110/80 mmHg. He had acanthosis nigricans on axillary and cervical regions. Renal, cardiac, cerebral and endocrinological causes of hypertension including hyperthyroidism, hyperaldosteronism and cushing syndrome were excluded. There were no findings of end-organ damage. On 24-h monitoring, mean and maximum blood pressure measurements were 137/86 mmHg (95–97 p) and 153/92 mmHg (>99 p+5 mmHg) respectively. Despite enalapril treatment, he had hypertensive attacks. Plasma and 24-h-urinary catecholamine levels and metanephrine levels were within normal levels. MIBG scanning was also normal. After exclusion of phaeochromocytoma, pseudophaeochromocytoma was considered in this patient. **Conclusion:** In the differential diagnosis of paroxysmal hypertension, phaeochromocytoma should be considered first and investigated thoroughly. However, pseudophaeochromocytoma should be kept in mind in patients clinically suggesting phaeochromocytoma but with no laboratory findings.

P3-621

A Case of X-Linked Adrenal Hypoplasia Congenita – Adrenal Hypoplasia Congenita, Glycerol Kinase Deficiency and Duchenne Muscular Dystrophy

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Introduction: X-linked adrenal hypoplasia congenita (AHC) is caused by mutations of the NR0B1 gene encoding DAX1 on chromosome Xp21. AHC also occurs as part of a contiguous gene deletion syndrome together with Duchenne muscular dystrophy, glycerol kinase deficiency (GKD), mental retardation, or a combination of these conditions. Here, we report a male 5 years old with AHC who presented with adrenal insufficiency, GKD, and duchenne muscular dystrophy due to a mutation in the DAX-1 gene. **Case:** A 5 years old male patient who presented with vomiting, bruising, fainting, growth and failure to thrive was hospitalized. He was dehydrated, lethargic. His external genitalia was well developed with intrascrotal testes of 2 ml in volume. There was skin hyperpigmentation. The patient underwent a detailed clinical investigation including genetic testing. The initial laboratory tests showed sodium: 126 meq/l, potassium: 7.3 meq/l, glucose: 64 mg/dl, blood urea nitrogen: 32 mg/dl, basal cortisol level: 1.2 μg/dl, adrenocorticotropic hormone (ACTH) level: >1250 pg/ml, 17 hydroxyprogesteron (17-OHP): 0.1 ng/ml, dehydroepiandrosterone-sulphate: 0.1 μg/dl, testosterone: 0.1 ng/ml. Hydrocortisone, fludrocortisone and sodium chloride supplement were initiated. This treatment corrected electrolyte abnormalities and the patient improved. Adrenal glands were not visualized on abdominal ultrasound. The diagnosis was AHC. Further, we investigated for contiguous deletion syndrome. His creatinine phosphokinase (CK) (7592 U/L, normal: 35–195) and triglyceride (TG) (1045 mg/dl normal: 0–200) levels were elevated. Molecular analysis of the NR0B1 (DAX1) gene revealed a complete deletion. With these findings, we made a diagnosis of Xp21 contiguous gen deletion syndrome. **Conclusion:** DAX-1 deficiency should be kept in mind in male patients with primary adrenal insufficiency without congenital adrenal hyperplasia. Furthermore, CK and TG levels should be measured in all male patients with adrenal hypoplasia. These simple tests may help to make early diagnosis and appropriate genetic counselling for next pregnancy.

P3-622

Prenatal Treatment of Congenital Adrenal Hyperplasia: A Survey of Paediatric Endocrinologist

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Background: Prenatal dexamethasone (DXM) treatment has been proposed to prevent genital virilization in girls with congenital adrenal hyperplasia (CAH), however its safety has been questioned for potential adverse effects on the foetus and the mother. **Objective and hypotheses:** To analyse clinical practice and prenatal treatment experience with DXM during pregnancy at

risk of having her daughters with severe CAH. **Method:** An online survey to all members of SEEP was conducted to analyse the information process to parents, monitoring of prenatal and postnatal treatment and ethical issues raised by this action. **Results:** There were 49 responses from all over the country: 64% from reference centres for CAH, or tertiary hospitals. Three participants were treating more than 20 patients. 68% claim to have informed their patients, 93% focused on the efficacy of treatment, 89% on the risk for the affected foetus, 93% on the risk for the healthy foetuses and 78% on the risk for the mother. 52% were worried about treating healthy foetuses, and 21% about future cognitive impairment. 54% have ever been consulted about prenatal treatment of CAH. 34% said that this treatment was done at their hospital. 56% did not prescribe it because: they followed few patients (28%), considered it experimental (20%), referred to other canters (24%), the risks overweight the benefits (16%) or had no experience (12%). 38% conducted a meeting with endocrinologists, and/or gynaecologists to explain treatment; 35% provided verbal and written information to obtain an adequate informed consent. 70% respondents considered that treatment should be experimental. **Conclusion:** Index of response was very low; the majority have limited experience about CAH and/or prescription. Most practitioners consider this treatment experimental. It would be necessary that working groups who are investigating, publish their results and the best course to follow is clarified.

P3-623

A Case of ACTH Resistance with Generalized Hyperpigmentation at Birth

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Background: The MC2R gene (MC2R) encodes the receptor for ACTH, and MC2R mutations cause ACTH resistance. We describe a MC2R mutation-carrying ACTH resistance patient, who exhibited generalized hyperpigmentation at birth. **Objective and hypotheses:** The *MC2R* encodes the receptor for ACTH, and *MC2R* mutations cause ACTH resistance. We describe a *MC2R* mutation-carrying ACTH resistance patient, who exhibited generalised hyperpigmentation at birth. **Method:** Known genes associated with primary adrenal insufficiency were screened with use of next-generation targeted sequencing. The identified *MC2R* mutations were validated by conventional PCR-based sequencing. **Results:** Genetic analyses revealed compound heterozygous mutations: p.Asp103Asn and p.Gly226Arg. These mutations were previously reported in patients with ACTH resistance. **Discussion:** Most ACTH resistance patients were diagnosed after age 2 days due to developing of adrenal insufficiency-related symptoms (hypoglycaemia, seizures, and poor weight gain), while three patients were diagnosed during the neonatal period including our case. **Conclusion:** When we see neonates presenting symptoms suggesting adrenal insufficiency and hyperpigmentation, *MC2R* mutation should be considered as a differential diagnosis.

P3-624

Clinical and Genotypic Characterization of Simple Virilising Forms of Congenital Adrenal Hyperplasia

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Background: Congenital adrenal hyperplasia (CAH) is a recessive disease in 90% caused by 21-hidroxilase deficiency. The clinical manifestations are related with the severity of enzyme deficiency and are classified in classical and non classical forms. The classical form is the most severe with genital ambiguity in female newborns and universal virilisation. In 75% there is also aldosterone deficiency with salt wasting. **Objective and hypotheses:** To describe the phenotypical manifestations and genotype of a cohort with simple virilising (SV) form of CAH. **Method:** Retrospective analysis of 13 children with clinical SV CAH, with genetic confirmation followed in a pediatric endocrinology unit. **Results:** We analysed 13 children with SV CAH, six female. Age at diagnosis was 4.0 ± 1.05 years (mean $\pm$ S.D.), with earlier diagnosis in females. There was a prenatal diagnosis (because of family history) and a neonatal screening diagnosis. Presentation was variable with virilisation in all, precocious pubarche and growth acceleration. 66% of females with genital ambiguity needed surgical correction. Mean 17-hidroxiprogesterone at diagnosis was 121.5 ng/ml and total testosterone 179 ng/dl. The genotype included three homozygous for 1004T > A mutation (most frequent). Since diagnosis all were treated with hydrocortisone and 38.5% with fludrocortisone. LHRH analogue was used in seven patients (57% male), initiating at 6.3 ± 1.5 years and during 4.6 ± 2 years. In the five children with final height, the difference between target height and final height was -3.7 cm (S.D.: 2.9 cm). *z*-score was higher at diagnosis (mean 3.3), but similar to target height at the end of puberty (mean: -0.83). **Conclusion:** The concordance between final height and target height was related with relatively early diagnosis and treatment. Precocious virilisation in all and genital ambiguity with surgical correction need in 66% of females reinforce the attempted management. Our study supports inclusion of CAH in the newborn screening particularly for the classical form patients.

P3-625

'Reexpansion' of Testicular Tissue after Testis-Sparing Surgery in an Adolescent

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Background: Boys with 21-hydroxylase deficiency (21-OHD) develop testicular adrenal rest tumors (TARTs) at a high percentage. TARTs may lead to testicular structure damage and infertility. Treatment consists of increasing the glucocorticoid dose to suppress ACTH or surgery when necessary. **Objective and hypotheses:** We present an adolescent with TART who was treated by testicular sparing surgery at the age of 11. **Method:** A 13 -year-old boy with 21-OHD was admitted to our hospital for follow-up. He had been on hydrocortisone treatment since he was 3-years-old but his compliance to treatment was very poor. He had been operated for bilateral nodulary TARTs at the age of 11. The patient was dark skinned, with hyperpigmentation in the external genitalia. He had a testicle volume of 8 ml on each side. Laboratory examinations showed obviously increased levels of ACTH and 17-OH progesterone. Steroid dose was increased and he was advised to continue on treatment. **Results:** At the age of 15, scrotal examination and ultrasonography revealed a testicular volume appropriate for his age. **Conclusion:** Clinical examination and testicular ultrasonography should be performed in patients with 21-OHD, especially in puberty, regularly. Prompt evaluation and treatment of TARTs is mandatory. Testis sparing surgery is the choice of treatment for patients non-compliant to treatment since it may provide an appropriate testicular tissue size and prevent infertility in adulthood.

P3-626
Exogenous Cushing's Syndrome due to Misuse of Topical Corticosteroid Therapy

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Background: The development of Cushing's syndrome from topical corticosteroids in children is rare. It is most often reported in infants after misuse of high potency steroid creams for diaper dermatitis. 0.1% mometasone is a mild-strength topical steroid and so far to our knowledge no Cushing's syndrome in children after its usage was documented. **Objective and hypotheses:** The aim was to present a case of iatrogenic Cushing's syndrome in a 4-year old girl after topical mometasone treatment. **Case study:** We present a 4 year old girl who was admitted to our department because of short stature and symptoms of Cushing's syndrome. From birth she suffered from atopic dermatitis. From the 6th month till 4th year of life 0.1% mometasone cream had been applied 2–3 times a week (30 g/month) on face and body parts affected by the disease. On presentation, her height was −4.09 S.D.. She had central obesity with a moon face, redness, a buffalo hump, gluteal muscle atrophy and hypertension (BP 110/70 mmHg). No striae were observed. Blood glucose and lipids levels were within normal range. Morning and evening serum cortisol level was <22.1 nmol/l (N: 101–536). Urine free cortisol from a 24 h collection was decreased. ACTH serum levels were in normal ranges. ACTH stimulation test revealed secondary adrenal insufficiency. Abdomen ultrasound showed no adrenal abnormalities. Application of topical steroids was terminated. Replacement doses of hydrocortisone were administered (3 times/day). During the next 6 months hydrocortisone therapy was continued in gradually decreasing doses corresponding to the results of periodically performed ACTH stimulation tests. Her height velocity has increased during that time to 11.6 cm/year, she achieved height of −3.07 S.D. and normalized body proportions. **Conclusion:** Prolonged use of topical mometasone in children may result in iatrogenic Cushing's syndrome which initially presents ass growth failure. Parents of children treated with topical steroids should be thoroughly educated about their potential side effects and methods of application. The height of children with atopic dermatitis treated with topical steroids should be monitored.

P3-627
Familial Glucocorticoid Deficiency – A Case Report

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Background: Familial glucocorticoid deficiency (FGD) is a rare autosomal recessive disorder associated with isolated glucocorticoid deficiency. Melanocortin−2 receptor (MC2R), account for approximately 25% of FGD cases. **Case report:** 3 year old girl presented with recurrent hypoglycaemic episodes from day 2 of life. She was a product of consanguineous family born with a birth weight of 2.3 kg. At birth she was found to be dark in complexion from birth. Hyoglycaemic convulsion was noted on day 2 of life. There after she had three more episodes of convulsions associated with hypoglycaemia. All three episodes were associated with respiratrory tract infections associated with wheezing where she required hydrocortisone treatment. She had delay in achieving gross motor mile stones. She was at +1 S.D. for her height and −1 S.D. for her weight. Her genitalia were of normal female. Bone age was 7 years at the chronological age of 3 years. Short synacthen test revealed inadequate cortisol response. 17 hydorxyprogestreron and dihydroepiandrostenedione sulphate levels were undetectable. Both renin and aldosterone levels were normal. Adrenocorticotropic hormone level was >1400 pg/ml. Karyotype was 46, XX. There were no clinical features to suggest Allgrove syndrome. Hydrocortisone replacement therapy was started after investigations. There were no facilities to obtain a genetic confirmation of the disease. **Conclusion:** Possibility of MC2R mutation was considered due to advanced bone age together with glucocorticoid deficiency. Her diagnosis could have been considered at birth itself when she presented with hypoglycaemia together with dark complexion. Hydrocortisone treatment saved the child with acute episodes. Cortisol deficiency has to be excluded when children present with recurrent hypoglycaemia.

P3-628

Assessment of Ovarian Function and Reserve Based on Hormonal Parameters, Ovarian Volume, and Follicle Count in Euthyroid Girls with Hashimoto Thyroiditis

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Background: Among autoimmune disorders, autoimmune thyroid diseases are the most prevalent pathologies associated with premature ovarian failure. **Objective and hypotheses:** We aimed to investigate the ovarian function and reserve in euthyroid adolescents (TSH $<$ 2.5 mIU/l) diagnosed with Hashimoto thyroiditis (HT). **Method:** 30 adolescent girls (mean age 15.1 $\pm$ 1.4 years) newly diagnosed as HT with presence of high thyroid antibodies with gland heterogeneity in ultrasound and age-matched 30 healthy female subjects were enrolled the study. Anti-ovarian antibody, LH/FSH ratio, estradiol, anti-mullarian hormone (AMH), inhibin-B, and total testosterone were measured and the follicle count, ovarian volumes and uterine length were evaluated using pelvic ultrasound. **Results:** All patients were euthyroid and had normal thyroid volume. 33% (*n*: 10) of the patients had higher ovarian antibody above the limits without any ovarian dysfunction. There was no significant difference between the girls with HT and healthy controls regarding LH/FSH ratio, estradiol and inhibin-B levels. Anti-ovarian antibody (365 $\pm$ 311 vs 168.8 $\pm$ 148 ng/ml, *P*: 0.022), AMH (*P*: 0.007) and total testosterone levels were higher in HT group than the control group (*P*: 0.003). There were no significant mean measurements for total ovarian follicle count, total ovarian volume and uterine length between the groups. Anti-ovarian antibody was found to be positively correlated with LH/FSH ratio (*r*: 0.271, *P*: 0.036), AMH (*r*: 0.845, *P*: 0.0001) and inhibin-B (*r*: 0.633, *P*: 0.0001) in HT group. **Conclusion:** This study demonstrated that the HT girls had normal ovarian reserves based on measurements of AMH, inhibin B, FSH, LH/FSH ratio, estradiol and ovarian follicle counts.

P3-629

Early-onset Type 1 Diabetes and Multiorgan Autoimmunity in a Girl with Partial Monosomy 2q and Trisomy 10p

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Background: Genes in the HLA region confer about 50% of the genetic risk of type 1 diabetes (T1DM). More than 40 different genes give a minor contribution to T1DM risk, some of them are related to the immune function. **Case presentation:** A girl was referred at the age of 9 months with severe ketoacidosis in T1DM at onset. Anti-insulin autoantibodies were positive. She was the only daughter of unrelated Caucasian parents, born at term by vaginal delivery. The father suffered from Crohn disease. She showed hypotonia, facial dysmorphia with round face, prominent forehead, upslanting palpebral fissures, deep-set eyes, midface hypoplasia, and depressed nasal bridge. Methylation analysis for Prader-Willi syndrome was negative. At the age of 3 years mild mental retardation and eczema were evident and she developed juvenile idiopathic arthritis. Hypertriglyceridemia and anti-thyroperoxidase, anti-thyroglobulin autoantibodies were first detected at the age of 16 years, but thyroid function remained normal over time. She manifested growth retardation and pubertal delay with low bone mineral density and three fractures from mild trauma. Spontaneous menarche occurred at the age of 17 years. Final height was 154 cm ($-$1.7 SDS), significantly lower than mid-parental height (165 cm, 0.2 SDS). Recurrent seizures first appeared at the age of 16 years. CGH-array analysis showed a complex rearrangement involving chromosome 2q deletion and chromosome 10p duplication (2q37.3 (238.525.260–243.041.364) $\times$1, 10p15.3p14 (148.206–6.633.649) $\times$3). **Conclusion:** Analysis of 2q and 10p regions revealed that PDCD1 (programmed cell death one precursor) gene is located on chromosome 2, while IL-2RA (interleukin two receptor, alpha chain precursor/CD25) gene is located on chromosome 10. They are involved in the regulation of T cell function during immunity and tolerance. Duplication or deletion could be responsible for changes in T regulatory cells affecting their ability to suppress effector T cell function, finally increasing susceptibility for autoimmune diseases.

P3-630

CTLA4 A49G and C60T Genetic Polymorphism in Croatian Children and Young Adults with Autoimmune Thyroid Disease

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Background: Autoimmune thyroid disease (AITD), including autoimmune thyroiditis (AT) and Graves' disease (GD), is a complex autoimmune disease with a strong genetic component. The cytotoxic product of T-lymphocyte antigen-4 (CTLA4) gene, encoding a negative regulator of the T-lymphocyte immune response, was shown to be associated to AITD. **Objective and hypotheses:** To investigate the association of A49G and C60T polymorphisms of CTLA4 gene in population of Croatian children

and young adults with AITD. **Method:** The study comprised of 158 unrelated AITD patients (36 males, 122 females) with median age of 12.5 years (4.2–25.9), 127 with AT and 31 with GB. The control group consisted of 94 unrelated healthy subjects (46 males, 48 females) with median age of 12.0 years (4.6–21.5). SNP genotyping was performed using TaqMan probes (rs231775 and rs3087243) in a PCR ABI PRISM 7500 Sequence Detection System (Applied Biosystems by LT). **Results:** A49G disease associated G/G genotype of CTLA4 gene was detected more frequently in AITD patients (19.6%; OR 1.67, 95% CI 0.81–3.43; $P=0.16$), in AT patients (20.5%, OR 1.76, 95% CI 0.84–3.70, $P=0.13$) and GD patients (16.1%, OR 1.31, 95% CI 0.42–4.08, $P=0.76$) as compared to controls (12.8%), but no statistical significance for associations in none of the groups was found. Significant associations were found for the C60T disease-associated G/G genotype and AITD (OR 2.23, 95% CI 1.26–3.95; $P<0.01$), mainly for AT (OR 2.42, 95% CI 1.34–4.38; $P=0.003$), but not GB (OR 1.56, 95% CI 0.64–3.80; $P=0.33$). The risk allele G of both polymorphisms (A49G and C60T) was not significantly associated to AITD ($P=0.47$ and $P=0.10$ respectively). **Conclusion:** Our results do not indicate association of CTLA4 gene G49A polymorphism in the pathogenesis of AITD. However, the C60T polymorphism of CTLA4 gene was found to be associated to the risk of AITD, particularly to AT in our population.

P3-631

Oocyte Cryopreservation in a Patient with Premature Ovarian Failure due to Autoimmune Polyendocrine Syndrome Type 2

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Background: Autoimmune polyendocrine syndrome type 2 (APS2) is a complex disorder characterised by the obligatory occurrence of Addison disease in combination with thyroid autoimmune disorder and/or type 1 diabetes. APS 2 is the most common autoimmune polyendocrine syndrome and is primarily manifest in adult age. Premature ovarian failure (POF) is defined as sustained amenorrhea before the age of 40 years, FSH levels higher than 40 UI/l and hypoestrogenism associated with infertility, it may be due to autoimmune lymphocytic oophoritis and, when accompanied by other autoimmune diseases, may be part of APSs. **Case presentation:** We present a case of APS2 with POF that successfully underwent to oocyte cryopreservation. The patient has been followed up since the age of 5 years when she had been diagnosed for celiac disease. Since then she had strictly performed gluten free diet. She showed thyroid ultrasound suggestive for thyroiditis since the age of twelve and presented persistent anti-thyroid antibodies 2 years later, but never needed for L-thyroxine replacement. She had menarche at 14 years old with normal cycles for 4 years, followed by oligomenorrhea for 5–6 months and then secondary amenorrhea at the age of 21 years. Biochemical investigations showed hypergonadotropic hypogonadism and adrenal insufficiency with positivity of ovarian and adrenal autoantibodies. The patient underwent ovarian hyperstimulation with recombinant FSH (follitropin alpha) along with GnRH antagonist. Oocyte retrieval was performed after 57 days of stimulation. 13 oocytes were retrieved and cryopreserved with vitrification. **Conclusion:** To our knowledge this is the first case of POF due to APS2 that underwent successfully to oocyte cryopreservation. APS2 is a rare disorder that could involve many endocrine organs; in order to preserve fertility, it is important to screen periodically these patients to identify precociously women at high risk.

P3-632

Thyroid Function and Autoimmunity in Children with Newly Diagnosed Type 1 Diabetes Mellitus

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Background: Patients with type 1 diabetes (T1DM) are at a high risk of having other autoimmunological diseases. The most common coexisting disease is autoimmune thyroiditis, which is diagnosed in 15–30% diabetic patients. The incidence of the disease depends on the age, sex, and duration of T1DM. **Aims and objectives:** This study aims to assess the prevalence of anti-thyroid peroxidase antibodies and anti-thyroglobulin antibodies in children with newly diagnosed T1DM. **Method:** The analysis involved cases of new onset T1DM that were recorded from 01.01.2008 to 31.12.2014, in children $\leq$18 years from Wielkopolska Province, Poland. The measurement of the levels of TPO-ab, TG-ab and TSH, triiodothyronine and thyroxine (Immunoassay) were performed. The unpaired Student's *t*-test was used to compare continuous variables, and the χ^2 test was used to compare percentages among different patients subgroups. A P value <0.05 was considered significant. **Results:** 779 new cases of T1DM were identified. The mean age at diagnosis was 9.4 ± 4.5 years. 575 patients were positive for IA2-Ab, 519 for GAD-Ab, and 371 for IAA. 612 patients were tested for thyroid antibodies, of which 163 children were positive for at least one antibody. The prevalence of TPO-ab and TG-ab were 10.5 and 10.4% respectively. GAD-Ab has occurred most frequently in thyroid Ab positive patients ($P=0.04$) and IAA in thyroid Ab negative patients (P 0.001). TPO-ab was reported significantly more often among girls ($P=0.0008$) and children up to 10 years of age ($P=0.002$). Patients with thyroid Ab positive results revealed

elevated TSH level ($P=0.03$) and higher HbA1c level ($P=0.02$) compering to thyroid Ab negative individuals. **Conclusion:** Children with T1DM should be screened for autoimmune thyroiditis since the time of the disease onset. Risk factors for coexisting autoimmune thyroiditis are the age, sex, and positive titer of GAD-Ab.

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Hypercalcaemia as an Indication of Adrenal Insufficiency in a Patient with Autoimmune Polyendocrinopathy–Candidiasis–Ectodermal Dystrophy

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Background: Autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED), is a rare inherited disease of childhood, caused by the mutation of the *AIRE* gene on chromosome 21. It is characterized by three main diseases: chronic mucocutaneous candidiasis (CMC), chronic hypoparathyroidism (HP), and Addison's disease (AD), and can be associated with other autoimmune diseases and/or manifestations of ectodermal dystrophy. **Case presentation:** A 8-year-old girl, who was known to have HP and she was treated with calcium and calcitriol, presented at the Endocrinology Department, complaining of fatigue and abdominal pain for 5 days, without vomiting, nor fever. On examination she was pale with poor skin turgor, low normal blood pressure, and mildly tachycardic. The initial blood investigation revealed hypercalcaemia, hyponatremia, and hyperkalemia which suggested the possibility of adrenal failure. ACTH and cortisol levels, PRA, aldosterone, and anti-adrenal antibodies were requested. The patient was immediately treated with hydrocortisone, with marked clinical improvement. Calcium supplementation was initially discontinued and restarted after 24 h of hydrocortisone replacement. Lab results are as follows: Na: 125 mEq/l; K: 5.8 mEq/l; Ca: 11.6 mg/dl; cortisol: 5.84 μg/dl; ACTH: 3465 pg/ml; PRA: 148.2 ng/ml per h; and anti-androgen antibodies: positive. She was followed regularly, having nl electrolytes and low normal calcium. Eight months later a candidiasis scalp lesion was detected. In summary, this patient is diagnosed with HP, AD, and CMC, indicating the diagnosis of APECED. Molecular genetic analysis is anticipated. **Conclusion:** The presence of abdominal pain and hypercalcaemia in a patient with hypoparathyroidism should raise the suspicion of adrenal insufficiency which has to be investigated and treated on an emergency basis. Moreover, as the timing of the appearance of the individual disorders varies, a high level of suspicion regarding the development of associated endocrinopathies in particular adrenal failure, as well as informing parents of the possible symptoms is of outmost importance.

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Stevens Johnson Syndrome in a Case with Type 1 Diabetes Mellitus: Relation or Coincidence?

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Background: Stevens-Johnson syndrome (SJS) is an acute life-threatening dermatosis characterised by conjunctivitis, oral ulcerations, fever, and erythematous macules. The most important etiological factors are infections and drugs including anticonvulsants and nonsteroidal anti- inflammatories. **Objective and hypotheses:** Cases with both SJS and type 1 diabetes mellitus have been reported rarely in the literature. Herein, we report a diabetic case of recurrent SJS due to different causes. **Method:** A 10-year-old boy was admitted to our department with a 3-day history of fever, oral mucosal ulcerations and skin lesions. The patient was not under any treatment apart from insulin. He was diagnosed with type 1 diabetes 4 months ago. He has history of SJS with amoxicillin 3 years ago and clarithromycin 4 years ago. Physical examination revealed oral mucosal ulcerations, haemorrhagic crust on the lips, and bullose lesions on his thrunk and penis. Laboratory tests, including CBC, serum electrolytes, liver and renal function tests, urine analysis and sedimentation rate were within normal limits. Chest radiography was also normal. Mycoplasma PCR was negative. **Results:** The patient was diagnosed with unknown origin SJS and treated with methylprednisolone. The lesions progressively resolved in 5 days and methylprednisolone therapy was terminated. **Conclusion:** Type 1 diabetes mellitus is an autoimmune disease and associated with other autoimmune disorders such as thyroiditis and cealiac disease. SJS also occurs due to immune system defects. SJS may be associated with type 1 diabetes. New reports are required to define whether this association is a possible link in pathogenesis or coincidence.

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Radiologic Appearance is Important for Diagnosis of Autoimmune Hypophysitis

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Background: Aetiologic causes should be evaluated in patients with central diabetes insipidus. Inflammatory and malign diseases must be exclude. **Objective and hypotheses:** A 9-year-old girl suffered from polyuria and polydipsia was diagnosed CDI. Adenohypohysis height and infudibulum thickness were increased 8 and 9 mm respectively. Physical findings were consistent with Tanner stage 1, height SDS −0.48, and BMI 91 percentile. Tumor markers and adenohypophysis hormones were within normal ranges, IGF1 level was 98 ng/ml (−1/−2 SDS). Hypophysis autoantibodies and autoimmune endocrine diseases were not detected. Hypophysis gland was shrunk and infundibulary thickness was decreased to normal measurements at 18th month. However GH deficiency was detected with GH stimulation

test and 2.5 cm/year growth velocity. She was started to hGH treatment when her height SDS was −1.35 and has been grown up 9 cm/year. **Conclusion:** It can be suggested that patients with typical autoimmune hypophysitis radiologic findings such as symmetrical enlargement, intact sellar base, and nothing related with malign diseases can be followed without infundibulary biopsy.

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Functional Status of the Thyroid Gland in Children with Diabetes Mellitus Type 1

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Background and aims: To investigate the functional status of the thyroid gland in children with diabetes mellitus type 1. **Materials and methods:** In the study were included 29 (13 boys, mean age 11.3±2.7 years) patients with diabetes mellitus type 1 from iodine deficient region. The examination included thyroid ultrasound and assessment of the functional state of the thyroid system: thyroid-stimulating hormone (TSH), fT_4, fT_3, thyroid antibodies (TPO-Ab). Reference values of TSH were detected as 0.4–4.0 mkEd/ml, fT_4 9–20 pmol/l, and fT_3 4.4–9.3 pmol/l. **Results:** There were 20 (68.9%) patients with normal thyroid function. The 9 (31.1%) patients had subclinical hypothyroidism. There were not found differences in the age, sex and duration of the diabetes mellitus between group with subclinical hypothyroidism and normal thyroid function. The goitre was identified in 18 (62.1%) patients. Among children with subclinical hypothyroidism goitre was determined more often than in the group with normal thyroid function (100% vs 45%, $P=0{,}005$). The thyroid antibodies were identified in 7 (24.1%) children. In the group with subclinical hypothyroidism autoimmune thyroiditis took place in 3 (33.3%) patients but in the group normal thyroid function in 4 (20.0%, $P=0.620$). **Conclusion:** The results of the study have shown that every third children with diabetes mellitus type 1 from iodine deficient region had subclinical hypothyroidism. The goitre was identified in about 60% children and occurred twice as often in children with subclinical hypothyroidism. The autoimmune thyroiditis took place in about 25% children.

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About a Case of Basedow-Graves' Disease in a Infant

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Background: A disease of the immune system, responsible for 95% of cases of hyperthyroidism in children is very rare at this age, it affects one child in 10 million. **Presentation:** Khadija 3 year old girl admitted for goiter, no goitrogenic substances No drug Shot, No Inbreeding, goiter paternal aunt, The trouble was in the beginning 1 year a height and weight advance: +1 DS weight, height +3.2 DS, weakness, weight loss, Profuse sweating, tachycardia, irritability important, goiter, exophthalmos, cervical thyroid ultrasound increased size inhomogeneous echogenicity regular contours bilateral cervical lymphadenopathy. TSH: 0.05 uIU/ml, T_4: 100pm/l, anti-TG Ab: 82 IU/ml, anti-TPO Ab: 926 IU/ml, anti-TRAK Ab: 32 U/l. the throide scintigraphic increased size uniform intense fixation, hyper goiter capturing evoking Basedow'disease autoimmune diseases négatif. She is put under Propranolol, eye protection and Carbimazole 0.5 mg/kg per day for 3 months regression goiter, exophthalmos, T_4: 28 pmol/l, anti-TRAK Ab: 23 U/l. **Conclusion:** Need for improvements in the therapeutic management with identification of prognostic factors for disease remission, which could help to better define the optimum period of medical treatment and guide when choosing radical treatment when it will be necessary.

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The Autoimmune Polyendocrinopathies in Children and Adolescents

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Background: PEA is a rare disease characterised by the coexistence of two endocrine autoimmune deficiencies, sometimes with a non-endocrine autoimmune disease associated concomittente of occurrence or metachronous way. Depending on the age of onset of the disease and the characteristics observed, we can distinguish several subgroups. **Objective and hypotheses:** Search frequency of PEA in children and adolescents and study their phenotype. **Method:** This is a retrospective study of children and adolescents with PEA. All patients underwent a clinical examination, paraclinical exploration looking autoimmune diseases. Annual reassessments were performed. **Results:** 16 cases have been reported: 87.5% (14/16) PEA II, 12.5% PEA I. The age at diagnosis was 4 and 8 years in type 1 (both male) and 12 years (8–18) in type 2 (No sex predominance).The diabetes mellitus 1 was revealing PEA 2 with concomitant discovery ($n=4$) or metachronous (6) of autoimmune thyroiditis and other autoimmune diseases (adrenal insufficiency *n*: 2 pernicious anemia n: 1autoimmune oophoritis *n*: 3 hypoparathyroidism *n*: 1 after a mean of 12 years. adrenal insufficiency was revealing in type 1. Mucocutaneous candidiasis was present in two children with the hypoparathyroidism at diagnosis in the eldest but only appeared three years later in the younger. No other disease was observed (mean of 6 years). The PEA family were found in 25%. Therapeutically, monitoring was difficult with glycemic control poor in all cases of diabetic (Mean H A1C 8.6%), several ketotic decompensation and acute adrenal in case of adrenal insufficiency.

Discussion and conclusion: PEA is rare in children and are represented by PEA 1. Adrenal insufficiency is indicative in the majority of cases. PEA 2 can appear during adolescence. It combines Addison's disease and autoimmune thyroid disease and/or diabetes type 1. Illnesses that caused increased morbidity.

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Is Serum Serotonin Involved in the Bone Loss of Young Females with Anorexia Nervosa?

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Objective: Recent experimental data suggest that circulating serotonin interacts with bone metabolism, although this is less clear in humans. This study investigated whether serum serotonin interferes with bone metabolism in young women with anorexia nervosa (AN), a clinical model of energy deprivation. **Methods:** Serum serotonin, markers of bone turnover (osteocalcin (OC), procollagen type 1 N-terminal propeptide (PINP), type 1-C telopeptide breakdown products (CTX)), leptin, soluble leptin receptor (sOB-R), and IGF1 and its binding protein (IGFBP3) were assessed. Whole body, spine, hip and radius areal bone mineral density (aBMD) were assessed by dual-energy x-ray absorptiometry in 21 patients with AN and 19 age-matched controls. **Results:** Serum serotonin, leptin, IGF1, IGFBP3, OC, PINP and aBMD at all sites, radius excepted, were significantly reduced in AN whereas CTX and sOB-R were increased compared with controls. Serum serotonin levels were positively correlated with weight, BMI, whole body fat mass, leptin and IGF1, and negatively with CTX for the entire population. **Conclusions:** Low serum serotonin levels are observed in patients with AN. Although no direct link between low serum serotonin levels and bone mass was identified in these patients, the negative relationship between serotonin and markers of bone resorption found in all population nevertheless suggests the implication of serotonin in bone metabolism. Impact of low serum serotonin on bone in AN warrants further studies. **Funding:** This work was supported by the Centre Hospitalier Regional Universitaire (CHRU) of Montpellier (AOI UF 8751 and UF 8854) and a grant from the Société Française d'Endocrinologie Pédiatrique (SFEDP).

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Cranial MR Spectrometry Findings of Patients Aged 10–15 Years with Diagnosis of Rickets

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Objective: It is known that vitamin D has differential roles in cell proliferation, differentiation, neurotransmission and neuroplasticity in nervous system and exerts neurotrophic and neuroprotective effects, even different functions of vitamin D has been studied by advocating that vitamin D should be classified as a neurosteroid. It has been long known that vitamin D deficiency, VDR dysfunction, hyperparathyroidism and hypervitaminosis are potential causes for sensorineural hearing loss. Here, we aimed to detect pretreatment cranial spectrometry findings in patients with rickets. **Material and method:** This study included pretreatment cranial MR spectrometry evaulations of 30 patients (aged 0–15 years) who were diagnosed as rickets in Child Endocrinology department of Yüzüncü Yıl University, Prof. Dr Dursun Odabaş Medical Center between January 2014 and July 2014. **Results:** The study included 31 patients diagnosed as rickets. One patient was excluded due to declining participation. All patients underwent cranial MR spectrometry. Mean age was 2.15 ± 4.12 years (min–max: 0.07–15.13) in 30 patients with rickets. There were eight girls (25.8%) and 23 boys (74.2%). When biochemical and hormone values were studied in patients with rickets, the following results were observed: mean calcium value, 8.09 ± 1.52 mg/dl; mean phosphor value, 4.24 ± 1.53 mg/dl; mean magnesium value 1.95 ± 0.23 mg/dl; mean alkaline phosphatase value 838.23 ± 627.86;U/l; mean parathormone value, 314.82 ± 310.76 pg/ml; mean creatinine kinase value, 173.58 ± 239.73;U/l; mean albumin value 4.05 ± 1.41 g/dl; and mean 25 OH vitamin D level 5.52 ± 3.20 ng/ml. The following values were found in cranial MR spectrometry: mean choline, 105.14 (min–max: 5.99–173); mean creatinine, 84.08 (min–max: 2.96–126); N-acetyl aspartate, 127.69 (min–max: 0.01–206); mean choline/creatinine, 1.4 (min–max: 0.74–3.2) and N-acetyl aspartate/creatinine, 1.61 (min–max: 4.04). When cranial spectrometry and biochemical values were assessed by Pearson correlation, a positive correlation was detected between vitamin D level and N-acetyl aspartate/creatinine ratio. It was found that there was negative correlation between calcium level and creatinine value while positive correlation between calcium level and choline/creatinine ratio. **Conclusion:** Although this study is conducted on a limited sample size, we think that cranial MR spectrometry findings will provide useful data in monitoring patients with vitamin D deficiency and in studies investigating effects of vitamin D deficiency on brain.

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Evaluation of Bone Geometry, Quality and Bone Markers in Children with Type 1 Diabetes

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Background: Several studies have examined the relationship between type 1 diabetes and bone mass, which reported contradictory data on BMD, bone remodelling markers and bone quality. Nevertheless an incresead prevalence of osteopenia was observed among patients with duration of disease of >6 years. **Objective and hypotheses:** The aim of the study was to investigate the potential negative impact of type 1 diabetes on bone status in a group of children with type 1 diabetes, by evaluating bone geometry, quality and bone markers. **Method:** 82 children (47 males, 35 females), mean age 10.7 ± 3.0 years, height SDS 0.05 ± 0.94, BMI SDS -0.49 ± 0.87 with a mean duration of type 1 diabetes of 4.4 ± 2.9 years were studied. Bone geometry was evaluated on digitalized x-rays at the level of the 2nd metacarpal bone. The following parameters were investigated: outer diameter (D), inner diameter (d), cortical area (CA) and medullary area (MA), meanwhile bone quality was evaluated by ultrasound and expressed as amplitude dependent speed of sound (Ad-Sos) and bone transmission time (BTT). Data were converted to SDS and evaluated according to bone age. Bone markers (P1NP, CTX and BAP), sclerostin, Dkk-1, PTH and 25OHD were also assessed. Differences in bone geometry and quality were evaluated against zero, while the biochemical values of the patients were compared with a control group of 40 subjects of normal weight and height, which did not suffer of any chronic diseases. **Results:** D ($-0.99\pm$ 1,03), d (-0.42 ± 0.92), CA (-0.87 ± 0.82) and MA ($-0.46\pm$ 0.82) were all significantly smaller than in controls ($P<0.01$) while Ad-Sos (0.40 ± 1.22) and BTT (0.05 ± 0.92) were not significantly reduced. The bone markers were similar in children with type 1 diabetes and controls. When the patients were subdivided according to the HbA1c value ($<7.5\%$ and $>7.5\%$) no differences where found except for a BAP (106.43 ± 35.12 µg/l vs $84.99\pm$ 39.84 µg/l; $P<0.01$) which is a marker of bone formation. **Conclusion:** Type 1 diabetic children show a bone of reduced size but with conserved proportion and quality. Bone neoformation seems to be negatively affected by a suboptimal metabolic control.

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Comparison of Treatment Alternatives for Hypercalcemia due to Vitamin D Intoxication in Children

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Background: No large study comparing efficiency of prednisolone, alendronate and pamidronate has been conducted so far in children with hypercalcemia due to vitamin D intoxication. **Objective and hypotheses:** To perform a multicentre, retrospective study assessing clinical characteristics and treatment results. **Method:** A standard questionnaire was uploaded to an online national database system (www.favorsci.org) to collect data of children with hypercalcemia (serum calcium, >10.5 mg/dl) due to vitamin D intoxication (serum vitamin D, $>$ 150 ng/ml) who were treated in paediatric endocrinology clinics. **Results:** 74 children (mean age 1.4 ± 1.3 years, 45 males (60.8%)) from 11 canters were included. High doses of vitamin D intake was obvious in 77% of the cases. At diagnosis, mean calcium, vitamin D, and PTH levels were 15 ± 3.2 mg/dl, 400 ± 290 ng/ml, and 7.9 ± 7.8 pg/ml respectively. Calcium levels showed only mild correlation with vitamin D levels ($r=0.332$, $P=0.004$). Patients were designated into five groups according to the initial treatment regimens (See Table). During follow-up, pamidronate and calcitonin treatments were also given in three and four cases, respectively, in group 2. Initial median calcium levels were similar ($P=0.244$) among groups 2, 3, and 4 allowing comparison for treatment efficiency. The time to achieve normocalcaemia was comparable ($P=0.099$) among groups 2, 3, and 4. However, recurrence rate of hypercalcemia was significantly lower in group 4 compared to groups 2 and 3 (0 (0%), 2 (25%), and 3 (30%) respectively, $P=0.02$). **Conclusion:** In mild cases, hydration and furosemide are sufficient. For moderate cases, some of the patients given prednisolone require additional interventions (namely, pamidronate and calcitonin) to restore normocalcaemia. Pamidronate use is associated with a similar time to achieve normocalcaemia but with a lower recurrence rate. In severe hypercalcemia, physicians tended to start combination of treatments thus no comparison could be done with this group. **Funding:** This work was supported by a grant from the Pediatric Endocrinology and Diabetes Society, Turkey (2014-000522).

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Influence of Birth Weight and Total Body Less Head Bone Mineral Contents in 10–18 Korean Adolescents: Results from the Korea National Health and Nutrition Examination Surveys 2008–2010

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Background: In adolescents, as much as 51% of peak bone mass is accumulating and reaching 40% of bone mineral density (BMD) of adults. There are inconsistent reports on the associations between birth weight (BW) and bone mineral contents (BMC) in adolescents. **Objective and hypotheses:** We try to investigate the association between BW and BMC in adolescents. **Method:** Dual-energy x-ray aborptiometry assessment (DXA) of 10–18 adolescents (males = 474, females = 394) recorded in the 5th Korean National Health and Nutrition Examination Survey (KNHANES) 2008–2010 conducted by the Korean Ministry of Health and Welfare were assessed in this cross-sectional study. The subjects gestational age below 37 weeks and over 42 weeks were excluded. BW, current height, current weight, current BMI and clinical characteristics were compared according to quartiles of BMC and areal BMD of total body less head (TBLH), lumbar spine (LS) and femur neck (FN) according to age and sex. **Results:** According to TBLH BMC quartile groups, there were significant differences in BW (P for trend = 0.003 in males and <0.0001 in females), current height (P for trend = 0.0002 in males and <0.0001 in females), current weight (P for trend <0.0001 in males and <0.0001 in females), and BMI (P for trend = 0.003 in males and <0.0001 in females) and there were no significant differences in age, maternal age, and gestational age. According to LS BMC quartile groups, there were significant differences in BW (P for trend = 0.034 in males), current height (P for trend = 0.0001 in males and <0.0001 in females), current weight (P for trend <0.0001 in males and <0.0001 in females), and BMI (P for trend = 0.003 in males and <0.0001 in females) and there were no significant differences in age, maternal age, and gestational age. According to FN BMC quartile groups, there were significant differences in BW (P for trend = 0.008 in males and 0.020 in females), current height (P for trend <0.0001 in females), current weight (P for trend <0.0001 in males and <0.0001 in females), and BMI (P for trend <0.0001 in males and <0.0001 in females) and there were no significant differences in age, maternal age, and gestational age. In males, BW showed positive correlations with TBLH BMC ($r = 0.132$, $P = 0.0247$), NK_BMC ($r = 0.137$, $P = 0.0189$), TBLH BMD ($r = 0.108$, $P = 0.0458$) and NK_BMD ($r = 0.119$, $P = 0.0414$). However, BW showed only positive correlation with TBLH BMC ($r = 0.168$, $P = 0.044$) in females. In multivariate analyses, the odds ratio of having highest quartile TBLH BMC (OR = 2.157, 95% confidence interval (CI), 1.362–3.415) and highest quartile FN BMC (OR = 2.467, 95% CI, 1.183–5.144) in males and highest quartile TBLH BMC(OR = 1.985, 95% CI, 1.125–3.503) in females according to BW were significantly increased after adjusting for age, BMI, smoke, drink, exercise and gestational age. **Conclusion:** TBLH BMC is positively related to BW in Korean adolescents.

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Clinical and Molecular Characterisation of Patients with Pseudohypoparathyroidism

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Background: Pseudohypoparathyroidism (PHP) is a heterogeneous group of disorders characterized by hypocalcemia, hyperphosphataemia and Albright hereditary osteodystrophy (AHO), resulting from abnormalities of *GNAS*. **Objective and hypotheses:** This study investigated clinical features, outcomes, molecular characteristics of patients with PHP and pseudopseudohypoparathyroidism (PPHP). **Method:** Thirty one patients (15 males and 16 females) from 26 families with PHP1a, PHP1b, and PPHP were enrolled. *GNAS* mutation analysis and methylation-specific multiplex ligation-dependent probe amplification was performed to assess genetic and epigenetic alterations. Clinical data including presenting symptoms, outcomes, and endocrinologic findings were analysed retrospectively. **Results:** The age at diagnosis was 7.04 ± 5.2 years. Maternally-inherited *GNAS* mutations were identified in 14 patients of PHP1a, and paternally-transmitted mutations in 3 patients with PPHP. Twelve PHP1b patients harboured paternal uniparental disomy. Two patients of PHP1b demonstrated loss of methylation on exon 1A of *GNAS* by heterozygote deletion of nearby *STX16*. Serum total calcium and phosphorus levels at diagnosis were 7.24 ± 2.04 mg/dl and 7.2 ± 2.11 mg/dl respectively. The parathyroid hormone (PTH) and 25-hydroxyvitamin D3 levels were 367.70 ± 240 pg/ml and 28.54 ± 16.66 ng/ml respectively. The age at the start of calcium supplementation was 9.2 ± 5.6 years. Five patients (three PHP1a and two PHP1b) manifested subclinical hypothyroidism earlier than the onset of hypocalcaemia, requiring L-thyroxine therapy at age 2.0 ± 1.8 years. Two PHP1b patients were initially diagnosed with transient congenital hypothyroidism, and presented with hypocalcaemic seizure at age 10 and 17 years respectively. **Conclusion:** This study suggests that the mode of clinical presentation of patients with PHP is bimodal: hypothyroidism in the earlier age and hypocalcaemia later in childhood. Long-term follow-up for growth patterns, pubertal progression, obesity, thyroid functions, serum PTH, calcium, and phosphorus levels should be assessed on a regular basis in order to introduce appropriate treatment in these patients.

P3-645

Long Term Effects of Bisphosphonate Treatment in a Case with Infantile Onset Severe form of Juvenile Paget's Disease

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Background: Juvenile Paget's disease is a rare autosomal recessive osteopathy. Patients presenting in infancy develop severe bone deformities and may never walk. Bisphosphonate therapy is used to decrease bone turnover and it has generally good responses in milder forms of the disease. However there is no long-term experience of bisphosphonates in severe infantile forms. **Case report:** A 9 month-old boy was referred to our clinic for bone deformities. He was the third child of first degree cousins. He had bilateral sensorineural hearing loss and delay in neuromotor development. His height and weight were below the 3rd percentile. He couldn't move his extremities, even his mother couldn't cuddle him due to severe bone pain. Laboratory results showed normal serum calcium, phosphate, parathormon levels but very high alkaline phosphatase (1692 U/l; normal: 133–347). Bone ALP was also very high. Radiographic findings demonstrated bowing of femurs, widening of metaphysis and diaphysis of long bones, thickening calvarium, and periosteal reaction. Genetic analysis showed a large homozygous deletion in *TNFRSF11B* gene. Intravenous pamidronate therapy was started at a dose of 1 mg/kg every 3 months. The bone pain alleviated, motor development improved, ALP and periosteal reaction in bones decreased with the treatment. After 2 years of treatment, clinical findings began to deteriorate, so yearly dose of pamidronate was increased with a more frequent infusion schedule (every 2 months). At 4.5 years of age, bilateral humerus fractures developed and bone pain recurred restricting his movements. ALP was high (1577 U/l). Switching to another bisphosphonate zoledronic acid had a quick effect in alleviating bone pain. **Conclusion:** Intravenous pamidronate therapy is very effective in reducing bone pain, improving the bone deformities and motor development in infantile onset, severe form of juvenile Paget's disease. However this effect is transient. Changing to another bisphosphonate is an alternative treatment in case of resistance to pamidronate therapy.

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Diagnosis and Management of Gorham-Stout Disease: A Protocol Proposal

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Background: Gorham-Stout syndrome (GSD) is a rare disorder characterized by lymphangiomatosis, osteolysis and potentially lethal in the presence of chilothorax. **Objective and hypotheses:** As the management of GSD is not univocal and outcomes are unpredictable we build a multifaced protocol in order to study its natural history, biomarkers of bone disease and to treat uniformly patients. **Method:** Seven patients (five males, two females, 3 months–26.0 yrs) with GSD confirmed by biopsy underwent clinical, biochemical (Ctx, BAP, PTH, 25OHD, D-Dimer, karyotype, CGH-array) and imaging evaluations (total body- (TB) and spine DXA and STIR total body MRI) at baseline and than yearly. All patients presented osteolysis at baseline (clavicle $n=1$, ribs $n=2$, femur $n=1$, sternum $n=1$, omerus $n=1$, scapula $n=2$, ulna $n=1$, cranial basis) and one lately (parietal bone), three reported pathological fractures (clavicle $n=$one female, femur $n=$one male, rib $n=$one male) and four chylothorax. Three males underwent INFα2b treatment, two males pamidronate, two males and one female zolendronate therapy. **Results:** One male and female presented reduced TB and two males and one female reduced spine bone mineral density (z-scores between -2.8 and -1.1) with mildly increased bone turnover markers and elevated D-Dimer at baseline and during recidivism of bone or pleura. TB Stir MRI revealed aspecific involvement (hyperintensity in STIR and hypointensity in T_1) of multiple skeletal sites far from the primary localization in all and new foci of disease in two subjects. Five patients reached 4 years follow up; subjects on bisphosphonates displayed increase in BMD of about 1 z-score and all a sensible reduction of D-Dimer and pain. Karyotype and CGH were normal. **Conclusion:** As chilothorax may be the early complication of a massive osteolysis in GSD, a multidisciplinary team is warranted. Our preliminary findings suggest i) the potential usefulness of STIR TB MRI technique in detecting early skeletal foci of disease, although further studies are needed and ii) the potential of disease control by anti-angiogenic and anti-reabsorption therapies.

P3-647

Vitamin D Dependent Rickets Type 1A with Genetic Analysis in Three Chinese Children

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Background: Vitamin D dependent rickets type 1A (VDDR1A) is a rare disease caused by CYP27B1 mutations which encodes vitamin D 1α-hydoxylase. **Objective and hypotheses:** Vitamin D dependent rickets type 1A features of three Chinese cases with CYP27B1 mutations and report the experience of medication for severe hypocalcaemia. **Method:** Summarise their clinical features analyse the CYP27B1 and vitamin D receptor (VDDR) mutations. **Results:** There were one 1.2 years boy and two girls of 2 and 2.7 years old on their admissions. All of them had typical signs of rickets. Two had pathological fractures and predominant lower limbs deformities while one girl only presented with delayed walking until she was

Table 1. The CYP27B1 gene mutations in the three patients (for abstract P3-647).

Case	Mutation	Changed structure	Protein
1	485T > A/1086T > A	Missense/synonymous	162 V > D/362 T > T
2	1325CCCACCC,ins/1375,C > G	Frame shift/missense	Truncated/459R > G
3	1325 CCCACCC,ins/1442 A del	Truncated/frame shift	Truncated/protein changed

2 years old. They had hypocalcaemia (1.17–1.59 mmol/l), high alkaline phosphatase level (904.6–2240 U/l) accompanied with elevated PTH level (492.3–1238.4 pg/ml). Serum 25-(OH) D_3 levels were normal to high 27–105.2 ng/ml and 1.25–$(OH)_2D_3$ levels were low(3.21–10.02 pg/ml). In genetic analysis, they were all shown to have compound heterozygous mutations of CYP27B1 gene (see table 1). All patients were treated with calcium and calcitriol. Two of the female patient can stand up steadily 3 months after treatment and walk steadily 6 months later. A female patient suffered from 'bone hungry syndrome' was taken calcium intravenous infusion continuously for 3 days. The male patients died of severe pneumonia 1 month after discharged. **Conclusion:** Patients with VDDR 1A have a wide spectrum of clinical manifestations varying from mild to severe, even pathogenic fractures. They can be cured by high dose calcitriol and calcium supplementation. Intravenous injection may be needed because of severe bone hungry. The mutation of c.1325 CCCACCC might be a hot spot of CYP27B1 in VDRR1A, which has been reported in several of families.

P3-648

A Novel Mutation in CYP24A1 Gene in an Infant with Severe Hypercalcaemia and Unique Neurological Presentation

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Background: Loss of function mutations of CYP24A1, encoding vitamin D-24-hydroxylase, have been recently identified in idiopathic infantile hypercalcemia (IIH), a rare entity which may lead to severe complications. **Objective:** We describe a unique neurological presentation in an infant with IHH due to a novel CYP24A1 mutation. **Case presentation:** The patient was born at term after normal pregnancy to healthy non-consanguineous parents. He presented at age 7 months with weakness, failure to gain weight, and developmental arrest in the preceding 2 months. Physical examination revealed pale, thin, apathetic infant with severe hypotonia and tonic upward gaze. Laboratory investigation revealed severe hypercalcemia of 20.3 mg/dl (normal 7.2–10), ionized calcium 2.7 mmol/l (normal 1.0–1.2), phosphate 3.8 mg/dl (normal 4.7–8.0), PTH < 3 pg/ml (normal 16–87), 25-hydroxy-vitamin D 53 ng/ml (normal 30–100), and 1.25dihydroxy-vitamin D 92 pg/ml (normal 20–100). Urine calcium excretion was elevated, with calcium/creatinine ratio of 2.3 (normal for age < 0.8). Renal ultrasonography demonstrated normal-sized kidneys without nephrocalcinosis. After acute management with fluids, diuretics, pamidronate and calcitonin, calcium level decreased to 9.6 mg/dl, and the patient was discharged on low-calcium formula with no supplemental vitamin D. A month later, calcium level increased to 12.9 mg/dl and he received a second dose of pamidronate. Currently, the patient is 13 months old, with normal calcium level with no additional treatment; however, the neurological symptoms did not completely resolve. DNA was extracted from whole blood and full sequencing of the coding regions of the CYP24A1 gene was performed and revealed that the patient is a compound heterozygote of two mutations: E143del in exon 2 (a mutation that has been previously reported) and a novel truncating mutation in exon 8 (c.995_1001delCAAACAG). Each parent carried one of the mutations. The result of whole exome sequencing is pending. **Conclusion:** This patient presents a case of severe hypercalcaemia and to a novel CYP24A1 mutation associated with neurologic deterioration and tonic upward gaze that have not been previously reported in IHH.

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Continuous 1–34 rhPTH Therapy in a Girl with a PTH-Gene Defect

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Case presentation: We recently started a 9-year-old girl with hypoparathyroidism due to a mutation in the PTH gene on a pump therapy with 1–34 rhPTH. She has received calcitriol and calcium since the age of 4 months. Bilateral nephrocalcinosis stage II/III was diagnosed at a young age. So far, her renal function remains normal. During the last 18 months symptomatic hypocalcemic episodes have become more frequent despite increased calcium and calcitriol doses. Continuous rhPTH therapy was considered, encouraged by positive reports in the literature. 4 weeks before rhPTH therapy started, we gave her an i.m. depot with 100.000IU of 25-OH-D and stopped calcitriol therapy. The initial rhPTH dose was 0.5 μg/kg per day. Serum calcium, phosphate, crosslaps (CTX), osteocalcin and 1–34 PTH were measured every 2 h during the first 48 h of therapy. We observed mild nausea at the beginning of the therapy, when the calcium levels increased. The calcium: creatinine ratio in urine normalized

during the first 24 h and gradually increased over the next 48 h, which together with serum calcium levels in the upper normal range made a decrease in dose necessary. After 2 weeks, serum calcium levels of around 2.5 mmol/l have been established without additional oral calcium supplementation. However, urinary calcium excretion is still high. We documented interesting courses of endogenous calcium regulation in this human model of genetic PTH deficiency during the first days of exposure to rhPTH therapy. Both P1NP and osteocalcin levels increased by approx. 20% in the first 12 h of therapy in parallel with an initial increase in serum calcium. Levels then dropped to sub-baseline after 24 h. Regarding bone resorbtion, there was a biphasic elevation of CTX during continuous rhPTH application: CTX levels dropped after an initial peak in the first 24 hours but increased again after approx. 4 days. We speculate that after an initial effect on bone resorbtion, PTH-induced maturation of osteoclast precursors led to the delayed effects observed after 96 h. We hypothesize that activation of bone resorbtion rather than increased calcium uptake accounts for most of the initial increase in serum calcium during rhPTH treatment.

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Prevalence of Vitamin D Deficiency in Sickle Cell Anaemic Children in Jos, Nigeria

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Background: Children with SCA are six times likely to be vitamin D deficient. The prevalence of VDD in SCA is 65–100% (USA, Jeddah, Spain, England). Reasons for these include: recurrent illness, hospitalization, Increase resting energy expenditure, poor appetite, inadequate food intake, increased energy & micronutrient needs and probably excessive body covering. VDD in SCA is associated with increasing co morbidities. However, there are no studies from Nigeria the country with the highest burden of SCA. Assessing the vitamin D status of SCA children is the first step towards addressing this challenge. **Objective and hypotheses:** To determine the vitamin D status of children with sickle cell anaemia. **Method:** SCD-SS aged 2–18 years, who consent/assent to participate with no clinical evidence of extensive skin diseases, Liver disease, renal failure were enrolled into the study. Data was collected using a pre tested structured questionnaire. Blood samples for bone biochemistry (calcium, alkaline phosphatase & phosphorous) and 25 hydroxy vitamin D assay were collected and analyzed. Data was analyzed using Epi info CDC software version 3.6.1. A P-value < 0.05 was considered significant. Ethical review board of the Jos University Teaching Hospital. **Results:** The mean Serum 25 hydroxy vitamin D was $14.2 + 6.7$ ng/dl (range 6.35–34.8 ng/dl). Vitamin D deficiency was reported in 88.5%. 31% of subjects had vitamin D levels below 10 ng/dl. VDD was not associated with gender, religion, social class, but associated with age ($P > 0.05$). **Conclusion:** VDD is prevalent in 88.5% of children with SCA in Jos with 31.0% having severe deficiency (< 10 ng/dl). Children older than 10 years are more affected. **Funding:** PETCA research grant.

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Vitamin D Level and Vitamin D Receptor DNA in Children with Diabetes Mellitus Studying Sequence Analyse and Polimorphism

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Aım: İn this prospective planned study, it was aimed to study relationship between vitamin D level and vitamin D receptor gene polimorphism in patients with type l DM aged 0–18 years old. **Methods and materials:** We enrolled total 165 children in which 101 new and old diagnosed to WHO criterias TIDM patients from 0–18 years old and 64 chıldren as control group who were matched with gender and age. İn all cases serum Ca, P, PTH, ALP, Mg, albumine, 25-OH vitamin D and vitamin D receptor gne polimorphisms (Bsml, Apal, Taql, Fokl and Cdx-2) and also in patients insulin, C-peptide, HbA1c levels were studied. DNA izolations were obtained from patients and control group's peripheral blood samples for VDR gene polimorphism. Fındıngs: 43 (%42.6) of TIDM patients were female, 58 (%57,4) male. 30 (%46.9) of control group were female, 34 (%56.1). Mean age in patients was 11.69 ± 3.70 in control group was 10.7 ± 6.14 years. Mean vitamin D level in TIDM patients was 14.32 ± 6.14 ng/ml, in control group 14.17 ± 14.42 ng/ml and no statistical difference was found in vitamin D level between two groups ($P > 0.05$). Vitamin D level in %82.7 male TIDM patients was low. %55.1 of these patients were vitamin D insufficient, %27.5 vitamin D deficient. Vitamin D level was low in %81.3 of female patients with TIDM %39.5 of these patients were vitamin D insufficient and % 41.8 vitamin D deficient. No significant difference was found in low level of vitamin D between male and female patients with TIDM ($P > 0.05$). Altough there was no statistical significant difference in VDR gene polimorphisms with neither vitamin D quantative level nor categorical arrangement (deficient,insufficient and normal), in correlation analyses, significant positive correlation was confirmed between Fokl polimorphism and age, body weight and BMI level in control group. For Fokl polimorphism when adjustment was done to values above to patient and control groups, there was statistical significant difference in Fokl polimorphism in patient and control groups ($P > 0.05$). Also in correlation analyses while positive correlation was found between Fokl-Bsml and Bsml-Apal, negative correlation was found between Bsml-Taql and Apal-Taql. When patients with TIDM compared with control group no statistical significant difference was found in vitamin D gene polimorphism

(Bsml, Taql, Apal, Fokl and Cdx-2) ($P>0.05$). **Results:** İn our study while there wasn't any relationship between patients with T1DM vitamin D receptor gene polimorphisms (Bsml, Taql, Apal, Fokl and Cdx-2) it seemed as if polimorphism in Bsml or Apal and polimorphism in Taql effected each other adversly. Also while no significant difference was found in serum vitamin D level in both groups, no statistical significant correlation was determined between metabolic control and serum vitamin D level in patient group ($P>0.05$). Our study andn other contraversary studies results show that further clinical studies which will be done with same population and larger series are needed to assess anterograde vitamin D effect on TIDM development and VDR gene polimorphism. **Funding:** Proje 2014-TF-U059.

P3-652

Endocrine Function, Vitamin D and Bone Mass Status in β-Thalassemia Major

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Background: Thalassemia major is a hemoglobin disorder characterized by regular transfusion requirement. Despite the regular transfusions and advanced iron chelation protocols, endocrine complications have been reported as the frequent morbidities of the disease. **Objective and hypotheses:** The aim of the study was to i) investigate the prevalence of endocrine complications, ii) to examine the relationship between endocrine complications and metabolic parameters, iii) to investigate vitamin D status and bone mineral density in these patients. **Method:** Clinical data of 85 thalassemia major patients (46 females, 38 males) with a mean age 19.35 ± 9.5 years (3.48–53.90 years) were evaluated from the thalassemia clinic in a single centre, in Turkey. Height and weight measurement, pre-transfusion haemoglobin, serum ferritin, calcium, phosphorus, alkaline phosphatase, free thyroxine, TSH and vitamin D concentration were examined. Age, gender, disease history, drug usage, chelation protocol, bone mineral density data were recorded from case files. **Results:** Mean ferritin was 1991.14 ± 1789 ng/ml, mean haemoglobin was 8.84 ± 0.71. 73 (86.9%) of the patients were on chelation therapy with deferasirox, remaining were on deferiprone and/or deferoxamine treatment. Mean serum vitamin D concentration was 16.45 ng/dl, BMD was 0.85 ± 0.14 g/cm$^{2.}$ Lumbar spine corrected z-score was 0.44 ± 1.08 in children, T-score was -2.05 ± 1.11 in adults. There was a negative correlation between BMD and vitamin D, ALP levels ($r=-0.261$, $P=0.04$, $r=-0.48$, $P<0.01$ respectively). Three patients had diabetes and were on insulin therapy, three had impaired glucose tolerance, seven had hypogonadism, three had hypothyroidism. Among 84 patients, 45 (53%) were in pediatric age group ($\leq$18 years old), 16 out of 45 (35%) patients have short stature (height SDS ≤-2).One patient was on somatropine therapy. **Conclusion:** Most frequent complication was vitamin D deficiency and osteopenia/osteoporosis in our cohort. We want to highlight the importance of vitamin D replacement and early prevention of osteoporosis in thalassemia patients.

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Late Sequel of Meningococcemia: Presenting as Skeletal Dysplasia

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Background: Although there is considerable literature dealing with the diagnosis, initial management and early complications of meningococcemia, data about late complications is scarce. Growth plates may be influenced permanently by ischemia leading to late orthopedic complications such as leg length discrepancy, angular deformity and distorted body proportion. We present a patient with disproportionate short stature due to late squeal of meningococcemia who was misdiagnosed and followed as skeletal dysplasia for many years. **Case presentation:** A 12–year-8-month-old boy was referred for short stature, limb length discrepancy and angulation of legs which became apparent at 5 years of age who was diagnosed and followed as skeletal dysplasia before. He was born at term as child of healthy non-consanguineous parents. His birth weight was 3,250 g and height 50 cm. At 5 months of age he was hospitalized in an ICU for 20 days due to meningococcemia. He survived with phalangeal amputations. He later had surgery for the correction of genu varum at age 4 years. His height was 125 cm (-3.77 SDS), weight 57.8 kg (0.97 SDS) and BMI 37 kg/m^2 (3.68 SDS). Sitting height to height ratio (0.61) was increased, 'arm span-height' was decreased (-8 cm, <-2 S.D.) with mesomelic shortening of both upper and lower extremities.The right leg was 3 cm shorter than left leg with genu varum deformity despite corrective surgery. Second and fourth distal phalanges of right hand and distal phalanx of the fifth finger on the left were amputated. Soft tissue scarring of the scalp, both wrists, forearms and legs including ankles were also noted. Most striking radiological feature was early closure of epiphysis and resultant herniation into metaphyseal bone giving 'ball and socket' sign in extremities. In light of similar cases reported in literature and with almost identical radiological features mentioned above, we confidently conclude that he is suffering a post-meningococcal late skeletal sequelae. **Conclusion:** Epiphyseal growth plate injury secondary to ischemia during infantile meningococcemia may be insidious initially and may present years later with skeletal disturbances. Referrals for disproportionate short stature and possible skeletal dysplasia must not blind paediatricians in the field towards relevant clinical history taking.

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LRP5 Mutation in a Boy with Osteopetrosis and Normal Stature Despite Low IGF1 Levels

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Background: Osteopetrosis is a genetic disorder characterised by increased bone mass due to defective osteoclast formation and function. The genetic basis of this disease has been largely uncovered. Osteopetrosis is commonly associated with short stature but serum IGF1 and spontaneous or provocative GH levels are usually within the normal range. Thus, GH/IGF1 deficiency is unlikely to be the cause of the short stature of these patients. **Aim:** To study the underlying genetic mechanisms and the GH/IGF1 axis of a tall patient with radiological features of osteopetrosis. **Methods:** A 19 year-old male patient with osteopetrosis was studied. His final height was 179 cm (0.43 SDS), above family target height. The patient was first seen in the clinic at the age of 14 years due to delayed puberty (G1P1). Bone-age investigation showed increased bone mass and bone densitometry was performed. Blood samples were obtained for molecular analysis and laboratory tests for pituitary function were carried out. **Results:** Lumbar spine bone mass was increased (z-score $= +5.1$). Calcifications were present within the skull base but the brain MRI was normal. At the age of 16 years, the patient had a femural fracture with abnormal consolidation. Heterozygous mutation of LRP5 gene was detected: A1330V (GCG > GTG) (C/T). Serum IGF1 levels were consistently low (< -2 SDS) for his age and pubertal stage. Provocative tests performed after priming with sexual steroids (15 and 16 years) or testosterone replacement (19 years) resulted in undetectable GH but normal cortisol levels. **Conclusion:** This patient represents an uncommon case of osteopetrosis, with final height above the target height and very low GH/IGF1 concentrations. A de novo mutation was present in the LRP5 gene, which causes autosomal dominant type 1 osteopetrosis. However, further studies are necessary to evaluate the relationship between these molecular findings and the normal growth rate observed in spite of the extremely low serum GH and IGF1 levels.

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A Longitudinal, Prospective, Long-Term Registry of Patients with Hypophosphatasia

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Background: Hypophosphatasia (HPP) is a rare, inherited metabolic disease characterised by bone mineralisation defects and osteomalacia, and systemic manifestations, including seizures, respiratory insufficiency, muscle weakness, nephrocalcinosis, and pain. The biochemical hallmark of HPP is low serum alkaline phosphatase activity, resulting from loss-of-function mutations in the gene encoding tissue non-specific alkaline phosphatase. HPP presents a broad spectrum of disease severity classically defined by age at onset of symptoms (perinatal/infantile, juvenile, adult, odontohypophosphatasia (dental symptoms only), and 'benign' prenatal), with recognized overlap between, and range of severity within, these forms. The rarity of HPP combined with its variable expressivity presents considerable challenges in the diagnosis and understanding of the disease. **Objective:** Here we describe the design of an HPP Registry, which will enable better characterization and understanding of the epidemiology and clinical course of HPP through collection of demographic and longitudinal clinical data. **Method:** This multinational, observational, prospective, long-term registry will enroll $\geqq 500$ patients. Patients of any age with HPP will be included, except for those participating in Alexion-sponsored clinical trials. Sites will conduct the study in accordance with local regulations. Available patient data will be collected retrospectively *via* chart review at baseline and thereafter at intervals ≤ 6 months in the course of routine clinical care. Performance of new clinical procedures is not required. **Results:** Data collected will include patient demographics; diagnosis methodology; HPP disease history, including dates of onset and diagnosis; family history; clinical manifestations; and genotype. Data from medical and laboratory assessments specific to HPP will be recorded. Standardized questionnaire instruments will be used to quantify patient-reported burden of disease, functional status/disability, and quality of life. **Conclusion:** The HPP registry will provide a detailed longitudinal profile of patients with HPP, including demographics, diagnosis patterns, genotype-phenotype correlations, country-specific findings, and impact of HPP on daily activities and quality of life. **Conflict of interest:** Funded by Alexion Pharmaceuticals. All authors are members of HPP Registry Scientific Advisory Board. CB, KPF, AC are employees of Alexion. PK, CRG, LS, EM, WH received honoraria from Alexion. CL, KO, AL received consultancy fees from Alexion.

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Retrospective Evaluation of Patients Diagnosed as Nutritional Rickets: A Single Centre Study

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Background: Nutritional rickets continues to be an important health care problem. Its incidence has decreased in our country following the free vitamin D distribution that started in 2005 but

it continues to stay on the agenda as a preventable disorder. **Aim:** Our aim was to evaluate patients diagnosed with nutritional rickets following the vitamin D supplementation program. **Method:** We evaluated patients diagnosed with nutritional rickets between 2006 and 2011 at the Dr Sami Ulus Obstetrics and Gynecology and Pediatrics Training and Research Hospital. Nutritional rickets was defined with rickets-specific radiological findings and one of elevated alkaline phosphatase or decreased 25OHD in addition to hypocalcaemia and the response to treatment. **Results:** The 93 nutritional rickets patients consisted of 39 (41%) girls and 54 (59%) boys. The mean age was 19.1 ± 35.1 months. The patients had presented mostly in February and May and only 20% had been receiving vitamin D supplementation. A concurrent disorder was present in 46%. The most common sign at presentation was hypocalcaemic seizure (28%, *n*: 26). The physical examination usually revealed widened wrists and rachitic beads. Hypocalcaemia was present in 46 (*n*: 43) and stoss therapy had been administered to 53% (*n*: 49). **Conclusion:** The 400 IU vitamin D supplementation dose needs to be revised and the program made more widely available. The rickets incidence in infants aged 0-3 months has decreased but the fact that it continues to be present emphasises the importance of providing vitamin D supplementation to pregnant and nursing women.

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Discrepancy in Bone Age Rating Using Tanner-Whitehouse Rating and Automated Bone Age Determination in a Child Who was Later Diagnosed with Metaphyseal Dysplasia

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Background: In the last 50 years bone age has been manually evaluated using the method of Tanner and Whitehouse. Recently automated image analysis has been introduced for bone age determination. The automated method shows good agreement with manual evaluation; further, the precision of the automated method may be higher compared to the manual method. **Objective and hypotheses:** To report on the discrepancy of bone age determination using the manual TW2 method and the automated – boneXpert – TW3 method in a patient with metaphyseal chondrodysplasia. **Method:** A 4.8 year old girl was admitted due to nanismus with a height of 92 cm (−3½ S.D.) and a weight of 15 kg (−1.5 S.D.). Her birth weight was 3.6 kg and birth length was 48 cm. Parents were ethnic Danish and 183 and 180 cm respectively. The girl suffered no chronic diseases, had normal thyroid function, a normal growth provocative test and a normal female karyotype. She had a manual and automated bone age determination at the ages of 5.9 and 8.5 years. Further, she had a whole body x-ray examination and genetic examination. **Results:** At 5.9 years old the bone age was 6.7 years (manual) and 4.1 years (boneXpert) respectively, and the radiologist suspected bone disease. At 8.5 years old the bone age was 9.1 years (manual) and 5.4 years (boneXpert) respectively. Whole body x-ray examination was compatible with metaphyseal chondrodysplasia – McKusick type. Genetic examination confirmed the radiologic diagnosis with a homozygous pathogenic mutation-g.70A > G – in the RMRP gene. **Conclusion:** Children with metaphyseal dysplasia may show significant discrepancies in bone age when rated with the manual TW2 method and the automated – boneXpert – TW3 method. This may hamper adult height prediction. The manual method has the opportunity of evaluating bone structure and come up with proposals for further examinations.

P3-658

Vitamin Levels in Pregnant Women and in Cord Blood in Newborn in Our Area – Preliminary Results

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Background: There is increasing interest in vitamin D nutrition during pregnancy because of widespread reports of a high prevalence of low vitamin D status in pregnant women in high-latitude areas. It has been related to adverse events in mother and child. Neonates present a greater risk of hypocalcaemia, rickets and a higher incidence of infections during the 1st year of life. **Objective and hypotheses:** Real situation of pregnant women and newborn in relation of phosphorous-calcium metabolism. **Method:** Prospective descriptive study between January and July 2015 (preliminary results). Plasma 25(OH)D, calcium, phosphorous, magnesium and PTH levels were measured in third trimester of pregnancy and in cord blood at birth. Clinical history epidemiology data were collected and a nutritional survey was made on maternal vitamin D and calcium intake and degree of sun exposure. **Results:** 85 pregnant women and newborn were studied. 25OHD was analyzed mean 9.93 ng/ml (range 4–23.9), calcium 8.67 mg/dl (5–10.20). Mean 25(OH)D value in cord blood was 10.38 ± 5.8 ng/ml. Vitamin D deficiency (25(OH)D < 20 ng/dl) was present in 95,2% IC 95% (88.4–98.7)of pregnant women and newborns. We found a statistically significant relationship between maternal vitamin D levels and race, Africans had lower levels. We didn't find differences between vitamin supplementation during pregnancy. In 41% of women vitamin D and calcium intake was adequate. There was no association between 25OHD in pregnancy and birth somatometry. We didn't find differences in type of delivery or preterm birth. **Conclusion:** The prevalence of vitamin D deficiency in pregnant women was very high after the winter months and in their offspring. Calcium and vitamin D intake during pregnancy are inadequate in our area so it is necessary to develop healthy programs. Further studies are necessary to determine optimal vitamin D intakes for pregnant and lactating women as a function of latitude and race.

P3-659

Vitamin D Status in Romanian Children 0–18 Years – Should we be More Careful Regarding Supplementation?

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Background: In Romania (latitude 48°15'N to 43°40'N), vitamin D supplementation is a common practice mostly in 0–2 year old infants. No published information is available regarding vitamin D status in Romanian children. **Objective and hypotheses:** We aimed to evaluate the seasonal and age variation of vitamin D status in a large Romanian pediatric patient population. **Method:** 1 395 individuals, 0–18years, from across Romania had performed 1–699 vitamin D assessments (2012–2014) in a chain of private laboratories (Bioclinica). Vitamin D (25-hydroxyvitamin D2 and 25-hydroxyvitamin D3) was measured using High Performance Liquid Chromatography. Vitamin D levels were classified as severe deficiency <10 ng/ml, deficiency?10–20 ng/ml, insufficiency 21–29 ng/ml, sufficiency $\geqq 30$ ng/ml, potentially harmful 100–150 ng/ml and toxicity >150 ng/ml. **Results:** Female to male to ratio was 1:1.3. Mean vitamin D levels increased from April (36.9 ng/ml) to September (44.8 ng/ml) and decreased from October (43.9 ng/ml) to March (32.6 ng/ml). Mean vitamin D levels were 68.9 ng/ml before the age of one and 56.6 ng/ml in 1–2 years old's, significantly higher than for the older ages (mean 26.6 ng/ml ages 3–18 years). There was no gender difference for mean vitamin D. Children under the age of 1 year ($n=233$) presented the highest percentage of vitamin D toxicity (3.4%) and possibly harmful levels (9.4%). **Conclusion:** 25-hydroxyvitamin D levels >100 ng/ml were relatively prevalent in children 0–1 year old (12.8%). This might be attributed to supplementation errors and the fact that high-risk individuals were more likely to visit for medical check-up. Nonetheless, it stresses on the need to increase awareness on the importance of preventing Vitamin D supplementation administration errors in young age. **Funding:** Maria Puiu was financed under the Operational program: Development of existing infrastructure and creation of new infrastructure (laboratories, research centers). POSCCE-A2-O2.2.1-2013-1 in the Center of Genomic Medicine from the University of Medicine and Pharmacy 'Victor Babes' Timisoara.

P3-660

4 Years Follow-Up for 25OHD and iPTH in Vitamin D Substituted Patients with Diabetes Mellitus 1: An Unicentric Prospective Study

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Background: Vitamin D deficiency/insufficiency seems to occur frequently in children and teenagers but it is a matter of debate if limits (<20 ng/ml; <30 ng/ml) are correct. Besides its effect in bone metabolism Vit-D is also supposed to have a positive influence in diabetes mellitus 1 (DM1). **Objective and hypotheses:** To study 25OHD and iPTH values in a group of patients (pts) ($n=57$) with DM1 without Vit-D substitution (2011), with 1000 I.E./d (2012 and 2013) and 2000 I.E./d (2014). **Method:** $n=57$ pts (age: 7–17) followed for 4 years; 2011 no Vit-D, 2012, 2013, 2014 from October–March on Vit-D; one blood sample each year (January–March: iPTH and 25OHD). Pts and parents were asked about compliance. Subgroups due to 25OHD: i) <10 ng/ml (I.a. patients who refused to take Vit-D and I.b. Vit-D was taken.); ii) 10–20 ng/ml (II.a and II.b like before), iii) 20–30 ng/ml (III.a, III.b) and iv) >30 ng/ml (IVa, IVb.). **Results: 2011 (no Vit-D):** I: 19% of pts, iPTH: 51 pg/ml (30–99.5), II: 64% of pts, iPTH: 47.8 pg/ml (29.4–58.8), (83% of pts had 25OHD <20 ng/ml), III: 14.2% of pts, iPTH: 31.1 pg/ml (21.2–40.9), IV: 2% of pts, iPTH: 23.6. **2012: (1000 I.E./d):** I.b.: 1.7% of pts, iPTH: 38.9 pg/ml; II.a + II.b: 29.3% of pts, II.a, iPTH: 45.7 (27.7–62.6) pg/ml, II.b. iPTH: 51.2 (38.9–59.7) pg/ml, III.a + IIIb: 32.7% of pts, III.a.: 40.08 (34–55.6) pg/ml, III.b.: 40.8 (22.1–62.3) pg/ml, IV.a. + IV.b.:29.3% of pts, IV.a.: 42.4 (42.3–42.7) pg/ml, IV.b.: 39.1 (22.0–55.3) pg/ml. **2013 (1000 I.E./d):** data similar to 2012, **2014 (2000 I.E./d):** I.a. + I.b.: 4% of pts, I.a.: 35.7 (23.2–48.3) pg/ml, I.b.:none, II.a. + II.b.: 22% of pts, II.a.: 51.4 (42.4–56.2) pg/ml, II.b.: 69.6 (59.9–86.2) pg/ml, III.a + III.b: 47% of pts, III.a.: 40.1 (22.6–56.9) pg/ml, III.b.:43.5 (21.1–75.4) pg/ml, IV.a. + IV.b.: 28% of pts, IV.a.: 41.6 (28.7–61.8) pg/ml, IV.b.: 39.7 (23.6–69.9) pg/ml. Individual correlation between iPTH and Vit-D as well as changes during treatment will be shown. **Conclusion:** Due to actual limits of 25OHD, 83% of non-substituted DM1 patients had Vit-D deficiency (<20 ng/ml) and 97% had levels <30 ng/ml. Under 2000 I.E/d Vit-D during the autumn/winter period: 26% of patients had values below 20 ng/ml, 47% of patients below 30 ng/ml, and 28% of patients >30 ng/ml (max: 63), thus substitution with 2000 I.E/d significantly improved Vit-D status.

P3-661

Bone Mineral Density in Prader-Willi Females During the Transition Phase

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Background: Adult subjects with Prader-Willi Syndrome (PWS) have low Bone Mineral Density (BMD) and are at risk of osteoporosis. Several observations suggest that peak bone mass is usually achieved by late adolescence, in the presence of adequate gonadal hormone concentrations. Consequently, the altered bone characteristics of PWS patients may be related to inadequate sex steroid levels during pubertal development. **Aim:** To investigate BMD in PWS females during the transition phase. **Methods:** Thirty-two females with genetically confirmed PWS, aged 22.1 ± 0.4 year (mean + SE) (range 17.9–25.0 year), were studied.

Eleven subjects were undergoing sex steroids therapy (Group A), while the remaining 21 individuals were naïve to substitutive treatment (Group B). Twenty subjects had undergone GH treatment during childhood. In all patients dual-energy X-ray absorptiometry (DXA) (Lunar Prodigy) was used to measure BMD in the lumbar spine L1-L4 (gr/cm^2), BMD T-score, and BMD Z-score. **Results:** Four PWS had osteoporosis (T-score < -2.5: 12.50%), 14 had osteopenia (T-score from -1.0 to -2.5: 43.75%) and 14 had normal BMD (43.75%). Three subjects out of 11 of Group A had osteopenia (27.3%), while the remaining 8/11 showed normal BMD (72.7%). Four PWS out of 21 of Group B had osteoporosis (19%), 11/21 had osteopenia (52.4%), and 6/21 had normal BMD (28.6%). Mean lumbar BMD, BMD T-score and BMD Z-score were higher in Group A in comparison to Group B (BMD: 1.108 ± 0.02 g/cm^2 vs. 0.947 ± 0.03 g/cm^2: $P=0.006$; T-score: -0.69 ± 0.17 versus -1.51 ± 0.26: $P=0.04$; Z-score: -0.66 ± 0.24 versus -1.3 ± 0.28: $P=0.9$). Previously GH-treated patients had higher BMD T-score and BMD Z-score in respect to subjects naïve to GH treatment (-0.91 ± 0.22 vs. -1.72 ± 0.32: $P=0.04$ and -0.71 ± 0.25 vs -1.69 ± 0.32: $P=0.02$). **Conclusions:** We conclude that (1) delayed timing of sex steroids therapy should be avoided in PWS females, and (2) GH therapy during childhood seems to exert positive effects on BMD during the transition phase.

P3-662
Seasonal Differences in Plasma 25-OH Vitamin D Concentrations in Cord Blood

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Background: 25-OH vitamin D levels in newborns depend directly on their mother's status. In a previous study, 25-OH vitamin D levels were determined in cord blood in a cohort of women after winter months, showing deficient values in 94% of population (mean 25-OH vitamin D value 10.4 ± 6.1 ng/ml). Correlation between low 25-OH vitamin D levels and low sun exposure, dark skin phototype and Indo-Pakistani ethnicity were observed. **Objective and hypotheses:** The aim of this new study is to describe vitamin D status in pregnant women after summer months by determination in umbilical cord blood and to determine if there are differences with previous results. **Method:** Between October and early December 2014, 25-OH vitamin D plasma levels were measured in cord blood at birth in 103 pregnant women by chemoluminescence. Clinical history data were collected and a nutritional survey (Garabédian) was made on maternal vitamin D and calcium intake and sun exposure. **Results:** Mean 25-OH vitamin D value in cord blood was 12.36 ± 7.2 ng/ml. Vitamin D deficiency (25-OH vitamin D <20 ng/dl) was present in 83.4% of women. Low vitamin D levels in cord blood were significantly related to ethnicity (Indo-Pakistani and Maghreb) and dark skin phototype, use of traditional dress and low sun exposure ($P< 0.001$). No statistically significant differences were observed between 25(OH)D levels after winter and summer months ($P=0.108$), although there were differences between vitamin D intake and sun exposure in the two periods ($P<0.001$). **Conclusion:** There is a high prevalence of vitamin D deficiency in pregnant women at the end of gestation regardless of the season and increased sun exposure. Much more effective vitamin D preventive and therapeutic intervention should be implemented in this population, especially in certain risk groups (Indo-pakistani ethnicity and dark skin).

P3-663
Spondyloenchondrodysplasia with Immune Dysregulation and without Neurological Involvement: Report of Two Siblings with ACP5 Gene Mutation

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Background: Spondyloenchondrodysplasia (SPENCD) is a rare skeletal dysplasia characterized by metaphyseal enchondroma-like bone lesions and dysplasia of the vertebrae. SPENCD with immune dysregulation (SPENCDI) describes the syndrome of combined immunodeficiency, autoimmunity and spondyloenchondrodysplasia caused by the mutations in the *ACP5* gene on chromosome 19. Patients with SPENCDI and neurological manifestations including spasticity, developmental delay and cerebral calcifications have been reported. We present here two siblings born to consanguineous parents with genetically proven SPENCDI. **Case presentations:** 7 years 2 months old boy and his 9 yrs old sister were evaluated for short stature. On physical examination the brother had a round face, short neck, lumber lordosis and pes planus. Height was 100 cm (-4.43 SDS) with risomelia (arm span/height ratio: 0.97). He was diagnosed with autoimmune hemolytic anemia (AIHA) at the age of three months. He received glucocorticoid treatment for two months and required no further treatment thereafter. The sister's height was 113 cm (-3.29 SDS). She was diagnosed with AIHA at the age of 2.5 years and she was receiving methyl prednisolone ever since. Physical examination was normal except short stature and Cushingoid appearance of the face. Both patients were prepubertal. Both patients had AIHA, short stature, metaphyseal changes and platyspondyly compatible with SPENCD. The sister's AIHA was difficult to manage and required splenectomy. At the age of 8 years 4/12 the brother developed systemic lupus erythemasosus which was managed with steroids and immune suppressors. Both patients were of normal intellect and neither had intracranial calcification. Both patients and their parents had mutations in the *ACP5* gene. **Conclusion:** This rare skeletal dysplasia should be considered in patients with short stature and autoimmune disorders. SPENCDI should be included in the differential diagnosis of other skeletal dysplasias with immune involvement, such as Schimke type immuno-osseous dysplasia and cartilage hair hypoplasia.

P3-664

Short Stature in Osteogenesis Imperfecta is not Caused by Deficiencies in IGF1 or IGF-BP3

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Background: Osteogenesis imperfecta is a rare collagen related hereditary disease leading to recurrent fractures, reduced mobility, muscular weakness and short stature. **Objective and hypotheses:** It was always discussed if the reduced height is a consequence of the impaired collagen production, a reaction of the body to the brittleness of bones or if the patient might suffer from an additional deficiency of growth hormone (GH). **Method:** In a retrospective analysis 60 children (28 male; OI type 3 $n=22$, OI type 4 $n=38$) were investigated during their regular yearly examinations and stratified according to the clinical severity of the disease. **Results:** Results are presented in Table 1 showing severely reduced height z-scores with normal IGF1 and IGF-BP3 levels. **Conclusions:** Patients with OI III and IV have a severely reduced height with a significant difference of z-scores depending on the severity of the disease but without alterations of IGF1 and IGF-BP3. Therefore there is no evidence for a general GH deficiency in children with OI and a treatment with GH seems to be unreasonable.

	OI III	OI IV	p
Number of patients	22	38	
Height z-score	−6.43	−3.62	0.0011
Median [IQR]	[−7.939/−5.172]	[−4.576/−2.849]	
IGF1 z-score	−1.45	−0.95	0.2881
Median [IQR]	[−2.376/−0.913]	[−1.574/−0.883]	
IGFBP3 z-score	−0.13	0.05	0.6717
Median [IQR]	[−0.742/0.226]	[−0.321/0.152]	

P3-665

Vitamin D Status in Children in the Western Part of Turkey

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Background: An optimal vitamin D status is important for the growth and development of bones in children and adolescents. The prevalence of vitamin D deficiency is still high, even in low-latitude and industrialized countries, and vitamin D deficiency in childhood is reemerging as major public health issue. **Objectives:** To determine the frequencies of 25-hydroxyvitamin D (25(OH)D) deficiency and insufficiency in children and adolescents. **Methods:** A total of 556 children aged 0 to 18 years who visited tertiary medical center for health and growth status check-ups were included in the study. Serum 25(OH)D, calcium, phosphorous and alkaline phosphatase levels were measured. Vitamin D deficiency was defined as serum 25(OH)D levels less than <50 nmol/L (20 ng/mL); vitamin D insufficiency, as 50–75 nmol/L (20–30 ng/mL). **Results:** Prevalence of low vitamin D status was 63.5% for children aged 0 to 18 years; 219 children (39.3%) had vitamin D deficiency, while 134 of them (24.10%)had vitamin D insufficiency. Clinical vitamin D deficiency was not found in any children. The prevalence of vitamin D deficiency was higher among girls compared with boys, in adolescents compared with childhood stages and in autumn compared with seasons. **Conclusions:** 25(OH)D deficiency/insufficiency was found to be very common in the studied population. Routine screening and supplementation to prevent vitamin D deficiency in at-risk groups during winter and autumn months when vitamin D synthesis is scarce, may be required.

P3-666

Parathyroid Adenoma Should be Considered in the Management of Hypophosphataemic Rickets

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Background: X-linked dominant hypophosphatemic rickets (XLHR) is a rare hereditary metabolic bone disorder. Calcitriol and phosphates are used for the treatment and hyperparathyroidism rarely occurs as a complication. We report a case of XLHR who developed autonomous parathyroid hyperfunction during treatment and underwent surgery for that. **Case:** A male patient was presented with short stature and bone deformities at age 11 months and diagnosed with XLHR based on clinical and laboratory findings. The initial laboratory investigation results were as follows: Serum calcium: 9.6 mg/dl, phosphate: 2.8 mg/dl, alkaline phosphatase: 200 U/L, tubular phosphate resorption: 80%. 25-OH-vitamin D level was normal. Calcitriol and phosphate treatment was started. On follow-up, at the age of 13 years, his height was 151.4 cm (3–10p), weight 55 kg (50p) and physical examination findings were normal. On laboratory, serum calcium 12 mg/dl, P: 3.6 mg/dl, ALP: 180 U/L and parathormone: 588 pg/ml (5–65). Tc 99 m sestamibi scanning showed 1.5× 1 cm sized parathyroid adenoma at the right upper gland. Parathormone and calcium levels returned to normal after the excision of the adenoma. **Conclusion:** Autonomous parathyroid hyperfunction and hyperplasia is a rare but treatable complication of hypophosphataemic rickets. Although there is no consensus on phosphate dosage during the treatment, careful evaluation of phosphocalcic panel during treatment is important for the prevention, early diagnosis and intervention of parathyroid hyperplasia.

P3-667

Neurological Clinic Delays the Diagnosis of Pseudohypoparathyroidism

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Background: The pseudohypoparathyroidism (PHP) encompasses a heterogeneous group of clinical entities caused by a defect in the peripheral action of parathyroid hormone (PTH). Biochemically it manifests itself with hypocalcemia, hyperphosphatemia and elevated PTH. PHP-Ia is the most frequent and multiple hormone resistance, associated signs of Albright hereditary osteodisfrofia (OHA) and mutations in the gene encoding GNAS Gsa protein. **Case presentation:** 6 years old male suffering an episode of ataxia, incoordination and slowing. Familiy history: mother with short stature, normal phenotype. Personal history: preterm with normal birth weight. Neonatally presented hypoglycemia, early jaundice and congenital hypothyroidism, starting levothyroxine in the third week of life. Evolution: euthyroid with replacement therapy; rough phenotype, obesity and macrocephaly, brachydactyly, psychomotor retardation. At 5 1/2 years diagnosed possible benign childhood epilepsy. At age 6, episode of ataxia, incoordination and slowing. Highlights: Ca 4.6 mg/dl (ionic 0.67 mmol/l), P 10.8 mg/dl, Mg 1.3 mg/dl, i PTH 689 pg/ml, calciuria 0, fosfaturia high. Radiologically, bone hyperlucency, thinned cortical and correlation with chronological age. For suspected PHP1A by metabolic disorders and OHA phenotype initiates calcium and calcitriol therapy. The genetic study, showed deletion of 4 nucleotides in heterozygosity in exon 10 (c.568_571 of) the GNAS1 gene (20q13.2 Cr). Mother heterozygous carrier of the mutation, *de novo*. **Conclusions:** i) In a child with seizures or acute neurological symptoms, metabolic disorders should be ruled out. These may be responsible for a pathological EEG recording, as in our patient; EEG and clinical standards normalize when calcium and phosphorus metabolism. ii) In the PHP-IA various alterations in the GNAS locus determine variable phenotypes, and possibly combined with other hormones so these patients should be screened globally resistance. Our patient presented Albright phenotype and resistance to PTH and TSH.

P3-668

Treatment of Life Threatening Hypercalcaemia in Two Infants

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Introduction: Physicians often treat patients with high doses of vitamin D for various ailments and on occasion the prescribed doses far exceed the requirements of the patients. We present here two infants with vitamin D intoxication. **Case presentation:** A 6 month-girl child was brought to the hospital with complaints of persistent vomiting and refusal to feed. She was clinically dehydrated. She was administered 150.000 IU every day for 8 days. Serum calcium was 23.5 mg/dl, 25 (OH) vitamin D level 617 ng/ml and PTH <6 pg/ml. Urinary calcium/creatinin ratio was 3.4. Ultrasonography revealed no nephrocalcinosis. Intravenous hydration, furosemide and prednisolone was given. However, serum Ca level was 19.9 mg/dl, Pamidronate-disodium (0.5 mg/kg per day) for 3 days was also added. The patient was discharged on day 7 with a serum Ca level of 11.3 mg/dl. Serum Ca and vitamin levels were within the normal range at the follow-up visit. Case 2: A 10-month old boy was admitted with complaint of irritation, constipation, loss of appetite in the past two weeks. The medical history revealed that he had been 300.000 IU every week for 2 months. At presentation, the child was irritable and dehydrated. Serum Ca: 22 mg/dl, PTH: <6 pg/ml, 25(OH) vitamin D >600 ng/ml and urinary Ca/creatinin ratio:10. Ultrasonography showed bilateral nephrocalcinosis. Intravenous fluid and diuretics was started. When convulsive movements of the patient began pamidronate-disodium was given for 4 days. Peritoneal dialysis was performed for serum calcium levels remained stable (Ca:18 mg/dl). His serum calcium decreased and normalised (Ca:11 mg/dl). A follow up visit 6 months later revealed normal serum calcium and 25(OH)vitamin D (46.3 ng/ml). However, nephrocalcinosis was stable. **Conclusion:** Even if rarely applied of childhood, Pamidronate-disodium and peritoneal dialysis are best treatment modalities of the life threatening hypercalcaemia.

P3-669

Comparison of the Levels of Vitamin D in Children in Northern Spain (Domestic or Foreign)

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Background: In recent years, vitamin D is attracting increasing interest due to the resurgence of vitamin D deficiency and rickets in developed countries, identifying their extraesqueletics actions and greater understanding of its many benefits. Vitamin D deficiency in children prevalence of vitamin D deficiency in certain regions described up to 80%, especially at high latitudes (above 37) and some breeds. **Objective and hypotheses:** To study the degree of deficit VITD in our population (Location: 42° 51' north latitude 2° 41' west longitude) and check whether there are ethnic differences. **Method:** Cross-sectional observational study. Inclusion: Patients historical Endocrinology Unit Child-up over 2014. 1 wave/semester. Rating ethnic and outdoors origin. Excluded: Children with chronic disease and unable to fulfill. Reference Endocrine Society (2011) Levels of 25-OH-vitamin D (ng/ml), failure <30. Control performed within their own routine monitoring base. Study test (X2) and ANOVA, with a confidence interval of 95%. SPSS 19.0. **Results:** 152 cases initially selected (72/152♂–47%). Average age 9.24aDS3.27 (1–15). Pubertal (92/152) 60%. Distribution pathology (DM 36/152, 34/152 size, thyroiditis 15/152, forward/precocious puberty 23/152, 41/152

overweight, others 2/152). Distribution by ethnicity (Caucasian 108/152, black 8/152, 10/152 Maghreb, latina oriental 2/152 24/152). 35/42/28/47 quarterly distribution. No sex differences, pubertal status and pathology in the waves.78% in range 25OHD insufficiency average 21 ngr/ml DS (12–29). Significant differences between quarters (*P*: 0.01) and etnarios groups (*P*:0.001). Caucasian children deficit 68% (73/108) 25OHD average 24 ngr/ml DS (18–29) compared with 95% of foreign (42/45) 25OHD average of 12 ngr/ml DS (2–25), group deficit more severe. 1 case of tetanus hypocalcaemia. **Conclusion:** Children in our region have a prevalence of vitamin D deficit. Important. The exercise outdoors, extracurricular activities and a clearer skin could be responsible for the differences found, but given the high prevalence should make a general recommendation for prophylaxis VITD all the paediatric population in our latitude during school months.

P3-670

A Cause of Severe Hypercalcaemia: Overdose or Hypersensitivity to Vitamin D?

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Background: Hypercalcaemia is caused by many different conditions. Vitamin D intoxication with severe hypercalcemia is rare in the neonatal and infancy period. Here we described a 4-month-old male with severe hypercalcemia secondary to taking oral 600 000 units of vitamin D. He was diagnosed vitamin D 24-hydroxylase gene (CYP24A1) mutation after evaluation. **Case presentatıon:** He was admitted to our hospital with high serum calcium level (23 mg/dl). Serum vitamin D level was >250 ng/ml, parathyroid hormone level was 1.7 pg/ml. The treatment consisted of intravenous rehydration with treatment of hypercalcemia (diuretics and corticosteroids) at the beginning. Because serum calcium level decreased slowly, pamidronate treatment was added. Serum calcium returned to the normal range within 12 days, with weight gain progressively over the following weeks. Abdominal ultrasound objectified renal nephrocalcinosis. **Conclusion:** Mutations in the CYP24A1 gene cause reduced serum $24.25(OH)_2D_3$ to $25(OH)D_3$ ratio (<0.02), elevated serum 1,25-dihydroxyvitamin D ($1.25(OH)_2D_3$), hypercalcemia, hypercalciuria and nephrolithiasis. This case might accepted vitamin D intoxication because of high vitamin D intake. But severe hypercalcemia should be remarkable for CYP24A1 gene mutation.

P3-671

How are we Using Bisphosphonates in Children with Secondary Osteoporosis in a Tertiary Centre?

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Background: Bisphosphonates inhibit osteoclast activity, decreasing bone resorption and increasing bone mineral density (BMD). A Cochrane review in 2007 concluded further evidence is required for use of bisphosphonates in children with secondary osteoporosis. **Objective and hypotheses:** We appraised our current practice of bisphosphonate use in children with secondary osteoporosis (as defined by the 2013 International Society for Clinical Densitometry Position Statement) or with low BMD and significant symptoms. **Method:** 36 patients who were treated with bisphosphonates over a 7-year period were included. Data was collected on demographics, changes in BMD *z*-score, fractures rates and bone pain. **Results:** 86% of patients had cerebral palsy or a neuromuscular condition and 14% had respiratory or endocrine disorders. The mean age of commencing treatment was 12.3 years and patients were followed up for an average of 46.3 months (range 7–96). Prior to treatment, the mean baseline BMD *z*-score was -3.0 (SEM $\pm$ 0.33). 95% of patients had long bone and/or vertebral fragility fractures and 39% of patients reported bone pain. 75% of patients received <2 years of bisphosphonate treatment and no patient received >5 years. The majority initially commenced Pamidronate but at completion of therapy, only 50% were on Pamidronate with 36% on Zoledronic Acid. Treatment was tolerated well in 72% of patients. Infrequent complications, including venous access issues, were reported in a minority. The mean BMD *z*-score was -2.2 (SEM $\pm$ 0.28), following an average treatment period of 16 (SEM $\pm$ 2.20) months. On follow up, 86% of patients had no fractures and 50% of patients commented on decreased pain. **Conclusion:** Bisphosphonate use in a heterogeneous group of children with symptomatic low BMD or secondary osteoporosis resulted in increased bone density, and decreased fractures and pain. The treatment was well tolerated, and Zoledronic Acid is increasingly being used. Future prospective studies incorporating a larger cohort using quality of life data are needed.

P3-672

Pseudohypoparathyroidism: Clinical Heterogeneity Illustrated by Three Different Cases

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Background: Pseudohypoparathyroidism represents a group of clinical and molecular heterogeneous disorders, characterized by functional hypoparathyroidism, caused by end-organ resistance to the action of PTH. Pseudohypoparathyroidism manifests as hypocalcemia, hyperphosphatemia and elevated plasma levels of PTH. A combination of features, also known as Albright osteodystrophy including disproportionate short stature, obesity,

dysmorphia, may co-exist. **Case presentation:** We present three cases: The first case is a 13 years old boy who presented with fatigue and muscle cramps. During therapy he developed growth hormone deficiency and hypothyroidism. The second case is a 11 years old boy presenting with therapy-resistant absence epilepsy and intracerebral calcifications. The third case is a 5 years old girl with neonatal hypoglycemia and hypothyroidism. The girl's development was retarded, with evolution towards growth failure, severe early-onset obesity, osteodystrophy. Loss-of-function mutations in GNAS or epigenetic aberrations leading to failure of expression cause different types of pseudohypoparathyroidism (PHP). GNAS encodes GS alpha, a protein that is required for normal transmembrane signal transduction by many hormones. This gene is imprinted in a tissue-specific manner, being primarily expressed from the maternal allele in renal proximal tubules, whereas both alleles are expressed in bone. Maternally inherited deletions lead to the severe type, PHP Ia. These patients present resistance to other hormones other than PTH that act via Gsalpha-coupled receptors, as resistance to TSH, gonadotropins and GHRH. Patients typically have features of Albright osteodystrophy. Our third case was genetically proven to have PHP-Ia. PHP type Ib is associated with a GNAS imprinting defect in which both alleles have a paternal imprinting pattern on both alleles. Patients manifest renal resistance to PTH, without features of Albright osteodystrophy. Case 1 and 2 are believed to belong to this group of PHP, but genetic analysis is pending. **Conclusion:** Substantial clinical and molecular overlap occurs between PHP type 1a and type 1b, what makes it a challenging diagnosis.

P3-673

Successful Treatment of Severe Hypercalcemia in an Infant with Williams Syndrome Using a Single Infusion of Pamidronate Followed by Low Calcium Diet

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Background: 15% of patients with Williams syndrome develop hypercalcemia that is described as mild and transient. There are, however, reported cases with severe hypercalcemia that did not respond to traditional therapy. Pamidronate was used in the treatment of this condition, and was successful in the few reported cases in the literature. **Case presentation:** We report a 9 month old female who presented with failure to thrive, polyuria and polydipsia. She had the typical facial features of Williams syndrome, which was proven by genetic testing. She was found to have a calcium level of 19.5 mg/dl. The patient did not respond well to intravenous hydration and furosemide, so she received a single pamidronate infusion. Her calcium level normalized and she was kept on low calcium diet. Her calcium level is still normal 6 months after the treatment. **Conclusion:** Hypercalcaemia associated with Williams syndrome can be very severe with significant morbidity. In addition, Pamidronate intravenous infusion proves to be effective in the treatment of this condition.

P3-674

25-Hydroxy Vitamin D Levels in Patients with Chronic Diseases on Corticosteroid Treatment

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Background: Corticosteroids are medicines that are used to treat many chronic diseases. They are very effective anti-inflammatory drugs by suppressing the immune system, and are also used as a replacement therapy in conditions with low levels of endogenous cortisol. Glucocorticoid effects on bone metabolism include: reduced absorption of calcium in the intestine; increased calcium urinary excretion; increased bone resorption and reduced bone density. Corticosteroid treatment increase the activity of the 24-hydroxylase (CYP24A1), and thereby reduce the level of 25-Hydroxy Vitamin D (25-OH-D). Patients on a long term treatment with oral glucocorticoids have significantly lower levels of 25-OH-D, decreased mineral bone density and osteoporosis. Measuring the level of serum 25-OH-D is very important to determine vitamin D status in this group of patients. **Case:** We present five children with chronic diseases on a long term treatment with corticosteroids. Three of them are with progressive muscular dystrophy and two children are with chronic arthritis. The first studies in all patients showed low level of 25-OH-D–35 to 45 nmol/l, normal range is 80–200 nmol/l. This required the application of vitamin D3. The tests after treatment showed normal level of 25-OH-D, parathyroid hormone, alkaline phosphatase and calcium in the serum, and normal calcium/creatinine ratio in the urine. **Conclusion:** Vitamin D is very important for calcium homeostasis and for optimal bone metabolism and health. Children treated for a long period with oral corticosteroids often have low levels of 25-OH-D. In these patients it is necessary to check 25-OH-D levels regularly and treat the impaired vitamine D status with oral vitamin D supplementation.

P3-675

Pseudohypoparathyroidism Type 1b, a Rare Diagnosis in Adolescents

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Background: Pseudohypoparathyroidism (PHP) is a rare group of disorders characterised by end-organ resistance to parathyroid hormone (PTH), and possibly TSH, with or without features of Albright's hereditary osteodystrophy.

Case presentation: A 14-year-old boy presented with fatigue and spontaneous carpal spasms in association with a febrile viral infection. Past medical history was significant for an episode of asymptomatic hypocalcemia treated with calcium and alphacalcidol. He had discontinued therapy and he was lost to follow-up. Family history was remarkable for episodes of hand numbness for the mother, muscle cramps for maternal grandfather and carpal spasms and multiple fractures for maternal great grand mother. Physical examination revealed an adolescent with no dysmorphic features, normal height and weight, fully pubertal, with no skeletal abnormalities except for mild genu valgum. He had positive Chvostek and Trousseau signs. Laboratory investigation revealed markedly low serum calcium (5.3 mg/dl), phosphate (5.6 mg/dl), while magnesium, albumin, ALP and TSH were normal. There were also markedly elevated PTH levels (299.4 pg/ml) and vitamin D deficiency (16.5 μg/lt). ECG showed prolonged corrected QT interval. The patient was initially treated with calcium and alphacalcidol. In summary, this patient presented with PTH resistance, and no phenotypic signs of Albright's osteodystrophy, normal puberty, thyroid function and cortisol production, consistent with the diagnosis of PHP-I. A molecular genetic analysis was performed that revealed loss of methylation at the GNAS locus consistent with the diagnosis of PHP type 1b. **Conclusion:** PHP-Ib is the result of defects in the methylation pattern of the complex GNAS locus and can be inherited in an autosomal-dominant manner or may occur sporadically. The human GNAS gene is located on chromosome 20q13 and defects are heterogeneous. Genetic counselling is important for the patient and the family, as well as the need for life-long treatment with calcium and activated vitamin D.

P3-676

What Lies Beneath: An Enigma of Missed Opportunities and Calcium Problem

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Aim: To highlight the importance of tangential thinking in unusual clinical presentations, and tracking of family history with emergence of index case. **Methods:** A case review of three siblings presenting with varied symptoms and diagnosis to the different speciality clinic and noted to have Hypocalcaemia. **Results:** 14 year old boy, diagnosed at age of 3 years with Duchenne's muscular dystrophy (DMD), confirmed with identification of a mutation in the DMD gene (deletion of exons 46, 37 and 48). He presented with persistent hypocalcaemia and low vitamin D, normal Alkaline Phosphatase (ALP) and marginally raised Parathormone (PTH). Medicinal compliance and dysfunctional family dynamics were an issue and were thought to be major factors in persistent hypocalcaemia. 7-years old girl presented for excessive weight gain, clumsiness and frequent falls. She had a round face, significant brachydactyly of hands and feet and increased lumbar lordosis. She had marginally low calcium, normal ALP. Initial PTH was not assayed in view of sampling error. Subsequent PTH was raised. Index patient is a 12-years old boy presenting with acute hypocalcaemic tetany with 6 month history of pins and needles in hands and lips, recurrent spasm of hand and jaw. He was earlier treated for epilepsy. He had a round face with normal hands and feet. He had normal ALP, raised PTH, low vitamin D. In all 3 patients, Vitamin D levels and calcium levels normalised with supplementation, however, PTH still remained high. **Conclusion:** Pseudohypoparathyroidism (PHP) is a condition with PTH resistance, due to defective PTH receptor arising from defective G protein (α subunit). Rare causes should be considered especially with persistent hypocalcaemia. Complete biochemical evaluation is required in the absence of typical phenotypic features of PHP. Family history is important and needs to be carefully considered in the context of clinical presentation.

P3-677

A Novel Homozygous Six Nucleotide Deletion in GLUT2 Gene in a Fanconi–Bickel Syndrome Family

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Background: Fanconi–Bickel syndrome (FBS) is a rare autosomal recessive disorder characterised by hepatorenal glycogen accumulation, proximal renal tubular dysfunction, impaired utilization of glucose and galactose, rickets, and severe short stature. It has been shown to be caused by mutations in GLUT2 gene, a member of the facilitative glucose transporter family. **Results:** Here, we report an Iranian family with two affected siblings. The clinical findings in the patientinclude developmental delay, failure to thrive, hepatomegaly, enlarged kidneys and rickets. **Conclusion:** A novel six nucleotiddeletion (c.1061_1066del6, p.V355_S356del2) is shown to be segregated with the disease in this family.

P3-678

Final Height in a Patient with Fanconi Syndrome and GH Deficiency Treated with GH

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Background: The Fanconi syndrome (FS) and GH deficiency (GHD) is a rare association. The FS is a dysfunction in the proximal tubule that can be idiopathic or primary. This dysfunction leads to renal loss of bicarbonate, phosphate, glucose,

potassium and amino acids. One of the clinical feature is a delay in body growth. The correction of acidosis can protect the loss of growth. According to the prevalence of idiopathic GHD, it would be expected that 1 in 4 000 patients and, with FS may have both conditions. **Case report:** A 1.6-year old girl with FS, presented sweating, rickety rosary, tabes skull, chest keel, signs of rickets, muscle atrophy, enlargement of fists and knees. At this stage H-SDS: −4.49; blood tests showed metabolic acidosis, hiposfatemia, aminoacidúria, glycosuria, phosphaturia. Was excluded from inborn errors of metabolismo. The target height (TH)-SDS was −0.61. The patient received potassium, phosphate, and sodium bicarbonate replacement therapy. Clinical signs of rickets disappeared with this treatment. At 7.5 years, H-SDS: −2.89; HV-SDS: 1.54. At 9 years, H-SDS: −3.72; presented growth velocity reduction(HV-SDS: −3.89), with appropriate therapeutic compliance; IgF1: 12 ng/ml (22.1–383 ng/ml); IgFBP–3:1.3 μg/ml (2.6–5.5 μg/ml), GH stimulation test revealed inadequate response. Karyotype 46XX, euthyroid and tubular losses were appropriately replaced, no intestinal malabsorption. MRI of the pituitary gland and hypothalamus was normal. The GH replacement therapy was began at 10 years (H-SDS: −3.85). She presented catch-up growth, HV-SDS: 4.9. GH treatment was maintained for 5.9 months. Menarche occurred at 15.2 anos. At 18 years with 156 cm (H-SDS: −1.03) the patient has no signs of rickets, she continues to use citrate, phosphate, hydrochlorothiazide. **Conclusion:** With adequate control of the tubular eletrolyte losses in FS, it is expected an increase in growth rate. Even though uncommon, should be suspected GHD when there is a reduction in growth velocity. In this patient, treatment with GH, citrate and phosphate allowed to reach final height (FH) compatible with the TH.

P3-679

Carpal Spasm in Hypophosphataemic Patient

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Background: Phosphate is an essential ion and plays a vital role in many physiological processes. Carpopedal spasm is known as a symptom of hypocalcaemia, or rarely, hypomagnesemia. We present an unusual case of carpal spasm seen in hypophosphataemia. **Case presentation:** 14 year old boy was admitted with acute onset of both carpal spasm. He had shrimp salad made 2 days ago, and two times of vomiting and large amount of diarrhea was developed before carpopedal spasm. Biochemical investigation revealed only moderate hypophosphatemia without hypocalcaemia. Other laboratory finding including hormone tests related with phosphate regulation was normal. Carpal spasm improved with correction of hypophosphatemia. **Conclusion:** The phathophysiology of neurologic dysfunction in hypophosphatemia is not clear yet. But it has been suggested that physiological effects of phosphate is related. Careful observation of phosphate is recommended when the patient has neurologic symptoms.
☆No illustration from any novel.

P3-680

Efficacy and Safety of Oral Alendronate Treatment in Children and Adolescents with Osteoporosis

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Background: Osteoporosis is very rare in childhood and main reasons are growth retardation, immobilisation, calcium and vitamin D deficiency, long term steroid therapy. There is no concensus about the treatment of children and adolescents with osteoporosis. Biphosphonates have been important in the treatment of osteoporosis. **Objective and hypotheses:** To evaluate the efficacy and safety of oral alendronate on bone mineral density (BMD) in children and adolescents with osteoporosis. **Method:** Oral alendronate was given to 22 patients with an average age of 13.3×3.9 years (range 4.3–19 years) and BMD *z*-score < −2.13 of them were treated with steroids. DEXA was used to measure lumbar vertebral BMD before and 14×7.75 years after treatment. Auxological, biochemical (Ca, P, ALP) and densitometric parameters before and after treatment were compared for all patients. Responses of the patients taking steroids were compared with those who did not. **Results:** Posttreatment *z*-scores of patients were significantly higher than basal values ($P<0.001$). Average annual BMD increase with treatment was 32.74×52.57% (5.17–255.42%). *z*-score and annual BMD increase in patients taking no steroids were significantly higher than the others (*P*: 0.02and *P*: 0.006 respectively). Post treatment serum ALP levels were significantly lower than pretreatment levels (*P*: 0.007). After 1 year of treatment osteoporosis completely recovered in 6 patients (28.6%), improved to osteopenia levels in seven patients (33.3%). No significant difference observed between height SDS of patients before and after treatment (*P*: 0.022) and no side effects detected. **Conclusion:** Oral alendronate increases BMD without any side effects in osteoporotic children and adolescents. It is cheaper and easier to use than i.v. biphosphonates.

P3-681

A Case of Vitamin D Deficient Rickets Showing Resistance to the Treatment of Active Vitamin D: Severe Calcium Deficiency Cause Vitamin D Resistance

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Case presentation: A 2-year-boy was referred tour hospital for the rickets. He was the first son between non-consanguineous parents and fed with breast milk. But after weaning, he was avoided from taking egg, dairy products including cow's milk.

He was also suffered from developmental delay and had strong food preference. He could take only two kinds of foods, steamed rice and soy bean product, tofu. X-ray findings showed typical rachitic change on long bone metaphysis. Laboratory findings showed hypocalcaemia, hypophosphatemia, increase ALP activity (4595 IU/l), and increased intact PTH (729 pg/ml). 25 Hydroxyvitamin D was 13.2 ng/ml. From these results, vitamin D deficient rickets due to restricted food intake was diagnosed. After diagnosis, 2.5 μg/day of alphacalcidol was started. Although serum calcium and phosphorus levels were normalized, high PTH and ALP activity had not been corrected even by increased amount of alphacalcidol up to 8 μg. Genetic analysis of vitamin D receptor could not show any mutations. Functional analysis of VDR using 1,25 dihydroxyvitamin D3 induced 24 hydroxylase mRNA in the patient's peripheral lymphocytes could not show any differences between patient and control. Although, his serum calcium levels were normal, his oral calcium intake seemed to be less than 100 mg/day. Then we added 1 g of calcium lactate. After this treatment, his PTH and ALP activity were improved rapidly. 4 months treatment of calcium lactate and small amount of active vitamin D almost completely cured rickets. **Conclusion:** In conclusion, severe calcium deficiency induces vitamin D resistance in vitamin D deficient rickets. In the mechanism of the resistance the severe secondary hyperparathyroidism due to severe calcium deficiency may play an important role but detail mechanism should be unveiled.

P3-682

Metadiaphyseal Dysplasia Associated with Confirmed GH Deficiency: Family Report

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Background: Skeletal dysplasias are a heterogeneous group of more than 200 disorders characterised by abnormalities of cartilage and bone growth, resulting in abnormal shape and size of the skeleton. **Case presentation:** We present two children (brother 7 years and sister 11 years), investigated for growth retardation, part of five children brotherhood from apparently healthy non-consanguineous couple (mother's height = 158 cm and father's height = 163 cm). They had normal birth weight and the delayed growth development was progressively observed from early childhood. Brother's clinical examination revealed low height −4.08 S.D. (104.5 cm), hypopigmentation areas on face and body (diagnosed as vitiligo), curved tibia and radius, with limited extension in the joints. The sister presented similar clinical phenotype: low height −4.65 S.D. (118 cm), curved long bones in the forearm and leg, but no vitiligo lesions. Both children associated enamel dysplasia. Bone X-rays revealed delayed bone age and confirmed the clinical aspect, but could not plead for a certain diagnostic. Family history revealed a paternal grandmother with similar phenotype, indicating a recessive autosomal transmitted genetic disease. The investigation of somatotropic axis showed low IGF1, low basal GH with no stimulation at insulinemic induced hypoglycaemia, in both children. The IRM of the pituitary revealed an 'empty sella' aspect in the boy and a small hypophysis in the girl. Parameters of phospho-calcium metabolism were within normal range. The suspicion of a mucolipidosis was invalidated by enzymatic testing. A suspicion for Pile's disease was raised, with few data in the literature to compare and the positive diagnosis was not possible due to lack of diagnostic markers. **Discussion:** Taking into account the documented GH deficiency, the necessity of GH replacement therapy was raised. Owing to the important bone deformities (suggesting a metadiaphyseal bone disease), the treatment was delayed and we chose to closely monitor the growth rate and, if possibly, further investigate the genetic mutations implied.

P3-683

Hypocalcaemia by Parathyroid Dysfunction in Children and Adolescents

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Background: Dysfunction of the parathyroid gland is a rare cause of hypocalcaemia. It may be caused by a deficiency or resistance to PTH. Generally symptomatic It can be hereditary, congenital or acquired. **Objective and hypotheses:** Analysis of clinical, paraclinical, etiological and progressive children's and adolescents hypocalcaemia by parathyroid dysfunction. **Method:** This is a retrospective study of hypocalcaemia by parathyroid dysfunction observations in children and adolescents from 1980 to 2015. All patients underwent a complete physical examination, laboratory tests (phosphocacique, PTH), morphological explorations (cervical and kidney ultrasound), ophthalmologic examination, cardiovascular assessment (ECG and heart Doppler), and cerebral CT. Exploration was completed based on the patient context. **Results:** Twelve children (ten boys and two girls) are listed. Diagnostic average age: 5 years (2–14). The discovery of circumstances convulsions (four cases), growth retardation (four cases), systematic research (three cases), and cataract (one case). Clinical presentation was symptomatic in all cases (muscle spasms, tingling, cramps and tetany, defective enamel, and lack of dental development). The assessment of complications found a cataract ($n = 2$) and calcifications of the basal ganglia ($n = 3$), intracranial hypertension ($n = 1$). In 25% of cases, hypoparathyroidism is family. The mean serum calcium is 65 mg/l (60–70). The aetiologies found were: idiopathic hypoparathyroidism (three cases), postoperative hypoparathyroidism (three cases), a polyglandular autoimmune type I (three cases), DiGeorge syndrome (one case), and a pseudo hypoparathyroidism (two cases). Treatment with an alpha and calcium has improved symptoms in all cases. **Conclusion:** The Hypocalcaemia by parathyroid dysfunction is a rare disease in children. it may be due to varying etiologies. It is characterized by a symptom picture which can be grafted life-threatening. Its diagnosis and its treatment should be early and effective.

P3-684

VDR Gene Analysis Results of Four Patients with Hereditary 1,25-Dihydroxyvitamin D Resistant Rickets

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Background: Hereditary 1,25-dihydroxyvitamin D resistant rickets (HVDRR) caused by vitamin D defective receptor. **Objective and hypotheses:** We performed VDR gene analysis four patients with alopecia, skeletal dysplasia, and hypocalcaemia. **Method:** Genomic DNA extracted from peripheric blood. Whole gene sequence analysis was performed. **Results:** We found homozigot p.Q152* (c.454G>T) mutation three patients. Two of this three patients were siblings. There is homozygous p.R50* (c.148C>T) mutation in one patient. **Conclusion:** HVDRR is a rare autosomal recessive disease caused by the mutations in *VDR* gene. Here we report clinical and laboratory findings of four patients.

P3-685

Nutritional Rickets in a Bottle-Fed 2 Months Old Baby

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Background: Nutritional rickets (NR) is the most common growing bone disease, and vitamin D deficiency (VDD) may predispose to other diseases (diabetes mellitus, cancer, and multiple sclerosis). Maternal VDD and exclusive breastfeeding without supplementation are the most frecuent causes of NR in the neonate. VDD is still a problem in Europe. There are few reports of maternal hypovitaminosis D and rickets in bottle-fed infants during early infancy. We report a case of Nutritional Rickets in a bottle-fed baby at 2 months of age. **Case report:** A 2-month-old boy referred for irritability, episodes of hypertonia, cianosis and eye movements of 20–30 s of duration. Mother born in Philippines (1 year in Europe). Normal delivery at term. Adecuate pregnancy follow-up. BW 2660 g. Little sun exposure. She took vitamins. Bottle feeding since the 1st month of life, with intake of vitamin D 200 UI daily. Physical exam: BW, BL, and HC p25. Dry skin, sparse, fine hair, craniotabes, hyperexcitability, hypertonia, wide fontanel, enlargement of wrists, and frontal bossing. Blood test: (CaT 6.8 mg/dl (8.2–10.8), I.Calcio 0.79 mmol/l (1.12–1.23), and normal phosphoremia. Hyperparatiroidism (PTH: 329 pg/ml) and 25-OH-vitamin D (9.08 ng/ml). Hypocalciuria. X-ray: 'radiolucent' line in distal ulnar region, expansion and irregularity of the metaphyseal margin, brush-like appearance, cupping of distal region of femur, tibia, fíbula, radius, ulna and proximal of tibia and fibula, and general osteopenia. We started endovenous calcium and vitamin D3. Serum calcium is normal at the 4th day. Recuperation physical and radiological. Maternal blood test: calcium 10.3 mg/dl (8.5–10.5), phosphorus 3.1 mg/dl (2.6–4.8), intact PTH 86 pg/ml (10.0–65.0), and 25-OH-vitamin D 14.2 ng/ml. She started also treatment with vitamin D 800 UI + 1000 mg calcium. **Conclusion:** Control of calcium levels and vitamin D intake in the pregnant woman should be an important objective during pregnancy, to avoid clinical and radiologic anomalies in the neonate.

P3-686

A Rare Reason of Hyperinsulinism: Münchausen Syndrome by Proxy

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Background: Drug intoxication is one of the rare reasons of hyperinsulinism; it may occur not only accidentally but also deliberately. **Objective and hypotheses:** Herein, we report a case who presented with factitious hyperinsulinaemic hypoglycemia and diagnosed with Münchausen syndrome by proxy (MSBP) which is an uncommon condition of child abuse. **Method:** A 7-year-old girl was referred to our department due to hyperglycemic and hypoglycemic episodes. Her father has been treated with metformin and several sulphonilureas for more than 10 years. Blood glucose monitoring showed hyperglycaemia reaching 300 mg/dl and no hypoglycaemia. We didn't detect any other clinical or laboratory findings so that gliclazide (1 mg/kg per day) was initiated and increased to 2 mg/kg per day because of persisting hyperglycemia. However, episodes of hypoglycemia occurred during the patient follow up, thus gliclazide treatment was stopped. Few weeks later she was admitted to the emergency room with hypoglycemic seizure. Plasma levels of insulin (156 mIU/ml) and C peptide (6 ng/dl) were discordant with the concurrent blood glucose level (33 mg/dl) and urinary ketones were negative, suggesting endogenous hyperinsulinism. Diazoxide and dextrose (10%) was administered and hypoglycemia was prevented. Computed tomography and MRI of the abdomen was normal. In spite of diazoxide therapy, hypoglycemia was detected, so octreotide therapy was initiated and dose was increased to 35 μg/kg per day gradually due to resistant hypoglycemia. However, the mood of the patient's mother was discordant with the situation. Blood and urine samples were sent to toxicology laboratory in order to investigate hypoglicemic agents. Toxic levels of gliclazide were detected. **Results:** Patient was immediately isolated. Glucose infusion was decreased gradually. Finally on the 4th day of isolation, gliclazide was not detected in urine and blood samples. The patient was diagnosed as MSBP. **Conclusion:** MSBP is an unusual and difficult to identify cause of child abuse. It should be considered in the differential diagnosis of hyperinsulinism particularly in cases without apparent origin.

P3-687

Correlation of Vitamin D Levels with Glycaemic Control, Total Daily Insulin Dose, BMI, and Ethnicity in Paediatric Patients with Type 1 Diabetes Mellitus

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Background: Type 1 diabetes mellitus (T1DM) is an autoimmune and inflammatory process and vitamin D (VD) is thought to reduce inflammation and prevent autoimmune destruction. Studies have shown that VD has an effect on insulin secretion and sensitivity in rats. And it has been shown that adult T2DM with normal levels of VD have decreased insulin requirements. Two prior studies in Turkey looked at the relationship between VD levels and daily insulin requirement in paediatric patients with contradictory results. **Objective and hypotheses:** In this study, we will determine if there is a significant correlation between VD levels and HbA1c, daily insulin requirement, BMI, and ethnicity in paediatric T1DM. Our hypothesis is that patients with low VD levels will have increased daily insulin requirement. **Methods:** A retrospective chart review of 162 T1DM paediatric patients ages 3–20 years old was conducted. Age, gender, ethnicity, BMI, HgA1c, VD level (25(OH)D), and total daily insulin requirement (units/kg per day) were obtained. VD levels were divided into three groups: <20 ng/ml was considered deficient, 20–29.9 ng/ml insufficient, and >30 ng/ml was sufficient. Multivariate linear regression analysis (using STATA13.1) was used to assess the association between insulin requirement and VD levels adjusting for the following confounders: age, gender, ethnicity, BMI, and HA1c. **Results:** The study included 84 girls, 78 boys, 30 African Americans, 27 Hispanics, and 99 Caucasians. Analysis of the data showed that patients with a low VD had a statistically significant ($P=0.02$) increase in insulin requirement independent of HbA1c levels, age, gender, ethnicity, and BMI. **Conclusion:** These findings may suggest that lower levels of VD may contribute to the need for higher insulin doses, which may be related to insulin resistance and suboptimal glucose control in paediatric patients with T1DM.

P3-688

Management of Children with Type 1 Diabetes During Illness (Sick Days): Is There a Need for National Consensus Guideline?

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Background: Adequate sick day management at home may reduce the risk of progression to diabetic ketoacidosis (DKA) and admission to hospital. The UK does not have a consensus guideline for sick day management advice to children and young people with type 1 diabetes mellitus (T1DM). Children's diabetes services vary in their practice of education and advice in the use of urine or blood ketone monitoring during illness. **Objective and hypotheses:** The aim of this project was to review the variation of management of diabetes during illness. **Method:** A survey was conducted by the Association of Children's Diabetes Clinicians (ACDC) who sent out questionnaires to all paediatric diabetes units managing children and young people with T1DM including: local sick day management rules, out of hours diabetes support for families and information about the local diabetes service. **Results:** 93/127 (73%) of the units responded to the survey. There were 14 tertiary centres. Median number of children per service was 161 (range 73–450). The majority of units (93%) have a sick day management guideline in place. **Conclusion:** There was a wide variation in the practice of monitoring and advice given during illness. All guidelines advised increased doses of insulin during sick days but there was no consensus on how to calculate increased doses. There were also variations in the use of ketone testing and frequency on blood glucose monitoring. Some units still use urine ketone testing routinely. There is a need for evidence based national guidance to be in place.

Table 1. Results of survey.

Advice on extra insulin	72% Based on total daily dose, 24% units/kg, and 23% other locally derived rule
Ketone monitoring	58% Blood ketones, 3% urine ketones only, and 40% used both
Out of hours advice for diabetes patients	49% Paediatric registrar, 16% diabetes nurse specialist or diabetes consultant, 27% diabetes nurse specialist/diabetes consultant on a joint rota, and 14% from diabetes team in the evenings/weekends and paediatric on-call overnight

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Incretin Secretion was not Impaired in Obese Korean Children and Adolescents with Type 2 Diabetes

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Objective: The role of incretins in type 2 diabetes (T2D) is controversial. This study investigated the association between incretin levels in obese Korean children and adolescents with T2D. **Patients and methods:** We performed a 2-h oral glucose tolerance test in obese children and adolescents with T2D and with normal glucose tolerance. Twelve obese children and adolescents with newly diagnosed T2D (DM group) and 12 obese age-matched subjects without T2D (NDM group) were included. An oral glucose tolerance test (OGTT) was conducted and insulin, C-peptide, glucagon, glucagon-like peptide 1 (GLP1), and glucose-dependent insulinotropic polypeptide (GIP) were measured during the OGTT. Follow-up OGTT was done to six patients of the DM group (DM2 group) after 3 days discontinuation of oral hypoglycaemic agent. **Results:** The mean age of the patients was 13.8 ± 2.0 years, and the mean BMI *Z*-score was 2.1 ± 0.5. DM and NDM groups were comparable in age, sex, BMI *Z*-score, and waist:hip ratio. The DM group had significantly lower homeostasis model assessment of beta (HOMA-β) and insulinogenic index (IGI) values ($P<0.001$). The HOMA of insulin resistance (HOMA-IR) index was not different between the two groups. Insulin and C-peptide secretions were significantly lower in the DM group than in the NDM group ($P<0.001$). Total GLP1 (TGLP1) secretion was significantly higher in the DM group while intact GLP1 (iGLP1) and GIP secretion values were not significantly different between the two groups. Comparing DM and DM2 groups, FBS, BMI, HbA1c, HOMA-IR, and IGI values were significantly lower in the DM group than in the DM2 group ($P<0.05$). HOMA-β was higher in the DM group than in the DM2 group ($P=0.017$). TGLP1 and GIP secretion values were not significantly different in the DM and DM2 group, however, iGLP1 secretion was significantly lower in the DM2 group than in the DM group ($P=0.017$). Comparing DM2 and NDM groups, TGLP1 secretion was significantly higher in the DM2 group than in the NDM group ($P=0.04$), however, iGLP1 and GIP secretion values were not significantly different. **Conclusion:** Impaired insulin secretion might be important in the pathogenesis of T2D in obese Korean children and adolescents, however, which may not be attributed to incretin secretion. Although, patients had wash-out period, oral hypoglycaemic agent might be able to influence on incretin secretion.

P3-690

Neonatal Diabetes Mellitus: Clinical Feature and Outcome

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Background: Neonatal diabetes mellitus (NDM) is a rare (1:300 000–400 000 newborns) but potentially devastating metabolic disorder characterized by hyperglycemia combined with low levels of insulin. Two main groups have been recognized on clinical grounds, transient NDM (TNDM) and permanent NDM (PNDM). **Objective and hypotheses:** To describe clinical features and laboratory manifestations of patient with NDM and evaluate outcome of management. **Method:** Case series study, clinical features, biochemical finding, mutation analysis, and management outcome of 20 cases from 20 unrelated families were study. All exon of *KCNJ11, ABCC8*, and *INS* genes were amplified from genomic DNA and directly sequenced. If the mutation of *KCNJ11, ABCC8*, and *INS* has failed to detect, methylation – specific PCR will be done to detect the loss of methylated region on chromosome 6q24. Patients with ABCC8/KCNJ11 will transfer to sulfonylurea from insulin. **Results:** Twenty-one cases (11 girls and ten boys) onset at 7–357 days (median 45) of age with gestation age of 38.8 ± 2.3 weeks and birth weight of 2676.2 ± 592.4 g. Ten cases of them admitted with the feature of polydipsia, polyuria and 13 cases with diabetes keton acidosis with pH of 7.15 ± 0.18, HCO_3^- of 10.0 ± 9.0 mmol/l, BE of −16.1 ± 10.3 mmol/l, blood glucose of 35.7 ± 10.4 mmol/l, and HbA1c of 7.66 ± 2.86%. Mutation analysis showed six have heterozygous for a *KCNJ11* missense mutation, five patients with *ABCC8* mutations, four patients have abnormal of chromosome 6, five patients with *INS* mutation, and one patient with *EIF2AK3* mutation. The patients have duration of 53 ± 46 months. Four patients with TNDM stop insulin: now all cases have normoglycemic (blood glucose: 5.0 and 5.9 mmol/l), one patient has mild development delay and two patients have normal development. 17 patients with PNDM: 11 cases successfully transferred to sulfonylureas and did not need insulin injections, six cases require insulin, 2/17 cases with DEND syndrome, and 15/17 cases have normal development. **Conclusion:** It is important to perform screening gene mutation for patients with diabetes before 12 months of age to control blood glucose and follow up the patients.

P3-691

Acute Kidney Injury as a Severe Complication of Diabetic Ketoacidosis

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Background: Diabetic ketoacidosis (DKA) in children and young adults carries significant morbidity and mortality relating to complications such as cerebral oedema. Acute kidney injury (AKI) is a rare but potentially fatal complication of DKA. We present three cases of DKA complicated by AKI. **Case 1:** A 9-year-old girl presented with severe DKA at diagnosis. She was treated with intravenous fluids and insulin as per protocol. She had oliguria and haematuria 36 h after admission. She was hypertensive with evidence of enlarged kidneys on ultrasound (USS). She was transferred to the renal unit where she needed two cycles of

hemodialysis before making full recovery. **Case 2:** A 14-year-old girl presented with severe DKA and altered consciousness at diagnosis. She developed oliguria 24 h after starting treatment for DKA. USS of abdomen showed enlarged kidneys. Her renal function improved with haemofiltration and recovered fully by 1 week. **Case 3:** A 17-year-old girl with poorly controlled type 1 diabetes presented with severe DKA. She showed evidence of AKI with very high plasma creatinine, oliguria and low plasma phosphate. She was managed conservatively with individualised fluid plan and phosphate supplementation with recovery in 7 days. **Conclusion:** Patients with severe DKA can develop AKI due to a number of possible causes, hypovolaemia being the most likely primary cause. Appropriate management of hypovolemia and electrolyte disturbance in these patients can be very challenging. These cases highlight the importance of early recognition of AKI (rising plasma creatinine, oliguria, and haematuria) and discussion with paediatric nephrologist to formulate individualised fluid therapy in order to prevent deterioration in renal function. It is uncertain if recent modification in fluid management of DKA has led to a change in the incidence of AKI.

P3-692

BMI in Children and Young People with Type 1 Diabetes in England and Wales

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Background: BMI in childhood is an indicator of future health. **Objective and hypotheses:** To assess BMI distribution among children and young people with type 1 diabetes. **Method:** The National Paediatric Diabetes Audit (NPDA) collates height and weight data on children and young people with diabetes in England and Wales. BMI centiles were calculated using the UK 1990 reference population. Underweight was defined as $<$5th centile, overweight 85th – 95th centile and obesity $>$95th centile. **Results:** The 2013/2014 NPDA included data on 25 357 patients with type 1 diabetes. 1.6% Underweight, 57.5% healthy weight, 19.8% overweight, and 21.1% obese. Comparison to national data shows a higher prevalence of overweight and/or obesity in type 1 diabetes than in the general population. Living in more deprived areas are associated with obesity compared to the least deprived areas (odds ratio (OR) 1.71, 95% CI 1.54–1.89). Risk of obesity increased with age (OR 1.05, 95% CI 1.04–1.06/additional year) and being female (OR 1.26, 95% CI 1.17–1.34). A reduction in HbA1c of 1 mmol/mol was associated with an OR of 1.003 (95% CI 1.001–1.005). Duration of diabetes and ethnicity were not associated with obesity. Male gender (OR 1.95, 95% CI 1.53–2.47) and Asian ethnicity (OR cf. White ethnicity 2.14, 95% CI 1.45–3.16) were associated with increased risk of being underweight. An increase of 1 mmol/mol in HbA1c was associated with an OR 1.008 (95% CI 1.002–1.014). Deprivation, duration of diabetes and age were not associated with underweight. **Conclusion:** There is a trend towards higher BMI in children and young people with type 1 diabetes. The trend towards obesity in girls and in the most deprived areas is recognised in the general population and suggests the importance of lifestyle factors. The significant OR of being obese with every 1 mmol/mol decrease in HbA1c suggests confounding influences of diabetes control which requires further evaluation. **Funding:** This work was funded by the Healthcare Quality Improvement Partnership.

P3-693

Blood vs Urine Ketone Monitoring in a Pediatric Cohort of Patients with Type 1 Diabetes: a Crossover Study

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Background: Diabetes ketoacidosis (DKA) is the most severe complication in type 1 diabetes (T1D) but patient education and ketone monitoring may help decrease its frequency. However, the influence on glucose homeostasis of systematic ketone monitoring and of the nature of monitoring (urine vs blood) is unclear. **Objective and hypotheses:** To determine whether the use of blood ketone monitoring, as compared to urine ketone testing, decreases the duration of hyperglycemia, the occurrence of ketosis events and of DKA in the daily management of T1D in paediatrics. **Method:** Our single-site, controlled and randomized study was done on prepubertal patients with T1D outside of remission phase. Over 118 patients screened, 28 were actively enrolled. Patients were asked to test blood ketones during hyperglycemic episodes (HE), being two consecutive (but 1 h delayed) capillary glycaemia $\geq$250 mg/dl, during two periods of 6 months alternatively with a blood ketone meter and urine ketone test strips. **Results:** Our cohort was homogeneous for gender (F/M ratio: 1), age (mean 10.4 years) and diabetes duration ($\geq$2 years). During the study period, no episodes of DKA or severe hypoglycemia were noticed. Patients experienced a mean of 4.6 HE/month (range 0–9). They adequately controlled ketones 1.6 times/month (36% of HEs) and inadequately (when no HE occurred) 1.5 times/month. Missed ketone bodies measurements (2.9/month) tended to be higher with blood meter (3.7/month) than with urine strips (2.1/month) ($P=0.05$). Duration of hyperglycaemia during HEs was not different when patients measured or not ketones (4.3 ± 1.9 h vs 4.3 ± 2.0 h respectively), meaning that ketone monitoring did not allow rapid normalisation of glycaemia. The proportion of severe ketosis ($>$3 mM for blood and $>$28 mM for urine tests) was similar between the two groups (4% for urine and 5% for blood monitoring). Also, no difference was noticed in mean blood glucose or HbA1c levels before and after the study period. **Conclusions:** Whereas ketone monitoring is part of standardized diabetes education, its implementation in the daily routine remains difficult. Although, we did not observe DKA, ketone monitoring did not impact glycemic control during our study. Further research is necessary to evaluate how ketone monitoring may impact long-term diabetes control and complications.

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Elastargene 3C Helps to Improve HbA1c in Children and Adolescents with Type 1 Diabetes Using Insulin Pump Therapy

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Background: Elastargene 3C (E3C) is a cream specifically designed to improve lipoatrophy in patients with diabetes. It is made by many ingredients, among whom are elastin, arnica, collagen, caffeine, and L-carnitine. **Objective and hypotheses:** We started a 6-month, double-blind, randomized trial to test the efficacy of E3C in children with type 1 diabetes (T1D) using insulin pump (CSII), in whom infusion set usually left little withe scars. **Method:** Forty children and adolescents using CSII, were randomized into two arms: i) $n=20$ E3C once a day on the skin of abdomen or other sites where infusion sets have been placed, administered before sleeping; ii) $n=20$ placebo once a day on the skin of abdomen or other sites where infusion sets have been placed, administered before sleeping. BMI, HbA1c, and insulin requirement were determined in each child before at baseline and after 6 months. **Results:** At the end of the study, five patients dropped using the E3C or placebo and were excluded from the analysis. In elastargene group, 18 patients with T1D were evaluated: age 15.2 ± 4.8 years, diabetes duration 8.0 ± 5.3, time using a pump 4.1 ± 3.0; in the placebo group, 17 patients with T1D were evaluated: age 15.1 ± 5.7 years, diabetes duration 8.3 ± 5.8, time using a pump 4.7 ± 3.0. No significant difference has been observed for age, disease duration, and time since insulin pump started. HbA1c significantly improved in patients using E3C (baseline $8.08\pm0.80\%$, after 6 months $7.51\pm0.53\%$, $P=0.005$, Δ -0.53%), but not in placebo group (baseline $7.98\pm0.74\%$, after 6 months $7.76\pm0.79\%$, $P=0.19$, Δ -0.22%). No difference has been observed regarding BMI or insulin requirement. In the E3C group, withe scars completely disappeared in eight patients and improved in ten; in the placebo group withe scars did not change in any of the patients. **Conclusion:** To our knowledge this is the first time that a direct effect of E3C have been shown in improving little withe scars that appear on the skin after infusion set removal in children with T1D using CSII. Moreover, HbA1c significantly improved only in the E3C group, probably because improved insulin absorption.

P3-695

Intraosseous Infusion: Sometimes the Only Way to Treat Severe Diabetic Ketoacidosis

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Background: The diabetic ketoacidosis (DKA) represents one of the most frequent causes of death in childhood. The first therapeutic step is a quick rehydration, whereby a venous access must be ensured in every child with DKA, in order to infuse liquids immediately. The children conditions (state of shock, obesity) can make access extremely difficult. We present two cases of patients with severe DKA, where finding a venous access was almost impossible. **Clinical cases:** F.A., M, 18 m, and E.G., F, 3 y, arrived in our Department in coma state. Arterial sampling documented severe DKA. The children needed a venous access for their clinical conditions. After several infructuous attempts, we decided to proceed with intraosseous access. After premedication with EMLA, we inserted a needle for intraosseous injection on the level of the right tibial plate, using the Vidacare EZ-IO. The time for procedure execution was 3 min. The children began saline 0.9% solution and, after 1 h, started insulin therapy and continued rehydration by marrow needle, according to a computerized protocol in use in our department. Twelve hours later, we cannulated successfully two peripheral veins and the intraosseous device was removed. There were no treatment complications. **Discussion:** For critically ill patients, intraosseous access (IOA) represents a quick and fairly safe mode to ensure liquids when peripheral venous access is difficult; it could be a lifesaving procedure. By IOA, you can infuse glucosaline solutions and many drugs employed in the intensive care. The IO route can also be used to get mixed blood samples for blood tests. Intraosseous insulin is scheduled in resuscitation protocols, but not assessed in that recently proposed by ISPAD. The absorption and duration of action are the same as those obtained through a peripheral or central vein. The complications of this procedure are rather rare (0.6 per cent) The use of this procedure requires careful and continuous monitoring. IO needle should be removed as soon as the children conditions permit and, in any case, not later than 24 h.

P3-696

Influence of hypoglycemic episodes on attention and behavioural abnormalities in diabetic children

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Background: Type 1 diabetes may have an influence on concentration, attention and behaviour. These effects are relevant, as they may affect school performance and later career options for paediatric diabetes patients. **Objective and hypotheses:** This study examined attention, concentration and behavioural difficulties in diabetic children aged 5–13 years and their association with hypoglycaemic episodes and HbA1c. **Method:** 48 children with type 1 diabetes mellitus (age 5–13 years, 28 boys, 20 girls) were stratified for HbA1c over the last 2 years (good diabetes control HbA1c $<7.5\%$; average or bad diabetes control HbA1c $>7.5\%$), number of hypoglycaemia per month (<1 episode/month, 1–5 episodes/month, >5 episodes/month). Parents answered the

Strengths and difficulties questionnaire (SDQ, screening for behavioural abnormalities and difficulties). KiTAP, a computer based test, was used to test selectivity, intensity, flexibility and control of impulse in the patients. School grades were assessed. Differences between groups were tested for significance using Mann–Whitney *U* tests. Correlations were calculated using Spearman's rank correlation coefficients. **Results:** Attention (tested with the KiTAP tool) was significantly better in patients with 1–5 hypoglycaemic episodes compared to patient with >5 episodes. There was no overall statistic difference in patients with <1 compared to >5 hypoglycaemic episodes/month. SD-questionnaire did not show increased behavioural abnormalities or correlation with HbA1c in diabetic children. Attention did not correlate with HbA1c. There was no significant difference for attention between the low HbA1c group and the high HbA1c group. **Conclusion:** These results suggest that the frequency of hypoglycaemia exerts an influence on attention. Although literature shows that hypoglycaemia does not cause permanent cognitive impairment, recent hypoglycaemia seems to influence attention. Diabetic children do not have behavioural abnormalities. Good diabetes control with absence of hypoglycaemia should be achieved.

P3-697

Recurrent Ketosis after Prolonged Exercise in Type 1 Diabetes: The Need for Glycogen Replacement Strategies: Case Report

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Background: In diabetic athletes, glycogen depletion can contribute to the early development of starvation ketones as is demonstrated by our patient. **Case presentation:** Our patient, a 15-year-old male triathlete with type 1 diabetes for 5 years was referred to our tertiary center because of suboptimal regulation on continuous subcutaneous insulin infusion (CSII). He frequently awoke with nausea and ketosis, which was initially attributed to failure of insulin delivery. With optimalisation of administration materials and initiation of concomitant s.c. injections of a long acting insulin analogue, morning ketosis persisted on a weekly basis. After thorough examination of his insulin pump records, it stood out that ketosis developed when few carbohydrates were consumed after exercise. Rapid ketosis developed in the early morning hours when physical activity was resumed before breakfast. To rule out other metabolic causes of ketosis, the patient was admitted. During the 1st day, he performed his usual physical activity, took a last meal at 1900 h and fasted afterwards. The fasting would be stopped when ketones >1 mmol/l developed or in case of complaints. After 13 hours of fasting, ketone bodies developed in the presence of relatively normal glucose levels and normal fasting insulin levels. Serum acylcarnitines were normal and urine organic acids confirmed diabetic keto-acidosis. Our working diagnosis was ketosis due to glycogen depletion, and 2 g/kg corn starch late in the evening was added to his diet. Consecutively, no ketosis occurred. **Conclusion:** In diabetic athletes, glycogen depletion can contribute to the early development of starvation ketones as is demonstrated by our patient. Therefore, glycogen replacement strategies need to be discussed with our diabetic athletes.

P3-698

Adherence to Diabetic Ketoacidosis Management Protocol: a Paediatric Centre Experience

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Background: Paediatric diabetic ketoacidosis (DKA) management should be regulated by specific protocols. Following the Canadian Diabetes Association recommendations, our paediatric tertiary care hospital was provided with such a protocol in 2009. **Objective and hypotheses:** Assess the proportion of DKA episodes that are marked by non-adherence to our DKA management protocol (DKAp). We suspected a moderate non-adherence rate. **Method:** We conducted a retrospective study on all patients admitted with DKA between March 2009 and September 2013. Deviations to DKAp were classified as major or minor according to their potential impact on patient outcome. Non-adherence to acute management DKAp was defined as the occurrence of greater than or equal to one major or greater than or equal to two minor deviations. **Results:** Seventy-nine patients were included (mean age: 9.7 ± 4.9 years; 53.2% females). Most cases were new-onset diabetes (60/79, 75.9%). Within known diabetic patients, the DKA precipitating factor was poor treatment compliance in 10/19 (52.6%) and insulin pump dysfunction in 4/19 (21%). Mild DKA (pH: 7.21–7.30) occurred in 24 (30.4%) patients, moderate DKA (pH: 7.11–7.20) in 30 (38.0%) and severe DKA (pH $\leq$7.10) in 25 (31.6%). Continuous insulin drip was used in 73/79 (92.4%) cases. We observed greater than or equal to one major deviation to DKAp in 37/73 (50.7%) cases, mostly failure to monitor hourly neurological status (32/69, 46.4%, four missing values) and inappropriate administration of 0.9% NaCl i.v. bolus in well-hydrated patients (5/73, 7%). Minor deviations (≥ 2) occurred in 66/73 (90.4%) patients; mostly failure to monitor urine ketone levels every 4 h (66/73, 90.4%) and blood gas and serum electrolytes every 2 h (33/73, 45.2%). Overall, non-adherence to DKAp occurred in 69 (94.5%) cases. The following complications were observed: 7/73 (9.6%) hypoglycemia, 55/73 (75.3%) hyperchloremic acidemia, and 1 (1.4%) CT-scan suspected cerebral edema. No deaths occurred. **Conclusion:** Non-adherence to DKAp was observed in the majority of cases without unusual complication rate. The establishment of a protocol does not guarantee its adherence and surveillance of its application is needed.

P3-699

Continuous Intersticial Glucose Monitoring in Early Detection of Glucose Tolerance Abnormalities in Adolescents with Cystic Fibrosis

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Background: Cystic fibrosis-related diabetes (CFRD) and glucose abnormalities have a negative impact on pulmonary function and survival in cystic fibrosis (CF) patients. Oral glucose tolerance test (OGGT) is the screening test of choice for CFRD, although undetected high glucose levels can be missed with this test. The use of a continuous intersticial fluid glucose monitoring system (CGM) can be useful in these patients. **Objective and hypotheses:** To determine the role of CGM in the early detection of glucose abnormalities in CF. **Method:** All CF children aged 10–17 years without known diabetes and followed by our hospital CF team were included. Those with infections or under a corticosteroid treatment course in the last 6 weeks were excluded. OGGT in the last year was reviewed with special attention in intermediate values over 200 mg/dl. CGM system was placed during 5 days. **Results:** Among 13 children, six girls, we found: High glucose levels in OGGT in three patients, none CFRD. Two of them had intermediate values over 200 mg/dl; glucose excursions above 200 mg/dl in CGM in six patients, four with normal OGGT. The patient with impaired glucose tolerance in OGGT showed in CGM a glucose mean of 136 ± 28 mg/dl and 10% of time above 190 mg/dl with excursions above 200 mg/dl. Mean level of 24 h blood glucose values for all patients was 109 ± 14 mg/dl. The patients with normal CGM had lower mean levels than those with impaired CGM (99.8 ± 9.3 mg/dl vs 119.6 ± 10.6 mg/dl, $P = 0.005$). **Conclusion:** CGM could be a useful tool to detect glucose excursions in CF children with normal OGGT. The CGM systems are a comfortable way to detect hyperglucemia in a real situation. It is still unknown how the development of CFRD in these patients with impaired glucose can be delayed.

P3-700

Health-Related Quality of Life in Children and Adolescents with Type 1 Diabetes Mellitus in Spain: Results From the CHRYSTAL Study

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Background: Costs and health related quality of life study for type 1 diabetes mellitus (CHRYSTAL) pediatric patients in Spain is an observational study conducted in 2014 on a representative sample of 275 patients aged 1–17 years with type 1 diabetes mellitus (T1DM) in Spain. The study collects diabetes specific health related quality of life (HRQoL) using the Diabetes Module of the Pediatric Quality of Life Inventory (PedsQL). This scale has been identified to be one of the best scales to describe HRQOL in pediatric population. **Objective and hypotheses:** The objective was to describe the HRQoL for pediatric patients with T1DM in Spain and to compare results by HbA1c level. **Method:** PedsQL is modular instrument composed of 28 items comprising five dimensions (diabetes, treatment I, treatment II, worry, and communication) graded on a scale from 0 to 4. Scores were converted from 0 to 100, where higher scores indicate higher HRQOL. The questionnaire was self-administrated on patients 8–17 and proxy completed by the caregiver for children two to seven. The overall and itemized mean scores by age ranges were calculated. Results by HbA1c level (HbA1c $<7.5\%$ vs HbA1c $\geq 7.5\%$) were analyzed by Mann–Whitney *U* test. **Results:** Valid results were obtained for 268 patients. The proxy results indicated an overall HRQoL of 65.5 for patients with HbA1c $\geq 7.5\%$ and 70.6 for those with HbA1c $<7.5\%$ in patients aged 2–7. For patients 8–17, the self-report indicated an overall HRQoL of 72.0 for patients with HbA1c $\geq 7.5\%$ and 73.2 for those with HbA1c $<$ 7.5%. Results by age range were consistently lower among patients with HbA1c $\geq 7.5\%$, although differences by HbA1c level were not statistically significant. The 'Worry' dimension had the highest negative score on QOL across all age ranges. **Conclusion:** CHRYSTAL is the first study to evaluate HRQoL in a representative sample of children and adolescents with T1DM in Spain. Interventions are needed to include HRQoL measures as part of the regular practice while managing diabetes for better assessment of diabetes care. **Funding:** This work was supported by Eli Lilly and Company.

P3-701

HbA1c Rather Than BMI Lifestyle and Adherence to Mediterranean Diet is the Major Determinant of Triglyceride/HDL Cholesterol Ratio in Adolescents with Type 1 Diabetes

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Background: Triglyceride (TG)/HDL ratio has recently been considered a index of cardio-metabolic risk in healthy and obese subjects. Diet, lifestyle indexes, anthropometric parameters, and metabolic control are the variables with possible influence on belonging to a certain cardio-metabolic risk group. **Objective and hypotheses:** To identify whether HbA1c *per se* has an influence on TG/HDL and to study other possible variables influencing the ratio. **Method:** We evaluated 85 adolescents with type 1 diabetes (T1D). Inclusion criteria were age range 12–19.9 years and T1D with at least 2-year duration. All patients underwent clinical

Table 1.

TG/HDL ratio	<1.2 ($n=53$)	≥ 1.2 and <2.0 ($n=23$)	≥ 2.0 ($n=9$)	*P* value
BMI–SDS	0.09 ± 0.95	0.73 ± 0.76	0.16 ± 1.44	0.015[a]
SBP (mmHg)	112 ± 9	117 ± 10	122 ± 11	0.005[a]
DBP (mmHg)	70 ± 8	74 ± 8	78 ± 10	0.016[a]
Chol (mg/dl)	168 ± 29	183 ± 35	200 ± 42	0.030[a]
HbA1c (%)	8.10 ± 1.0	8.40 ± 0.97	9.90 ± 1.20	0.001[a]
Gender (M/F)	22/31	11/12	8/1	0.022[b]

examination and measurement of HbA1c and lipid profile, as well as filled-in the KIDMED questionnaire investigating Mediterranean diet quality index and a questionnaire on socio-economic and lifestyle indexes. The patients were subdivided according to Di Bonito *et al*. TG/HDL ratio tertiles (*Diabetes Care* 2012). The Kruskal–Wallis (a) and χ^2 (b) tests were applied. **Results:** The Table 1 shows mean $\pm$ S.D. values of variables significantly different among TG/HDL ratio classes. Age, waist/height ratio, mediterranean diet adherence, socioeconomic, and lifestyle parameters were not significantly different among the three groups. A stepwise multinomial logit model identified HbA1c as the parameter with the highest independent influence on belonging to the highest cardio-metabolic risk group ($P=0.002$), followed by SBP ($P=0.034$), while BMI and waist/height ratio disappeared after SBP entered the model. **Conclusion:** In our group of adolescents with T1D, showing a fair level of adherence to Mediterranean diet and on average a correct lifestyle, HbA1c, and male sex were the major determinant of belonging to a low cardio-metabolic risk group.

P3-702

Non-HDL Cholesterol in Diabetic Children: Treatment Recommendations Considering Glycaemic Control, BMI, Age, Gender, and Generally Accepted Cut Points

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Background: Non-high-density lipoprotein cholesterol (non-HDL-C) has been shown to be a suitable predictor of cardiovascular risk. **Objective and hypotheses:** We aimed to investigate factors influencing non-HDL-C levels in children with type 1diabetes (T1D, registered at the German/Austrian DPV database, $n=26358$) in order to increase the rare use of lipid-lowering therapies. Recommendations for acceptable (<120 mg/dl), borderline-high (120–139 mg/dl), and high (≥ 140 mg/dl) non-HDL-C levels in children at high cardiovascular risk were considered. **Results:** Non-HDL-C levels were generally higher in children aged >10 years than ≤ 10 years and also higher in females than in males. Non-HDL-C levels increased with worsening glycaemic control, elevated non-HDL-C levels and age. The rate of non-HDL-C levels ≥ 120 mg/dl was more than 25% and of levels ≥ 140 mg/dl still 10%, irrespective of glycaemic control, weight, age, and gender. However, the rate of non-HDL-C levels ≥ 140 mg/dl was even 25% in overweight girls aged >10 years. **Conclusion:** Considering the non-HDL-C treatment goal <120 mg/dl for children with diabetes-related high cardiovascular risk, it can be assumed that more than a quarter of children with T1D require intensified lifestyle interventions. Further 10% of all T1D children and even 25% of overweight adolescent girls need immediate lipid-lowering treatment in parallel with lifestyle changes, because there is no reasonable perspective of reaching their non-HDL-C goal by improved glycaemic control or weight loss alone. **Funding:** DPV initiative was supported by the German Federal Ministry of Education and Research as part of the competence net diabetes (grant FKZ 01GI1106) integrated into the German Center for Diabetes Research (DHZ), the German Competence Net Obesity (grant FKZ 01GI1130), and the European Foundation for the Study of Diabetes (EFSD).

P3-703

A 1-year Follow-up Study to Evaluate Efficacy and Compliance of Continuous Glucose Monitoring in Children with Type 1 Diabetes Mellitus

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Background: Self monitoring of blood glucose (SMBG) is an important part of diabetes management. Continuous glucose monitoring system (CGMS) provides the real time measurements of users' glucose levels. The NICE guideline recommends use of CGMS if there is persistent hypoglycaemia unawareness or repeated hypoglycaemia or hyperglycaemia. In our paediatric diabetes clinic within a large DGH, we have a cohort of 12 children who were funded for the CGM use for a minimum of 1 year. **Objective and hypotheses:** To assess the effects of CGM on metabolic control, hypoglycaemic episodes and overall compliance over a period of 12 months. **Method:** Data from cohort of 12

Table 1. Comparison of HbA1c prior to CGM use to Hba1C at different months

	Mean (S.D.) mmol/mol	95% Confidence Interval	*P*-value
Pre-CGM HbA1c	70.7 (13.4)		
1 months	59.3 (10.9)	3.6–19.1	0.008
3 months	60.0 (12.9)	2.8–18.6	0.012
6 months	60.5 (11.0)	2.8–18.6	0.061
9 months	59.8 (4.2)	1.92–20.0	0.022
12 months	64 (9.6)	−2.9–16.4	0.150

patients who were commenced on CGMS was collected retrospectively. We compared HbA1c and frequency of hypoglycaemic episodes over 12 months. We also report their compliance and side effects related to CGMS use. **Results:** 12 patients (eight males), with median age 14.5 years (5–18 years) used CGM over a year. There was significant improvement in the HbA1c within 1 month of usage that was sustained over 9 months (Table 1). Proportion of hypos over 12 months was reported to be low at a mean 3.8% (range 1.6–5.3%). There were issues with non compliance with five patients using the CGMS sensor intermittently after 8 months of continuous usage. Two of the five patients reported problems with allergy to plaster and CGM device not sticking well. **Conclusion:** In clinical practice use of CGMS showed improvement in control within a short period of time but this was not sustained over 12 months. Hypoglycaemic episodes were infrequent during the 12 months CGMS use. Compliance of long-term use of CGMS was low at 58% even in a healthcare that funds its use.

P3-704

Diabetic Ketoacidosis Treatment: Experience from a Paediatric Tertiary Centre (2004–2014)

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Background: Diabetic ketoacidosis (DKA) is a medical emergency. The most physiologic fluid/electrolytes replacement rates and insulin dosis are still controversial. **Objective and hypotheses:** To evaluate the effectiveness and security of DKA treatment. Our protocol consists of 2 h' rehydration with 0.9% sodium chloride (NaCl), followed by insulin infusion (0.1 U/kg per h) associated to 0.45% NaCl with 5% glucose. Potassium is replaced with monophosphate potassium associated to potassium chloride in first 12 h. Lower insulin doses are used in children under 5y and mild DKA (0.05 U/kg per h). **Method:** Retrospective study including children and adolescents with DKA at 1 DM diagnosis, attended at our hospital since 2004. DKA and severity groups were defined according to international literature. Data collected included insulin infusion, glycaemia, pH, osmolarity, corrected sodium, potassium and phosphate along the first 12 h. Statistical analysis with SPSS 21th ($P<0.05$). **Results:** Since 2004 we admitted 142 new cases of 1DM. We included 38 children with DKA, 23 males (60%) with mean age of 8.2 ± 4.0 years. Severe DKA occurred in 11 (28.9%), moderate DKA in 11 (28.9%) and mild DKA in 16 (42.2%). At admission, mean glycaemia was 554 ± 154 mg/dl, mean osmolarity 310 ± 12 mosm/kg, mean corrected sodium 146 ± 5 mmol/l, mean potassium 4.5 ± 0.72 mmol/l and mean phosphate 1.5 ± 0.45 mmol/l. Insulin was started at a mean dose of 0.07 ± 0.02 U/kg per h. Along 12 h, mean glucose supply was 4.8 ± 1.8 g/U per h, mean potassium provided was 0.13 ± 0.05 mmol/kg per h and mean phosphate was 0.11 ± 0.06 mmol/kg per h. Potassium anf phosphate was started simultaneously with insulin infusion in 32 (84%) children; hypokalemia (<3.5 mmol/l) occurred in 16 (42%) children, and hypophosphatemia (<0.9 mmol/l) occurred in 10 (26%) cases. There was no hypocalcemia. Variation along 12 h had statistical significance for glycaemia, pH, corrected sodium and osmolarity ($P<0.0001$), without variation of corrected sodium. There were no cases of cerebral oedema. **Conclusion:** Our protocol allowed an adequate and safe approach to DKA treatment at 1 DM onset. Hypocalcaemia should be corrected with higher potassium supply. There was a gradual correction of dehydration and acidosis, without complications.

P3-705

Treatment of Dyslipidemia in Children and Adolescents with Diabetes Mellitus Type 1

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Background: Cardiovascular disease (CVD) is the major cause of mortality in diabetes mellitus type 1 (T1DM). Dyslipidemia will increase this risk. Several guidelines have been published, how to treat dyslipidemia in T1DM, yet some studies have shown that the number of patients who are treated according to these guidelines is low. **Objective and hypotheses:** To investigate the frequency of dyslipidemia in children and adolescents with T1DM and if they are treated according to recent guidelines and if not, to identify the reason why guidelines were not followed. **Method:** All children and adolescents with T1DM from the pediatric and transition diabetes outpatient clinic of the University Medical Center Groningen were retrospectively investigated. 210 persons with T1DM (112 male and 98 female), 3–24 years old were included. Data of lipid profiles, HbA1c, smoking and BMI and in patients with dyslipidemia (LDL-c$\geqq$ 2.6 mmol/l), tracking of LDL-c (defined as $\geqq$75% of the LDL-c results $\geqq$ 2.6 mmol/l), blood pressure, family history for dyslipidemia and CVD, were collected. We investigated if patients were treated according to the guidelines and asked the treating physician for possible reasons to deviate from it. **Results:** 41.9% ($n=88$) of the patients had dyslipidemia. Dyslipidemia was significantly associated with age, female sex, HbA1c and BMI. In patients with dyslipidemia 65.6% showed tracking of LDL cholesterol, 42.5% had a positive family history for CVD and 28.8% for dyslipidemia. 11.4% of the patients with dyslipidemia were treated with a diet and 5.7% with statins. The most important reasons for not treating dyslipidemia were mild increase of LDL cholesterol (46.6%) and bad compliance with high HbA1c (28.4%). **Conclusion:** Dyslipidemia is frequently seen in patients with T1DM, yet treatment percentage is low. Awareness for early intervention is important. Research to investigate the benefit of treatment is needed.

P3-706

Hearing Changes in Children and Adolescents with Type 1 Diabetes Mellitus

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Background: There have been reports that patients with diabetes have hearing loss greater than those without. Suggested pathogenesis for diabetes-associated hearing loss has included cochlear microangiopathy, hyperglycaemia of cerebrospinal fluid, auditory neuropathy and diabetic encephalopathy. **Objective and hypotheses:** This study is aimed to investigate hearing changes in children and adolescents with type 1 diabetes mellitus and to examine if hearing changes is associated with glycaemic control. **Method:** Pure-tone thresholds were measured in both ears of children and adolescents with type 1 diabetes mellitus (T1DM) ($n=53$) and their sex and age-matched healthy controls ($n=33$) at frequencies from 125 Hz to 8 000 Hz. **Results:** There was greater hearing loss in T1DM subjects compared to controls at 6 000 Hz. Significant greater hearing loss was also found in poorly-controlled T1DM subjects (HbA1c≧9%) ($n=25$) compared to well-controlled subjects (HbA1c <9%) ($n=28$) at 2 000, 4 000 and 6 000 Hz. **Conclusion:** T1DM is associated with an increased risk of hearing loss in children and adolescents and this difference seems to be related to blood glucose control states. Hearing evaluation and interventions are required in the management of T1DM in children and adolescents.

P3-707

A Novel Genetic Mutation in a Turkish Family with GCK-MODY

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Background: Maturity-onset diabetes of the young type 2 (MODY2) is an autosomal dominant inherited disease caused by heterozygous inactivating mutations in the glucokinase (GCK) gene. It mostly presents with mild fasting hyperglycaemia. MODY2 accounts for 2%–5% of all diabetes cases. It is treated with diet only, and complications are extremely rare. We presented here a family with MODY2 caused by a novel heterozygous p.E51*(c.151.G>T) mutation of the GCK gene. **Case:** A 17-year-old girl was admitted to our department because of fasting hyperglycaemia. Parents had no consanguinity. Father and grandfather were diagnosed with diabetes. On physical examination Body mass Index was 30.2 kg/m^2 (>95 p) She had not acanthosis nigricans. Pubertal assessment revealed Tanner V. Serum autoantibodies against glutamic acid decarboxylase, islet cell antibodies, and anti-insulin autoantibodies were negative. Blood glucose level was repeatedly checked and showed fasting hyperglycaemia (132 mg/dl) as well as an elevated haemoglobin A1c level (6.6%; reference range, 4.8%–5.9%). A standard oral glucose tolerance test with 75 g of glucose equivalent was performed with a fasting glucose of 130 mg/dl and a 2-h glucose of 159 mg/dl. The fasting insulin concentration was 6.9 μU/ml and 27 μU/ml after 2 h. Considering the clinical and family history, mutation analysis of the GCK gene was performed. Complete sequencing of coding exons and intron-exon boundaries of the GCK gene was carried out in the patient. Genetic analysis of case identified a heterozygous mutation (c.151.G>T) leading to stop codon (p.E51*) in GCK gene. Family members were screened for this mutation. The same mutation and mild hyperglycaemia were found in the patient's father and the two-sisters but was absent in the mother. **Conclusion:** GCK mutation screening should be considered in patients with mild early-onset hyperglycaemia, family history of impaired glycaemia, and negative ß-cell antibodies. In addition family members of patients with MODY should be screened.

P3-708

Incidence and Risk Factors of Diabetic Nephropathy in Children and Adolescents as Per Republic of Uzbekistan National Register

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Aim: To study incidence and risk factors of diabetic nephropathy (DN) in children and adolescents as per the Republic of Uzbekistan National Register. **Method:** An information list (card) and appropriate software were developed on the basis of the DN register. The cards were collected in every region of Uzbekistan to be introduced into a computer database. **Results:** DN screening performed in children by Alikhanova N M in 1998 showed that 4+5 degree DN incidence in children and adolescents was 20.4 and 51% respectively. In 2007 on the basis of specially developed register card data on incidence of DN in children and adolescents with one type diabetes mellitus was assessed in the Republic of Uzbekistan. four and five degree DN incidence in children was found 17.0 and 0.6%, to be 31.7% in adolescents and lower than the one in 1998, but higher that the one in the 2006-year Register. It was 11.2 and 20.7% respectively, to show that there is 1.5–time difference between actual and registered DN incidence. Inheritability by diabetes mellitus and by arterial pressure, mean daily hyperglycaemia, increase in HbA1c, body mass and cholesterol, reduction of blood fibrinolytic activity and both daily and nocturnal increase in arterial pressure as well as growth in manifestations of autonomic neuropathy are among the risk factors of onset and progression of DN in children and adolescents. Cow milk feeding, low weight at birth and disease duration differed insignificantly. **Conclusions:** Rate of registration of late diabetic complications, DN and chronic renal insufficiency (CRI) in particular remains low, though in 50% and 100% children and adolescents respectively, CRI is the main cause of death.

P3-709

Elevated HbA1c and Cardiometabolic Risk Factors in Korean Children and Adolescents: Data from the Korean National Health and Nutrition Examination Survey, 2011–2012

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Background: Prediabetes often precedes type 2 diabetes, which is associated with obesity and increased risk of developing cardiovascular disease. Haemoglobin A1c (HbA1c) has been recently recommended as a useful tool for the diagnosis of diabetes and prediabetes. **Objective and hypotheses:** We investigated whether prediabetes according to HbA1c was associated with cardiometabolic risk factors in Korean children and adolescents. **Method:** We used data from the 2011–2012 Korean National Health and Nutrition Examination Survey (KNHANES), which is the nationally representative database. In total, 1 581 subjects aged 10–19 years were assessed. We classified the subjects into two groups based on HbA1c level (the normoglycaemia group with HbA1c of $<5.7\%$; the prediabetes group with HbA1c of 5.7–6.4%). Clinical characteristics and cardiometabolic risk factors between the normoglycaemia and prediabetes groups were compared. **Results:** According to HbA1c levels, 305 subjects (171 boys and 134 girls) had prediabetes. In the prediabetes group, obesity, waist circumference (WC), WC to height ratio (WHtR), total cholesterol, triglyceride (TG), fasting glucose, AST and ALT were significantly higher than those in the normoglycaemia group ($P<0.001$). Metabolic syndrome by IDF definition was 3.5% in prediabetes group and 1.4% in the normoglylcaemia group (statistically non-significant, $P=0.098$). In the both normoglylcaemia and prediabetes groups, overweight/obese subjects had higher BMI, WC, WHtR, blood pressure, TG, AST and ALT ($P<0.05$) and lower HDL cholesterol ($P<0.001$) than those with normal weight. Age-, sex- and income-adjusted logistic regression analysis showed that the subjects with prediabetes had increased risk of having obesity (OR 1.52, $P<0.001$), abdominal obesity (OR 2.75, $P<0.001$), hypertriglyceridemia (OR 2.02, $P=0.005$), high ALT (OR 2.53, $P<0.001$). **Conclusion:** Prediabetic HbA1c levels in Korean children and adolescents were strongly associated with increased cardiometabolic risk factors. HbA1c might be a useful marker to assess cardiometabolic risk in children and adolescents.

P3-710

How Appropriate are the Lengths of Syringe Needles Used for Subcutaneous Injections to the Children at School Age

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Aims: To define the normal ranges of the thicknesses of the skin and subcutaneous tissues *via* ultrasonography, and to determine whether the current syringe needle-lengths used for the subcutaneous injections were appropriate. **Methods:** The thicknesses of the skin and subcutaneous tissues of 2 244 students were measured at the left arm using ultrasonography. Patients were divided into three groups based on age: 6–8, 9–12 and 13–17 year. **Results:** The thicknesses of the skin, subcutaneous tissue and skin-subcutaneous tissue were found to be positively correlated with age, BMI and body surface area. All these were observed to be gender related. There is a possibility to make intramuscular injections for the 50, 25 and 25% of boys with age groups of 6–8, 9–12 and 13–17 year respectively. For the girls, the risk of intramuscular injection is 25% for all age groups. **Conclusions:** Our study has shown that the skin and skin-subcutaneous tissue thicknesses varies as a function of age, gender, BMI and body surface area.

P3-711

Heterogeneous Presentation of Paediatric Hyperglycaemic Hyperosmolar State – A Case Series

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Background: The hyperosmolar hyperglycaemic state (HHS) is rare, but recognised, life-threatening clinical entity in children with type 2 diabetes (T2DM). It is also reported as presenting feature in other types of diabetes and metabolic disorders. The estimated mortality in HHS is 10–20%, ten times higher than Diabetic Ketoacidosis (DKA).The mainstay of management involves aggressive fluid therapy with insulin and managing complications namely; rhabdomyolysis, multi-organ failure, cerebral oedema and malignant hyperthermia. **Objective:** We report three cases, where HHS was the presenting feature, only one of which has confirmed T2DM, highlighting the challenges for early diagnosis and management. **Case-series report:** i) 16-year-old-Asian female, with neurodegenerative disease, immobility, pubertal delay and obesity (BMI 42) presented acutely unwell. Examination revealed Acanthosis Nigricans. She had a complicated course with acute kidney injury, vascular thrombosis and cerebral oedema. ii) 4.5-year-old-Black African male, BMI 16.5, previously well, presented with abdominal distention and collapse (GCS 3/15). Aetiology of presentation was unclear; fluids and insulin were stopped within 4 days. Recovery was complete. iii) 8-year-old Caucasian girl with quadriplegic cerebral palsy and Haemophagocytic Lymphohistiocytosis, receiving pulsed steroid therapy, presented with stupor and severe dehydration. Recovery was to premorbid state. Management in all cases involved aggressive isotonic fluid resuscitation and insulin therapy. Investigations consistent with HHS are shown below.

Table 1.

Investigations	Case 1	Case 2	Case 3
pH	7.27	6.8	7.32
Blood glucose (mmol/l)	33	47	38
Sodium (mmol/l)	172	163	152
Serum-Osmolality (Osm/Kg)	392	400	368
HbA1C (mmol/mol)	104	<40	82
Blood Ketones (mmol/l)	1.8	Negative	2.4

Conclusion: This heterogeneous case series includes new-onset T2DM, steroid induced and transient HHS with complete recovery. The latter two have not been previously described in the literature. Significant neurodevelopmental delay in two of our patients delayed diagnosis similar to other case reports. There is imperative need for increased awareness and evidence-based paediatric guidelines for management of HHS to avert adverse outcomes.

P3-712

A Novel Compound Heterozygous Mutation in an Adolescent with Insulin-dependent Diabetes: A Case Report of Wolfram Syndrome

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Background: Wolfram syndrome (WS) is an autosomal recessive neurodegenerative disorder characterized by non-autoimmune diabetes mellitus and progressive optic atrophy. WS includes other possible disorders, such as diabetes insipidus, sensorineural deafness, genitourinary tract problems, neurological or psychiatric disorders and others. **Case presentation:** A 12-years-old boy presented with glicosuria and shortly developed insulin-dependent diabetes mellitus. Autoimmune markes for diabetes were negative, insulin requirement ranged from 0.22 to 0.43 U/kg per day) and HbA1c from 53 to 59 mmol/mol). Family history for autoimmunity was negative. Genetic tests for monogenic diabetes were performed and no mutations for GCK-MODY 2 and HNFA1-MODY 3 were found. At age 16 years metabolic control worsened and optic atrophy was identified during a routinary eye examination and confirmed by MRI. Wolframin (WFS1) gene was analysed and compound heterozygosity for a missense and a frameshift mutations in exon 8 was found: c.(2104G>A)+(2155_2168dup14); p.(Gly702Ser)+(Phe725fs). The missense mutation, paternally inherited, is annotated by Human Gene Mutation Database (HGMD), but no phenotype description is available. The frameshift mutation, also detected in the mother, is a 14 bp duplication, not previously reported. It causes a frameshift which results in a premature stop codon, predicting a truncated protein of 25 amino acids shorter than the wild-type wolframin. No mutation was shared by the twin brother. No signs of central diabetes insipidus or any other diseases associated with WS were found. Our report of a novel inactivating mutation increases the spectrum of WFS1 defects and contributes to establish phenotype-genotype relationship. **Conclusion:** WS diagnosis is often delayed and misdiagnosed as autoimmune diabetes. The rarity of the condition and the absence of other diseases at diabetes diagnosis makes extremely challenging the recognition of WS. However the compound heterozygosity for the here reported mutations, even markedly altering the protein structure, seems to confer a mild phenotype among the spectrum of WS manifestations.

P3-713

Sirolimus Therapy in an Infant with Persistent Hyperinsulinaemic Hypoglycaemia

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Background: Persistent hyperinsulinaemic hypoglycaemia (HH) of infancy (PHHI) is a rare condition which presents with severe hypoglycaemia during the neonatal period. For medically unresponsive forms of diffuse HH, subtotal pancreatectomy was previously the only treatment option, with the potential consequences of recurrence of hyperinsulinism, diabetes mellitus and exocrine pancreatic insufficiency. The novel use of sirolimus treatment was recently reported in four infants who achieved good glycaemic control. We report our experience with Sirolimus in an infant with PHHI. **Case presentation:** A neonate was diagnosed with PHHI when she presented with severe refractory hypoglycemia at birth. She was initially treated with diazoxide at 20 mg/kg per day and a carbohydrate-rich diet. She responded well with minimal hypoglycaemia until 7 months of age when she started having episodes of recurrent hypoglycaemia. The side effects of diazoxide she experienced were hypertrichosis and decreased appetite. Mutational analysis demonstrated that she was heterozygous for a novel missense mutation on the ABCC8 gene. An 18-F DOPA PET scan showed that she had diffuse disease. At 18 months, she was commenced on sirolimus at an initial dose of 0.5 mg/m^2 per day, gradually increasing weekly until the dose was 4.8 mg/m^2 per day, with a therapeutic trough between 20–30 ng/ml. Diazoxide was eventually discontinued 2 months

after sirolimus was started. She has continued on sirolimus for the past 8 months. She only experienced one episode of severe hypoglycemia contributed by viral gastroenteritis, during which the sirolimus trough was suboptimal at 13 ng/ml. Side effects included mild elevation of transaminases and asymptomatic elevation of creatine kinase level. **Conclusion:** Sirolimus therapy is an alternative to subtotal pancreatectomy in severe diffuse PHHI, avoiding the side effects of hypertrichosis and fluid retention associated with diazoxide therapy. However, the duration of therapy in PHHI and the long term side effects have yet to be established.

P3-714

Permanent Neonatal Diabetes Mellitus in Beckwith Wiedemann Syndrome: An Unusual Co-Occurrence

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Background: Diabetes mellitus is not characteristic of Beckwith Wiedeman Syndrome (BWS). If anything, BWS is associated with hypoglycaemia secondary to hyperinsulinaemia. A case of permanent neonatal diabetes mellitus and BWS have never been reported from our setting. **Objective and hypotheses:** To report on a 17 years old boy with BWS diagnosed with permanent neonatal diabetes mellitus at 4 months of age and to determine the molecular genetics study which may associated with diabetes and BWS. **Method:** He was a term baby, weighing 5.25 kg, born by caesarian section (CS) for cephalo-pelvic disproportion. He had earlobe crease, protruded tongue and omphalocoele requiring immediate surgical repair. He stayed in-patients for 2 months post operation. He suffered recurrent hypoglycaemia until 4 months of age, and then developed persistently elevated glucose requiring insulin therapy. He was tested for DNA methylation at the imprinted KCNQ1OT1/H19 loci and PLAGL1 locus as well as the sequence analysis of coding and flanking intronic regions of the ABCC8 and KCNJ11 gene. **Results:** In addition to the clinical features of protruding tongue, macrosomia, omphalocoele, earlobe creases and persistent hyperglycaemia requiring insulin, his DNA showed complete hypomethylation at KCNQ1OT1. His DNA methylation was normal at H19 and the TND locus. There was no mutations detected in the KCNJ11 and KIR6.2 genes. The complete hypomethylation at KCNQ1OT1 is consistent with a diagnosis of BWS and the normal methylation at H19 is inconsistent with paternal uniparental disomy at chromosome 11. The absence of KCNJ11 and KIR6.2 is inconsistent with a diagnosis of neonatal diabetes. The combination of clinical signs with molecular genetic studies confirms the diagnosis of BWS in our patient, however, the mutational analysis of the K-ATP channels fails to confirm the cause of diabetes mellitus. **Conclusion:** Diabetes mellitus in BWS occurs rarely and future studies should aim to identify possible causes of diabetes in BWS.

P3-715

Prevalence of Vascular Complications in Children with Type 1 Diabetes in Ireland

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Background: Screening guidelines for vascular complications in children with type 1 diabetes (T1DM) are based on results from Diabetes Control and Complications Trial (DCCT) and its follow-up, the Epidemiology of Diabetes Interventions and Complications (EDIC) trial. These studies established conclusively that early and intensive diabetes care improves long-term outcomes. **Objective and hypotheses:** To establish screening practices and prevalence of vascular complications in a cohort of paediatric patients with T1DM in Cork University Hospital (CUH). **Methods:** A retrospective review of all data currently available over the last 24 months in the paediatric diabetes clinic in CUH was carried out and compared to ISPAD Guidelines 2014. HbA1c, blood pressure (BP), fasting lipid profile, urine albumin to creatinine ratio (UACR) and retinal screening for each patient were recorded. **Results:** 313 children with T1DM (148 girls, 165 boys) aged 1–18 years (mean 11.99 ± 3.7) were analysed. The mean HbA1c was 68.3 ± 15.02 mmol/mol. 235 patients (75%) had HbA1c above the optimal concentration 58 mmol/mol with 26% (81 patients) at the high risk (>74.9 mmol/mol). Retinal screening showed 2% (six children) as having background retinopathy. BP screening was obtained for 87% (272 children) with 26% (81 cases) having an elevated systolic BP ($>140/90$). Lipid screening was documented for 75% (235 children), with 32% (100 children) displaying elevated total cholesterol, 33% (103 children) elevated LDL cholesterol, 11% (34 children) elevated triglycerides and 3% (ten cases) with suboptimal HDL cholesterol. UACR was recorded for 65% (203 cases), with 4% (12 cases) having a UACR >3 mg/mmol (ISPAD 2014). **Conclusion:** The results of this cohort study are consistent with the international literature. They identify what routinely happens in the Paediatric Diabetes Clinic and highlights the vascular risk profile of these children. These baseline data will be followed prospectively for the next 10years and will help to inform clinical care and service development of children with T1DM in Ireland.

P3-716

Hyperglycaemia During Chemotherapy for Acute Lymphoblastic Leukaemia Among Taiwanese Children

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Background: Hyperglycaemia is a common occurrence during the treatment for paediatric acute lymphoblastic leukaemia (ALL). Emergence of new evidence exhibits conflicting results. The incidence of hyperglycaemia during chemotherapy has not been well described in the Asian population. **Objective and hypotheses:** The aim of study is to delineate the characteristics of paediatric patients at risk for hyperglycaemia during chemotherapy. **Method:** This retrospective study involved chart review of consecutive patients aged younger than 18 years with diagnosis of ALL in a medical centre in Taiwan in 1997–2008. Hyperglycaemia was defined by random plasma glucose levels 200 mg/dl or fasting glucose levels 126 mg/dl at least two separate samplings. Risk factors for hyperglycaemia were described with crude and adjusted odds ratios (OR) with 95% confidence intervals (CI) in the univariate and multivariate regression analysis. **Results:** A total of 137 patients with mean age were included for analysis. Mean age at diagnosis was 7.4 years (range 2.1–17.9 years) with male predominance ($n=79$). Among the subjects, 27 (19.7%) were overweight or obese, 42 (30.7%) were aged older than 10 years, and 13 (9.5%) had family history of diabetes. Overall 24 (17.5%) patients experienced hyperglycaemia during ALL treatment. Age was the most important predictor of hyperglycaemia (adjusted OR = 14.22, 95% CI 2.99–67.65). Patients with fasting glucose concentration 100 mg/dl were also 9.85 folds more likely to develop hyperglycaemia (95% CI 2.25–43.05). **Conclusion:** Age and fasting glucose have the highest predictive value on subsequent occurrence of hyperglycaemia during chemotherapy. Cautions in clinical care should be given to those patients at high risk for hyperglycaemia, particularly in the case of obese adolescents with disarranged glucose homeostasis.

P3-717

Seip-Berardinelli Syndrome in a Patient Referred by Low Weight Gain

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Background: Seip-Berardinelli syndrome is a rare form of congenital lipodystrophy. **Objective and hypothesis:** To report a patient later diagnosed with Seip-Berardinelli syndrome referred initially for evaluation due to low weight gain. **Population and/or methods:** We performed the report of the case along with a literature review. **Results:** The patient was referred due to low weight gain. She was the second daughter of a non-consanguineous couple. She was born vaginally at 36 weeks of gestation, measuring 46 cm, weighing 2 685 g, with head circumference of 32 cm and Apgar scores of 9 and 10 at first and fifth minutes. The patient developed neuropsychomotor and speech delay. On physical examination, at 3 years and 8 months, her weight was 19 kg (P90–97); length was 108 cm (P90–97) and head circumference was 49 cm (P50). She had general reduction of subcutaneous tissue, leaving the musculature visible; acanthosis nigricans in neck and axillary regions; umbilical hernia and hirsutism in face, back and limbs. Her laboratory tests showed VLDL dosage of 166 mg/dl (Normal up to 40), triglycerides of 829 mg/dl (Normal up to 160), cholesterol of 151 mg/dl (Normal up to 200); glucose of 83 mg/dl (Normal: 70–110) and insulin of 37 IU/ml (Normal <30). Echocardiography showed concentric hypertrophy of the left ventricle. **Conclusions:** Clinical and laboratory findings were compatible with the diagnosis of Seip-Berardinelli syndrome. These patients have almost complete absence of adipose tissue from birth, which causes them to have an undernourished appearance. The treatment of this disease is based on diet and drug therapy for dyslipidemia control and avoiding its consequences.

P3-718

Effect of Reward-based Motivation on Metabolic Control in Children and Adolescents with Type 1 Diabetes Mellitus

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Background: Metabolic control is important in prevention and delay of microvascular and macrovascular complications of type 1 diabetes mellitus (DM). Psychological disorders and, a lack of motivation may negatively affect metabolic control. Therefore, motivational and psychological support can be needed as a part of medical treatment to improve metabolic control in patients with type 1 DM. **Objective and hypotheses:** To investigate the impact of reward-based motivation on metabolic control in type 1 DM children. **Method:** 44 type 1 DM patients with a mean age of 12.3 ± 2.8 years and mean diabetes duration of 4.7 ± 2.7 years were enrolled in the study. Before the study, patients were informed that three patients who will have the best metabolic control at the end of 1 year would be rewarded. Number of control visits and hypoglycemic episodes, daily insulin requirement and mean HbA1c values were compared before and one year after study. **Results:** During the study period a statistically significant decrease in the mean HbA1c value, number of hypoglycemic attacks and daily insulin requirement were determined ($P<0.05$). Decrease in the mean HbA1c value was significant in both sexes and especially in the pubertal group ($P<0.05$). It was observed that the patients had more frequent control visits during the motivation study. The positive impact of motivation has been maintained throughout 6 months after completion of the study. **Conclusion:** This study showed that reward-based motivation might provide significant improvement in the metabolic control in type 1 DM children with a more evident effect seen in the pubertal group.

P3-719

Fanconi-Bickel Syndrome due to a Novel SLC2A2 Mutation Presenting with Transient Neonatal Diabetes

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Background: Fanconi-Bickel syndrome (FBS) is a glycogen storage disease caused by the homozygous mutations of SLC2A2 gene which codes GLUT2 protein. It is characterized by growth retardation, hepatomegaly and hypophosphataemic rickets. While most of the cases with FBS have fasting hypoglycaemia and postprandial hyperglycaemia, only few cases had been shown to have neonatal diabetes (ND). **Case presentation:** A 14 days old girl was admitted to hospital with difficulty in feeding. She was born 2620 g from consanguineous parents. She had hyperglycemia (bloodsugar: 651 mg/dl) and metabolic acidosis (blood pH: 7.1 HCO3: 11); intravenous fluid and insulin treatment were started with diagnosis of ND. She had increased parenchymal echogenicity in renal ultrasonography but her renal functional tests (RFT), serum and spot urine electrolytes were normal and she did not have proteinuria. She was discharged with subcutaneus NPH insülin. At the age of four months insülin was discontinued and ramipril was started because of newly diagnosed proteinuria. Molecular genetic study showed her homozygous for a novel missense mutation (p.A127D, c.380C > A) in SLC2A2 gene. Her parents were heterozygous for that mutation. When she was evaluated for FBS findings in addition to present growth failure and proteinuria at nine months of age; RFT and serum electrolytes were normal but tubular phosphate reabsorption was decreased. Unlike increased renal echogenicity compatible with diffuse parenchymal disease, there wasn't liver involvement in abdominal ultrasonography. **Conclusion:** ND can be the initial finding of FBS. After excluding frequent causes, FBS should be kept in mind for differential diagnosis for ND. Cases with homozygous SLC2A2 mutations should be followed for growth retardation, hepatomegaly and hypophosphataemic rickets.

P3-720

Cardiovascular Autonomic Neuropathy and Early Atherosclerosis in Adolescent Type 1 Diabetic Patient

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Objective: To evaluate cardiovascular autonomic neuropathy (CAN) in type 1 Diabetics and to detect its relation to coronary artery calcification. **Patients and methods:** It is a cross sectional study included 62 diabetics and 30 controls. Clinical, laboratory assessment and 24 h holter were done for all patients and controls and coronary artery calcium (CAC) scoring by multisclice CT was done for all patients only. *t*-test, Mann–Whitney U-test and stepwise multiple regression were used for statistical analyses. **Results:** CAC score was positive in 8.1% of patients. Heart rate variability (HRV) was significantly lower in diabetics. All parameters of HRV were insignificantly lower in diabetics with positive CAC score. Patients with microalbuminuria had a significantly lower HRV. HRV had a significant correlation with age of patients, duration of disease, HbA1, and Qtc in diabetics. **Conclusion:** Percentage of arrhythmia and early atherosclerosis is high in adolescent type 1 diabetic patients. CAN is associated with early atherosclerosis. Cardiac autonomic neuropathy is associated with older age, longer duration, and poor glycemic control and microalbuminuria.

P3-721

GAD Antibodies Negative Type 1 Diabetes and Dravet Syndrome

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Background: An association between type 1 diabetes mellitus (T1DM) and idiopathic generalized epilepsy is reported. Some authors suggest an autoimmune mechanism mediated by antibodies to glutamic-acid-decarboxylase (GAD), that is an enzyme involved in the synthesis of the neurotransmitter GABA. Dravet syndrome (DS) is a rare, severe epilepsy disorder characterized by febrile hemiclonic seizures or generalized status epilepticus starting at 6 months of age. In classical DS, a delayed development and a motor impairment are often described. Mutation or deletions of SCN1A account for 85% of DS cases. SCN1a mutations alter sodium channel activity that can predispose the SNC to abnormal excitability. **Objective and hypotheses:** To discuss the association of antibodies negative T1DM and DS in a patient. **Method:** Case report and literature review. **Results:** We report the case of a 9-year-old boy with T1DM and DS. No familial history of epilepsy or diabetes was reported. The patient was a first-born at the 37th week from a normal pregnancy. He presented a normal adaptation at birth. At 8 months, he developed febrile seizures, then at 2.5 years he presented afebrile generalized tonic-clonic seizures. A DS was

clinically diagnosed, confirmed by a positive test for a SCN1A gene mutation (heterozygous c.560_563inv).Epilepsy has proved to be drug-resistant (valproate, gardenal, topiramate, levetiracetam and then stiripentol). A mild improvement of seizures was reported with stiripentol treatment. At the age of 7, the boy developed a T1DM. Blood examinations revealed glycaemia 536 mg/dl; glycated haemoglobin 86 mmol/mol (n.v.20–38), venous pH 7.29, bicarbonate 10.7 mmol/l, base excess −17.1 mmol/l; phosphotyrosine antibodies positive, negative anti-GAD and anti-insulin antibodies. The antibody panel was confirmed after 2 years. **Conclusion:** A concordance between GAD-antibody titres and clinical manifestations of myoclonic encephalopathy was reported in some patients, in whom a pathogenetic role of GAD autoimmunity was suggested. In the presented case, we can hypothesise an autoimmune aetiology but not GAD-antibodies mediated.

P3-722

Social Risk Assessment in Children with Diabetes Mellitus to Plan Medical and Social Care

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Background: According to the World Health Organization, the social determinants of health, the conditions in which people are born, grow, live and work – significantly influences on health. The CAF Foundation, the Endocrinology Scientific Center and the Institute for Family Health under the Alfa-Endo Program studied prevalence of some social determinants in families of children with type 1 diabetes mellitus. **Objective and hypotheses:** Investigate social conditions of families with children with type 1 diabetes mellitus to plan social care. Research question: does the social conditions of families influence on diabetes control in children? **Method:** The study was conducted in 2014 in the six Russian regions. In total, 221 mothers of children with type 1 diabetes mellitus (diabetes) were interviewed in health facilities (187 included in the analysis). The indicator of poor control of diabetes was glycated haemoglobin (HbA1C) higher than 8% (the Russian National Recommendations). **Results:** Mean age of the children, whose mothers were interviewed, was 10.2 years (from 2 to 18), mean duration of diabetes – 4 years, 60% were girls. About 18% of the families had income < mean live-wage; 16% with single parent. One parent works in 52% of families; mothers can't work mainly because of the child diseases. Both parents are unemployed in 3% families. All children are provided by the State with complete medical care. The most needed social support: financial (50%), better housing condition (39%), psychological counseling (39%), legal advice (35%). Half of children with diabetes had level of HbA1C higher than 8%. No one independent social factor correlated with poor diabetes control. However, combination of poverty, single maternity, parent unemployment in 3% of families correlated with high HbA1C (Pearson Chi-Square 5 510, the minimum expected count is 2.82, $P=0.025$). **Conclusion:** The study confirmed necessity of screening social risk factors in families of children with diabetes to provide comprehensive social and health care. **Funding:** This work was supported by the Alfa Banking Group (Donation Agreement #48, 2013).

P3-723

The Investigation of Frequency of Diabetic Ketoacidosis in Children with New-onset Diabetes Mellitus Type 1

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Background and aims: The aim of this study was to investigate the frequency of diabetic ketoacidosis and diagnostic mistakes in onset diabetes mellitus type l in children and their relationship with age. **Materials and methods:** In this study were included 269 patients (from 7 month to 17 years) in onset diabetes mellitus type l since 2010–2013. All patients were divided in to two groups. The first group consists of 92 patients (children were younger than 5 years) and the second group consists of 177 patients (children were more senior than 5 years). **Results:** Diabetic ketoacidosis was revealed at 137 of 269 (50.9%) patients: 56 children younger 5 years and 81 more than 5 years. In the first group the frequency of diabetic ketoacidosis was 60.8% (56 from 92) and in the second group 45.7% (81 from 177, $P=0.026$). Among 269 patients with diabetes mellitus type l in 25 (9.3%) children was wrong diagnose. In the same time 24 (17.5%, $P=0.05$) from 137 children with diabetic ketoacidosis had wrong diagnoses. Wrong diagnoses among patients with diabetic ketoacidosis were: 56% – appendicitis, 20% – pneumonia or bronchial asthma, 20% – meningitis, 4% – pyelonephritis. In the first group the frequency of diagnostic mistakes was 25% (14 from 56), in the second group – 12.3% (ten from 81, $P=0000$). **Conclusion:** The frequency of diabetic ketoacidosis in new-onset diabetes mellitus type l in children was high (50.95%). Diagnostic mistakes were more often among children with diabetic ketoacidosis. Diabetic ketoacidosis occurred more often in children under 5 years. Diagnostic mistakes also took place more often in children under 5 years.

P3-724

Study of Adiponectin Level in Diabetic Adolescent Girls in Relation to Glycaemic Control and Complication of Diabetes

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Objective: To determine the influence of adolescent girls with type 1 DM on circulating levels of adiponectin and to study the relation between adiponectin level with glycemic control and complication of diabetes. **Patients and methods:** The study included 40 female adolescent type 1 diabetic patients and 40 healthy volunteer of the same age and sex. Blood sample was taken for assessment of glycosylated haemoglobin, lipid profile and adiponectine. Urine sample was taken for assessment of albumin/creatinine ratio. *t*-test for independent variables, Pearson's correlation analysis were used. **Results:** The mean age of our patients was 14.4±2.5, mean duration of disease was 10.1±2.8 and mean insulin dose was 1.4±0.5. Diabetic patients had a significantly higher diastolic blood pressure, triglyceride, total cholesterol, LDL and adiponectin than controls. Patients with diabetes complication had a significant lower BMI and HDL. On the other hand, they had higher disease duration, total cholesterol, HbA1, albumin/creatinine ratio and adiponectin. Patients with microalbuminuria had a lower BMI, higher disease duration, diastolic blood pressure and adiponectin. Patients with diabetic retinopathy had higher disease duration, insulin dose, HbA1, microalbuminuria and adiponectin. Adiponectin in diabetic patients had a significant negative correlation with BMI and positive correlation with systolic blood pressure and microlabuminuria. **Conclusion:** Serum adiponectin level is high in adolescent type 1 diabetic girls. It can be used as a predictor of diabetes complications rather than a sensitive biochemical marker for glycaemic control.

P3-725

Frequent and Prolonged Daytime Hypoglycemia in Diabetic Children Detected by Continuous Glucose Monitoring: A Problem of Hypoglycaemia Unawareness?

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Background: Hypoglycaemia represents a common issue in diabetic children, and the achievement of good metabolic control together with the avoidance of hypoglycemia remains a tightrope walk. As hypoglycaemia is not always recognised, data about hypoglycemia frequency are limited. **Aims:** We previously reported about nocturnal hypoglycaemia in diabetic children. This study now focusses on the frequency and duration of hypoglycemia at daytime and risk factors for such episodes. **Patients and methods:** 60 diabetic children were included. The data of 51 patients (29 males, 22 females, mean age 12.1 years, 2.4–17.6 years, 36 with multiple insulin injection therapy and 15 on insulin pump) could be analysed. Glucose was measured by continuous glucose monitoring (CGMS) (iPro®, Medtronic) for 6 days. Subjects had to perform four blood glucose measurements per day for calibration and to keep notes about insulin doses, bed time and wake up time and symptoms of hypoglycaemia. HbA1c was calculated as average of four values measured preceding the study. Daytime hypoglycemia was defined as glucose excursion <3.7 mmol/l during daytime. **Results:** Hypoglycaemia remains frequent in diabetic children, and most of the episodes are asymptomatic and often prolonged. Tight metabolic control or high insulin dosage however did not increase the risk for hypoglycaemia. In contrast longer diabetes duration could be identified as a risk factor for prolonged hypoglycaemia. These data suggest that hypoglycemia unawareness and decreasing counterregulation are a relevant problem already in childhood. **Conclusion:** Hypoglycaemia remains frequent in diabetic children, and most of the episodes are asymptomatic and often prolonged. Tight metabolic control or high insulin dosage however did not increase the risk for hypoglycaemia. In contrast longer diabetes duration could be identified as a risk factor for prolonged hypoglycaemia. These data suggest that hypoglycaemia unawareness and decreasing counterregulation are a relevant problem already in childhood.

P3-726

Neonatal Diabetes Mellitus due to Insulin Gene Mutation

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Background: Neonatal diabetes is a rare disorder with an incidence of between 1 in 215 000–500 000 live births with approximately 50% having permanent neonatal diabetes (PNDM). Insulin gene (*INS*) mutations have recently been described as a cause of PNDM. **Objective and hypotheses:** To describe clinical features and laboratory manifestations of patient with PNDM due to INS gene mutation and evaluate outcome of management. **Method:** Case series study, clinical features, biochemical finding, mutation analysis and management outcome of five cases from five unrelated families were study. All exon of INS genes were amplified from genomic DNA and directly sequenced.

Results: Five cases (three girls and two boys) onset at 152.2 ± 129.4 days of age with gestation age of 37.6 ± 3.3 weeks, birth weight of 2840 ± 856 g. Four out of five cases admitted with the feature of diabetes keton acidosis, blood glucose of 35.6 ± 13.8 mmol/l, HbA1C of 8.98 ± 3.4%. Analysis of all coding regions and exon/intron boundaries of the INS gene showed heterogygous mutation: two patients with splicing mutation at c.188-31G > A, one patient with missense mutation at c.265C > T (p.R89C), one patient with missense mutation at c.127T > A (C43S), one patient with missense mutation at c.286T > C (p.C96R). The oldest patient who has been treated for 12 years has bad blood glucose control for a long time so he has physical retardation but normal mental development and not yet complication. Four smaller patients who have duration of 21 ± 13.8 months have quite normoglycaemic with blood glucose in 5–8 mmol/l and HbA1C of 6.7 ± 1.4%. All of them have normal motor and mental development. **Conclusion:** *INS* mutation screening is recommended for all diabetic patients diagnosed before 1 year.

P3-727

Single Centre Experience of Neonatal Diabetes

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Background: 6 patients with neonatal diabetes presenting to a single centre from April 2014 to March 2015 were studied for clinical presentation, biochemical findings of the disorder, genetics and treatment outcomes. **Objective and hypotheses:** Six children presenting to a single centre in South India were studied for correlation of disease with clinical features and genetics, suitability of current treatment regimens and treatment outcomes. **Method:** Neonatal diabetes was defined as 'A Diagnosis of Diabetes prior to 9 months of age.' Ages at recruitment ranged from 5 days to 18 years. Detailed history and investigations ere obtained and included HbA1C, blood glucose, liver and renal function tests and autoimmune markers. Genetic samples were sent to the Genetics Lab of University of Exeter Medical School. **Results:** Genetic mutations were identified in five of the six children. Two children had mutations in INS gene (*INS* missense mutation, *p.R89C*; a novel INS intronic mutation, c.188-40C > A), one child in ABCC8 (*ABCC8* nonsense mutation, *p.W232**, and an *ABCC8* missense mutation, *p.P254S*) and another in KCNJ11(*KCNJ11* missense mutation, *p.R201C*). In another infant with a mutation in KCNJ11,(novel *KCNJ11* missense variant, *p.R29H*) a causal association of the mutation with diabetes could not be proven. Two children with INS mutations and the child without an identified mutation have been continued on insulin. ABCC8 and KCNJ11 mutation children are being transitioned onto Sulphonylurea. The neonate with the non-causal KCNJ11 mutation died on 11th day of life, of a massive cerebral infarct, most probably consequent to very high blood sugars at presentation. **Conclusion:** With proper genetic analysis, basic research findings can be translated into accurate treatment decisions and good clinical outcomes in neonatal diabetes and especially, the outcomes of transition onto sulphonylurea can be improved.

P3-728

Assessment of the Effect of the Diagnosis of Type 1 Diabetes Mellitus in the Nutritional Habits of Unaffected Family Members

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Background: Type 1 diabetes mellitus (T1DM) is a chronic and demanding disease affecting not only the patient's life but also the whole family's perspective. Many studies have explored the effect of T1DM on the emotional and social life of the family; however, a small amount of evidence for the dietary habits of the unaffected members of the family currently exists. **Objective and hypotheses:** To explore the effects that T1DM has on the dietary habits of the unaffected members of the family. **Method:** The survey was performed during the regular visit of patient and family at the outpatient paediatric diabetic clinic of our department. Unaffected family members (parents and non-diabetic children) were asked to participate in the study. Changes in dietary habits were assessed using a standardized questionnaire (family eating and activity habits questionnaire, FEAH) and a questionnaire of demographic, anthropometric and nutritional data of family that was specifically designed for this study. Height and weight were measured and BMI was calculated for each unaffected member of the family during the visit, whereas previous measurements were retrieved either by health records or by memory. **Results:** Members of fifty families were interviewed. Differences in dietary habits before and after the diagnosis of T1DM were documented to affect predominantly mothers. A statistically significant intra-familial difference in dietary habits was observed with mothers being affected more than fathers ($P = 0.001$). This effect was more prominent in mothers whose child was diagnosed with T1DM at a younger age than later in life. Assessment of family activity revealed a low percentage of physical activity for most of the families. **Conclusion:** Mothers and especially those with children diagnosed with T1DM at the age of 5.5 years or earlier changed their dietary habits in a higher proportion. A significant number of families retained their unhealthy nutritional habits after the diagnosis of T1DM and in conjunction with the reported low level of physical activity indicate areas for intervention.

P3-729

Lifestyle and Metabolic Control in Adolescents with Type 1 Diabetes

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Background: In type 1 diabetes (T1D) adolescents it is necessary to design effective interventions to take care of their health and psychological problems. This leads to effective transition to an adult unit. **Objectives:** Evaluate the relationship of lifestyle with metabolic control in diabetic adolescents. **Methods:** Retrospective study of 42 T1D adolescents managed in a Pediatric Diabetes Unit. Patients completed a questionnaire on lifestyle and results were correlated to metabolic control. **Results:** Patients included 20 males, 22 females with a mean age 15.8 ± 1.6 years (13–18.49) and 7.3 ± 3.4 years after diagnosis (1–14.62). Mean HbA1c 7.7 ± 1%, 4.6 ± 0.99 glycaemia/day, insulin dose 0.93 U insulin/kg per day and 4.2 ± 1.22 injections/day. 90.5% received treatment with multiple doses of insulin (MDI). Comparing continuous subcutaneous insulin infusion (CSII) and MDI: number of injections/day: 4.07 MDI vs 6.8 CSII ($P = 0.01$), insulin dose/day, HbA1c, blood glucose/day between groups was non significant. Number of boluses was significant negative correlated with HbA1c level ($P = 0.021$); as well as number of glycaemia/day with HbA1c and blood glucose variability (p NS). Teens who exercise ≧3 times/week (64.3%) had better metabolic control than those who did not exercise (HbA1c 7.4% vs 8.3%; $P = 0.02$). 9.5% of adolescents reported smoking and 38.1% reported drinking alcohol. Smoking ($P = 0.026$) and drinking (P NS) were associated with poor metabolic control. 64.3% of adolescents always performed glycaemic check prior to insulin injections. 12.2% were seen by psychologists, and 75% of those would like to have a specific unit for adolescents with T1D. 64.95% of patients thought psychologist would help them and the worst controlled were the most demanding. **Conclusions:** Exercising ≧3 times/week was associated with good metabolic control. Drinking alcohol, smoking, lower insulin injections and glucose determinations were associated with poor metabolic control. It exists a high demand, especially by those in poor control, to create specific units to provide psychological support.

P3-730

β-Cells' Functional Exhaustion at Type 1 Diabetes Onset may Lead to Early Microvascular Complications

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Background: Diabetic ketoacidosis (DKA) is a severe and often the inaugural clinical manifestation of type 1 Diabetes (T1D). Diabetic nephropathy is one of the most devastating chronic complications of T1D and its' early diagnosis is traditionally based on microalbuminuria. **Objective and hypotheses:** The aim was to investigate the possible associations between the initial clinical manifestations and the chronic complications of T1D. **Method:** Retrospective study of data acquisition on clinical manifestations during the long-term follow-up from the archives of the Diabetes Centre, 'Aghia Sophia' Children's Hospital from 1990 to 2013. We studied 567 individuals with T1D. Fifty-seven percent of these patients presented DKA at diagnosis. The 24-h urinary albumin excretion (UAE) ((nephelometer Turbox) Orion, Finland), was assessed in 196 of the 567 patients and microalbuminuria (MA) was defined with values between 30–300 mg/day, measured on at least two measurements over a three-month period. Statistical analyses were performed using MedCalc statistical software. **Results:** 30.6% of the patients examined for UAE, had microalbuminuria. The mean age of MA occurrence was 15.7 years and was not correlated with DKA. Kaplan-Meier survival curve showed a mean age of microalbuminuria 13.6 years for the patients who presented DKA at T1D onset, while the mean age for MA for those who had no DKA at onset was 17.4 years ($P = 0.024$). **Conclusion:** The mean age of microalbuminuria was significantly younger for those patients who initially presented DKA and this finding may reflect a genetic or environmental predisposition regarding the severity of the course of T1D. It has been supported that decreased C-peptide levels are associated with microvascular complications in T1D. Apparently, the early and severe pancreatic β-cells' secretory exhaustion, results not only in DKA but may trigger the initiation of the pathophysiologic phenomena that lead to the microvascular complications at a younger age.

P3-731

Influence of Pancreatic Autoinmunity in the Onset and Progression of Diabetes in Paediatric Population

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Background: Anti-islet autoantibodies are predictive and diagnostic markers for type 1 diabetes (T1D). The most frequently determined pancreatic autoantibodies in T1D are anti-glutamic acid decarboxilase (GAD), anti-tyrosine phosphatase (IA-2) and anti-insulin (AAI). **Objective and hypotheses:** To study whether the pancreatic autoimmunity profile influences the initial presentation of diabetes, its metabolic behaviour and the presence of other autoimmune disorders in T1D. **Method:** Retrospective study of 210 paediatric patients with T1D. We analyzed age, sex, age at diagnosis, type of clinical presentation (hyperglycaemia/ketosis/ketoacidosis (KAD)), HbA1c (HPLC-Menarini, NV 5.31 ± 0.31%), C-peptide levels and pancreatic autoimmunity (GAD, IA2, AAI). Additional autoimmune disorders were screened with an antibody array at diagnosis and at follow-up. The metabolic control (last year mean HbA1c and acute complications) were also analysed. Data are reported in percentages, median and interquartile ranges. Statistical analysis was performed with SPSS 22.0. **Results:** At diagnosis, mean age was 7 years (3.3–10.5), 53%

Table 1. (for abstract P3-731)

	GAD+	IA2+	GAD+/IA2+	AAI+	GAD−/IA2−/AAI−
n (%)	45 (21%)	45 (21%)	92 (44%)	2 (1%)	26 (12%)
Years at DM1 onset	5.0 (2.1–10.5)	6.8 (3.6–9.8)	8.3 (4.7–10.9)	7.0 (3.8–10.3)	4.1 (2.7–8.2)
Sex (F%)	44	62	52	50	54
DM1 debut (%) HG/Ketosis/KAD	29/38/33	20/32/48	29/38/33	50/0/50	19/58/23
HbA1c at DM1 debut (%)	10.6 (8.7–12.1)	10.7 (9.6–12.6)	10.7 (9.8–11.9)	9.9 (6.8–13.0)	11.0 (9.9–12.1)
Basal C-Peptide (ng/ml)	0.4 (0.3–0.5)	0.5 (0.3–0.6)	0.5 (0.3–0.7)	0.5 (0.4–0.7)	0.3 (0.1–0.6)
Celiac antibodies (%)	11	9	7	0	19
Anti-thyroid antib (%)	9	9	9	0	8
Anti-parietal cells antibodies (%)	0	2	2	0	0
Follow up (years)	4.4 (2.6–8.3)	4.5 (2.2–7.8)	4.0 (2.1–6.6)	3.6 (2.6–4.6)	5.3 (3.0–9.2)
Mean HbA1c in the last year (%)	6.5 (6.2–7.2)	6.7 (6.2–7.1)	6.6 (6.3–7.0)	6.4 (6.3–6.5)	6.7 (6.3–7.1)

female, Hb1Ac 10.7% (9.6–12.2), C-peptide 0.5 ng/ml (0.3–0.7). Initial presentation: hyperglycemia 23%, ketosis 40%, ketoacidosis 37%. Associated autoimmunity at follow-up: anti-thyroid antibodies 9%, celiac disease 10%, parietal cells antibodies 2%. Celiac disease was diagnosed in five patients before T1D. GAD+ patients showed more rapid progression to celiac disease. Other autoimmunity markers: one patient had adrenal antibodies (GAD+/IA2) with normal adrenal function, 4% of the patients presented positive ANA, one of them with olygoarthritis (IA2+) and another with associated autoimmune thyroiditis (GAD+/IA2+). Another patient was diagnosed with autoimmune hepatitis 3.7 years after T1D (GAD+). Within the last year follow-up no patient presented episodes of severe hypoglycaemia or ketoacidosis. No significant differences were found between patient-groups with isolated, combined or absence of pancreatic autoantibodies (table 1). **Conclusion:** In our cohort 88% of patients have pancreatic autoimmunity markers, which did not influence the debut, the subsequent] metabolic outcome of T1D or the prevalence of other autoimmune diseases.

P3-732

Severe Insulin Resistance and Dyslipidaemia with Unremarkable Fat Distribution in an Adolescent Girl due to Mutation in the PPARG Gene (Familial Partial Lipodystrophy Type 3)

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Background: Mutations in the PPARG gene, encoding peroxisome proliferator-activated receptor-gamma (PPARG) are associated with Familial lipodystrophy type 3. PPARG regulates fatty acid storage and glucose metabolism. The genes activated by PPARG stimulate lipid uptake and adipogenese by fat cells. In cases of lipodystrophy and defects of adipogenesis lipoid accumulates ectopically in the liver, skeletal muscle, pancreas and cardiovascular tissues and impairs the function of these tissues causing metabolic disease. **Objective and hypotheses:** A 16 year old girl with a BMI on the 90th centile presented with severe insulin resistance, acanthosis nigricans and unremarkable fat distribution. She was first treated with metformin and with a current HbA1c of 8.5% started treatment with insulin glargin. Extensive hypertriglyceridaemia up to 5000 mg/dl [56 mmo/l] developed within 1.5 years treated by Omega-3-acids, MCT fat and fenofibrate. Transaminases were elevated and the liver was hyperechoic on the ultrasound. Father was healthy with triglycerids around 300 mg/dl. An insulinresistance syndrome was suspected and a genetic analysis performed. **Method:** DNA from the patient has been screened for mutations in the PPARG gene by fluorescent sequence analysis and multiplex ligation dependent probe amplification (MLPA). **Results:** A heterozygous sequence variant was found in the PPARG gene (c.609G>T in exon 3) as cause for the severe insulin resistance and dyslipidaemia. The therapy is a low fat diet as well as pharmacotherapy. **Conclusion:** Closely work up should be done if a severe metabolic syndrome is diagnosed without obesity in childhood or adolescence with extensive hypertriglyceridaemia regarding rare forms of lipodystrophy.

P3-733

Use of Smartphone, a Cellular Glucometer and Social Media App in the Management of Type 1 DM in the Adolescent Population: The Future of Diabetes Care

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Background: The integration of technology in health care has led to improved medical care and better compliance, especially in chronic diseases such as diabetes. Despite these advances, compliance has always been an issue in caring for adolescents

with diabetes. Text messaging has become a popular way to communicate with peers especially for teens. Multiple studies support the theory that texting is an easy and affordable resource that health care providers can utilise to educate youth about health care issues. Other modalities such as web based apps and social media that reinforce diabetes education can also help patients. **Objective and hypotheses:** To use a smartphone, a cellular glucometer and social media app to help improve diabetes care in adolescents. **Method:** Each participant received a smartphone and a cellular glucometer. The cellular glucometer automatically uploads blood sugars to a website portal that the participants and health care provider can access. We also created a private social media website, as a type of online support group. Each week, our group, which consists of a physician, nurse and social worker, reviewed the blood sugars and texted the participants advice to help improve their blood sugars. Each provider in our group carried a phone, so that participants could contact us. Hemoglobin A1C (HBA1C) values were measured at baseline and after study intervention. We enrolled 30 patients from 12 to 22 years with Type 1 DM. **Results:** Out of 30 participants: one withdrew; 12 had a decrease in HBA1C; eight had an increase in HBA1C; nine maintained their HBA1C. Survey done of participants who had a decrease in their HBA1C directly attributed the improvement to the study. **Conclusion:** This study demonstrates that an integrated technology program to aid in the management of Type 1 DM in adolescents can be used to help improve diabetes control in this population. **Funding:** This work was supported from the Verizon Foundation(grant number:10180631).

P3-734

A Boy with Wolfram Syndrome

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Background: Wolfram syndrome, also known as Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, Deafness (DIDMOAD), is a rare neurodegenerative disease of autosomal recessive inheritance with incomplete penetrance. In addition, it may present with different endocrine and metabolic abnormalities such as pituitary dysfunction. We reported clinical features, biochemical features and mutational analysis of a boy with Wolfram syndrome. **Case presentation:** A 7-year-old boy presented to ophthalmologist for bilateral blurred vision and found to have bilateral cataract. On further enquiry, the family noted 3-month history of polyuria, polydipsia and nocturia. There was no consanguinity and only paternal grandfather had type 2 diabetes at old age. Fasting glucose was 18 mmol/l. He had ketosis but no acidosis. HbA1c was 18.2% at presentation. Anti-islet cell antibody was negative. He received basal-bolus insulin at 0.8 unit/kg/day. He had undergone bilateral phacoemulsification of cataract and implant of intraocular lens soon after diagnosis. His vision remained clear after operation. His glycemic control was also satisfactory with HbA1c ranged 6.5% – 7.7%. He started to have onset of puberty at 9 years 8 months. However, he presented to ophthalmologist again at 11 years for drop in vision. Examination revealed bilateral pallor optic disc rims with increased cup-to-disc ratio. Visual field demonstrated moderate field constriction. In view of diabetes mellitus and bilateral optic neuropathy, Wolfram syndrome was suspected. Mutational analysis detected a compound heterozygous c.1999C>T (Q667X) and c.2170C>T (P724S) mutations in WFS1 gene. Mutational analysis of parents confirmed their carrier status. He is now 17 years 6 months and achieves his final height comparable to mid-parental height. He did not develop diabetes insipidus or hearing impairment. **Conclusion:** Although no clear genotype-phenotype correlation has been drawn for Wolfram syndrome, it is speculated that inactivation of both WFS1 alleles may be associated with an early onset of diabetes mellitus.

P3-735

Cardiovascular Risk Factors in Children and Adolescents with Type 1 diabetes

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Background: Diabetics have an increased risk of cardiovascular disease. In young adults with type 1 diabetes mellitus (T1DM), cardiovascular events are more often the cause of premature death than nephropathy. In pediatric T1DM population, 35% have 2 or more cardiovascular risk factors (cvRF). **Objective and hypotheses:** This study aimed to determine the prevalence of traditional cvRF in children and adolescents with T1DM, and their association with the degree of glycemic control. **Method:** We performed a retrospective hospital-based analysis that included all children and adolescents with the diagnosis of T1DM, for at least one year, followed in pediatric consultation of a single secondary hospital. The cvRF assessed were BMI, blood pressure (BP), triglycerides (TG), high-density lipoprotein cholesterol (HDL) and low-density lipoprotein cholesterol (LDL). IBM SPSS®21 was used for statistical analysis. **Results:** A total of 59 T1DM patients were included in this study, with a predominance of male gender (59%) and an average age of 13±4.2years. The mean diagnosis age was 8±3.8years, and the mean follow-up time was 5±3.3years. Actually, 10% had other autoimmune (AI) disease, and 93% are doing multiple daily insulin injection. Regarding to disease control, 25% had an HbA1c under 7.5%. Traditional cvRF were present in 47.5% of T1DM patients. Of these patients, 7% have elevated BP, 18.5% elevated TG, 52% elevated LDL, 25% decreased HDL and 52% overweight/obesity. The presence of cvRF was associated with an early age of disease diagnosis (7 vs. 10) ($P<0.05$), but was not associated with duration of disease. Presence of cvRF was not associated with current age, gender, glycemic control and other AI diseases. **Conclusion:** This study demonstrates a high frequency of cvRF in children and adolescents with T1DM. It therefore emphasizes the importance of early and systematic screening for these risk factors. Early intervention should be considered in all patients at risk.

P3-736

Megaloblastic Anaemia and Diabetes in a Young Girl

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Background: Rogers syndrome or thiamine responsive megaloblastic anaemia (TRMA) with diabetes mellitus (DM) and deafness is an uncommon autosomal recessive disorder. We report the case of an eleven-month-old girl with TRMA. **Case presentation:** She was admitted to the hospital with paleness, hypotonia, diarrhoea and fever. She was born to first degree consanguineous Moroccan parents. Our patient medical history was relevant for hemolytic anaemia at the age of 1 month, not followed up. Laboratory investigations revealed hemoglobin 7 g/dl, folic acid 22 μg/l (N 3–20 μg/l), vitamin B12 628 ng/l (N 180–500 ng/l), iron 74 μg/dl, ferritin 202 μg/l. Blood smear showed anisocytosis with a predominance of macrocytic cells. The bone marrow aspirate showed hypercellularity, ringed sideroblasts and abnormal erythropoiesis with megaloblasts. Hemoglobin electrophoresis was normal. On admission, serum glucose was 429 mg/dl, HbA1c 9.4% (N 4.0–6.2%) and C peptide level 0.8 μg/l (N 0.5–3.0 μg/l). IAA, ICA, GADA and IA2A were negative. Auditory evoked brainstem responses revealed deep to total sensorineural hearing loss. Severe macrocytic anaemia and hyperglycemia led us to the diagnosis of TRMA and oral thiamine was given 100 mg/d. The diagnosis was confirmed by molecular analysis (homozygote mutation in the nucleic acid sequence of exon 2 introducing a premature stop codon). **Conclusion:** Our patient presents a TRMA with DM, anaemia and deafness associated with ophthalmologic disorders. Treatment with pharmacological doses of vitamin B1 improved the clinical features but had no effect on the hearing loss. The causal gene of TRMA is SLC19A2, encoding a high-affinity thiamine transporter. Diabetes is a non-type 1 DM. Various types of anaemia, which respond to therapy, are described in TRMA. Hearing loss is irreversible. Ocular symptoms are inconsistent in association with TRMA. TRMA should be kept in mind in the differential diagnosis of DM and/or megaloblastic anaemia especially if consanguinity is present.

P3-737

Audit Assessing Glycaemic Control in Children Aged Less than 16 Years with Type 1 Diabetes in Malta Over the Period 2013–2014

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Background: Suboptimal glycaemic control in type 1 diabetes, measured by HbA1c, increases the risk for long-term complications. **Aims and objectives:** To calculate and compare glycaemic control in children with Type 1 Diabetes in Malta in 2013 and 2014. To identify any need to change the way services are structured and delivered. **Methods:** Almost all diabetic children less than 16 years of age in Malta fall under the same paediatric diabetes team, based at the main state hospital. The demographic and clinical data of all patients newly diagnosed with T1DM are collected on a Microsoft Excel spreadsheet and updated annually. The average HbA1c of all measurements taken every 3 months with an HbA1c analyser is calculated. **Results:** In 2013, 43.8% (95% CI 35–52%) of our patients achieved a target HbA1c of $<7.5\%$. Another 26.6% (95% CI 19–34%) achieved an HbA1c of 7.5 – 8% which still reflects relatively good control. The percentage of patients with an HbA1c of $>9.5\%$ was 4.6% (95% CI 1–8%). The mean HbA1c was $7.69 \pm 0.16\%$. Boys had a mean HbA1c of $7.76 \pm 0.19\%$ while girls had a mean HbA1c of $7.59 \pm 0.26\%$. The mean HbA1c in the 0–10.9 year age group was $7.53 \pm 0.16\%$ with a comparable mean HbA1c in boys of $7.51 \pm 0.23\%$ and in girls of $7.55 \pm 0.28\%$. The mean HbA1c in the 11–16 year age group was $7.85 \pm 0.26\%$. The boys had a mean HbA1c of $8.04 \pm 0.3\%$ while girls had a better mean HbA1c of $7.63 \pm 0.44\%$. In 2014, 49.6% (95% CI 41–58%) of our patients achieved an HbA1c of $<7.5\%$. 18.9% (95%CI 12–26%) achieved an HbA1c of 7.5 – 8%. 3.9% (95% CI 0.6–7.3%) had an HbA1c of $>9.5\%$. The mean HbA1c was $7.67 \pm 0.17\%$. The mean HbA1c in the 0–10.9 year age group and in the 11-15.9 year age group were comparable to the 2013 data. **Conclusion:** Glycaemic control in our cohort of patients was similar in both years. The results are compared to other European data.

P3-738

Prestarium Pharmacogenetic Efficacy in Predicting Diabetic Nephropathy in Children and Adolescents

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Aim: The work was initiated to study efficacy of prestarium in normoalbuminuric patients with type 1 diabetes mellitus by ACE genotype upon primary diabetic nephropathy (DN) prevention. **Materials and methods:** We examined normoalbuminuric 22 patients with type 1 diabetes mellitus aged from 12 to 17 years with DN duration $\geqq$ 10 years divided into two groups by ACE polymorphism, that is, the one with II genotype ($n=11$) and the one with DD genotype ($n=11$). Activity of urinary neutral α-glucosidase was measured by rate of glucose production from maltose. PCR was performed by means of GenePackTM PCR Core reagent kit. All patients were prescribed with prestarium in the dose of 2.5 mg/day for 6 months. **Results and discussion:** Systolic arterial pressure and diastolic arterial pressure were found reduced by 4.2% and 3.6%, respectively, heart rate decreasing by 6.4%. Pre- and post-therapy blood fibrinolytic activity was $15.3 \pm 0.8\%$ and $14.9 \pm 0.6\%$, respectively, fibrinogen concentrations being respectively, 3.02 ± 0.2 g/l and 3.08 ± 0.2 g/l. Total cholesterol was found decreased by 4.4%, HbA1c being reduced by 16.7%. There was 7.1% and 6.8% reduction in proteinuria in the first and second groups of patients, respectively. Glomerular filtration rate and creatinine were found decreased by 9.2% and 4.6% in the 1st group, reducing by 2.2% and 1.2% in the 2nd one. Urinary neutral α-glucosidase in patients with II genotype was

registered reduced by 63.6%, confident reduction by 10.5% being found in patients with DD genotype to be 8.5 times higher (P4 = 0.0001) than the parameter in the 1st group. **Conclusions:** In normoalbuminuric diabetic patients with II genotype prestarium facilitated moderate reduction in systolic and diastolic arterial pressure as well as in heart rate. In these patients total cholesterol reduced by 4.4% versus 0.8% in patients with DD genotype. There was 16.7% and 4.7% reduction in HbA1c level, respectively.

P3-739

Assessment of Quality of Life in Adolescents with Type 1 Diabetes; a Pilot Study

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Background: Diabetes as a disease and its treatment can have a profound effect on the quality of life (QoL) in terms of social and psychological well-being as well as physical ill health. Current goals of diabetes management focus on optimising metabolic control, along with preserving a good QoL. **Aims and objectives:** To assess QoL in adolescents with type 1 diabetes (T1D) at the Diabetes Endocrine and Metabolism Pediatric Unit at Cairo University. **Methods:** One hundred and fifty adolescents (10–18 years old) with T1D duration more than 1 year were studied regarding socio-demographic data, duration of DM, insulin therapy, and monitoring of glycaemic control in terms of frequency of self-monitoring of blood glucose (SMBG) and mean HbA1c. They were asked to complete the "QoL for youth" questionnaire (provided by Novo Nordisk), formed of 22 questions evaluating six domains (symptoms related to diabetes, treatment, activities, parent issues, worries about diabetes and health perception). Score of each domain was calculated. **Results:** Study included 82 males and 68 females with mean duration of diabetes of 3.6 ± 2.7 years. Score was better in males, urbans, with higher educational level and with family history of diabetes. Scores were significantly better with lower mean HbA1c in domain 1 (DM related symptoms) and domain 6 (health status), $P = 0.001$ and < 0.001 respectively; and with more frequent SMBG in Domain 1 (DM related symptoms), domain 2 (Impact of treatment), and domain 4 (Parent issues), $P = 0.03$, 0.01 and 0.02, respectively. **Conclusion:** QoL was more favorable in males, urbans, higher educational level, SMBG more than 3 times daily and HbA1c below 7.5%.

P3-740

Mody3 Early Identification and Diagnosis

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Background: MODY is monogenic. About 1% of diabetes has a monogenic cause but is frequently misdiagnosed as DM1 or DM2. **Objective and hypotheses:** It is important to study family history of patients with atypical diabetes forms for verification of diagnosis and prognosis. **Method:** Genetic, biochemical and hormonal testing, 2 patients were examined. **Results:** At pre-school medical examination a general practitioner noticed positive family history of diabetes of an 8 year old boy and sent him to an endocrinology centre. It was noted that the proband's father had fasting hyperglycaemia without symptoms of diabetes and obesity at the age of 18. He was not examined for 16 years as he did not have any diabetes symptoms. When he was 34, occasionally FPG 7.4 mmol/l and after meal 12.3 mmol/l without ketosis was detected. He was diagnosed DM1 and insulin was prescribed. At the moment of examination he had diabetes for 6 years and received insulin in dose 0.1 U/kg/day. HbA1c was 6.6%. FPG was 6.6 mmol/l, stimulated glucose (after standard carbohydrate breakfast without insulin injection) was 14 mmol/l (1 h), 12.8 mmol/l (2 h). Basal insulin serum was 2.4 U/l, stimulated insulin serum was 20.9 U/l (1 h), 23.7 U/l (2 h). The boy's paternal grandmother had GDM at the age of 23 years. At the moment of examination she had diabetes for 40 years without complications and received insulin in dose 32 U/d (0.5 U/kg/day). Her two sisters had DM. At the moment of examination the proband did not have hyperglycaemia and diabetes symptoms. FPG was 4.2 mmol/l, stimulated glucose (OGTT) was 7.7 mmol/l (1 h), 6.4 mmol/l (2h). Basal insulin serum was 4.2 U/l, stimulated insulin serum was 13.7 U/l (1 h), 10.3 U/l (2 h). Genetic testing revealed that the proband and his father had mutation S355X in the HNF1A gene. The proband's father was prescribed sulphonylurea tablets instead of insulin and this resulted in glycaemia stabilization. **Conclusion:** Correct genetic diagnosis is important for proper patients' treatment and prognosis and it enables predictive genetic testing for their asymptomatic relatives.

P3-741

Low fT3 Syndrome due to Metabolic Acidosis/Ketoacidosis in Type 1 Diabetes Mellitus (Type 1 DM)

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Background: Type 1 DM is an autoimmune disease, characterized by destruction of the insulin-producing beta-cells in the islets of Langerhans. The absolute insulin deficiency leads to metabolic imbalance with hyperglycaemia, acidosis and proneness to ketosis. This acute disturbance can change thyroid hormone metabolism. **Objective and hypotheses:** To examine the influence of metabolic acidosis/ketoacidosis in type 1 DM on thyroid hormone levels. **Method:** In this retrospective study, we analysed 48 patients (pts) treated at our hospital between 2010 and 2014. Lab data of this 48 pts (30 female, 18 male, mean age 9.4 ± 4.1 years) were examined for influence of pH, BE, anion gap, HbA1c, insulin antibodies and BMI on the fT3 level. **Results:** A significant correlation could be identified between BE and fT3

level. Low fT3 was noted in 86% and normal fT3 in 14% of 28 pts with metabolic acidosis. In 12 pts diagnosed for ketoacidosis only 1 patient had normal and 11 pts had low fT3 level. Thyroid hormone levels became normal after the stabilisation of metabolic status (mostly during 3–5 days. **Conclusion:** Low fT3 syndrome should not be interpreted as hypothyroidism, but as a protective mechanism during an acute stressful event in type 1 DM. The level of fT3 partly reflects in the metabolic derangements.

P3-742

Coping Styles of Adolescents with Type 1 Diabetes and their Parents: Association with Metabolic Control and Disease Duration

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Background: Coping skills are very important for the management of developmental changes among young people, and especially so, for adolescents with chronic diseases such as type 1 diabetes (T1DM). **Objective and hypotheses:** To study the various coping behaviours in a sample of children and adolescents with T1DM and to evaluate their association with metabolic control and duration of disease. **Method:** The study population consisted of 65 children and adolescents with T1DM (male/female: 22/43) with a mean ($\pm$S.D.) age of 12.6 ($\pm$5.2) years, disease duration of 4.8 ($\pm$4.4) years and HbA1c of 8.1 ($\pm$1.6)%, who attended the diabetic clinic of the University Department of a Tertiary Children's Hospital. The 'Ways of Coping Questionnaire' (Lazarus and Folkman), adapted and standardized in Greek population, was completed by all adolescents, 36 fathers (67.9%) and 17 mothers (32.1%). Coping was categorized as: i) active coping, ii) seeking social support, iii) wishful thinking, iv) problem avoidance, and v) aggressive coping. **Results:** There was a significant association between fathers' and adolescents' coping styles in respect of 'active coping' ($r=0.41$, $P=0.016$) and 'seeking social support' ($r=0.38$, $P=0.023$). Female adolescents used more the 'seeking social support' way compared to males (1.92 ± 0.73 vs 1.39 ± 0.99, $P=0.041$). Duration of disease was positively associated with the 'active coping' style ($r=0.36$, $P=0.014$). Mean HbA1c levels were positively correlated with 'aggressive coping' ($r=-0.36$, $P=0.014$) and negatively associated with 'active coping' ($r=-0.31$, $P=0.035$), which means that more constructive behavior has a positive impact on glycaemic control. **Conclusion:** Active coping was associated with better metabolic control and longer diabetes duration in adolescents with T1DM. Female adolescents with T1DM used more the 'seeking social support' strategy compared to males, which is also reported in healthy adolescents. Assessment of coping behaviour might be useful in the identification of adolescents in need of particular support and counselling.

P3-743

Examination of Diabetes Nurse Educator Guided Diabetes Care Team in Pediatric Type 1 Diabetes

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Objective: To establish a diabetes nurse case manager guided care team in a tertiary hospital paediatric diabetes outpatient clinic. Disease-management programs have demonstrated effectiveness for improving glycaemic control in adults with diabetes. Currently, there is an absence of published literature exploring this model of care in paediatric type 1 diabetes. **Methods:** Using a before–after research design, the nurse case manager model of care was initiated in the paediatric diabetes program at McMaster Children's Hospital (Hamilton, ON, Canada) in October 2013. In the new model, youth with type 1 diabetes receive outpatient diabetes care from their nurse case manager every 3 months in collaboration with the staff physician, dietician, and mental health specialist as needed. Primary outcomes are caregivers and participants' diabetes self care scores and the burden of diabetes care measured using validated surveys that are administered at baseline and 6 months after exposure to the nurse case manager model. Secondary outcomes include glycaemic variability and health care utilisation. **Results:** Recruitment was completed in 3 months, during which 201 youth-caregiver pairs with type 1 diabetes greater than 1 year were enrolled; mean age 11.9 ± 3.4 (S.D.) years; 46% males and 54% females. Mean HbA1c was 8.5 ± 1.3% (non diabetes range 4–6%). Only 18% of participants achieved ISPAD target HbA1c at baseline. Baseline problem areas in diabetes score was 57% indicating significant parental care burden and mean youth daily self management score was 23/35 indicating inadequate self-management routines. **Conclusions:** A diabetes nurse case manager guided care team can be successfully implemented in a paediatric diabetes outpatient clinic. This model may provide an opportunity to improve diabetes care for youth with type 1 diabetes. Analysis of 6-month primary outcomes will begin in June 2014.

P3-744

Transition During Adolescence, is there Room to Improve?

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Background: Transition is a difficult period for adolescents with type 1 diabetes. The non-linear development of the adolescent brain along with increasing insulin resistance, increasing autonomy and risk of psychopathology means that

adolescents are vulnerable to poor mental and physical health and ensuing deterioration in metabolic control. It is also during this period of turmoil that adolescents often transfer from paediatric to adult services. **Objective and hypotheses:** The aim of this study was to assess the levels of satisfaction with the current transition process among adolescents with type 1 diabetes in our hospital and to investigate how the process could be improved and reasons for disengagement post transition. **Method:** We developed a questionnaire to assess the satisfaction of adolescents who had transitioned to adult services within the last 5 years which was distributed to both the adolescents and their parents. Participants were recruited either at outpatient appointments or by phone contact. **Results:** A total of 22 patients were eligible for inclusion. Of these, 14 patients (63%) responded. Eight patients (57%) felt that they were ready at the time of transfer while six patients (42%) felt that the current system worked well. Five patients (35%) had previously attended paediatric clinic appointments on their own. Five patients (35%) would have preferred to have been more involved with the decision for transition. Nine patients (64%) admitted to having missed adult clinic appointments because 'they didn't want to go' or 'couldn't make it' due to college or work commitments. Freetext suggestions for improvements were completed by participants. **Conclusion:** The results of this study highlight a need for improved communication between paediatric and adult Ted areas for improvement in the transition process for adolescents with chronic disease. This includes teams, jointly staffing young adult clinics, appropriate scheduling of young adult clinics during college breaks and encouraging participation and independence of adolescents during clinic visits.

P3-745

Vitamin D Status in Egyptian Children with T1D and the Role of Vitamin D Replacement on Glycaemic Control

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Background: Many epidemiological studies have found high prevalence of vitamin D deficiency in children with type 1-diabetes mellitus (T1D). 1,25(OH)2D is a potent immune-modulator that also enhances the production and secretion of several hormones, including insulin. The association of low serum 1,25(OH)2D levels with high glucose level and diminished insulin sensitivity suggests that vitamin D may modulate insulin metabolism. **Aim and objectives:** To screen for vitamin D deficiency in paediatric patients with T1D and to study the effect of vitamin D supplementation on glycaemic control and insulin requirements in those patients. **Methods:** Our study was a prospective cohort study that included 50 patients with T1D above 5 years of age with onset of T1D >1 year, with no hepatic or renal problems or any drugs that may affect vitamin D metabolism. 25-hydroxyvitamin D (25(OH)D) level was assessed initially and after 3 months of vitamin D supplementation (in those with vitamin D deficiency). Glycaemic control (HbA1c) and insulin requirements were studied at 0 and 3 months of vitamin D therapy. **Results:** Thirty-five patients (70%) had vitamin D deficiency, 33 of them received vitamin D supplementation for 3 months (two were non-compliant). 25(OH)D levels improved after therapy (from a mean of $11.2+5.7$ to $31.4+11.5$). Mean HbA1c at 0 and 3 months of therapy was $9.4+1.9$ and $8.7+1.5$ respectively. However, mean insulin requirements were not reduced after therapy ($1.13+0.3$ and $1.18+0.4$ at 0 and 3 months respectively). **Conclusion:** Checking the serum 25(OH)D levels in children and adolescents with T1D and providing replacement for children with low levels improved glycaemic control at 3 months after therapy with no reduction in insulin requirements.

P3-746

Residual C-Peptide in Paediatric Patients with Type 1 Diabetes

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Background: Preservation of C-peptide is important and has become regarded a relevant endpoint as already a quite small residual C-peptide seems to be related to both less acute and late diabetes complications. **Objective:** To assess the residual C-peptide secretion in pediatric patient with T1D. **Method:** Cross-sectional study of 157 patients with T1D. We analyzed: age at diagnosis, age at time of study (years), sex, diabetes duration (years, ≥ 1 year of T1D), HbA1c (HPLC-Menarini, mean 6 last months), and fasting C-peptide levels (chemiluminescent immunoassay, minimum detectable 0.01 ng/ml). Data reported in percentage, mean $\pm$ S.D.; C-peptide levels in median and range. Statistical analysis was performed with SPSS 17.0. **Results:** 58% patients had undetectable C-peptide; in this subgroup duration of T1D was significantly longer, with younger, but not significantly, age at diagnosis. Minimum and maximum diabetes evolution: 1–16.7 years in undetectable and 1–11.8 years in detectable

Table 1. (for abstract P3-746)

C-peptide	*n* (%)	Age debut (years)	HbA1c (%)	Age study (years)	T1D evolution			C-peptide levels (ng/ml)
					Years	<5 years	>10 years	
Global	157 (100%)	6.5 ± 4.0	6.8 ± 0.7	12.2 ± 4.6	5.6 ± 3.8	83 (53%)	24 (15%)	–
Undetectable	91 (58%)	5.1 ± 3.4	6.9 ± 0.8	12.4 ± 4.6	7.2 ± 3.8	31 (37%)	21 (88%)	–
Detectable	66 (42%)	8.5 ± 3.9	6.6 ± 0.7	11.9 ± 4.6	3.3 ± 2.6	52 (63%)	3 (12%)	0.14 (0.01-1.4)
P	–	0.188	0.855	0.927	0.004	<0.001	0.001	–

C-peptide subgroup. Only 3/24 patients with >10 years T1D evolution had detectable C-peptide (10.0–11.7 years evolution, C-peptide 0.01–0.09 ng/ml); 5/27 patients with <2 years T1D evolution had undetectable C-peptide (1.0–1.6 years evolution, age diagnosis 5.1 years (0.6–10.9)). HbA1c was lower in detectable C-peptide subgroup but not significantly. C-peptide levels were negatively correlated with diabetes evolution and HbA1c levels. **Conclusion:** The natural course of T1D in paediatric age is heterogeneous. Lower C-peptide levels are associated with longer duration of diabetes and earlier age at diagnosis.

P3-747

A Novel Nonsense Mutation in the *WFS1* Gene Causes Wolfram Syndrome

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Background: Wolfram syndrome is a rare autosomal recessive neurodegenerative disorder caused by mutations in the *WFS1* gene. The *WFS1* gene is active in cells of body, with highly expression in the, brain, lungs, heart, inner ear, and pancreas. Within cells, *WFS1* gene encodes wolframin protein that is located in a structure of endoplasmic reticulum. Endoplasmic reticulum has critical role in protein folding and material transportation within the cell or to the surface of cell. Although the actual function of wolframin protein is unknown, but based on location, defect of this protein may cause the problem in protein folding or cellular transportation. **Case presentation:** In this study DNA sequence of *WFS1* gene was analysed in a 9 years old boy, to confirm wolfram syndrome. **Conclusion:** We found the novel pathogenic nonsense mutation in exon 4 of *WFS1* gene (c.330 C > A). The heterozygosity for parents also confirmed by Sanger sequencing.

P3-748

Health Literacy of Caregivers of Children with Type 1 Diabetes: A Pilot Study on Impact on Glycaemic Control in an Arabic-Speaking Population

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Introduction: Health literacy has been linked to poorer diabetes control and outcomes. Caregivers with poor health literacy may fail to comprehend various elements of diabetes education leading to poor glycaemic control of their children. No studies to date had investigated the link between caregivers' health literacy and their children's glycaemic control in an Arabic-speaking population. **Objectives and hypothesis:** Our aim is to study the link between caregivers' health literacy level and their children's glycaemic control. We hypothesise that children of caregivers with poor health literacy will have poorer glycaemic control. **Methods:** This is a cross-sectional study of a pilot of caregivers of children with type 1 diabetes in a Diabetes centre in Kuwait. Health literacy was assessed through administering the Arabic version of the Newest Vital Sign (NVS) tool. The child's glycaemic control was measured through the level of HbA1C within 3 months of the test administration. **Results:** Twenty caregivers were recruited with a median age of 37.0 years (IQR 35.5 – 41.5). The median age of their children was 8.9 years (IQR 6.2 – 11.1) with a BMI SDS of 0.6 (IQR −0.5 – 1.7). Median HbA1C was 8.6 (IQR 7.8 – 9.2) with children of caregivers with high likelihood of limited health literacy having poorer glycaemic control compared to those without (HbA1C 9.3, and 8.3 respectively, $P = 0.02$). **Conclusion:** This study highlights the possible link between caregivers' health literacy and their children's glycaemic control in Arabic-speaking populations. This should be confirmed in future studies with larger samples.

P3-749

Achievement of Therapy Targets in Children and Adolescents with Type 1 Diabetes Mellitus at the "Diabetes School"

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Objective and hypotheses: The work was initiated to assess efficacy of training and achievement of therapy targets in children and adolescents with type 1 diabetes mellitus in "Diabetes Schools". **Method:** The five-day training course was conducted in "Type 1 Diabetes School" at the Center for the Scientific and Clinical Study of Endocrinology, Uzbekistan Public Health Ministry (Tashkent). The training was conducted by means of a structured program containing all appropriate sections. Before and after training course all participants were tested with a questionnaire containing 30 key questions for self-control. On the basis of the findings children and adolescents with type 1 diabetes mellitus were divided into groups. 54 of 80 children and 38 of 57 adolescents were preliminary trained, 26 children and 19 adolescents got no training. DCA Vantage Siemens (USA) was used to measure glycated haemoglobin (HbA1c) by means of latex agglutination inhibition. Certified by the National Glycohemoglobin Standardization Program this method became the reference

one. It helps demonstrate the predicting role of HbA1c level as a criterion for assessment of chronic glycaemia and achievement of therapy targets in children and adolescents with type 1 diabetes mellitus. **Results:** Frequency of target HbA1c level ($\leq$ 7.5%) achievement in the trained patients was 68%. Among children who got no preliminary training target HbA1c level was found in 12%. Among trained adolescents 58% achieved compensation. The target HbA1c level was found in 11% of adolescents who got no training. **Conclusion:** Frequency of target HbA1c level ($\leq$ 7.5%) achievement was found in 68% of children with type 1 diabetes mellitus having received preliminary training at "Diabetes School" to be significantly higher ($P<0.001$) than the one in the group of patients who got no preliminary training (12%). Among adolescents target HbA1c level achievement was observed in 58% of the trained patients to be significantly higher ($P<0.001$) as compared with those who got no preliminary training (11%). Better compensation and higher frequency of target HbA1c level achievement in children as compared with those among adolescents confirms the role of family in the type 1 diabetes mellitus control.

P3-750

Oral Glucose Tolerance Test as a Routine Tool to Discriminate High Risk Individuals of Type 2 Diabetes in Child Obesity

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Background: It is debated whether oral glucose tolerance test (OGTT) should be routine in child obesity units to identify high risk individuals for impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). **Aims:** To investigate the prevalence of some signs of metabolic syndrome in child obesity. **Methods:** All consecutive newly referred obese children (BMI > 30) at a Swedish university unit were evaluated with fasting glucose, insulin, apolipoprotein A1 and B, HbA1c, cholesterol and triglyceride (TG). An OGTT was performed and glucose was measured before and 120 minutes after intake of 75 gram oral glucose. Fasting glucose > 6.0 mmol/L was defined IFG and >7.0 mmol/L diabetes. IGT was defined as glucose >8.8 mmol/L at 120 minutes. Correlations were performed with Spearman test. **Results:** 134 children (60% females), mean $\pm$ SD age 12.5 $\pm$ 2.9 years, BMI 30 $\pm$ 5.6 (BMI SDS range 2.8–5.0) were examined at referral and after one year working in a life-change program. Four of these were found to have diabetes and ten IFG. Only five had IGT despite the majority (75%) having insulin levels >20 mU/L. Fasting insulin correlated strongly to TG ($r=0.6$, $P<0.01$), and to less degree to low HLD and high LDL cholesterol (both $r=0.3$, $P<0.05$), maybe due to some outliers with low HDL but normal insulin levels. Interestingly, heredity for type 2-diabetes was the strongest risk factor correlating to pathological OGTT, followed by low HDL cholesterol levels below 1.0 mmol/L. Despite decreased BMI, HDL cholesterol stayed almost unchanged over the years and correlated with high TG as well as apolipoprotein B/A1 > 0.7 as a marker of cardiovascular risk in 30 children. **Conclusion:** Despite OGTT being a routine examination yearly at our university unit, it is the complex combination of high fasting glucose, low HDL and high TG that will discriminate for those with increased risk of developing diabetes, IGT or IFG.

P3-751

Fasting the Holy Month of Ramadan in Older Children and Adolescence with Type 1 Diabetes in Kuwait

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Background: Ramadan is the holy month of fasting for Muslims. New evolving technology in the treatment of type 1 diabetes (T1DM) had encouraged Muslim diabetics to pursuit the practice of fasting. There are limited data on fasting of children and adolescence with T1DM during the holy month. **Objective and hypotheses:** Our aim is to investigate the ability, effect and safety of children and adolescence with T1DM to fast the Holy Month of Ramadan 2014. **Method:** This was a prospective observation study of children and adolescence with T1D for at least one year who intended to fast the Holy month of Ramadan 2014. Pre Ramadan, children and their families were evaluated and educated about diabetes management during Ramadan. The following clinical outcomes were investigated before, during and after the Holy month: glycosylated haemoglobin A1C (HbA1C), number of days fasted, number of hypoglycaemia and hyperglycaemia episodes, and number of emergency hospital visits. **Results:** A total of 50 children and adolescence were recruited with a mean age of 12.7 $\pm$ 2.1 years, 23 (46%) were males and 27(54%) were females. 27(54%) of cases were on multiple daily injections (MDI) insulin regimen and 23(46.0) were on pump therapy and there was no significant difference between two groups as regards mean age, gender, duration of diabetes, and HbA1C prior to Ramadan. The children fast a mean of 20.0 $\pm$ 9.9 days. Most common cause for breaking the fast was mild hypoglycaemia (mean blood sugar during the attacks (3.04 $\pm$ 0.31). Two patients had had one episode of DKA during fasting due to lower respiratory tract infection and pump failure respectively. HbA1C after Ramadan was predicted by pre-Ramadan HbA1C ($r=0.533$). **Conclusion:** Fasting in children with T1DM above the age of 10 years is feasible and safe in both pump and non-pump users. Pre-Ramadan education of the families and their children along with intensive monitoring of fasting children during the month is crucial.

P3-752

The Long-Term Insulin Management with Premixed Insulin in Neonates and Infants with Diabetes

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Objectives: To describe a new therapy protocol for the long-term insulin management in neonates and infants with diabetes. **Methods:** All the infants were fed with 3 hours intervals. The patients were started insulin therapy with 0.6 U/kg per day divided equally into four doses. All the insulin doses were given as premixed insulin (25% insulin lispro and 75% neutral protamine Hagedorn (NPH) insulin) when the number of breast feed was more than three during the night, while if the patient had less than three breast feeds, only the last insulin (night) dose was administered as NPH insulin. Nine-point plasma glucose profiles, HbA1c, and the weight gain were evaluated at the last visit. **Results:** The study was completed with 11 patients who had neonatal diabetes (ND) or type 1 diabetes (T1D). During the follow-up, all the patients had enough weight and length gain, and none of them had episode of ketoacidosis. None of the patients had rapid fluctuations for the blood glucose levels. Hypoglycaemia, normoglycaemia and hyperglycaemia were reported by 8%, 81%, and 11% of all the blood glucose measurements, respectively. Severe hypoglycaemia was not experienced by any patients. The mean HbA1c levels of the patients with ND and T1D at the last visit were %7.0 $\pm$ 0.2 and 7.6 $\pm$ 0.55, respectively. **Conclusion:** This study describes a specific protocol for long-term insulin management of neonates and infants with diabetes. The findings suggest that the method is effective, convenient, and successful.

P3-753

Gestational Diabetes Mellitus: How Well-Established are the AWMF Guidelines and Which of the Cord Blood Parameters Suggest an Experienced Gestational Diabetes?

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Objective: The number of heavy newborns is increasing steadily. Often the gestational diabetes (GDM) has not been identified even though an increasing number of pregnant woman are being screened. We examined in a circumscribed area how often the pregnant women passed through an oral glucose tolerance test (oGTT) and had it been realized and interpreted according to the AWMF guidelines. **Methods:** In this prospective study we analyzed the OGTT results from 132 pregnant woman overall, separated in 3 groups: Women with detected GDM ($n=64$), mothers from macrosom newborns but normal OGTT ($n=17$), control-group ($n=47$). Finally we included 4 special cases, women with a high risk for GDM but undetected or missing OGTT. **Results:** The prevalence for gestational diabetes mellitus was 12.4% during the period of the study. Overall 71/132 women, which means 53.8%, were screened for GDM according to the AWMF guidelines. In due consideration of a 2 week tolerance (= gestational age 24+0 till 27+6 (+/− 1 week)) 70.5% conformed to the guidelines. Reasons for not carrying out an oral glucose tolerance test according to the AWMF guidelines were that the measurement point was too early or too late, the use of capillary measurement, incorrect interpretation of the test values, no initiation of therapy despite pathologic test values, absence of oGTT after pathological GCT. the values were not tested over 2 hours. **Conclusions:** By involving a 2 week tolerance the AWMF guidelines are established very satisfactorily but there is room for improvement.

P3-754

Thyroid Function and Prevalence of Celiac Disease in Children with T1D in Lithuanian Pediatric Population

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Background: Patients with type 1 diabetes (T1D) are at higher risk for developing coexisting autoimmune diseases. **Objective and hypotheses:** To evaluate thyroid and celiac disease prevalence in children with T1D in Lithuanian paediatric population. **Method:** 777 patients (49.7% males) <18yrs with T1D, covering all T1D pediatric Lithuanian population, were examined. Serum free thyroxine (FT4), thyrotropin (TSH), antithyroid peroxidase (ATPO) and tissue transglutaminase antibodies (tTG-A) were measured. **Results:** Mean age of patients was 12.1 $\pm$ 4.4 years (0–4 years 7.9%, 5–9 years 23.4%, 10–14 years 36.9%, 15–18 years 31.8%). Mean duration of T1D was 3.9 $\pm$ 3.9 years, in 68.1% duration of disease was <5 years. The average level of HbA1c was 8.75 $\pm$ 2.22%. 33.7% of children had HbA1c <7.5%. Thyroid dysfunction was detected in 17.6% of cases. Hypothyroidism was evident in 0.4%, subclinical hypothyroidism – in 16.6%, hyperthyroidism – in 0.6% of cases. Thyroid dysfunction was significantly more prevalent in females ($P=0.053$). ATPO were positive in 12% of cases. There was a significant association between positive ATPO and thyroid dysfunction ($r=-0.165$, $P<0.001$). No significant associations between thyroid dysfunction and metabolic control were found. Positive tTG-A were found in 4%. No significant correlations between positive tTG-A and HbA1c or duration of T1D were found ($P=0.947$ and $P=0.062$, respectively). **Conclusion:** Thyroid dysfunction was more common in females and in patients with positive ATPO antibodies. The prevalence of positive tTG-A in Lithuanian children with T1D is similar to data from most other countries.

P3-755

Severe Hypertriglyceridaemia in a Child with Severe Diabetic Ketoacidosis

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Background: Severe hypertriglyceridemia (HTG) is a very rare complication of childhood diabetic ketoacidosis (DKA). The exact mecanism is unclear but transient insulin deficiency may cause a decrease in the activity of lipoprotein lipase. We report a case of girl with DKA and HTG. **Case report:** A 14-year-old girl, previously healthy and nonobese, presented with DKA following two months malaise, two weeks of polyuria and polydipsia. She was found to have DKA with her initial blood gas showing a pH of 6.80, HCO3 4.1 mmol/l, and anyon gap 28 on arrival to our PICU. Her physical examination revealed severe dehydration, decreasing level of consciousness, and her blood gas continued to show a severe metabolic acidosis. The colour of her serum was milky. Other biochemical values at admission could not be accurately measured because of severe HTG. The girl was treated with insulin and fluid according to the standard DKA treatment protocol. After 38 hours, blood gases had normalised and subcutaneous insulin was commenced. Her plasma triglyceride level was 2106 mg/dl after 12 hours of treatment without abdominal pain and declined 1521 mg/dl at second day. Serum amilase was 178 U/l on day 2 and decreased to 55 U/L at 4th day. Serum triglyceride levels were monitored and gradually reduced to 362 mg/dl at fifth day and normalised on day 10. On outpatient follow-up, no underlying lipid disorders were found and serum triglyceride level stayed normal. **Conclusion:** HTG results from absolute insulin deficiency and increases the risk of acute pancreatitis. Abnormalities in the gene for lipoprotein lipase could be implicated of severe HTG. Although experience regarding HTG in DKA is very limited in pediatric patients, our patient recovered with DKA treatment protocol without plasmapheresis or special medical treatment and no primary lipid metabolism disorders were found.

P3-756

Factors Related to Progression to Macroalbuminuria in Type 1 Diabetic Children with Microalbuminuria

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Background: Microalbuminuria is usually the earliest sign of diabetic nephropathy. However, it does not always progress to macroalbuminuria,and may regress to normoalbuminuria. Mean HbA1c and HbA1c variability was known to be independent risk factors for microalbuminuria in children with type 1 diabetes. **Objective and hypotheses:** We hypothesised that both mean and variability of HbA1c could affect the progression to macroalbuminuria in children with type 1 diabetes. **Method:** Thirty eight patients with type 1 diabetes who developed microalbuminuria were included in the study. Patients who had progressed to macroalbuminuria were categorized as progression group and Other patients were grouped as non-progression group. Data were collected 2 years prior to the onset of microalbuminuria in all patients to the onset of macroalbuminuria in progression group and to the last follow up date in non-progression group. **Results:** Eleven patients (29%) had progressed to macroalbuminuria and 27 patients had not progressed. Follow up duration were 6.4 ± 5.2 years and 6.2 ± 3.8 years, respectively. Mean HbA1c before the microalbuminuria ($P = 0.004$), mean ($P < 0.001$) and variability ($P = 0.003$) of HbA1c after microalbuminuria, total cholesterol ($P = 0.009$) at diagnosis of microalbuinuria were related factors on the progression to macroalbuminuria in univariate analysis. In multivariate analysis, mean HbA1c after microalbuminuria was the only significant risk factor for the progression to macroalbuminuria and hazard ratio for progression was 17.9 (95 percent confidence interval, 2.12 to 151). **Conclusion:** Poor glycaemic control was the unsurpassed risk factor for the development of diabetic nephropathy. In our study, HbA1c variability after onset of microalbuminuria was not the major contributor for the progression to macroalbuminuria after adjusted by mean HbA1c.

P3-757

Acute Painful Neuropathy in a Teenager with Type 1 Diabetes (T1D) and Eating Disorders

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Background: Acute painful neuropathy (APN) is a rare manifestation of diabetic neuropathy (DN) in T1D adolescents, associated with poor metabolic control. Eating disorders (ED) often present in T1D patients in association with metabolic derangement, leading to the development of diabetic complications. **Case presentation:** A teenage girl aged 12 years with a recently diagnosed T1D (duration: 9 months) was admitted with diabetic ketoacidosis (DKA), also complaining of pain and numbness in the limbs. During the last 3 months she reduced food intake and insulin doses (0.3 IU/kg per day) in order to lose weight, leading to metabolic deterioration (HbA1c: 11%). On

admission, her height was 150 cm (50th–75th centile), weight: 34 Kg (3rd centile), BMI: 15.1 kg/m^2 (3rd centile). She had impaired vibration sensation thresholds (VPT) in upper and lower limbs and abnormal sensory peroneal nerve measurements (amplitude: 2.7 mV, velocity: 35 msec), with a marginally impaired pupillary adaptation in darkness (58.3%, normal: 54.2–78.6%). She was put under long term psychiatric support. Six months later binge eating episodes were reported, with no neurologic symptoms. Her weight (41.5 kg) (25th–50th centile) and BMI (17.7 kg/m^2) (<25th centile) were increased and her metabolic control was improved (HbA1c: 7.5%), as well as her VPT measurements at all sites (index finger: 3.5 vs 10.5V, big toe: 4.0 vs 8.0V). During the following 2 years she had a progressive metabolic deterioration (HBA1c: 7.6–9.4%) and periodical symptoms of DN. Her previously abnormal peroneal nerve parameters were slightly improved (amplitude: 5.1 mV, velocity: 38.6 msec), with additional abnormal sural nerve values (amplitude: 6.5 uV, velocity: 40 msec), and no indices of other microvascular complications. **Conclusion:** A teenager with a short T1D duration and eating disorders developed APN. DN symptoms and electrophysiological findings were temporarily improved after BMI and HbA1c improvement, but were subsequently deteriorated with poor metabolic control. APN may present in T1D adolescents during a period of acute weight loss and cannot be reversed unless optimal metabolic control is achieved in the long term.

P3-758

A Case of Tacrolimus Related Posttranslated Diabetes Mellitus (PTDM)

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Background: Tacrolimus is highly potent immunosuppressant agent. Despite it is quite prophylactic effect on renal allogreft rejection, the most marked side effect of tacrolimus is lead to posttranslated diabetes mellitus. There are some predictive risk factors which are determined on development of tacrolimus related diabetes mellitus: Advanced age, familial history, genetic factors, ethnicity, impaired glucose tolerance or metabolic syndrome in pre-transplantation period, obesity or overweight, immunosuppressant dose, additional other immunosuppressants,presence of associated hepatitis. **Objective:** We present a case of tacrolimus related diabetes mellitus to pay attention predictive risk factors before renal transplantation. **Case:** 15 years old boy had choronic renal failure due to vesicouretheral reflux. He was referred by Deparment of Pediatric Nephrology because of blood glucose level higher than normal. His weight was 42 kg and his height was 144 cm and his BMI was 22. Blood tension was arterial: 130/90 mm/Hg. When his health records of pre-transplantation period were revised, we realised that he had metabolic syndrome: Blood glusose test were as high as 280 mg/dl. LDL: 167 mg/dl. Triglyceride was 190 g/dl. He had hypertension. HbA1C was 4.1. when he was admitted to our clinic, his laboratory test were following: Glucose: 501 mg/dl, LDL: 182 mg/dl, triglyceride was 164 g/d,. HbA1C: 14.3,insulin: 2,2 U/mlC-peptide: 1.4. Islet cell antibodies (Anti-GAD, Anti-ICA, Anti-IA) were negative. After translanptation, he was given tacrolimus 0.15 mg/kg/day and prednisolone 0.5 mg/kg/day plus mycophenolate mofetil 1200 mg/m^2/day. In the 12th weeks, he was diagnosed tacrolimus related diabetes mellitus. The our case had metabolic syndrome that is mentioned one of predictive risk factors. **Conclusion:** We suggest to screen and be monitored predictive risk factors in pre-transplantaiton period. Measures should be taken to prevent modifiable risk factors.

P3-759

Short-Term Use of Continuous Glucose Monitoring System in Paediatric Patients with Type 1 Diabetes Mellitus and Correlation with Short-Term Improvement in Glycaemic Control

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Background: Several studies show there may be a relationship between the use of continuous glucose monitoring systems (CGMS) and improved glycaemic control in patients with type 1 diabetes mellitus (t1dm). **Objective and hypotheses:** The purpose of this study was to determine if there is a significant correlation between the clinical (office based) use of short-term CGMS and improvement in glycaemic control in paediatric patients with t1dm. **Method:** Retrospective chart review of 28 t1dm patients that were non-randomly chosen to use the short-term CGMS (ages 5–18 years, 17 males and 11 females) in a paediatric diabetes clinic. Reasons to recommend the CGMS were: hyperglycaemia (7), hypoglycaemia (4), glucose fluctuations (8), sports-related (4), to improve control (4), insurance request (1). The variables investigated in this study were: haemoglobin A1c (HgA1c) before and after the use of the CGMS, age and gender. **Results:** The average HgA1c pre-CGMS was 9.17%, and in the follow up visit (average time between visits was 94.5 days) was 8.70%. Differences in HgA1c between pre and post-CGMS vistis were not statistically significant ($P=0.10$). **Conclusion:** While HgA1c was lower after short-term CGMS in paediatric patients with t1dm, the difference was not statistically significant. This may be due to the small number of patients in our study.

P3-760

Neonatal Diabetes – the Great Masquerader: Experiences from One Hospital

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Background: Neonatal diabetes can present from birth to six months of age. This can often be confused with sepsis as there is considerable overlap of symptoms in this age group as illustrated below. **Objective and hypotheses:** The cases described illustrate the importance of blood glucose monitoring in sick infants presenting to emergency care settings we recommend an initial check of blood glucose concentrations in all sick infants who present to Accident and Emergency. **Method:** A 7 week old, born to nonconsanguineous parents presented with a temperature of 38.6C and a one day history of poor feeding. Clinical examination was unremarkable. The working diagnosis was possible sepsis. A blood gas that was done for monitoring of electrolytes showed a glucose concentration of 39 mmol/l with a normal ph. The baby was started on an insulin infusion and then managed on an insulin pump. Genetic analysis showed a KCNJ11 mutation. Insulin was stopped and baby is on Glibenclamide. A second baby, born to consanguineous parents (birth weight of 2.7 kg) presented at 24 days of age with a one day history of vomiting and poor feeding. The baby was mildly tachypnoeic. A diagnosis of sepsis was made. Again an incidental blood gas showed the baby to be in ketoacidosis with a blood glucose of 43 mmol/l. Insulin infusion was commenced and the baby was subsequently managed on a pump. Genetic analysis revealed a recessive non coding *INS* mutation. The baby went into remission in two weeks and is currently off insulin. **Results:** Both infants were clinically well and the diagnosis could have been missed. **Conclusion:** The cases illustrate the importance of blood glucose monitoring in sick infants presenting to emergency care settings and we recommend this. The phenotype of the diabetes in both infants correlated with the respective mutations.

P3-761

Daily Subcutaneous Insulin Requirements of Children with Type 1 Diabetes after Diabetic Ketoacidosis Treatment

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Background: There is no specific guideline for management of children with type 1 diabetes just after diabetic ketoacidosis (DKA) treatment. There are different insulin dosage practices (from 0.8 to 2.0 U/kg per day) in different centres based on personal experiences. **Objective and hypotheses:** To assess daily subcutaneous insulin requirements and frequency of hypoglycaemic events (blood glucose $<$ 50 mg/dl) just after DKA treatment of children with type 1 diabetes. **Method:** This was a cross-sectional study of 30 patients admitted to our hospital with the diagnosis of DKA between June 2013 and March 2015. All were placed on multi-daily injection of insulin and regular blood glucose monitoring after treatment for DKA. The initial dose of subcutaneous insulin was calculated by 1.5 U/kg perday (40% of the total dose for basal insulin with insulin glargine and 60% for bolus insulin with insulin lispro divided in three doses). Follow-up doses were adjusted according to blood glucose monitoring. **Results:** The mean age of patients was 10.3 $\pm$ 5.0 years (1.6–17.4), and 20 of patients were female. From the analysis, the mean daily insulin requirement gradually declined from 1.62 $\pm$ 0.33 U/kg per day on 1st day to 1.25 $\pm$ 0.33 U/kg per day on day 7th after treatment for DKA. Only one hypoglycaemic episode was observed during fasting in one patient and four postprandial hypoglycaemic episodes were observed in three patients. No severe hypoglycemia was detected. **Conclusion:** Initial dose of 1.5 U/kg per day subcutaneous insulin just after DKA treatment was supposed to be fairly safe and sufficient for management of most of the patients with type I diabetes.

P3-762

Metabolic Control and Glycemic Variability in Pediatric Patients with Type 1 Diabetes in Multiple Daily Injections Therapy Using Automated Bolus Calculator Glucometer

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Background: The management of type 1 diabetes is complex, requires a multidisciplinary team and knowledge of the possible advantages of new technologies such as insulin bolus calculators. **Aims and objectives:** To assess if the use of an automated bolus calculator glucometer Accu-Check Aviva Expert® improves the diabetes control in paediatric patients in multiple daily injections (MDI). To identify which patients benefit most from its use. **Methods:** We evaluated 41 diabetic patients treated with MDI (mean age 14.15 $\pm$ 3.4 years, 53.7% male) using the calculator. Metabolic control (HbA1c, DCA, Siemens®) and glycaemic variability (standard deviation (SD), mean glycaemia (MG) and number of hypoglycaemia) were assessed at baseline and after 6 and 12 months. Patients were classified into three groups: prepubertal group ($<$ 12 years, $n=11$), pubertal group (13–15 years, $n=12$) and postpubertal group ($>$16 years, $n=18$). We define as sufficient use of the device if the daily frequency of insulin boluses or intake $>$ 2.5. **Results:** 75.6% of cases had poor metabolic control at baseline (HbA1c$>$ 7.5%). We have data for 12 months follow-up of 19 patients and 6 months follow-up of 30 patients. 61% use the calculator correctly. Patients with poor metabolic control at baseline had significantly worse glycaemic variability (DS and MG). In the overall sample, HbA1c statistically improved from baseline at the follow-up (initial: 8.4 $\pm$ 1.2%DE, 6m: 8.1 $\pm$ 1.1%DE, 12m: 7.7 $\pm$ 0.6%DE, P 0.001) mostly in pubertal group and in patients with poor metabolic control. There was no improvement in glycaemic variability. **Conclusions:** In our study the use of the calculator helped to improve metabolic control, especially in pubertal patients and in patients with poor metabolic control at baseline. The glycaemic variability did not improve, perhaps due to the small sample size and because we don't have baseline data on glycaemic variability parameters.

P3-763

Maturity Onset Diabetes of the Young: Just Think about It

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Background: Maturity Onset Diabetes of the Young (MODY) is a monogenic form of diabetes with onset before 25 years. It is a heterogeneous disorder due to heterozygous monogenic mutations with an autosomal dominant transmission. It represents 2 to 5 percent of diabetes but is often underdiagnosed. We report three cases of MODY highlighting the features of different subtypes, two without associated abnormalities and one with renal disorder. **Cases presentation:** Case 1: a nine-year-old boy with a BMI of 24.5 kg/m^2 (> P97) presented with diabetes. IAA, ICA, GADA and IA2A were negative. Mutation c.392G>A (p.Arg131Gln) was found in the hepatocyte nuclear factor-1-alpha, which causes MODY 3. Initial treatment consisted of repaglinide but after two years, the patient requires insulin (0.8 U/kg/d). Case 2: a thirteen-year-old girl with a BMI of 22.8 kg/m^2 (P 90–97) presented with pre-diabetes. There were no insulin resistance. IAA, ICA, GADA and IA2A were negative. Mutation c.898G>A (p.Glu300Lys) was found in the glucokinase gene, which causes MODY 2. Metformin was given three times a day. Case 3: a nine-year-old Caucasian girl presented with diabetes. Medical history revealed bilateral renal dysplasia with renal insufficiency and renal graft. Homozygous mutation c.1235C>G (p.Pro412Arg) was found in the hepatocyte nuclear factor-1-beta gene, which causes MODY 5. Insulin was given twice daily (0.5 U/kg/d). **Conclusion:** In MODY, mutations concern genes that are directly involved in the beta cell function. The symptoms manifest slowly with the absence of obesity and ketosis in most cases. MODY is usually treated by diet, oral diabetes medications and insulin. Treatment and prognosis vary depending on the genetic mutation. Clinicians should keep in mind the possibility of MODY, especially in antibody-negative youth with familial diabetes. Making a diagnosis of MODY can have important implications for the guidance of appropriate treatment, prognosis and genetic counselling.

P3-764

The Role of KCNJ11 Gene in Neonatal Diabetes

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Background: Neonatal diabetes mellitus (NDM) is a monogenic form of diabetes that occurs in the first 6 months of life. Infants with NDM do not produce enough insulin, leading to hyperglycaemia. An identified and potentially treatable form of monogenic diabetes is the neonatal diabetes caused by activating mutations of the KCNJ11 gene, which codes for the Kir6.2 subunit of the beta cell of the ATP sensitive potassium channel (KATP). The identification of KCNJ11 mutation has important therapeutic implications, as many patients can replace insulin injections with sulfonylurea tablets. **Objective:** To identify mutations in the KCNJ11 gene as a cause of permanent NDM in order to identify patients carrying this mutation and modify their treatment regimen. **Patients and methods:** Sequencing the KCNJ11 gene in 17 Egyptian probands with permanent neonatal diabetes diagnosed with diabetes before the age of 2 years. **Results:** One case with a mutation in the KCNJ11 gene (p. R201H) was identified. The patient was successfully shifted from insulin therapy to sulfonylurea. Four previously recognized polymorphisms E23K, I337V, L270V and A190A were detected. **Conclusion:** NDM secondary to KCNJ11/Kir6.2 activating mutations has potentially important therapeutic consequences leading to transfering those patients from insulin therapy to sulfonylurea.

P3-765

A Case of DEND (Developmental Delay, Epilepsy, and Neonatal Diabetes) Syndrome with Heterozygous *KCNJ11* Mutation Successfully Treated with Sulfonylurea Therapy

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Background: Permanent neonatal diabetes mellitus is caused by mutations in the K_{ATP} channel subunits. DEND (Developmental delay, Epilepsy, and Neonatal Diabetes) syndrome is the most severe form of permanent neonatal diabetes. We experienced a patient with DEND syndrome, who was initially misdiagnosed as type 1 diabetes, who has been successfully switched from insulin injection to oral sulfonylurea therapy. **Case presentation:** A 50-day-old male presented with fever and seizure, complicated by persistent hyperglycemia. He was born at 38 weeks of gestation with a birth weight of 2.75 kg. Laboratory findings were consistent with diabetic ketoacidosis, and insulin therapy was initiated with conventional regimen. Also, antiepileptic drug was administered to control seizure. At 10 months of age, he cannot hold his head up or make eye contact with others, and electroencephalography showed spike discharges from right central and left central area. At age 17.9 years, direct sequencing of *KCNJ11* identified a

heterozygous mutation of c.602G>A (p.R201H). Since then, gliclazide was initiated and the insulin dose was gradually reduced. After 3 months, insulin was discontinued with a gliclazide dose of 2.4 mg/kg. He continued to have excellent glycaemic control with HbA1c level of 5.9% at age 18.7 years. However, his psychomotor retardation was not improved. Currently, he is 18.8 years old and still not able to talk with others because of severe intellectual disability. The patient had neonatal diabetes, epilepsy, and pronounced severe developmental delay. **Conclusion:** We described clinical course of a case of DEND syndrome caused by an activating mutation of *KCNJ11*. **Novel insights into clinical practice:** This study emphasizes the necessity to screen K_{ATP} channel mutations in diabetes diagnosed before 6 months, especially if combined with developmental delay and epilepsy.

P3-766

Two Permanent Neonatal Diabetes Mellitus Cases due to Mutation in abcc8 Genes in Vietnam: Clinical Features and Long – Term Outcome in Treating by Sulfonylurea (2008–2014)

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Background: Neonatal diabetes mellitus (NDM) is a rare insulin-requiring form of diabetes, diagnosed in the first six months of life. Unlike type 1 diabetes mellitus, it is caused by the mutation genes involved in the development and secretory function of the pancreas. ABCC8 gene mutation, resulting in both transient and permanent NDM, increases the sensitivity to the stimulatory actions of ADP, so it remain the potassium channel open and prevent insulin release. Sulfonylurea acts by an ATP-independent mechanism to close these channels and insulin release. It is therefore the best choice for treating permanent neonatal diabetes mellitus due to ABCC8 and KCNJ11 gene mutation. **Objective and hypotheses:** We report two cases of NDM due to ABCC8 gene mutation about clinical features and good long-term outcome in management by Sulfonylurea. **Method:** We collect data base on the interview their parents and the medical record about diagnosed-age, signs and symptoms, family history and laboratory test (Glucose, HbA1c, Anti-GAD, ICA, C-peptide, Insulin), Insulin regimen (dose, type, duration), Sulfonyurea (dose), side effects and complication at the beginning and after 3 months. **Results:** Two girls, diagnosed diabetes mellitus before 6 months of age, one was incidentally discovered amd one was hospitalized in ceton acidosis. They were healthy before and there was no family history. The blood glucose and HbA1c were very high, C-peptide were 0.282 and 0.278 ng/ml respectively, ICA and Anti-GAD were negative. They were treated with subcutaneous injection Insulin but the blood glucose is in wide variance, and there were several hypoglycemic times. After gene analysis, with ABCC8 gene mutation, they have been transfered to Sulfonylurea and we rapidly stopped using Insulin after 2 weeks. The treament is more simplex, the blood glucose is stable in the long term, HbA1c dropped from 8,3% and 6,8% before Sulfonylurea to 5.8% and 6% respectively and there are no side effects up to now. **Conclusion:** We should do gene analyze in all diabetes children diagnosed before 6 months of age. The changing management from Insulin to Sulfonylurea is much effective and safe in ABBC8 and KCNJ11 mutation NDM.

P3-767

Type 1 Diabetes in Pediatric Patients: Demographic and Clinical Characterisation

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Background: Type 1 diabetes is one of the most common chronic disease in pediatric age. The incidence is increasing worldwide, with significant variations between countries. In Portugal, the prevalence in pediatric age is about 0.16%. **Objective and hypotheses:** This study aims to characterize a pediatric population with type 1 diabetes and to identify factors influencing the metabolic control. **Method:** Retrospective analysis of children and adolescents diagnosed with type 1 diabetes, between January of 2001 and December of 2013 that were followed in a secondary care hospital, in Portugal. Demographic, clinical and laboratorial data were collected. IBM SPSS20 was used for statistical analysis. *P* values below of 0.05 were regarded as statistical significant. **Results:** Between 2001 and 2013, 59 pediatric patients were diagnosed with type 1 diabetes. The incidence was higher in males (59.4%) and during autumn and winter (62.1%), and an increasing number of patients were diagnosed in the recent years. The average age at diagnosis was 8.34 ± 3.82 years and there was no statistical difference between genders. Although at diagnosis the majority of patients had no diabetic ketoacidosis (61.5%), eight patients (13.6%) had subsequent hospitalization for treatment of diabetic decompensation. Six patients (10.2%) had at least another autoimmune disease (three with coeliac disease, three with thyroiditis, one with hepatitis).Regarding the current clinical state, the majority had normal weight (72.4%) and normal blood pressure (96.7%) and only two patients had microvascular complications, namely microalbuminuria. HbA_{1c} $<7.5\%$ was achieved in 25.4%. No statistical differences were found between HbA_{1c} value and the current age, age at diagnosis, gender, follow-up time or current BMI. **Conclusion:** This study corroborated the increasing incidence of type 1 diabetes, which enhances the importance of a better knowledge of this disease. The majority of new cases were diagnosed in males and during autumn and winter. There were not identified factors influencing the metabolic control, maybe because of the little dimension of our sample.

P3-768

The Missing Link in Neonatal Diabetes

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Background: Neonatal diabetes mellitus (NDM) presents within 6months of life, is either permanent (PDM) or transient (TND). The incidence is 400 000/live births. Monogenic accounts for the majority of cases. We describe the case of what appears to be a familiar NDM with no current known cause. **Case report:** EM presented at 3 weeks old. She was born at term, IUGR (2.3 kg) with one day history of diarrhoea, vomiting and anorexia. There was no history of polyuria, polydipsia or weight loss. Blood glucose: 37 mmol/l, blood ketones: 4.5 mmol/l and metabolic acidosis (PH: 6.8, PCO2: 3.4, bicarbonate: 0.6, BXS: −30). She commenced on Actrapid insulin 0.05 units/kg per h and transferred to PICU where she was started on CSII. Her paternal uncle had NDM presenting aged 4 weeks, requiring insulin from onset. He went into remission aged 2 years old, and represented at 15 years in DKA and has remained on insulin henceforth. There is no other family history of diabetes. EM's results showed HbA1c: 7.6%, C-peptide: 145 pmol/l (370–1470), insulin: 114 pmol/l (18–173) and negative diabetes antibodies (Anti-GAD, Islet, insulin autoantibodies). Sequence analysis of 6q TND, and KCNJ11, ABCC8 and INS genes for PND did not identify a pathogenic mutation. Mutation analysis of all known NDM genes have been undertaken in both EM and her uncle and so far have not identified any mutations. Analysis for whole genome sequencing is being undertaken. She is doing well on CSII (0.25 units/kg per day), HbA1c:7.2%. **Conclusion:** Most commonly monogenic NDM is due to heterozygous activating mutations in *KCNJ11* and *ABCC8* genes encoding the Kir6.2 and SUR1 subunits of the K_{ATP} channel. Mutations in the *INS* gene are reported as the second most common cause. So far all these mutations were excluded. We present the case of what appears to be a familiar cause of NDM which remains under investigation.

P3-769

Cutaneous Manifestations among Type 1 Diabetic Patients in DEMPU

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Background: Almost all diabetic patients eventually develop skin complications from the long-term effects of diabetes mellitus. Cutaneous manifestations generally appear subsequent to the development of diabetes but may be the first presenting sign, or even precede the diagnosis. **Objective and hypotheses:** To detect the prevalence and spectrum of skin manifestations in type 1 diabetic (T1D) patients attending the Diabetes Endocrine and Metabolism Pediatric Endocrinology (DEMPU) clinic, Cairo University and to investigate the effect of the disease duration on these dermatoses. **Method:** A prospective observational study was performed on 4221 subjects with T1D patients attending the DEMPU clinic were enrolled between December 2010 and September 2011. The overall prevalence of dermatologic manifestations was 3.6% (152 T1D patients; 74 males and 78 females) attending the DEMPU clinic. A detailed dermatological examination was carried out by a dermatology team and the cutaneous findings were recorded. **Results:** The overall prevalence of skin manifestations was 3.6% (152 T1D patients; 74 males and 78 females). The mean age of the patient 8.38 ± 3.79 years (range 1.5–15 years) and the mean total duration of diabetes was 2.80 ± 2.86 years. Cutaneous adverse effects related to insulin injections (28.9%), cutaneous infections (bacterial, fungal and viral infections) (25%), allergic skin diseases (19.1%) and pruritus (15.1%) were the most prevalent cutaneous disorders among T1D diabetic children. **Conclusion:** Early referral to the dermatologist helps to detect skin complications of diabetes in T1D patients and is essential for both prevention and management of these conditions.

P3-770

Particularités de la prise en charge du diabète Type 1 chez des enfants dont la révélation est survenue avant l'âge de five ans

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Background: The most common endocrinopathy which affects children is diabetes type 1. Its incidence is increasing around the world. **Objective and hypotheses:** We determined the specificities of diabetes on children whose stated age is <5 years, and trying to define a relations (HbA1c) – IGF1. **Method:** This is an observational cross-sectional epidemiological study of diabetic children whose diabetes was diagnosed before 5 years of age, followed by specialist consulting and hospital of the day at the Department of Pediatrics of the CHU of Tlemcen. We also determined the General characteristics; sex, age, family history of DT1, DT2, personal medical history, age of revelation, circumstances of discovery, clinical examination data, biological results, schemes with the insulin doses received, monitoring of glycemic control by glycated hemoglobin and the comfort of the child's life. **Results:** *61 diabetic children <5 years of age; sex ratio: 1.10, average age: 6.9 years, age of discovery is around 2.85 years, for the mode of revelation; Ketoacidosis: 34.42%, polyuro-plydisique

syndrome in 32.78%, fortuitous discovery in 8% of the patients. 95.09%, patients are under schema basal bolus. Also 36.06% presented symptomatic hypoglycemia, 13.11% hospitalized with 6.56% for Ketoacidosis during the last 6 months, associated diseases found in seven patients: which two thyroiditis, and five celiac disease. About the impact of the rate of IGF1 known glycemic control: 81.25% of patients with low levels of IGF1 had a high HbA1c, theses patients haven't any stature and weight deficit. The majority of patients had BMI in the standards except for six cases presenting obesity four of whom have a history of T2D. **Conclusion:** We must try to optimize the IGF1 levels so as to improve secondarily the HbA1c, glycemic control and quality of life of diabetics.

P3-771

Evaluation of Boluses Delivered by Insulin Pump in Type 1 Diabetes Mellitus Paediatric Patients

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Background: Insulin pump (IP) is very popular and efficient mean for T1DM treatment in paediatric population. Delivery of basal insulin is automatically regulated 24 h basal set up. But, boluses must be delivered in meal time and their number and type are different. **Aims and objectives:** To evaluate number and type of boluses in IP treatment of T1DM children and to correlate them with clinical features of the patients and metabolic control of their T1DM. **Methods:** T1DM patients from Pediatric Clinic in Sarajevo with insulin pump treatment were participants in this study. We used two consecutive download data and data from corresponding two controls. **Results:** We analyse data from 41 patients (24 males/17 females), mean age 13.5 years, 15 prepubertal/26 pubertal, mean diabetes duration 7.1 $\pm$ 2.4 years, mean HbA1c 8.9 $\pm$ 1.3%., delivered mean 5.4 $\pm$ 1.65 boluses daily. Lowest HbA1c (7.6 $\pm$ 1.0%) was in patients delivered 8–10 boluses daily, and the worst HbA1c (11.1 $\pm$ 2.1%) was in patients with 1–3 boluses daily. NS difference was between bolus number (5.6/5.3) in prepubertal and pubertal patients. Only 12 patients (29%) used bolus wizard (BW) calculation in everyday pump use, and they had significantly lower HbA1c than non BW users (8.22/8.99%, $P < 0.05$). Patients delivered more insulin of total daily insulin intake in bolus form had significantly lower HbA1c level ($P < 0.05$). There was no significant difference in correlation of number of delivered boluses and diabetes duration, and with duration of insulin pump treatment. **Conclusions:** Frequent downloading and analysing data from IP memory especially bolus delivery evaluation are very important for better regulation of T1DM in paediatric patients with IP treatment.

P3-772

Insulin Therapy in the Pediatric Age–Group

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Objective: Continuous subcutaneous insulin therapy (CSII) and therapy with insulin analogues are considered to provide physiological insulin replacement, which results in improvement of diabetes control. Rate metabolic compensation of diabetes mellitus (DM) in children on IPT and basal-bolus insulin therapy on the level HbA1c and self-control of glycemia. **Methods:** We analyzed retrospectively 88 histories of disease children with type 1 DM. The patients were divided into three groups: group 1 – CSII users (19 patients, age 13.02 $\pm$ 3.75 yrs, DM duration 5.36 $\pm$ 4.11 years, duration of CSII using 1.25 $\pm$ 1.15 years); group 2 – BPR-A users (39 patients, age 10.70 $\pm$ 4.08 years, DM duration 5.34 $\pm$ 3.68 years, duration of BPR-A using 2.58 $\pm$ 2.14 years), group 3 – BPR-H users (31 patients, age 13.99 $\pm$ 3.54 years, DM duration 4.47 $\pm$ 3.29 years). HbA1C levels; frequency of blood glucose measuring; the presence of hypo-, hyperglycemia and diabetic coma were evaluated. The statistical analysis were made using Excel 2010. The results were statistically significant if $P < 0.05$. **Results:** After transition to CSII, group 1 children showed to have lower HbA1C levels (6.99 $\pm$ 0.74% vs 7.81 $\pm$ 0.86%, $P = 0.004$). We didn't find difference of HbA1C levels before and after transition to BPR-A in group 2 (7.68 $\pm$ 1.20% vs 7.78 $\pm$ 2.04%, $P > 0{,}05$). BPR-H users had higher HbA1C levels in comparison with CSII (9.04 $\pm$ 2.29%, $P = 0.0001$). The frequency of blood glucose measuring were significantly higher in CSII users (9.00 $\pm$ 3.60 times a day) than in BPR-A (5.32 $\pm$ 1.52, $P = 0.0001$) and BPR-H users (4.37 $\pm$ 0.98, $P = 0.0001$). BPR-H users had five cases of ketoacidosis, BPR-A users – one case of severe hypoglycemia and none – in CSII users. **Conclusions:** CSII was the only way of insulin supply that resulted in decrease of HbA1C levels, absence of severe hypoglycemia and diabetic coma.

P3-773

Mauriac Syndrome, a Rare Complication of Type 1 Diabetes Mellitus

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Background: Mauriac syndrome (MS) classically involves hepatomegaly (hepatic glycogenosis), growth impairment and cushingoid features in a patient with poorly controlled type 1 diabetes mellitus (T1DM). The typical age of presentation is adolescence. With the advent of improved insulin regimens, MS has seen less frequently. However, new cases appear each year in medical literature. **Clinical case:** We report the case of a 9 years and 9 months of age male, with T1DM onset al 20 months of age. During the last 2 years he hadn't had medical control of T1DM; he was receiving treatment with NPH human insulin and short-acting insulin analogue (lispro), total dose: 0.8 UI/kg per day. Physical examination: Weight: 22.7 kg (−1.5 S.D.). Height: 117 cm (−3.58 S.D.). Rounded face. Abdominal swelling, liver 3 cm below RCM, he had no splenomegaly Lypodistrophia in both arms. His target height was 165±5 cm (P^3, −1.95 S.D.). Abdominal ultrasound: diffuse hepatomegaly with homogeneous echogenicity. No intrahepatic focal lesions, normal-sized gallbladder with thin and smooth walls. Haemoglobin A1C 13.1%; fasting glucose 302 mg/dl; triglycerides 156 mg/dl; AST 43 UI/l; ALT 51 UI/l. No microalbuminuria. Bone age: 6 years (delayed; −4–5 S.D.). Treatment and diabetologic training were intensified. 4 and a half years later his insuline regimen is glargine once a day and lispro at breakfast, lunch, night tea and dinner; total dosis: 0.9 UI/kg per day. Physical examination: Weight: 53.8 kg (−0.82 S.D.). Height: 152 cm (−2.63 S.D.), growth rate: 7.6 cm/years (+3.6 S.D.). Normal phenotype, no goiter, No abdominal masses or hepatomegaly. Pubertal stage: Tanner III (Right teste of 12 cm^3 and left 10 cm^3; adrenarche II-III. Left arm and left thigh lypodistrophia. HgA1c 7.1%. Bone age according to chronological age (BA: 14 years CA: 15 years). **Conclusions:** Despite improvements in the therapeutic treatment of T1DM, MS continues to appear in cases of poor control, even before puberty. Most of the clinical findings are reversible with a good metabolic control.

P3-774

Is Autoimmunity on the Increase in Type 1 Diabetes Mellitus? Presentation of Multiple Auto-Immune Disorders at Diagnosis of Type 1 Diabetes Mellitus

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Background: Globally approximately 8%[1] of children have type 1 diabetes mellitus (TIDM) with an incidence of 24.5 in every 100 000 children (0–14 years)[2]. TIDM is an autoimmune condition causing the destruction of beta islet cells and is associated with other autoimmune conditions such as coeliac disease (10% of children with TIDM test are positive for TTG) and hypothyroidism (25% have thyroid autoantibodies). We would like to report a case series of patients presenting with all three conditions at diagnosis. **Case 1:** A 9 years old girl presented with 3 months history of anxiety and polyuria, polydipsia for a few weeks. She had generalised abdominal tenderness, multiple scabbed skin lesions and was in diabetic ketoacidosis (DKA). Initial TSH 97.5 mU/l (normal range (NR) 0.3–5.0), fT_4 1.3 (NR: 12–22). In view of associated thyroid abnormalities with DKA, a repeat blood test was done and this showed a TSH 75.6 mU/l and fT_4 of 3.8. Anti-thyroid peroxidase antibody was normal. Tissue Transglutaminase (TTG) >128 U/ml (NR: <7). She was heterozygous for HLA-DQA1*05:01/DQB1*02:01 and negative for HLA-DQ8 (HLA-DQB1*03:02) consistent with a diagnosis of coeliac disease. **Case 2:** A 10 years old girl presented with a two week history of polyuria, polydipsia. She had high blood sugars with glycosuria. Diabetic workup screening blood tests show initial TSH 9.2, the repeat blood results a month later 63.3 (NR: 0.3–5.0). She was also found to have a TTG 170 U/ml and a family history of coeliac disease. Biopsy showed features of villous atrophy confirming coeliac disease. **Conclusion:** Currently there is no literature available for all three conditions presenting at diagnosis. Is the increasing incidence of TIDM and autoimmune disorders precipitating the presentation of multiple autoimmune disorders at diagnosis? Furthermore, does the presentation of all three autoimmune conditions affect the diabetic control in these patients?

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P3-775

Type 1 Diabetes Mellitus and Precocious Puberty: Rare Association

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Background: Precocious puberty is defined as pubertal development that begins at an earlier age than expected; most paediatric endocrinology subspecialists use cutoff ages of 8 years for girls and 9 years for boys. **Objective and hypotheses:** We reported in this case, rare association between type 1 diabetes mellitus and precocious puberty. **Method:** We present a girl with type 1 diabetes developed at the age of 3 years, with good glycaemic control using insulin. She also had a developmental. At the age of 6 years child had breast enlargement, height increase, and an increase in growth velocity. On examination, she was found

to have Tanner stage 3 breast development, and her vaginal mucosa was oestrogenised. Her height was above the 97th percentile. **Results:** Biochemically, she was diagnosed as having central precocious puberty, and magnetic resonance imaging of her pituitary gland diagnosed central precocious puberty idiopathic. Treatment with leuprolide resulted in normalisation of her growth rate and regression of the breast development; the vaginal mucosa also became unoestrogenised. **Conclusion:** Precocious puberty and type 1 diabetes is a rare association. The relationship has not been determined.

P3-776

School Aged Presentation of Diabetes Mellitus Type 1 with Repeat Hyperglycaemia, Positive Pancreatic Autoimmunity and Related Genetic Risks

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Background: Type 1 diabetes mellitus has three common presentations: Typical (hyperglycaemia with cardinal symptoms), ketoacidosis and asymptomatic hyperglycaemia. **Case presentation:** A 7.5-year-old girl with a history of bronchial asthma presented to the emergency department with acute-onset diabetic symptoms. The previous year she was admitted to the Paediatric Ward for a pneumonia complicated by pleural effusion. She then developed hyperglycemia (400 mg/dl) related to IV corticosteroid administration and glycosuria without ketonuria. Insulin therapy (maximum 0.86 IU/kg per day) was administered for 5 days. On discharge preprandial glycaemia was normal but her postprandial hyperglycaemia (230–240 mg/dl) persisted for another week. Outpatient follow-up labs revealed positive HLA DR3, normal insulin and C-peptide, HbA1c 5.4% (NGSP), positive antiGAD (2 000 U/ml), pancreatic islet cell, positive antitransglutaminase and antiendomysium antibody levels, negative anti-insulin antibody and a normal oral glucose challenge test. 6 months later she was admitted for acute bronchospasm which required treatment with oral corticosteroids. A hyperglycaemia (400 mg/dl) with glycosuria absent ketonuria was detected. Corticosteroids were suspended and SC insulin was started (maximum 0.75 UI/kg per day) for 3 days, which resulted in normalization of glycemic values. 4 months postdischarge she was readmitted with a 3 days history of polydipsia and nocturnal enuresis. At home her blood glucose measured 500 mg/dl. Hospital labs revealed: a normal venous pH, a venous blood glucose of 511 mg/dl, glycosuria absent ketonuria or ketonemia, glycohemoglobin 8.5%, positive microsomal antibody levels, normal thyroid function, appropriate bone age and a normal fundoscopic exam. Repeat pancreatic autoinmunity tests and antitransglutaminase antibody levels remained positive. **Conclusion:** Close monitoring of iatrogenic hyperglycaemia may help in early detection of type 1 diabetes and to prevent further complications.

P3-777

Clinical Changes Observed After System Implementation of JUNIORSTAR Systems in Children with Dm1a

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Background: Several drugs and pharmaceutical formulations not sold in our country for different reasons: economic, market requirements or the prevalence of the disease. Like occur in so-called orphan treatments, diabetes mellitus (DM) children may be deprived of pharmaceutical presentations for its lower numerical prevalence vs the number of adult patients affections DMtipo2 One of the problems that young children face DM1 is its high sensitivity to insulin. Since May 2014 marketing begins in Spain vials for JUNIORSTAR system that allows the administration of glargine and glisulide in pens 0.5 UI. **Objective and hypotheses:** To evaluate the impact of using vials for device JUNIORSTAR 0.5/0.5 UI in young children with DM1 and compare it with our previous experience and published *Rev Esp Pediatr Endocrinol* 2013; **4**(Suppl) device imported from abroad. **Method:** DM1 children over 2 years with at least 6 months duration from debut. Age $>$ 2a. Sensitivity index $>$ 100 mGrs/dl/IU. Desire of parents to not use syringes. Rejection Insuflow® type devices. No possibility ISCI. Using glisulide insulin and/or insulin glargine and comparison with the data (Farmaco Foreign Ministry authorization code 011813) RAPID NOVO PenFill CARTUCHOS®. Study comparativo. IBM Stastistics SPSS 19.0, Nonparametric paired samples $n < 30$. Health Survey Questionnaire SF-36 (Spanish and summarised). **Results:** Ten children (5♂), mean age 5.8 to (5–8.5). Prior è HbA1c (DCA): 8.1% (6.4–8.8) needs: 0.72 IU/kg per day (0.45–0.88), sensitivity 168 mg/dl/UI (135–280) and Survey 7.2 points (6–8). After 6 months of use è HbA1c (DCA): 7.5% (6.8–7.9) *P*: 0.38, needs 0.88 IU/kg per day (0.77–1.05) p differences: 0.01 95% CI (0.12–0.34), sensitivity 145 mg/dl/UI (125–205) *P*: 0.001, and Enc 8.5 points (7–9). Improvement score similar to previous study. **Conclusion:** Improving quality of life perceived by parents with the low cost of operation defines the potential of this dosage form as a transition to adult-type devices.

P3-778

Metabolic Control in Children in Northern Spain DM1A with Deficit of Vitamin D

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Background: 1 000 million people worldwide presenting vitamin D deficiency in children prevalence of vitamin D deficiency in certain regions described up to 80%, especially at high latitudes (above 37). Has been postulated role of vitamin D in

the immune system and in clinical variability DM1. **Objective and hypotheses:** To study the degree of deficit VITD in our population (Location: 42° 51'north latitude 2° 41'west longitude) with DM1 and check whether this influences the metabolic control. **Method:** Prospective open intervention. DM1a with 12 months duration. 1st wave study months April-May 2014 – 6 months intervention (insolation 3 months + 3 months treatment) – revaluation Q4 November–December 2014. Intervention three summer months inducing activities 'outdoors' and posterior shock treatment 3 months one unidosis 2.5 ml bottle. 25 000 IU of cholecalciferol (vitamin D), equivalent to 0.625 mg. (DELTIUS)/ one every 3 weeks. Reference Endocrine Society (2011) Levels of 25-OH-vitamin D (ng/ml), failure < 30 (student t), with a confidence interval of 95%. SPSS19.0. **Results:** Initially selected 57 cases (26/57♂–46%). Average age debut 8.24aDS4.27 (0.3to15). 11.11% HbA1c debut DS2.37 (8–15.5). Age current average 11.5aDS3.67 (2–17). SDS1.16 average HbA1c 7.95% (5.8–9.6) in 1 wave. No differences between sexes. 93% basal-bolus regimen (4/57 ISCI). 89% Caucasian (3/57 Maghreb, Latin 3/57) 98% in range 25OHD insufficiency average 18 ngr/ml DS (10–28). Normality ♀ caucasian 12a (37 ngr/ml) Intervention in 56 cases. On average HbA1c 7.68% revaluation SDS1.18 (5.6–9.2) *P*:0.12. Mean 25OHD 33 ng/l DS (26–52) *P*:0.01. Improvement in 52/56 cases (93%). No differences between sexes or races. **Conclusion:** Children DM1 in our region have a severe deficiency of vitamin D. The exercise outdoors in summer and a shock treatment with depot preparations is shaping effective in correcting this deficit. Although no significance in improving metabolic control HbA1c levels seem to improve in these cases. An assessment and comprehensive intervention of this pediatric population is needed compared with a deficit of vitamin D.

P3-779

Effects of Educational Interventions for Children and Adolescents with Type 1 Diabetes Mellitus

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Background: Is to evaluate of the quality of the current education program for diabetic children and their parents at Diabetes Endocrine and Metabolism Pediatric Unit (DEMPU). **Objective and hypotheses:** Is to evaluate of the quality of the current education program for diabetic children and their parents at DEMPU. **Method:** The present study was an observational longitudinal study conducted on 100 cases of T1D admitted in DEMPU inpatient section, using a questionnaire covering all aspects of the program solved before and after attending 5 days education sessions. **Results:** Marked increase in diabetic knowledge after attending education program, as 95% of interviewed parents knew how to prevent hypoglycaemia at night, 97% of them knew that diabetic parents were not responsible for affection of their children with diabetes, 94% of them mentioned that their schools were aware about the child disease and 92% of them allow their children to share in school activities. There was no significant difference between different social classes in understanding education program. Linear regression analysis showed that the only factor which has an effect on HbA1c was total post education score. **Conclusion:** The efficient points of the education program at DEMPU were identified and included knowledge about nature of T1D, role of family history in developing T1D, awareness of symptoms of hypoglycaemia, how to prevent hypoglycaemia during sports and at night, school awareness of the disease and sharing school activities, while the weak point in this program was defective.

P3-780

Clinical Findings, Endocrine Profile and Genetic Features of 5α-Reductase-2 Deficiency

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Background: The 5α-reductase-2 (5R2) deficiency is a rare 46, XY disorder of sex differentiation caused by mutations in the 5R2 gene. Diagnostic and clinical management is not well definite. **Aims and objectives:** To describe relevant features of 5R2 deficiency in a large sample. **Methods:** Retrospective records of persons with 5R2 deficiency were reviewed and clinical, endocrinological, genetic data analysed. **Results:** A total of 25 individuals with certain diagnosis of 5R2 deficiency was collected (age at first clinical observation 0.4 ± 1.0 years). About 50% had a misdiagnosis before diagnosis. Mean period from first observation to definitive diagnosis was 9.1 ± 10.8 years. Gonadal removal was performed before certain diagnosis in eight subjects. Initial sex assignment was female in 64% and male in 36%. After diagnosis, sex re-assignment was performed in five babies: four girls to male sex and one boy to female sex. Baseline testosterone/DHT ratio was diagnostic in six/12 subjects, while post-hCG T/DHT ratio was diagnostic in all tested patients by setting the cut-off value at 15 or lower. 18 different mutations in 5R2 gene were identified (homozygous 12/25; compound heterozygous 11/25; monoallelic missense mutation 1/25; homozygous V89L variant associated with high progestin administration during pregnancy 1/25). Five mutations have never been reported (p.G13D, p.P79L, c.281 + 1G > A, c.331_332delCT, p.V124D). In some individuals, the same mutations were associated with different phenotypes. **Conclusions:** Consistent time-lag may persist before the diagnosis of 5R2 deficiency is established. Sex assignment and gonadal removal may be done before certain diagnosis. Sex re-assignment

is usually to male sex, but the contrary may occur. Accurate endocrine evaluation is recommended, since the use of appropriate cut-off values of T/DHT ratio may permit to select individuals with 5R2 deficiency. Large genetic variability is present and a clear genotype-phenotype correlation is lacking.

P3-781

Aromatase Deficiency due to Novel CYP19A1 Mutation in an Egyptian Patient with Ambiguous Genitalia

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Background: Mutations in CYP19A1 gene have been described in both females and males and to date only 20 cases with aromatase deficiency have been reported. In newborns, aromatase deficiency should be considered in the aetiology of 46, XX DSD, after ruling out congenital adrenal hyperplasia. **Objective and hypotheses:** Report of a case with CYP19A1 mutation. **Method:** Here we report a patient who was presenting at the age of 20 years old reared as boy, he had no palpable testis, hypoplastic scrotum, phallus was penis like = 3–cm, there was a penoscrotal hypospadias, he was a product of consanguineous parent, his karyotype was 46, XX and SRY was negative. Pelvic sonar showed a small hypoplastic uterus and no testis could be identified. Testosterone and its precursors were normal excluding congenital adrenal hyperplasia, pathology of gonadal biopsy showed ovarian stroma negative for oocytic follicle. All these data were suggestive of aromatase deficiency that was confirmed by molecular investigation of the *CYP19A1* gene. **Results:** A novel splice site mutation in the donor splice site of exon 9 was identified in our patient, c.1263 + 1G > T (IVS9 + 1G > T). The mutation was found in the homozygous form in the patient and both parents were heterozygous for the mutation. Further, the mutation was not found in 200 normal chromosomes of Egyptian origin and was predicted to be disease causing by various bioinformatic tools. **Conclusion:** This is the first report of such a rare disorder in an Egyptian patient with 46, XX DSD emphasising the importance of mutational analysis of *CYP19A1* gene for appropriate management and better choice of sex. **Funding:** This work was supported by the fund of IRD in collaboration with STDF in Egypt.

P3-782

The Time of First Presentation at the Department of Paediatric Endocrinology of Patients with 46, XY DSD

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Background: The atypical appearance of the external genitalia in a neonate, defined as the external masculinization score (EMS) less than 11, should incline the clinicians to perform diagnostic procedure ideally managed by a multidisciplinary team in a tertiary centre. Among the patients with disorders of sex development (DSD), the most challenging subgroup in terms of aetiology, is the subgroup with 46, XY karyotype. **Objective and hypotheses:** To study the time of first presentation at the department of paediatric endocrinology of 46, XY DSD patients with atypical genitalia after birth and to assess whether there is a correlation between the time of first presentation and the EMS in those raised as males. **Method:** We performed a retrospective analysis of 28 patients (25 raised as males, three raised as females) with 46, XY DSD that presented for the first time at our department over the last 15 years. We excluded those patients in whom the reason of undescended bilateral testis was obvious (i.e. CHARGE syndrome, prune belly syndrome, omphalocele). The analysed group was not deprived of selective bias as these patients were enrolled into further genetic study. **Results:** The median time of first presentation at the department of paediatric endocrinology was 7.5 months (range: 1–153). The time of first presentation was not correlated with the EMS in those raised as males ($r_s = 0.0$). The consensus on DSD issued in 2006 does not seem to influence the time of first presentation as the median time was 3 months (1–21) in the group that was diagnosed before 2006, and 10 months (1–153) after 2006 respectively. **Conclusion:** There is a strong need to study the reasons of those patients with late presentation to the paediatric endocrinologist and to promote the knowledge on DSD management in regional neonatal departments.

P3-783

Impact of Neonatal Exposure to Different Doses of Bisphenol A on the Hypothalamic-Pituitary-Testicle Axis in Male Rat

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Background: Male genital abnormalities may be associated with environmental endocrine disruptors. **Objective and hypotheses:** To observe the hypothalamic kiss-1 gene and the testis androgen acceptor (AR) gene expression level changes and the level of serum luteinizing hormone (LH), follicle stimulating hormone (FSH); testosterone (T) and Inhibin B (INH B) in neonatal rats which exposure to different doses of bisphenol-A (BPA). In order to explore the effects of neonatal exposure to different doses of BPA on the hypothalamic-pituitary-testis axis and the testis function in toddler and adolescent male rat. **Method:** Neonatal male Sprague-Dawley (SD) rats were randomly divided into five groups: blank control, low-dose BPA (25 ug/kg per day), medium-dose BPA (50 ug/kg per day)) and high-dose BPA (250 ug/kg per day). The rats were subcutaneously injected with respective agents on postnatal days 1–7 (PND1-7). Pups were weaning on postnatal days 21 (PND21) and randomly

sacrificed on postnatal days 22(PND 22) and postnatal days 50(PND 50)and collected blood.The hypothalamus and testis were taken and weighed. The hypothalamic Kiss-1 mRNA and the testis AR mRNA were measured by Real-Time PCR., The level of serum LH, FSH and T and INH B were measured. **Results:** There was no significant difference between the control group and other five drug groups on the weight of rats. The medium- and high-dose BPA groups compared with the controls, the organ coefficient of testis decreased significantly in PND 50.In PND22 male pups, the medium and high dose BPA groups compared with the controls, the serum LH were decreased significantly The level of serum T obviously decreased in PND22 and PND 50.In high dose group of PND 22, the expression of hypothalamic Kiss-1 mRNA increased compared with the rest of the groups while in PND50, compared with control group,the medium and high dose groups Kiss-1 mRNA decreased. There were no significant difference in the mRNA expressions of testis AR with control group in PND 20 and PND 50. **Conclusion:** Neonatal exposure to the low-dose BPA does not have a significantly influence on the hypothalamus–pituitary- testis axis and the testis function. Neonatal exposure to the medium- and high-dose BPA affect the expression level of the hypothalamic kiss-1 mRNA in toddler and adolescent male rat and may impair the function of testis and hypothalamus–pituitary-testis axis.

P3-784

A Cross-Sectional Growth Reference and Chart of Stretched Penile Length for Japanese Boys Aged 0–7 Years: Ethnic Differences and Secular Changes

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Background: Reference values for penile length have not been established for Japanese boys. **Objective:** We aimed to develop percentiles and means with standard deviations of stretched penile length (SPL) in Japanese boys. **Method:** We conducted a cross-sectional study in 1 628 Japanese boys aged <9 years from 2007 through 2014. The LMS method was used to develop a growth reference and chart for SPL in boys aged 0–7 years. Inter-observer variation in the SPLs was assessed in 32 boys (median, 3 years of age; range, 0–11 years). The correlation between SPL and stature, weight, or BMI was analyzed by the Pearson's test. The SPLs determined in the present study were compared with those of other ethnicities or those in previous Japanese studies. **Results:** SPL increases continuously during prepubertal period, and most rapidly in the first 4 months of life. No significant fixed or proportional bias was found for inter-observer variation ($P=0.5$; $r=0.33$, $P=0.06$). There was no significant correlation between SPL z-score and stature z-score ($r=0.14$, $P<0.001$), weight z-score ($r=0.09$, $P<0.001$), or BMI z-score ($r=0.01$, $P=0.71$). The SPL in current Japanese boys was significantly shorter than that in US Caucasian or Turkish boys, and longer than those reported by previous Japanese studies. **Conclusion:** These data serve as an updated growth reference and chart for SPL in Japanese boys aged 0–7 years. SPL needs to be assessed by a growth reference for the same ethnicity and generation. **Funding:** This work was supported by Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science, by Health Science Research Grant for Research on Applying Health Technology (Jitsuyoka (Nanbyo)-Ippan-014) from the Ministry of Health, Labor and Welfare, Japan, and by FGHR Clinical Research Grant.

P3-785

Recurrent Orchitis in a Patient with True Hermaphroditism

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Background: Ovotesticular Disorder of Sex Development (OTDSD – true hermaphroditism) is rare, characterized by the presence of both presence of both testis and ovay tissue. Usually, these patients seek medical attention due to ambiguous genitalia. **Case presentation:** A 15-year-old boy, with 'atypical' genitalia and breast enlargement came for surgical correction. His genitalia had a more masculine aspect at birth and he had been submitted to six corrective surgeries. Karyotype is 46, XX(20). His complaint was recurrent episodes of painful testicular swelling and gynecomastia for the last five years. Tanner stage G4P3 and breast enlargement (T_4), hyperpigmentedscrotum fused with palpable gonads and a penis 6 cm long with distal hypospadia. Lab work-up: Estradiol = 73.4 pg/ml (<20), Pubertal LH and FSH levels. Testosterone = 156 ng/dl. Ultrasound revealed testes with microlitiasis, bilateral hydrocele and cysts in the left testis. A structure which could resemble a rudimentary uterus or vaginal fornix was also shown. Bilateral mastectomy and a laparoscopy was performed in order to explore the gonads, which turned out to be *ovotestis*. The left gonad was totally excised, whereas inthe right one, the macroscopic testis component was preserved. **Conclusion:** In OT DSD, the ovarian portion of the gonad in the scrotum may enlarge during the ovulatory phase, which may be misdiagnosed as 'orchitis', but the cyclical nature of the episodes should raise the possibility of ovarian tissue present in the gonad. In the ovotestis, the testicular component may be dysgenetic, opposing to the usual normal function of the ovarian portion, which favors the maintenance of the ovarian portion when possible. In our patient, the social male gender was well established therefore testicular tissue was preserved. The possibility of neoplastic degeneration is minimized once Y chromosome was not present but follow-up is mandatory, with the dosage of markers of malignization.

P3-786

Isolated Persistent Pubertal Gynecomastia in Three Adolescent Males as the Only Phenotypic Expression of PAIS with Androgen Receptor Gene Mutations

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Background: Pubertal gynecomastia is observed in up to 65% of adolescent males. It is usually idiopathic and tends to regress within 1–2 years, although sometimes pubertal gynecomastia persists. **Case presentation and methods:** We investigated three adolescent males with isolated persistent pubertal gynecomastia: twin brothers and an unrelated adolescent boy. The twins (17 years) had normal male external genitalia. Biological testing showed normal testosterone concentration (4.1 and 3.8 ng/ml respectively) and normal response to the HCG stimulation test (10.3 and 13 ng/ml respectively). The gonadotropin level was normal. Spermatogenesis investigations revealed azoospermia in one of the brothers and oligospermia in the other. The third adolescent boy (16 years) presented normal male external genitalia. Biological investigations showed normal testosterone level (3.6 ng/ml) and no other sign of alteration. No evidence of spermatogenesis failure was documented. **Results:** For the twins, genetic analysis of the AR gene revealed a c.1937C > A mutation in the hinge region leading to a substitution of an alanine by aspartic acid: p.Ala646Asp. This mutation was transmitted by their mother. She presented no sign other than very sparse pubic hair. For the third adolescent, genetic analysis of the AR gene identified the c.134C > G substitution resulting in a p.Ala45Gly change in amino acid. This mutation was transmitted by his mother. The maternal family history revealed a first cousin with bilateral mastectomy for persistent and prominent bilateral gynecomastia. **Conclusions:** These data suggest that persistent pubertal gynecomastia should be investigated to identify a possible defect of the AR gene.

P3-787

Identical Twins Raised as Sister and Brother

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Background: Disorders of sex development (DSD) can be caused by many hormonal and genetic defects. One rare condition is a mutation of the SRY-gene disturbing normal sex differentiation. Identical twins with this disorder of varying degree are presented to learn how difficult social sex assignment may be in such a case**. Case presentation:** Identical 46, XY twins were born in 1985 from non consanguineous, healthy parents of German origin. The newborns were healthy but showed DSD. Child I presented female external genitalia. Streak gonads with muellerian structures were found by laparotomy. This is the clinical picture of Swyer's syndrome. Consequently she was raised as a girl receiving estradiol since the age of 12 years. Child II demonstrated a male-like phallus with hypospadia, flat scrotum with two palpable gonads and inguinal hernia. Laparotomy detected two testes with epididymides, a normal vagina, uterus and tubes but no ovarian tissue. All inner structures including dysgenetic testes were resected. This is the clinical picture of oviduct persistence. In consequence he was raised as a boy. At the age of 4 years he was operated for phallus curvature correction. With 5 years of age he got a urethroplasty for hypospadia repair. With 8 years the first artificial testes were inserted. With 13 years testosterone therapy was initiated. **Conclusion:** A mutation in SRY-gene is postulated. It disturbed physiologic gonadal development in identical 46, XY twins in different manifestation: In the girl no gonads developed leading to streak gonads and persisting muellerian structures like in Swyer's syndrome. This twin therefore was raised in a social female sex. In the second twin dysgenetic testes were found with diminished testosterone- and no AMH- production. Accordingly he was born with a vagina and persisting muellerian structures. In respect of his well developed phallus he socially was raised as a boy. Both of the identical twins are very content with their social female and male sex assignment. They live with heterosexual partners, they have a normal vita sexualis, and they wish to have children. They cannot think to have lived up to 30 years in a undefined so called third gender. In their opinion the early gender assignment during infancy was correct.

P3-788

Persistent Müllerian Duct Syndrome Associated with Anorchia Caused by a Compound Heterozygous Mutation in the AMHR-II Gene

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Background: The persistent Müllerian duct syndrome (PMDS) is a rare 46-XY disorder of sex development, characterized by the persistence of Müllerian derivatives (uterus, Fallopian tubes) in otherwise normally virilised males. The condition is transmitted as a recessive autosomal trait and is caused in most cases by a defect in either the anti-Müllerian hormone (AMH) or the AMH type-II receptor (AMHR-II) genes. **Case report:** We present a 9 years old male who was born with bilateral cryptorchidism, scrotum hypoplasia and normal penis. There were no relevant conditions in his familiar (no consanguinity), or personal history. Blood karyotype showed normal result (46 XY; SRY +). Two beta-hCG stimulation tests (1000 U × 3 doses) were performed. First at 2.3 years of age (Testosterone post-hCG = 150 ng/dl) and then at 8.9 years (Testosterone post-hCG = 15.8 ng/dl; normal values > 200 ng/dl). Basal AMH was also low (3.1 ng/ml (44–173 mg/dl)). Postnatal ultrasonography detected a tubular-shaped structure close to the urinary-bladder.

Laparoscopy was performed at the age of 9. Structures resembling rudimental uterus and Fallopian ducts were found behind the urinary-bladder and were resected. The histological- inmuno-histochemistry examination confirmed the müllerian origin of both structures. No gonad tissue was found with the exception of epididymis tissue. Karyotype was performed in both structures with a normal 46-XY result. Sequencing of the AMHR-II confirmed compound heterozygosity. One of the mutations was the recurrent 27 bp deletion in exon 10th. The other was a c.6101 C>T (p.Arg423Cys), in the intracellular serine/threonine kinase domain of the receptor. This mutation is described for the first time. **Conclusion:** We present a case of PMDS caused by a mutation in AMHR-II. The association with anorchia is occasionally seen, and is thought to be caused by the increased risk of torsion and subsequent degeneration of the testes. In this patient we hypothesize that the testicular degeneration occurred in the first years of life.

P3-789

A Novel Mutation in Steroidogenic Factor Gene in a Patient with 46, XY DSD without Adrenal Insufficiency

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Introduction: Steroidogenic factor-1 (SF1/NR5A1) is a nuclear receptor, which regulates genes that have functions in the development of adrenal glands and gonads, reproduction, and other metabolic functions. **Case presentation:** A 20-day-old infant was admitted due to ambiguous genitalia. Physical examination revealed a 2×1 cm phallus, bifid scrotum, and hypospadias. Both gonads were palpable in the inguinal canal. Serum levels of adrenal androgens (17-OH progesterone, DHEAS, androstenedione) and gonadotropins were within normal limits. Uterus could not be visualized on pelvic ultrasonography. In peripheral blood chromosome analysis 46, XY karyotype was detected. Initially, partial androgen insensitivity and 5α-reductase deficiency were suspected. The patient was reared as male according to the decision of Gender Assignment Council. After decision, he underwent orchiopexy and surgical repair for hypospadias. At the age of 11 years, his pubertal development was normal with pubic hair Tanner stage III and both testes palpable as 6 ml. Hormonal evaluation revealed: LH: 7.1 IU/l, FSH: 23.1 IU/l, total testosterone: 164 ng/dl, and testosterone/dihydrotestosterone ratio was 22. After hCG stimulation test (3 000 IU/day, 3 days), total testosterone level was measured as 368 ng/dl (Δtestosteron = 204 ng/dl). Next generation sequencing of SF1 gene revealed a novel heterozygote mutation at T272P (c.814A>C). Analyses of the parents detected 17% mosaicism in the father's leukocyte DNA. Buccal smear sample to confirm mosaicism status of the father also detected the same level of mosaicism. Adrenal insufficiency was excluded with a standard dose ACTH stimulation test, which revealed a peak cortisol level of 27.8 μg/dl. **Conclusion:** We report a novel mutation in SF1 gene in a patient with 46, XY DSD without adrenal insufficiency. Additionally, we detected a low-level paternal mosaicism with next generation sequencing.

P3-790

Evaluation of Two New Anti-Müllerian Hormone Assays for the Investigation of Disorders of Sexual Development in Neonates

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Background: Anti-Müllerian hormone (AMH) inhibits the in utero growth of the Müllerian structures in female fetuses. In neonates with suspected disorders of sexual development (DSDs), the presence of testicular tissues and functioning Sertoli cells can be investigated by testing for serum AMH concentration. **Objective:** To evaluate the performance of two new AMH assays in a hospital laboratory. **Method:** The technical performance of two new assays for AMH (Beckman Coulter and Roche) was evaluated and compared with each other using standard laboratory protocols. Serum AMH concentrations were also measured in 44 neonates with no suspected DSDs. **Results:** AMH results generated by the two assays are highly comparable (Pearson correlation coefficient = 0.966). Both assays were linear within their reportable ranges. Precision studies showed that coefficients of variation (CVs) at the limits of quantitation (LOQ) were <7%. In the female neonates ($n = 24$; aged 0–29 days; mean age = 5.9 days), AMH concentrations (Beckman Coulter assay) ranged from 0.02 to 2.28 ng/ml (mean ± S.D., 0.22 ± 0.47 ng/ml). In comparison, in the male neonates ($n = 20$; aged 0–30 days; mean age = 11.7 days), AMH concentrations ranged from 15.5 to 157.6 ng/ml (mean ± S.D., 70.5 ± 48.7 ng/ml). **Conclusion:** There is no overlap between serum AMH concentrations in the two gender groups of neonates. All AMH concentrations measured in the male and female neonates fall within their respective reference intervals provided by one of the manufacturers (males <60 days, 15.1–266.6 ng/ml; females <60 days, 0.01–3.39 ng/ml). In conclusion, both AMH assays were analytically sensitive enough to be used in neonates, and differential AMH concentrations in male and female neonates render this test a useful tool for the investigation of DSDs.

P3-791

'Female', 'Male', or 'Between' in a 46, XY-Patient with a 17ß-HSD3-Mutation

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Background: 46, XY-disorders of sex development (DSD) are due to different causes like androgen insensitivity, gonadal dysgenesis, defects in testosterone metabolism and others. Exact diagnosis is mandatory prior to medical advice, therapeutic steps, or even surgical procedures. To show the difficulties of gender assignment before and also after a correct diagnosis we describe a patient who waited 35 years for the complete diagnosis, but was advised, treated and operated before. **Case presentation:** A 46, XY-child was born with ambiguous genitalia with clitoris hypertrophy, short vagina and palpable gonads. Under the impression of partial 'androgen insensitivity' or 'gonadal dysgenesis' gonadectomy and shortening of the phallus was performed at the age of 5 and 6 years respectively. Estrogen substitution therapy was initiated at the age of 13 years resulting in good breast development giving her together with her long hair a female appearance. But she felt a deficit of libido and clitoral arousal. According to her chromosomal gender of 46, XY she started at the age of 34 years with additional testosterone gel by self-medication and got the impression of feeling stronger and more energetic. At the age of 35 years it was possible to establish his/her diagnosis of a homozygote 17ß-HSD type 3 splice site mutation. This is the cause of the congenital lack of virilization mimicking partial androgen insensitivity syndrome. After gonadectomy and phallus reduction there was no tissue for spontaneous male puberty. Currently the patient is unable to decide for a male or female social sex but prefers to live between the two standard genders. **Conclusion:** In retrospect it would have been better to wait for the correct diagnosis, since in 17ß-HSD-patients a considerable number of individuals develop significant male testosterone levels and demonstrate spontaneous phallic enlargement during puberty.

P3-792

Physical Assessment and Growth Curve of 46, XY Disorders of Sex Development Children Who Aged 0–16-Years-Old

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Background: The growth pattern of normal children was inappropriately used to evaluate those who with DSD. **Objective:** To understand growth and development of the 46, XY disorders of sex development (DSD) children, drawing height, weight and BMI curve of children with 46, XY DSD at the age of 0–16. **Method:** The registration database was used in this study. Non- CAH 0-16 years old 46, XY DSDs were collected. Growth curves were fitted by LMS application within 0–3 years old and 3–16 years old group and were compared with the curves of normal boy. According to the results of HCG standard test, the children were divided into good response group and poor response group, the differences of height between the two groups of children with normal boys were analyzed. The HtSDS and WtSDS were calculated and compared with normal boys at same age. **Results:** 431 cases of non-CAH 46, XY DSDs were included in the study. 56.6% (244 cases) of children aged 0–3 years old. The HtSDS was -0.25 ± 1.206, WtSDS was 0.44 ± 1.282, BMI was $18.10 \pm 2.926\ kg/m^2$ for 46, XY DSD children. HCG standard test was conducted among 360 cases. Good response 250 cases, HtSDS and WtSDS were -0.16 ± 1.211 and 0.57 ± 1.346; 110 cases were classified into poor reaction group, HtSDS and WtSDS were -0.38 ± 1.200 and 0.26 ± 1.245. Height of 46, XY DSD children generally lower than normal boys in infant period, 46, XY DSD children without soared growth at 12-16 years old, this phenomenon was more obvious in poor response group. **Conclusion:** The growth retardation of non-CAH 46, XYDSD was observed at infant period, and it is more obvious in pubertal period. The level of retardation related with testicular interstitial cell function.

P3-793

A Novel Mutation of the AR Gene Causes Androgen Insensitivity Syndrome: A Case Report

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Background: A 8-year-old Chinese girl was referred by the endocrinologist of our hospital because of ambiguous external genitalia.Physical examination revealed breast and axillary hair and pubic hair at Tanner stage 1, There had two mass located within two side of inguinal regions,labia fusion, the size of clitoris was 2.0×1.0 cm, there was a vaginal opening. US images revealed a solid nodile suggestive of testicular tissue located in both inguinal regions. The MRI exam confirmed a testicle in the deep inguinal ring on both sides. The uterus and Fallopian tubes were absent.The blind-ended vagina length was 4.0 cm. The baseline testosterone (T) and dihydrotestosterone (DHT) and androstenedione ($\triangle 4A$) concentration were 0 nmol/l, 0.51 ng/ml, 21.66 pg/ml respectiverly, After the HCG stimulation test, T and DHT and ($\Delta 4A$ concentration were 4.69 nmol/l, 0.628 ng/ml, 99.88 pg/ml respectiverly. The T/DHT ratio was 14.2, The T/$\Delta 4A$ ratio was 2.4. Her karyotype was a normal 46, XY complement. **Objective and hypotheses:** The aim of the study was to verify the mutation of the AR gene to molecular cause of this patient of 46, XY DSD. **Method:** DNA was extracted from peripheral leukocytes and all exons of the AR genes were amplified by PCR. The AR gene was sequenced (exons 1 to 8 with intronic flanking regions) in patient and his parents. Amino-acid substitutions were studied in silico to predict the effects using Polyohen2 and SIFT software **Results:** A c.1685 T > C mutation (p.Ile562Thr) on exon 2 of the AR gene was identified in the patient. But the locus mutation of the AR gene had never been reported was found in the one thousand – genome database dbSNP database and BGI internal database.The structure prediction of the mutated protein was significantiy changed. All three in silico algorithms predicted affected protein function with a conserved amino acid throughout species (Polyohen2: probably damaging with a 0.99 score; SIFT :damaging with a 0.0 score; Mutation Taster: disease causing). By verifying the site of patients parents, the mother carried the same mutation, The father was found to be normal, which is consistent with an x-linked patter of AIS. **Conclusion:** A c.1685 T > C mutation (p.Ile562Thr) on exon 2 of the AR gene could result in androgen insensitivity syndrome.

P3-794

A Novel Androgen Receptor Gene Mutation in a 46,XY Patient: Complete Androgen Insensitivity Syndrome

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Background: Androgen insensitivity syndrome is the most common cause of 46,XY disorders of sex development. This condition is inherited in an x-linked recessive pattern and the most common causes are inactivating mutations in the androgen receptor (*AR*) gene. **Objective and hypotheses:** In this study, we report a novel *AR* gene mutation in an adolescent patient presenting with primary amenorrhea. **Method:** A 16-year-old patient was admitted to our department for primary amenorrhea. According to the past medical history her breast development began 12 years old. **Results:** Physical examination revealed that external genitalia structure was totally consistent with a female phenotype; breast development was Tanner stage 5 and pubic hair was Tanner stage 1. Laboratory tests revealed that basal LH: 24.44 mIU/ml; FSH: 1.36 mIU/ml; total testosterone: 5.29 ng/ml; E2: 37 pg/ml; Karyotype analysis was reported to be 46,XY. Pelvic ultrasonography failed to identify bilateral gonads, an image in 30×7 mm which could be related to hypoechoic rudimentary uterus was obtained. As a result of serial analysis of gene expression, a novel heterozygous mutation was identified in the *AR* gene. The gonads were removed in order to avoid the malignant risk. **Conclusion:** As a result, with this case report we emphasized that, i) 46,XY disorders of sex development should be considered in differential diagnosis of the patients with female phenotype presenting with bilateral inguinal hernia in the period and, ii) CAIS should be considered in differential diagnosis of the patients with female phenotype and breast development presenting with primary amenorrhoea.

P3-795

Polymorphisms and Mutations of the Genes *INSL3* and *HOXD13* in the Pathogenesis of Isolated Cryptorchidism in Greece

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Background: Current literature suggests an important role of both endocrine disruptors and genetic factors in the occurrence of cryptorchidism. **Objective and hypotheses:** The aim of the study is to investigate the impact of variants in *INSL3* and *HOXD13* genes in the pathogenesis of isolated cryptorchidism in Greece. 43 boys with isolated cryptorchidism and 50 healthy non-cryptorchidic boys (control group) were enrolled. **Method:** Genomic DNA was extracted from peripheral blood leukocytes and genetic analysis was conducted using PCR and direct sequencing of *INSL3* and *HOXD13* gene regions. **Results:** Two apparently novel variants, the *−109 T>A of the *INSL3* 5′ UTR and the *528_529inv of the *HOXD13* 3' UTR were disclosed in two unrelated patients. None of these variants was revealed in the control group ($P=0.32304$). Conversely, multiple previously described polymorphisms of both genes (*INSL3*: c.27G>A, c.126A>G and c.178A>G/*HOXD13*: c.*311C>T, c.*360A> T and c.*359_*360insT) were detected in both the cryptorchidic patients and the control group with no statistically significant difference between groups. 'In silico' analysis for the two as yet unreported findings indicated possible alterations of the cDNA sequences but with no comprehensible impact on the coding procedure. A combination of polymorphic alleles in these two genes was observed in both patients and controls without any statistically significant difference between groups ($P=0.30873$). **Conclusion:** Neither the presence of specific polymorphisms in the *INSL3* and *HOXD13* genes, nor their combination could account for the pathogenesis of isolated cryptorchidism. The effect of endocrine disruptors or variations in non-examined genes in the pathogenesis of cryptorchidism, as well as the better delineation of the role of the new detected variants should be further investigated in larger populations. **Funding:** Master Degree Course 'Research on Female Reproduction' taking place in Aretaeio General Hospital of Athens. Department of Medical Genetics of Choremio Research Laboratory.

P3-796

Tumours of Gonads in Patients with Disorders of Sex Development – 46,XY Gonadal Dysgenesis

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Background: Disorders of sex development, especially with Y chromosome material, are the main factor of an increased risk of gonadal tumour. The main idea of this study was to investigate the prevalence of gonad tumours in patients with 46,XY gonadal dysgenesis. **Methods:** This study included 9 patients with 46,XY gonadal dysgenesis: seven patients with partial and two with total

gonadal dysgenesis. Among nine patients there were two patients with Frasier syndrome and one with Denys-Drash syndrome. In six cases the patients had bilateral gonadectomy. In five cases gonadectomia was performed at the moment of primary detection of disorders of sex development. (0.4; 1; 2.7; 14; 16 years). One patient hade gonadectomy a bit later at teenage age (17 years) due to the high risk of gonadal tumour. **Results:** Pathologic examination revealed gonadal tumours in two (33%) of six patients. All patients with gonadal tumours had an unambiguous female phenotype. That's why the diagnosis was made only at teenage age and therefore operation was also performed only at teenage age. (14, 16 years). In one case was revealed gonadoblastoma and in other was Sertoli-Leydig cell tumour. **Conclusion:** In our study of disorders of sex development with 46,XY gonadal disgenesis the risk of gonadal tumour was high. Patients with a total gonadal dysgenesis 46,XY had the highest risk of tumours of gonads. The maximum risk of a tumours of a gonads arised at teenage age. Therefore gonadectomy should be considered soon after the diagnosis of 46,XY gonadal dysgenesis.

P3-797

Screening for Y Microdeletions in Patients with Hypergonadotropic Hypogonadism due to Disorder of Sexual Development

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Introduction: Hypergonadotropic hypogonadism is mainly characterised by streak or dysgenetic gonads. It is primer gonadal insufficiency which occurs as a result of chromosome abnormalities, gonad developmental and steroid synthesis defects. However, Y microdeletions associated hypergonadotropic hypogonadism due to disorder of sexual development has been reported, there are no many studies. Moreover, it is not known enough to contribution for development of sexual ambiquity. Aim of this study is to screen presence of Y microdeletion in hypergonadotropic hypogonadism and to investigate relationship between disorder of sexual development. **Method:** All patients (*n*: 66) were monitored by Pediatric Endocrinology Clinic of Medical Faculty of Gaziantep University. They had disorders of sexual development. **Findings:** Of 66 all hypergonadotropic hypogonadism, 41 had female kartotype, 25 had male karyotype.of all patients, 34 choromosome abnormalities (28 Turner syndrome, four Klinefelter syndome, two Noonan Syndrome) 15 testicular differentation defects (11 anorchia, four atrophia), six testesteron synthesis defect, 11 ovarian agenesis or dysgenesis. Of 46,XY karyotype, six had complet female phenotype (Snicker five point), eight had ambiquous genitale (Snicker three points), one Turner syndrome had ambiquous genitale. Of all patients, 7 (%10.6) had Y microdeletion (two Turner syndrome; five had 46,XY karyotype). **Conclusion:** Y microdeletion can associate associated hypergonadotropic hypogonadism due to disorder of sexual development. We consider that Y microdeletion may be related to sexual ambiquity or aggravate its severity.

P3-798

'I am a Boy Since 8-Years-Old': Female During Childhood, Virilization at Puberty

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Background: 5α-reductase-deficiency is an autosomal recessive disorder with clinical spectrum ranges from a male phenotype with hypospadias to a female phenotype. Many different mutations of SRD5A2 gene has been described in affected patients and clinical signs can vary depending on the degree of enzyme deficiency. **Case presentation:** 14-years-old girl admitted to our clinic because of feeling as a boy since 8-years-old. Parents were first degree cousins. She was born at home. Physical examination showed remarkable facial acne and thick voice. In genital examination phallus was 4×1.5 cm and bilaterally gonads were palpable in labia major with volume of 15 ml. Breast development was Tanner stage 1, pubic hair development was Tanner stage 4. In pelvic ultrasound there was no uterus and testes were observed in distal inguinal canal. Standard dose ACTH test was normal. In laboratory analysis; basal LH was 5.62 mIU/ml ($N = 1.24–8.62$), FSH was 10.2 mIU/ml (N: 1:27–19:26), total testosterone was 4.31 ng/ml ($N = 1.75–7.81$) and anti-müllerian hormone was 9.81 ng/ml (N: 1.3–14.8). After βhCG stimulation test; testosterone:androstenedione ratio was 3.27 ($N > 0.8$), testosterone: dihydrotestosterone ratio was 433.7 ($N < 10$). Karyotype was 46,XY. SRD5A2 gene analysis revealed a homozygous mutation in exon 1 (c.193g> C, p.ala65pro) confirming the diagnosis of 5α-reductase deficiency. Psychiatric evaluation was consistent with male sexual identity. Patient eventually underwent to sex-change hormonal therapy and gender reassignment surgery by the decision of Gender Committee. **Conclusion:** 5α-reductase-deficiency, although rare, should be suspected in any girl presenting with pubertal virilization. In patients with 5α-reductase-deficiency diagnosed so late, the management is highly problematic and requires extensive psychological evaluation and support of the patient and his family for the final decision of gender assignment. Experienced multidisciplinary approach is extremely important for good clinical management.

P3-799

A Novel Mutation in Human Androgen Receptor Gene Causing Partial Androgen Insensitivity Syndrome in a Patient Presenting with Gynecomastia at Puberty

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Background: Partial androgen insensitivity syndrome (PAIS) typically presents with micropenis, penoscrotal hypospadias, bifid scrotum with descending or undescending testes and gynecomastia. It is x-linked recessive disease resulting from mutations in androgen receptor (*AR*) gene. **Objective and hypothesis:** To present clinical characteristics of a novel mutation in the *AR* gene in an adolescent boy with PAIS who presented with gynecomastia at puberty. **Results:** A 16-year-old boy was admitted with the complaints of gynecomastia and sparse facial hair. On physical examination, his height SDS was 2.84 and weight SDS was −0.5. His external genitalia was phenotypically male with pubic hair Tanner stage IV and normal axillary hair. Stretched penile length was measured as 8 cm accompanied with *penoscrotal hypospadias* and *bifid scrotum* in which both testes were palpable as 2 ml. There was bilateral gynecomastia compatible Tanner's stage III. Family history revealed male relatives from maternal side with similar clinical phenotype. He had elevated gonadotropins with a normal testosterone level. Chromosome analysis revealed a 46,XY karyotype. Due to the family history suggesting a disorder of X-linked trait, PAIS was considered and molecular analysis of *AR* gene was performed. DNA sequence analysis revealed a novel mutation hemizygous p.T576I (c.1727C>T) in the *AR* gene. **Conclusion:** The diagnosis of PAIS is based upon clinical phenotype and laboratory findings, and must be confirmed by detection of a defect in the AR gene. An accurate approach including a detailed family history suggesting an x-linked trait is an important clue to arrive at a quick diagnosis.

P3-800

A Novel Mutation of the AMH in an Egyptian Male with Persistent Mullerian Duct Syndrome

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Background: Persistent Müllerian duct syndrome (PMDS) is a relatively rare autosomal recessive disorder of sex development (DSD), characterized by the presence of Müllerian duct derivatives in 46,XY phenotypic males. PMDS is due to mutations in the AMH gene or its type II receptor gene AMHR2. To date; more than 50 different mutations of the anti-Müllerian hormone (AMH) gene have been reported. **Case report:** Here, we report a novel mutation of AMH in an Egyptian patient with PMDS. A 3-year-old male presented with bilateral cryptorchidism and normal male external genitalia. A laparoscopic surgery revealed a uterus and fallopian tubes. Serum AMH was very low (0.1 ng/ml). The patient's uncle had infertility, bilateral cryptorchidism and very low serum AMH (>0.1 ng/ml). Genetic analysis of AMH gene showed a homozygous novel frameshift mutation c.203delC (p.L70Cfs*7) in exon 1. This mutation is predicted to result in early truncated protein. Both parents were heterozygous for the mutation. **Conclusion:** In conclusion, PMDS should be included in differential diagnosis of cryptorchidism. **Funding:** This work was supported by the IRD (France) and STDF (Egypt).

P3-801

Pseudo-Precocious Puberty in Androgen Insensitivity Syndrome Secondary to a Prepubertal Oestrogen Producing Sertoli Cell Tumour

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Background: Androgen insensitivity syndrome (AIS) is an X-linked hereditary disease with *AR* gene loss-of-function mutations in 46,XY patients. They undergoes poor development of secondary sex characteristics, except for breast development at puberty. AIS patients are prone to develop germ cell cancer, even though with lower incidence than in dysgenetic gonads secondary to defects in organogenesis. **Case presentation:** We described a 3-years-old girl referred because growth acceleration and progressive breast development. She had fully developed female phenotype without sexual ambiguity. Pelvic ultrasound (PU) revealed Mullerian structures and two gonads resembling ovaries. Physical examination revealed: Height (H): 116.3 cm (HSDS: +3.8), Bone age (BA): 7 years, Breast development (Tanner IV) and scarce pubic hair. Endocrine studies revealed serum basal pubertal oestradiol (25 pg/ml) but pre-pubertal testosterone, LH and FSH levels failing to respond to acute GnRH stimulation. Diagnosis of pseudo precocious puberty (PPPUB) secondary to excessive steroid production was made. The source of the abnormal sex steroids was undetermined. At 8.2 years she was readmitted to the Hospital. H: 148.1 cm (HSDS: +4), BA: 16 years. The diagnosis of central precocious puberty was made. However; the aetiology of her early sexual development remained undetermined. Patient was lost in follow-up until 20y of age. H: 150 cm (HSDS: −1.75) Referred because of primary amenorrhea. CAIS diagnosis was suspected. PU discarded the presence of Mullerian structures**.** Karyotype was 46,XY**.** Molecular studies revealed a loss-of-function mutation in the androgen receptor gene, c.1972delC (p.Q658fs*2). Bilateral gonadectomy was performed. Histologic study of both gonads showed abundant signs of testicular dysgenesis and in one, a tubular structure with cylindrical epithelium, characteristic of a Sertoli cell tumour (SCT), was observed. Positive inmunoexpression of CYP11A1 and CYP19 aromatase was found only in the SCT. **Conclusion:** In conclusion, we are reporting for the first time PPPU in an AIS patient. Early sex development can be secondary to oestrogen synthesis by a SCT.

P3-802

Gender Reassignment in Muslim Communities

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Background: The commonest cause of 46, XX disorders of sex development (DSD) is congenital adrenal hyperplasia (CAH). We report two female virilised siblings with uncontrolled CAH who were reared as boys since birth. Different team members were involved in management. We discuss here gender reassignment and the psychosocial implications from Islamic perspectives. **Case reports:** An eight and 11 years old severely virilised CAH Yemeni girls were raised as boys since birth. They were referred to Saudi Arabia for further management. Parents are consanguineous and there is a family history of neonatal death. The gender was first assigned when parents were under social and cultural pressures. They were unsatisfied of the assignment and, therefore, have kept a balance in counseling their children and the way they brought them up, in order to help easier gender reassignment in the future. The dilemma has reached a peak when children started to menstruate at the age of 7.5 years. They will now be reassigned as girls. **Discussion:** Similar to western societies, gender assignment in Muslim communities, as per Islamic guidance, follows the best available evidence and parents should be well informed. The dominant role of male gender in a Muslim community shouldn't over rule Islamic laws. Management shouldn't be influenced only by how easy to reconstruct the genitalia, but sexual function and better chance of fertility should also be considered. Should gender-reassignment is required; the Islamic recommendation is to perform surgery as early in life as possible to avoid serious psychosocial implications. Gender transfer is totally prohibited, and even considered criminal in Islam. **Conclusion:** Management of patients with DSD requires a multidisciplinary team approach, owing to make the best decision to help patients entertaining more or less usual gender role, sexual life, fertility and psychosocial wellbeing. Cultural and religious perspectives should not be overlooked.

P3-803

A Case of Klinefelter Syndrome with an Atypical Presentation

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Background: Klinefelter syndrome, also known as 47, XXY, is a disorder characterized by tall stature, hypogonadism and mental retardation which is caused by nondisjunction events during meiosis and occurs in 500–1 000 live male birth. Here we report a patient with Klinefelter syndrome who presented with short stature, in contrast to common tall stature presentation and was diagnosed with GH deficiency. **Case:** A 7-year-old male presented with short stature. He was born to an advanced aged mother with a birth weight of 1430 g at 33 weeks gestation. His height was 104.7 cm (−3.7 S.D.) and weight 17 kg (−1.5 S.D.). Anthropometric measurements were otherwise normal. He was prepubertal and had no dysmorphic findings on physical examination. His growth rate was 4 cm/year during the previous year. On laboratory investigations; total blood count, blood chemistry, and thyroid function tests were within normal limits. Autoantibodies for celiac disease were negative. Serum IGF1 was 101 ng/ml (2.5–25 p), and IGFBP3 was 1480 ng/ml (<2.5 p). Karyotype analysis revealed a 47, XXY genotype. Bone age was 4 years and pituitary MRI was normal. GH stimulation tests using clonidin and L-dopa revealed peak GH responses of 3.5 ng/ml and 3.92 ng/ml respectively. He achieved 10 cm growth during the 1st year of GH treatment. **Conclusion:** Although tall stature is a well-known feature of Klinefelter syndrome, patients may present with short stature and can be diagnosed with GH deficiency.

P3-804

A Practical and Integrative Approach to Differential Diagnosis between 46,XY Disorder of Sexual Development

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Introduction: 46,XY disorder of sexual development can cause clinical spectrum varying from complete female phenotype to isolated micropenis. However, the most common reasons are androgen synthesis and resistance, choromosome abnormalities, testicular dysgenesis, steroid synthesis defects, it is usually idiopathic. The accurate and differential diagnosis is crucial in respect of treatment, monitoring, sex determination, surgical correction. Moreover, it sometimes can be medical urgency. **Method:** In this study, a total of 160 patients presenting disorder of sexuel development symptoms or findings were enrolled in Pediatric Endocrinology Department of Medical Faculty of Gaziantep University. We accepted following including criteria: i) Patients with XY karyotype ii) Ambiguous genitale iii) undescended testes iv) Hypospadias v) Micropenis vi) Puberta tarda we performed following tests all patients: FSH, LH, T, DHT, DHEAS, SHBG, AMH, karyotype, Y microdeletion, androgen receptor mutations 5α reductase mutations, LHRH stimulation test (choosen cases), HCG stimulation test. **Findings:** Of the 160 children, 42 androgen insensitivity, 33 undescended testes, 24 isolated micropenis, 21 atrophic testis, 15 hypogonadotropic hypogonadism, 11 anorchia, six puberta tarda, four 5α reductase deficiency (5SRD), two gonadal dysgenesis, one 17-β hydroxy streroid dehydrogenase deficiency. Im terms of CAG or GGC repeat length, there was no statistically significant between patient groups. The mean CAG and GGC length in the AR gene were respectively 22 and 16. 114 patients had 5SRD gene polymorphism in exon1. 27 had no polymorphism. Anti mullerian hormone (AMH) was found highly correlated with testicular tissue volume, testicular function and determination of the presence of testicular tissue. **Conclusion:** We consider that integrative evaluation of clinical characteristics, standard and dynamic tests with guiding algoritm of AMH provides considerable contributions in diagnosis of DSD, whereas genetic analysis has defining characteristics.

AMH seems as a guite useful hormonal marker in determination of presence testicular tissue and its function during prepubertal period in terms of DSD.

P3-805

Patient with Primary Amenorrhea and Glomerular Nephropathy

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Background: Primary amenorrhoea is a rare condition characterised by absent menarche. Based on gonadotropin levels, we distinguish hyper from hypogonadotropic hypogonadism forms. **Objective and hypotheses:** Herein, we present a case of primary amenorrhea with hypergonadotropic hypogonadism and glomerulopathy. **Method:** A 27-year-old female presented for evaluation of primary amenorrhea and incomplete pubertal development. Her past medical history was positive for glomerulopathy during adolescence resulting in end-stage renal failure and hemodialysis 8 years ago. Family history was unremarkable. At examination, she was phenotypically female, no acne, no hirsutism, normal weight, height 173 cm for an arm span 179 cm, breast development Tanner 3, pubic hair Tanner 4, female external genitalia with clitoromegaly. Reproductive profile showed elevated LH (151.8 UI/l) and FSH levels (179.4 UI/l), low oestradiol levels (0.07 nmol/l) and serum testosterone (T) at 2 nmol/l. Karyotype was 46,XY with no *SRY* mutations. Pelvic ultrasound and MRI showed a small uterus and normal vagina, consistent with absent AMH levels yet the gonads were not identified. Laparoscopy identified two gonads of 1.5×1 cm with fallopian tubes. Gonads were removed given the high risk of malignancy with the presence of a dysgerminoma arising in a gonadoblastoma in the left gonad. Clusters of Leydig cells hyperplasia were present in both gonads producing some testosterone as indicated by serum T decreasing from 2 to 0.5 nmol/l after the gonadectomy. The patient was started on oestrogen replacement therapy. **Results:** This 46,XY DSD patient presented with a female appearance, female internal reproductive tract, with gonadal dysgenesis associated with gonadoblastoma and dysgerminoma. The association of DSD with progressive glomerulopathy is reported in Frasier syndrome (FS), caused by mutations in Wilm's tumour gene (*WT1*). The genetic analysis of *WT1* is underway. **Conclusion:** This case points to the high risk of gonadoblastoma in FS and the need for precocious screening of proteinuria in case of 46,XY DSD in order to improve clinical prognosis of these patients.

P3-806

The Advent of Disorders of Sexual Differentiation Team at a Major Teaching Nigeria: Impact on Patient Management and Outcome

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Background: Disorders of sexual differentiation (DSD) constitute a great challenge in patient management especially in a low resource settings with inadequate manpower in various specialities, as it involves critical reasoning, careful evaluation, multidisciplinary involvement and making difficult decisions such as rearing sex and gender issues. **Aim:** To highlight the importance of forming a DSD team in the management of these children and to document our initial experience in the Paediatric Endocrine/Genetic unit of UCH, Ibadan, Nigeria. **Method:** The DSD team of the hospital was formed in the year 2010 with members from Paediatric endocrinology, Paediatric surgery, Psychiatry, Radiology and Obstetrics & Gynaecology and held jointly bimonthly clinics. We present patients with DSD managed in the unit between 2010 and 2014. Information was obtained from patients' records and from the Endocrinology register. Details of bio data, clinical history, investigations, treatment and outcome were retrieved. **Results:** The team saw 13 patients during the period, aged one day to 13 years. Four patients did not have palpable gonads on examination and were raised as females. Eleven patients (85%) had pelvic ultrasound scan done to visualise internal organs while, karyotype could only be evaluated in three (23%) patients who could afford to pay. In the two patients (15%) that had mutational analysis done, results confirmed a diagnosis of Partial androgen insensitivity syndrome (PAIS) and 5α reductase deficiency respectively. Interventional surgery was performed in five while two await surgery. Commonest DSD was congenital adrenal hyperplasia (CAH) seen in three patients (23%). There were two deaths while one case of CAH defaulted. **Conclusion:** The presence of a DSD team on ground has caused an integrated approach to the management of these children despite the intense limitations in terms of inability to get important hormonal and genetic tests done in every case because of financial constraints.

P3-807

An Interesting Case of a Phenotypic Female with a 46,XY Karyotype, Uterus and Menstruation

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Background: This is a case of an 18 year old phenotypic female of Bolivian origin with a 46,XY karyotype, uterus and menstruation with estrogen replacement. She was initially diagnosed with androgen insensitivity based on Leuprolide and HCG stimulation testing results. With menstruation, other etiologies are being considered. **Case presentation:** She presented with clitoromegaly and moderate posterior labial fusion (Prader III). Laboratory evaluation at 6–7 months showed a 46,XY karyotype from peripheral blood. Leuprolide stimulation testing showed a baseline LH concentration of 19.6 ng/dl which stimulated to 105.3 ng/dl. HCG stimulation testing showed an elevated baseline testosterone of 161 ng/dl which further stimulated to 553 ng/dl. The presence of a uterus was shown by pelvic ultrasound and confirmed by MRI. The patient was initially diagnosed with androgen insensitivity and the decision was made to rear the patient as a female. She then underwent bilateral gonadectomy, clitoral reduction, and correction of the urogenital sinus by urethral advancement and flap vaginoplasty. Pathology of the gonads showed infantile testes bilaterally. The karyotype from cells cultured from skin and gonads was 46,XY. Genetic testing for androgen receptor defects was negative. Transdermal oestradiol was administered starting at 14 years to induce breast development and continued. She received two courses of progesterone without menstrual bleeding. She later had a menses 11 months after her last course of progesterone. **Objective and hypotheses:** The aim is to elucidate a genetic defect leading to this patient's presentation. **Method:** SNP array analysis was performed and whole exome sequencing is being performed. **Results:** SNP array analysis was unremarkable. Whole exome sequencing results are pending. **Conclusion:** The presence of a functional uterus is unusual in this patient with a 46,XY disorder of sexual differentiation and biopsy confirmed testes. SNP array analysis and whole genome sequencing may be useful in determining the etiology of DSD in this patient and other atypical cases of DSD.

P3-808

Characteristic of Children with Mixed Gonadal Dysgenesis

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Background: Mixed gonadal dysgenesis (MGD) is a DSD with variations of 45,X/46,XY caryotype and different phenotype. **Objective and hypotheses:** To describe the features of six patients (three raised as boys and three as girls). **Method:** The mean patients' age at the time of the report is 11.7 ± 4.0 years old. Molecular diagnosis was made in utero and confirmed after birth in two boys (for maternal age and because one mother had thyroid cancer), in one child in neonatal period due to sexual ambiguity and in three children (one boy and two girls) around 10 years of age. **Results:** At birth, three patients. had ambiguous genitalia (one male – chriptorchidism, one male – penile hypospadia, one – scrotal hypospadia with bilateral chriptorchidism for wich the sex of the child was initially established as male). One boy had normal genitalia since birth, two babies were raised as girls. In three girls and one boy at the age about 4 years old growth retardation became evident, further in life those girls had laparoscopic gonadectomy to decrease the risk of gonadoblastoma. All four children received GH treatment. In boy growth GH was interrupted due to the progression of bone maturation and spontaneous puberty. However, the puberty was not completed at age of 16 (testicular volume reached 10 ml, at US microlitiasis was seen), and during FISH analyzes microdeletions of the AZF-regions of Y-chromosome associated with oligo-/azoospermia were found. Another boy was referred to paediatric endocrinologist for obesity and also entered spontaneous puberty and is still under GH treatment. One boy was diagnosed and treated with hydronephrosis, two girls had horseshoe kidney. Girls with MGD had Turner-like features but were taller than those with classic TS caryotype. No one child had typical for TS cardiac malformations. One girl was operated for cholesteatoma. **Conclusion:** Children with MGD present with variable phenotype and require closed follow-up by the team of the specialists.

P3-809

A 19-Year-Old Adolescent with Short Stature and Scrotal Tumour

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Introduction: Primordial short stature can have many different causes. In addition to maternal factors (e.g. placental insufficiency), genetic or skeletal disorders may be found in the child. It is important to identify the underlying aetiology in time, since not only the risk of diabetes is increased, but also the prevalence of insufficient gonadal function and malignancy, e.g. in mixed gonadal dysgenesis (MGD). **Case report:** A 19 year old adolescent presented with primordial short stature (2500 g, 47 cm at birth, GA 40 weeks). History revealed urinary tract infections in earlier childhood and double kidneys as well as mildly impaired intelligence. Puberty was delayed with an onset at the age of 16 years. Phenotype was male with well-proportioned short stature, except for a broad chest. He presented dysmorphic signs like low-hairline, low-set ears, multiple pigmented naevi; there were no cardiovascular or renal anomalies. The external genitals showed a normally formed penis with two intra-scrotal hypotrophic testes with a volume of 5 ml each, in the presence of nearly adult pubertal stages P5, G4-5. The palpation of the scrotum revealed an indolent scrotal tumour well separated from the testes. Endocrinological investigations identified a MGD with 46,XY (75%)/45,X (25%) karyotype in lymphocytes and normal testosterone production. Elevated FSH was indicative of testicular dysgenesis. Ultrasound investigation of the tumour showed a tubular structure suspected to be a hypoplastic uterus. Surgical exploration showed a circumscribed tumour histologically proved to be a rudimentary uterus without evidence of malignancy. Because of sufficient gonadal function and male phenotype the testes remained intra-scrotal and will be checked by ultrasound regularly. **Conclusions:** In male and female children with primordial (or non-familial)

short stature and even discreet dysmorphic signs of Ulrich-Turner's syndrome, a karyogram should be performed in time, since several types of gonadal neoplasms have been described in MGD. MGD conditions are accompanied by a wide phenotypical range and comprise the entire spectrum from normal testes or ovaries, unilateral streak gonads with contralateral testis, ovary or uterus to bilateral streak gonads. This is the first report of an intra-scrotal uterus which is well delimited from the testis in a male patient with MGD. Furthermore, there is a controversial discussion of the proceeding in male patients with MGD because of the increased risk of testicular malignancy. Though fertility may be already impaired, we decided not to perform orchiectomy in this patient since there were no indicators of malignancy, a well-accessible intra-scrotal location of the testes and an otherwise normal gonadal function. Regular clinical and ultrasound examinations should detect malignant degeneration in time.

P3-810

An Atypical Case of Mayer-Rokitansky-Kuster-Hauser Syndrome with Hyperandrogenemia

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Background: Mayer-Rokitansky-Kuster-Hauser syndrome (MRKH) is characterized by utero-vaginal atresia in patients with a normal female phenotype and 46, XX karyotype. Various anomalies may accompany MRKH. The number of cases with accompanying hyperandrogenemia is limited. **Case presentation:** We describe a combination of Mullerian agenesis and hyperandrogenemia (total testosterone level 0.85 ng/ml) in a patient presenting with primary amenorrhea and mild hirsutism. **Conclusion:** Mullerian agenesis describes a broad spectrum that may also be accompanied by hyperandrogenemia. Androgen levels should be investigated in patients with Mullerian agenesis when even mild findings of clinical hyperandrogenemia are present, and these case should be monitored to see whether or not hyperandrogenemia accompanies the syndrome.

P3-811

Cushing's Syndrome due to Ectopic ACTH Secretion by a Germline Tumour in the Cross-tail Area in a 7 Month Old Female Infant

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Background: Ectopic ACTH syndrome is very rarely seen in infancy, usually occurring in older children. **Case presentation:** A female infant was born by Caesarean section (BW 4280 g) with congenital anal atresia and a large tumour surrounding the cross-tail region. CT imaging identified a heterogeneous pelvic mass ($76 \times 49 \times 38$ mm) below the sacrum. On day 1 of life, a sigmoid colostomy was established and at age 1 week, part of the tumour with the coccyx was removed. Control CT abdomen and pelvis scan showed residual tumour ($27 \times 21 \times 28$ mm). Histopathology showed a grade three teratoma immaturum. α-fetoprotein (AFP) pre-surgery was 59 000 ng/ml and post-surgery 6 339 ng/ml (normal range 500 ng/ml). There were no metastases. For 3 months, the child was well, then tumour size increased on imaging. Chemotherapy-3 blocks VBP (vinblastine, bleomycin, cisplatin) normalised AFP and decreased tumor size. At age 7 months the child had increased appetite, weight gain ($>97^{th}$c), Cushingoid appearance, hypertension (BP) (210/160 mmHg), hypokalemia (2.85 mmol/l), hypercortisolemia (09.00 h; 1794 nmol/, 13.00 h; 1794 nmol/l), increased ACTH (121 pg/ml) and LDH (1.005 U/l). Dexamethasone suppression test showed absent cortisol suppression: 1.054 nmol/l (basal), 1.056 nmol/l (post-dex). Imaging studies (CT CNS, chest, adrenal scintigraphy with octreotide) excluded metastases. Immunohistochemical staining of the tumour was positive for ACTH in cancer cells. Ketoconazole, metyrapone, anti-hypertensive therapy induced only temporary, control of hypercortisolism (09.00 h cortisol 1453 nmol/l, ACTH 700 pg/ml) and BP. At age 12 months, a significant part of the tumour was removed at surgery. Currently, the patient does not require supplementation of steroid hormones. **Conclusion:** An extremely rare cause of Cushing's syndrome (CS) due to ectopic ACTH syndrome is described in a female infant.

P3-812

Uterine Bleeding: A Rare Side Effect of Mitotane Treatment for Recurrent Adrenal Carcinoma

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Introduction: Mitotane is an adrenal-specific agent available for treatment of residual adrenocortical carcinoma (ACC) after surgery, due to a specific, direct effect on adrenal cell mitochondria impairing adrenal steroidogenesis being associated with increased SHBG and modulates their disposal for target cell. We report a rare case of uterine bleeding during mitotane treatment in a girl with recurrent ACC. **Case report:** A 2.6 year-old girl was diagnosed with underlying right ACC Stage II disease (tumor size: 100 g). *TP53* mutational analysis was performed and R337H and P72R were detected (primary tumor and peripheral blood). Same mutations were identified in her maternal peripheral blood. She had a tumor recurrence nine months after the first surgery and was submitted to a total resection surgery. Chemotherapy (Cisplatin,

Etoposid, Doxorubicin and Mitotane) was initiated. A second recurrence was detected 12 months after the second surgery. Radiotherapy was indicated followed by a third surgical total tumor resection. Since the last surgery, when she was 4.9 years old, she is on Mitotane only and glucocorticoid and mineralocorticoid replacement, with normal DHEA-S blood levels. At 6 year-old, she was referred due to bilateral breast enlargement and pigmentation of areola, without pubic hair, followed by daily vaginal bleeding for at least 15 days. Pelvic ultrasound showed uterine enlargement and thickened endometrium with no ovarian abnormality. Hormonal study confirmed pre pubertal response at baseline (LH <0.1 mIu/ml, FSH <0.3 mIu/ml), without rise of LH/FSH after LHRH stimulation test. SHBG: 482 mmol/L (22–130). Vaginal bleeding ceased after progestogen depot treatment. Since then, she has few relapses of uterine bleeding that has been ceased with progestogen depot. **Conclusion:** Uterine bleeding can occur during mitotane therapy, maybe due to increased binding capacity of SHBG, with hormonal investigation being consistent with pre pubertal response. Symptomatic treatment is important in managing such rare cases.

P3-813

Metabolic Syndrome in Childhood Acute Lymphoblastic Leukaemia Survivors

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Background: A significant number of long-term complications are reported in childhood acute lymphatic leukemia (ALL) survivors, and among them metabolic syndrome (MetS). **Objective and hypotheses:** To evaluate the prevalence of features of MetS. In addition, we evaluated the presence of steatohepatitis which is described in association with MetS in otherwise healthy subjects. **Method:** We assessed waist circumference, triglycerides levels, blood pressure, HDL cholesterol, serum blood glucose and liver ultrasound in 92 (44 males) off therapy childhood LLA survivors (age at diagnosis 5.6 ± 3.8 years, age at recruitment 10.6 ± 4.2 years). IDF criteria for MetS were used. **Results:** We found a waist circumference pathological in 54 (58.7%), hypertriglyceridemia in 6 (6.5%), hypertension in ten (10.9%), low HDL cholesterol in four (4.3%) and hyperglycemia in two (2.1%) patients. Hepatic steatosis was found in 24 (26.1%) patients, mild in 18 (19.5%), moderate in four (4.3%) and severe in two (2.1%) survivors. Only one patient presented the three criteria for the diagnosis of MetS, 16 patients only two and 43 only one. At least one metabolic abnormality was found in about 60% of our patients. **Conclusion:** Survivors of childhood ALLL are prone to develop MetS, which can predispose to cardiovascular disease. A prevalence of 13.1% (95% CI 8.4–17.7) has been reported in these patients. In this study the rate of MetS is 1.1%, lower than what reported. Some reasons may account for that, overall lifestyle and age at recruitment. Our patients, living in South of Italy, have Mediterranean diet which is well acknowledged to prevent MetS. However we cannot exclude that a younger age at diagnosis in this study as compared to other study populations may play a role. Further studies focusing on the risk factors for MetS are mandatory in these patients.

P3-814

Results of GH Treatment in Childhood Brain Tumours Survivors

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Background: GH deficiency is the most common endocrine disorder in childhood brain tumours survivors. **Objective and hypotheses:** To examine results and safety of GH treatment in patients with childhood brain tumours. **Method:** 118 patients (72 craniopharyngioma, 29 medulloblastoma, 17 germ cell tumours) received hGH in the dose 0.03–0.034 mg/kg per day for 2.3 ± 0.8 years. The mean chronological age at the start of the treatment was 12.6 ± 2 years, bone age 9.9 ± 2.1 years, remission time 2.4 ± 1.3 years, height SDS -2.8 ± 1.2. **Results:** Height SDS after the 1st year of treatment increased from -3.0 to -2.3 in patients with craniopharyngioma, from -3.5 to -2.8 in patients with germ cell tumors and from -2.2 to -2.1 in medulloblastoma patients. 37/118 (31%) achieved final adult height, and it was -0.2 ± 1.2 in craniopharyngioma group, -1.1 ± 1.0 in germ cell tumours group, -1.7 ± 1.4 in medulloblastoma patients. The initial serum IGF1 was -2.1 ± 0.9, and increased till -0.6 ± 0.5 after 1 year treatment. Growth velocity was significantly ($P<0.001$) lower in patients received spinal irradiation (5.9 ± 2.2 cm/year) then in patients who didn't receive spinal irradiation (9.6 ± 2.3 cm/year) and positively correlated with IGF1 level ($r=0.41$, $P<0.05$) Tumour recurrence occurred in 21/72 (29%) patients with craniopharyngioma, which was similar to untreated group. The were no tumour recurrence in patients with medulloblastoma and germ cell tumours during GH treatment. No significant adverse events were registered. **Conclusion:** This data suggest that hGH treatment is effective and save treatment of GH deficiency in paediatric brain tumours survivors.

P3-815

Craniopharyngioma – Symptoms, Treatment and Follow Up – An Analysis of 100 Cases

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Background: Craniopharyngiomas are rare embryogenic malformations of the sellar area with low-grade histological malignancy. Its incidence is 0.5–2.0 cases per million persons per year, 30–50% of all cases become apparent in children. **Objective and hypotheses:** The aim of the study was to analyse the clinical symptoms and treatment efficacy in children diagnosed with Craniopharyngioma. **Method:** A retrospective analysis included 100 children with craniopharyngioma treated in Institute in years 1999–2011. **Results:** The sex ratio was 1:1 and the median age at primary diagnosis was 8.5 years (2 weeks – 18 years old). The symptoms observed included: cranial hypertension (57%), endocrine disorders (70%), vision disorders (54%), a growth failure and decrease of growth rate (50%), diabetes insipidus (8%), delayed puberty (including menstrual disorder) (22%), secondary hypothyroidism (14%), adrenal insufficiency (7%). Complete resection of tumour was achieved in 90% of patients, partial resection in 10%. Overall 23 patients underwent a second surgery due to a local recurrence with a median recurrence time of 2 years (7 months to 8 years old). Postoperative radiotherapy received 19 patients. Most of surgical interventions was made by the same operator (89%). A second recurrence was seen in 2 patients with a median time of 5 years. These patients needed decompression a cystic part of tumour. Postoperative complications included adenohypophysis (100%), diabetes insipidus (89%), visual acuity deterioration (73%), overweight and obesity (62%), and cognitive deficits (19%). The 5-year survival in our series is 90%, 89% at 10 years. However, 7 patients died between 0.5–5 years after surgery (median 2 years), 5 died due to severe hypothalamo-hypophyseal disturbances, two because of neurosurgical complications. **Conclusion:** Craniopharyngiomas are tumours, which can cause many different symptoms depending on tumour localisation, size and the diagnosis promptness. Surgical treatment is effective in most cases, especially if performed by experienced neurosurgeon. Long term survival is high, however complications have serious implications on the quality of life.

P3-816

Von Hippel-Lindau Disease in an Adolescent with a Newly Described Alteration in the VHL Gene

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Background: Von Hippel-Lindau (VHL) disease is an autosomal dominant disorder characterized by susceptibility to tumours including haemangioblastomas of retina and central nervous system, renal cell carcinoma and phaeochromocytomas. The disease is caused by mutations in the VHL tumour suppressor gene. **Objective and hypotheses:** We present an adolescent with VHL disease confirmed by genetic analysis which revealed the mutation p. A149P (PCC > GCC), which has not been reported to date. **Method:** A 16-year-old boy presenting with headache and nausea to another medical centre was referred to our clinic when diagnostic workup revealed bilateral adrenal masses. The patient's father also had had bilateral adrenal tumors, central nervous system tumor, renal cell carcinoma and had died after an operation. Family history revealed multiple tumors in the patient's uncle, aunt and grandmother. A magnetic resonance imaging of the abdomen showed bilateral adrenal tumors that were also positive on metaiodobenzylguanidine scintigraphy. Raised urinary catecholamines confirmed a diagnosis of phaeochromocytoma. **Results:** Bilateral adrenalectomy was performed. A heterozygous variant of the VHL gene, p. A149P (PCC > GCC), was verified. **Conclusion:** VHL disease should be clinically suspected in any individual presenting with bilateral phaeochromocytoma and a positive family history. Molecular analysis of the VHL gene is useful in the management and follow-up.

P3-817

Two Synchronous Central Nervous System Tumors in a Child with Neurofibromatosis Type 1

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Background: Synchronous, multiple central nervous system (CNS) tumors are usually rare in pediatric patients. Pilocytic astrocytomas are the major type of CNS tumors in neurofibromatosis type 1 (NF1). **Case presentation:** A 6.5-year-old boy was admitted to our hospital for severe emaciation. Profound fat and muscle wasting were the only prominent clinical features. His growth rate was preserved despite his rapid dramatic weight loss (HT: 118 cm, *P*. 0.50; WT: 16.5 kg *P*. 0.3, BMI: 11.9 kg/m^2 < *P*. 0.4, T.J. Cole 1995). IGF1 value was low (45 ng/ml). Physical exam also showed two café-au-lait spots (0.5 cm) and scoliosis. No headaches, vomiting, seizures, ataxia, blurred vision, diplopia, nistagmus or signs of progressing into puberty were present. Adrenal and thyroid tests were normal. Serum electrolytes were normal as well. Tests for Crohn, celiac disease, HIV and other hematologic malignancies were negative. On magnetic resonance imaging of the brain, two concomitant large masses (5 cm each) were identified. The first mass had a diencephalic location (with wide hypothalamic involvement) while the second mass was located outside the optic pathway (extra optic pathway tumors/ extra-OPT) in the posterior fossa (with extension towards the brainstem and 4th ventricle). Both proved to be pilocytic astrocytomas. **Conclusion:** The same histological type in both

tumors pointed out towards NF1 as the underlying medical condition even when the NIH diagnostic criteria for NF1 didn't seem to be met at the chronological age of the patient. In our case, the diencephalic syndrome (characterised by cachexia and preserved linear growth) might be considered the revealing metabolic signature of the hypothalamic tumor regardless of the paucity of the accompanying symptoms. Furthermore, even if the presence of two synchronous CNS tumors is certainly a rare event, this is not the case anymore in patients with NF1 regardless of the severity of their skin involvement.

P3-818

Endocrine Evaluation in Children and Adolescents Submitted to Allogeneic Bone Marrow Tranplantation

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Background: Paediatric bone marrow transplantation (BMT) can lead to endocrine dysfunctions due to common pre-procedure protocols involving chemo and radiotherapy. **Objective and hypotheses:** To evaluate the prevalence and time-of-onset of endocrine dysfunctions after BMT in children and adolescents. **Method:** A retrospective cohort-study design was performed. The inclusion criteria were: age range less than 18 years old at the time of their allogenic BMT program, which started in 2010 in our Institution. The patients started their follow-up 100 days after BMT (time zero) and every six months, when possible. Height (cm), Weight (Kg), BMI and respective *z*-scores (NCHS 2000) as well as their pubertal status (Tanner) were obtained. Lab and imaging data for endocrine diseases (GH deficiency; precocious/delayed puberty, thyroid dysfunctions, adrenal diseases, diabetes insipidus, bone diseases, and metabolic syndrome) were collected. **Results:** From 75 patients submitted to allogeneic BMT, 40 (21 females) were referred to endocrine evaluation. Their primary disease was diagnosed at 5.5 ($\pm$4.2) years old (Range: 0.0–15.0). BMT was performed at 8.5 ($\pm$4.5) ys (0.8–17.8). Bone marrow donors were: siblings (21), bone bank (nine), umbilicus cord (five), and parents (five). The patients were referred for endocrine evaluation at 9.9 ($\pm$4.4) ys (2.0–18.0). The prevalence of endocrine complications was: Growth disorders ((8), five with GH deficiency, under treatment), hypothyroidism (five) dyslipidemia (five), amenorrhea (three), obesity (two), puberty disorders (three), failure to thrive (one). 15 patients have been still under follow-up with no endocrine disease detected so far. **Conclusion:** These findings emphasise the importance of screening for endocrine complications in children and adolescents submitted to BMT, particularly growth, thyroid and metabolic. Children require an early and long follow up so that endocrine complications can be diagnosed and promptly treated.

P3-819

Early Endocrine Complications in Survivors of Childhood Malignant Tumours

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Background: The progress made in the treatment of childhood cancer has resulted in better long-term survival rates. Therefore sequelae of treatment have become more important. **Objective and hypotheses:** To investigate the prevalence of early endocrine disorders in survivors of a childhood tumour within the 1st years after diagnosis. **Method:** We performed a retrospective medical record review of survivors followed at the endocrine clinic of a tertiary paediatric centre. Outcome measures were frequency and types of endocrine dysfunction. **Results:** 57 patients (27 women) were included. The age at tumour diagnosis was 6.0$\pm$4.3 years and follow-up time was 7.6$\pm$3.5 years. Primary treatment for the neoplasm was chemotherapy in 55 cases and radiotherapy in 40. The proportion of patients with any endocrine disorder increased to 17/57 (29.8%) at the end of the follow-up period. The most common reported endocrine disorders were primary gonadal dysfunction ($n=10$), primary hypothyroidism ($n=4$), and pituitary dysfunction ($n=4$). **Conclusion:** Endocrine disorders are frequently seen within the 1st years after diagnosis of a childhood cancer. Inconsistent endocrine follow up leads to unnecessary delay in diagnosis and treatment.

P3-820

AIP Polymorphism in Familiar Isolated Pituitary Adenomas: Case Report

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Background: Familiar isolated pituitary adenomas (FIPA) encompasses the familiar occurrence of isolated pituitary adenomas outside the setting of syndromic conditions such as MEN1 and Carney's complex, and comprise about 2–3% of pituitary adenomas. About 20% of FIPA have mutations in the aryl hydrocarbon receptor interacting protein gene (AIP), usually associated with a worse outcome. **Objective and hypotheses:** Evaluate the presence of AIP gene mutations in 3 patients with clinical features of FIPA. **Case report:** A 13.9 years old boy was

referred because of short stature (Height – 2.44 S.D., Puberal Tanner stage G3, PH2, testicular volume 8cc). His mother had been diagnosed with no functional pituitary microadenoma, and his brother, who also had short stature, had a non functional macroadenoma. Workup revealed normal pituitary function and an MRI showed a pituitary image compatible with microadenoma. Due to his familiar background the AIP gene was studied. The promoter and exons 1–6 and intronic flanking regions were amplified by PCR using specific primers. The DNA fragments were sequenced by automatic sequencing. **Results:** We found the following polymorphisms (SNPs): **c. 468+111 C>T**, (intron 3) heterozygous in index patient and mother and homozygous in the brother and **c. 990+60G >C heterozygous**in 3' UTR and in the three patients. **Conclusion:** The molecular study of the AIP gene in families with pituitary adenomas is necessary, since it is associated with poor outcome. Due to the low frequency of the **c. 990+60G >C** polymorphism (3%) in healthy population, we suggest studying this polymorphism in the healthy family members.

P3-821

Primary Hypogonadism after Haematopoietic Stem Cell Transplant in Paediatric Patients with Cancer

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Background: Gonadal function is altered up to 25% in patients who suffered cancer in childhood. Cryopreservation of ovarian tissue (COT) is an option for preserving fertility. **Aims and objective:** To establish the prevalence of primary hypogonadism (PH) in children with cancer after hematopoietic cell transplantation (HCT). To analyse the variables that predict progression to PH. **Methods:** Retrospective cohort study. Patients aged 0 to 18 undergoing HCT from 2004–2014. Categorical variables in %, continuous normal in mean (S.D.), non-normal in median (P25–P75). Independent variables: age at transplantation, gender, total body irradiation (TBI), busulfan, cyclophosphamide, COT. Dependent variable: PH. Multivariable logistic regression (LR). Statistical significance *P*-value <0.05. **Results:** 75 patients underwent HCT, table 1. 30 developed PH, 19 women, 11 men. Age of onset of PH 11.97 years (S.D. 3.22). 9 women underwent COT, all developed PH. Characteristics: current age 15.58 years (S.D. 3.53), age at HCT 11.59 (S.D. 2.88), 44.4% received TBI, 11.1% abdominal radiotherapy, 33.3% busulfan, 11.1% melphalan, maximum FSH 79.63 mU/ml (S.D. 39.24). Characteristic of the other ten women with PH: current age 12.41 years (S.D. 4.88), age at HCT 5.98 (S.D. 3.61), 0% TBI, 30% abdominal radiotherapy, 90% busulfan, 40% melphalan, maximum FSH 43.75 mU/ml (S.D. 21.40). In LR model, sex ($P=0.000$) and age at time of HCT ($P=0.003$), independently predict progression to PH. RL was also performed excluding patients under ten and we found the same results. **Conclusions:** Women and patients older at time of HCT are more likely to develop PH. In girls with PH, FSH is greater in those who underwent COT, but these girls probably received a more gonadotoxic treatment.

Table 1.

Gender	25 women, 50 men
Current age	13.31 years (S.D. 4.26)
Age at HCT	7.81 (S.D. 4.23)
TBI	40%
Conditioning regimen	52.33% busulfan, 18.66% melphalan, 77.3% cyclophosphamide

P3-822

Galactocele: A Rare Case of Breast Enlargement Among Children

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Background: A galactocele is a retention cyst containing milk or a milky substance that is usually located in the mammary glands caused by a protein plug that block off the outlet. It is seen in lactating women on cessation of lactation and rarely in infants and children. It presents as a large, soft, fluctuating lump in the lower part of breast. This paper is intended to report a case of Galactocele in one of the paediatric patient. **Case presentation:** Galactocele in children is described as a rare cause of increasing in breast size and can appear in males. We reported case of a 2-year-old male presented with a progressive enlargement of bilateral breast mass for 6 months with no discoloration, pain or nipple discharge. Although a rare case, it is important to include galactocele in the differential diagnosis in paediatric patients presenting with benign breast masses. **Conclusion:** The report discussed the differential diagnosis in paediatric patient with benign breast mass and how they arrived to their conclusion.

P3-823

LHRH Analogues Successfully Suppress Menstruation During Chemotherapy in Teenagers and Young Adults

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Background: There are no available guidelines on hormonal therapy to suppress menstruation in teenagers and young adults (TYA) undergoing chemotherapy. **Objective and hypotheses:** To review the use of LHRH analogues (LHRHa) (Leuprorelin (L)) or continuous progesterone (Norethisterone (N)) to defer menses in TYA undergoing chemotherapy in a single Institution and

initiate guidance on its use. **Method:** Clinical notes of 27 TYA treated with L or N over a period of 1 year were reviewed with data collection on hormonal therapy, side effects and breakthrough bleeding. **Results:** Median age: 14 years (10–18years). >70% patients received L (3.75 mg, every 4/52 SC) with cyproterone acetate (CA) (50 mg BD PO) taken for the first 4/52 if more than 1/52 had elapsed from last period to suppress L-induced initial 'flare'; <30% patients received N (5 mg TDS PO). Only one patient on L had breakthrough bleeding despite appropriate management. Breakthrough bleeding in patients on N was related to poor GI absorption. No adverse reactions related to L occurred. No episodes of deep venous thrombosis were associated with N, although 2/6 of patients on N were already on Heparin before starting N. **Conclusion:** LHRHa successfully suppress menstruation during chemotherapy. Whilst awaiting national guidelines, L remains our first choice treatment at a dose of 3.75 mg every 4/52 SC with or without CA. Breakthrough bleeding is expected after the 1st dose of LHRHa and should be managed symptomatically. If breakthrough bleeding occurs after 2nd dose of L, interval between doses could be decreased to 3/52. If breakthrough bleeding occurs while on 3/52 regimen a pelvic US is needed. N remains our 2nd choice treatment; patients on asparaginase should never receive N. Breakthrough bleeding is not expected whilst on N; if it occurs patient's adherence, decreased absorption and/or drugs interaction should be looked for. If no explanations a pelvic US is needed.

P3-824

Suprasellar Brain Tumours Related Endocrinopathies

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Background: Brain tumours constitute the second most common tumours in childhood after leukaemia. Infra-tentorial tumours are more common. Most of the supra-tentorial tumours (STT) are in the supra or para-sellar regions. Malignant tumours are rare. The survival is 50–90% with appropriate management. However, STT and/or treatment may lead to traumatic brain injury (TBI) with endocrinopathic sequel. **Methods:** This is a retrospective hospital based study of 32 children with STT reviewed at King Khalid University Hospital (KKUH), Riyadh, Saudi Arabia (SA) (2001–2013). All patients underwent intracranial surgery and occasionally additional treatment such as radiotherapy. The patients' care has been followed throughout. **Results:** 32 children (1.5–17 years) (mean and median = 9.5, males = females) with STT were assessed at KKUH. Symptoms include: 68.8% headache, 43.8% vomiting, 37.5% clumsiness, 43.8% for each of neurological deficit and visual disturbances, 28.1% (n = 9/32) with pituitary-hypothalamic features. Preoperative imaging showed SST, 21.9% had hydrocephalus, and calcification. Preoperative endocrine investigations were only performed in 50–60% and were essentially normal. Five patients had dynamic tests: (triple tests, n = 4) (two failed all of the tests and one had a failed synacthen test). Post operatively, seven had DI, one required on table DDAVP and hyperglycaemia requiring insulin in one patient. 20 patients received dexamethasone for 3–7 days, four were discharged on hydrocortisone. PICU stay was for 1–3 days on average. Histopathology showed variety of tumours including: two teratoid rhabdoid tumour, six gliomas, six astrocytoma, four carniopharyngioma and three germinoma. 12 patients required radiotherapy including two who also required chemotherapy. Follow up reveiled two patients with evolving panhypopituitarism, and one developed hyperprolactinaemia and DM within 2 years of follow up. **Conclusion:** Children with STT are prone to develop TBI at all stages of their illness and management. It is crucial to have a multidisciplinary team approach with baseline and follow up endocrine workup.

P3-825

GH and Prolactin Secreting Adenoma in an Adolescent Boy

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Background: Pituitary gigantism is a rare disorder. Paediatric endocrinologists may see at most one or two patients during their careers. In one large series of 2367 children and adolescents with pituitary adenomas, only 15 (0.6%) had pituitary gigantism. Much of our understanding is derived from isolated case reports and extrapolation from the adult literature. No sex predilection is known. Gigantism may occur at any age, and has been observed as early as the first 6–9 months of age. **Case report:** A 13-year and 6-month old boy was admitted for chronic headache. Magnetic resonance imaging (MRI) detected a pituitary adenoma which is 15×9×7 mm in size. There was no history of a chronic disease, medication or familial malignancy. The height was 176.5 cm (+1.23 SDS), the weight was 53 kg (−0.04 SDS) and the blood pressure was 107/75 mmHg. Pubertal stage was Tanner stage-2. Laboratory findings were as follows: LH: 0.84 mIU/ml, FSH: 1.73 mU/ml, total testosterone: 0.4 ng/dl, TSH: 2.3 mcIU/l, fT_4: 1.02 ng/dl, prolactin: 13.02, cortisol: 10.5 µg/dl, IGF1: 656 (+2.6 SDS) ng/ml, GH: 6.1 ng/ml, fasting blood glucose: 102 mg/dl, insulin: 10.7 mU/ml. An oral glucose GH suppression test was performed. Minimum GH level was found as 3.6 ng/ml which was not an adequate suppression. Ophthalmologic assessment was normal. This pituitary adenoma was primarily thought to be a GH. A transsphenoidal adenomectomy was performed. Pathologic investigation revealed a GH and prolactin secreting adenoma. Clinical and laboratory findings recovered after surgery and still normal by the end of 3 months. **Conclusion:** This patient with GH and prolactin secreting adenoma was presented here, since it is a very rare condition in childhood. Despite the scarcity of disease, all patients with a pituitary adenoma deserve a comprehensive evaluation of pituitary functions.

P3-826

The Evaluation of Bone Mass Density in Patients after Therapy of Solid Tumours

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Backgrounds and objectives: Low bone mass density is an important problem in survivors of childhood cancers. The aim of this study is to determinate the influence of factors on bone mass density (BMD) and the prevalence of abnormal bone turnover. **Materials and methods:** The evaluation was performed in 67 patients (64.18% boys and 35.82% girls) at least 1 year after therapy of solid tumours, aged 4–27 years (median 12.67). The following parameters were assessed: BMD (*z*-score), level of PTH, IGF1 SDS, height SDS, BMI SDS. The relationships between different factors were examined. **Results:** The following disorders were found: BMD (mean -0.52 ± 1.29) with a value of < -2 in 8.96% patients, $< -1, -2 >$ at 20.89%; level of PTH decreased in 13.11%, increased in 4.92%; IGF1 SDS decreased in 8.93%; increased in 3.57%, overweight or obesity in 26.15%. Moreover, group with weight and/or height deficiency (20% of the study group) reached a lower average BMD than the rest of patients (avg. -1.56 ± 2.05 vs avg. -0.25 ± 0.9; $P = 0{,}033$) and lower IGF1 SDS value (avg. -0.91 ± 0.90 vs 0.11 ± 1.20; $P = 0.01$). No such difference was found in PTH levels ($P = 0.35$). Positive correlations for the entire study group between BMD and IGF1 SDS ($r = 0.39$, $P < 0.01$), BMD and level of PTH ($r = 0.27$, $P = 0.036$), BMD and height SDS ($r = 0.44$ $P < 0.01$), BMD and BMI SDS ($r = 0.25$, $P = 0.042$) were found. **Conclusion:** Disorders of bone mineral substrate are multifactorial. Patients with weight and/or height deficiency may be more likely to lose bone mass as a result of treatment. Disorders of bone mineral density can also be a problem in paediatric patients, especially after anti-cancer therapy.

P3-827

The Pathway to the True Diagnosis

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Case presentation: A 3 year old girl was admitted with the diagnosis of acute interstitial nephritis from the family doctor directly to our tertiary hospital. As an out-patient, the girl was treated with antibiotics with no result. She had polydipsia accompanied by day-time and night-time polyuria and enuresis that developed 2 weeks before admission. During the last year the girl showed increased appetite and escalating weight gain. At admission, her height was +3.5 SDS, weight was +2 SDS and BMI +3 SDS for age and sex. We diagnosed central diabetes insipidus (CDI) and she started treatment with Desmopressin. At first hormonal evaluation the patient had bilateral macular oedema and elevated levels of prolactin. MRI revealed one supraselar mass with a second mass in the right orbit, accompanied with lytic lesion of the zygomatic bone. The radiological diagnosis was 'Pituitary tumour'. The differential diagnosis included tumours with multiple sites development. The clinical presentation with CDI pointed at the possibility of Langerhans cell histiocitosis (LCH). Patients with LCH lesions of the facial bones or anterior/middle cranial fossae with a concurrent intracranial mass have a threefold increased risk of developing CDI. The histological result from pituitary surgical biopsy revealed eosinophilic granuloma. This confirmed the diagnosis of LCH. The patient started chemotherapy according to the established current protocol. Despite our efforts to decrease the weight gain velocity, the girl put on further 12 kg of weight since the therapy start (current height +3 SDS, weight +5.5 SDS, BMI +5 SDS). **Conclusion:** The frequent initial presentation of intracranial benign and malignant tumours to the Pediatric Endocrinologist requires step-wise multidisciplinary approach for ensuring better outcome.

P3-828

Long-Term Effects of a Ketogenic vs a Hypocaloric Diet in Children and Adolescents with Obesity

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Background: The prevalence of childhood obesity is high worldwide and predisposes to adult obesity and metabolic disorders. Many dietary approaches have been proposed to reduce this prevalence, but no single diet has proven to be superior to others in terms of long-term weight loss maintenance in children. **Objective and hypotheses:** To evaluate and compare long-term body weight changes among obese children and adolescents who had lost at least 10% of their initial weight with either a ketogenic (very-low carbohydrate) or a hypocaloric diet after 6.83 ± 1.7 years. **Method:** 38 obese children and adolescents after weight loss intervention with a ketogenic (55.26%) or hypocaloric diet (44.73%) between 2005 and 2010 were reassessed. BMI SDS was calculated at baseline (BMI SDS 0), after the weight loss (BMI SDS 1) and after approximately 6.8 years(BMI SDS 2). Differences were assessed according to type of diet, gender and difficulty to retain the weight loss. **Results:** The ketogenic children started older (14.87 ± 2.92 vs 12.87 ± 2.79, $P = 0.039$), had higher BMI SDS than the hypocaloric children (2.92 ± 0.76 vs 2.37 ± 0.58, $P = 0.019$) and 71.4% were morbidly obese (BMI SDS > 2.5). All children significantly decreased their BMI SDS 1 with a similar fold change (0.64). Assessment of BMI SDS according to time, type of diet or difficulty in retaining weight loss, revealed that BMI SDS decrease was irrespective of diet type or difficulty. All children decreased their BMI SDS by 0.4 in the last 6.8 years and this decrease was

significant for those on the ketogenic diet (2.26±0.81 vs 1.8±1.22, $P=0.005$), except for two children that underwent bariatric surgery. Most of the children that followed the hypocaloric diet (75%) are currently lean or overweight BMI SDS (<2) and showed no differences according to difficulty. **Conclusion:** Our data reveals the importance of life style intervention in childhood obesity. A BMI SDS decrease of approximately 0.5 is of great importance and can be retained and decreased further into young adulthood irrespective of the diet followed.

P3-829

Metabolically Unhealthy Obese Children Under the Risk of Exercise Induced Chronotropic Incompetence

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Background: There is a high incidence of acute cardiovascular events in obese subjects. **Objective and hypotheses:** We hypothesised that exercise tolerance is different in metabolically healthy (MHO) and metabolically unhealthy (MUO) obese adolescents. **Method:** 45 obese adolescents aged 10–17 (23 males and 22 females) were examined with an anthropometry, fasting blood glucose, insulin and lipids. IDF criteria were used for grouping for MHO and MUO. Multistage cycle protocol was offered to each participant with further analysis of cardiovascular parameters: resting heart rate (HRr), maximal heart rate (HRm), resting and maximal systolic and diastolic blood pressure (SBPr, SBPm, DBPr, DBPm respectively). Maximal predicted heart rate (MPHR) was calculated by Tanaka formula and HRm in patient was compared with MPHR as a percent of it (%MPHR). Standard statistical methods were used for the data analysis. **Results:** The chosen population was homogenous by gender, age, body composition, fasting glucose and insulin levels ($P>0.05$ for all), resting cardiovascular parameters HRr ($P=0.467$), SBP ($P=0.370$) and DBP ($P=0.477$). There was statistical difference in between groups by the fasting lipids (P for TC=0.003; TG<0.001; HDL=<0.001; FFA=0.002). There was predominantly chronotropic response in MHO with an increasing HRm till 152.714+18.611 vs 137.2+23.917 bpm ($P=0.041$) and predominantly inotropic response in MUO with an increasing SBPm till 171.222+18.123 vs 149.171+21.467 mmHg ($P=0.007$). Observed HRm was lower than expected (Chi-Square=767.8897; $P=0.0000001$). Statistic difference in groups by % MPHR (82.847+12.49 in MHO vs 71.167+10.144 in MUO ($P=0.019$). Multiple linear regression model was created to predict % MPHR at the top of exercising in obese children (MR=0.695; F (6.34)=5.53; $P=0.004$). The model includes Lean BMI (b=−0.72; $P<0.001$), ISI-FFA (b=−0.3; $P=0.02$), Cholesterol (b=0.52; $P=0.001$), HDL (b=0.36; $P=0.009$). **Conclusion:** There is an adequate chronotropic reactivity and moderate SBP increasing in MHO. MUO are under the risk of exercise induced chronotropic incompetence, which associated with acute cardiovascular events in studies.

P3-830

Determinants of Serum Interleukin 1 – Receptor Antagonist Concentrations in 12-Year-Old Children Born Small or Appropriate for Gestational Age

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Background: Elevated concentrations of interleukin 1 – receptor antagonist (IL-1Ra) have been found in adult subjects with the metabolic syndrome and type 2 diabetes as a marker of inflammation. **Objective and hypotheses:** Our aim was to study whether serum IL-1Ra associates with markers of reduced insulin sensitivity (IS) and dyslipidemia in 12-year-old children. **Method:** A total of 192 children (109 girls) were studied at the mean age of 12.25 years (range 12.01–12.73). 78 of them had been born appropriate for gestational age (AGA), 70 small for gestational age (SGA), and 44 from preeclamptic (PRE) pregnancies as AGA. Fasting serum IL-1Ra, high molecular weight adiponectin (HMW-adipo), leptin, sex-hormone binding globulin (SHBG), insulin, IGFBP1, HDL cholesterol, triglycerides and blood glucose were measured. IS was estimated by Quantitative IS Check Index (QUICKI). **Results:** The means of serum IL-1Ra, HMW-adipo, IGFBP1, SHBG, leptin, insulin, blood glucose and QUICKI did not differ between the children born SGA, AGA or from PRE pregnancies ($P>0.05$ for all). In the whole study population, serum IL-1Ra correlated negatively with SHBG and positively with triglycerides ($P<0.01$ for both). The children in the highest IL-1Ra tertile had significantly lower QUICKI ($P=0.001$), IGFBP1 ($P=0.001$), SHBG ($P<0.001$) and HDL cholesterol concentrations ($P=0.016$), and higher BMI, weight-for-height, serum insulin, leptin ($P<0.001$ for all) and triglyceride concentrations ($P=0.037$) when compared to the children in the lowest IL-1Ra tertile. Pubertal development or sex distribution did not differ significantly between the highest and lowest IL-1Ra tertile subjects. **Conclusion:** The children with the highest IL-1Ra levels had lower IS and HDL cholesterol, and higher triglycerides than those with the lowest IL-1Ra levels suggesting that high IL-1Ra concentrations associate with unfavourable metabolic features.

P3-831

Evaluation of Renal Functions in Obese Children and Adolescents with Cystatin-C and Creatinin Based GFR: is Increasing GFR Reflected Hyperfiltration and Possible Renal Damage in Future?

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Introduction: There is a growing interest in the relationship between obesity and renal damage. Chronic kidney disease is accepted as an important complication of obesity in adulthood.

However, information on association between childhood obesity and renal functions is limited. In this study, It is aimed to investigate the renal functions in obese children and adolescents. **Patients and methods:** We enrolled 107 obese children and adolescents as a study group and 47 normal-weighted children as a control group. Serum cystatin-C, serum creatinin levels, 24 h proteinuria, creatinin clearance (CrCl) and glomerular filtration rate (GFR) were evaluated in groups. Estimated GFR was measured by both creatinin based (Schwartz, Counahan-Barratt) and cystatin–C based (Filler) formulas. Metabolic parameters (blood glucose, insulin, lipids) were analysed in obese subjects. IDF criterias was used to determine of metabolic syndrome (MetS). **Results:** The mean age of obese patients was 12.57 years; and 15 of 95 obese children (>10 years of age) had MetS. Proteinuria and serum cystatin–C levels were not different between obese and control groups. Obese patients with MetS have higher Cystatin-C level than without MetS. CrCl, Filler, and Counahan-Barratt measurements showed statistically significant increase in GFR of obese subjects than control subjects (147 vs 117, 138.8 ± 26.1 vs 118.06 ± 26.6, 137.2 ± 26.9 vs 122.9 ± 27.7 respectively). These increase is negatively correlated with duration of obesity. Only Filler equation showed statistically significant decrease of eGFR in patients with metabolic syndrome. **Conclusions:** In obese children and adolescents renal damage seems to be at functional level reflecting glomerular hyperfiltration without proteinuria. However, as obesity duration is incresed, eGRF is began to decrease, possibly beginning with nephropathy. Although serum cystatin-C levels can be useful for prediction of nephropathy only in obese children with MetS, GFR measurement is advantageous for detecting unfavourable effect of childhood obesity on renal functions either with or without MetS.

P3-832

The French Experience in Bariatric Surgery 'Laparoscopic Adjustable Gastric Banding' in Adolescence

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Background: Because the success rate of lifestyle interventions is modest in severely obese adolescents, surgical treatments are now proposed. Laparoscopic adjustable gastric banding (LAGB) represents an attractive treatment with minimal morbidity and reversible procedure. **Method:** All adolescents were included in prospective longitudinal assessment and entirely managed by a pediatric team. Surgery was proposed only after at least 1-year lifestyle intervention in a multidisciplinary program. 3 years after surgery, an adult transition plan has been implemented. **Results:** Since 2008, 44 adolescents have undergone LAGB. The mean age and mean BMI at surgery was 16.6 ± 0.9 years and 45.1 ± 5.2 kg/m^2, corresponding to a mean weight of 127.6 ± 19.8 kg. Base line comorbidities data demonstrated a high incidence of insulin resistance (IR), and 75% of metabolic syndrome. An average of 12 visits in the first year, nine in the second and five in the 3rd year were recorded. 52% of patients had more than 3 years of follow-up (median 28, range 3–84 months). 3 years after surgery median weight loss was 41 kg (2–57) corresponding to a percentage of excess weight lost of 77% (3–100), the majority of weight loss was evident after the 1st year. Mean BMI tends to stabilize after the second year (33.3 ± 6.6 vs 32.8 ± 8.2 at 2 and 3 years respectively, P=ns). An improvement in metabolic status was demonstrated (HOMA-IR decreased from 5.5 ± 3.3 to 1.4 ± 1.1, $P<0.005$). In multivariate analysis only the mean number of consultations/year, was found significant on weight loss, significant differences were found between patients who had 6 or less consultations/year and those with 12 consultations/year for final weight ($P=0.004$) or EWL ($P=0.005$). **Conclusion:** Among severe obese adolescents there was substantial weight loss and an improvement of metabolic profile 3 years after LAGB. But these require a high degree of patient cooperation and professional support. However this technique appears to be a primary choice for bariatric surgical procedure. Long-term outcomes are still lacking.

P3-833

Correlation of Serum FGF-21 Levels with Metabolic Parameters in Korean Obese Children

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Background: Serum FGF-21 levels are increased in adults with obesity, type 2 diabetes and nonalcoholic fatty liver disease (NAFLD). Serum FGF-21 levels have been implicated as a potential biomarker for early detection of the metabolic syndrome (MetS) and type 2 diabetes in adults. However, there are only a few studies about the correlation between FGF-21 levels and metabolic parameters in children. **Aims and objective:** This study is aimed to evaluate the relationship between serum FGF-21 and metabolic parameters in obese children. **Method:** Our subjects included 37 lean and 78 obese children and adolescents aged 8–15 years. We analyzed fasting serum FGF-21, adiponectin by enzyme-linked immunosorbent assays and also fasting insulin, glucose, transaminases, lipids profile were measured. Independent t-test and univariate correlation analysis were used to evaluate the relationship between FGF-21 and other clinical and metabolic parameters. **Results:** Serum FGF-21 levels were significantly increased in the obese children compared to those of normal-weight children. Obese children also demonstarated significantly increased insulin, total cholesterol, LDL-C, alanine transaminase (ALT). Serum adiponectin and HDL-C were significantly decreased in obese children than in controls. Serum FGF21 levels were positively correlated with insulin ($r=0.326$, $P<0.001$), triglycerides ($r=0.444$, $P<0.001$) and ALT ($r=0.273$, $P=0.003$). But serum FGF21 levels were negatively correlated with HDL-C ($r=-0.334$, $P<0.001$). **Conclusions:** Serum FGF-21 was higher

in obese children and significantly correlated with metabolic parameters. Our results suggest that FGF-21 may be potentially used as early biomarker for obese children with metabolic disorders.

P3-834

Liver Steatosis in Obese Children Courses with Enhanced Insulin Resistance and Dyslipidaemia, Which are Influenced by Gender, Puberty, Race and Body Fat Distribution

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Background: Liver steatosis (LS) is diagnosed in obesity at very early ages, not exclusively related to overweight severity. **Objective and hypotheses:** To investigate the features of patients diagnosed with obesity associated LS (ultrasonography). **Method:** We retrospectively studied 88 obese (BMI $> +2$ SDS) children with LS (LS-OB) and 88 age, gender, race and puberty matched obese children without LS (no-LS-OB). BMI-SDS, body composition (DXA) and abdominal fat distribution (MRI; $n=27$ in LS-OB), baseline and after OGTT glucose, insulin and derived indexes (HOMA, WBISI), HbA1c, lipid profile, apoprotein-A1 and B, liver enzymes, and uric acid were studied. **Results:** LS was mainly diffuse (97.7%) and mild (65.9%). In LS-OB mean age was 12.07 ± 2.81 years and BMI 4.60 ± 2.81 SDS, with 71.6% males/29.4% females (61.2% pubertal) and 56.5% Caucasian and 41.2% Hispanic. LS-OB showed higher AST/ALT ($P<0.001$), insulin/HOMA ($P<0.05$) and triglycerides/VLDL ($P<0.01$) than no-LS-OB; with an IR prevalence of 65.8%, mean HOMA 4.62 and HbA1c $>5.7\%$ in 35.9% LS-OB. LS-OB with moderate-severe LS (31.8%) had lower WBISI/HDL ($P<0.05$), higher AST ($P<0.05$), ALT ($P<0.01$), apoprotein-B ($P<0.05$) and LDL/HDL-ratio ($P<0.05$) than LS-OB with mild LS; showing higher trunk/lower-limb fat-ratio (trunk/LL, DXA) and visceral/subcutaneous abdominal fat-ratio (Vis/Sq, MRI) ($P<0.05$). Serum liver enzymes were increased in 40.5% LS-OB, with lower levels in females vs males and prepubertal children vs adolescents ($P<0.05$). These patients had higher glucose and insulin at 30 min in the OGTT ($P<0.05$ and $P<0.01$), cholesterol, apoprotein-B, cholesterol/HDL and LDL/HDL-ratios ($P<0.05$) and higher trunk/LL and Vis/Sq ratios ($P<0.05$). Over 30% LS-OB had dyslipidemia (mainly decreased HDL and increased VLDL) and 79.4% low vitamin D (<20 ng/ml), both alterations were more severe in Hispanics ($P<0.05$), as was *acanthosis nigricans* ($P<0.01$). **Conclusion:** LS in obese children courses with enhanced insulin resistance and dyslipidemia. Severe OB-LS is associated with greater visceral adiposity and metabolic impairment, which are also influenced by race, sex and pubertal stage. **Funding:** This work was supported by the CIBER Fisiopatología de la Obesidad y Nutrición (CB06/03) and the Instituto de Salud Carlos III, Fondo de Investigación Sanitaria (FIS: grant number PI10/00747 and PI13/02195).

P3-835

How Early are Vascular Changes in Obese Children Among North Indian Population?

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Background: Obese children are known to be at high risk for vascular complications and there is paucity in Indian literature regarding the onset and magnitude of vascular complications. Carotid intima media thickness (cIMT) and Brachial artery distensibility are known to predict future atherogenesis. **Objective and hypotheses:** To compare vascular parameters of obese children aged 5–18 years with age and sex matched controls and its relationship with pubertal age. **Method:** 80 children, 40 obese and 40 age & sex matched controls 5–18 years recruited after approval from Institutional Ethics Committee and informed assent/consent. cIMT &brachial artery distensibility measured by echocardiography. Endothelial independent vasodilatation measured using sublingual glycerlytrinitrate spray (GTN) and endothelial dependent vasodilatation by reactive hyperemia. **Results:** Mean age was similar in both cases and controls – 11.15 ± 2.52 (M:F = 23:17). 19 (47.5%) were pre-pubertal (M:F = 10:9) and 21 (52.5%) were post-pubertal (M:F = 13:8). BMI significantly higher in obese vs controls (26.58 ± 1.88 kg/m^2 vs 17.58 ± 1.72 kg/m^2 – $P<0.001$). Flow mediated vasodilatation significantly lesser in obese group (2.0 ± 0.06 vs 2.2 ± 0.05 – $P=0.05$). GTN induced vasodilatation less in obese but not significant (4.6 ± 0.23 vs 6.2 ± 0.31 – $P=0.07$). cIMT significantly higher in obese (0.57 ± 0.14 vs 0.38 ± 0.07, $P<0.001$). On comparing prepubertal and postpubertal obese, FMD and GTN induced vasodilatation were comparable ($P=0.49$, 0.22). cIMT significantly higher in postpubertal obese (0.60 ± 0.13 vs 0.44 ± 0.14, $P<0.01$) in comparison to prepubertal obese. 27/40(67.5%) obese (24 postpubertal and three prepubertal) had cIMT greater than the normal cutoff of 0.49 mm. **Conclusion:** Cohort of obese children have evidence of subclinical vascular alterations as observed by decreased endothelial independent vasodilatation and increased carotid intima media thickness. cIMT is higher with pubertal onset indicating that with age and puberty, there is further progression of atherogenesis. Thus indicating need for early screening and intervention for cardiac morbidities.

P3-836

Prader-Willi Syndrome – A General Picture of 51 Cases

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Objective and hypotheses: To describe the morphological characteristics of patients with Prader-Willi Syndrome (SPW) who have been followed in a Pediatric Endocrinology Outpatient Clinic. **Method:** We performed a retrospective study on 51 patients evaluating the age of diagnosis, genetic mutation, use of GH (rhGH), age of beginning of follow-up, and *z*-score of weight, height and BMI. Data on their first and latest visit to our clinic were compared. **Results:** 51 patients were analysed, and the mean diagnosis age was 3.43 (±3.28) years old. The mean age of their first appointment was 4.95 (±4.26) years old and the average time of follow up was 6.45 (±5.24) years. The mean *z*-BMI at the beginning and at the latest visit was 2.26 (±2.61 S.D.) and 2.97 (±1.58 S.D.) respectively. At the latest visit, their mean age was 11.3 (±6.31) years old and the mean height was $z-1.41$ (±1.52 S.D.). Eighteen patients have never used rhGH, 15 had it irregularly and 18 regularly for more than 2 years. Genetic diagnosis: 17 of the patients have chromosome deletion, 14 have maternal uniparental disomy. Nineteen patients did only the methylation test. **Discussion:** Despite the early diagnosis of PWS, it is noteworthy the delay between the diagnosis and the start of follow-up, postponing the measures to minimize the weight gain. An adequate coping since the time of diagnosis could introduce the basic concept of the disease in order to avoid obesity and raise adherence to accomplish diet restriction and effective rhGH treatment. **Conclusion:** SPW is a rare disease that needs specialized attention and a multidisciplinary team struggling to minimise the deleterious effects of obesity, which is the cause of bad quality of life and early death in these patients.

P3-837

Comparison of Two Family-Intervention (Parents Only vs Parent and Child) in the Treatment of Childhood Obesity

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Background: Obesity in adolescence is associated with a 70% likelihood of obesity or overweight in adulthood. Hence, effective intervention programs for childhood obesity in high-risk populations are needed. **Objectives:** i) To compare the efficacy of two intervention strategies, involving parents only vs parent and child, to a control group, in the treatment of childhood obesity. ii) To identify clinical demographical and biochemical predictors for decreased BMI-SDS. **Methods:** 247 children with BMI: 85–99 percentile, 5–11 years, were recruited to the study. The participants were randomized into three groups: parents only ($n=84$) or parents and child group ($n=89$), who participated in 12-week meetings with a dietician and a psychologist, and a control group ($n=74$). Follow-up continued for 2 years. Changes in anthropometric and clinical outcome were assessed. **Results:** 46 (52%), 45 (54%), 37 (50%), in the parents only, parents and the control groups respectively, had completed 2 years follow-up. At 12 weeks, the decrease in BMI-SDS was significant only in the intervention groups, and decreased from 1.74 ± 0.31 to 1.66 ± 0.36 in the parents' group ($P<0.001$), and from 1.83 ± 0.33 to 1.76 ± 0.36 in the parents and child group ($P=0.012$), with no significant change in the control group (1.73 ± 0.32 to 1.70 ± 0.31, $P=0.301$). After 2-years, decrease in BMI-SDS was significant only in the parents and child group (BMI-SDS after two-years follow up: 1.56 ± 0.46, $P=0.006$). According to a stepwise linear regression analysis, older age ($\beta=0.282$, $P=0.012$), lower baseline TSH levels ($\beta=-0.214$, $P=0.049$) and higher adiponectin levels at the end of the intervention ($\beta=0.345$, $P=0.002$), were associated to greater decline in BMI-SDS during the intervention. **Conclusions:** A behavioural intervention program for the prevention and treatment of childhood obesity that focuses on parents and children was found to have significant positive short and long term effects on BMI-SDS. Lower baseline TSH levels might predict better short-term outcomes. **Funding:** Grant from the Institute of research, Clalit Health Services.

P3-838

Bioavailable Vitamin D in Obese Children: The Role of Insulin Resistance

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Background: Studies examining vitamin D levels in association with childhood obesity usually do not concurrently measure levels of vitamin D-binding protein and do not calculate the unbound, bioavailable vitamin D, that is considered the fraction of 25-hydroxyvitamin D able to exert biological activity. **Objective and hypotheses:** To evaluate in a group of children for the most part obese i) the concentrations of both total 25-hydroxyvitamin D and of the bioavailable fraction ii) the potential role of insulin resistance in modulating the concentrations of bioavailable vitamin D. **Method:** 63 obese children and 21 lean controls were enrolled and the main metabolic parameters were investigated. Total 25-hydroxyvitamin D and vitamin D-binding protein were measured, two SNPs in the coding region of the vitamin D-binding protein (rs 4588 and rs 7041) were studied and, using these data, the vitamin D bioavailable fraction was calculated. **Results:** Obese children showed total 25-hydroxyvitamin D levels lower compared to not-obese children (21.3 ± 6.7 ng/ml vs 29.6 ± 11.7 ng/ml; *P*: 0.0004). Bioavailable 25-hydroxyvitamin D levels, on the contrary, were not different among obese and not obese children (3.1 ± 1.6 ng/ml vs 2.6 ± 1.2 ng/ml; $P>0.05$). Insulin

resistant children showed higher bioavailable levels of 25-hydroxyvitamin D compared to not insulin resistant children (3.4 ± 1.4 ng/ml vs 2.0 ± 0.9 ng/ml; *P*: 0.013) and an inverse correlation between insulin resistance and vitamin D-binding protein was found (*r*: −0.40; *P*: 0.024). **Conclusion:** Our data i) show that obese children, although have low concentrations of total 25-hydroxyvitamin D, present levels of bioavailable 25-hydroxyvitamin D similar to those of normal weight children ii) demonstrate that this finding is due to a reduced concentration of vitamin D-binding protein iii) suggest that the increased insulin resistance usually present in obesity may be associated to this reduction.

P3-839

Age at Menarche in Relation to BMI. Data from the Hellenic Action Plan for the Assessment, Prevention and Treatment for Childhood Obesity

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Background: A secular trend towards earlier menarche has been observed. **Objective and hypotheses:** The correlation of age at menarche with the BMI as well as the maternal age at menarche and their BMI. **Method:** This is a cross-sectional study conducted from October 2012–December 2013. A pre-selected, representative elementary and high school cohort was derived, using stratification and PPS methodology. Parents responded to questionnaire and students were measured with high sensitivity methods. IOTF cut offs were used. Data were analysed for 12 986 mothers and for 2 272 adolescents for which age at menarche was available. All the variables used are binary (binomial, dichotomous) in nature. The menarche age of the subject and her mother is Normal vs Early (<12 years). **Results:** Analysing the whole group 'early menarche' had 27.5% of the girls as compared to 15.0% for the mothers (OR=2.1 95% CI=1.9–2.4). For the sample of 2 272 girls with known age at menarche for the girl and the mother, 'early menarche' had 32.9% of the girls and 17.7% of the mothers (OR=2.395% CI=2.0–2.6). The correlation coefficient between the mother's and the daughter's age at menarche equal to 0.375 ($P<0.01$).The percentage with 'early menarche' was 28.8% for normal weight girls and 43.1% for overweight/obese girls (OR=1.9, 95% CI=1.6–2.3). 'Early menarche' had 61.0% of the girls whose mother had early menarche as compared to 26.9% of the girls whose mother had normal menarche (OR=4.395% CI=3.4–5.3). In both generations the OR of the association between age at menarche and BMI is of the same order. **Conclusion:** The most significant association is the effect of the mother's age at menarche to the daughter's age at menarche. This generation has 'early menarche' in higher proportion than their mothers. BMI is positively correlated with mother's BMI and negatively associated with age at menarche. **Funding:** This work was supported by an EU grant MIS301205.

P3-840

Are Age and Initial BMI-SDS in Obese Children and Adolescents Associated with the BMI-SDS Courses During and after the Attendance of an Inpatient Weight-Loss Program (LOGIC-Trial)?

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Background: It has been discussed in literature, that being severely obese and adolescent are predictive for failure in a behavior based weight-loss program. **Objective:** To investigate the association between age and initial BMI-SDS with BMI-SDS courses during and after the attendance of an inpatient weight-loss program. **Design:** The LOGIC-trial involves overweight and obese children and adolescents (6–19 years), who participate in an inpatient weight-loss program for 4–6 weeks. Height and weight values were taken at the start (T_0), at the end of the intervention (T_1) and one year after start of the intervention (T_2). The study sample includes $n=1.046$ participants (T_0). The recall rate at T_2 was relatively high (54.6% of the original cohort). Missing BMI values were replaced by baseline observation carried forward method. Age at baseline (years) was grouped: 7–11 ($n=214$); 12–14 ($n=501$); ≧15 ($n=331$). BMI-SDS values at baseline were grouped by using the 75th internal percentile (low vs. high). Linear mixed effects model (piecewise linear function with a knot at T_1) was calculated. **Results:** BMI-SDS courses are significantly determined by age and BMI-SDS at baseline. Older children (≧15 yrs) improved the least in reducing BMI-SDS under short-term intervention compared to the younger participants (independent of BMI-SDS at baseline). During 1-year follow-up BMI-SDS increased in all participants. The strongest increase was observed in 12–14 year-old children with a high BMI-SDS at baseline. 12–14 years old children showed the smallest BMI-SDS reduction during FU compared to the younger and older age groups, independent of BMI-SDS at baseline. The BMI-SDS difference (T_0–T_2) was −0.15 in children (12–14 years) with a low

BMI-SDS and −0.05 in children with a high BMI-SDS at baseline. **Conclusion:** Age and BMI-SDS at baseline determine the BMI-SDS courses during and after the attendance of an inpatient weight-loss program. The long-term success of an inpatient weight-loss program was lowest in 12–14 years old children. **Funding:** The LOGIC-study is funded by the non-profit organization Else Kröner-Fresenius-Stiftung, Bad Homburg, Germany and the German statutory pension insurance scheme, Landshut, Germany.

P3-841

Turn off and Turn in: The Influence of Television Viewing and Sleep on Lipid Profiles in Children

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Background: Physical activity is beneficial to lipid profiles, however the association between sedentary behaviours and paediatric dyslipidaemia remains controversial. Understanding these associations is critical given that youth are increasingly engaging in sedentary pursuits, and are sleeping, on average, 1 h less than children were 20 years ago. **Objective and hypotheses:** To investigate whether various forms of sedentary behavior/sleep predict lipid profiles in children over a 2-year period. Our hypothesis is that sedentary behavior will adversely impact lipid profiles in childhood. **Method:** Data from 630 children living in Quebec, Canada, with at least one biological parent with obesity (QUALITY cohort) were collected at both 8–10 years and 10–12 years. Sedentary behaviour, sleep time and moderate-to-vigorous physical activity (MVPA) were measured over 7 days using accelerometry, with sedentary behaviour defined as the average minutes daily at <100 counts/min. Sleep time was derived from accelerometer non-wear time. Screen time, computer/video game use and TV viewing over the past 7 days were self-reported. Adiposity was measured using DXA scan and dietary carbohydrate/fat intake by an average of three 24 h dietary recalls. Outcomes included fasting total cholesterol, triglycerides, HDL-cholesterol and LDL-cholesterol. Multivariable models adjusted for MVPA, fitness, adiposity and diet. **Results:** Every additional hour of TV time at baseline predicted a 7.4% (95% CI = 3.9; 10.9) increase in triglycerides and 2.1% (95% CI = −3.7; −0.5) decrease in HDL. These findings held true for triglycerides after adjusting for adiposity, dietary carbohydrate and sugar-sweetened beverages. Every additional hour of sleep predicted a 4.1% (95% CI = −7.9; −0.3) decrease in LDL even after controlling for sedentary behaviour and dietary fat intake. **Conclusion:** Higher time spent engaged in TV watching and lower sleep appear to be deleterious to childhood lipid profiles over time, even when taking into account other major lifestyle habits. **Funding:** This work was supported by the Canadian Institutes of Health Research (#OHF-69442, #NMD-94067, #MOP-97853, #MOP-119512), the Heart and Stroke Foundation of Canada (#PG-040291) and the Fonds de Recherche du Quebec – Sante.

P3-842

Hepatic Steatosis Influences Significantly the Cardiovascular Risk in Children with Metabolic Syndrome

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Background: Despite the metabolic syndrome in pediatrics is a well recognized entity, there is no unanimous consensus on exact value of MS to predict long-term cardiovascular risk. Hepatic Steatosis (HS) is another emerging condition associated to pediatric obesity. **Objective and hypotheses:** To evaluate the prevalence of MS in a large pediatric obese population, assess the relationship between MS and HS, and evaluating the possible role of HS in defining the syndrome and modulating the cardiovascular impact. **Method:** We studied 803 overweight and obese children (395 girls and 408 boys, mean age 9.43 ± 2.5 years, BMI z-score 2.23 ± 0.53 with complete clinical and biological assessment. MS was defined using criteria of American Heart Association. The diagnosis and severity of HS was based on ultrasound scan. All patients underwent an ultrasonography to measure carotidal intima-media thickness (cIMT), a validated marker of subclinical atherosclerosis. **Results:** The overall prevalence of MS was 13.07% and was significantly higher in patients with MS: 40.9% vs 18.5% ($P<0.0001$). Spearman's correlation between HS grade and the number of MS criteria was significant ($\rho=0.285$ $P<0.0001$). No statistical difference was recorded about cIMT and cIMT z-score between patients with or without MS, until inclusion of HS as additional criterion for the diagnosis of MS. In this case, there was significant difference in cIMT and cIMT z-score between the two groups. In multiple stepwise linear regression analysis, cIMT z-score was better predicted by using HS grade and ($\rho=0.279$, adjusted R^2: 2.6%, $P<0.0001$), than using only MS cluster. **Conclusion:** HS should be used as additional criterion in detecting pediatric MS phenotype at higher risk for long-term cardiovascular morbidity.

P3-843

Increased Glucagon-Like Peptide-1 Response to Oral Glucose in Prepubertal Obese Children

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Table 1. (for abstract P3-843)

	Obese group	Control group	P-value
Fasting insulin (μU/ml)	15.9±10.6	6.5±2.0	0.02
Insulin AUC (μU/ml×120min)	8485±4354.8	3057±1195.3	0.005
GLP-1 AUC (ng/ml×120 min)	505.4±225.6	335.2±83.1	0.04
HOMA-IR	3.7±2.5	1.4±0.4	0.02
WBISI	4.7±2.5	9.3±2.7	0.002
HOMA-p	3.6±2.4	1.5±0.5	0.03
Insulinogenic index	4.8±3.8	0.6±0.4	0.007

Background: Over the last years a role for gastrointestinal hormones, such as glucagon-like peptide (GLP-1), in the pathogenesis of obesity and its complications, has been hypothesized. However, there are few data for the paediatric population. **Objective and hypotheses:** To assess whether there is a difference in post-load GLP-1 response in obese children compared to normal-weight peers and to assess the relationship with insulin responses. **Method:** Ten prepubertal obese children (five boys; mean age (±S.D.): 10.5±1.6 years; BMI-SDS: 2.2±0.5) and ten controls (eight boys; age: 9.9±1.2 years; BMI-SDS: −0.7±0.5) underwent a modified oral glucose tolerance test (OGTT) to evaluate post-load (0–5–10–15–20–30–60–90–120 min) glucose, insulin and GLP-1 responses. Insulin sensitivity (HOMA-IR, WBISI) and secretion (HOMA-ß, insulinogenic index) indexes, area under the curve (AUC) for glucose, insulin and GLP-1 were calculated. **Results:** Obese children showed an increased post-load GLP-1 release along with higher AUC insulin and insulin secretion and resistance indexes. GLP-1 AUC was associated with BMI-SDS ($r=0.45$, $P=0.04$), HOMA-IR ($r=0.53$; $p=0.01$) and fasting glucose ($r=0.68$; $P=0.001$). **Conclusion:** Obese children showed an increased GLP-1 response to oral glucose. The increased GLP-1 response might likely represent a compensatory mechanism to avoid post-prandial hyperglycaemia and allow a normal glucose tolerance.

P3-844

The Risk of Metabolic Syndrome among Dyslipidemic Children and Adolescents

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Background: Lipid assessment is emerging as a useful and easy detectable tool to define the overall cardiovascular risk in children and adolescents. Nevertheless, no all dyslipidemic patients suffer the same cardiometabolic consequences. **Objective and hypotheses:** To compare anthropometric, biochemical and blood pressure variables among dyslipidemic children and adolescents according to the presence of metabolic syndrome (MetS). **Method:** 700 dyslipidemic children and adolescents (median age 9.75, range 2.00–17.50 years) referred to our endocrine outpatient clinic were screened for MetS according to Weiss' definition. Anthropometric parameters (BMI-SDS and waist-to-height ratio (WHeR)), systolic blood pressure (SBP), lipid profile including LDL/HDL and TC/HDL ratios, fasting glycaemia (G), insulin (Ins), G/Ins ratio (GInsR) and HOMA index were collected for all the enrolled patients. **Results:** Among dyslipidemic patients, the prevalence of MetS was 8.71% (61/700). Children and adolescents with MetS presented higher BMI-SDS and WHeR than no-MetS patients (BMI-SDS 2.34±0.32 vs 1.29±1.35, $P<0.00$; WHeR 0.62±0.05 vs 0.58±0.05, $P<0.00$). In MetS, level of TG (150.11±66.43 vs 90.25±55.42 mg/dl, $P<0.00$), TC/HDL (4.62±1.43 vs 3.69±1.18) and LDL/HDL (2.93±1.12 vs 2.34±0.98) ratios were higher and HDL-cholesterol levels were lower (39.80±13.92 vs 53.04±13.66, $P<0.00$) than no-MetS. Glucidic metabolism was more altered in MetS than no-MetS (GInsR 6.63±7.04 vs 9.84±8.70, $P<0.00$; HOMA index 4.94±4.23 vs 2.86±1.82, $P<0.00$). High SBP values defining hypertension were found in 74% MetS and in 22.5% no-MetS. Among all dyslipidemic children, TG levels together with GInsR and HOMA index were identified as independent predictive factors for MetS. **Conclusion:** In our outpatient setting of dyslipidemic children, the finding of high TG and low HDL levels helps in discriminating patients with MetS, especially when associated with increased BMI-SDS, insulin resistance and high SBP. Our data highlight the presence of a cluster of conditions that concurrently increased the cardiovascular risk already in childhood and, therefore, that had to be globally investigated.

P3-845

RNAi as Tool to Study Molecular Mechanisms of Metabolic Adverse Reactions in Caenorhabditis Elegans

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Background: The introduction of second generation antipsychotic (SGA) drugs for the treatment of bipolar disorders has been associated with metabolic adverse reactions. Many studies cite significant weight gain as a common side effect, which is often attributed to dysfunction of glucose homeostasis and the development of dyslipidaemia. This in turn may trigger the early pathogenesis observed for example in type-2-diabetes. Factors

controlling energy metabolism are largely conserved between mammals and the nematode *Caenorhabditis elegans (C. elegans)*, thereby providing a powerful model to delineate the molecular pathways that lead to metabolic disorders. **Objective and hypotheses:** Daf-3 is responsible for storage of fat. **Method:** We established a tissue-specific molecular method (RNA Interference; RNAi) in our lab for controlled and cell type-specific silencing of protein synthesis in *C. elegans*. With this method it is possible to block protein synthesis in specific development stages of the worms. We used different *C. elegans* mutant strains which lack key regulator proteins of the Insulin- and TGF-β-signaling pathway to study the effects of their absence on tissue lipid accumulation and other metabolic disorders. **Results:** Using GFP silencing we confirmed the suitability of the RNAi-method to study lipid metabolism at a single-cell-level. Further, studies in our lab have shown that treatment of *C. elegans* with olanzapine, a common antipsychotic drug resulted in significant weight gain just as in human patients. A regulatory protein DAF-3 is thought to be involved. Initial experiments indicate DAF-3 is necessary but not sufficient for this side effect. **Conclusion:** *C. elegans* represents a powerful model-system for medical research. Molecular mechanisms leading to excessive storage of fat upon medication are very complex. At least two or more proteins operate in concert to cause this metabolic adverse reaction.

P3-846

Hypertriglicerydaemia in a Boy with Bardet-Biedl Syndrome – Case Report

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Background: Bardet-Biedl syndrome (BBS) is a rare autosomal ciliopathy characterised by retinal dystrophy, obesity, postaxial polydactyly, renal anomalies, mental retardation and hypogonadism as well as minor features, which include diabetes mellitus, cardiac dysfunction and behavioural abnormalities. Hypertriglyceridaemia in BBS patients has not been reported to date. **Objective and hypotheses:** Presentation of the diagnosis and treatment of hypertriglicerydaemia in a boy with BBS. **Method:** Analysis of the clinical course on the basis of medical records. **Results:** Male patient, at the age of 16 month with postaxial polydactyly, obesity, recurrent upper airway infections, isolated IgA deficit and severe gastroesophageal reflux disease has been diagnosed with BBS type 2. Further examinations revealed left ear hearing insufficiency, and severe mental, motor and speech retardation, with accompanying autism. At the moment of BBS diagnosis (16 months) laboratory testing revealed isolated hypertriglyceridemia (triglycerides –TGL, 3.01 mmol/l, N: 0.31–1.41 mmol/l), with with normal total cholesterol (5.4 mmol/l, N: 2.75–5.95 mmol/l), LDL cholesterol (3.11 mmol/l, N: 1.65–3.41 mmol/l), and HDL cholesterol (0.94 mmol/l, N: 0.60–2.05 mmol/l). Treatment with low fat diet was unsuccessful, subsequent laboratory testing at the age of 10 years and 11 years and 11 months revealed permanent elevated level of TGL (2.98 and 8.41 mmol/l respectively, N: 0.27–1.86 mmol/l), with normal total, LDL and HDL cholesterol levels. There were no clinical, nor laboratory features of insulin resistance: normal fasting serum glucose level 4.4 mmol/l, fasting serum insulin level 2.13 μIU/ml, HOMA index – 0.4. Family history was negative. Therefore familial form and secondary hypertriglyceridemia were excluded. Treatment with fenobirate has been started. Control laboratory tests after 2 months revealed significant decrease of TGL (1.82 mmol/l). No adverse effects of fenofibrate have been noticed. **Conclusion:** This case study describes the first case of BBS with hypertriglyceridemia which is a novel sign to the syndrome that cannot be explained by accompanying diseases, diagnosed up to date. Treatment with fenofibrate in BBS patients may be effective and safe.

P3-847

Uric Acid and Triglycerides/HDL Ratio as a Predisposing Factor for Metabolic Syndrome in Children

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Background: Uric acid and Triglycerides/HDL ratio are an important risk factor for cardiovascular diseases. **Aim:** To investigate how Triglycerides/HDL ratio and uric acid are correlated with children's biochemical and anthropometric characteristics, depending on the predisposition for metabolic syndrome (MetSyn). **Methods:** 110 students, 6–12 years old, living in Sparta-Greece, participated in our research. Anthropometric and biochemical analyses were performed. **Results:** 39.1% of children had BMI%$\geqq$85% and 71.7% had waist circumference (WC) %$\geqq$95%. 3.64% had uric acid $\geqq$5.5 mg/dl, 8.2% glucose $\geqq$100 mg/dl, 3.64% triglycerides $\geqq$150 mg/dl, 12.7% cholesterol $\geqq$200 mg/dl while there was no child with HDL$\leq$40 mg/dl. The triglycerides/HDL ratio was 2:1 in 3.6% and $\geqq$3:1 in 3.6% of children. 17.27% of them were predisposed for MetSyn. With statistical importance ($P<0.05$) we found that in the total population: the Triglycerides/HDL ratio was positively correlated with cholesterol, LDL, ALT/SGPT, GGT and CAD (cholesterol/LDL); while uric acid increased WC% and triglycerides and decreased HDL. With statistical importance ($P<0.05$) we found that in the population of children without predisposition for MetSyn: Triglycerides/HDL ratio was positively correlated with body weight, uric acid, CAD and white blood cells; while uric acid increased WC% and cholesterol and reduced HDL. In children with predisposition for MetSyn, Triglycerides/HDL ratio was positively correlated with CAD ($P<0.001$), while uric acid was positively correlated with triglycerides ($P=0.003$) and negatively

with HDL ($P=0.023$). **Conclusions:** Despite the fact that HDL was normal in all children, triglycerides and uric acid levels were increased in a small percentage of children, making them important predisposing factors for the acquisition of metabolic disorders. The deposition of visceral fat can supercharge the lipid profile and raise the concentration of insulin, reducing renal clearance, resulting in hyperuricemia. At the same time, uric acid has a mechanistic role in atherosclerosis through the removal of nitric oxide which may be an early indicator of endothelial dysfunction and cardiovascular diseases.

P3-848

Increased Prevalence of 25-Hydroxyvitamin D Insufficiency and Deficiency among Overweight and Obese Children and Adolescents in Greece

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Background: The prevalence of childhood obesity has increased dramatically in the last decades and accounts for a significant increase in morbidity and mortality in adulthood. **Objective and hypotheses:** To determine the prevalence of 25-hydroxyvitamin D insufficiency and deficiency in overweight and obese children and adolescents. **Method:** 350 ($n=350$) children and adolescents (153 males (M), 197 females (F)) were recruited to participate in the study during the autumn months. Of those, 34 had normal BMI (age: 9.66 ± 0.47 year; BMI: 20.04 ± 0.39 kg/m^2, F: 26, M: 8), 111 were overweight (age: 10.23 ± 0.27 yr; BMI: 23.02 ± 0.31 kg/m^2, F: 64, M: 47) and 205 were obese (age: 10.28 ± 0.23 year; BMI: 28.48 ± 0.38 kg/m^2, F: 107, M: 98). The concentrations of 25-hydroxyvitamin D and cardiometabolic parameters were determined at 08:00 h following a 12-h fast. Systolic and diastolic blood pressure was determined twice and the mean was calculated. The study was approved by the Ethics Committee and written informed consent was obtained by the parents. **Results:** The concentrations of 25-hydroxyvitamin D were sufficient ($\geqq$30 ng/ml; 36.87 ± 0.7 ng/ml) in 63 (18%) children and adolescents, insufficient (20–29 ng/ml; 24.5 ± 0.24 ng/ml) in 132 (37.71%) and deficient ($<$20 ng/ml; 14.98 ± 0.29 ng/ml) in 155 (44.28%) subjects. Serum 25-hydroxyvitamin D concentrations were significantly lower in overweight and obese children and adolescents compared with their normal counterparts (Normal BMI: 24.06 ± 1.48 ng/ml; Overweight: 23.94 ± 0.84; Obese: 21.48 ± 0.61 ng/ml, $P<0.03$). **Conclusion:** 25-hydroxyvitamin D insufficiency or deficiency was observed in 82% of overweight and obese children and adolescents. These findings suggest that serum 25-hydroxyvitamin D concentrations should be determined regularly in this population and substitution therapy should be commenced when necessary. **Funding:** This work was supported by the National Strategic Reference Framework (NSRF) 2007–2013.

P3-849

The Triglyceride-to-High Density Lipoprotein Cholesterol Ratio in Overweight Korean Children

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Background: Dyslipidaemia is related with the initiation and progression of atherosclerosis in children, and the total cholesterol (TC) and non-high density lipoprotein cholesterol (non-HDL-C) are commonly used screening tools for identifying children with dyslipidaemia. The triglyceride-to-high density lipoprotein cholesterol (TG/HDL-C) ratio has recently been reported as a marker of insulin resistance in obese children and adolescents. **Objective and hypotheses:** To describe the TG/HDL-C ratio and related factors in overweight and normal weight Korean children. **Method:** Data from 405 Korean children (144 overweight children, aged 9.1 ± 1.9 years, and 261 normal weight children, aged 8.8 ± 1.8 years) were retrospectively evaluated. Glucose, insulin, TC, HDL-C and TG levels were measured after overnight fasting, and the TG/HDL-C ratio, non-HDL-C (TC – HDL-C) and homeostasis model assessment of insulin resistance (HOMA-IR, insulin (μU/ml) $\times$ glucose (mmol/l)/22.5) were calculated. Overweight was defined by BMI $\geqq$85th percentile. Hypertriglyceridemia was defined by TG$\geqq$130 mg/dl ($\geqq$10 years of age) or $\geqq$100 mg/dl ($<$10 years of age), and hypo-HDL-cholesterolemia was defined by HDL-C$<$40 mg/dl. **Results:** Overweight children showed higher TG (100.0 ± 69.6 vs 73.9 ± 40.0 mg/dl, $P<0.001$) and lower HDL-C (52.1 ± 11.3 vs 57.9 ± 10.8 mg/dl, $P<0.001$) levels than normal weight children. The prevalence of hypertriglyceridemia (35.4% vs 13.8%, $P<0.001$) and hypo-HDL-cholesterolemia (13.2% vs 3.1%, $P<0.001$) was increased in overweight children compared to normal weight children. The TG/HDL-C ratio was higher in overweight group than normal weight group (2.16 ± 2.06 vs 1.35 ± 0.87, $P<0.001$), and the TG/HDL-C ratio correlated with HOMA-IR after adjusting for age and sex ($r=0.567$, $P<0.001$). The sensitivity of TC $\geqq$200 mg/dl and non-HDL-C$\geqq$145 mg/dl for identifying those with TG/HDL-C ratio$\geqq$3 was 8.2% and 23.4% respectively. **Conclusion:** The TG/HDL-C ratio is increased in overweight children, and it seems to be related with parameters of insulin resistance. However, the TC and non-HDL-C is not a sensitive screening tool or identifying those with increased TC/HDL-C ratio.

P3-850

Waist Height Ratio as a Marker of Obesity and Insulin Resistance in Adolescents

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Background: Recent studies have shown a rising trend in pediatric obesity. However, studies dealing with the ultimate metabolic consequences of pediatric obesity and the means of accurately predicting these consequences are limited. **Objective and hypotheses:** To study the utility of WHtR as a marker of insulin resistance. To validate the presently used cutoffs ($\geqq 0.5$) and validate its utility in populations studies. **Method:** 96 children of both sexes in the 11–16 years age group were evaluated for lifestyle factors conducive to obesity, BMI, WC, WHtR, triceps skin fold thickness and fat percentage measured and fasting samples drawn for fasting insulin, glucose, lipids, adiponectin, hs-CRP; & HOMA-IR was also calculated. **Results:** Waist height ratio showed significant association with lifestyle factors, other anthropometric markers and biochemical markers, ($P < 0.05$), except for adiponectin. 40 children out of the total 96 had a BMI $<$85th centile, among whom, eight children had raised WHtR and greater incidence of frequent snack consumption, family history of obesity and increased fat percentage ($P < 0.05$). When the entire study group was divided into tertiles, the tertile with WHtR – 0.49–0.53 had HOMA-IR and hs-CRP values similar to cut-offs determined in previous studies. **Conclusion:** WHtR performed as well as BMI and WC in assessing obesity and insulin resistance in children. Children with normal BMI and high WHtR can still have increased central obesity & consequent metabolic risks. The presently used WHtR cutoff $\geqq 0.5$ for central obesity, correlates well with insulin resistance and future cardiovascular risk. WHtR has the potential to become 'the anthropometric marker' to define insulin resistance and cardio-vascular risk in future community studies. **Funding:** This work was supported by a research grant from the Endocrine Society of India.

P3-851

Genotype and Clinical Characteristics in Korean Patients with Prader-Willi Syndrome: A Single Centre Study

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Background: Prader–Willi syndrome (PWS) is characterised by neonatal hypotonia, hypogonadism, progressive obesity, short stature, and mental retardation. This syndrome arises from a loss of expression of paternally derived genes on chromosome 15q11–13 region. **Objective and hypotheses:** The aim of this study was to investigate clinical characteristics and their genotypes in Korean patients with PWS. **Method:** The study included 46 PWS patients diagnosed by clinical features and methylation test. And genetic subtypes were distinguished by using fluorescence *in situ* hybridisation (FISH). Birth history, auxological profile, clinical features, neurodevelopmental state, radiologic findings, and medication were reviewed, retrospectively. And BMI was analysed in patients more than 2 years old age. **Results:** Total 46 PWS patients, 27 patients were male and 19 patients were female. Their age at diagnosis was 1.8 ± 3.7 years. 39 patients (84.8%) were diagnosed within 1 year of age due to hypotonia and feeding difficulty, but other seven patients were diagnosed at 3–15 years old. FISH was performed in 39 patients and 29 paternal deletions (73.7%) and ten maternal UPDs (26.3%) were noted. 21 males (77.8%) undergone orchiopexy. 36 patients (78.3%) had received recombinant human GH therapy, and the mean age at the start of GH and duration of therapy were 2.7 ± 2.9 and 3.3 ± 2.4 years. 19 patients were obese (2.34 ± 0.86, 19/37, 51.4%) and among them, GH group was less obese than non-GH group (41.9%, 100%, $P < 0.05$). In GH group, early start group, who received GH from one year of age, were less obese than later starte group (7.7% vs 66.7% $P < 0.05$). 20 patients (43.5%) had scoliosis. One patient had hip dysplasia, and one patient had pes planus. Six patients received anti-epileptic drugs for epilepsy, and all of them were paternal deletion. Two patients performed tonsillectomy due to sleep apnoea. **Conclusion:** Our study showed that deletion was common, and early GH therapy improved BMI of Korean PWS patients. As PWS is a multi-systemic disorder, and there are different manifestations according to time, persistent and systemic monitoring should be needed.

P3-852

Comparison of the Insulin Resistance Index HOMA-IR between Obese and Normal Children

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Background: Adult obese subjects are susceptible to an excess of cardiovascular events due to insulin resistance through the metabolic syndrome or hyperinsulinism itself. These deleterious factors go on and amplify from childhood into adulthood. To the best of our knowledge no comparison of insulin resistance indices has been performed between obese and normal children. **Objectives:** The main objective of this study is to compare the insulin sensitivity index (HOMA-IR) of two cohorts of obese vs non-obese children. The secondary goals consist in checking the Gaussian distribution of the HOMA-IR index in non-obese and in obese children, in one hand, and comparing components of the metabolic syndrome in obese children with normal or with increased HOMA-IR values, in the other hand. **Methods:** We analysed 463 non-obese children (cohort FLVS) from 256 families who were compared with 850 obese children from 602 families (cohort OBE). Gaussianity (normality) distribution of HOMA-IR was checked by Quantile-Quantile plot (Q-Q plot). Assuming normality we considered as extreme children whose log HOMA-IR values deviate plus or minus two standard deviations from the mean. **Results:** When adjusted for sex, age and BMI, we found that the 3rd and 97th centiles of HOMA-IR were 0.61 and 0.69 respectively in FLVS cohort. Using these thresholds, we classified children in OBE cohort as hypersensitive to insulin (IH) (one out of 850 children (0.1%)); sensitive to insulin (IS) (224 out of

850 children (26.3%)); and resistant to insulin (IR) (625 out of 850 children (73.5%)). Normality of HOMA-IR was observed in both FLVS and OBE cohorts, with few outliers. Components of the metabolic syndrome are more present in the IR class than in both IH and IS classes. **Conclusions:** For the first time an insulin resistance has been compared between obese and normal children. Given the variability of the definition of the metabolic syndrome, the classification of obese children with respect to their HOMA-IR values provides a useful tool especially with relevance to future potential complications.

P3-853

Nonalcoholic Steatohepatitis Leading to Cirrhosis of the Liver as a Complication of Hypothalamic Disorders in a Course of Craniopharyngioma – Case Report

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Background: Craniopharyngioma is low – grade malignant tumour with high survival rate. Its incidence is 0.5–2.0 cases per million persons per year. 30–50% of all cases occur in the childhood. The tumour location leads to numerous complications like deficits of pituitary function, impairment of vision, neuropsychological deficits and obesity. Excess body fat is observed in 40–50% of craniopharyngioma patients. **Case presentation:** We present two patients after neurosurgery carried out as treatment of craniopharyngioma with extreme obesity and liver cirrhosis secondary to NASH. The first patient is a 17-years-old girl and the second patient is now 27-years-old male who was under the care of the Department of Endocrinology in the period from 6 to 18 years of age. In the history both of them were in good condition till age of 6. Since then the symptoms of CNS tumour appeared. In case of the girl episodes of severe headache, vomiting were observed and the tumour around the optic chiasm and in the third ventricle was diagnosed. In case of the boy there were diabetes insipidus, weight loss and hypersomnia. CT showed cystic tumour of the suprasellar region. After total resection of craniopharyngioma symptoms of panhypopituitarism, diabetes insipidus, hyperphagia and steady weight gain were observed. In first six months after the operation the boy has put on weight by 35 kg. Attempts to modify the diet were unsuccessful. In a girl at 11 years of age the following examination revealed carbohydrate intolerance, hyperinsulinism and features of fatty liver. In the 8th year after the neurosurgery relapse of craniopharyngioma was diagnosed. Patient underwent endoscopic fenestration of tumour cyst.The rest of tumour has been identified, but her parents refused radiotherapy. Both of them at 13–15 years of age began to show the symptoms of hepatopulmonary syndrome and liver failure. Based on liver biopsy diagnosed with NASH, after that they underwent liver transplantation. In the long term observation patients are still obese. A qualification for the bariatric surgery is considered. **Conclusions:** The aim of our study is to highlight fatty liver disease as a significant problem in obese children with hypothalamic damage caused by tumour. Thorough, long-term observation of patients and performed examinations may allow for early detection of progress from simple steatosis to steatohepatitis and finally cirrhosis of the liver.

P3-854

Association of Sleep Habits and Risk Factors for Metabolic Disorders in Children

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Background: Sleep is a complex and essential biological process that is required on a daily basis for all humans, playing a vital role in the maintenance of the homeostasis in short and long term. **Aims and objectives:** To investigate the role of sleep hours in correlation with risk factors for metabolic disorders in a children population. **Methods:** The program was implemented in 949 children (5–12 years old) living in Sparta-Greece. The lifestyle was determined by using specially designed questionnaires. Anthropometric measurements were made. In 480 of them a determination of the haematological and biochemical profile was conducted. **Results:** 58.8% of the children go to sleep between 19.00–22.00 h, 37.8% between 22.00–2.00 h, and 3.3% after midnight. After correlating all the measurements with sleep habits with statistical significance ($P \leq 0.05$), we arrived at the following findings. Children that have breakfast start their night sleep earlier than those who do not have breakfast. Children that consume more fruits, vegetables and dairy products per week tend to sleep earlier. Children who eat non-homemade food or consume fast-food sleep early in the night less often. Children that were prematurely born start their night sleep later. Children having less anxiety or stress tend to sleep earlier in the evening. Furthermore, it was found that the earlier a child goes to bed in the night the less tired it feels when it wakes up in the morning. Children who sleep late (after 22.00 h) were presented with higher BMI%, hip circumference, WC%, blood pressure and glucose and urea levels. Children who sleep after midnight have decreased platelets and plateletcrit. **Conclusions:** In an effort to maintain body weight and to prevent the metabolic, immunological and haematological complications it is necessary not only to preserve an appropriate diet and exercise program but also to keep adequate sleep hours.

P3-855

Plasminogen Activator Inhibitor-1 as a Marker of Insulin Resistance in Obese Adolescents

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Background: Obesity is considered to be a chronic inflammatory state in which the dysfunction of adipose tissue plays a central role. Adipose tissue is known to express and secrete a variety of products known as 'adipokines' including leptin, adiponectin, resistin, and visfatin, as well as cytokines and chemokines such as tumor necrosis factor-α (TNF-α), interleukin-6, and monocyte chemoattractant protein-1. **Objective and hypotheses:** The aim of this study is to evaluate the inflammation markers and their correlation with insulin resistance in obese adolescents. **Method:** 78 obese children (38 male; age 14.3 ± 1.8 years) and 60 healthy adolescents (21 male; age 14.9 ± 2.2 years) were included in the study. BMI-SDS, waist/hip circumference, blood pressure were recorded. Serum fasting lipid profile, glucose, insulin, plasminogen activator inhibitor-1 (PAI-1), TNF-α, adiponectin levels of obese adolescents were compared with healthy controls. The homeostasis model assessment for insulin resistance (HOMA-IR) was calculated as a marker of insulin resistance. **Results:** Obese adolescents had significantly higher serum triglyceride, LDL cholesterol, insulin, HOMA-IR and PAI-1 and lower HDL-cholesterol and TNF-α levels compared with controls. Serum PAI-1 levels positively correlated wih HOMA-IR whilst serum TNF-α negatively correlated with BMI and HOMA-IR in obese adolescents ($P < 0.05$). The insulin resistant group had higher BMI, insulin, PAI-1 and lower TNF-α levels ($P < 0.05$). **Conclusion:** Obese adolescents had significantly increased PAI-1 levels as compared with the control group. A positive correlation between PAI-1 levels and indices of insulin resistance was demonstrated in this study. Our results suggest PAI-1 can be used as a marker of insulin resistance in obese adolescents.

P3-856

Relationship between Visceral Obesity and Plasma Fibrinogen in Obese Children

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Background: The prevalence of obesity in children and adolescents has increased significantly worldwide with an alarming rise of its co-morbidities. The excess of visceral adipose tissue is associated with hypertension, prothrombotic and pro-inflammatory states leading to cardiovascular diseases. **Aim of the study:** To find possible associations between visceral obesity and plasma fibrinogen, as one of the cardiovascular risk factors, in obese children. **Subjects and methods:** Our study included 43 obese children and 40 non-obese age and sex matched controls who were subjected to a detailed history taking, complete physical examination, anthropometric assessment, body composition analysis, ultrasonographic measurement of visceral adipose tissue and subcutaneous fat as well as laboratory measurement of plasma fibrinogen. **Results:** The present study revealed significant higher levels of fibrinogen in obese children than control (14.5 + 5.1 mg/ml and 2.9 + 0.52 respectively) with P-value < 0.01. Moreover, the obese group had highly statistical significant differences in visceral fat (5.96 + 0.77 cm) and subcutaneous fat (2.66 + 0.70 cm) than control (2.45 + 0.65 and 0.70 + 0.18 mg/ml respectively) with P-value < 0.01. In addition, fibrinogen had significant positive correlation with BMI ($r = 0.327$), Waist/Hip ratio ($r = 0.394$), fat percentage ($r = 0.301$), visceral adipose tissue ($r = 0.323$) and subcutaneous fat ($r = 0.301$). **Conclusion:** There is highly significant increase in the fibrinogen level, visceral and subcutaneous abdominal fat in the obese group than controls with insignificant sex differences. Fibrinogen had significant positive correlation with the different adiposity markers, blood pressure, visceral and subcutaneous fat. Visceral adipose tissue is a stronger predictor for cardiovascular risk compared to subcutaneous fat.

P3-857

Influence of GNRH Analogue on BMI in Girls with Precocious Puberty

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Background: Treatment with the gonadotropin – releasing hormone (GnRH) agonist is the treatment of choice for central precocious puberty (CPP). **Objective and hypotheses:** Concept have been expressed that GNRH treatment may be associated with increased BMI and it is controversial in some studies. **Method:** We studied the height, weight, and BMI of 52 girls that the majority of them had CPP. All patients were treated with GNRH analogue over 12 months. The variables were evaluated at 0.6 and 12 months after initiation of treatment. **Results:** Before the initiation of therapy the girls had a mean BMI S.D. score for chronological age of 0.8 ± 1.18 after 6 months of therapy. BMI S.D. s was 0.82 ± 1.15 and after 12 months was 0.82 ± 1.28, the P-value is 0.909 and it is not statistically significant. Height S.D. score for chronologic age was 0.41 ± 1.65 before the initiation of therapy and was 0.41 ± 1.65 after 6 months and 0.43 ± 1.6 after 12 months of therapy. The P-value is 0.66 and it is not statistically significant. **Conclusion:** GNRH analogue treatment in CPP is safe for BMI and is increasing of BMI is not significant.

P3-858

Prevalence of Asthma Symptoms and Association with Obesity, Sedentary Lifestyle and Sociodemographic Factors: Data from the Hellenic National Plan for the Assessment, Prevention and Treatment of Childhood Obesity

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Background: The parallel increase in prevalence of asthma and obesity in childhood has led to an increasing body of evidence about a possible link between the two conditions. **Objective and hypotheses:** To assess the prevalence of asthma symptoms in a representative sample of Greek schoolchildren and to evaluate its association with overweight/obesity as well as other socio-economic, demographic and lifestyle factors. **Method:** This is a cross-sectional study conducted from October 2012–December 2013. A pre-selected, representative elementary school cohort (N = 11.751, age range 5.9–12.3 years) was derived, using stratification and PPS methodology. Parents responded to questionnaire and the approved Greek version of the ISAAC core questionnaire and students were measured with high sensitivity methods. IOTF cut offs were used to classify the children. Socio-economic status index was calculated (SES index range 0–13) on years of parental education, rented vs owned residence, m^2/person, number of vehicles Logistic regression was applied using STATA 11.0. **Results:** The prevalence of asthma symptoms was documented in 31% of population. Boys were 1.22 (CI: 1.13–1.33) times more likely to present with asthma symptoms Overweight (odds ratio: 1.13, 95% CI 1.03 TO 1.25) and obesity (odds ratio: 1.27, 95% CI: 1.11–1.46) were related to the presence of asthma symptoms. Moreover, 1 year increase of age increased the odds of asthma symptoms by 9.6% (CI: 0.94–0.98) and an increase of 5 h/week of sedentary activities increased the odds of asthma by 10.7% (CI: 1.01–1.13). **Conclusion:** A strong association between presence of asthma symptoms and obesity and sedentary activities was documented irrespectively of socio-economic and regional (urban vs rural) factors. The findings stress the importance of public health policies towards obesity prevention and enhancement of physical activities in paediatric populations in our country.

P3-859

Long-Term Effects of Neonatal Over-Nutrition on Metabolic Equilibrium are Age and Sex Dependant

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Background: Neonatal over-nutrition (NON) can have a long-term effects on energy homeostasis and some of these effects may be sexually dimorphic. **Objective and hypotheses:** We aimed to determine how NON affects body weight (BW), body composition and cytokine levels throughout development and if these changes are sexually dimorphic. We hypothesised that the effects would be both age and sex dependant. **Methods:** At birth, Wistar rats were organized into litters of four (NON) or 12 (control) pups (equal number males/females) and killed on postnatal days (P) 10, 21 (weaning), 30, 50, 85 or 150. Serum levels of adiponectin, leptin, insulin, interleukins (IL) six and 1β and TNFα and cytokine mRNA levels in s.c. and visceral (V) adipose tissue were measured. **Results:** At P10 BW was greater in NON rats of both sexes ($P < 0.0001$), continuing until P60. After P90 NON again increased BW in males ($P < 0.0001$). At P10 SC was increased by NON, with females more affected than males ($P < 0.0001$). These effects were not found after P21, but at P150 NON again increased SC in males. At P21 NON increased V ($P < 0.001$) and males had more V than females ($P < 0.0001$). The effect of NON disappeared after P50 and returned in later adulthood, but only in males. At P10 serum glucose ($P < 0.02$), insulin ($P < 0.0001$), leptin ($P < 0.03$) and adiponectin ($P < 0.0001$) were increased and IL1β ($P < 0.05$) and TNFα ($P < 0.0006$) levels decreased by NON, with similar changes in cytokine expression in s.c. None of these effects were found at P30. Thus, there is an early effect of NON that dissipates and then reappears in males after P90, increasing BW, V, s.c., serum leptin levels and TNF-α gene expression in V. **Conclusion:** Early nutritional modifications can have long-term effects that are both age and sex dependant and that may possibly affect the aging of metabolic homeostasis. **Funding:** This work was funded by grants from Fondos de Investigación Sanitaria (grant numbers PI100747, PI1302195), Ministerio de Ciencia e Innovación (grant number BFU2011–27492), Centro de Investigación Biomédica en Red Fisiopatología de Obesidad y Nutrición (CIBEROBN), Instituto de Salud Carlos III, and Fundación de Endocrinología y Nutrición.

P3-860

Metabolic Syndrome in Greek Adolescents and the Effect of 6-Month Educational/Behavioural School Interventions

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Background: Data regarding the prevalence of metabolic syndrome (MS) in Greek adolescents and the effect of school interventions are scarce. **Objective and hypotheses:** To study the prevalence of MS in a representative sample of Greek adolescents and evaluate the impact of a 6-month educational-behavioral intervention. **Method:** Cross-sectional anthropometric data ((height, weight, waist circumference (WC)), blood pressure (BP), fasting blood glucose (BG), triglycerides and HDL-cholesterol, were assessed at baseline and following the intervention in adolescents aged 12–17 years, as part of a 'screening program for MS characteristics in adolescents attending 27 high schools in three municipalities of Attica, with the use of portable telemedicine' funded by the European Union. Intervention consisted of educational sessions promoting healthy lifestyle by a dietitian, exercise physiologist and psychiatrist, at the school setting to all participants. Half of the students were randomized to receive an additional intervention of daily consumption of one fruit in classroom. **Results:** A total of 1 142 adolescents participated in the study, of whom 572 received the added fruit intervention. The prevalence of MS in the total sample was 2.7% at baseline and 2.3% post-intervention. There was no change in MS prevalence (2.5%) in the fruit intervention group, however there was a statistically significant increase in HDL-cholesterol (15.5%, $P<0.001$) and a decrease in WC (0.7%, $P=0.028$) and diastolic BP (2.8%, $P<0.001$) post-intervention. The prevalence of MS in the 570 adolescents who did not consume fruit, decreased from 2.8 to 2.1%, following the intervention, but this difference was not significant. In this group, significant decreases were found in WC (0.7%, $P=0.037$), diastolic BP (2.6%, $P<0.001$) and triglycerides (3.4%, $P=0.009$). Interestingly, BMI and BG increased significantly in both groups post-intervention. **Conclusion:** A 6-month school intervention had a significant impact on abdominal obesity, diastolic BP and lipids, but did not improve BMI and BG in the short term.

P3-861

Decreased Insulin Sensitivity and Secretion in Obese Youth with High OGTT Derived 1 h Blood Glucose

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Background: Obese adults with normal glucose tolerance (NGT) but 1-h post load glucose (1 hPG)≧155 mg/dl have an increased cardiometabolic risk. In children, preliminary data suggest that 1hPG≧132.5 mg/dl might identify those at higher risk of type 2 diabetes. **Objective and hypotheses:** To assess whether NGT obese youth with 1hPG ≧132.5 mg/dl (High-NGT) have worse insulin sensitivity and secretion compared to obese youth with 1hPG <132.5 mg/dl (low-NGT). **Method:** Oral glucose tolerance tests (OGTTs) were performed in 202 obese children (83 males, 82 prepubertal, mean age (SD): 11.1±2.8 years, BMI-SDS: 2.23±0.52). Indexes of insulin sensitivity (HOMA-IR, WBISI) and secretion (insulinogenic index), and the area under the curve (AUC) for glucose and insulin during the OGTT were calculated. **Results:** Ten (5%) youth had impaired glucose tolerance. Among those with NGT, 38 (19.8%) were classified as high-NGT (age: 10.9±2.7 years) and 154 as low-NGT (age: 11.2±2.9 years). High-NGT youth showed higher fasting glucose and AUC glucose and insulin, lower insulin sensitivity (WBSI) and insulin secretion. **Conclusions:** These data suggest that 1hPG ≧132.5 mg/dl may identify NGT youth with impaired insulin secretion and insulin sensitivity, at increased risk for type 2 diabetes and other cardiometabolic complications.

P3-862

Diagnosis and Treatment of Familial Hypercholesterolemia in Children – A Preliminary Report

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Background: Heterozygous familial hypercholesterolemia (FH) is an autosomal dominant genetic disorder occuring in

Table 1. (for abstract P3-861)

	Whole study group	Low-NGT	High-NGT	*P*
Fasting glucose (mg/dl)	92.9±9.4	91.9±9.8	95.9±7.2	0.02
Fasting insulin (μU/ml)	15.6 (10.3–22.6)	15.6 (10.0–22.7)	15.1 (10.3–21.4)	0.99
AUC glucose (mg/dl)	111.5±15.8	105.9±11.2	125.9±11.5	<0.001
AUC insulin (μU/ml)	70.4 (100.5–120.4)	65.2 (41.3–99.0)	106.4 (55.9–127.1)	0.007
HOMA-IR	3.5 (2.4–5.1)	3.4 (2.3–5.1)	3.7 (2.5–5.2)	0.66
WBISI	0.32 (0.20–0.48)	0.34 (2.37–4.99)	0.26 (0.18–0.38)	0.016
Insulinogenic Index	2.5 (1.4–5.3)	2.7 (1.5–6.5)	1.7 (1.2–2.9)	0.009

1:500 people. Patients with FH have a high risk of premature cardiovascular diseases. Today effective lipid-lowering therapies are available and it is a chance to extend the life of patients. **Aims and objectives:** The aim was to analyse the clinical data of children with FH from the Clinic of Pediatrics, Diabetology and Endocrinology and preliminary assesment of the effects of treatment. **Materials and methods:** The study included children with elevated cholesterol level. In 210 patients who had excluded secondary causes of hypercholesterolemia, molecular testing for mutation in LDLR and APOB genes was performed. **Results:** From the 210 patients with hypercholesterolemia, aged between 3 and 18 years, FH was confirmed in 79 patients. In all patients, history of cardiovascular diseases in family was positive. In physical examination no specific symptoms for FH were seen. Age of patients with FH was 9.8±4.1 years, and initially the average total cholesterol level was 275±40 mg/dl, LDL 223±39 mg/dl, HDL 57±15 mg/dl, triglycerides 99±25 mg/dl. In 79% of patients in the LDLR gene and in 21% in the APOB gene, mutations were found. All patients with FH started diet. Treatment with statins in 59 patients and with statin and ezetimibe in four patients with FH was started. The average level of total cholesterol in the control tests after 12 weeks of treatment was 214±23 mg/dl, LDL 136±18 mg/dl, HDL 55±12 mg/dl, triglycerides 89±27 mg/dl. In the group of patients treated with pharmacological therapy, no adverse side effects of the treatment were reported. **Conclusions:** Hypercholesterolemia should be diagnosed and treated as soon as possible. Therapy consisting of diet, statins and ezetimib is a safe form of therapy in children. It is necessary to continue monitoring the efficacy and safety of therapy. **Fundingl:** Narodowe Centrum Nauki UMO-2013/09/B/NZ5/02786.

P3-863

Metabolic Syndrome Risk Factors in Obese Children and Adolescents

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Objective and hypotheses: The work was initiated to perform integral assessment of metabolic syndrome (MS) risk factors in obese children and adolescents. **Method:** We examined Uzbek 100 children and adolescents with exogenous-constitutional obesity (ECO) aged from 6 to 16 years (mean age 11.7±0.25); 54 (54.0%) boys and 46 (46.0%) girls among them. To develop prediction scale we used a modification of Bayesian probability, method for standardization of intensive parameters. **Results:** MS risk is 8.5 times higher with triglycerides (TG) ≧1.7 mmol/l; it is 5.3 times higher with HDL <1.03 mmol/l, 3.1 times higher with BMI>97th percentile and 2.6 times higher with HbA1c>6.7%. MS risk increases by 2.7 times with early onset of obesity (under 10 years), by 3.4 times with ECO duration >5 year, and by 2.9 times with SHBG<70 nmol/l for boys and <100 nmol/l for girls. Analysis of relative risk (RR) and etiological fraction (EF) of MS risk factors demonstrated that TG≧1.7 mmol/l (RR=8.47; EF=88.19%) and HDL <1.03 mmol/l (RR=5.30; EF=81.15%) almost completely precondition MS. Very high and high precondition of MS could be seen with BMI>97th percentile (RR=3.07; EF=67.44%), and HbA1c>6.7% (RR=2.60; EF=61.54%) and IA >3.0 (RR=2.16; EF=53.64%), respectively. MS is moderately preconditioned by obesity duration ranging from 5 to 10 years, obesity onset age >10 years, MAU ranging from 30 to 100, fasting glycemia (≧5.0), diastolic blood pressure ≧85 Hg mm, SHBG<20 for boys and <30 for girls. **Conclusion:** Children and adolescents aged under 16 years with high TG, low HDL, BMI>97th percentile, high HbA1c and obesity duration >5 years are at MS high risk. TG≧1.7 mmol/l and HDL<1.03 mmol/l almost completely precondition MS. BMI>97th percentile, and HbA1c>6.7% and IA>3.0 are associated with very and high MS precondition.

P3-864

A Systemic Approach for the Management of the Program Entitled 'Development of a National System for the Prevention and Management of Overweight and Obesity in Childhood and Adolescence in Greece'

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Background: The prevalence of obesity has increased dramatically in Greece in the last two decades, and more than 35% of children and adolescents are currently overweight or obese. Prevention could be the key strategy for controlling the current epidemic of obesity. **Objective and hypotheses:** Prevention is the main scope of the Program entitled 'Development of a National System for the Prevention and Management of Overweight and Obesity in Childhood and Adolescence in Greece' (MIS 370545), which is funded by the National Strategic Reference Framework (NSRF) 2007–2013. The Program is endorsed by the Ministry of Health and the Research Center of the National and Kapodistrian University of Athens Medical School. It is implemented by the Division of Endocrinology, Metabolism and Diabetes, First Department of Pediatrics, 'Aghia Sophia' Children's Hospital, which serves as a National Center for the Prevention and Management of overweight and obesity in childhood and adolescence. **Method:** The soft systems methodology (SSM) is a systemic approach for dealing with real-world complex or problematic situations. SSM is used to manage the complexity raised by the interaction of the center, the primary stakeholders and the external environment consisting of the hosting hospital, other hospitals, paediatricians, partners, collaborating

organizations, societies and others, which all together form an integrated whole. Applying SSM's CATWOE statement (Clients, **A**ctors, Transformation, Worldview, Owner, Environmental Constrains) and modelling the problem at different abstraction levels, also serves as a means to understand the whole system. **Results:** The methodology was instrumental in augmenting our understanding of the systemic interaction of the system's elements and the underlying structures associated with the Center's internal and external operating environment. **Conclusion:** The methodology illustrated the communication arrangements, which contribute to delays in system flows that impact the operating effectiveness of the procedures associated with the management of overweight and/or obese children. **Funding:** The Program entitled 'Development of a National System for the Prevention and Management of Overweight and Obesity in Childhood and Adolescence in Greece' (MIS 370545), is funded by the National Strategic Reference Framework (NSRF) 2007–2013.

P3-865

Waist Circumference to Body Height is a Suitable Measure of Cardiovascular Risk in Overweight and Obese Children

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Background: Several methods have been used to evaluate the risk of cardiovascular diseases in obese children. Both BMI and waist-to-hip ratio were suggested as risk factors. However, they did not prove to estimate the risk for cardiovascular events in adulthood. Recent studies suggest that the ratio of waist circumference to body height (WHtR) is a more reliable predictor for cardiovascular risk in 6-10-year old children (Kuba *et al.* 2013). **Objective and hypotheses:** To evaluate WHtR as an indicator for cardiovascular risk factors in 8–18 year old children with overweight and obesity. Furthermore changes in WHtR during an obesity intervention program were studied. **Method:** The study included 93 children and adolescents between 8 and 18 years with a BMI above the 85th percentile who participated in an outpatient obesity program. WHtR was considered critical if it exceeded a value of 0.5. The children received individual nutritional and exercise counseling and were examined before start of the program and after 6 months. **Results:** The mean WHtR was $0.58 + 0.07$ in obese children, and significantly lower in overweight children ($0.51 + 0.04$, $P < 0.001$) before the intervention. It decreased significantly after weight loss in obese children ($0.55 + 0.08$) as well as in overweight participants (0.47 ± 0.03). WHtR correlated significantly with HOMA index, leptin, uric acid, adiponectin, and systolic blood pressure. Weight loss also lead to an improvement in these cardiovascular risk factors. **Conclusion:** In summary, our data indicate that WHtR is a reliable marker for cardiovascular risk factors in children and adolescents. **Funding:** This work was supported by DAAD, Germany (grant number A/11/96804).

P3-866

The Effectiveness of a Comprehensive and Personalized Plan of Action in the Prevention and Management of Overweight and Obesity in Childhood and Adolescence

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Background: Obesity in childhood and adolescence represents a major health problem of our century, and accounts for a significant increase in morbidity and mortality in adulthood. **Objective and hypotheses:** To investigate the effectiveness of a comprehensive and personalized plan of action in the prevention and management of overweight and obesity in childhood and adolescence. **Method:** 470 children and adolescents (mean age $\pm$ SEM: 9.9 ± 0.2 years; 205 males, 265 females; 274 prepubertal, 196 pubertal), who attended an out-patient clinic for the prevention and management of overweight and obesity, were studied prospectively for one year. According to their BMI, subjects were classified as obese, overweight or of normal BMI. All subjects were evaluated by a multi-disciplinary team at frequent intervals, and received comprehensive personalized advice on diet, exercise and psychologic management. Detailed endocrinologic evaluation was performed at the beginning and the end of the study. The study was approved by the Ethics Committee and written informed consent was obtained by the parents in all cases. **Results:** At initial evaluation, 64% of subjects were obese, 29% overweight and 7% of normal BMI. A significantly higher number of boys were obese compared with girls (74% vs 56%, $P < 0.001$), while a higher number of girls were overweight compared with boys (33% vs 23%, $P < 0.001$). Preadolescent children were more likely to be overweight than adolescents (32% vs 25%, $P = 0.044$). The onset of weight gain had been observed beyond the age of 5 years and was progressive throughout childhood and adolescence. Following 1 year of the multi-disciplinary management interventions, obesity decreased from 64 to 51%, normal BMI increased from 7 to 16%, and cardiometabolic indices improved substantially. **Conclusion:** A comprehensive and personalized multi-disciplinary management plan is effective in decreasing the prevalence of obesity in childhood and adolescence. **Funding:** This work was supported by the National Strategic Reference Framework (NSRF) 2007–2013.

P3-867

Insulin Resistance in Adolescents with Screen Addiction and Attention-Deficit/Hyperactivity Disorder

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Background: Screen (TV, tablet, smartphones, internet, video games, PC etc.) addiction is a growing problem in child health. The effect on insulin-glucose metabolism is not well known yet. **Objective and hypotheses:** To investigate the insulin resistance in screen addicted children. **Method:** We studied 108 children and adolescents aged 13.72 ± 1.95 years (range 11–17 years). Participants were divided into three groups according to ADHD and Computer Addiction scales (group 1: ADHD and screen addicted group 2: ADHD group 3: control group). There were an equal number of obese and non-obese cases in these three groups. Clinical assessments included insulin resistance measured by HOMA-IR, auxology, blood lipids, body fat analysis. All cases wore pedometer for 3 days to measure the daily physical activity. Carbohydrates, fat and calorie intake was calculated with a nutrition program. **Results:** The mean weight and BMI SDS was 1.75 ± 2 and 1.6 ± 1.7 respectively. Daily active energy consumption was 747 ± 532 kcal in screen addicted group and 511 ± 384 kcal in non-addicted group ($P < 0.05$). Duration of physical activity was 2.6 ± 1.7 h in computer addicted group and 1.7 ± 1.1 h in non-addicted group ($P < 0.05$). Mean energy intake was 2051 ± 656 kcal in computer addicted group and 1778 ± 536 kcal in non-addicted group ($P < 0,05$). HOMA-IR values of the patients ranged from 0.62 to 16.46 while the average was 3.45 ± 2.7. There was no effect of ADHD and computer addiction to the HOMA-IR values (*P*: 0.228). HOMA-IR value of the computer addicted non-obese ADHD cases was 1.9 ± 0.6 whereas non addicted non-obese ADHD cases was 1.3 ± 0.5 (*P*: 0.012). In order to show the effect of ADHD on HOMA-IR values, non obese ADHD cases were compared with cases without ADHD. The HOMA-IR values of ADHD cases was 1.3 ± 0.5 while cases without ADHD was 2.7 ± 1.9 (*P*: 0.006). **Conclusion:** Computer addiction causes insulin resistance whereas activity decreases this effect. **Funding:** Ege University Scientific Research Committee 2013-BAP-017.

P3-868

Ketogenic Diet in Paediatrics: Work in Progress

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Background: The effects of carbohydrate-restricted (ketogenic) diets on metabolic parameters in children have been incompletely assessed. **Objective and hypotheses:** Effective treatment options for childhood obesity are limited and the risk of significant co-morbidities increase sharply with age, especially in paediatric population where growth is normally still occurring. The purpose of this study was to evaluate the feasibility, the efficacy and the safety of a high-protein, low-carbohydrate, low-fat ketogenic diet (K diet) in the treatment of morbidly obese children. **Method:** Eight children, aged 10–15 years, were recruited to follow a K diet. Anthropometric data (waist, neck, abdomen, hips, thighs, arm circumference, weight, height, BMI) were collected at enrolment, after 10 days of diet, during reintroduction of food and throughout the course of the whole study during the various visits. The study is still ongoing. Diet composition was monitored and recorded at each visit and ketosis was kept under control. Blood tests and liver ecography were performed at the beginning of the study. The multiphase dietetic protocol was combined with a nutritional supplement for alkalinisation. **Results:** The observed clinically meaningful reduction of body weight, in the subjects included in the study, was primarily associated with a reduction of the waist circumference. The K diet appears to be an effective method in overweight children and may be a feasible and safe alternative for children's weight loss.

P3-869

Severe Hypothalamic Obesity in a Girl with Craniopharyngioma – Case Report

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Background: Hypothalamic obesity is a form of obesity syndrome associated with a variety of hypothalamic disorders including intracranial tumors, infections, trauma, vascular problems and hydrocephalus and acquired or congenital functional defects in central energy homeostasis. The pathogenetic mechanisms underlying hypothalamic obesity are multifactorial. Weight gain results from the hypothalamus damage, which leads to excessive apetite and low metabolic rate, multiple pituitary hormonal deficiency, hypomobility and insomnia. **Aims:** The aim is to present a 20-year-old female who underwent neurosurgical operation in the age of 11 years because of craniopharyngioma and manifested severe obesity thereafter (BMI > 50 kg/m^2). **Case presentation:** The girl in the age of 10 years was referred to endocrinologic outpatient clinic because of height deceleration and weight gain. In the age of 11 years craniopharyngioma (max. diameter 30 mm) was diagnosed. Postsurgically she developed multihormonal pituitary insufficiency and excessive appetite. The girl was on hormonal substitution therapy. With time the disturbed energy balance led to severe obesity with complications like insulin resistance, scoliosis, knee valgus and low self-assessment. The pharmacological treatment with metformin, orlistat, alpha-glucosidase inhibitor and psychological therapy did not bring weight loss. The BMI was critical 52 kg/m^2. In the

age of 19 years she underwent very unique neurosurgical operation. The stimulator for deep brain stimulation into the nucleus accumbens septi of the brain was installed. The aim of this intervention was to modify the appetite control. The operation was successful. The weight loss was significant - from a total weight of 150–130 kg. Since that time the weight is stable. The most important fact is that the self-assessment has been changed. The motivation improved and there is no obsessive thinking about eating. The treatment of hypothalamic obesity is very difficult. The deep brain stimulation gives a chance of better appetite control which seems to be the main problem in the disease.

P3-870

The Changes of Neuroendocrine Status in Children with Different Forms of Obesity

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Background: Obesity is accompanied with the development of serious complications, including behavioural disorders. Obesity with impaired neuroendocrine status confirmed, but papers describing these interactions are a bit. **Objective and hypotheses:** To compare the state of neuroendocrine status in children with various forms of obesity and normal weight control to the evaluation of central hormonal regulators of energy balance. **Method:** We examined 315 children (236 obese, age 14.56±2 years, BMI 32.86±5.1 kg/m^2; 79 normal weight (control), 14.51± 2.2 years (P=0.95), 19.9±2.5 kg/m^2 (P=0.0001)), observed in the endocrinology department of University clinic (Minsk) in 2013–2015. Obese children were divided into subgroups: simple (14.35±2 years, BMI<35 kg/m^2) and morbid obesity (15.6±1.6 years, >35 kg/m^2)). Patients underwent determination of dopamine, ghrelin, serotonin, neuropeptide Y, leptin and insulin levels with calculation of HOMA-IR. Results were processed using SPSS 18.0. **Results:** Obese children showed a significant increase of dopamine values increase with increasing BMI as compared with the control ((pa-k=0.012), (pm-k=0.0001) (pa-m=0.009)). Leptin levels children with morbid and alimentary obesity were significantly higher than control ((pa-k=0.0001) (pa-m=0.0001), (pm-k=0.0001)). There were a significant decrease in the values of ghrelin in obese children ((pa-k=0.0001), (pm-k=0.0001)). A reduction of neuropeptide Y levels were showed in children with morbid and alimentary obesity compared to control ((pm-a= 0.0001), (pa-k=0.0001) (pm-a=0.1)). Leptin levels positively correlated with BMI (alimentary – rs=0.26, P=0.005; morbid – rs=0.57, P=0.0001) and HOMA-IR (alimentary – rs=0.24, P=0.04, morbid – rs=0.41, P=0.002). Serotonon, ghrelin and NPY levels in severe obese patients were correlated with the presence of parental obesity (rs=0.43, P=0.0 2, rs=−0.26, P=0.03 and rs=−0.39, P=0.03 respectively). **Conclusion:** Obese children had higher levels of dopamine and leptin with the reduction of NY and ghrelin concentrations.

P3-871

Body Composition and Metabolic Risk Factors in Preschool Children

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Background: Recently childhood obesity shows trends of lowering age at start. Preschool children are still very physically active. A possible association between total and abdominal obesity and metabolic risk at preschool age could be of value for preventive measures. **Objective and hypotheses:** To investigate the relationship between body composition and some metabolic risk factors at preschool age. **Method:** A total of 40 (50% boys) healthy preschool children were invited for participation (mean age 5.31±0.74 years). Body weight, height and waist circumference (WC) were measured using standard procedures. BMI was assessed by CDC references. A questionnaire was filled in by the parents. Children's physical activity was measured by pedometry. Fasting blood samples were collected and lipids, BGL, insulin, SHBG, adiponectin (ADN), leptin were measured. DXA of the fat mass (FM) was performed. **Results:** Children with overweight/ obesity were 30% of all (17.5% obese), and 10% were underweight. Children completing the recommendation for at least 10 000 steps/daily during the week were 9.7%, and during the weekends – 16.1%. FM (g) correlated positively with BMI and WC (P<0.001). When the IDEFICS reference (www.ideficsstudy.eu) was used to rank ADN results as low (first quartile), lower levels of adiponectin correlated with weight, BMI and WC (P<0.001), with fasting insulin (r=0.458, P=0.032) and HOMA-IR (r=0.533, P=0.015). There was a significant correlation between FM and lower ADN (r=0.737, P<0.001) and with the same approach with elevated leptin levels (r=0.602, P=0.005), as well as with elevated triglycerides (r=0.461, P=0.041), controlled for sex and age. Lower ADN correlated also with tissue fat (r=0.432, P=0.045), FM (r=0.469, P=0.028), and with WC (r=0.490, P=0.021), after controlling for physical activity. SHBG correlated inversely with weight (r=−0.428, P=0.033), BMI (r=−0.449, P=0.025) and WC (r=−0.540, P=0.005). **Conclusion:** To summarise, metabolic risk in preschool children is established and highly associates with both FM and physical activity. **Funding:** This work was supported by the Ministry of Health Fund 'Medical Science'.

P3-872

Evaluation of Alternatives to OGTT to Assess Glucose Intolerance and Diabetes in an Obese Paediatric Population

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Background: Screening for glucose intolerance (GI) or type 2 diabetes (T2D) is recommended for obese children over 10 years of age (or onset of puberty) in the presence of ≧2 of the following risk factors: family history of T2D in a first- or second-degree relative, high risk ethnicity, signs of insulin resistance (IR) or associated conditions, or maternal gestational diabetes. The diagnostic importance of HbA1C levels is still controversial in children and adolescents. **Aims and objectives:** To evaluate the prevalence GI and T2D among a cohort of obese paediatric patients in Switzerland using Oral Glucose Tolerance Test (OGTT), and to assess the utility of alternative tests (i.e. single fasting blood sample for glucose, insulin, HOMA-IR and HbA1C) as compared to the OGTT. **Methods:** All the patients with a BMI *z*-Score above +2 S.D.s (WHO references) had OGTT and HbA1C measurement performed. Risk factors for diabetes were evaluated. **Results:** 148 patients included: mean age was 12 (range 3.2–18) and mean BMI *z*-score was +2.92 S.D.s (range 2.0–12.9). 34 patients (23%) had normal OGTT, 84 (57%) had IR, 28 (19%) had GI and 2 (1.4%) had T2D. 19 patients (68%) of the GI group and both T2D patients had normal fasting glucose levels. Ten patients (7%) had HbA1C ≧7.5% and poor correlation with OGTT diagnosis of GI or T2D. Among the patients diagnosed with GI, 13 (46%) did not belong to the risk-group according to the ADA guidelines, nor did the two patients diagnosed with T2D. **Conclusions:** 20% of this large cohort of obese Swiss children had either GI or T2D when tested with OGTT. Remarkably, more than half would have been missed using fasting glucose measurements alone. Further, HbA1C level in children does not seem to correlate well with the diagnosis obtain with OGTT. Additional statistical analysis is ongoing to further elucidate these results.

P3-873

Sex Differences in the Pubertal Response to High-Fat Diet

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Background: It is well known that ingestion of a high fat diet (HFD) can induce rapid weight gain and metabolic imbalances. However, males and females are not equally susceptible to these effects. Furthermore, an individual may be more prone to gain weight during specific developmental periods. **Aims and objectives:** We aimed to analyse the response to the acute exposure to a HFD during pubertal/adolescent period and to determine whether males and females respond differently. **Methods:** Adolescent C57bl/6 mice of both sexes were placed on a HFD or low fat diet (LFD) for eight days. Body weight, adipose tissue mass and glycaemia were measured at sacrifice and serum was collected. Serum insulin, leptin, interleukin (IL)6 and TNFα levels were determined by multiplex assays. **Results:** A greater number of kilocalories were ingested by the HFD group compared to the LFD groups of both sexes, with this being significant in females ($P<0.03$), and with males eating more than females regardless of diet ($P<0.0001$). No significant effect on weight gain or adipose tissue mass was found. However, HFD increased glycaemia in males (HFD: 132±7 vs LFD: 100±5 mg/dl; $P<0.002$), but not in females (HFD: 106±6 vs 100±3 mg/dl). Although insulin, leptin and TNFα levels increased with the HFD, especially in males, this was not significant. In contrast, IL6 levels decreased with HFD in males ($P<0.002$). **Conclusion:** During the pubertal/adolescent period in mice, there is a rapid response to HFD intake with males being more susceptible than females. **Funding:** This work was funded by grants from Fondos de Investigación Sanitaria (PI100747; PI1302195), Ministerio de Ciencia e Innovación (BFU2011–27492), Centro de Investigación Biomédica en Red Fisiopatología de Obesidad y Nutrición (CIBEROBN), Instituto de Salud Carlos III, and Fundación de Endocrinología y Nutrición.

P3-874

Relation between Thyroid Function Tests and Cardiometabolic Risk Factors in Childhood Obesity

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Background: It is known that obese children are at higher risk in terms of cardiovascular diseases when compared with normal weight children. Recent studies emphasizes on the fact that there is a relation between TSH and several cardiovascular risk factors in obese children. **Objective and hypotheses:** The aim of the study is to investigate the relation between cardiometabolic risk factors and thyroid function tests in obese children. **Method:** 148 obese children with a BMI > 95 percentile, 128 overweight children with a BMI between 85 and 95 percentile and 142 children with a BMI < 85 percentile were evaluated in terms of thyroid function tests and cardiometabolic risk factors. The mean age of patients was 11.2±2.3 years (range: 7–18 years). BMI, waist circumference, systolic and diastolic blood pressures, serum lipid levels, fasting blood glucose and insulin levels, CRP, homocystine, lipoprotein A, fibrinogen levels were evaluated as cardiometabolic risk factors. OGTT was done in order to evaluate glucose metabolism disorders. **Results:** When compared with normal weight children, TSH levels were higher, sT_4 levels were lower and sT_3 levels were higher in obese children. When the obese patients were divided into three groups according to the severity of obesity as slight-moderate–severe, sT_4 levels were lowest and TSH levels were highest in the severely obese group when compared with the other

two groups and control group. A significant positive correlation was found between TSH levels and BMI-SDS, waist circumference, systolic blood pressure, HOMA-IR, serum triglyceride, total cholesterol, LDL, homocystein, lipoprotein a levels. When corrected according to age, gender, puberty stage and BMI-SDS, it was found that TSH was correlated with impaired glucose tolerance, impaired fasting glucose and insulin resistance. **Conclusion:** The thyroid function dysfunction and increased TSH levels in obese children could be related to dyslipidaemia, insulin resistance, impaired glucose metabolism and other increased cardiometabolic risk factors.

P3-875

İnsulin Infusion Treatment Option in Severe Hypertriglyceridaemia Induced Pancreatitis

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Background: The risk of pancreatitis increases when triglyceride levels rise above 1 000 mg/dl. This requires particular attention in subjects with type 2 diabetes, which is accompanied by elevated triglyceride levels in one in every two patients. Apheresis, a treatment option in pancreatitis developing secondary to hypertriglyceridemia, is expensive and not available in every centre. Another option, heparin administration, may result in rebound hypertriglyceridaemia. Thirdly, continuous insulin infusion is an alternative option in these patients. **Case presentation:** Continuous insulin infusion was applied in the treatment of pancreatitis developing secondary to severe hypertriglyceridemia (6 695 mg/dl) in an adolescent who had been diagnosed with type 2 diabetes several years previously but had been left untreated. He was screened for lipoprotein lipase mutation and no mutation was detected. At the 14th h of infusion, triglyceride levels decreased by 80% (to 1 110 mg/dl), with no complications. **Conclusion:** Insulin infusion is an inexpensive, fast and safe form of treatment in severe hypertriglyceridaemia induced pancreatitis.

P3-876

Obesity has a Significant Impact on Hyperandrogenemia Only after Puberty in Korean Girls

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Background: As metabolic complication and polycystic ovarian syndrome due to childhood obesity is rising, the role of hyperandrogenemia (HA) and hyperinsulinism is receiving attention. **Objective and hypotheses:** The aim of this study was to investigate the presence or absence of obvious HA according to pubertal status and to find potential etiologic determinants of HA in Korean obese girls. **Method:** We analysed 91 subjects aged 6–17 years (prepuberty, $n=54$; puberty, $n=37$). Each girl was classified as being either normal weight (NW) or obese (OB) according to Korean growth standard. Blood test was performed early in the morning after at least 8 h of fasting to measure glucose, insulin, androgens, gonadotropins, and sex hormones. **Results:** Hyperinsulinaemia and high homeostasis model assessment of insulin resistance (HOMA-IR) values were found regardless of pubertal status in OB girls. The plasma levels of free testosterone (FT) and dehydroepiandrosterone sulfate (DHEAS) were markedly higher in OB girls compared to NW girls in puberty (FT, $P=0.018$; DHEAS, $P=0.060$) but not in prepuberty (FT, $P=0.127$; DHEAS, $P=0.180$). The significant related factor to HA in puberty was the body mass index z-score ($P=0.002$) and progesterone level ($P=0.003$). But HOMA-IR, luteinising hormone levels were not relevant to HA in pubertal girls. **Conclusion:** Since OB pubertal girls had HA, further follow-up is mandatory to see the metabolic and reproductive consequences and to determine whether weight control is the important factor for prevention of HA-related complications. And OB prepubertal girls did not show HA in the present study but they should be regularly monitored because they already had hyperinsulinaemia.

P3-877

Higher Hb1Ac in Obese Prader-Willi Syndrome Patients vs Obese Controls

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Background: Obesity in Prader-Willi Syndrome has peculiar features associated to reduced lean body mass which could confer different metabolic characteristics. **Objective and hypotheses:** The aim of this study is to describe and to compare the metabolic profile in obese patients and obese Prader-Willi syndrome patients (OPWS) followed in a Pediatric Endocrinology outpatient clinic. **Method:** 45 obese and 22 OPWS patients between 8 and 20 years old were evaluated in a cross-sectional study. We compared them according to cholesterol and triglycerides levels, as well as glycated hemoglobin (A1c) and fasting glucose. **Results:** The mean age of the 67 patients was 14.1 ($\pm$3.2) years old, 45 are male and the mean z-BMI was $+$3.1DP ($\pm$0.6DP). Both groups did not differ in gender, age and z-BMI. The metabolic profile in OPWS vs obese patients showed: higher LDL-c level (LDL-c$\geqq$130 mg/dl) 18.2$\times$11.1%, lower HDL-c level ($<$40 mg/dl) 36.4$\times$46.7%, and lower hypertriglyceridemia ($\geqq$150 mg/dl) 13.6$\times$24.4% respectively; but there was no significant difference between both groups. There was a significant difference ($P<0.001$) in abnormal Hb1Ac ($\geqq$5.8%) between OPWS (73.3%) and obese patients (7.1%). Only one patient in each group had high fasting glucose ($>$100 mg/dl). **Conclusion:** There is a high prevalence in both groups of inappropriate cholesterol levels. Moreover, Hb1Ac could be an important tool to evaluate glycemic profile in OPWS patients.

P3-878

Obese Children and Adolescents: Reasons for Non-compliance with Follow-up Scheduling

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Background: Non-compliance is a major issue for treatment failure in childhood obesity. **Objective and hypotheses:** To identify the barriers of adherence to weight management programs, of obese children and adolescents. **Method:** A descriptive, ongoing study based on phone recorded questionnaires with the use of information from the medical records. The study group consisted of 85 overweight and obese children and adolescents (M/F = 46/39) with mean present age 15.5 years (S.D. = 2.6), that failed to complete their weight management programs in a hospital based pediatric outpatient clinic. Analyses were conducted using SPSS statistical software (version 19.0). **Results:** 56% of the interviewees declared that they first visited the outpatient clinic on parents' initiative and 40% of them after a pediatricians' referral. 20% attended in order to investigate whether there was any medical pathology, 40% only for nutritional support and consultation and 40% for both. Mean percentage of fat at 1st visit was 38.3. Most common reasons for treatment abandonment were children's denial to return to the clinic (32.9%), difficulties in scheduling consultations due to parents and patients activities (29.4%) and long time of transportation (20.0%). In almost half of the cases (50.6%) there was a weight reduction in comparison to the one they had during treatment. However in 71.8% of the cases parents reported that their child was still overweight. In 15/85 children there were related disorders with most common being psychological ones and difficulties in getting dressed (ten/15 children). **Conclusion:** Time limitations both for the children and parents and practical difficulties are the main reasons for not completing the weight management program. Pediatric endocrine departments can collaborate with primary care providers and offer obesity clinics or group therapy at a local level in order to assure increased compliance with minimal inconvenience for the family.

P3-879

Cardiometabolic Risk Factors in Overweight/Obese Children and Adolescents and Family History of Cardiovascular Disease

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Background: Global prevalence of childhood obesity has increased from 4.2 to 6.7% in recent decades. Dyslipidaemia predisposes to cardiovascular disease (CVD) in adults. Family history (FH) of CVD is used as a screening tool for dyslipidaemia in children/ adolescents, however with controversial sensitivity. **Objective and hypotheses:** Purpose of the study was to identify and examine the effects of possible cardiovascular (CV) risk factors in overweight/obese (OW/O) and normal weight (NW) children/ adolescents with FH of CVD. **Method:** Anthropometrical, biochemical indices, FH of CVD were obtained from 68 healthy children/adolescents aged 7–13 years old. SPSS software was used for statistical analysis. **Results:** 35/68 were OW/O, 33 were NW.15/35 OW/O and 8/33 NW had positive FH of CVD. Systolic blood pressure (SBP), waist circumference (WC), triglycerides (Tg), hsCRP, fasting blood insulin (FBI) and HOMA-IR were found statistically significantly higher in the OW/O group compared to the NW one. High density lipoprotein (HDL-C), apolipoprotein A (Apo(A)) were statistically significantly lower in the OW/O children /adolescents compared to their normal peers. Paradoxically, total Cholesterol (TCh) was statistically significantly higher in the NW children/adolescents. FBI, hsCRP levels and WC were significantly higher in the OW/O children/ adolescents with FH of CVD compared to the ones without. No difference was found between OW/O and NW groups in low density lipoprotein (LDL-C), fasting glucose, apolipoprotein B (Apo(B)) and diastolic blood pressure (DBP). TCh and SBP were found to be independently associated with obesity (negatively, OR = 1.965(1.935, 2.97), $P < 0.031$ and positively OR = 1.045(1.016, 1.074), $P < 0.002$ respectively). FH of CVD was not related to any CV risk factors. There was a trend that controls have breastfed longer and their parents had lower BMI values. **Conclusion:** Dyslipidaemia, insulin resistance, elevated SBP and increased WC appear in OW/O children/adolescents. Using a FH of CVD to screen for dyslipidaemia misses a significant percentage (30–60%) of children with dyslipidaemia. Universal screening of lipid profiles in children is recommended. Preventing obesity can lead to lower CV risk in children/adolescents.

P3-880

Healthcare Professionals' Perception of Overweight in Preschool-aged Children

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Background: Childhood obesity is still increasing worldwide. Early recognition of overweight or obesity in children by healthcare professionals is of utmost importance, allowing interventions to start at a young age. **Objective and hypotheses:** We studied whether healthcare professionals adequately perceive preschool children's overweight and whether this is influenced by their own BMI. **Method:** Healthcare professionals received a

questionnaire containing pictures and sketches of seven preschool children with body weights ranging from underweight to morbidly obese. The professionals rated the pictures on a five-point scale from 'too heavy' to 'too light'. Concurrently, at each picture, healthcare professionals assigned one from sevne sketches most adequately depicting the child's body shape. Healthcare professionals' height and weight were self-reported and BMI was calculated. Groups were made based on quartiles: low (Q1), average (Q2 and Q3), or high BMI (Q4). **Results:** Of the 716 questionnaires, 353 (49.3%) were returned and 346 (48.3%) were used for analysis. Healthcare professionals most often chose sketches lighter than the correct one. Depending on the healthcare professionals' BMI group, the overweight child was perceived as 'normal weight' by 74–79% of the healthcare professionals. The obese children were rated correctly by 44–52% of the healthcare professionals, but as 'normal weight' by 14–15% of them. The morbidly obese child was adequately assessed by 93–98% of the professionals. Healthcare professionals in the lowest BMI group less frequently perceived the underweight child as too light, compared to professionals in the average BMI group ($P=0.01$). **Conclusion:** Independently of their own BMI, healthcare professionals are unlikely to adequately perceive overweight in preschool-aged children. The lack of identifying overweight or obese children may hinder early intervention. **Funding:** The study was sponsored by an unrestricted grant from Hutchison Whampoa Limited, Hong Kong. The study sponsor had no role in i) the study design and conduct; ii) the collection, management, analysis and interpretation of the data; iii) writing the abstract; and vi) the decision to submit the abstract.

P3-881

Evaluatıon of the Relationship between Serum Adropın Levels and Blood Pressure in Obese Children

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Background: The prevalence of obesity and related cardiovascular comorbodities are increasing rapidly. Adipokines play the major role on the pathogenesis of obesity related inflammation and hypertension. **Objective and hypotheses:** The aim of the study was to evaulate the serum adropin levels in obese children and to determine the relationship between adropin levels and blood pressure in pediatric age group. **Method:** 40 obese children (mean age: 12.5 ± 2.5 years; male/female ratio: 18/22) and 15 healthy control (mean age: 15 ± 3.14 years; male/female ratio: 5/15) were included to the study. Serum adropin levels, laboratory and clinical variables were compared. Ambulatory blood pressure monitoring were performed to obese subjects. Relationship between adropin levels and blood pressure variables were examined. **Results:** Serum adropin levels were significantly lower in obese subjects than healthy controls (193.56 ± 94 vs 289 ± 187 pg/ml, $P=0.03$). Adropin levels were correlated negatively with BMI z-score ($r=-0.56$, $P=0.034$). There were no correlation between serum adropin levels and laboratory data in obese subjects. Five of the patients (12.5%) were non-dipper, nine of the patients (22.5%) had hypertension. There were no significant correlation between serum adropin levels and blood pressure data. **Conclusion:** Serum adropin levels were significantly lower in obese children, however there were no correlation between serum adropin levels and blood pressure variables. Further studies are needed to determine the role of adipokines on blood pressure.

P3-882

Adipocyte Fatty Acid Binding Protein is Related to Weight Status and Metabolic Risk Markers in Childhood Obesity

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Background: Adipocyte fatty acid binding protein (aFABP) regulates intracellular transport of fatty acids and seems to be involved in the pathogenesis of the Metabolic Syndrome. aFABP overproduction leads to increased cholesterol and triglyceride accumulation and to higher expression of pro-inflammatory genes. In adults aFABP seems to promote insulin resistance and atherosclerosis, and aFABP levels are significantly higher in obese compared to lean subjects. Fat mass, lipid markers and inflammatory markers are also associated with aFABP levels. However, metabolism of aFABP in children/adolescents is poorly understood. **Objective and hypotheses:** We investigated the correlation between circulating aFABP and several markers of weight status and of metabolic risk in a well characterized cohort of overweight or obese adolescents. **Method:** 28 adolescents aged 13.5–18.5 years with a BMI $\geqq$ 90th percentile according to national reference values were included. Weight, height, waist and hip circumferences were measured following standardized procedures, and a fasting blood sample was taken to measure insulin, glucose, transaminases, lipids, free fatty acids, uric acid and aFABP. Pearson's correlation and linear models were determined using the R package. **Results:** aFABP was correlated with BMI-SDS (0.48 (0.13, 0.72); $P=0.0095$) and waist-to-height ratio (WHtR) (0.63 (0.33, 0.81), $P=0.00036$). A correlation was also observed with HOMA-IR (0.52 (0.19, 0.75), $P=0.0044$) and the dependence remained significant after correcting for sex and pubertal stage. Some markers of metabolic risk were significantly correlated (γGT 0.48 (0.13, 0.73), $P=0.0091$; uric acid 0.46 (0.11, 0.71) $P=0.013$; HDL-C -0.39 (-0.66, -0.01) $P=0.043$; triglycerides 0.38 (0.01, 0.66), $P=0.047$), whereas others were not (cholesterol $P=0.32$; LDL-C $P=0.12$; free fatty acids $P=0.68$). aFABP did not depend on gender, age or pubertal stage in obese adolescents. **Conclusion:** Our data provide evidence that aFABP in obese adolescents – as in adults – is associated with weight status as well as insulin resistance and metabolic risk markers. **Funding:** This work was supported by the Federal Ministry of Education and Research, Germany (Integrated Research and Treatment Center IFB 'AdiposityDiseases,' FKZ: 01EO1001).

P3-883

Investigating Predisposing Factors for Childhood Obesity

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Background: Childhood obesity is considered to be an epidemic in developed countries that can negatively affect children's health and psychology. **Aims and objectives:** To investigate the nutritional and environmental factors that lead to the presence of childhood obesity and its complications. **Methods:** A total of 949 students, 3–12 years old, living in Sparta–Greece, have participated in our research. Their lifestyle and eating habits were determined by using specially designed questionnaires. Anthropometric and blood pressure measurements were performed. **Results:** 33% of children were classified as overweight or obese, while 65% had waist circumference (WC) % $>$90%. 36% of the boys and 29.9% of the girls were found overweight or obese ($P=0.05$). As for the eating habits, 8% of the total population does not eat breakfast, 15.5% eat 'fast-food' more than four times a week, 30% consume one fruit per week and 44% consume vegetables in a daily basis. With statistical significance ($P\leq0.05$) we observed all the following findings. BMI% was greater in children who skip breakfast, consume fruits, legumes, grains, rice, pasta, bread and dairy products as well as during a decreased consumption of vegetables. Overall, obese children tend to skip breakfast, consume more olive oil/olives per week, exercise less and have elevated levels of blood pressure. In boys, WC% was found to increase as the time of exercise per week decreases, while it seems to be affected by stress and anxiety as well. Females that breastfed had a decreased BMI%. BMI% was increased by 12 units in children that had an obese relative. **Conclusions:** In Greece, the high prevalence of overweight and obese children is regarded as a bizarre finding, since Mediterranean diet has been always associated with good health status. Consequently, there is rising awareness towards adopting proper health habits during childhood.

P3-884

Vitamin D Status in Iranian Obese and Non-obese Children

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Background: Vitamin D deficiency is now a critical issue due to its high prevalence and side effects. **Objective and hypotheses::** We assessed the serum vitamin D status of obese and non-obese children and comparing their therapeutic response to identical oral vitamin D consumption in Iran. **Method:** This study was performed in children aged 2–14 years at Children Medical Center of Tehran in Iran. At first, the serum 25-hydroxy vitamin D level was measured in 45 obese and 45 non-obese children. Afterward, all the children with low serum 25-hydroxy vitamin D were treated by 50 000 IU of vitamin D3 as a pearl once a week for 6 weeks. Meanwhile, the prevalence of vitamin D deficiency before and after treatment was determined. **Results:** The study revealed that 95.6% of obese and 66.6% of non-obese children were suffering either vitamin D deficiency or insufficiency ($P<0.001$). After oral treatment of 74 cases, measuring of the vitamin D level illustrates promising improvement for the latter group (decreased from 66.6 to 3.3%) while 55.8% of the obese group are still suffering low vitamin D level ($P<0.001$). **Conclusion:** This study demonstrates a high prevalence of vitamin D deficiency among Iranian children, particularly the obese ones. Moreover, low therapeutic response in the obese group was witnessed.

P3-885

Is vitamin D Important Player in Hepatosteatosis in Childhood Obesity?

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Background and aim: Childhood obesity is one of the most serious public health problem. Obesity-related complications such as hepatic steatosis or type 2 diabetes can now be monitored even during early childhood. The aim of the study was to examine the relationship between vitamin D levels and obesity with hepatosteatosis (HS) in children. **Methods:** A total of 128 children with obesity were included in this study. HS was diagnosed using ultrasonography. HS was graded. 25-hydroxyvitamin D, calsium, phoshate alkaline phosphatase, parathormone, serum lipid level, glucose and insuline level were measured. Data were analysed using two categories; obesity with HS and obesity without HS. **Results:** A total of 128 children were studied. In our study group 42% was male and the mean age 12.1 + 3.1 (range 4–18 years) HS was identified in 39% (*n*: 50) There was a high prevalence (122/128 95%) of vitamin D deficiency or insufficiency; however, there were no significant associations between vitamin D level and HS. Uric acide, ALT, trigliseride level were significantly different in two groupes. **Conclusions:** There is a high prevalence of vitamin D deficiency and insufficiency in children with HS however, no association was found between vitamin D deficiency and HS.

P3-886

Obesity in School Children of Zahedan-Iran; Double Burden of Weight Disorders

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Background: Obesity has a permanent effect on children's health and acts as a major risk factor for chronic diseases. Therefore considering the children's BMI is a vital parameter at each visit. This study was performed to measure prevalence of obesity and its determinants in school children of Zahedan in Iran; Zahedan is the capital of Sistan-and-Balouchestan province which is known to have the highest prevalence of underweight in Iranian children. **Methods:** This cross-sectional study was performed on 3 582 school children among which 1 786 were girls and 1 796 were boys. The students were aged between 6 to 13 years old and were selected based on a stratified random method. The BMI was measured for each student and being overweight/obesity was determined based on CDC 2000 definitions. Prevalence proportions were estimated by weighing the sample. The study was done at the primary and guidance schools of Zahedan; samples were stratified from two geographic regions of Zahedan (zone 1 & 2). **Results:** In the sample, 78.9% were under 85th percentile, 11.8% were overweight (85th–95th percentile) and 9.3% were obese (>95th percentile). Weighted estimate for prevalence of obesity/overweight in girls, boys and all 6–13 years old students were 16.2, 18.4 and 17.4% respectively. Presence of overweight/obesity was related to school type (private to public schools OR=2.13, 1.80–2.52) and increasing age (OR=1.12, 1.04–1.20). **Conclusions:** A high prevalence of obesity was found in Zahedan students. Concurrent high prevalence of obesity/overweight and underweight demonstrates amplitude of weight problems in school children. The results of this study show an urgent need for special health programs to conduct proper diagnosis and management of obesity in Zahedan.

P3-887

Sports Regulated and Lipid Profile in Children and Adolescents with Overweight

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Introduction: Obesity is the most common nutritional disorder in the paediatric age. Decreased physical activity and increased inactivity are important factors that are involved in this pandemic. The highest prevalence of obesity in Europe is in the South. **Objective:** To study the relationship between the practice of a regulated sport and lipid profile in overweight children and adolescents. **Material and methods:** 318 overweight children, age range 3–17 years (11.07±2.7), attending the Pediatric Nutrition consultation of a tertiary hospital. 42.5% are male. Anthropometry was performed and the sample was stratified according to the international standard of Cole. Physical activity is assessed using a validated questionnaire that collected belonging to a sports club and time spent at the same. Serum cholesterol (CT) and triglycerides (TG) are determined by ADVIA 2400 and HDL-C and LDL-C by cellulose acetate electrophoresis HELENA. Statistical Analysis SPSS19. **Results:** 61.9% of children are obese. 36.8% of the sample belongs to a sports club. Children belonging to a sports club have a lower BMI (25.4 vs 27.1 k/m^2, ns) and lower CT(162.7 vs 168.2 mg/dl, ns) and LDL-c (97 vs 101.7 mg/dl, ns) and HDL-c (48.3 vs 44 mg/dl, $P=0.001$) significantly higher. In the group of children belonging to a sports club and play sports more than 3hr a week showed no differences in BMI (25.2 vs 25.7 k/m^2, ns). However, these children showed higher serum levels of HDL-c (49.7 vs 46.3 mg/dl, ns) and lower levels of LDL-c (101.3 vs 103.3 mg/dl, ns) and TG (66.7 vs 73.5 mg/dl, ns) than children playing less than 3 h a week. **Conclusion:** Regulated sport improves lipid profile in overweight children, independently of BMI and specially by increasing HDL-c levels. The spent time in sport seem play an important role in the improving of lipid profile. Therefore the promotion of the regulated physical activity during a adequate time should form part of strategies for prevention of metabolic risk in paediatric obesity. **Funding:** Proyecto De Investigacion En Salud (FIS2011). 'Asociación Entre Biomarcadores De Estrés Oxidativo, Inflamación, Riesgo Cardiovascular Y Variantes Génicas En Niños Obesos'. Investigador coordinador: Dra M Gloria Bueno Subproyecto i) Dra. Gloria Bueno, Subproyecto ii) Dra Rosaura Leis Trabazo, Subproyecto iii) Dra M[a] Concepción Aguilera. Número de expediente:PI11/02059. Años:2012–2014. Cuantía: 35.530,44.

P3-888

Weight and the Factors Influencing it in a Cohort of School Aged Children

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Background: Weight disturbances in children are an important problem, both underweight and obesity having important health consequences. There is an ongoing debate about their cause, the risk factors involved and the need for public health policies focused on their prevention. **Objective and hypotheses:** The aim of this study was to estimate the prevalence of weight disturbances in a cohort of school-aged children and to analyse some factors considered to play a role in their aetiology. **Method:** An observational study was conducted in 16 schools in Mures County, Romania, between November 2013 and May 2014, on a random sample of 1923 children 6–14 years of age. Variables analysed: ages, sex, environment, birthweight, gestational age, and BMI S.D. score. **Method:** Each child was measured and weighted using metrological checked instruments and a legal representative had to fill in a questionnaire regarding perinatal factor upon signing the written consent. The WHO and Swiss BMI charts were used for anthropological assessment. Statistical analysis used M.O. Excel and MedCalc v. 12.5 with a level of significance of 0.05. **Results:** The prevalence of underweight was 2.81% (WHO) and 2.86% (Swiss). Overweight and obesity had a prevalence of 9.57 and 5.04% respectively (WHO charts). Boys have a higher probability of being overweighed (OR 1.45, CI 1.06–1.97, $P=0.01$), but not underweight (OR 1.14, CI 0.68–1.92, $P=0.61$). Prematurity or low birth weight are not associated with higher odds of weight disturbances. Children from rural areas have higher odds of being underweight (OR 2.15, CI 1.27–3.65, $P=0.0014$). There is a significant difference in the prevalence of overweight adjusted for age ($P=0.005$). **Conclusion:** From the various factors analysed sex was the only significant one influencing weight disturbances in school aged children.

P3-889

Dietary Patterns in a Group of Obese Children

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Background: Obesity and overweight are important disturbances, considering their consequences, especially in children. Diet composition is an important factor involved in weight management. **Objective and hypotheses:** The aim of this study was to analyse the food pyramid and dietary patterns of obese children. **Method:** An observational study was conducted targeting obese children from Romania. The study included 63 children, age 3–18, who presented to the endocrinology clinic from February 2013–April 2014. Variables: age, sex, environment, food pyramid. Method: each legal representative filled a food frequency questionnaire with 126 items regarding the child's diet and each child had his height and weight measured using validated tools. A web-based nutritional assessment tool was used for FFQ analysis, which returned the food pyramid and diet composition analysis. **Results:** Sex ratio favoured girls (1.36:1) and the mean age was 9.4 ± 3.5 years. All the children were above the 99th percentile in BMI. The average food pyramid followed the recommended number of portions for cereals and fruits & vegetables, but for sweets, fat and meat the number of portions was above recommendations. There are only minor differences in dietary patterns of boys vs girls (oranges as the most often fruit), but on a more detailed analysis, girls eat more vegetables than boys and healthier cereals. Children in rural areas tend to choose unhealthier foods. **Conclusion:** Obese children eat too many portions of sweets, fat and meat, choose the unhealthy options from the cereal and eat fruits more likely than vegetables. Web-based nutritional assessment tools are an easy option for diet evaluation, even in small children.

P3-890

Does Vitamin D Influence Energy Metabolism in Children and Adolescents?

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Background: Recent years bring a lot of data of the important role of vitamin D in different physiological processes, including a prevention from pathological states. **Objective and hypotheses:** The aim of the study was to analyze associations between serum level of vitamin D and some markers of glucose and lipid metabolism but also as well bone-related molecules as adipokines and in children and adolescents. **Method:** 57 patients, 40 with type 1 diabetes mellitus (T1DM), 17 with obesity, and 11 control, healthy age- and BMI-matched children were included in the study. Fasting blood samples for measurement of vitamin D, lipid profile, glucose, HbA1c concentrations, but also as well bone derived sclerostin, osteocalcin (OC) and Receptor Activator of Nuclear Factor NF-κB ligand (RANKL), as fat tissue-derived leptin and adiponectin were taken at 0800 h. Vitamin D was measured by HPLC, hormones by immunochemistry, and other parameters by routine chemistry methods. Statistical analysis was performed in all groups using ANOVA with post-hoc Turkey test and multiple regression analysis. **Results:** Vitamin D levels did not differ among three groups: patients with T1DM, obese patients, and healthy ones. There were significant differences regarding C-peptide, HbA1c, fasting glucose, leptin, LDL-cholesterol, HDL-cholesterol, HDL-cholesterol/total cholesterol levels among groups $P<0.001$. In multiple regression analysis vitamin D was negatively related to HOMA index in obese children ($p=0.01$). The partial regression coefficient of vitamin D for HOMA-IR was strong ($r=-0.64$). In the group of patients with T1DM vitamin D correlated negatively with HbA1c ($r=-0.3$, $P=0.03$). In the control group vitamin D was positively related to OC ($P=0.028$). **Conclusion:** The results of our study suggest that vitamin D could influence energy metabolism in children and adolescents. Its action seems to be associated with as well insulin action as with bone-derived OC. **Funding:** This study was supported by a grant nr K/ZDS/001812, from Medical College, Jagiellonian University in Cracow.

P3-891

Bone Age Assessment and Glucose Metabolism in Overweight and Obese Children

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Background: Bone age (BA) tends to exceed chronological age (CA) in obese children. There are studies showing that insulin may directly influence skeletal growth. Objective: To determine whether there is an association between BA and glucose metabolism in a group of overweight and obese children. **Methods:** The study included 55 obese or overweight children, mean age: 11.56 ± 3.07 years old. Anthropometric indexes (weight, height, BMI, waist circumference, weight to height ratio), glucose metabolism (fasting insulin, fasting glucose, oral glucose tolerance test, HOMA-IR) were evaluated. Advanced BA maturation was defined as the third percentile with BA: CA > 1.2. **Results:** BA was significantly advanced only in 10.90% ($n=6$) of the children in the studied group. All were in the prepubertal stage, with a mean age of 10.53 ± 1.43 years and the male to female ratio was 5:1. Hyperinsulinaemia was found in 23.63% ($n=13$) of children but only one (7.69%) of these, had a significantly advanced BA. Children with advanced BA and hyperinsulinism or alterations of the glucose metabolism had a lower Height *z*-score than children with bone advancement in the lower tertiles. No correlation between BMI *z*-score, HOMA – IR and advanced BA was found ($P \geqq 0.05$). **Conclusion:** Hyperinsulinaemia and alteration of the glucose metabolism could be associated with advanced BA in obese children independent of the degree of obesity. Further studies are needed to establish other metabolic factors that are involved in modulating the skeletal growth in obese children.

P3-892

The Triglyceride-to-HDL Cholesterol Ratio is Associated with Insulin Resistance in Obese Boys But Not in Obese Girls

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Background: Children and adolescents with obesity often have insulin resistance (IR) and are at increased risk to develop coronary heart disease (CHD) in adulthood. The triglyceride to HDL-cholesterol (TG/HDL-C) ratio reflects small, dense low-density lipoprotein (LDL), an atherogenic lipoprotein particle that strongly predicts CHD. **Objective and hypotheses:** To evaluate the TG/HDL-C ratio in obese children and adolescents and study the relationship with age, the degree of obesity and IR. **Method:** Data from 125 obese children and adolescents (71 girls; mean ± S.D. BMI SDS: 2.9 ± 0.4) aged 10–18 yrs (13.7 ± 1.8 years) were studied. Fasting plasma glucose, serum insulin, HDL-C and TG concentrations were measured. IR was assessed by the HOMA-IR. **Results:** 18 (25%) girls and 17 (23%) boys had TG levels above 150 mg/dl. 23 (32%) girls and 28 (38%) boys had HDL-C levels below 40 mg/dl. TG levels were inversely related to HDL-C in girls ($r=-0.283$; $P=0.017$) and in boys ($r=-0.329$; $P=0.004$). The TG/HDL-C ratio was not related to age, neither in girls ($r=0.113$; $P=0.349$) neither in boys ($r=0.136$; $P=0.249$), nor to BMI-SDS, neither in girls ($r=-0.048$; $P=0.689$) neither in boys ($r=-0.081$; $P=0.494$). The TG/HDL-C ratio was significantly related to the HOMA-IR in boys ($r=0.299$; $P=0.010$), but not in girls ($r=0.129$; $P=0.288$). **Conclusion:** The TG/HDL-C ratio is not associated with the degree of obesity nor with age in obese children and adolescents. In obese boys it is associated with the HOMA-IR, but not in girls. Our findings suggest that in obese boys the TG/HDL-C ratio may serve as a clinically useful determinant to identify those patients who are IR and at increased risk to develop future CHD. **Funding:** This study is part of the Limburg Clinical Research Program (LCRP) UHasselt-ZOL-Jessa, supported by the foundation Limburg Sterk Merk, Hasselt University, Ziekenhuis Oost-Limburg and Jessa Hospital.

P3-893

Experience with Sleeve Gastrectomy in Adolescent Obese Subjects and in Prader-Willi Syndrome

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Background: Prader Willi syndrome (PWS) results from the loss of paternally imprinted genes on chromosome 15q11–15 and is characterized by neonatal hypotonia, short stature, hypogonadism, aggressive food-seeking behavior, hyperphagia, and obesity with difficult in losing weight only with nutritional approach. **Objective and hypotheses:** We report our experience on sleeve gastrectomy in PWS and obese subjects during 12 months of follow-up. **Method:** Three PWS (two males; aged 15.9 ± 4.4 years; range 10.9–19.3) and six age matched obese controls (OB; one male; aged 15.6 ± 2.8; range 10.5–18.5). PWS showed basal mean BMI 43.1 ± 0.9, BMI S.D. 4.5 ± 1.4, waist circumference 107 ± 21 cm, HbA1c 44.7 ± 8.3 mmol/mol, HOMA-IR 13.8 ± 19.4. OB showed basal mean BMI 57.2 ± 17.8 ($P<0.05$ vs PWS), BMI S.D. 7.5 ± 2 ($P<0.05$ vs PWS), waist circumference 120 ± 9.1 cm, HbA1c 36.4 ± 2.4 mmol/mol, HOMA-IR 5.0 ± 2.0 ($P<0.01$ vs

PWS). One PWS has type 2 Diabetes treated with biguanides and GLP1 agonists and one OB showed IGT. None of pts was treated with GH. Ethic Committee and informed consents were obtained. **Results:** After 12 months from surgery, PWS pt with type 2 Diabetes normalized glycaemia and HbA1c and stopped therapy, as pt obese with IGT. One PWS pt did not lose weight during follow-up. After 1 year PWS showed mean BMI 37.6±4.6, BMI S.D. 3.7±1.7, waist circumference 98±15.5 cm, HbA1c 38±6.2 mmol/mol, HOMA-IR 2.0±0.9. OB showed mean BMI 39.5±7.4, BMI S.D. 6.1±0.6 ($P<0.05$ vs PWS), waist circumference 106.8±8.8 cm, HbA1c 33.0±1.7 mmol/mol, HOMA-IR 3.5±2.3. One obese pt developed reflux and vomiting controlled by diet and anti-reflux therapy. **Conclusion:** Our data, although preliminary showed that sleeve gastrectomy in adolescent with PWS, as in obese patients, improve positively BMI, and may normalize glycemic control and insulin resistance. No statistically difference were found among parameters but this result can be influenced by the very small sample and the widespread distribution of data. These results need to be confirmed on higher number of pts with a longer follow up.

P3-894

Metabolic Syndrome and Inflammatory Markers in Obese Children at Chiang Mai University Hospital

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Background: Inflammatory markers in obesity with metabolic syndrome (MS) have been postulated to be associated with development of CVS diseases in adults. **Objective:** To study inflammatory marker levels in obese children. **Method:** A cross-sectional study of obese children was conducted. Children with history of endogenous obesity, chronic diseases, drug ingestion/any acute illnesses within two weeks prior to enrolment were excluded. Fasting blood sugar (FBS), OGTT, insulin, lipid profiles, and inflammatory markers were studied. **Results:** 58 obese children (20 females/38 males) with a mean BMI *z*-score of 5.1±2.2 were enrolled. The prevalence of pre-diabetes and MS were 17.2 and 31% respectively. No case met the criteria diagnosis of diabetes. Although FBS, OGTT, lipid profiles, and HS-CRP level were not statistically different between obese children with and without MS, 69% of the cases had high hs-CRP level compared to normal values. **Conclusion:** Obesity without MS could be at risk to develop CVS diseases due to high level of the inflammatory marker, HS-CRP. Early weight reduction in children with obesity should be emphasized on primary care physicians and their families. **Funding:** This study has been fully supported by the Faculty of Medicine Endowment Fund from the Faculty of Medicine of Chiang Mai University, Chiang Mai, Thailand.

P3-895

Evaluating Liver Enzymes and Cholesterol Levels in Newly Diagnosed Obese Children Attending the University of Port Harcourt Teaching Hospital

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Background: Increasing obesity epidemic is not limited to the developed world, but is gradually gaining grounds in the developing countries. The attendant metabolic syndrome is one major complication but liver disease seems to be attaining significant proportion in adult and adolescent obese patients. **Objective and hypotheses:** To evaluate the extent of liver damage in obese children attending the Paediatric endocrinology clinic using liver enzyme levels. **Method:** Weight, height and BMI with Serum liver enzymes, alanine transferase, aspartate transaminase and cholesterol levels were measured in 13 newly diagnosed obese children attending the endocrinology clinic of UPTH. Hip and waist circumference were measured and waist:hip ratio calculated. **Results:** Males were smaller than females (weight 70.02 kg vs 74.66 kg, $P=0.707$ and BMI SDS; 30.95 kg/m^2 vs 33.82 kg/m^2; $P=0.782$). Though males had wider waist circumference, 100.80 cm vs 95.37 cm, female had wider hips, 102 cm vs 100.60 cm but the differences were not significant. Seven (54%) children had ALT levels greater than the laboratory reference values, but no child had elevated AST and cholesterol. There was no significant difference in liver enzyme and cholesterol levels between the genders and between those with waist circumference <95th percentile and those >95th percentile. There was significant positive correlation between AST and waist hip ratio, BMI, cholesterol and BMI SDS. **Conclusion:** Liver enzyme derangement was recorded in newly diagnosed obese children and there is positive correlation between AST and waist hip ratio.

P3-896

Prevalence of Excess Weight in Adolescents at Primary Health Care Units in South Brazil

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Background: In the past decades Brazil has experienced a nutritional transition process characterised by a significant reduction in malnutrition and progressive increase in overweight and obesity. Nutritional education and precocious interventions are useful strategies to combat excess weight in childhood and adolescence. According to the World Health Organization (WHO),

there were more than 40 million children overweight in the world in 2011. In Brazil, the prevalence of excess weight in the population aged 10–19 years was 21.7% in boys and 19.4% in girls in 2008–2009. **Objective and hypotheses:** To estimate the prevalence of overweight and obesity in adolescents at primary care units (ESFs) in order to identify those eligible for weight control programs. **Method:** Quantitative cross-sectional study in adolescents (10–19 year) who lived in the geographical area of four ESFs in the Brazilian Public Health System (SUS) in Blumenau-SC. All adolescents were called to assess weight, height and BMI. It was excluded those who did not attend the call and those who were pregnant. Overweight and obesity was defined by WHO criteria (BMI for age and gender). Epiinfo2000 and Epidata were used in statistical analysis. The Human Ethnic Comity of the Blumenau University approved the study. **Results:** There were 1351 adolescents in the geographical area covered by the study. A total of 840 adolescents were evaluated. Excess weight was observed in 26.8% ($n=225$). Overweight in 14.8% ($n=124$) and obesity in 12.0% ($n=101$). There was difference in excess weight between two ESFs (24.8% vs 35.9%; qui-squared 4.1, $P=0.04$). Almost 100% of them were not involved in health care programs to weight control. There were no differences between age groups 10–14 and 15–19 years (27.1% vs 26.3% respectively). **Conclusion:** The prevalence of excess weight in adolescents in a South Brazil city was 26.8%. The majority of them were not involved in programs to weight control. Differences in geographical distribution of excess weight were observed. **Funding:** This work was supported by the Brazilian Ministry of Heath - PROPET-SAÚDE - Edital n° 24 da SGTES/MS 12/15/2011.

P3-897

Effect of Overweight and Obesity on Spinal Deformities for Children 5–7 Years

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Background: Obesity is one of the factors of musculo-skeletal disorder by its weight stress. It can change body shape and axis of weight balance, especially in growth, which can affect skeletal curvature. **Objective and hypotheses:** The objective of this study was to determine the prevalence of spinal abnomalies in elementary school entry children and evaluate some cofactors related to obesity in child. **Method:** In a cross-sectional study of 1 450 people between 20 000 and pre-school pupil arriving in Qom province was selected as a cluster (Sons: 830, and girls: 620) and examined. the variables of height, weight, BMI, percent body fat, waist-hip ratio were measured. Based on the cut off were classified to four groups underweight, normal, overweight and obese. Then, using the checkerboard test, three students in New York and plummet height lateral, posterior and anterior were assessed. The data using descriptive and inferential statistics, χ^2, t-test and correlation analysis were used. **Results:** Most abnormalities of the lumbar lordosis in the obese group with 6/69% and minimum flat back 6/0% in under weight..regression results indicate that the incidence of spinal deformities, only two variables, BMI and gender effects and 179% higher in obese children compared to children who are underweight and 45% more girls than boys are affected. **Conclusion:** This study demonstrates the high prevalence of spinal deformities in children before school age. Also can be normal BMI as a significant protective factor against known skeletal disorder.

P3-898

A Case of Rapid Onset Obesity, Hypoventilation, Hypothalamic Dysregulation and Neuroendocrine Tumours-ROHHADNET Syndrome

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Background: Rapid-onset obesity with hypoventilation, hypothalamic dysfunction, and autonomic dysregulation (ROHHADNET) is a rare disorder which presents in early childhood. **Case presentation:** Four years old girl was referred to endocrinology unit with a history of excessive weight gain. Parents noticed a rapid weight gain from 3 years of age with increase food seeking behaviour and daytime somnolence. Her weight was >95th centile and her height was on 25th centile. Bone age was 1 year and 6 months at the chronological age of 4 years 2 months. Ultrasound scan of the abdomen revealed a mixed echogenic lesion in right suprarenal area. Right kidney was 8.1 cm and left kidney was 7.6 cm. She had normal endocrine work up. Urinary Vanyllylmandelic acid levels were with thin normal range. Her blood pressure was normal. She underwent tumour excision and histology confirmed ganglioneuroma. During surgery she had excessive bleeding. Post operatively she was found to have hypertension. She admitted with repeated episodes chest infections due to hypoventilation and frequent febrile episodes without any focus of infection. Subsequent ultrasound scan revealed small kidney on right side and dimercaptosuccinic acid (DMSA) scan revealed a nonfunctioning right kidney most likely due to ischemic infarction of the right kidney during surgery. Child's blood pressure is controlled with two anti hypertensives. **Conclusion:** Child is under close follow up for developing endocrinopathies. Hypoventilation results in repeated infections and child needs oxygen and antibiotics during such episodes. Overall she has a poor quality of life. Hypertension has resulted as a part of surgical complication rather than the disease. Great clinical suspicion is needed to diagnose this condition with increased morbidity and mortality.

P3-899

The Influence of Physical Activity and Physical Fitness in the Metabolic Profile and Microcirculation of Eutrophic, Overweight and Obese Children 5–12 Years of Age

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Background: Obesity is a worldwide epidemic affecting adults and children. Social changes throughout history have contributed to modifications in nutrition and physical activity levels. These changes in lifestyle affected health, increasing the number of metabolic and cardiovascular diseases. Obese children already have a low grade systemic inflammation as well as markers of increased cardiovascular risk. The endothelial function is an important and early marker of atherosclerotic disease. **Objective and hypotheses:** To assess whether physical activity and fitness levels affect low grade inflammation and endothelial function in children. To investigate the influence of physical activity and fitness on the metabolic profile and microcirculation of prepubertal or early pubertal children classified according to the BMI. **Method:** After physical examination, 62 school children answered a questionnaire about activity level (physical activity questionaire for older children) and performed a physical fitness test (yoyo test). Twelve-hour-fasting blood samples were collected for lipidogram, glucose, insulin, leptin, interleukin-6 and adiponectin levels. The microcirculation was evaluated by noininvasive plethysmography after venous occlusion. Body composition was assessed by DXA. **Results:** Significant differences were detected in obese vs eutrophic children regarding metabolic profile, serum level of inflammatory citokines and vasodilation capacity. Even though less active children had higher levels of inflammatory markers and worse endothelial function in comparison with more active children, the main predictor of metabolic endothelial dysfunction and increased inflammatory markers was the weight excess. **Conclusion:** Young children (Tanner 1–2) already exhibit metabolic abnormalities due to excessive weight. Physical fitness seems to reduce these abnormalities, although the main determinant seemed to be the weight excess. Based on this data it can be suggested that diet management in combination with regular exercise to increase physical fitness should be stimulated in prepubertal children to reduce the risk for the development of future metabolic or cardiovascular diseases. **Funding:** This work was supported by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (Capes), Brazil and by Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro – (FAPERJ), Rio de Janeiro, Brazil.

P3-900

Predicting Early Cardiovascular Risk in Obese Children Based on Anthropometry

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Background: Early predictors of cardiovascular risk using anthropometric and laboratory variables available in the general practice in obese children are poorly identified. **Objective and hypotheses:** To identify best predictors of early cardiovascular risk in obese children between anthropometric and laboratory parameters. **Method:** Cardiovascular risk was determined by measuring intima-media thickness of the right common carotid artery (cIMT) in 43 severely obese children aged 5.10–16.11 years. Anthropometric and laboratory parameters were also measured in all subjects. Multiple linear regression was used to identify which of the anthropometric or laboratory parameters contribute more to the determination of cardiovascular risk, valued with cIMT. A P-value < 0.05 was considered as statistically significant. **Results:** The analysis shows a statistically significant correlation between cIMT and anthropometric parameters: waist circumference and hip circumference. **Conclusion:** The easy and non-invasive measurement of waist and hip circumferences may help paediatricians to estimate early cardiovascular risk in obese children in the clinical practice.

Table 1.

Dependent variable	Independent variable	P-value
CIMT	Waist circumference	0.0012
	Hip circumference	0.0124
	F-ratio = 7.26; P-value = 0.0026	

P3-901

Metabolic Syndrome Rates Among Adolescents of the Greek School Community

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Background: Adolescent obesity constitutes a phenomenon with epidemic prevalence in a worldwide context. Increased rates of metabolic syndrome represent a consequence of this epidemic, leading to high risk for chronic diseases in adolescence. The study herein, presents the primary outcomes of a school-based

intervention trial regarding the control of the metabolic syndrome among adolescents of Northern Greece. **Aims and objectives:** To investigate the prevalence rates of the metabolic syndrome. **Methods:** A total of 424 adolescents, aged 14.10 ± 1.78 years were recruited. Anthropometric values were recorded. All participants underwent a school-based laboratory investigation including glucose cholesterol and triglyceride levels and body composition determination, *via* telematic health care devices. **Results:** In the total sample (59% girls), BMI was 21.82 ± 3.25 kg/m^2 while waist circumference was 78.78 ± 9.29 cm. Systolic (SBP) and diastolic (DBP) blood pressure were 121.21 ± 11.89 and 73.88 ± 10.54 mmHg respectively. Mean cholesterol levels were 172.42 ± 27.48 mg/dl, triglycerides levels 88.07 ± 40.15 mg/dl and glucose levels 100.89 ± 15.11 mg/dl. After examining the components of the metabolic syndrome in adolescents according to IDF, 24.4% of the sample presented abdominal obesity. Hyperglycemia was found in 52.2% of the sample, hypercholesterolemia in 15% and elevated triglycerides in 6.3% of adolescents. Increased SBP presented the 22% of participants, while increased DBP was apparent in 11.7% of them. Finally, almost one out of six adolescents (15.9%) presented metabolic syndrome. **Conclusions:** A significant proportion of the Greek adolescent population fulfills the criteria of the metabolic syndrome or presents abnormal value to one of its components. Implementation of prevention and intervention strategies are considered as priority actions. **Funding:** Integrated System for Promotion and Education of Health of the Municipality of Ampelokipoi-Menemeni to combat obesity and eating disorders in adolescents ESPA European Community fund.

P3-902

Identification and Management of Obesity by General Paediatricians in the UK

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Background: A third of children in the UK are obese or overweight. The majority are not in contact with medical services. Presentation to general paediatricians for unrelated condition may pose an opportunity to identify children with obesity. The UK obesity services for Children & Adolescents (OSCA) group have produced guidelines for management of obese children in secondary care. **Objective and hypotheses:** Determine the prevalence of obesity in general paediatric out-patients. Describe the rate of identification of obesity. Compare practice with OSCA guidelines. **Method:** Retrospective review of all patients attending general paediatric out-patient department during 1 calendar month. BMI centile was calculated for each child using British 1990 growth reference (UK90). History, investigations performed and management was compared to OSCA guideline standards. **Results:** 186 patients attended out-patient clinic. 138/186 (74%) notes were available for review. 13/138 (9.4%) of children were obese (BMI > 98th centile) with mean age 9.6 (± 5.3) years and mean BMI SDS 3.6. Of the obese children, 5/13 (39%) were identified by clinicians; Focused history was documented in 3/13 (23%); 2/13 (15%) had the full set of investigations and 2/13 (15%) had fasting glucose, insulin & lipids measured. Secondary obesity was identified in one obese child (congenital hypothyroidism). 3/13 (23%) had co-morbidities including psychological, joint problems, abnormal glucose metabolism and precocious puberty. 1/13 (8%) of obese children were referred to a paediatric endocrinologist. In addition, 7/138 (5.1%) of children were overweight (BMI 91th − 98th centile) with mean age 8.2 (± 4.9) years and mean BMI SDS 1.8. 2/7 (29%) who were overweight had been identified by clinicians. **Conclusion:** Around 10% of children attending general paediatrics out-patients are obese. But there is under-recognition. Investigations and management of these children is frequently incomplete.

P3-903

Genotype and Phenotype Characterisation in Two Patients with MEHMO Syndrome

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Background: MEHMO (microcephaly, epilepsy, hypogenitalism, mental retardation, obesity) is a rare disorder with X-linked inheritance. Only three families with this disorder were described previously, with the linkage to a region on X chromosome. No specific gene has been identified so far. **Aims and objectives:** The aim was to identify the genetic etiology in two unrelated Slovak male probands (4.5 and 1.5 years old respectively) with the clinical diagnosis of MEHMO and describe the genotype-phenotype correlation. **Methods:** Blood samples of both probands and their parents were obtained. DNA analysis by the whole exome sequencing (WES) approach was performed. Subsequent analyses of identified variants were focused on the chromosome X. Candidate sequence variants were verified by direct sequencing by Sanger. **Results:** Analysis of exome in proband 1 has identified 18 variants on chromosome X. Haplotype analysis showed that only three of them were found also in the mother and the mother's mother of the proband 1, and only one variant – in the gene *EIF2S3* – was located in the previously described region of the chromosome X associated with MEHMO. The variant is a frame-shift mutation with premature stop codon influencing eight last amino acids of the protein. The same mutation was found also in the proband 2 and his mother. The phenotype of the probands had several common features, i.e. microcephaly, mental retardation, epilepsy, growth retardation, obesity, and diabetes. Nevertheless, the phenotype was more severe in the older proband 1 including panhypopituitarism and frequent respiratory infections. **Conclusion:** This is the first identification of a gene (*EIF2S3*) causing MEHMO syndrome. *EIF2S3* encodes the γ subunit of the eukaryotic translation

initiation factor 2 (eIF2), which is involved in protein synthesis. Point mutations in this gene have been previously identified in several families with microcephaly and impaired intellect (i.e. milder phenotype than MEHMO). **Funding:** This work was supported by the Slovak Research and Development Agency (APVV 0187-12).

P3-904

Generalized Idiopathic Benign Acanthosis Nigricans in Childhood

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Background: Acanthosis nigricans (AN) is a dermatosis characterised by velvety hyperpigmentation, skin thickening, and papillomatosis. AN is generally associated with endocrine disorders (diabetes mellitus, obesity, polycystic ovary syndrome), drugs, and malignancy. In rare cases, it can be unrelated to any systemic disease. Here, we report on a 5-year-old boy from Turkey with diffuse, progressive skin hyperpigmentation. **Case report:** He was born in a non-consanguineous marriage with normal growth and developmental milestones. Hyperpigmentation started at the age of 2 months, around the neck and axilla and spread to other body parts. The main complaint was the cosmetic appearance. He appeared well on physical examination. His blood pressure was within the normal range. Body weight (90 p) and height (90 p) were normal for the patient's sex and age. Upon skin examination, velvety skin with hyperpigmentation and thickening were observed, especially involving periscrotal areas, armpits, neck, abdominal wall, and lumbar region. No change was detected in nails, teeth, and mucous membranes. Tests for the assessment of biochemical, hormonal, and haematological parameters showed no abnormalities. The test results for blood count, B12, thyroid hormones, insulin, C-peptide, HbA1C, cortisol, prolactin, total/free testosterone levels, IGF1, growth hormone, lipid profile, complete liver and renal function, and oral glucose tolerance were all within normal limits. Tumour markers were negative. Chest x-ray and abdominal ultrasound were normal. Skin biopsy was consistent with the diagnosis of AN, which revealed marked hyperkeratosis, acathosis, and papillomatosis. **Conclusion:** Benign, generalised AN, in the absence of systemic disease in children, is rare. We found only nine case reports in literature. It is very important to exclude underlying causes of AN.

P3-905

Potential Connection of Dyslipidaemia with BMI and Associated Disorders in Obese Children and Adolescents

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Background: It is used to define body weight status in children and adolescents using age- and gender-corrected for BMI-SDS. Also excess body weight (EBW) is increasingly applicable to children and adolescents (BMI 99-th percentile). BMI seems to be informative for the severity of obesity, but not for relevant risks of dyslipidaemia. **Objective and hypotheses:** To reveal the potential connections between absolute levels of lipids and BMI, as well as several associated disorders. **Method:** 34 children and adolescents with obesity and EBW (99%.) were included in the investigation with average age of 11.31 years, male/female ratio was 20/14. HOMA index of insulin resistance, as well as the levels of insulin, pro-insulin, thyroid status, lipids were measured. Dyslipidaemia was defined as abnormal levels of more than two lipid fractions. **Results:** No any correlation has been found between absolute levels of lipid fractions and BMI ($r < 0.02$). Also there were no significant connection of dyslipidaemia with gynecomastia, steatohepatosis, hypothyroidism, sex, and pubertal delay ($P > 0.05$). Interestingly in 70.6% of investigated patients the insulin resistance and hyperisulinaemia were found, 91.7% from which had statistically significant dyslipidemia ($P < 0.05$) without sex predominance. Insulin resistance and hyperinsulinaemia positively associated to BMI-SDS > 2.5. **Conclusion:** Hyperinsulinaemia and insulin resistance are connected with severity of obesity (BMI-SDS > 2.5) and are mostly associated with dyslipidaemia in obese children and adolescents. We assume that there are marginal lipids' levels above which the BMI doesn't have interaction on them or other regulator mechanisms are triggered. Further investigations should be done to evaluate the relationships between other associated endocrine and somatic disorders and hyperinsulinaemia and/or insulin resistance and BMI severity in obese children and adolescents.

P3-906

Deficiency of 25-(OH) D-Vitamin in Adolescents with Obesity

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Objective: To evaluate the level of 25 (OH) D – vitamin in obese adolescents living in the South of Russia. **Materials and method:** We examined 20 obese adolescents with varying degrees of severity, aged 15.5 ± 0.3 years, ten girls and boys. The comparison group consisted of ten healthy adolescents matched for age and sex. Obesity was calculated by BMI. Level of 25-(OH) D – vitamin was studied in the laboratory by ELISA (nmol/l). Furthermore, the fasting blood glucose, fasting insulin was investigated, insulin resistance index was calculated (HOMA). **Results:** Excess body weight was diagnosed in 20% (two) boys and 30% (three) girls (BMI 25–30), I degree of obesity (BMI 30–35) were detected in 70% (seven) boys and 60% (six) girls, II obesity degree in 10% (one) boys and 10% (one) girls. Level of 25-(OH) D – vitamin was significantly lower in the intervention group compared with the control group (25.2 ± 0.12 nmol/l, 63.7 ± 0.24 nmol/l respectively). Thus sex differences haven't been identified. In assessing the level of 25-(OH) D – vitamin according to WHO classification revealed that 65% (13) of the main group of adolescents had vitamin D deficiency, which amounted to

20.4±0.86 nmol/l. Insulin resistance was detected in all the surveyed boys and girls of the main group, HOMA index was 3.4±0.14. As a result, the correlation analysis was found a positive relationship between the level of 25-(OH) D – Vitamin and the degree of obesity, as well as index HOMA. **Conclusion:** In adolescents with obesity and insulin resistance showed a reduction in the level of 25-(OH) – vitamin D, despite the the South place of residence.

P3-907

The Correlation Study on Childhood Obesity, Insulin Resistance and Androgens

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Background: Adolescent hyperandrogenemia is prophase of polycystic ovary syndrome. Obesity is one important cause of hyperandrogenemia. Whether hyperandrogenemia has happened in obese children is need to explore. **Aims and objectives:** To investigate the levels of insulin and androgens in obese children, analysis the correlation between insulin resistance and androgens, and comparison on the differences of androgens levels between obese boys and girls, and between prepubertal and pubertal obese children. **Methods:** 110 obese children and 70 normal weight children were recruited in the outpatient department of endocrinology of Children's Hospital of Chongqing Medical University in China in 2013–2015. Weight, height, waist circumference and blood pressure were measured in all children. Fasting glucose (FPG) and insulin (FINS) dehydroepiandrosterone sulphste (DHEAS), androstenedione (A4), testosterone (T), luteinising hormone (LH), follicle stimulating hormone (FSH), and estradiol (E2); blood lipids were measured. 2 h postprandia glucose and 2 h postprandia insuin were measured in obese children. HOMA-IR index was calculated. **Results and conclusions:** i) Serum DHEAS in obese group, normal group were 3.08±2.52 umol/l, 2.40±1.67 umol/l respectively, $P<0.05$. Serum A4 in obese group, normal group were 6.27±7.42 nmol/l, 4.10±3.08 nmol/l respectively, $P<0.05$. Serum DHEAS, A4 in obese children were higher than normal children. There were showed no significant difference in T, LH, FSH, LH/FSH, E2 between obese and normal group. Correlation analysis showed that both DHEAS and A4 had a positive relationship with BMI, WC, FINS, 2 h INS, HOMA-IR. ii) Serum A4 in obese girls was higher than obese boys, but there was no significant difference in DHEAS levels between obese boys and obese girls. iii) The serum T, DHEAS, A4, LH, FSH, LH/FSH in children were higher in pubertal than prepubertal obese children. In conclusions i) The androgens are increasing in obese children, especial in pubertal obese girls. ii) A4 is more common androgen than T and DHEAS in obese children. iii) Hyperandrogenemia is associated with insulin resistance in obese children.

P3-908

The Prevalence of Obesity in Children and Adolescents in the Udmurt Republic

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Background: Obesity is an increasing problem among children and adolescents in recent decades however official statistics are contradictory. **Objective and hypotheses:** The purpose of this epidemiological study was to determine the prevalence of obesity in children and adolescents in the Udmurt Republic – the region in European part of the Russian Federation with a child population of 300 thousand people. **Method:** According to the experiment 5732 children 1–17 years (boys – 2 845, girls – 2 887), among them the inhabitants of the cities– 1 090, rural inhabitants–4 642, were examined. Diagnostic criteria of obesity in children is recommended by the World Health Organization were used. **Results:** The prevalence of overweight was 16.7±0.7%, the prevalence of obesity was 7.1±0.3%. Gender features were characterized by a significantly higher ($P<0.001$) frequency of obesity in boys (9.0±0.5%) compared with girls (5.2±0.4%), with no differences in the frequency of overweight (17.4±0.7% and 16.1±0.7% respectively). In accordance with the age, two peak prevalence of obesity were registered: children 1–3 years (12.2±1.7%) and 7–12 years (8.6±0.6%). There were not any significant differences in the frequency of obesity among urban and rural residents (7.4±0.4% and 5.9±0.7%, $P>0.05$). In the structure of obese patients 57.0% had BMI in the range of 2 to 2.5 S.D., 27.5% had BMI in the range of 2.6–3.0 S.D., 13.0% had BMI in the range of 3.1–3.9 S.D. and 2.5% had BMI in the range of ≧4.0 S.D. **Conclusion:** The results motivate paediatricians to devote more time to the problem of obesity.

P3-909

Survey Serum 25-Hydroxyvitamin D Concentration in Obese Children and Clinical Significance in Chinese Population

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Background: Simple obese is a worldwide public health problem. Recent studies suggested a possible relationship between obese and vitamin D deficiency. **Objective and hypotheses:** To discuss the relationship between 25-Hdroxyvitamin D with glucose and lipid metabolism of simple obese in Chinese children. **Method:** 65 children with obeses (35 mild-to-moderate, 50 severe) and sixty-two children with normal weight were enrolled in this trial. The Serum 25-hdroxyvitamin D, insulin, cortisol and C peptide were measured by CLIA. **Result:** There was significant difference between obeses and normal children in serum 25-(OH) D ($P<0.001$). Serum 25-(OH) D was inversely related with BMI ($r=-0.456$, $P<0.001$), BMI SDS ($r=-0.447$, $P<0.001$). Serum

25-(OH) D was inversely related with triglyceride obsess children ($r = -0.389$, $P < 0.001$). Moreover, triglyceride in obese children with serum 25-(OH) D ≤ 50 nmol/l was higher than that in obese children with 25-(OH) D>50 nmol/l ($P < 0.05$). Serum 25-(OH) D was not statistically significant with blood total cholesterol and low density lipoprotein cholesterol (hdl-c), blood glucose, insulin, haemoglobin A1c in obese children ($P > 0.05$). **Conclusion:** Serum 25-(OH) D in obese children are lower than normal weight children, Serum 25-(OH) D was inversely related with height and BMISDS, 25-(OH) D was inversely related with triglyceride level in obeses, which imply that 25-(OH) D maybe a risk factor of obesity and abnormal blood lipid.

P3-910

Clinico-Biochemical Correlation Among Children with Obesity and Metabolic Syndrome

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Background: Childhood obesity associated with risk of developing metabolic syndrome (MetS) and paucity in Indian literature regarding correlation between clinical and biochemical parameters in obese and MetS. **Objective and hypotheses:** Comparing clinical and biochemical correlation of obese children, controls and MetS. **Method:** Eighty children (40 obese and 40 age and sex matched controls) 5–18 years recruited after approval by Institutional Ethics Committe. BMI, Waist circumference (WC) and blood pressure (BP) recorded after informed consent/assent. Lipid profile measured using auto analyser and Insulin levels by electrochemiluminescence and Fasting blood sugar by glucose oxidase method. **Results:** Mean age of study population was similar in both cases and controls-11.15 ± 2.52 (M:F = 23:17)with 19(47.5%) prepubertal (M:F = 10:9) and 21 (52.5%) postpubertal (M:F = 13:8). BMI and WC higher in obese (26.58 ± 1.88 vs 17.58 ± 1.72–$P < 0.001$), (72.34 ± 6.24 vs 65.03 ± 5.89–$P < 0.001$) respectively. Mean Systolic and diastolic BP in obese was comparable 100 ± 5.73 and 64.70 ± 4.65. Calorie intake higher in obese (1893.55 ± 329.96 vs 1657.60 ± 290.30–$P = 0.001$). S.Cholesterol (Chol) were comparable ($P = 0.22$).STriglyceride (TG) raised in obese (135.50 ± 43.32 vs 89.08 ± 12.46) $P < 0.001$ and low density lipoprotein (LDL) was 86.58 ± 22.18 in obese vs controls 68.83 ± 9.68 ($P < 0.001$). Serum high density lipoprotein (HDL) low in obese than controls (37 ± 4.37, 42.70 ± 6.42-$P < 0.001$). Fasting blood sugar in obese was 93.78 ± 7.08 and comparable. Insulin levels higher in obese (11.51 ± 4.73 vs 6.08 ± 2.46–$P < 0.001$). Age, BMI and WC correlated positively with insulin and LDL. 4 (21%) prepubertalobese and 14 (66%) postpubertalhad MetS. Mean BMI (29.45 ± 3.08 vs 26.58 ± 1.88), WC (77.17 ± 4.5 vs 72.34 ± 6.2), FBS (97.02 ± 2.2 vs 93.78 ± 7.08), Chol (158.31 ± 17.7 vs 142.87 ± 13.96), TG (165.69 ± 44.6 vs 135.5 ± 40.9) and LDL (95 ± 26.1 vs 79.21 ± 22.4) significantly higher among obese with MetS, $P < 0.01$. BMI and WC had significant positive correlation with dyslipidemia and FBS, $P < 0.05$. **Conclusion:** Obese children have high BMI, increased WC and higher prevalence of dyslipidaemia putting them at high risk of MetS. High BMI and increased WC correlated strongly with increased LDL and high insulin levels. With **o**nset of puberty WC and BMI increases significantly and worsening of dyslipidaemia. Children with MetS had significantly higher BMI and WC, Lipid parameters and Insulin levels than obese.

P3-911

Clinical and Phenotypic Patterns of Overweight and Obese School Children

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Results of epidemiological studies of 540 9–17 years old school children in Ternopil city are presented in this article. The aim is to determine the incidence of overweight, obesity, metabolic syndrome and hypertension among Ternopil schoolchildren and to trace clinical and phenotypic features of these pathological conditions among them. The results showed that the incidence of overweight among schoolchildren is 11.1% and obesity is 4.8% (11.8% of girls and 14.8% of boys). Boys develop obesity three times more often than girls and are overweight 1.4 times more often than girls, while frequency of underweight is independent of gender. In pubertal period boys develop obesity three times more often: 7.3% of boys and 2.3% of girls ($F = 0.523$ $P < 0.05$) and more often are overweight (11.1 and 6.4% respectively). In general, abdominal obesity of children and adolescents was found in 4% of boys and in 1.9% of girls. The incidence of abdominal obesity (as a marker of metabolic syndrome) among overweight schoolchildren is 19.3% among the examined boys and 18.5% among girls. There is direct relationship between BMI and blood pressure values, which is more pronounced among boys than among girls. Every second obese boy has labile hypertension, while among obese girls 50% had normal blood pressure, and only every sixth girl had high normal blood pressure.

P3-912

In Different Method of the Evaluation of State of Feeling of Obese Children; Goodenough Harris 'the Draw-a-person' Test

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Objective: Psychosocial problems which the obesity caused is one of the most important reasons that impede success of treatment. Researches indicate that, majority of all obese children have depression. In this study, the effect of obesity on state feeling (*cognitive functions and socioemotional adaptation)* were

investigated in a different special test. To this end obese and nonobese young patients were compared by a special test determines the ability of mind and concepts. **Materials and method:** The study included 26 patients between the ages of 4–14 years. Organic obesity, chronic disease and medication history were excluded from the study. After received a detailed history and physical examination in all cases *Goodenough Harris Draw a Man Test (GEH BIC)* test was performed. Interpretation of the test was performed by the same specialist. **Results:** 14 obese and nine nonobese patients mean ages were respectively 8.86 ± 2 years and 9.86 ± 0.89 years. According to *GEH BIC Test*, eight of 14 cases did not draw hand, and 11 cases of the obese patients did not draw finger.despite that, only five cases of the nonobese group drew less numbered fingers. Six of the obese cases drew little figures. **Conclusion:** In obese group, tiny figure drawing and drawing figures without hand-finger, were significantly higher than in nonobese group. According to GEH BIC test, drawing figures without hand-finger is the sign of sense of guilt, and tiny figure drawing is also symbolize the lack of self-confidence. These data suggests that, obese child have intense feelings of guilt and lack of self-confidence.

P3-913

Phenotypic Study of Obesity in Children and Adolescents

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Background: Child Obesity is a major health problem. It is mainly due to a high diet and low physical activity. In some cases, they may be due to genetic causes. It must be detected and treated precociously due to an increased risk of early onset of diseases, including diabetes and heart disease. **Objective and hypotheses:** Search the frequency, clinical and etiological characteristics of obesity in children and adolescents. **Method:** This is a retrospective study of 48 cases of obese children, hospitalized between 1995 and 2014. All patients underwent an examination and a complete physical examination. The exploration was completed by a general and endocrine balance. Depending on the results, a paraclinical exploration was made. **Results:** 48 cases were reported. the sex ratio G/F: 2. The mean age was 10 ± 5.8 years for males and 12 ± 1.04 in girls. Obesity is more common among boys age < 6 years (50%) and at age between 12 and 18 years (37.5%). Obesity is more common among girls whose age is between 12 and 18 years (58.3%) and between 6 and 12 years (25%). In adolescence, obesity is greater among girls than boys (58.3% vs 37.5%) whereas before the age of rebound weight, it is more important for boys 50% vs 16.66%. 50% of boys and girls have moderate obesity. Severe and morbid obesity are in proportion equal to 25%. The causes are common 60.71%, syndromic obesity 21.43%, endocrine obesity 10.72% and iatrogenic7.14%. Complications are more common in boys 35.71% vs 32.14% (*P*: 0.01). Visceral and neuropsychiatric complications are predominant. **Conclusion:** Aetiological factors of childhood obesity are complex and involve epigenetics and behaviour. Early and éfficace support is based on growth monitoring and prevention by dietary and lifestyle rules.

P3-914

Association of Serum Levels of 25(OH) Cholecalciferol and Childhood Obesity

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Background: Vitamin D is now recognised as a prohormone, essential for the maintenance of mineral homeostasis, calcium metabolism and normal skeletal architecture. 30 ng/ml or greater can be considered sufficient serum levels. The prevalence of vitamin D deficiency among severely obese children is almost 49% caused by the fact that it is sequestered in the larger body pool of fat of such individuals, being vitamin D fat soluble. Vitamin D deficiency has been recently associated with cardiovascular disease and metabolic syndrome in morbid obesity. Particularly, 25(OH) D levels were inversely correlated with HbA_{1c}, insulin, LDL, triglycerides, total-cholesterol and insulin resistance. **Objective:** To investigate the action of this hormone in obese children visited in Pediatric Endocrinology and Adolescentology Clinic of L'Aquila and to examine the relationship between 25(OH) D concentration and other parameters commonly altered in obesity. **Methods:** Prospective study envolving 23 obese children (Ob) (13 girls; 11.06 ± 3.98 years, BMI > 95 °C) and 21 normal weighted children (C) (12.23 ± 3.54 years). An OGTT was performed and serum insulin was obtained to calculate the glucose/insulin ratio and the HOMA-index. All had undergone an assessment of weight, height and pubertal status; cholesterol, triglycerides, liver enzymes and serum 25(OH) D were measured at the baseline visit. **Results:** Mean 25(OH) D levels were highest in Ob, with a statistically significant difference, respect to C. The BMI level was inversely correlated with vitamin D levels. An important inverse relationship was found when vitamin D levels were compared with basal

Table 1. (for abstract P3-914)

		BMI	Basal insulin	Triglycerides	GPT	γGT
VIT D	Rho	−0.41	−0.40	−0.30	−0.43	−0.42
	P	0.005	0.02	0.05	0.004	0.009

(obese patient)

insulin, GPT, GGT, triglycerides. **Conclusions:** Comparing the vitamin's D concentration with the lipemic and metabolic parameters, largely confirm the few existing data in the literature, that such metabolic alterations are linked to a high prevalence of vitamin D deficiency in obese children.

P3-915

Comparison of Lipid Profile in Active and non Active Obese Children in Qom-Iran

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Background: Obesity and nonactivity particularly in child hood can associated in cardiovascular disease in adult hood. **Objective and hypotheses:** Aim of this study was comparison of lipid profile in active and non active obese children. **Method:** The participants in this study who where obese children 8–10 years, according to cut off BMI > 85% percentile, that selected by cluster sampling method. After obtaining consent.they complete PAQC queastionair and divided to two groupse active and non active. Sample blood test whas taken for measure and compair level of TC, TR, HDL and LDL factores in active and non active obese. Data were analyzed byspss and in dependent Ttest, chi square test with significant level confidence at 0/05. **Results:** Finding showed that the two groups active and non active were statistically diference in triglycerides (MD: 13, $P=0.005$),cholesterols total (MD: 34, $P=0.001$), LDL-cholesterols (MD: 13, $P=0.002$) and only HDL cholesterols (MD: 56, $P=0.019$) were higher in non active groupe. Also LDL/HDL = 4.15, $P<0.0001$, TC/HDL: 4.31, $P<.0001$ were shown. **Conclusion:** Obesity is not alone but with immobility may be a risk factor for increased lipid profile in children.

P3-916

Vitamin D Deficiency can Modulate GH/IGF1 Axis in GH Deficient Children

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Background: According to the latest studies vitamin D has an effect on the production and/or secretion of IGF1 in the liver, but the exact mechanism regulating these relationships has not been thoroughly explained. **Objective and hypotheses:** Evaluation of the relationship between 25(OH)D and IGF1 levels in the serum of children with GH deficiency (GHD). **Method:** The study group consisted of 76 GH deficient children qualified for GH therapy. The GHD was defined as GH secretion in stimulatory tests below 10 ng/ml. 25(OH)D and IGF1 concentrations were evaluated before the start of GH treatment. The study group was divided into two subgroups, depending on the concentration of 25(OH)D: deficient children in need of treatment (25(OH)D < 20 ng/ml; $n=33$) and non-deficient children (25(OH)D > 20 ng/ml; $n=43$). The two subgroups did not differ significantly in terms of GH deficiency defined as the maximum secretion of GH in tests. IGF1 concentration was expressed as an S.D. normalized for bone age. **Results:** It was only in the group of children with 25(OH)D deficiency that a weak positive correlation between 25(OH)D concentration and IGF1 concentration was found ($P<0.05$). There was no significant correlation between the concentrations of 25(OH)D and IGF1 in the group without vitamin D deficiency or in the whole study group. **Conclusion:** The results suggest that low serum 25(OH)D concentrations can influence IGF1 concentrations. Therefore, in vitamin D deficient patients their vitamin D status should be normalized before their IGF1 concentrations are evaluated.

P3-917

Serum IGFI Concentration and Growth During Infancy Correlate to Polyunsaturated Fatty Acid Pattern

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Background: IGF1 is important for fetal and infant growth and is influenced by nutrition. In young pigs, docosahexaenoic acid (DHA)-enriched food is associated with higher IGF1 levels but studies in human infants are lacking. **Aims and objectives:** To assess levels of polyunsaturated fatty acids (PUFA) relate to IGF1, birth size and growth during infancy. **Methods:** The setting was a population-based longitudinal cohort comprising 126 full-term, normal size infants (50% females) followed prospectively with anthropometric measurements as well as blood sampling from cord blood, serum at 2 days of age and at four and 12 months. Only those which had complete series of PUFA analyses were included. Parents completed food questionnaires on each occasion. At 1 month of age, 95% were given some breastfeeding and at four months 64% were exclusively breastfed. IGF1 were assessed using the IDS-iSYS-technique and leptin using RIA (Linco Research). Essential fatty acids were analysed with masspectrometry technique. **Results:** Cord IGF1 correlated negatively to cord omega n6/n3 ($r=-0.25$, $P<0.01$) and cord arachidonic acid (AA) ($r=-0.34$, $P<0.001$). At birth, AA had a negative correlation to birth length (BL) ($r=-0.29$, $P=0.001$) and weight (BW) ($r=-0.25$, $P<0.01$). The unsaturated PUFA mead acid from cord blood and at two days of age correlate closely to BW ($r=0.45$, $P<0.001$), BL ($r=0.34$, $P<0.001$) and head

circumference ($r=0.35$, $P<0.001$). At 2 days of age, there was a negative correlation between IGF1 and AA ($r=-0.52$, $P<0.001$) and a positive correlation to linoleic acid (LA) ($r=0.46$, $P<0.001$) respectively. At 4 months of age IGF1 still correlated positively to LA ($r=0.39$, $P>0.001$) but negatively to omega n3/n6 ratio ($r=-0.40$, $P<0.001$) and to AA ($r=-0.36$, $P<0.001$). **Conclusions:** During infancy, essential fatty acids correlate to IGF1 and to birth size. Whether this is through GH level or nutrition *per se* remains to be elucidated.

P3-918

Are Short Children with Low GH Secretion Metabolically Different from Children of Normal Height?

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Background: Severe GH deficiency (GHD) leads to several metabolic effects in the body ranging from abnormal body composition to biochemical disturbances such as high insulin sensitivity. However, less is known regarding these parameters in children with a milder deficiency in GH secretion. **Objective and hypotheses:** To analyse if short children with a relatively low GH secretion differ metabolically from healthy children of normal height. **Method:** We examined insulin sensitivity index (Si), body composition and fasting levels of glucose, insulin and HbA1c in short children (<-2.5 SDS) between 7–10 years of age ($n=35$) and compared the results with an age- and sex-matched control group of normal height ($n=12$). We also performed a subgroup analysis comparing these parameters for short children above and below a peak GH secretion level of 10 μg/l during GH-stimulation test. **Results:** The group of short children had a higher mean Si compared to the control group (12.9 vs 10.4 $(\text{mu/l})^{-1}\times\text{min}^{-1}$) but the difference was non-significant unadjusted ($P=0.079$) and only borderline significant when adjusted for sex ($P=0.059$). The comparison of body composition adjusted for sex showed that the short children had a lower percentage of abdominal fat (AF, 13.3% vs 16.6%, $P=0.05$) and higher percentage of lean body mass (LBM, 80.6% vs 77.5%, $P=0.04$) compared to the controls. No significant difference of fasting glucose or HbA1c was detected between the groups but fasting insulin was significantly lower in the short children (22.4 vs 32.0 pmol/l, $P=0.05$) when adjusted for sex. When comparing short children above and below GH-peak level of 10 μg/l the children with lower GH secretion were shown to have a significantly lower fasting insulin level (16.8 vs 27.8 pmol/l, $P=0.04$) and the other comparisons showed tendencies towards higher Si, lower AF and higher LBM, but these results were non-significant. **Conclusion:** Short children with mildly impaired GH secretion are very heterogeneous in terms of their metabolic profile compared with healthy children of normal height. They show higher Si and lower fasting insulin levels than the healthy children but in contrast to the phenotype of GHD the short children have low AF and high LBM, which might have contributed to the differences in insulin sensitivity. **Funding:** The work was supported by Eli Lilly Sweden AB, Swedish Heart-Lung Foundation, Swedish Research Council for Health, Working Life and Health Care and Karolinska Institute-Stockholm County Council Research Support.

P3-919

Familial Short Stature Associated to Terminal Microdeletion of 15q26.3: Variable Phenotype not Involving the IGF1 Receptor Gene

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Background: Terminal deletions of chromosome 15q are associated with different degrees of pre- and post-natal growth failure, dysmorphic features, functional impairments and congenital anomalies. Although monosomies of 15q26 do not represent a classical contiguous gene syndrome, candidate genes for selected features have been identified. Short stature is referred to deletions of the IGF1-R gene, located on 15q26.3. We demonstrate evidence of phenotype comparable with 15q26 monosomy in a family with microdeletion of 15q26.3 not involving IGF1-R gene. **Case presentation:** An 8 years old girl was referred for short stature and minor dysmorphic features. Past history showed congenital hearth defect, repaired at 1.75 years, and infantile spasms since 6 months. IQ was mild impaired on verbal scales. After birth, height presented a progressive decline, achieving -3 S.D., far from the target height (S.D. – 1.44). Bone age was mildly delayed. She presented minor dysmorphisms including mild down-slunting eyelid, micrognathia, overjet with prominent incisors, short philtrum, arched palate. GH and IGF1 productions were normal. Array-CGH showed a microdeletion of the 15q chromosome, on the sub-terminal region 15q26.3 (chr15: 100167695–102364500) of about 2.5 Mb not involving the IGF1-R gene. The same deletion was found in the father. Father's final height was found on the lowest part of the normal range. His past history was characterised by mild learning difficulties. He also presented truncal obesity and nocturnal sleep apneas. **Conclusion:** To the best of our knowledge, this is the first case of terminal 15q deletion with a phenotype similar to others reported, not involving the IGF1-R gene. Deletion's size seems not to be a predictor of the breadth of the phenotypic spectrum and the wide clinical variability suggests that other genetic mechanisms may be involved and need to be investigated.

P3-920

Is the Insulin Secretion in Pancreatic Beta Cells Related with IGF-1/IGFBP-1 Axis in Korean Children?

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Background: The IGF system is involved in the development of metabolic and cardiovascular disease. This study aimed to investigate the association of insulin-like growth factor-1 (IGF1), IGF-binding protein-1 (IGFBP1) and IGFBP3 with insulin resistance and type 2 diabetes in children. **Methods:** We included 36 children aged 10 to 16 years without known diabetes, medication, chronic disease. They were classified into three groups according to the results of oral glucose tolerance test and other clinical/laboratory findings. We performed anthropometric measurement and laboratory tests. The fasting levels of serum IGF-1, IGFBP-1 and IGFBP-3 were measured. **Results:** i) Serum IGF1, IGFBP3 and IGF1/IGFBP1 molar ratio levels were significantly higher in glucose intolerance group. Serum IGF1 ($r=-0.396$, $P=0.023$) and IGFBP3 ($r=-0.628$, $P<0.001$) had negative correlation with IGFBP1. ii) Serum IGFBP1 was negatively correlated with age, BMI, systolic blood pressure, serum c-peptide, insulin, and HOMA-IR. And serum IGF1/IGFBP1 was significantly related with serum c-peptide, insulin and HOMA-IR. iii) Serum IGFBP1 had no correlation with fasting plasma glucose level, lipid profile, apoprotein A/B and HbA1c. It was not different between normal glucose tolerance group and glucose intolerance group. iv) In normal glucose tolerance group, serum IGFBP1 and IGF1/IGFBP3 was no significantly different between obese and non-obese groups. But IGFBP1 had negatively associated with age, BMI, systolic blood pressure, serum c-peptide, IGFBP3 and HOMA-IR. **Conclusion:** Serum IGF1/IGFBP1 molar ratio was significantly elevated in Korean children with glucose intolerance sate and especially, serum IGFBP1 correlated with serum c-peptide. These findings suggest that IGFBP1 may related glycemic control and insulin secretion in children.

P3-921

Severe Isolated Growth Hormone Deficiency and Myopathy in Two Brothers with RNPC3 Mutation

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Background: We present two brothers with very distinct phenotype, possibly constituting a novel clinical and genetic entity. The common phenotype included red hair, obesity, myopathy, severe IGHD and, growth without growth hormone. **Case presentation:** At the age of 28 months the older brother had a height of 68 cm (−9 SD), his bone age was 6 months. The younger brother had a height of 62 cm at the age of 20 months (−5 SD), bone age 10 months. Two tests of pituitary GH reserve showed severe growth hormone deficiency (GHD) in both patients (<0.3 ng/ml). All other pituitary hormones were within normal levels. Rapid growth in the first two years got them on the 30th and 40th percentile on the growth curve. IGF-I and IGFBP3 were not initially available, but under treatment were normal. Leptin measurement was not available. Unsteady gait, falling increased muscle enzymes lead to a diagnosis of myopathy. Two muscle biopsies were inconclusive (Macedonia and Germany). Remarkably, after GH treatment was interrupted growth continued normally and they both reached normal adult target height. Retesting the GH pituitary reserve showed low GH levels <0.3 ng/ml. Extensive genetic investigation included sequencing of the GH1, POMC, MC4R, SMN1, dystrophin and dynactin genes, as well as the complete mitochondrial genome. No gene alterations were detected. The karyotype of the patients is normal 46, XY. Whole exome sequencing (WES) identified a compound heterozygous mutation in the RNPC3 gene, where each parent is heterozygous for one of the variants (RNPC3:NM_017619: exon6:c.613C>T: p.R205X, and RNPC3:NM_017619: exon13:c.1420C> A:p.P474T. **Conclusions:** Mutations of the RNPC3 gene encoding 65K protein that is a part of the U12-type spliceosome were identified. At present it is not clear how the mutations cause the IGHD and the myopathy in the patients. Additional functional studies will follow.

P3-922

Gigantism Secondary to Growth Hormone Secreting Pituitary Macrodenoma

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Background: Pituitary gigantism is an extremely rare disorder characterised by GH excess that occurs before fusion of the epiphyseal growth plates. **Case summary:** A 13 years 6 month old Chinese boy presented to the paediatric endocrine outpatient clinic with tall stature. He was noted by his parents to have a continued growth spurt since 9 years old, and he required new shoes and clothes every school term. He had no headaches or visual disturbances. There is no family history of tall stature. On examination, his height measured 191.3 cm (> 2 SD above the 97th percentile) and his weight measured 66.0 kg (90th-97th percentile). He had no gynaecomastia or features of Marfan syndrome. There was mild prognathism. He was Tanner Stage 4 for pubic hair and his testicular volumes measured 15 ml bilaterally. His bone age was 14 years with a predicted height of 206.0 cm. An oral glucose suppression test (OGTT) showed a failure of GH suppression with a paradoxical rise after 60 min to

a peak GH of 25.0 ug/L and an elevated IGF1 of 877.0 ug/L (183–850). Serum prolactin was normal at 198 mIU/L (72.0–320.0). A pituitary MRI showed a pituitary macroadenoma measuring 12×9×7 mm. Perimetry was normal. He underwent endonasal transphenoidal hypophesectomy and he developed central diabetes insipidus post operatively. Histology confirmed a pituitary adenoma which was positive for growth hormone and prolactin. A repeat OGTT 3 months after surgery showed adequate suppression of GH levels of 0.73 ug/L with normalisation of IGF1 to 228 ug/L (183–850) and a pituitary MRI showed no tumour recurrence. **Conclusion:** We report a case of GH excess secondary to a pituitary macrodenoma which achieved surgical and biochemical cure with transphenoidal surgery.

P3-923

IGFI and Relation to Growth in Infancy and Early Childhood in Very-Low-Birth-Weight Infants and Term Appropriate for Gestational Age Infants

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Background: IGFI regulates early postnatal growth of preterm infants and also plays an important role in growth in childhood. Very-low-birth-weight (VLBW) infants are at risk for reduced growth in early childhood. **Objective and hypotheses:** To compare IGFI and the correlation to growth parameters in infancy and early childhood in VLBW and term appropriate for gestational age (AGA) infants. **Method:** We included 41 VLBW children and 64 term born AGA children. Anthropometry was performed at 0, 3, 6, 12 and 24 months of (corrected) age. IGFI was measured at 6 and 24 months corrected age (CA) in the VLBW children and at 3, 12 and 24 months in the term born children. **Results:** VLBW children are lighter and thinner than term AGA children at all ages and are shorter until 12 months CA. VLBW children have lower head circumference than term AGA children at all ages. At 24 months CA IGFI in VLBW children is significantly higher than in term AGA children (13.0 vs. 10.3 nmol/L resp.; $P=0.013$). In VLBW children IGFI at 6 months CA was significantly correlated to weight and length at 6 months CA and to change in weight and length between 0 and 6 months CA; IGFI at 24 months CA was significantly correlated to head circumference and to change in length between 0 and 24 months CA. In term AGA children IGFI at 3, 12 and 24 months was correlated to weight and length at the same age and to change in weight and length in the preceding period. **Conclusion:** In infancy and early childhood IGFI is correlated to preceding growth in both VLBW and term children. At 2 years CA IGF-I in VLBW children is higher than in term AGA children indicating an important role in the catch-up growth in length.

P3-924

Severe Isolated Growth Hormone Deficiency and Myopathy in Two Brothers With *RNPC3* Mutation

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Background: We present two brothers with very distinct phenotype, possibly constituting a novel clinical and genetic entity. The common phenotype included red hair, obesity, myopathy, severe IGHD and, growth without growth hormone. **Case presentation:** At the age of 28 months the older brother had a height of 68 cm (−9 SD), his bone age was 6 months. The younger brother had a height of 62 cm at the age of 20 months (−5 SD), bone age 10 months. Two tests of pituitary GH reserve showed severe growth hormone deficiency (GHD) in both patients (<0.3 ng/ml). All other pituitary hormones were within normal levels. Rapid growth in the first two years got them on the 30th and 40th percentile on the growth curve. IGFI and IGFBP3 were not initially available, but under treatment were normal. Leptin measurement was not available. Unsteady gait, falling increased muscle enzymes lead to a diagnosis of myopathy. Two muscle biopsies were inconclusive (Macedonia and Germany). Remarkably, after GH treatment was interrupted growth continued normally and they both reached normal adult target height. Retesting the GH pituitary reserve showed low GH levels <0.3 ng/ml. Extensive genetic investigation included sequencing of the *GH1, POMC, MC4R, SMN1*, dystrophin and dynactin genes, as well as the complete mitochondrial genome. No gene alterations were detected. The karyotype of the patients is normal 46, XY. Whole exome sequencing (WES) identified a compound heterozygous mutation in the *RNPC3* gene, where each parent is heterozygous for one of the variants (*RNPC3*:NM_017619: exon6:c.613C>T: p.R205X, and *RNPC3*:NM_017619: exon13:c.1420C> A:p.P474T. **Conclusions:** Mutations of the *RNPC3* gene encoding 65K protein that is a part of the U12-type spliceosome were identified. At present it is not clear how the mutations cause this particular phenotype. Additional functional studies will follow.

P3-925

Influence of the -202 A/C IGFBP3 Promoter Polymorphism on Individual Variation in Body Height in Korean Girls

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Background: The most common single nucleotide polymorphism in the IGFBP3 promoter region occurs at position -202.

This polymorphic variation occurs frequently and may influence GH responsiveness and somatic growth. **Objective and hypotheses:** This study aimed to assess the effects of IGFBP3 promoter polymorphism on growth in children. **Method:** Restriction fragment length polymorphism (RFLP)-based genotyping of the -202 single nucleotide polymorphism was performed in 146 Korean girls aged between 15 and 16 years, who were selected randomly from the Seoul School Health Promotion Center. The participants were divided into three groups (tall, medium, and short) according to the height percentile established from normal reference values for Korean children. The serum levels of IGF1 and IGFBP3 were then compared according to genotype. **Results:** The genotype distribution in the participants was 79 AA (54.1%), 60 AC (41.1%), and 7 CC (4.8%). The C allele frequency at the -202 IGFBP3 position was 25.4% in this group. The mean serum IGFBP-3 concentration in girls with the AA genotype was higher than that in girls with the AC genotype in the medium ($P=0.047$) and short ($P=0.035$) groups respectively. There was no difference in the IGF1 to IGFBP3 molar ratio between the AA and AC genotype groups ($P=0.161$). **Conclusion:** The -202 polymorphism in the IGFBP3 promoter region is assumed to affect the serum concentration of IGFBP3 in children as well as in adults. However, it is unclear whether this affects physical development according to the concentration of IGFBP3.

P3-926

Usefulness of Priming with Gonadal Steroids Prior to GH Stimulation with Clonidine in the Evaluation of the GH Status of Short Children

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Aim: To determine the usefulness of priming with gonadal steroids prior to GH stimulation with clonidine in the evaluation of the GH status of short children. **Method:** 21 males were studied, with a mean chronological age of 13.2 ± 1.5 years (range 11–16 years), mean bone age 11.0 ± 1.4 years, Tanner stage 1–2, with height 135.8 ± 7.4 cm (Ht-SDS -2.8 ± 0.5), and an inadequate response to an initial GH stimulation test with clonidine (peak GH <10 ng/ml). A second stimulation test with clonidine was performed in the same patients after gonadal steroid priming: 50 mg i.m. testosterone propionate daily for 3 days. **Results:** 15 of 21 children (71%) increased their GH response to a level of >10 ng/ml following priming with gonadal steroids. Mean peak GH after priming was 11.32 ± 5.6 ng/ml compared to a peak GH level of 3.9 ± 2.8 ng/ml prior to gonadal steroid priming (peak GH 14.45 ± 2.0 ng/ml in the responders vs 6.2 ± 2.4 ng/ml in the non-responders). **Conclusion:** Priming with gonadal steroids significantly improves GH secretion following GH stimulation with clonidine and diminishes the possibility of a false diagnosis of GH deficiency.

P3-927

Comparison of Two IGF1 Assays in Patients Treated with GH

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Background: IGF1 measurements are used to diagnose and monitoring GH related disorders. GH dose is titrated against IGF1 concentrations which should be kept within the age-and sex-related normal range. However, IGF1 results vary widely depending on the immunoassay used. International guidelines advise to report IGF1 results as S.D. scores from an assay-specific age-related reference population. **Objective and hypotheses:** Our objective was to assess whether the change in immunoassay lead to different clinical interpretation in prepubertal children, followed-up in our paediatric unit and treated with similar dose of GH. **Method:** We collected 101 samples of 58 patients (23 girls and 35 boys) with tanner 1. IGF1 was measured by the Immulite 2000 (Siemens Diagnostics) immunoassay until February 2013 and by the Liaison (DiaSorin) from this date onwards. IGF1 data from 51 determinations were obtained with the Immulite (group A) and from 50 with the Liaison (group B). **Results:** No differences were found in age (7.96 ± 2.2 vs 8.38 ± 2.2 age; $P=$ N.S:), dose of GH (0.2165 ± 0.031 vs 0.2096 ± 0.034 mg/kg·week, $P=$N.S), absolute IGF1 concentrations (290.5 ± 118 vs 281.9 ± 78.3 ng/ml, $P=$N.S.), or SDS-IGF1 (1.22 ± 1.04 vs 1.25 ± 0.69, $P=$N.S.) between both groups. We took a subgroup of 16 children with determinations by both methods, where no significant differences in the levels of SDS-IGF1 were found. **Conclusion:** In our group of prepubertal GHD patients treated with GH the change in the immunoassay for IGF1 was not associated to changes in clinical decisions. In both groups the same GH dose of GH was maintained as there were not significant changes in SDS-IGF1 regardless of the method used.

P3-928

Acute Effects of a Training Session on IGF1 and IGFBP3 Concentrations in Brazilian Jiu-Jitsu Fighters

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Introduction: The relationship between sports intensity and growth has become a concern in teenagers. Changes in the GH/IGF1 axis have been studied as biomarkers for training intensity in adolescents; however, reports on the effects of physical effort on GH and IGF1 levels are discordant and studies on GH and IGF1 responses in combat sports are scarce. **Aim:** To investigate the effects of a Jiu-Jitsu training session on serum

IGF1 and IGFBP3 concentrations. **Methods:** Nine male Jiu-Jitsu fighters (25±4.7 years), representing a sample of the National Elite in the sport in Brazil with 5.4±2.7 years of practice, were studied. Blood samples for serum IGF1 and IGFBP3 determinations (ELISA) were collected at the beginning (after 30 min rest) and immediately after the training session, which consisted of six 7.5-min fights. The fighters' perception of the intensity of the effort was recorded. Data was analyzed by Wilcoxon test at 5% significance ($P<0.05$). **Results:** The intensity of the effort was rated 'hard' and 'very hard' by the athletes. No significant difference was observed on IGF1 ($P=0.57$) or IGFBP3 ($P=0.73$) levels before or after the training session. Seven athletes had IGF1 levels below the 25th centile (<P10 in two of them) and six showed IGFBP3 levels lower than 4 mg/l. **Discussion and conclusion:** Differently to previous studies, which reported reductions in IGF1 in wrestling fighters after training, a hard training session by National Elite Brazilian Jiu-Jitsu fighters did not have a significant effect on IGF1 or IGFBP3 concentrations. This was probably due to the training status of the fighters, who were at their maximum level of performance in the season and/or to their already low levels of IGF1 and IGFBP3 before training session. Furthermore, our findings support the use of acute changes in GH/IGF1 as biomarkers for training intensity/status in combat sports.

P3-929

Biochemical Profiles Differentials by SGA Children Catch Up

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Background: SGA cohort study in analytical and metabolic variables at 3 and 12 months of age with somatométrica situation. **Material and methods:** Live births in singleton pregnancies in our hospital during 2012–2014, PEG were studied according EG and weight/height (Spanish Tablas 2008). Tours are conducted at 0, 3, 6, 9, 12 months, with measurements of weight, height and perimeter. Blood samples are obtained at least fasting discussed 4h and excess stored for further studies. Catch poor if *P* and/or T< P10 or Δ<0.5 SDS, catch faster if *P* and/or T>P75 or Δ>1 SDS. Methods IGF1 study (2013 – IMMULITE inmunoluminiscencia IRR WHO NIBSC 87/518), glucose/PCR Oquinasa ABBOT 2013, chemiluminescence insulin-ABBOT CMIA 2013, lipids Enzymatic CHOD-BAP 2013 ABBOT. Multivariate ANOVA study and test (X2) with a confidence interval of 95% is made. SPSS 19.0 for paired samples ($P<0.05$). **Initial results:** 80 PEG recruited in 18 months (♂44, 55%). Cases at 3 months follow-up 74 cases (45 samples BQ) and at 12 months follow-up 48 patients (27 samples BQ). At 3 months catch up distribution under/normal/fast (8/40/26), at 12 months Distribution (4/13/10). **Conclusions:** Although the power of the test is medium-low in a group and are not final data (12 months to catch up poor) differences between the different branches are evident, presenting the poor catch values of insulin, glucose, lipids and IGF1 below normal and fast catchp significantly higher, including PCR. These values could help to determine how early the possible behavior of a SGA. Somatometric child in the first months of life and/or demonstrate an early stage and changes in the metabolic profile of the same. **Funding:** Pfizer International research grant was used to buy a personal computer and clinical facilities.

Table 1. (for abstract P3-929)

Age/study media (SDS)	Normal catch-up	Low catch up	High catch up	Signification
Age os study	***3 mouth***	***3 mouth***	***3 mouth***	***3 mouth***
Glucose (mgrs/dl)	72 (8)	58 (6)	81 (5)	0.01
Insulin (mCU/ml)	6 (1)	4 (2)	10 (3)	0.03
PCR (mgrs/dl)	1.8 (0.5)	1.1 (0.3)	2.1 (0.6)	0.55
LDL (mgrs/dl)	58 (8)	49 (6)	68 (10)	0.04
IGF1 (ng/ml)	38 (3)	<25	46 (8)	0.01
Total cases (45)				
Age os Study	***12 mouth***	***12 mouth***	***12 mouth***	***12 mouth***
Glucose (mgrs/dl)	80 (7)	67 (6)	95 (4)	0.001
Insulin (mCU/ml)	9 (2)	6 (2)	15 (4)	0.01
PCR (mgrs/dl)	1.5 (0.3)	1.2 (0.2)	5.8 (1.3)	0.005
LDL (mgrs/dl)	74 (8)	66 (5)	88 (8)	0.01
IGF1 (ng/ml)	88 (7)	35 (5)	124 (18)	0.0001
Total cases (27)				

P3-930

IGF1 Deficiency: An Important Differential Diagnosis in Severe Growth Failure and Its Excellent Response to rhIGF1 Replacement Therapy

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Table 1.

Glucagon stimulation	Peak GH level-6.33 μg/l
IGF1 generation	IGF1 undetectable (<3.3 nmol/l) after GH (33 μg/kg per day×4). IGFBP3 increased from 0.5 to 1.3 mg/l(0.5–2.9)
GH receptor gene sequencing	Normal

Background: IGF1 is the key effector peptide in the control of normal growth. IGF1 deficiency in the presence of normal GH is associated with growth failure. This may be caused by primary defects in the GH-IGF1 axis or by conditions such as malnutrition or chronic inflammation. Severe primary IGF1 deficiency (height <-3 S.D., serum IGF1 <2.5th centile, GH normal) is an European Medicines Agency (EMA) licensed indication for rhIGF1 therapy. We report a patient with severe failure to thrive, short stature and unexplained IGF1 deficiency who showed an excellent response to rhIGF1 therapy. **Case:** A 10 month old girl was referred with severe failure to thrive (weight: 4.2 kg, -7.95 S.D.s, length 60.1 cm, -4.40 S.D.s). She was born to non-consanguineous Caucasian parents at 36 weeks gestation weighing 2.85 kg. She was not dysmorphic or micro cephalic, had gross motor delay, no recurrent infections and a very good caloric intake. Russell-Silver syndrome, skeletal dysplasia, malabsorption and chronic illness were excluded. Cranial MRI was normal and IGF1 was persistently undetectable. Further investigations are as follows (see Table 1): GH therapy (37 μg/kg per day) caused severe diarrhoea with no increase in height velocity or IGF1 level. She was treated with rhIGF1, 120 μg/kg twice daily. After 1 years of treatment, height improved from -4.40 to -1.48 S.D.s and weight from -7.95 to -0.94 S.D.s. The serum IGF1 level normalised (20.9 nmol/l) and age-appropriate motor milestones were achieved. Exome sequencing results are awaited. **Conclusions:** This child with IGF1 deficiency associated with severe failure to thrive of unknown aetiology has shown excellent linear and developmental response to within-label use of rhIGF1 therapy and continues to benefit from this treatment.

P3-931

5-Year Response to GH in Children with Noonan Syndrome and GH Deficiency: Our Experience and Review of the Literature

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Background: Noonan syndrome (NS) is an autosomal dominant disorder characterized by specific features including short stature, distinctive facial dysmorphic features, congenital heart defects, hypertrophic cardiomyopathy, skeletal anomalies and webbing of the neck. Molecular screening has shown that the majority of individuals with NS have a mutation in the PTPN11 gene. Noonan syndrome children may show an impaired GH/IGF axis. Moreover, recombinant human GH (rhGH) has been shown to improve growth rate in patients with NS, although data are still limited. **Objective and hypotheses:** We assessed growth response following GH therapy in GH-deficient NS patients (NSGHD) and compared it with idiopathic GH deficient (IGHD) sex and age-matched patients. We also evaluated the safety of rhGH therapy in NS patients with GHD. **Method:** We enrolled five (two males and three females) GH-deficient NS patients (NSGHD, mean age 8.5 years) and in five (two males and three females) idiopathic GH deficient (IGHD, mean age 8.6 years) patients and followed them for the first 5 years of GH therapy (0.25 mg/kg per week). We also evaluated the safety of rhGH therapy in NS patients with GHD. **Results:** At the beginning of GH treatment, height and growth rate were statistically lower in NSGHD children than in IGHD ones. During the first 3 years of rhGH therapy, NSGHD patients showed a slight improvement in height (from -2.71 to -2.44 S.D.s) and growth rate (from -2.42 to -0.23 S.D.s), although the values were always significantly lower than in IGHD children. After five years of rhGH treatment, height gain was higher in IGHD children (mean 28.3 cm) than in NSGHD patients (mean 23.6 cm). During the first 5 years of rhGH therapy, regular cardiological and haematological check-ups were performed, leading to the conclusion that rhGH therapy was safe. **Conclusion:** Pre-pubertal NS children with GHD slightly increased their height and growth rate during the 1st years of GH therapy, although the response to rhGH treatment was significantly lower than in IGHD children. Furthermore, the therapy appeared to be safe since no severe adverse effects were reported, at least during the first 5 years. However, a close follow-up of these patients is mandatory, especially to monitor cardiac function.

P3-932

Modification of Cardiovascular Risk Factors in Children Treated with GH

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Background: The administration of GH on paediatric patients to optimize the longitudinal growth, can modify some cardiovascular risk factors due to their effects on metabolism. **Objective and hypotheses:** Evaluation of the effect of GH on total cholesterol blood levels (TCBL), fasting blood glucose concentration (FBGC), blood pressure (BP) and BMI, comparing these variables before starting treatment, after a year and at the end. And

it also assesses whether there are differences according to sex, duration and the treatment indication. **Method:** Retrospective longitudinal observational study. Includes 72 patients treated with GH. The group comparison is performed using Chi-square test for categorical variables and Mann Whitney U for continuous variables. Comparison of changes in BMI, glucose, cholesterol and BP from baseline to a year and to the end of treatment was performed with the Wilcoxon *W*-test. **Results:** TCBL descends after a year of treatment ($P=0.03$) and at the end ($P=0.01$). FBGC increases after a year of treatment ($P=0.001$); but the difference is not significant between the start and the end of treatment. BMI decreases after a year of treatment ($P=0.007$) and at the end ($P=0.007$). No differences were found in Systolic BP or Diastolic BP, between different moments of treatment. No differences were observed in any of the analysed variables according to sex or treatment indication at any time. At a longer duration of treatment the decrease of BMI is greater ($P=0.069$) and also rises the decrease of TCBL ($P=0.072$); but the duration of treatment has not resulted in a greater increase in FBGC. **Conclusion:** GH in children improves BMI and TCBL; these changes increase as the treatment duration is longer, due to the lipolytic effect. There are also elevation of FBGC but only during the 1st year of treatment. There are no changes in BP.

P3-933

Adult Height in Children Born Small for Gestational Age and Treated with GH: Data from the French KIGS Database

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Background: Treatment with GH in children born small for gestational age (SGA) increases height velocity (HV) but data on adult height (AH) are scarce. **Objective and hypotheses:** To report AH in a group of SGA children treated with GH. **Method:** This is a post-marketing longitudinal analysis of SGA children treated with GH and included in France in KIGS. Selection criteria were children followed at least one year and having reached AH based on chronological age (CA) in 2013 and HV as defined by a French scientific committee. Median values and 25th; 75th percentiles are shown. **Results:** Out of 432 enrolled SGA patients, 73 children, including 34 (47%) boys, achieved AH and were included in the analyses. At birth, gestational age was 39 (37; 40) weeks and height SDS was −3.08 (−3.68; −2.74). Target height (TH) SDS was −1.08 (−1.64; −0.30). CA at start of GH treatment was 8 (6; 11) years: 21 (54%) girls were older than 9 years and 4 (12%) boys were older than 11 years. GH dose at start of treatment was 0.06 (0.04; 0.06) mg/kg per day. Median CA was 16 (14; 17) years in 2013. Height increased to −2.08 (−2.63; −1.79) SDS after one year and up to −1.73 (−2.27; −1.04) at time of GH withdrawal. AH SDS was −1.92 (−2.42; −1.30) overall 43 (59%) children had reached an AH >-2 SDS. Difference between height and TH at start of GH treatment was −1.74 (−2.68; −0.96) SDS when difference between AH and TH was −0.66 (−1.92; −0.02) SDS at final analysis. No new safety concerns were reported during follow-up. **Conclusion:** In a group of children with severe growth retardation at birth, and treated with GH enabled an AH was slightly lower than the TH. Nearly 60% of the SGA children reached an AH >-2 SDS. **Conflict of interest:** Author received honoraria from Pfizer. **Funding:** This work was supported by Pfizer.

P3-934

Psychosocial Functioning and Self-Perception of Children and Adolescents Treated with GH

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Background: Coping with a chronic medical condition requiring prolonged treatment may have an effect on psychological adaptation and self-esteem of patients. **Objective and hypotheses:** To identify key factors that influence self-perception and well-being in children and adolescents on GH therapy. **Method:** A prospective study with the use of validated questionnaires SPP (the Greek version). The patient cohort included 272 Greek children and adolescents (183 males, 89 females), with mean age 13.7 (5.5) years and mean duration of GH treatment 3.4 (3.1) years. Student's *t*-tests and ANOVA were computed for the comparison of mean values. Pearson correlations coefficients were used to explore the association of two continuous variables. **Results:** Mean score for 'Relationships with peers' was 3.13 (S.D. = 0.53), for 'Relationships with parents' was 3.03 (S.D. = 0.60), for 'Athletic competence' was 3.16 (S.D. = 0.66), and for 'Physical appearance' was 2.83 (S.D. = 0.60). Also, mean score for 'Self-esteem' was 3.28 (S.D. = 0.50), for 'Attitude' was 2.96 (S.D. = 0.57), for 'Close friends' was 3.00 (S.D. = 0.62) and for 'Emotional relationships' was 2.73 (S.D. = 0.61). All scores were positively correlated with each other indicating the close relationship among all studied parameters ($P<0.050$). Males were found to have better relationship with peers, better athletic competence and worse attitude than females ($P=0.010$; $P=0.013$ and $P=0.023$ respectively). Participants living in urban areas had significantly better relationship with their parents compared to those living in rural areas ($P=0.034$). Mothers' high educational level was positively related with participants' self-esteem and opinion about their physical appearance ($P=0.025$ and $P<0.001$ respectively). Fathers' low educational level was negatively associated with patients' attitude ($P=0.043$). Age and socio-economic status were not significantly associated with any of the self-perception scores. **Conclusion:** Children on GH therapy score above average concerning relationships with parents and peers and have good athletic competence. Sexual dimorphism

was appreciated regarding relationships with peers, athletic competence and attitude.

P3-935

Do IGF1 Generation Test Results Predict 1st-Year Growth Response to GH Treatment in Idiopathic Short Stature?

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Background: It is well-known that human GH (hGH) treatment increases growth rate in idiopathic short stature (ISS) in the short term which might predict the overall height gain. However,the fact that ISS might involve a heterogeneous group of individuals with individual benefits from hGH treatment makes the decision to treat or not to treat difficult. **Objective and hypotheses:** The aim of this study was to investigate retrospectively whether an IGF1 generation test (IGFGT) might be used as a tool to predict the first year growth response to GH treatment in individuals with ISS. **Method:** 57 subjects with ISS who had at least %20 increase in IGF1 levels with an IGFGT and who were treated for at least one whole year with GH were included in the study. Of these 57 subjects, 29 were girls. The mean age of the patients was 11.47 ± 1.95 years and 38 were prepubertal. IGF1 levels were measured by a chemiluminescence immunoassay. IGF1 levels and heights were expressed as SDS both for age and gender. Bone age was evaluated by Greulich Pyle method. The increase in IGF1 levels were expressed both as the percentage of the initial value and delta IGF SDS. **Results:** Height SDS increased significantly both in pubertal (-2.78 ± 0.88 vs -2.03 ± 0.80) and prepubertal (-2.77 ± 0.54 vs -2.50 ± 0.64) subjects; however, bone age increased 2.12 ± 1.54 years and 2.00 ± 1.32 years in 1 year respectively. There was a negative correlation between delta height SDS and basal IGF1 SDS ($r = -0.434$, $P = 0.001$). There was a positive correlation between delta height SDS and delta IGF1 SDS ($r = 0.372$, $P = 0.004$) but the same was not true for percentage increase in IGF1. **Conclusion:** Our results suggest that in individuals with ISS, the lower basal IGF1 SDS is and the higher increase in IGF1 SDS(in an IGFGT) is, the more the height gain after one year of GH treatment is.

P3-936

Adherence to GH Treatment: Impact of Actual Height, Treatment Duration, and Puberty

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Background: Adherence to GH treatment is a challenge. **Objective and hypotheses:** We analysed the impact of treatment duration, treatment success, treatment indication, age, gender, pubertal stage, and height on treatment adherence (TA) to optimise treatment success. **Method:** Based on the easypod autoinjector used in the Saizen-online prospective, multicenter, open-label, noninterventional study we analyzed TA in 6 months periods. TA was evaluated using proposed cut-offs (good adherence: <1 missed dose/week; medium adherence: 1–3 missed doses/week; poor adherence: >3 missed doses/week)[1]. **Results:** 168 children treated with GH (71% GH deficiency, 7% Turner-Syndrome, 2% chronic renal insufficiency, 20% small-for-gestational age) were included (641 6-months observations periods). TA did not differ significantly between treatment indications ($P = 0.713$) or gender ($P = 0.167$). Younger age, prepubertal stage, and lower height-SDS were associated with better TA, while better treatment success and longer treatment duration were related to lower TA (table 1). **Conclusion:** Especially in pubertal children with good treatment success so far, TA should be critically reviewed. **Funding:** This work was supported by a grant from Merck Serono GmbH, Darmstadt Germany. Study design, data collection and analysis, decision to publish, and preparation of the manuscript are solely the responsibility of the authors.

Table 1 (for abstract P3-936).

	Good adherence	Medium adherence	Poor adherence	*P*-value
Number of 6-months observation periods	373 (58.2%)	135 (21.1%)	133 (20.7%)	
Age (years)	11.6 ± 3.2	13.4 ± 3.1	12.0 ± 3.1	$<0.001^{1,2,4}$
Actual height-SDS	-1.9 ± 1.1	-1.7 ± 1.2	-1.3 ± 1.3	$<0.001^{1,3}$; 0.038^{2}; 0.017^{4}
Prepubertal	57.3%	32.2%	48.7%	$<0.001^{1,2}$; 0.012^{4}
Treatment success (actual height-SDS–height-SDS at onset of GH treatment)	+0.8 (IQR 0.2–1.4)	+0.7 (IQR 0.2–1.3)	+1.0 (IQR 0.5–1.5)	0.004^{1}; 0.002^{3}; 0.005^{4}
Treatment duration (y)	1.8 (IQR 0.8–3.6)	3.0 (IQR 1.5–4.5)	2.5 (IQR 1.6–3.6)	$<0.001^{1,2,3}$

Data as *n* (%), mean ± 1 S.D., or median and interquartile range (IQR); *P*-values: 1) overall; 2) good versus medium; 3) good versus poor; 4) medium vs poor TA, Fisher's exact, Wilcoxon–Mann–Whitney and Kruskal–Wallis tests were used as adequate.

P3-937

The Blood Oxidant System and Insulin Resistance in Girls with Turner Syndrome after 1 Year of GH Therapy

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Background: The effects of recombinant GH therapy on development of oxidative stress and insulin resistance in girls with Turner syndrome (TS) were observed. **Objective and hypotheses:** The aim of this study is to examine the longitudinal relationships of oxidative stress markers with the development of insulin resistance during GH treatment in girls with TS. **Method:** Ten prepubertal girls (aged 12–14 years; median 13.0 years) with TS were included in the study. All of them have not been treated with GH before. Blood antioxidant system was examined using activity of superoxide dismutase and catalase, thiobarbituric acid reactive substances (TBARS), ceruloplasmin level and total antioxidant capacity (TAC) of plasma. Levels of lipids, glucose, insulin, HbA1c and IGF-1 were measured in blood plasma before and after 1 year of GH treatment (0.05 mg/kg per day). The insulin resistance assessed using the homeostasis model assessment of insulin resistance (HOMA-IR). **Results:** The concentration of plasma insulin level in girls with TS after 1 year treatment GH was significantly higher than before (7.2 ± 3.4 vs 14.5 ± 4.9 mU/l, $P = 0.003$). The values of HOMA-IR in girls with TS after treatment GH was significantly higher than before (1.6 ± 0.8 vs 3.2 ± 1.22, $P = 0.008$). Before treatment value of HOMA-IR was less than 3.2 (upper reference limit) from all patients, after treatment it was more than 3.2 in five of ten patients (max value of HOMA-IR was 4.7). Also after treatment the value of TBARS was significantly greater (about 40%) and the catalase activity was significantly lower (about 30%) than before treatment. **Conclusion:** So GH treatment in girls with TS after 1 year GH treatment promoted insulin resistance accompanied by the development of mild form of oxidative stress.

P3-938

An Open-Label Phase 2 Dose-Finding Study Comparing Three Different Doses of Weekly TV-1106 and Daily Recombinant Human GH (Genotropin®) in Treatment-Naive, Pre-Pubertal, GH-Deficient Children

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Background: TV-1106 (Teva Pharmaceuticals) is a genetically fused human GH and human serum albumin, in development for treatment of GH deficiency (GHD). TV-1106 has an extended duration of action compared to daily GH treatment and thus it is believed that treatment with TV-1106 can reduce the frequency of injections and improve compliance and quality of life for those requiring growth hormone replacement therapy. The efficacy and safety data from adult studies with TV-1106 support initiation of the pediatric phase 2 study. **Objective and hypotheses:** The aim of the phase 2 study is to evaluate the safety and efficacy of three different weekly doses of TV-1106 and a daily dose of Genotropin as a treatment of pediatric GHD. **Method:** 60 treatment-naïve pre-pubertal children with GHD will be randomized (1:1:1:1) to one of 3 doses of TV-1106 (0.554 mg/kg per week, 0.924 mg/kg per week, and 1.2 mg/kg per week) administered s.c. injection or a daily dose of Genotropin (0.033 mg/kg per day s.c. injection). The open-label study consists of four periods: screening, 6-month core study, 6-month efficacy extension, and 12-month safety extension. Primary endpoints are safety and tolerability; secondary endpoints are height velocity (HV), HV S.D. scores (HV-SDS), and height S.D. scores (H-SDS). Exploratory endpoints include IGF1 and bone maturation as measured by ratio of bone age to chronological age (BA/CA), patient adherence and quality of life outcomes. **Results:** For the 24 patients currently enrolled in TV-1106 groups (0.554 0.924 and 1.2 mg/kg per week) and Genotropin group, mean peak GH level (mcg/l) at baseline are 6.7, 4.7, 1.8 and 6.7 and mean IGF1 SDS scores at baseline are -0.83, -0.7, -1.7, and -1.25 respectively. Demographics for all study participants will be presented. **Conclusion:** This study will provide essential data towards understanding how once weekly administration of TV-1106 safely and effectively treats pediatric patients with GHD. **Funding:** This work was supported by the Research and Development Divsion of Teva Pharmaceuticals Ltd Israel.

P3-939

Increasing Lean Body Mass, Phase Angle, and Total Body Water But Decreasing Body Fat Among Short-statured Children Born Small-for-Gestational Age on GH Treatment

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Background: There is a small proportion of children born SGA without postnatal catch-up growth who are presented with persistent short stature, low BMI, and decreased lean body mass (LBM). Data on body composition are rarely reported in the literature. Our study addresses the question whether human recombinant GH treatment could affect body composition in these SGA children or not. **Design:** We included 58 SGA children ($n = 20$ females) with SGA (birth weight and/or birth length < -2.0 SDS). At start of GH treatment, chronol. ages varied between 3.5 and 12 years (median 9 years). GH was administered daily s.c. in a mean GH dose of 35 μg/kg BW). Body composition was measured by single-frequency bioelectrical impedance analysis (BIA) at start of GH, and thereafter annually for

4 years. LBM, phase angle (PA), total body water (TBW), and body fat (BF) values were converted into SDS. Additionally, IGF1 and IGFBP3 levels were obtained. **Results:** (median (IQR: 25th; 75th percentile): Height SDS and BMI SDS significantly increased (H: start −3.4 (−3.6, −3.0); 1st year −2.4 (−2.5, −2.0); 4th year −1.1 (−1.8, −0.7); BMI: start −1.1 (−1.4, −0.5); 1st year −0.8 (−1.3, −0.3); 4th year −0.4 (−1.1, −0.7)). Serum IGF1 SDS and IGFBP3 SDS increased after start of GH (IGF1: start −1.3 (−1.9, −0.4); 1st year 1.2 (−0.1, 2.4); 4th year 1.5 (0.3, 2.5); IGFBP3: start −0.2 (−0.9, 0.4); 1st year 1.5 (0.6, 2.3); 4th year 1.3 (0.2, 1.9)) . Parameters derived from BIA showed decreasing body fat SDS (start −0.7 (−1.4, 0.2); 1st year −1.7 (−2.5, −0.9); 4th year −1.6 (−2.1, −0.9)), increasing LBM (start −1.9 (−2.4, −1.4); 1st year −0.76 (−1.3, −0.2); 4th year −0.2 (−0.7, 0.6)), increasing TBW (start −1.8 (−2.1, −1.6); 1st year −0.9 (−1.3, −0.7); 4th year −0.6 (−1.0, 0.5)), and – as a measure for sufficient cell metabolism – an increasing phase angle (start −0.3 (−1.0, 0.5); 1st year 0.2 (−0.4, 0.8); 4th year 0.8 (0.3, 1.5)). **Conclusions:** In SGA children on GH treatment, our data show a significant improvement of body composition in terms of body fat, lean mass and general cellular integrity.

P3-940

GH Dosing Patterns in Children with Isolated GH Deficiency and Multiple Pituitary Hormone Deficiency Enrolled in the NordiNet® International Outcome Study

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Background: Long-term monitoring of GH treatment in children is very important. **Objective and hypotheses:** To describe patterns of GH dosing in clinical practice in children with isolated GH deficiency (IGHD) and multiple pituitary hormone deficiency (MPHD). **Method:** We analysed 7 years of GH treatment data from NordiNet® International Outcome Study (IOS) (NCT00960128), an observational study evaluating the long-term effectiveness and safety of Norditropin®. Dosing analysis was performed by gender, diagnosis (MPHD/IGHD), age, baseline height SD score (SDS) and BMI SDS. GH dose was categorised by mean dose in the full treatment period (μg/kg/day): low (0–25), medium (>25–40) and high (>40–≤70). **Results:** At baseline, (mean±SD) patients with IGHD ($n=5\,503$) were younger (9.1±4.0 years) and shorter (height SDS, −2.6±0.9) than patients with MPHD ($n=794$; 9.8±4.3 years, height SDS, −2.2±1.3). Mean GH dose (μg/kg/day) during the 7-year period (IGHD, 32.0±6.6; MPHD 29.1±8.6) was similar between sexes (Table 1). Proportionally more patients with MPHD than with IGHD were in the low-dose group (Table 1). During year 1, GH dose was unchanged for most patients (IGHD 82.0%; MPHD 82.7%). During year 2, GH dose increased for 24.7 and 20.1%, and decreased for 10.4 and 15.8% of patients with IGHD and MPHD respectively. Baseline BMI SDS was significantly inversely correlated with average GH dose in the full treatment period (IGHD and MPHD, $P<0.0001$). GH doses tended to decrease at age ∼14 years (girls) and ∼15 years (boys). **Conclusion:** Patients with MPHD received lower mean GH doses than patients with IGHD. Over 75% of patients with IGHD and >50% with MPHD were in the medium-dose group. **Conflict of interest:** M Šnajderová and O Blankenstein are members of the NordiNet® IOS International Study Committee. E Pournara and B Tønnes Pedersen are employees of Novo Nordisk. **Funding:** This study was sponsored by Novo Nordisk Health Care AG.

P3-941

Decrease of Small Dense LDL and Lipoprotein-Associated Phospholipase A2 due to Human GH Treatment in Short Children with GH Deficiency and Small for Gestational Age Status

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Objectives: GH deficiency (GHD) and small for gestational age (SGA) status are associated with cardiovascular risks. We therefore investigated antiatherogenic effects of GH. **Methods:** Subfractions of LDL and HDL, lipoprotein-associated phospholipase A2 (Lp-PLA2), and high-sensitivity C-reactive protein (hsCRP) were measured at baseline, after 8 and 52 weeks of GH

Table 1 (for abstract P3-940).

		Low, %	Medium, %	High, %	Mean±SD dose, μg/kg per day
IGHD	All	11.2	78.6	10.2	32.0±6.6
	Boys	11.5	78.7	9.9	31.9±6.6
	Girls	10.7	78.5	10.9	32.4±6.8
MPHD	All	28.3	63.6	8.1	29.1±8.6
	Boys	25.8	66.9	7.3	29.3±8.0
	Girls	32.2	58.7	9.2	28.7±9.4

treatment in 51 short children born SGA ($n=33$) or with GHD ($n=18$). **Results:** For the overall group, we found post-treatment reductions of LDL cholesterol ($P=0.016$), small-dense LDL cholesterol ($P<0.001$), Lp-PLA2 ($P<0.001$), and hsCRP ($P=0.005$), but increases of HDL2a cholesterol ($P=0.025$). SGA children showed reductions of small-dense LDL cholesterol ($P=0.02$), Lp-PLA2 ($P=0.002$), hsCRP ($P=0.037$) and increases of HDL2a cholesterol ($P=0.004$). GH deficient children had non-significant decreases of small-dense LDL cholesterol, Lp-PLA2, hsCRP and increases of HDL2a cholesterol. **Conclusions:** Children with GHD or born SGA may benefit from GH treatment by growth acceleration and simultaneous reduction of their latent cardiovascular long-term risk.

P3-942

Long-Term Insulin Sensitivity and β-Cell Function in Short Children Born Small for Gestational Age Treated with GH and GnRHa: Results of a Randomised, Dose-response Trial

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Background: Pubertal children born small for gestational age (SGA) with a poor adult height (AH) expectation can benefit from treatment with GH 1 mg/m^2 per day (~0.033 mg/kg per day) in combination with 2 years of GnRH analogue (2 years GnRHa) and even more so with 2 mg/m^2 per day (~0.067 mg/kg per day). Concerns haven been raised about the effects of GH and GnRHa on insulin sensitivity on the long-term. **Objective and hypotheses:** To investigate insulin sensitivity and β-cell function during long-term GH treatment, either with or without 2 years of GnRHa. To study whether GH 2 mg/m^2 per day results in a less favorable insulin sensitivity at AH than GH 1 mg/m^2 per day. **Method:** Longitudinal, randomised, dose-response GH trial involving 110 short SGA children (59 girls) treated with GH until AH; 67 received also 2 years GnRHa. Frequently sampled intravenous glucose tolerance (FSIGT) tests were performed and insulin sensitivity (Si), glucose effectiveness (Sg), acute insulin response (AIR) and disposition index (DI) were calculated using Bergman's MINMOD MILLENIUM software. The GH-dose effect was evaluated in a subgroup of 48 children who started GH treatment in early puberty (random 1 or 2 mg/m^2 per day) with 2 years of GnRHa. **Results:** At AH, Si, Sg and AIR were similar between children treated with GH/2 year GnRHa and those treated with only GH. In the pubertal subgroup there was no GH dose-effect on Si, Sg, AIR and DI. In addition, we performed an FSIGT in 15 children at start and after 3 months of only GnRHa. There was no significant change in Si, Sg, AIR and DI during only GnRHa treatment. **Conclusion:** Combined GH/2 years GnRHa has no long-term negative effects on insulin sensitivity and β-cell function compared to only GH. Started in early puberty, a GH-dose of 2 mg/m^2 per day results in a similar insulin sensitivity at AH as a dose of 1 mg GH/m^2 per day. **Funding:** This study was an investigator initiated study, supported by an independent research grant from Pfizer B.V. The Netherlands.

P3-943

Influence of the Application of the POI Score on the Results of GH Therapy in Prader-Willi

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Background: According to international guidelines Prader-Willi children during GH treatment must be closely monitored by polysomnography, ENT evaluation and IGF1 levels. **Objective and hypotheses:** The study aims to determine whether the modulation of GH therapy in children and adolescents with Prader-Willi Syndrome with a specific decisional score (POI score; Salvatoni A., Horm Res Paediatr. 2012) changes and to what extent the results of the therapy. **Method:** We compared retrospectively 40 prepubertal children (21 boys), aged 4.1 (3.8) year, with genetically confirmed Prader-Willi syndrome, in treatment with GH for at least 3 years. Twenty patients (group A) were treated with a GH standard dose of 0.09 U/kg per day, and treatment was discontinued according to the Italian pharmaceutical agency (AIFA) recommendations (BMI over 95th percentile and/or OSAS); in the other 20 patients (group B) the dosage of GH treatment was modulated according to the POI score. We compared in the two groups of patients the trend of the following aspects in the last 2 years of GH treatment: times of discontinuation of the treatment, dosage of GH, IGF1 levels, height-SDS and BMI-SDS. The results are reported as (median (IQR). Mann-Whitney Rank test was used for statistical analysis. **Results:** The group B resulted to be treated with significant lower dose of GH (0.08 (0.06) mg/kg per week vs 0.31 (0.03) mg/kg per week; $P<0.0001$)). The two groups showed at the end the 2 years of treatment similar changes in BMI-SDS (group A+1.2(1.6) vs group B+0.1 (2.6); $P=$ns), height-SDS (group A+0.66 (1.36) vs group B+0.10 (1.01); $P=$ns) and times of discontinuation of the treatment (one case in each group). The change in IGF1-SDS resulted significantly higher in group A (group A 2.39 (1.78) vs group B 1.36 (1.82); $P<0.02$). **Conclusion:** The use of the POI score even reducing GH doses and IGF1 levels does not significantly alter the therapeutic results. **Conflict of interest:** The study was supported by a grant Provided by Pfizer. **Funding:** This work was supported by Pfizer - Ref Pfizer WI180070.

P3-944

The Impact of GH Therapy in Noonan Syndrome Children with Identified Mutations in RAS/MAPK Pathway

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Objective: To evaluate the response to recombinant human GH (rhGH) treatment in NS children with short stature and previously identified mutations in the RAS/MAPK pathway genes. **Methods:** 23 patients with NS (17 males; 19 *PTPN11*, 3 *RAF1* e 1 *SHOC2*) were daily treated with rhGH (mean rhGH dose of 47 μg/kg per day). The main outcome measures were 1st year growth velocity, change in height SDS (Noonan syndrome specific), change in IGF1 levels and adult height SDS. **Results:** At the start of rhGH treatment, the mean age was 10.7 ± 3.7 years, bone age was 8.6 ± 3.2 years and 18 children were prepubertal. All subjects presented a height SDS < -2 for reference population (H-SDS = −3.4 ± 0.8) and appropriate BMI-SDS. Noonan syndrome specific height SDS (HNS-SDS) was −0.8 ± 0.7. Growth velocity (GV) during the 1st year of therapy was 7.0 ± 2.0 cm/year, an increment of 2.9 ± .3.2 in baseline GV. Height SDS significantly improved after 1 year of rhGH therapy (mean change in HNS-SDS of 0.5 ± 0.4, $P < 0.001$). IGF1 levels also increases during the first year of therapy (99.7 ± 56 μg/l to 237 ± 104 μg/l, $P < 0.001$). Adult height was achieved in eight patients (six *PTPN11*, one *RAF1*, one *SHOC2*) after 3.5 years of treatment. The total height SDS gain in relation to Noonan syndrome specific growth chart was 1.0 ± 1.3, equivalent of 7 cm. No clear genotype influences on treatment outcomes were observed. **Conclusions:** The use of rhGH to promote linear growth in short children with NS is still controversial. The increment of height SDS in relation to population matched Noonan syndrome specific growth chart support a benefit of this therapy to improve the adult height. **Funding:** This work was supported by the FAPESP 2014/09410-0.

P3-945

As Great Intra as Interindividual Variability in Uptake of s.c. GH Injections in Longitudinally Followed GH Treated Children

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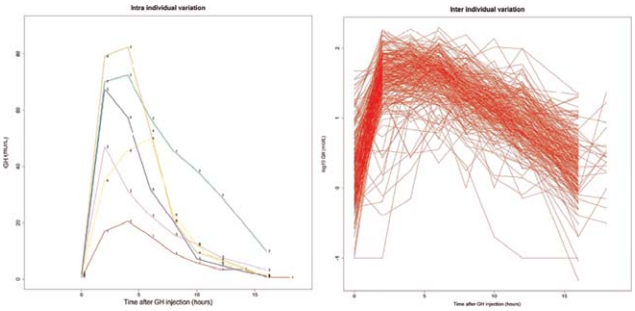
Background: The variation in uptake of daily sc GH-injections is hardly known. **Objective and hypotheses:** There is a considerable variability in uptake of s.c. GH-injections both within and between children. **Method:** 65 children used (Genotropin® pen 4/16, needle 12 mm), dose 0.08–0.14 mU/kg per day within trials: TRN 87–010; 88–080; 88–177; followed yearly two–eight times 1992–1999 ($n = 214$). GHserum-sampling every 2nd h, before and until 16 h after the s.c. GHinj at 18.00 h, given by patient/parent under nurses' supervision: 90° deep sc in femoral muscle. GH was analysed by Pharmacia Polyclonal assay, IRP 80–505, with CV 10%. Pharmacokinetic estimates were Tmax (h), Cmax (ug/l), AUC 16 h. The GH-curves divided into group A: back-to-baseline within 16 h ($n = 46$), group B: did not return ($n = 70$), group C: suspected GHpeak from endogenous secretion ($n = 74$). Values given as median (coefficient of variation, CV %). **Results:** *Interindividual variation:* group A: with Cmax 64 (45) at Tmax 4 (42), AUC1 6 h 407 (40) and back-to-baseline after 16 h (43). Group B: Cmax 61 (50), Tmax 4 (38), AUC 16 h 420 (40). Group C: Cmax 60 (56), Tmax 4 (60), AUC 16 h 431 (52). *Intra-individual variation*: **group A + B + C**: 51 subjects with 2–8 times = 190 curves: Cmax 63 (36), Tmax 4 (41), AUC 16 h 426 (32). **Conclusion:** As great intra and inter-individual variability in GH uptake from s.c. injection was found. The impact on growth and IGF1 response remains to be elucidated. **Funding:** These investigator-initiated and sponsored studies (TRN 88-080; TRN 88-177; TRN 89-071; TRN 98-0198-003) were supported by unrestricted research grants from Pharmacia/Pfizer, the Swedish Research Council grant no 7509, the Foundation Växthuset for Children, Sahlgrenska University Hospital (ALF), West Sweden Region (VGR) grants, and the County Council of Östergötland.



P3-946

The Correlation between the Increase in IGF1 and the Growth Improvement Induced by GH Treatment in Short Children Born Small for Gestational Age

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Background: IGF1 is an important marker of GH treatment and is used to titrate the GH dose. **Objective and hypotheses:** We report the correlation between the GH treatment induced increase in IGF1 and growth improvement in short children born small for gestational age (SGA). **Method:** We recruited 13 prepubertal SGA children (eight boys, five girls) who received GH treatment. Eight continued treatment for >2 years. We retrospectively analyzed the correlation between the following parameters: i) IGF1 S.D. score increase (ΔIGF1 SDS) at 24 h, 1 or 2 years after GH treatment initiation; ii) height S.D. score increase (ΔHSDS) at 1 or 2 years. **Results:** There was a significant positive correlation between ΔIGF1 SDS at 1 year and ΔHSDS at 1 year ($r=0.61$, $P=0.027$), and a positive correlation between ΔIGF1 SDS at 2 years and ΔHSDS at 2 years ($r=0.65$, $P=0.079$). Serum IGF1 levels were significantly elevated 24 h after the initiation of GH treatment ($P=0.016$). Although there was no significant correlation between ΔIGF1 SDS at 24 h and ΔHSDS at 1 year ($r=0.075$, $P=0.82$), there was a significant correlation between ΔIGF1 SDS at 24 h and ΔHSDS at 2 years ($r=0.72$, $P=0.045$). **Conclusion:** As previously reported, the ΔIGF1 SDS induced by GH treatment was positively correlated with ΔHSDS. Importantly, there was also a correlation between the IGF1 increase 24 h after the initiation of treatment and growth improvement. Although IGF1 is affected by various factors such as nutrition status, the IGF1 increase 24 h after the initiation of GH treatment should reflect GH responsiveness independently of such factors. We conclude that IGF-1 at 24 h could be an important predictive factor for GH treatment-induced growth improvement.

P3-947

Medical and Biochemical Effects of Intervention Program in Patients with Poor Adherence to rhGH Treatment

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Background: Optimising adherence to treatment in paediatric patients is important, since non-adherence may lead to incorrect interpretation of growth results and in the treatment course. It has been found that injection frequency is correlated with growth response and final height among children treated with rhGH. **Objective and hypotheses:** The main aim of this study was to evaluate IGF1 levels and growth velocity before and after a medical intervention in non-adherent patients group of our service. **Method:** This was an observational, longitudinal study. We used the issued-uncharged rhGH presctiptions of the last 6 months to evaluate compliance. Medium-low adherence was defined as a rate below 92%. 33 patients were included. We contacted their families in order to inform them about the importance of the treatment, exposing the reasons for poor adherence. Twice monthly monitoring was carried out during 6 month. Furthermore, patients were asked to bring their empty vials in each visit. Growth velocity and IGF1 values were calculated before the intervention and were re-calculated afterwards, expressed in S.D.S. **Results:** The initial adherence rate was 80.8%. No differences were found in relation to GH deficiency diagnosis, age, gender or duration of treatment. After intervention the adherence rate was 91.7% ($P<0.001$). Mean S.D.S IGF1 before intervention was 1.44 (± 0.75) vs 1.70 (± 0.86) 6 months after intervention (P: 0.031). Similar results occur with mean S.D.S growth velocity -0.20 (± 1.3) vs 0.66 (± 1.48) before and after intervention respectively (P: 0.02). A positive relationship was observed between changes in S.D.S IGF1 (Final S.D.S IGF1 minus initial S.D.S IGF1) and changes in adherence to treatment, however the correlation coefficient did not reach formal statistical significance ($r=0.355$; $P=0.059$). **Conclusion:** Adherence to rhGH treatment is efficaciously improved by an educational intervention that involves patients and their families, and this improvement has visible and relevant consequences on clinical and biochemical outcomes in a relative short period of time.

P3-948

Favourable GH Treatment Response in a Young Boy with Achondroplasia

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Background: Achondroplasia is a skeletal dysplasia being the most common cause of rhizomelic dwarfism. **Case presentation:** We present a 10 years old boy who was first diagnosed prenatally. He had a mutation c1138G>A in the gene FGFR3 in a heterozygotic constellation. His IGF1 levels and IGFBP3 were normal. Two stimulation tests for GH were performed with normal levels of the hormone. His psychomotor development was adequate for his age except for speech difficulty. He started with recombinant hGH (r-hGH) at the age of 3.4 years in a dose of 0.06 mg/kg. His mean Height SDS (HtSDS) was -2.2. The growth increased to 10 cm/year in the 1st year of therapy (HtSDS – 1.1). It decreased during the second year to 4 cm (HtSDS – 1.7) and again increased during the 3rd year to 8 cm/year (HtSDS – 1.3). In the next years the growth was constant (6.5, 2.3, 3.5 cm/year). He is still growing in the 3rd percentile of the growth curve (HtSDS – 1.2). The body disproportion did not aggravate during treatment. **Conclusion:** The growth was satisfactory in the first 4 years of treatment, although he still continued to grow. The young age at the start of treatment was also of importance. Our other patients with achondroplasia who started treatment older had a poor response to GH.

P3-949

Plexiform Neurofibroma and Demielinisant Lesions in a Patient with GH Deficiency Treated with rGH

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Case report: A 13-year old boy treated with rGH for short stature due to isolated GH deficiency was submitted in our clinic in June 2014 for regular follow-up. From his medical history we note that he was diagnosed with GH deficiency in 2009 (−4.5 S.D.) and started treatment with rGH 0.035 mg/kgc per day since February 2009. The physical exam showed H=149.9 cm (−0.74 S.D.), 39 kg, Tanner P3G3 and a subcutaneous left paravertebral tumour in the toracal region reported to be painful by the patient. The tumour had hard consistency, was mobile and had no sign of inflammation. A spinal MRI was performed that showed a left paramedian toracal tumour located from T7 to T9 with extension in the left VIIIth foramen that raised the suspicion for a toracal neurofibroma with intra and extraforamen extension. He was sent to surgery and the biopsy revealed a plexiform neurofibroma. In October 2014 (4 months later), a spinal MRI was performed that showed no signs of restant tumour or relapse. Taking into account the patient's family complaint of child's poor scholar performance and memory loss, a cerebral MRI was done revealing some demielinisant supratentorial lesions; consequently, the patient is currently under evaluation in the paediatric neurology department. **Particularity:** In this case, a keypoint resides in the fact that the tumour was discovered early due to the periodic follow-up for GH therapy but another issue might be the continuance of the GH-therapy. **Funding:** This paper is partly supported by the Sectorial Operational Programme Human Resources Development (SOPHRD), financed by the European Social Fund and the Romanian Government under the contract number POSDRU 141531.

P3-950

Growth, Development and Puberty of Patients with Congenital Multiple Pituitary Hormone Deficiencies

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Background: The congenital form of congenital multiple pituitary hormone deficiencies (cMPHD) is rarely differentiated from the acquired type. cMPHD is due to impaired production of several pituitary hormones, caused by mutations in the pituitary transcription factors genes: PROP1, POU1F1 (PIT1), HESX1, LHX3, LHX4. It includes short stature, delayed puberty, cognitive impairment, obesity and metabolic abnormalities. **Objective and hypotheses:** To evaluate in a retrospective study the effects on growth and development during hGH replacement therapy alone and in combination with sex hormone therapy in patients with cMPHD. Out of 49 patients with MPHD, 29 were congenital. 15 belonging to consanguineous families and inbred clans, three of these families have more than one affected sibling. **Method:** All patients were diagnosed, treated and followed in our clinic. **Results:** Mean birth weight of 21/29 neonates was 3126+536 g (2500–3600). Mean birth length of 7/29 neonates was 48.7+2 cm (45–50). By history neuromotor development was normal or slightly delayed. Age at referral was 9.5+7 yearsears (0.3–21.4) (m) and 6.7+3.5 years (1.4–15.1) (f). Height (S.D.s) before treatment was −2.8+1.0 (−4.4 to −0.9) (m) and −2.8+1 (−4.8 to −1.7) (f). Mean age at initiation of hGH treatment was 9.9+6.7 years (0.5–22.5) (m) and 10.3+4.2 years (0.8–16.5) (f). Mean age at initiation of sex hormone treatment was 17.0+3.5 years (13.1–23.8) (m), 17.1+2.3 years (13.8–21.9) (f). Penile and testicular sizes were below normal before and after treatment. Head circumference (S.D.) was −1.9+0.9 before and −0.63+1.8 at end of treatment. Final height (S.D.s) reached −1.1+0.6 for both males and females. **Conclusion:** Despite the fact that cMPHD can be recognised immediately or short time after birth, the age at referral by parents or family physician was late. Nonetheless, the final height was higher than patients with cIGHD, most probably due to the late onset of induced puberty.

P3-951

Predictors of Response to rhGH Treatment in 125 Children with Short Stature of Various Aetiologies

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Background: Response to rhGH treatment is extremely variable in pediatric growth disorders; predictors of the response are not yet clearly determined, due to disomogeneity of studied cohorts. **Aims and objectives:** To investigate the correlation between clinical parameters and height gain after the 1st year of rhGH treatment and at the last visit in eight different aetiologies of short stature, with the aim of identifying predictors of response to rhGH treatment. **Methods:** We selected 125 prepubertal children showing hormonal and clinic alterations (0< IGF1 <−2 S.D.s and/or GH stimulated peak secretion < 8 μg/l AND H<−3 S.D.s or HV <−2 S.D.s or H <−2 S.D.s+HV <−1.5 S.D.s) and treated with rhGH for a mean period of 5.298 years (range 2–15.66 years). Patients have eight diagnosis: 19 Organic GH-Deficiency (GHD), 19 Isolated idiopathic-GHD, 16 neurosecretory disfunction, 14 radio-treated GHD, 15 ISS, 11 SGA, 11 SHOX-Deficiency, 20 Turner Syndrome. We evaluated the correlation between

clinical and hormonal parameters and height gain S.D.s after the 1st year and at the last visit. **Results:** There was strong correlation between height gain sds at the 1st year and pre-treatment IGF1 levels (P: 0.045 r: 0.19) and between height gain sds at the last visit and three parameters: height gain sds at the 1st year ($P<0.0001$ r: 0.47), pre-treatment IGF1 values (P: 0.0033 r: −0.28), HV S.D.s at 1 year of therapy ($P<0.0001$ r: 0.37). **Conclusions:** Predictors of response to rhGH treatment could guide rational use of this therapy, in particular to decide which patient could benefit of treatment on the long period. Our data show that children having a very low value of IGF1 are those that will benefit most from the treatment. Furthermore, the effectiveness of rhGH therapy can be evaluated by estimating the standardized height gain and the height velocity after 1st year.

P3-952

Linear Regression Model of Final Height Prediction Based on Pre-Treatment Data in Children with GH Deficiency Treated with GH

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Background: Prediction of GH therapy effectiveness in children with short stature is an important issue in paediatric endocrinology. **Objective and hypotheses:** The aim of the study was to create a linear regression model of GH therapy effectiveness, based on the data available before treatment. **Method:** Retrospective analysis comprised the data of 150 short children (101 boys), diagnosed with isolated GH deficiency, who were treated with GH up to the attainment of final height (FH). The following parameters (input variables) were assessed before treatment for each patient: gender, chronological age (CA), bone age (BA), BA/CA ratio, height (expressed as hSDS), mothers' and father's height (expressed as mhSDS and fhSDS respectively), height velocity (HV), pubertal stage (labelled: prepubertal – 0, pubertal – i), GH peak after falling asleep and in two stimulation tests (all GH values log-transformed), IGF1 (expressed as S.D.s for age and sex), IGF1/IGFBP3 molar ratio, birth weight (expressed as S.D.s for gestational age). The output variable was FHSDS. **Results:** The model was created on the data of 100 patients (learning group) and validated on the remaining 50 cases (testing group). The best model was described by the equation: FHSDS $=0.683+0.529$*hSDS-0.286*IGF1 SDS-0.152*HV$+0.146$*mhSDS$+0.163$*fhSDS The mean error (RMSE) of predicted FH S.D.s was 0.59 S.D. (3.5 cm) for learning group and 0.63 SD (3.8 cm) for testing group. The model explained 44% of variability of FH SDS in learning group and 36% in testing group. **Conclusion:** Auxological indices and IGF1 secretion before treatment but not GH peak after failing asleep and in stimulation tests were significant predictors of GH therapy effectiveness in children with isolated GH deficiency. Relatively high amount of variability of FH S.D.s remains unexplained by the model, probably in part due to nonlinear dependencies between variables.

P3-953

Vitamin D Levels and not Vitamin A are Correlated with Height Velocity in Children with GH Deficiency Who are Under GH Treatment

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Background: It has been suggested that Vitamin A intake may affect height velocity in children with GH deficiency (GHD) who were under GH replacement (GHR). **Objective and hypotheses:** Aim of the study was to evaluate vitamin A levels in GHD children under GHR. **Method:** Vitamin A levels were measured in 38 children (23 males, mean age 10.8 (S.D. 3.3) years) with GHD, after mean duration of GH treatment of 3.1 (S.D. 2.6) years. Height, weight, BMI, height S.D.s, height velocity S.D. were evaluated at the time of vitamin A measurement and 1 year before. Vitamin D and PTH levels were also measured at the same time. **Results:** Linear Regression analysis showed that height velocity and height velocity S.D.s were not correlated with vitamin A levels. Furthermore no difference could be detected in height velocity S.D.s between children with low (11 subjects) or children with normal vitamin A levels (25 subjects). Males had significantly higher levels of vitamin A compared with females (mean S.D.) 0.43 (0.14) vs 0.33 (0.09) μg/ml respectively ($P=0.014$) Height velocity S.D.s had a positive correlation with vitamin D levels (R^2 adjusted 0.382 B$=0.246$, SE 0.072, $r=0.671$, $P=0.004$). **Conclusion:** Vitamin D levels and not vitamin A are correlated with height velocity in children with GHD who are under GH treatment.

P3-954

Long-Term Effects of GH Replacement Therapy on Hematopoiesis in GH Deficient Children

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Background: Among their metabolic effects, GH and its mediator IGF1 have been reported to influence hematopoiesis. Indeed, GH/IGF1 axis promotes erythropoiesis and GH deficiency (GHD) has been associated with a normochromic and normocytic anemia both in adults and in children. In contrast, *in vivo* data on the effects of GH/IGF1 axis on leukocytes and platelets are scanty. **Objective and hypotheses:** To evaluate the effects of 4-years GH replacement therapy (GHRT) on hematopoiesis in GHD children.

Method: 100 GHD children (64 males) aged 9.74±3.95 years were enrolled in the study. Anthropometric measures, serum IGF1 levels and blood count were evaluated at baseline and then annually during the first 4 years of GHRT. 100 healthy children sex- and age- comparable to the patients were enrolled as controls and evaluated annually. **Results:** At the start of the study GHD children showed levels of hemoglobin (Hb) (12.5±1.1 g/dl) and hematocrit (Hct) (36.7±4.0%) lower than controls (Hb 13.0± 1.0 g/dl, $P<0.002$; Hct38.1±4.3%, $P<0.02$). 4 years of GHRT were associated with a significant increase in Hb (13.2±1.0 g/dl, $P<0.0001$) and Hct (39.0±3.4%, $P<0.0001$) which became comparable to controls (Hb13.3±1.3 g/dl; Hct39.7±7.8%). Hb levels significantly correlated with IGF1 serum levels ($r=0.32$, $P<0.0001$). At baseline seventeen GHD children (17%) showed a normochromic, normocytic anemia while after 4 years of GHRT only two patients (2%) were still anaemic. No difference in leukocytes and platelets count was detected between patients and controls neither at baseline nor during the study. **Conclusion:** GHD in children is associated with a significant reduction in Hband Hct.Long-term GHRT improves these anomalies. Neither GHD nor GHRT have effects on leukocytes and platelets parameters.

P3-955

Thyroid Function in Children Treated with rhGH for GH Deficiency

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Background: The relation between thyroid function and treatment with recombinant human GH (rhGH) has been the subject of many studies which indicate a decrease of fT_4 levels and a compensatory TSH increase at rhGH therapy onset. On the other hand, we have identified a number of patients with documented primary hypothyroidism (either on treatment with L-thyroxine or not) before the onset of rhGH treatment. **Objective and hypotheses:** To assess thyroid function in all children treated with rhGH for GH deficiency and detect the percentage of children with primary hypothyroidism before the onset of rhGH. **Method:** We retrospectively analyzed thyroid function in all patients receiving rhGH for GH deficiency in our department. Other indications for rhGH treatment (e.g. chronic kidney disease, Turner syndrome, Prader-Willi syndrome) were excluded. **Results:** 129 children (77 boys and 52 girls) with GH deficiency on rhGH were identified. 29 (22.5%) were detected to have thyroid dysfunction. Of those, ten patients had central hypothyroidism (in two patients it was secondary due to brain tumor, whereas in the rest eight patients, four had also ACTH deficiency). Patients with additional ACTH deficiency were diagnosed at neonatal age whereas patients with TSH and GH deficiency were diagnosed later in life. 19 children were found to have primary hypothyroidism (TSH values >5 μU/l). Only four (all pubertal boys) out of the 19 patients developed compensated primary hypothyroidism after the onset of rhGH treatment (mean time since rhGH treatment: 28.5 months). Fifteen patients were identified to have primary hypothyroidism before the onset of rhGH treatment. Four patients (three girls and one boy had a confirmed genetic defect) and one girl had clinical and biochemical manifestations of pseudohypoparathyroidism. In one girl, thyroid dysfunction was attributed to treatment with valproic acid. In nine patients, no cause for thyroid dysfunction was identified. **Conclusion:** A significant number of patients with GHD (7%) were identified to manifested primary subclinical hypothyroidism of unknown cause before the onset of rhGH.

P3-956

A 5-year Follow-up of Adults, with Childhood-Onset GH Deficiency, Treated with GENOTONORM® in France

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Background: Young adult patients with childhood-onset GH deficiency (GHD) whose GH replacement therapy (GHRT) is discontinued exhibit negative metabolic and physiological effects, reversible through GHRT. **Objective and hypotheses:** To report the characteristics and 5-year GHRT in adults with childhood-onset GHD. **Method:** Analysis of the subgroup of adults with childhood-onset GHD included between March 2003 and October 2006 in KIMS. In France, KIMS was conducted in all centers with at least one adult treated with Genotonorm® (Genotropin®). **Results:** Overall 120 patients (56 (47%) females) were included; GHD was acquired, congenital and idiopathic in 64 (53%), 41 (34%) and 15 (13%) patients respectively. All patients had severe GHD, associated with one or more other pituitary hormone deficiency in 104 (87%) patients. Median age at inclusion was 22 years (interquartile range 19; 30). Median GHRT dose prescribed at inclusion, was 0.20 mg/day (0.20; 0.40); in 95 (79%) patients inclusion corresponded to adult GHRT initiation. Overall, 23 (19%) patients were lost to follow-up. The percentage of patients treated with GHRT decreased over time especially after 2 years and was 77% at 5 years. In 29 (24%) patients GHRT was permanently discontinued (patient's request in 17 (59%) cases). Prescribed GHRT dose increased up to 2 years (0.60 mg/day (0.40;0.80)). IGF1 level was available, at each visit, in more than 80% of the patients, except at 5 years where IGF1 data was available in 70% of the patients. Median IGF1 level was 80 μg/l (40; 164) at inclusion, 199 μg/l (116; 306) after 1 year and 172 μg/l (78; 220) after 5 years. Body mass index increased from 25.4 kg/m^2 (21.9; 30.7) at inclusion up to 27.2 kg/m^2 (24.0; 32.4) after 5 years. Increase in pituitary tumor size was reported in one female. No new safety concern was reported. **Conclusion:** The relatively weak prescribed doses may preclude highlighting long-term benefit of GHRT. **Funding:** This work was supported by Pfizer.

P3-957

Somatotropic Pituitary Insufficiency in Kearns-Sayre Syndrome – The Clinical Picture, Genetic Diagnosis and Efficacy of rhGH Therapy

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Background: Kearns-Sayre syndrome (KSS, OMIM #530000) is a rare disease belonging to a heterogeneous group of mitochondrial cytopathies. KSS is caused by deletions and/or duplications in the mitochondrial DNA, which lead to the dysfunction of the respiratory chain and to disorders in tissues with a high energy demands (muscle, nervous system). **Case presentation:** The girl was admitted to the hospital at the age of 13 years with the suspision of KSS. Progressive body mass deficiency has been noticeable since the age of 4–5 years. Beginning of the eye movements disorders were difficult to ascertain. Neurological examination revealed limitation in both eyes abduction, significantly reduced upward movement, bilateral ptosis, without cerebellar symptoms, and features of myopathy or neuropathy. MRI of the head and serum lactate levels were normal. EMG revealed discrete myogenic features. Pubertal stage was assest as A1, P1, Th1. Retinal pigmentary retinopathy characteristic for KSS was found. Somatotropic pituitary insufficiency was diagnosed. At the age of 14 years rhGH treatment was started (Omnitrope) (height 149.3 cm; $<$3rd percentile, weight 26.5 kg, bone age 10 years, the rate of growth 3.4 cm/year) which ended at the age of 16 years 4/12 (height 164.2 cm, $\sim$50 percentile). The current height at the age of 17 years and 2/12 is 165.9 cm ($>$50 percentile). Molecular studies confirmed the presence of the common deletion in mtDNA. **Conclusion:** i) KSS is usually detected after the diagnosis of a variety of endocrine disorders, ii) clinical course of the disease is variable, but the growth deficiency is dominant in childhood, iii) the final confirmation of the diagnosis KSS may be set by molecular studies, iv), PCR can be used as a quick and easy method for the analysis of mtDNA rearrangements, v) In our patient improvement of growth velocity was observed.

P3-958

The Correlation between the Increase in IGF1 24 h after the First Injection of GH and the Improved Growth

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Background: IGF1 is a biomarker of GH, and is often used to titrate the dose of GH therapy. However, IGF1 production is regulated by not only GH but also other factors. **Objective and hypotheses:** We investigated whether the increase in IGF1 at several time points after the commencement of GH therapy could be a predictive factor for the improved growth. **Method:** We studied 45 pre-pubertal patients with GH deficiency (GHD) that had continued with GH treatment for more than 2 years (29 boys and 16 girls). GHD was mild in 20 patients, moderate in 18, and severe in seven. We statistically analyzed the correlation between the following values: i) The increase in IGF1 (ΔIGF1) at 24 h, 4 months, 1 or 2 years after GH therapy was started; ii) The increase in height S.D. score (ΔHSDS) at 1 or 2 years. **Results:** The ΔIGF1 24 h after GH therapy was started was significantly correlated with ΔHSDS at 2 years in mild and moderate GHD patients ($P=0.021$, $r=0.511$ and $P=0.008$, $r=0.602$ respectively). The ΔIGF1 at 4 months, 1 or 2 years in the mild and moderate GHD patients and at any time points in the severe GHD patients was not correlated with ΔHSDS. **Conclusion:** This study clarified that the ΔIGF1 24 h after the initiation of GH therapy was significantly correlated with the improved growth of GHD patients. Since IGF1 is affected by various factors, i.e. nutrition and pubertal stage, its value immediately after the initiation of GH therapy is important to reflect the efficacy of GH. IGF1 24 h after the first injection of GH is an early and useful predictive factor for the efficacy of GH in GHD patients.

P3-959

Late Diagnosis of a Type II/III Mucolipidoses Treated with GH Replacement Therapy

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Background: Mucolipidoses II/III (ML) are rare autosomal recessive lysosomal storage disorders (incidence: 1/325 000 live births). They have overlapping clinical phenotypes with mucopolysaccharidosis disorders and include growth retardation, facial dysmorphism, skeletal abnormalities, respiratory and heart diseases, hepatosplenomegaly and abdominal hernias. There is no specific treatment and the management has been limited to supportive care. **Case presentation:** A.M., aged 18, boy of an young non-consanguineous apparently healthy couple, suspected by the Genetics Department for mucopolysaccharidosis, was first addressed to the Endocrinology Department at the age of 14 years 4 months for investigations of growth retardation. The clinical examination revealed short stature (-4 S.D.), 'elf' facies, limited extension and abduction of the upper limbs with bilateral tendon retraction of the fingers and also in the radiocarpal and elbow joints, decreased mobility of the spine and waddling walk with wide support base; no signs of pubertal onset. Wrist radiography revealed delayed bone age of $\sim$6 years. Somatotropic axis investigations revealed low IGF1 (62.4 ng/ml, N = 220–972, GH = 0.42 ng/ml, without stimulation at the arginine test:

GH = 2.75 ng/ml) pleading for GH deficiency. Since there were not known contraindications, GH replacement therapy was started with an initial dose of 0.035 mg/kg per day followed by biannual reassessments. After 4 years of treatment the medium growth rate was 0.42 cm/month and no side effects were reported. The last wrist radiography revealed delayed bone age (11 years 6 months) permitting treatment continuation. Further investigations (the enzymes α-iduronidase, iduronate-2-sulfatase, arylsulfatase B, β-galactosidase) confirmed MLII/III. **Conclusions:** Corroborating the clinical phenotype, biological data and evolution, this case can be included in MLIII. We haven't found in the literature any case of MLIII treated with GH replacement therapy. In our case the treatment was effective and improved the patient's quality of life.

P3-960

Does Applying Regular Questionnaire to Patients on GH Increase the Compliance?

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Background: Compliance of patients on GH treatment is very important for the success of the treatment. In a multicentre study done in Turkey we had shown that compliance decreased at the end of 1st year of treatment which had an adverse effect on growth rate and IGF1 levels. **Objective and hypotheses:** To evaluate whether doing regular questionnaire to patients on GH has an effect on compliance at long term. **Method:** A questionnaire form was prepared with 14 questions. The patients on GH treatment who were followed from our Unit filled a form at the 3rd and 6th month of their follow-up consecutively. Spectrum of diagnoses were GH deficiency (86.3%), Turner syndrome (5.7%), intrauterine growth retardation (3%) and others (5%). **Results:** 301 patients filled the first form and 198 patients filled the second form on follow up. Mean age was 11.6 ± 3.5(1–18) years and duration of GH treatment was between 0.25–14 years. 98.5% of the children answered the questions regarding technical issues (GH application technique and time, storage conditions etc) correctly. However 56% of the patients stated that, not infrequently, after injection drug spilled back. 62% of GH injections were done by parents or under parental guidance. After the first questionnaire it was shown that 71.3%of the patients had absolute compliance to treatment. This ratio was 82.4% in girls, 67.5% in boys. Treatment duration was much longer in incompliant patients (2.1 ± 1.6 years and 1.8 ± 1.7 years respectively). Injection by the parents resulted in a higher compliance rate than injection by the patient (79.5 and 68.3% respectively). After the second questionnaire, compliance rate increased from 74.2 to 80.7%. Compliance of girls was much higher than boys (83.9 and 77.8% respectively). **Conclusion:** Applying regular questionnaire to patients on GH increases the compliance to treatment. More education should be given to boys in this matter.

P3-961

Characterisation of Children Born Small for Gestational Age within the Australian Indications for GH (GH) Therapy: An OZGROW Analysis

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Background: Small for gestational age (SGA) without subsequent catch up growth is an indication for GH treatment in Europe, the US, and Korea but not in Australia. However, many SGA are likely to be included under the 'short stature and slow growth' (SSSG) indication. It is unknown to what extent children born SGA are included in the Australian indications or how they differ from non-SGA patients within each indication and gender. **Objective and hypotheses:** To characterise and compare birth, parental auxology, and initial GH-treatment data of SGA patients with respect to non-SGA patients by gender and Australian indication. Analyses are confined to SSSG, GH deficiency (GHD), Turner syndrome (TS), and Prader-Willi syndrome (PWS). **Method:** SGA was defined as birthweight below the 10th Australian centile for gestation period. Frequencies of SGA for males (M) and females (F) were calculated for each indication. Frequencies were compared to an expected frequency of 10% (Chi square). Means for SGA and non-SGA were calculated for M and F of each indication for gestation period (GP), birth weight S.D. score (BWtSDS), father's height S.D.s (FHtSDS), mother's height S.D.s (MHtSDS), mean parental height S.D.s (MPHtSDS), and GH starting age (SAge, years), height S.D.s (SHtSDS), and Dose (SDo, mg/m^2 per wk). Means were compared using *t*-tests. **Results and conclusions:** SGA was overrepresented: GHD-22%, PWS-55%, SSSG-41%, TS-48% ($P < 10^{-6}$). SGA BWtSDS was always lower ($P < 10^{-10}$) but GP similar. SGA MPHtSDS was always shorter ($P = 0.28$ (M PWS) – 10^{-4} (M SSSG)). As was SGA SHtSDS ($P = 0.4$ (F PWS) – 10^{-8} (M SSSG)). However SAge was similar although younger for SSSG (F 8.7 vs 9.4, $P = 0.005$; M 8.8 vs 9.9, $P = 10^{-7}$). SDo was similar although lower for M SSSG (4.9 vs 5.1, $P = 10^{-4}$). SGA forms a major and significantly different subpopulation of Australian GH-patients. Further analyses will address treatment response. SGA-specific GH treatment may be advocated.

P3-962

Effectiveness of rhGH Treatment in a Boy with Nephrogenic Diabetes Insipidus

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Background: The majority of children with primary nephrogenic diabetes insipidus grow below the third centile. **Objective and hypotheses:** Effect of rhGH treatment on growth in a patient with primary nephrogenic diabetes insipidus.

Results: The patient is an 11-years and 2 month old Caucasian boy of unrelated healthy parents. At the age of 7 years and 9 month he was admitted to our hospital for evaluation of polydipsia and polyuria. His body height was 116.0 cm (−1.78 S.D.s). Urine volume was 4165 ml/day (5.2 l/m^2). During a water deprivation test, urine osmolality was below 200 mosm/l while plasma sodium and plasma osmolality increased to 140 mmol/l and 305 msom/l respectively. Administration of desmopressin revealed no increase in urine osmolality and a mutation in the Aquaporin two gene was found during molecular analysis (c.732del C in exon 4 of the AQP2 gene). Treatment with hydrochlorothiazide (2 mg/kg per day) and amiloride (0.2 mg/kg per day) led to a decrease of urine output to 2800 ml/day (3.5 l/m^2). At the age of 9 years and 6 months his height was 125.3 cm (−1.59 S.D.s). Levels of IGF1 and IGFBP3 were 90 µg/l (−2.05 S.D.s) and 2.0 mg/l (−1.41 S.D.s), two GH stimulation tests revealed low GH levels below 8 ng/ml and GH treatment was started with 0.8 mg/day s.c. (0.029 mg/kg). He showed a good catch-up growth. At the age of 11 years and 2 months his height was 140.3 cm (−0.55 S.D.s). Levels of IGF1 and IGFBP3 were within the normal range (181 µg/l (−0.34 S.D.s) and 2.71 mg/l (−0.52 S.D.s) respectively). **Conclusion:** Our patient had a GH deficient state and rhGH treatment induced impressive catch-up growth. GH deficiency should be investigated in short children with nephrogenic diabetes insipidus.

P3-963

The Easypod™ Connect Observational Study: Comparison of Results from Interim Analyses

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Background: The Easypod Connect Observational Study (ECOS) observational study follows children with GHD, SGA and Turner syndrome receiving r-hGH therapy for up to 5 years, with interim analyses each year. The easypod electromechanical auto-injector device enables accurate, real-world digital records of patients' adherence to rhGH to be collected for evaluation. **Objective and hypotheses:** The primary objective of ECOS is to evaluate the level of adherence of paediatric patients receiving rhGH *via* easypod™; secondary objectives are to assess the impact of adherence on clinical outcomes and concentrations of IGF1 and to identify factors that may influence adherence to this form of treatment. **Method:** Demographic, auxological and diagnostic data are obtained from medical notes, with adherence data obtained directly from the patients' easypod™. Adherence is defined as days with injections received, divided by days with injections planned, expressed as a percentage. An interim global analysis was completed in 2014. Interim analyses have also been completed for the Nordic countries (Norway, Sweden, Finland), France and Canada. The real-world use of easypod™ (routine visits/year, local easypod™ data upload methodology, etc) in these analyses was compared to assess any country-specific differences. **Results:** At the time of analysis, 1 972 patients had been enrolled globally, mean age 9.8 years; Canada $n=204$, mean age 10.9 years; France $n=220$, 9.4 years; Nordic $n=150$, 8.6 years. Individual levels of adherence prospectively measured with easypod™ (median (Q1, Q3), 93.0% (82.8%, 97.5%)) were higher than those previously reported in retrospective studies based on questionnaires and were maintained over time. Median 9-month adherence rates in the countries analysed were similarly high: Canada 96.9, France 94.9, Nordic 97.3%. **Conclusion:** Adherence rates with the easypod™ device are high and maintained over time. Different age range at baseline and possible differences in clinical practice did not appear to have any major impact on easypod™ adherence rates in different countries. **Conflict of interest:** Professor Peter Davies has received a research grant as an investigator and honoraria as a committee member from Merck Serono. **Funding:** This study is funded by Merck KGaA, Darmstadt, Germany.

P3-964

Evaluation of the Facility of Use of a New GH Administration Device – Study DAGH2014

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Background: One of the limiting factors in adherence to GH therapy, is satisfaction with the administration device used. **Objective and hypotheses:** With the emergence of a new biosmiliar GH (BGH) administration device, we will assess the simplicity, ease of use, management and pain perceived by the patients. **Method:** Prospective through survey caregivers and children treated with BGH at least for 6 months. Signed informed consent was required. The questionnaire consists of 13 questions analysing four components: preparation, fixing of the dose, injection of the medication and maintenance. The perception of pain was measured by visual analogue scale expressed in numerical score. **Results:** 23 patients/caregivers were interviewed; The dose average receiving was 0.78 mg/day. 60.8% were female. three patients did not complete the second questionnaire. 33.3% of the patients increased their participation in the self-administration of medication 89.5% of the patients prefer the new device and 10.5% the old device. On the pain scale, the average score for the old device was 2.1 (maximum: 6; minimum: 0); in 75% of patients, the

Table 1. Shows the differences between old and new device responses (for abstract P3-964).

	Old device $n=23$	New device $n=20$	P
General scale	Very easy 56.5%	Very easy 70%	ns
Preparation (three questions)	Very easy 55.1%	Very easy 73.3%	$<$ **0.05**
Fixing dose (three questions)	Very easy 63.8%	Very easy 70%	ns
Injection (four questions)	Very easy 46.7%	Very easy 66.25%	$<$ **0.05**
Maintenance (two questions)	Very easy 69.6%	Very easy 87.5%	ns

score was <2. With the new device the average scale was 1.7 and 80% of patients scored <2 (P: ns) **Conclusion:** The new device analysed has good acceptance among patients. Preparation and injection is easier with the new device. One of the most important effects is the increase in self-administration.

P3-965

Effect of Human Growth Hormone on Growth Rate of Short Stature Children with Low Birth Weight

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Background: If children with intrauterine growth retardation (IUGR) are stunt after birth, they will not have the desired height. Short stature is not fatal but affects personality and social and physical development of children. **Objective and hypotheses:** The aim of this study was to determine the effect of human GH on growth rate of short stature children with history of low birth weight. **Method:** This study was conducted on 148 children (3 – 13 years old), 106 girls and 42 boys, with diagnosis of IUGR and a height SD score of -2 SD or less in Qazvin, Iran. Parents' height was in the normal range for adults. Other causes of short stature were ruled out. The study subjects were treated with 4 IU/m^2 per day GH for at least 6 months. Height growth rate was measured and compared before and after the treatment. **Results:** At the start of the study mean age was 8.73 ± 2.84 year. Height growth rate was 0.41 ± 0.17 and 0.87 ± 0.23 cm/month before and after the treatment, respectively and the difference was statistically significant. Height SD score was significantly decreased. Furthermore, the results of boys and girls were not statistically different ($P < 0.001$). **Conclusion:** GH therapy can improve height growth status in children with low birth weight.

P3-966

Gene expression profiles in growth hormone deficient (GHD) children relate peak GH levels to circadian clock, chromatin remodelling and WNT signalling pathways

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Background: GH deficiency is classically defined on the basis of a cut-off applied to the peak GH level during stimulation tests; a process with recognised limitations. Identifying the functional role of genes whose expression is associated with pGH may help with our understanding and classification of GHD. **Objective and hypotheses:** Identify patterns of gene expression (GE) related to pGH and to describe the function, and regulation of these genes. **Method:** Pre-pubertal children with GHD ($n=98$) were enrolled from the PREDICT study (NCT00256126). All children enrolled had two GH stimulation tests both with pGH levels <10 μg/L. Whole blood GE was determined prior to GH treatment using Affymetrix U133v2 microarrays. GE was correlated with pGH using rank regression [gender, ethnicity, age and body mass index (BMI) as co-variates]. Network models were generated (Biogrid/Cytoscape) and the hierarchy of gene modules determined (Moduland); upstream activity in the network model was assessed using causal network analysis (Ingenuity Pathway Analysis). **Results:** Rank regression identified 347 genes that were correlated with pGH: 188 positively and 159 negatively ($R > \pm 0.28$, $P < 0.01$). Hierarchical clustering identified five distinct clusters of GE (2 clusters positively correlated with pGH and 3 negatively correlated). For the positively correlated GE clusters one cluster associated with network modules related to cell cycle and the second with chromatin remodelling and circadian clock ($P < 0.01$). For the negatively correlated GE clusters two associated with network modules related to circadian clock, DNA replication and WNT signalling while the third associated with apoptosis ($P < 0.01$). Upstream regulators of these modules were PIK3R3 (circadian clock), *SIRT2* (growth factor signalling) and *APC2* (WNT signalling) ($P < 7.7 \times 10^{-3}$). **Conclusion:** GE profiling identified a genomic signature related to pGH levels functionally linked to circadian clock and growth factor signalling and regulated by PIK3R3, SIRT2 and APC2.

P3-967

Usefulness of Reevaluation of Growth Hormone Secretion During Puberty

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Background: Endogenous GH secretion physiologically increases during puberty. In particular, a correlation between GH levels and pubertal stages can be stated. Therefore, it is possible that some patients with childhood-onset GH deficiency (GHD) at puberty normalize their GH secretion. Finally, there are not so far assessed potential predictors of persistent GHD in patients during puberty. **Objective and hypotheses:** Our study aims evaluating the normalisation of GH secretion during puberty in a cohort of GHD adolescents. Secondly, we intend to verify if it is possible to pinpoint some factors which may predict the GH sufficiency at puberty. **Method:** We enrolled 72 patients (40 boys, 32 girls) with history of childhood-onset GHD who had received >1 year of GH treatment and had reached the pubertal Tanner stage 3. All of them were submitted to arginine re-test to evaluate the GH secretion. Auxological and hormonal data at diagnosis and at reevaluation of GH secretion were analysed. **Results:** At retesting, 42 subjects (58.3%) normalized GH secretion and 30 subjects (41.7%) confirmed a GHD. No predictive factors of GH sufficiency were identified. In particular, IGF1 levels were no significantly different in both groups. Interestingly, at the puberty onset the adolescents with sufficient GH secretion decelerate their growth velocity, whereas the GHD adolescents maintain their regular and progressive growth. Finally, the adolescents that normalized their GH secretion showed a BMI significant lower (18.75 kg/m^2) than GHD patients (20.58 kg/m^2). **Conclusion:** The majority of childhood-onset GHD patients acquires a sufficient GH secretion at puberty. Although no predictive factors of GH sufficiency are emerged, to retest GH secretion during puberty may be recommended, in particular in cases of GHD adolescents with a mild GHD at diagnosis.

P3-968

Bone Age Maturation in Prader-Willi Syndrome on GH Treatment is Accelerated in Pre-Pubertal Age without Affecting Final Height

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Background: In children with Prader-Willi Syndrome (PWS) on Growth Hormone treatment (GHT) bone age (BA) acceleration is often observed. Little is known on reasons and consequences. **Objective and hypotheses:** To quantify BA acceleration in pre-pubertal PWS children on GHT and to investigate how BA correlates with weight gain and age at onset of GHT. To assess how final height depends on pre-pubertal bone maturation, weight gain and age at onset of GHT. **Method:** In 19 pre-pubertal PWS children, starting GHT (6 mg/m^2 per week) before age 3, longitudinal anthropometric and BA readings up to age 10 were retrospectively analyzed. In 21 adult PWS patients final height was retrospectively correlated with age at onset of GHT, pre-pubertal weight gain and bone maturation. **Results:** In pre-pubertal PWS catch-up growth is completed after 2 years of GHT. Thereafter, between the age of 5 and 10 years, bone maturation was accelerated, BA velocity (years CA/years BA) amounted to 1.33 years per year. The mean increase of bone maturation of 1.6 SD between the age of 5 and 10 years exceeded the increase in height of 0.5 SD considerably. BA maturation was positively correlated with overall weight gain, but not with age at onset of GHT. In the adult group, mean final height was within the parental target height range, but significantly below mean parental target height. The earlier GHT was started, the taller they were. Final height was negatively correlated with pre-pubertal weight gain, but not with BA acceleration. **Conclusion:** BA maturation exceeds growth in the pre-pubertal phase considerably without reducing final height.

P3-969

Evaluating First Year Response and Final Height to Growth Hormone Treatment in Growth Hormone Deficiency Based on Peak GH Levels on Testing

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Background: Diagnosis of GH deficiency (GHD) is a complicated issue especially in isolated GH deficiency. Auxological evaluation, IGFI, IGFBP3 levels and GH response to provocative testing are all considered in the diagnosis. However, cut-off values for GH levels at stimulation tests are controversial. We aimed to evaluate the response to rhGH treatment in patients with different GH peak levels in stimulation test. **Objective:** We aimed to evaluate the response to rhGH treatment in patients with different GH peak levels in stimulation test. **Method:** 149 patients (60F) with GHD who had been followed for minimum of 1-year with rhGH therapy were included in this retrospective study. Patients with chronic illness and Turner syndrome were excluded. Patients were divided into two groups according to peak GH level under 5 ng/dl (Group I) and 5–10 ng/dl (Group II). **Results:** The mean age at beginning of rhGH therapy was 11.6 ± 3.5 years, the mean height standard deviation score (SDS) was -2.9 ± 1.2. The ratio of SGA born patients (6.7% vs. 19.4%) and the having normal pituitary MRI (44.1% vs. 83.8%) were significantly higher in group 2 ($P < 0.05$). At the beginning of the therapy; there was no significant difference in chronological age (CA) (11.3 ± 3.9 vs. 11.7 ± 3.1) and "Δ CA-BA was (2.8 ± 2.0 vs 2.4 ± 1.6) in group I and II respectively. Height SDS (-3.4 ± 1.4 vs -3.0 ± 0.9, $P = 0.034$) and IGF1 SDS (-1.52 ± 0.87 vs -0.94 ± 0.55, $P < 0.001$) were lower in group I. BMI SDS levels were higher in group I (0.27 ± 1.43 vs -0.47 ± 1.37, $P = 0.002$). Although lower

Final/Near Final	Group I (*n*:21)	Group II (*n*:36)
Initial height SDS*	−4.0±1.9	−2.9±0.7
PAH SDS at initiation	−1.7±1.1	−1.2±1.0
MPH SDS	−1.3±0.7	−1.3±0.8
Final height (FH) SDS	−1.2±0.7	−1.4±0.8
FH SDS – Initial Ht SDS*	2.7±1.7	1.5±0.7
FH SDS – MPH SDS	0.2±0.9	−0.2±1.0
FH SDS – PAH SDS*	0.5±1.1	−0.2±1.2

*$P<0.001$.

rhGH doses were given in group I (30.0±5.4 vs 34.5±4.9, $P<0.001$), the first year response was better in this group (Change in height SDS +1.0±0.7 vs +0.6±0.3, $P<0.001$). At the end of first year, BMI SDS was reduced in group I (0.27±1.43 vs −0.04±1.40, *P*:0.015); but not changed in group II (−0.47±1.37 vs −0.39±1.10, $P=0.360$). First year height response had a negative correlation with peak GH level (r:−0.479, $P<0.001$) and with IGF SDS (*r*:−0.340, $P<0.001$). The final/near final height was available in 57 patients and final height SDS was −1.2±0.7 and −1.4±0.8 in group I and II, respectively (Table). Total gain of height (Final height SDS-Initial height SDS) was significantly higher (2.7 vs 1.5 SDS) in group I and group II respectively. **Conclusion:** In GHD, patients with peak GH levels under 5 ng/dl had better first year response and final height gain with rhGH treatment.

P3-970

Growth Hormone Therapy in Children: Predictive Factors and Short-Term and Long-Term Response Criteria in an Italian Cohort

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Background: The correct diagnosis of growth hormone deficiency (GHD) and the definition of growth response in the management of growth hormone (GH)-treated children is controversial. **Objective and hypotheses:** To evaluate: i) short-term and long-term efficacy of GH treatment; ii) various criteria commonly used to define poor response to GH therapy and compare them in the same cohort of GHD patients. **Method:** Our study includes 94 children (66 boys and 28 girls), affected by GHD and treated with GH until final or near-final height. We assessed data recorded at the start, at 1 year, at 2 years and at the end of GH therapy. The criteria used for detecting poor responders after the first year were: ΔHt SDS (gain in height) <0.5, <0.3 for less severe or <0.4 SDS for severe GHD, a height velocity (HV) <mean −1 SDS. The final height was considered satisfactory if ΔHt ≧ 1 SDS. **Results:** After one year of treatment we could define "poor responders" 55.3% of patients (ΔHt SDS <0.5), 40.9% (HV < mean −1 SDS) and 23.4% (ΔHt SDS <0.3 for less severe GHD or <0.4 SDS). At the end of the treatment poor responders were 22.3%, even if 97.9% of our population achieved midparental target height. The median final height was −1.11 SDS, with a total height gain of +1.5±0.6 SDS. Our analysis revealed also a negative association between height gain (after 1 year and at the end of treatment) and chronological age at diagnosis, and a statistically significant positive correlation between final ΔHt and duration of therapy. **Conclusion:** A clear definition of satisfactory growth response after replacement therapy is still lacking. We suggest to evaluate the individual patient and not only a statistic parameter. Most of patients have pubertal delay and a potential for spontaneous catch up growth, which must be taken into account when measuring the effect and cost-effectiveness of treatment.

P3-971

Patients with Childhood Onset Growth Hormone Deficiency Treated with rhGH – Reevaluation in the Transition Period between Childhood and Adulthood – Preliminary Study

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Background: More than two thirds of teenagers with childhood-onset GH deficiency (CO-GHD) documented normal GH response when retested at final height. **Objective and hypotheses:** To identify potential predictors for persistent GHD after reaching final height under rhGH with a particular accent on children with isolated GHD (IGHD). **Method:** Prospective study: reevaluation CO-GHD in the transition period; cohort of 27 CO-GHD patient who received rhHG and reached final height; cohort has 20 boys (74%) and 7 girls aged 14–20 years, the mean duration of therapy =7.06 years (3 to 12.4 years); average time to cessation of therapy =1.63 years (0.3 to 5.4 years); antropometric parameters were analyzed and GH-IGF1 axis was retested with ITT test. The main outcome measures were sensitivity, specificity, positive and negative predictive values of clinical and hormonal factors for persistent GHD (GHD-P) defined as peak GH <5 ng/ml. **Results:** 60% of patients are isolated GHD, 40% are multiple pituitary deficiency (MPD); 32% of IGHD are persistent GHD (IGHD-P) and 68% are reversible IGHD (IGHD-R) (peak GH in ITT > 5 ng/ml). Patients with IGHD-P had a significant initial growth retardation,a significantly lower initial GH response in ITT and significantly better recovery for growth retardation than IGHD-R patients. ≧1 additional pituitary hormone deficiency predicts 100% persistence of GHD status at reevaluation. **Conclusion:** Approximately one third of IGHD patients are GHD-P after final height achievement; GH peak value in ITT ≤3 ng/ml at initial diagnosis – 100% positive predictive value for status of persistent IGHD; IGF1 value <−1.5 SD at reevaluation requires retesting all pituitary axes given that the combination of

additional pituitary deficiency can occur gradually; IGF1 ≤ -2.5 SD at reevaluation - oriented the diagnosis of MPD with 100% specificity in selecting the cases that do not require dynamic tests.

Conflict of interest: HG Dörr, J Bramswig: none to declare. M Šnajderová: member of NordiNet® IOS International Study Committee. E Pournara, S Meckes-Ferber, B Tønnes Pedersen: employees of Novo Nordisk. **Funding:** This study was sponsored by Novo Nordisk Health Care AG.

P3-972

Time Trends in Baseline Characteristics (2006–2014) in Short Children with Growth Hormone Deficiency (GHD), Born Small for Gestational Age (SGA) and with Ullrich-Turner Syndrome (TS) Enrolled in Nordinet® International Outcomes Study (IOS) in Germany and Czech Republic

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Background: Early diagnosis of growth disorders and initiation of GH therapy at a younger age improves clinical outcomes. **Aims and objectives:** To analyse time trends in baseline parameters at GH treatment start (2006 – 2014) in short children with GHD, SGA and TS from Germany and Czech Republic enrolled in NordiNet® IOS (NCT00960128). **Method:** Baseline data (chronological age, height, weight, BMI, GH dose) from paediatric patients (<18 years) enrolled in NordiNet® IOS in Germany and Czech Republic were analysed using a multiple regression model including country and year. Standard Deviation Scores (SDS) for height and for BMI were calculated using national and WHO references, respectively. **Results:** In Germany ($n=2113$) significant decreases (2006: 2014) in mean (SD) age at treatment start for GHD (9.96(3.86): 8.31(4.08); $P<0.001$) and SGA (7.52(3.19): 6.63 (2.40);$P=0.025$), and a reduction in baseline (SD) GH dose (μg/kg/day) in GHD (29.42(7.41): 26.27(3.70); $P=0.029$) and SGA (34.67(4.40): 30.89(4.41); $P=0.012$) were observed over time. In Czech Republic (n=581) significant decreases in mean (SD) age for GHD (11.37(3.57): 6.87(4.09); $P<0.001$) and mean (SD) GH dose for TS (45.61(3.67): 41.59(3.54); $P=0.005$) were observed over time. Significant between-country differences in GH dose (GHD $P<0.001$; SGA $P<0.001$; TS $P=0.006$) and HSDS (GHD $P=0.013$; TS $P=0.018$) over time were also shown. Increasing proportions of females with GHD (2006: 2014) (16.7%: 32.4%) and SGA (21.4%: 66.7%) were enrolled in Czech Republic during the study bringing proportions closer to overall proportions observed in Germany (GHD 30.4%; SGA 40.9%). BMI SDS did not differ significantly between both countries. **Conclusion:** Significantly earlier age at treatment start in both countries and improvements in the proportion of females with GHD and SGA treated with GH in the Czech Republic may indicate raised awareness of diagnosing children with short stature and suggest optimism for improving clinical outcomes with GH therapy.

P3-973

A Patient with an 13q Deletion Syndrome, Important Growth Delay and Somatotropine Insufficiency Undergoing Growth Hormone Therapy–Case Report.

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Background: Growth deficiency is a common symptom of many genetic syndromes. 13q deletion is a very rare genetic syndrome described in almost 200 cases. Growth reduction is a constant symptom along with mental retardation, congenital defects varying according to the deleted region of chromosome 13. **Objective and hypotheses:** The aim of this paper was to present the case of a 12 year old patient with an interstitial deletion 13q (22.3–31.1), important growth delay and somatotropine insufficiency treated with hrGH. The patient is a first child of young non-consanguineous Polish parents. They had a history of a miscarriage in the first trimester. The patient was born at term with 2550g weight (<10th c), 47 cm length (10th c). In the neonatal period she showed failure to thrive, delayed psychomotor development and reduced muscle tone. Before one year of age she was diagnosed with 13q deletion syndrome (karyotype: 46XX, del 13q (22.3–32.?). She is a patient of numerous medical clinics for her diverse needs (dysgammaglobulinemia, fructose intolerance, Asperger Syndrome). **Method:** She has been a patient of the Endocrinology and Diabetology Clinic of the Children's Health Memorial Institute since the age of 3 years. Growth delay is a constant symptom of the 13q deletion syndrome therefore hormonal tests haven't been performed. Visits were discontinued from 2008 to 2013. At the age of 11 years and 7 months she appeared again presenting facial dismorphic features, scoliosis, lumbar hyperlordosis, weak postural and limb muscles, fifth toe clinodactyly, Ax1, Pub1, Th1, Me (−). Height: 119.0 cm, $hSDS_0$: −5.11, $hSDS_0$-mpSDS: −4.25, GV_0:2.7 cm/year, IGF-1:142 ng/dl (N), BA: 9–10 years. GH secretion was low in 3 tests performed, i.e.: maximum GH concentrations were: in the night profile: 3.63 ng/ml, arginine test: 0.9 ng/ml, glucagone test: 7.47 ng/ml. Pituary MRI: dimensions AP 6 mm, h: 3 mm, transverse 12 mm), without pathological enhance after gadoline administration. She was diagnosed with somatotropine deficiency. Other growth delay causes were excluded. **Results:** With the permission of the Growth Hormone Treatment Coordination Group, in terms of a trial the patient was started with hrGH in a doses of 0.5 U/kg per week (May 12- Dec. 9), and afterward

0.34 U/kg per week. After 10 months we achieved a GV improvment from 2.7 cm/year to 7.2 cm/year and centile position change from $hSDS_0$: −5.11 to $hSDS_1$: −4.89, ΔhSDS:0.22. After 3 months of rhGH therapy the girl was supplied with orthopedic support in terms of prevention of major back worsening. In the Genetics Department of The Children's Health Memorial Institute a CGH array assay showed the 13q deletion containing 34 genes, including Waardenburg type 4A Syndrome and Hirschprung Syndrome, which she doesn't display the symptoms of. **Conclusion:** hrGH treatment might bring satisfactory results in children despite growth deficiency being a standard symptom in 13q deletion syndrome. This is the second reported patients undergoing rhGH treatment and the oldest one.

P3-974

Linear Growth in a Child with Ellis Van Creveld Syndrome: Positive Effect of Growth Hormone Therapy

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Background: Ellis van Creveld syndrome (EVC) (chondroectodermal dysplasia) is a rare, multisystem disorder. It probably affects only around 1 in every 150,000 individuals. It is characterized by a long, narrow trunk and shortened arms and legs; extra fingers (postaxial polydactyly), and abnormalities of the oral region and teeth. In infants, non-bony manifestations, particularly congenital heart defects, may be health or life-threatening. **Case presentation:** This boy was born at term by lower segment CS due to transverse presentation. His length = 41 cm and weight = 2.2 kg, Hc = 33 cm. He had features of EVC syndrome including: rhizomalic short stature, post-axial polydactyly in hands and feet, multiple frenulae in the mouth, hypoplastic nails, congenital heart disease (small PDA), long filtrum, and thick upper lips. **Growth assessment:** His growth chart showed an initial spontaneous catch up during the first year of life which was followed by progressive deceleration of growth till the age of 6 years (htSDS = −3.6) with normal BMI (= 16 kg/m^2). Investigation showed: normal echocardiographic evaluation, normal renal and hepatic functions, and normal hemogram. Hormonal evaluation showed: normal thyroid function, IGF-I = 78 ng/ml (IGFI SDS = −1.7) and normal 8 AM cortisol concentrations. Clonidine stimulation test for GH release showed a peak of 18 ug/l. Human GH therapy was started and improved his linear growth (0.05 mg/kg) (HtSDS) increased from −3.6 to −2.2) after two years of treatment. This is the first case of EVC with normal GH response to provocation that responded well to GH therapy. Previously, the association of growth hormone deficiency and ECV has been reported in one patient and, in this case, the growth hormone treatment had a favorable effect on growth. **Conclusion:** It appears that growth hormone therapy improves linear growth in GH sufficient patients with EVC syndrome.

P3-975

Factors Effecting Response to Growth Hormone Treatment in Children with Turner Syndrome

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Background: Short stature is the most common presenting symptom in Turner Syndrome (TS). GH treatment helps alleviating short stature in TS, although response to treatment varies significantly. **Objective and hypotheses:** We aimed to evaluate the response to GH treatment and factors affecting this response in children with TS. **Method:** Forty-nine patients with TS diagnosed by cytogenetic analysis and who had been followed minimum of 1-year with GH therapy were included in the study. Clinical and anthropometric parameters were obtained retrospectively from patients files. Height SDS changes > 0.5 SD in first year of treatment was considered as good response. **Results:** The mean age at diagnosis was 9.9 ± 3.8 years of age, the mean height standard deviation score (SDS) was −3.2 ± 1.3. The most common karyotype was 45X (40.8%) followed by 45X/46XX (14.3%) and 46X,i(X)(q10) (12.2%). 40% of patients had intrauterine growth retardation (birth weight < 2500 gr). The initial GH dosage was 41 ± 1 μg/kg per day. The average height SDS at the beginning, first year and second year of therapy were −3.0 ± 1.1, −2.5 ± 1.0 (*n*;49) and −2.3 ± 1.1 (*n*:40), respectively. 27 patients had good response to treatment. Target height (TH), presenting age, birth weight, chronological age-bone age difference and change in IGFI SDS after treatment were not different between good and poor responders. However, good responders had lower height SDS at presentation (−3.2 ± 1.3 vs. −2.6 ± 1.0, $P < 0.05$) and lower peak GH response to stimulation (6.5 ± 4 vs. 8.9 ± 5 mg/dL, $P < 0.05$) and lower IGF-I SDS (−2.1 ± 1.1 vs. −1.7 ± 1.3) although the latter was nonsignificant. The final height was available in 15 patients and was 150 ± 4.9 cm (−2.0 ± 0.8 SDS). Good responders reached final height of 152.5 ± 2.3 (*n*:7) which was higher than poor responders [147.1 ± 5.6 cm (*n*:8), $P < 0.05$]. Final heights in poor responders were significantly lower than their target height [147.1 ± 5.6 vs. 158 ± 7 cm ($P < 0.01$)], whereas, this was not significant in good responders (152.5 ± 2.3 vs. 156 ± 6 cm, *P*:0.07). **Conclusion:** Only significant factor affecting first year response to GH treatment was GH levels on provocative testing in children with TS. In those, who reached final height, height gain was also better in good responders.

P3-976

Thyroid Function in Children with Prader-Willi Syndrome, the First 12 Months of GH Therapy

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Background: Normal thyroid function is necessary for the optimal growth promoting effects of GH. Changes in the hypothalamic-pituitary-thyroid (HPT) axis following GH have been reported in subjects initially thought to be euthyroid. A specific group of patients, children with Prader-Willi syndrome (PWS), are thought to have a 'vulnerable' HPT axis. **Objective and hypotheses:** To evaluate the impact of paediatric GH therapy on thyroid hormone status, with a particular interest in children with PWS. We hypothesised that GH in PWS children would result in hypothyroidism that is central in origin. **Method:** 137 and 147 test encounters for fT_4 or TSH respectively, were analysed from the OZGROW database, prior to and during GH, for individuals who were receiving GH therapy since 2009. Where a reference range was provided, fT_4 or TSH was standardized by expressing them as a % of the given reference range. We did a general analysis and a comparative analysis of individual patients' test results (where available) before GH and afterwards. **Results:** 16 and 13 encounters of fT_4 and TSH respectively had tests before GH and within a year afterwards. Of these, 12 and ten patients respectively had PWS. Overall there was no significant difference in fT_4 or TSH results after GH was commenced ($P=0.98$ for fT_4 and $P=0.24$ for TSH). However, for PWS patients there was a significant reduction in median TSH results after GH commencement using standardised % reference ranges (32.17% before to 25% after, $P=0.01$). There was also a significant decrease in TSH within 12 PWS patients who had both before and after tests (paired *t*-test $P=0.002$); there was however no evidence of a reduction in fT_4 in these patients. Of note four of these PWS patients in the latter group had been treated with thyroxine. **Conclusion:** This study showed that overall there was no significant change in TSH and T_4 levels post GH therapy. However, PWS patients showed a significant decrease in TSH levels, where GH therapy may unmask a state of central hypothyroidism. Whether these changes in TSH were clinically significant, remains unclear.

P3-977

Congenital Hypopituitarism and Severe Developmental Delay Associated with Homozygous *POU1F1* Mutation

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Background: Mutations in *POU1F1* is a rare cause of combined pituitary hormone deficiency, which commonly includes GH, TSH and prolactin deficiencies and characterised by hypoplastic anterior pituitary. **Objective and hypotheses:** To present a case of severe short stature and developmental delay 1.5 years old girl, who was admitted to our hospital because of short stature. **Method:** Hypopituitarism panel' genes were sequenced using a custom Ion Ampliseq gene panel and PGM semiconductor sequencer (Ion Torrent). **Results:** The girl was born at term from consanguineous healthy parents. Her birth length and weight were 47 cm and 2220 g respectively. Psycho-motor delay were noted during first months of life. Cardiac echo showed patent ductus arteriosus at 1st week of life and patient underwent surgery at 5 months. She was diagnosed with central hypothyroidism at 2 months of age and started on Levothyroxine. Since then her fT_4 levels were always normal. At 1.5 years her height was 58 cm (S.D.s −7.3) and her weight was 3.8 kg (BMI S.D.s −7.4), she had severe developmental delay and some mild dysmorphic features (sparse hair, prominent forehead, saddle nose and blue sclera). Laboratory testing revealed recurrent asymptomatic ketotic hypoglycaemias (1.4–2.6 mmol/l), low IGF1 (3 ng/ml), undetectable prolactin (<30 mU/l), but normal random cortisol and ACTH levels (495 nmol/l and 12.7 pg/ml respectively). Brain MRI showed anterior pituitary hypoplasia. Genetic analysis revealed homozygous R256W mutation in *POU1F1* gene. The girl was started on GH therapy (Rastan) and carbohydrate rich diet. For the first 5 months of GH therapy she grew 9 cm (height velocity 19 cm/year) and showed some improvement in psychomotor development, but remained hypotrophic (BMI S.D.s −5.2). **Conclusion:** *POU1F1* mutations is a rare cause of hypopituitarism, which may present with failure to thrive and extremely short stature, showing a good response to GH therapy. Severe developmental delay, seen in our case, may be a result of untreated neonatal hypoglycaemia, hypothyroidism or be a part of a syndrome.

P3-978

GH Therapy in Lery-Weill Syndrome: Report of Three Cases

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Background: SHOX deficiency is a frequent cause of short stature. GH therapy has been approved for growth promotion in individuals with SHOX mutations by FDA and EMEA. **Case report:** Three patients with Leri-Weill syndrome (LWS) started GH therapy at different chronological ages (CA). Patient 1 started GH + LHRHa at the CA of 13.4 years, height 148.4 cm (−1.5 S.D.), Tanner stage 4, bone age (BA) 13 years. Target height (TH) 160.5 cm (−2.5 S.D.); mother affected by LWS 140.7 cm (−3.7 S.D.). After 3 months of therapy height was 151.7 (−1.3 S.D.), after 6 months height was 153.4 cm (−1.2 S.D.). After 1 year on LHRHa + GH, height 158 cm (−1 S.D.), BA 13.5 years. His sister, patient 2, started GH at the CA of 3.5 years, height 88 cm (−2.6 S.D.), BA 2.5 years. TH was 147.5 cm (−2.6 S.D.). After 3 months height was 90.7 cm (−2.3 S.D.) and after 6 months 92.8 cm (−2.2 S.D.). After 1 year, height was 98 cm (−1.7 S.D.), BA 3.5 years. Patient 3 was referred for short stature at the CA of 9.3 years, prepubertal, height 127.4 cm (−1.2 S.D.), BA 10.5 years. TH was 164.5 cm (−1.8 S.D.). His brother (18 years) with a final stature of 150 cm presented the same mutation. Patient started GH therapy at the CA of 9.5 years. After 6 months height was 136 cm (−0.5 S.D.). After 10 months height was 139 cm (25°–50°ct), Tanner stage 2, BA 12.5 years. Due to the accelerated skeletal

maturation LHRHa was associated. After 6 months of combined therapy height was 143 cm (50°ct), but BA was 13 years. **Conclusion:** GH therapy significantly improves growth rate and final height in children with SHOX deficiency. Height gain is higher in children who start GH therapy early, as confirmed by our data, despite the small size of our sample.

P3-979

The Assessment of Quality of Life and New Technologies for Therapeutic Monitoring in a Cohort of Paediatric Patients Treated with GH

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Background: Short stature may represent a significant psychosocial problem. The rationale for GH treatment has traditionally rested upon the clinical improvement in terms of growth and well-being. Great importance is also associated with the adherence to the therapy. **Objective and hypotheses:** We have investigated the benefits obtained by GH treatment, the factors that positively influence growth, the differences between 'objective' and 'subjective' adherence and finally the health related quality of life (HrQoL) linked to the condition of short stature and to the treatment both from the children and the parents' point of view. **Method:** The target population were short stature children and adolescents with a diagnosis of GH deficiency (GHD) and/or SGA, in therapy with GH using an electronic device (easypod, Merck Serono) for the administration of the therapy. We evaluated the anthropometric parameters, automatically recorded adherence and responses to three different questionnaires on the knowledge of the treatment, the reported adherence, and the evaluation of the HrQoL. **Results:** 87.5% of all patients had good adherence according to the definition of Cutfield/Hartmann and 79.5% revealed adherence rates greater than 90%. Comparing recorded against reported adherence showed that more children had higher reported adherence than recorded adherence. We also found a general good HrQoL, both from the child and from the parent's point of view. Nevertheless, parents generally have a more pessimistic opinion of their children's conditions. Finally 100% of patients with a better growth response during the 1st year of treatment present at the same time a better psychological adaptation, as compared to the others with an unsatisfactory response. **Conclusion:** New technologies capable of accurately recording/monitoring adherence give the possibility to collect objective and consistent data. They also allow the clinician to evaluate the possibility of changes in the therapeutic regimen. Pediatricians have to consider if benefits actually ride out the discomfort, difficulties and limitations and if going on with treatment, especially in poor responders.

P3-980

Final Height in Patients with Isolated GH Deficiency and Multiple Pituitary Hormone Deficiencies, Treated with GH

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Background: To date a lot of data on the efficacy of GH treatment of children with short stature was accumulated. GH is the major but not exclusive endocrine regulator of linear growth. Influence of multiple pituitary hormone deficiencies on the final growth remains poorly understood. **Aim:** To compare the results of treatment with GH in patients with isolated GH deficiency and multiple pituitary hormone deficiencies. **Methods:** 15 patients with isolated GH deficiency and ten patients with multiple pituitary hormone deficiencies were included. All children received GH ('Rastan', Russia) in a dose of 0.033 mg/kg per day and other hormonal replacement therapy if necessary. Final height was determined when patient's bone age achieved 16 years (according to the atlas Greulich). **Results:** Height of patients with isolated GH deficiency was 159,8 (148.0–166.5) cm. The same indicator in children with multiple pituitary hormone deficiencies was 161.5 (157.8–164.0) cm. The difference was not significant ($P=0.65$ using Mann–Whitney U-test). Decimal age of the end of treatment in patients with isolated GH deficiency was 16.0 (15.0–17.0) years and in children with multiple pituitary hormone deficiencies – 18.0 (17.0–18.0) years. The difference between two groups was significant ($P=0.01$ using Mann–Whitney U-test). **Conclusions:** Our results show that final height in patients with GH deficiency does not depend on the presence of multiple pituitary hormone deficiencies if its replacement therapy is appropriate. Final height in patients with multiple pituitary hormone deficiencies is achieved later, than in patients with isolated GH deficiency.

P3-981

Current Practice in Diagnosis and Treatment of GH Deficiency in Childhood: A Survey from Turkey

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Background: Diagnosis and treatment of GH deficiency(GHD) in children are different between countries, and even among centres in the same country. **Objective and hypotheses:** To evaluate current practices in diagnosis and treatment of GHD in the process of preparing the new consensus on GHD by Turkish Society for Pediatric Endocrinology and Diabetes. **Method:** A questionnaire was sent out to all paediatric endocrinology centres. **Results:** 24 centres returned the questionnaire. The most frequently used GH stimulation test was L-dopa and second one was clonidine. 18 centres used a cut-off value of GH of 10 ng/ml, four centres 7 ng/ml, and two centres 5 ng/ml for the diagnosis of GHD. The most frequently used assay was immunochemiluminescent for GH, IGF1 and IGFBP3. Sex steroid priming in both sexes was used by 19 centres. The most frequently used starting dose in prepubertal children was 0.025–0.030 mg/kg per day and 0.030–0.035 mg/kg per day in pubertal children. Growth velocity was used in the evaluation for growth response to recombinant human GH (rhGH) therapy in all centres. Anthropometric measurements of patients every 3–6 months, fasting blood glucose, bone age and thyroid panel evaluation were used by all centres at follow-up. Therapy was stopped primarily according to decreased height velocity and advanced bone age. 14 centres used combined treatment (rhGH and gonadotropin releasing analogues) to increase final height. **Conclusion:** Although conformity was found among centres in current practice, it is very important to update statement and modify the approach to GHD with new evidence based clinical studies.

P3-982

Experience of the Use of Genetically Engineered GH 'Rastan' by Children in Clinical Practice

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Objective: To evaluate the efficacy of the drug 'Rastan', (manufacturer JSC 'Pharmstandard-Ufa Vita'), in children with GH deficiency at the beginning of treatment at different ages. **Materials and methods:** We examined two groups of patients with GH deficiency who receive the drug for 3 years. In group 1, nine boys and two girls with age at debut of therapy 5.88 ± 1.35 (from 3.3 to 7.1 years); in the 2nd group of ten boys and two girls at the beginning of treatment in 10.57 ± 1.76 (from 8.3 to 13.7 years). The diagnosis is established on the basis of the standard stimulus samples, the maximum release of GH in the sample with clonidine in group 1 3.46 ± 2.81 ng/ml were evaluated by growth rate, bone age S.D.s of growth. **Results:** At the start of treatment age in group 1 5.88 ± 1.35, bone age 2.39 ± 0.56, S.D.s growth 4.11 ± 0.83; respectively in group 2, the patients' age 10.57 ± 1.76, bone age 6.87 ± 2.0 S.D.s growth – 3.201 ± 0.34. For 1 year of treatment, the growth rate in group 1 amounted 8.04 ± 3.30 cm, in group 2 9.05 of 2.72 cm, which has no significant differences ($P = 0.75$). S.D.s of growth did not change significantly and amounted to -3.48 ± 0.97 cm ($P = 0.28$) in group 1, -2.82 ± 38 cm ($P = 0.077$) in group 2. For 3 years in the growth one and group 2 added 23.46 ± 6.87 cm and 22.30 ± 6.44 cm ($P = 0.28$) respectively. SDs growth decreased from -4.11 ± 0.83 cm to -2.43 ± 1.139 cm ($P = 0.007$) in group 1 and in group 2 with- 3.20 ± 1.34 cm to -2.02 ± 1.21 cm ($P = 0.045$). Bone age increased in group 1 comparison with 2.39 ± 0.56 to 5.76 ± 1.57 ($P = 0.007$) and in group 2 with 6.87 ± 2.0 to 11.01 ± 1.91 ($P = 0.013$). **Conclusions:** These clinical observations demonstrate a significant effect of the drug 'Rastan' in the treatment of GH deficiency by children for 3 years regardless of the age of the patients at the beginning of therapy. Experience of the use of genetically engineered GH 'Rastan' by children in clinical practice.

P3-983

GH Therapy in Kuwait: First Report on Characteristics and Response in Treated Children

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Background: Recombinant GH (rGH) treatment is approved in many countries for treatment of short stature in a number of childhood diagnoses. rGH was first introduced in Kuwait in the 1990s. Since its introduction, there has been no reported data on the clinical profile of treated children. There is a huge gap in knowledge of use and response to Paediatric rGH therapy in Kuwait and the region. **Objective and hypotheses:** The objective of this study is to report the clinical profile and response of children treated with rGH by the Endocrine Division at an academic centre in Kuwait. **Method:** This study is a retrospective chart review of children treated regularly with rGH by the Pediatric Endocrine Clinic at Mubarak Al-Kabeer Hospital in Kuwait between December 2013 and December 2014. **Results:** A total of 64 children were treated with rGH in the centre. Mean age

at rGH initiation was 8.3 years (±3.0). There was no significant gender difference between treated children, males were 33 (47.6%) and females were 33(52.4%). The most common indications for therapy were in order; GH Deficiency GHD (49.1%), small for gestational age (SGA) (16.9%) and Turner syndrome (TS) and variants TS (11/9%). Pre-GH height S.D.s were −2.8 (±0.52), −2.5 (±0.53), and −2.8 (±0.70) for GHD, SGA, and TS respectively. Mean height S.D.s difference at 1st year of therapy were +0.55 S.D.s, +0.62 S.D.s, and +0.54 S.D.s respectively for GHD, SGA, and TS. 1-year significant response to therapy (≧0.5 S.D.s difference in height) was associated with younger age of rGH initiation (*P*-value=0.03). **Conclusion:** The clinical profile of use of rGH in children in Kuwait was similar to other reported studies internationally. Similar to reported literature, younger age of initiation of therapy predicts significant response at 1 year follow-up. Such report will be enriched with investigating data at 2 years follow-up from multiple centres in the country.

P3-984

Management of Prepubertal Gynecomastia in Two Patients with Peutz-Jeghers Sydrome: Use of Aromatase Inhibitors

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Background: Peutz-Jeghers syndrome (PJS) is a rare autosomal-dominant disorder frequently caused by the serine-threonine-kinase-11(STK11) gene mutation and characterized by hamartomatous polyps throughout the gastrointestinal tract, mucocutaneous hyperpigmentation and predisposition to several malignancies. Rarely, PJS may be associated to an oestrogen producing large cell calcifying Sertoli cell tumour that may result in gynecomastia and increased growth velocity (GV). **Objective and hypotheses:** We present data of two boys affected by PJS, treated with the aromatase inhibitor (anastrozole) for gynecomastia. **Method:** Patient 1 (P1-9 years old) and patient 2 (P2-6 years old) came to our observation for bilateral gynecomastia. Physical examination showed pigmented lesions of the lips, testicular volume of 7 ml bilaterally for P1 and 4 ml for P2; pubic hair corresponding to a Tanner stage of 2 in P1 and of 1 in P2 and an infantile penis in both. GV was 7.5 cm/year (>97th percentile) in P1 and 7 cm/year (75th-90th percentile) in P2. Bone age was consistent with chronological age for both patients. The mammary gland ultrasound showed a bilateral diameter of 8 cm in P1 and 6 cm in P2. Testicular ultrasound revealed a benign bilateral multifocal microcalcification pattern. Plasma levels of LH, FSH, 17β-oestradiol, testosterone, DHEAS, α-fetoprotein and β-HCG were normal while oestrone, anti-mullerian hormone and inibin-B were elevated in both patients. Genetic analysis discovered a partial deletion of chromosome 19p13.3 incorporating the STK11 gene in P1 and a deletion of STK11 gene in P2. Both patients started treatment with anastrozole: 1 mg/day. **Results:** P1: after 1 year GV decreased to 5.7 cm/year and gynecomastia decreased to 4 cm. P2: after 6 months GV decreased to 4.8 cm/year and gynecomastia decreased to 4 cm. Estrone and anti-mullerian-hormone levels decreased in both patients. No side effects were described. **Conclusion:** Anastrozole seems to be efficient in treating gynecomastia in PJS prepubertal male patients by controlling oestrogen excess and may represent an alternative to orchidectomy.

P3-985

Age at Menarche in Chronic Respiratory Disease: Cystic Fibrosis and Asthma – Comparison with a Large Cohort of Healthy Girls Living in Verona

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Background: Menarche is a milestone in human sexual development as it denotes the achievement of fertility. Few studies have evaluated the age at menarche (AAM) in chronic respiratory disease. **Objective:** The main aim of this study is to investigate AAM and menarcheal determinants in girls affected by Cystic Fibrosis or Asthma, and to compare their AAM with healthy girls' one. **Subjects and method:** The study was conducted on 1207 girls living in Verona aged 11–24: 1062 healthy girls, 47 girls affected by Cystic Fibrosis and 98 asthmatic girls. Data collection was done using self-administered questionnaires about AAM. There were two types of questionnaire: one for healthy and asthmatic girls, and the other one for girls affected by cystic fibrosis. Girls with asthma was also administered an asthma control test (ACT). **Results:** The average AAM among girls affected by cystic fibrosis (FC) (*n*. 36) is 13.24±1.44 significantly higher ($P<0.0001$) than healthy girls' average MA 12.49±1.2 years. Also asthmatic girls (*n*. 86) experienced delayed menarche compared with the healthy ones ($P<0.05$): the average MA among girls affected by asthma is 12.79±3.0 years. **Conclusion:** The basis of delayed menarche among patients affected by chronic diseases is multifactorial. We analysed many variables such as Asthma severity, type of mutation in FC, chronic infection and pancreatic insufficiency. None of these explains delayed menarche in girls with chronic respiratory disease. Chronic inflammation and malnutrition seem to be the main causes of delayed onset of menarche. The issue of growth and puberty in children affected chronic respiratory disease requires further investigation.

P3-986

Optimal Strategy for Ovarian Function Assessment in Girls with Central Precocious Puberty before and During GnRH Analogue Treatment

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Background: The degree of suppression of the pituitary-ovarian axis in girls with central precocious puberty (CPP) under GnRH analogue (GnRHa) treatment is usually assessed at pituitary levels. However, the extent of ovarian function suppression under GnRHa treatment has not been evaluated. **Objective:** To evaluate ovarian activity in CPP girls before and during treatment with GnRHa. **Patients and methods:** In this prospective study, 11 CPP girls naïve of treatment were included. Serum LH, FSH, estradiol (E_2, ECLIA) and inhibin B (INH-B, ELISA) were measured at baseline, 3 and 24 h after depot Triptorelin acetate 3.75 mg IM administration at the first and after 4^{th}, 7^{th} and 13^{th} doses. Samples were obtained at 3 and 24 h at the time of maximal gonadotrophin and ovarian responses respectively. **Results:** 3 h after the first GnRHa dose LH and FSH (mean $\pm$ SEM) increased significantly over baseline (1.9 ± 0.79 to 22.2 ± 3.9 IU/l and 4.6 ± 0.46 IU/l to 19.9 ± 1.9 IU/l, $P < 0.001$ respectively); 24 h after, E_2 and INH-B increased ten and five times over baseline (24 ± 8–250 ± 42 pg/ml and 53 ± 5–263 ± 30 pg/ml respectively, $P < 0.001$). A positive correlation between E_2 and INH-B was observed ($r = 0.84$, $P < 0.001$). Throughout subsequent GnRHa doses, 3 h gonadotrophin responses were suppressed (LH < 4 IU/l), and 24 h after GnRHa, E_2 and INH-B levels fell below normal prepubertal levels and remained within the detection limit of the assays. Nevertheless, three patients with poor adherence to treatment protocol showed gonadotrophin, E_2 and INH-B responses to GnRHa at pubertal levels. **Conclusion:** After 24 h of the first dose of GnRHa, increased E_2 and INH-B serum levels confirm pubertal activation of ovarian function. Under sustained GnRHa treatment, when gondotrophin suppression is reached, ovarian endocrine function is almost negligible.

P3-987

From Prepuberty to Adulthood: Semen Quality and Its Predictors in a Prospective Cohort Study of Russian Young Men

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Background: We are not aware of other longitudinal cohort studies of boys with annual assessments of pubertal development and long term follow-up to adulthood to evaluate semen quality. **Objective:** To describe semen quality and investigate its predictors in a longitudinal cohort study of Russian boys followed from prepuberty until adulthood. **Design and methods:** From 2003 to 2005, 516 prepubertal 8–9-year-old boys were enrolled (86% of all eligible Chapaevsk boys, Russia) and underwent annual growth and sexual development assessments for ten years, including Tanner staging and measurement of testicular volume. At age 18, the young men collected two semen samples one week apart. 150 men provided two samples and nine men one sample (total 309) for 54% participation among those eligible. Semen samples were analyzed for volume, sperm concentration and motility by one technician (LS) according to the NAFA-ESHRE manual. A total of 67 samples were excluded due to severe chronic illness (six), lost semen (nine), age > 20 years (two) and long/short abstinence time (50). 98 matched pair samples were analysed by Wilcoxon signed-rank test to compare repeat semen parameters. **Results:** No differences were found between first and second samples. Based on second samples ($n = 129$), men had a median (interquartile range, IQR) volume, sperm concentration, progressive and total motility of 2.6 (2–3.7) ml, 48 (25.7–78.5) $\times 10^6$/ml, 56% (49–61%) and 64% (57–69%), respectively. Median (IQR) total sperm count and total motile sperm count were 126.0 (68.2–221.8) and 78.5 (38.4–144.4) $\times 10^6$/ejaculate respectively. 24, 16, 31 and 33% of men had semen parameters below 'normal' reference limits for volume (2 ml), sperm concentration (20×10^6/ml), total sperm count (80×10^6/ejaculate) and motility (60%) respectively. Data are being analysed for predictors of semen quality. **Conclusion:** This is one of the first prospectively designed studies to follow a large cohort of boys annually from prepuberty until adulthood and collect semen samples. **Funding:** This work was supported by the NIH (grants ## R01ES0014370, P30ES000002), the Russian Science Foundation (grant # 14-45-0065).

P3-988

Further Expansion of the CHARGE Geno-Phenotype: A Girl with a Novel Deletion of *CHD7* and with the Combination of Hypogonadotropic Hypogonadism and Agenesis of Internal Genitalia

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Background: CHARGE syndrome is a variable entity. Clinical diagnosis is based on the Blake-Verloes criteria and can be confirmed by identifying a mutation in *CHD7*. Hypoplasia of the genitalia is a common feature and is most often attributable to hypogonadotropic hypogonadism which is described in 81% of the males and 93% of the female patients. Other genital anomalies are rare. Combined agenesis of the uterus and ovaries is so far only reported in one patient with suspected CHARGE syndrome. **Case presentation:** A girl presented originally with cheilopalatoschisis, unilateral kidney agenesis, hearing problems attributed to bilateral hypoplasia of auditory ossicles and cochlea and aplasia of the semicircular canals. At age 18 years, the adolescent girl was seen in the endocrine clinic because of primary amenorrhea and subnormal breast development which were attributed to hypogonadotropic hypogonadism. Oestrogen treatment was initiated and gradually increased over 2 years into the range of oral oestro-progestagen contraceptives. Because of persistent amenorrhea, ultrasound and MRI examinations were performed and their results were compatible with combined agenesis of uterus (corpus and cervix) and ovaries. Genetic exploration disclosed a hitherto unreported c.3634_3637 deletion in exon 15 of *CHD7*, suggestive of CHARGE syndrome. **Conclusion:** In an adolescent girl with a newly recognised *CHD7* deletion and hypogonadotropic hypogonadism, the observation of persistent amenorrhea after prolonged oestro-progestagen treatment led to the sub-diagnosis of agenesis of uterus and ovaries thereby further expanding the geno-phenotype of so-called CHARGE syndrome.

P3-989

Metabolism and Gonadal Axis of Early Menarche Girls and Girls Treated with GnRHa During Puberty

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Background: Early menarche may be associated with diabetes, metabolic syndrome, cardiovascular disease and oligomenorrhoea in adults. While the state of metabolism and gonadal axis of early menarche girls and girls who treated with Gonadotropin-releasing hormone analogues (GnRHa) during puberty was not so clear. **Objective and hypotheses:** We assessed in a retrospective unicentre study the state of metabolism and gonadal axis of early menarche girls and girls who treated with GnRHa during their puberty. **Method:** 39 early menarche girls and 58 girls who had treated with GnRHa were enrolled in our study and 19 normal menarche girls were enrolled as control group. All of them were 2 years within puberty. Data were collected in height, weight, gonadal hormone, blood glucose, insulin, blood lipid, leptin, adiponectin and the size of uterus and ovary. **Results:** Both BMI S.D.S for chronological age (CA) and for bone age (BA) of early menarche girls were significantly higher than normal menarche girls ($P<0.05$). The ratio of insulin resistance in early menarche girls (20.5%) was also significantly higher than normal girls (0%). No significant difference in lipid metabolism and gonadal axis between two groups. In girls treated with GnRHa, BMI S.D.S, insulin, HOMA-IR and the ratio of insulin resistance (20.7%) were all significantly higher than normal group ($P<0.05$). Meanwhile, DHEAS, androstenedione and testosterone of GnRHa treated girls were significantly higher than early menache girls, and DHEAS was higher than normal girls. The size of uterus in treated group was larger than the other two groups. **Conclusion:** Early menarche and GnRHa treatment may take negative effect to BMI and glucose metabolism. Androgen was higher in GnRHa treated group. Therefore, suggestion was that BMI, insulin, blood glucose and androgen should be monitored in early menarche girls and girls treated with GnRHa.

P3-990

The Consequences of Polycystic Ovary Syndrome in Adolescent Girls

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Background: Polycystic ovary syndrome (PCOS) represents one of the most common complains for adolescent girls to present to endocrinologist. PCOS has the potential to affect the young person both metabolically, physically, psychologically and socially. **Objective:** To evaluate the metabolic and psychological consequences of PCOS in adolescent girls. **Method:** Adolescent girls admitted in the Endocrinology Department of Children Emergency Hospital, Timisoara for a period of 4 years were studied. They were evaluated after a complex protocol: clinically (blood pressure), anthropometric (height, weight, BMI), hormonal (estrogen, progesterone, testosterone, LH, FSH, SHBG, FAI), metabolic (glucose, OGTT, insulin, HOMA and lipid profile), ultrasound (polycystic ovaries) and psychological. **Results:** Out of 51 adolescent girls (mean age 17.1 ± 1.8 years) diagnosed with PCOS according to Rotterdam criteria, 70.58% of them had a body mass index higher than 75% percentiles for age, 9.80% were obese, while 37.52% were hypertension. Hirsutism and acne were encountered in 72.54% of adolescents, 58.82% had polycystic ovaries on ultrasound and 90.19% were associated with irregular cycle. Oral glucose tolerance test was altered in 64.70% patients, hyperinsulinaemia was found in 29.41% of them. Dyslipaemia was identified in 33.33% patients, moderate hepatosteatosis in 43.13% of them, while the metabolic syndrome was diagnosed in 25.49% cases. Anxiety (56.86%), depression (45%), eating disorders (52.94%) and reduced quality of life (80.39%) were also common in this group. Metformin was prescribed at adolescents diagnosed with insulin resistance (64.70%) and psychotherapy recommended in the majority of cases. **Conclusion:** Successful management of adolescent girls with PCOS consisted in the challenges of making the diagnosis of PCOS, lifestyle change, metformin treatment and psychotherapy.

P3-991

Pelvic MRI as Alternative to Pelvic us for the Diagnosis of PCOS in Overweight and Obese Adolescent Girls

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Background: Polycystic ovary syndrome (PCOS) is a common reproductive endocrinopathy in women of childbearing age, affecting 5–10% women in this age group. Its suggestive cardinal features are hyperandrogenism, ovulatory dysfunction and/or polycystic ovary appearance. The diagnostic gold standard tool is pelvic ultrasound (PUS) which may be limited in overweight and obese adolescent girls. **Objective and hypotheses:** To evaluate the contribution of pelvic MRI in diagnosis of PCOS in overweight and obese adolescent girls. **Method:** Six adolescent girls seen for signs and symptoms of hyperandrogenism and menstrual irregularity were biochemically screened (LH, FSH, testosterone, S-DHEA, Δ4 androstenedione, 17(OH) P, SHBG, TSH, fT_4 and lipid profile, fasting blood sugar and HOMA IR and HOMA-B). Each had PUS and/or pelvic MRI (PMRI) performed. Other causes of hyperandrogenism were excluded. **Imaging:** PUS performed with trans-abdominal transducer (Acuson scanner, using 3.5–7.5 MHz transducer; PMRI performed with phased array coil of 1.5 T Siemens MRI scanner, with T_1 and T_2-weighted axial and coronal images. The diagnosis of PCOS defined according to Rotterdam PCOS consensus Workshop (*Hum Reprod* 2004; 19: 41–7). **Results:** Six adolescent girls (mean age 15.2 years, mean BMI 34.91 kg/m^2, mean age at menarche 12.03 years), with menstrual irregularities, acanthosis nigricans (5/6), acne, hirsutism, and biochemical characteristics of PCOS (high plasma androgens, insulin resistance, glucose/insulin ratio <4.5, decreased SHBG) were identified. PUS was not contributive, but PMRI showed typical aspect with well delineated peripheral ovarian cysts, increased ovarian volume and stroma. **Conclusion:** PUS remains gold standard diagnostic tool for PCOS, its limitations in overweight and obese girls are real and should be known. Endo-vaginal transducer cannot, however, be utilized in young virgin girls. PMRI is a useful and accurate alternative, allowing greater delineation of structural components of the ovary and better appreciation of its volume or structural alterations.

P3-992

Syndromic X-Linked Ichthyosis

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Introduction: X-linked ichthyosis is an inherited disorder of keratinization due to steroid sulfatase deficiency. It may be part of a contiguous gene syndrome characterized by the presence of several clinical features including hypogonadism, Leri-Weill syndrome, short stature, chondrodysplasia punctata, mental retardation, epilepsy, Dandy-Walker malformation and ocular albinism. It is due to microdeletions of Xp22.3. We report observations of two siblings with syndromic x-linked ichthyosis. **Observation:** Two brothers aged 17 and 9 years with x-linked ichthyosis diagnosed at the age of 2 years were admitted for workup of cryptorchidism. Both had bad school results. The eldest brother had short stature (-3 S.D.s compared to age-matched children) and hypogonadotroph hypogonadism with bilateral cryptorchidism but without anosmia. Bone age was delayed at 13 years. Testes were located in intra-abdominal region. The youngest brother had also bilateral cryptorchidism with microphallus. Furthermore he had an attention deficit-hyperactivity disorder. He had not short stature nor anosmia. Testes were located in intra-abdominal region too. The two patients had not neurological abnormalities and their ophtalmological examination was normal. **Conclusion:** Most patients with steroid sulfatase deficiency have ichthyosis as the only clinical feature. Patients with more complex disorder or syndromic x-linked ichthyosis have a broader gene deletion or the so called contiguous gene syndrome with several genes involved. It is a heterogeneous entity with various clinical features. Although it is rare, affecting approximately 1/50 000–150 000 boys and men, it deserves to be known as an earlier diagnosis may optimize the care of patient, improve the prognosis of the disease and give genetic counselling to the family.

P3-993

The Effect of Aromatase Inhibitor in a Pubertal Patient with Aromatase Excess Syndrome

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Background: Aromatase excess syndrome (AEXS) is a rare autosomal dominant disorder caused by the overexpression of *CYP19A1* at 15q21. Patients with AEXS manifest various clinical features associated with oestrogen excess; gynecomastia, hypogonadotropic hypogonadism, and advanced bone age are the most salient features in this condition. **Objective and hypotheses:** The primordial treatment of the gynecomastia in patients with AEXS is surgical mastectomy, however long-term treatment with aromatase inhibitor for hypogonadotropic hypogonadism and short stature due to advanced bone age has not been established in children. We evaluated the effect of aromatase inhibitor for 2 years in a pubertal patient with AEXS. **Method:** The patient was 10-year-old boy. Comparative genomic hybridization analyses using a microarray identified about 200 000 bp heterozygous deletions included several exons of the neighbouring genes *DMXL2* and *GLDN*, which located upstream of the *CYP19A1* start codon in familial gynecomastia (father, elder brother and the patient). Because of psychological distress caused by gynecomastia,

the patient's father and elder brother had both undergone mastectomies. Endocrine examinations showed decreased gonadotropin and testosterone levels, and oestradiol level remained undetectable. His bone age was significantly advanced with 13 years old nine months, and his predicted final height according to the growth-potential method was 150 cm. Because of his predicted final height, the patient was treated with an aromatase inhibitor. **Results:** After 1 month of oral administration of 1 mg/day of anastrozole, the gynecomastia showed a tendency to improve and both LH/FSH (from 0.6/1.9 to 2.9/2.8 mIU/ml) and testosterone (from 19.5 to 389.6 ng/dl) levels were increased. Subsequently, 1 mg/day of anastrozole was continued every other day. His predicted final height was increased to 163 cm at 2-year evaluation. No adverse effects were evident during treatment. **Conclusion:** 2 years of anastrozole treatment for pubertal AEXS patient with a poor predicted final height was safe and effective for the improvement of gynecomastia and predicted final height. **Funding:** This work was supported by The Foundation for Growth Science 2013 in Japan.

P3-994

Homozygous *CYP17A1* Mutation Identified in a Chinese Family with 46, XX and 46, XY 17α-Hydroxylase Deficiency

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Background: Congenital adrenal hyperplasia due to 17α-hydroxylase deficiency is a rare autosomal recessive disorder, characterized by sexual infantilism, amenorrhoea, hypertension and hypokalemia,which is caused by CYP17A1 gene mutations. **Objective and hypotheses:** To provide a descriptive analysis of 17α-hydroxylase deficiency in two female siblings with different karyotype of 46, XX and 46, XY. **Method:** The clinical features and biochemical data of a pair of 46, XX and 46, XY Chinese siblings with 17α-hydroxylase deficiency from China were studied. Direct DNA sequence analysis of the *CYP17A1* gene was performed. **Results:** The two female siblings were evaluated for the same complaints of complete lack of female secondary sex characteristics at age of 15 years 8 months and 14 years respectively. Both of the older (46, XX) and younger (46, XY) had markedly reduced serum levels of cortisol, E2 and T, accompanied with increased serum levels of LH, FSH, P and ACTH. The older had normal blood pressure with normal serum K^+ level and PRA, while the younger had slight hypertension with serum K^+ and PRA in the low-normal range (3.48 mmol/l, 50 ng/l per h respectively). Pelvic ultrasonography revealed a pre-pubertal uterus in the older, and absence of ovaries and uterus in addition to a blindending vaginal tract in the younger. Cosyntropin administration did not cause a rise in serum cortisol and 17OHP levels but a rise in serum *P* (0.6–4.9 ng/ml, 1.8–4.9 ng/ml respectively) in the two sibings. The younger underwent bilateral orchidectomy,and the histology showed normal testicular tissues. The same homozygous mutations (c.1459_1467delGACTCTTTC(p.Asp487LysfsX20)) in *CYP17A1* gene were identified in both patients. **Conclusion:** We confirmed the diagnosis of 17α-hydroxylase deficiency in these two siblings.

P3-995

Puberty and Gonadal Function in Adolescents Girls after Renal Transplantation

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Background: Renal transplantation (RTx) is the most common solid organ transplant procedure. Several studies have reported on puberty and gonadal function in female RTx recipients with controversial results. **Objective:** We sought to describe puberty and gonadal function in adolescents after RTx before 16 years. **Methods:** We reported retrospectively the clinical signs of puberty, growth, medication and graft function of 20 girls aged 19.63 ± 4.21 years transplanted before 16 years old. Furthermore, hormonal and ultrasonographic characteristics were performed in these girls followed from 2014 to 2015 in Necker Hospital. **Results:** The age of onset of puberty was 12.4 ± 1.6 (10–16) years and the age of menarche was 14.1 ± 1.6 (11–17.5) years. Final size was significantly delayed compared to the target size (154.2 ± 3.1 vs 163.7 ± 1.1 cm, $P = 0.0035$). There was no significant correlation between age at telarche and age at RTx or with the corticosteroid dose. The patients with renal function below 60 ml/min/ 1.73 m^2 had a slightly delayed menarche (14 ± 2 years vs 12.5 ± 0.5 years, $P = 0.29$). Fifteen percents were amenorrheic, 21% spaniomenorrheic. The median FSH levels were 5.2 ± 2.75 (2.8–96) IU/l. Three patients had a low AMH level (< 1 ng/ml). All patients had an immunosuppressive therapy with a calcineurin inhibitor, an anti metabolite and corticosteroids. **Conclusion:** Pubertal development was normal in female adolescents after RTx with age at menarche slightly higher than that reported in the general population. Although she appears to be broadly conserved ovarian function may be impaired, but the mechanisms are not elucidated.

P3-996

Endocrine Disruptor and Premature Puberty, is There Any Association?

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Background: Endocrine disruptors (ED) can alter endocrine function. ED have become a part of everyday life and are found among phytoestrogens, active ingredients in pharmaceuticals, and additives or contaminants in food, personal care products, cosmetics, plastics and textiles. **Objective:** To describe cases of children with signs of early puberty who are exposed to ED. **Method:** Observational study of patients affected of premature puberty. Detailed medical history about exposition to ED such as parabens or tea tree oil through creams, wipes or food was made. **Results:** 12 girls who meet the criteria are described here. After removal of the product containing ED a regression of the signs of puberty was observed. **Conclusion:** It is very important to conduct a detailed history of environmental exposure. There is much conflicting epidemiological evidence regarding the involvement of ED in premature puberty. But more use of the precautionary principle could reduce exposure early and avoid children's health continued to be harmed.

P3-997

Abstract withdrawn.

P3-998

The Changes of Body Fat and Metabolic Parameters During GnRHa Treatment in Central Precocious Puberty or Early and Fast Puberty Girls

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Background: Oestrogen has positive effect to glucose and lipid metabolism. On the contrary, leptin has negative effect to metabolism. During GnRHa treatment, the secretion of oestrogen was suppressed and its effect will fade away. **Objective and hypotheses:** To observe the changes of body fat and metabolic parameters of central precocious puberty (CPP) or early and fast puberty (EFP) girls who treated with Gonadotropin-releasing hormone analogues (GnRHa). **Method:** 41 girls (25 CPP and 16 EFP), who treated with GnRHa for one year, were enrolled in our perspective study. BMI, body fat parameters (measure by ultrasound and body composition analyzer), serum lipid (Chol, TG, HDL and LDL), glucose metabolism (Fast blood glucose, Insulin, HOMA-IR), and adipokine (Lepin, Adiponectin) were obtained before treatment, after 6 months and 12 months of treatment. **Results:** Compare with data when GnRHa treatment, BMI and leptin, adiponectin started were significantly elevated after 6 months of treatment. After 12 months of treatment, the minimal thickness of the subcutaneous fat, BMI, BMI S.D.s, Leptin and insulin were significantly elevated compared with those at start and at 6 months. Fast blood glucose, HOMA-IR, Chol, TG, HDL and LDL didn't change significantly after 6 or 12 months of treatment. **Conclusion:** During GnRHa treatment in CPP and EFP, BMI, subcutaneous fat and insulin were elevated. It probably due to the withdrawal of estrogen and its positive regulation effect to the metabolism faded away, while leptin was not affected by GnRHa and still rised with development. So that leptin's negative effect to metabolism played a predominant role.

P3-999

Sertoli Cell Tumour in a Case of Androgen Insensitivity Syndrome

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Introduction: Complete androgen insensitivity syndrome (CAIS) is a sexual development disorder due to mutations that cause function loss in androgen receptors in 46, XY individuals. The risk of malignancy development until the age of 25 years in CAIS is 5–10%. We present a CAIS case where a Sertoli cell tumour was found, together with the USG and MR findings. **Case:** A 17-year-old female presented to our department complaining of amenorrhoea. She had a history of inguinal hernia surgery at the age of 2 years. The patient's niece of the same age had been diagnosed with CAIS at our department and gonadectomy had been performed 6 months ago. She had four other nieces with similar diagnoses. She was phenotypically female. On physical examination, height was 164.7 cm (−1.53 S.D.s), weight 54.5 kg (−2 S.D.), breast development Tanner stage 5, pubic hair Tanner stage 2 and there was scarce axillary hair. The gonad was palpated in the left inguinal region. Chromosome analysis revealed 46, XY, SRY positive. The LH level was 18.6 mIU/ml, FSH 0.7 mIU/ml, total testosterone 702 ng/dl, E2 31.3 pg/ml, Anti-müllerian hormone 8.2 ng/ml, and SHBG 59.7 nmol/l. Pelvic ultrasonography and MR imaging revealed 'Solid soft tissue 29×19×22 mm in size that could be from the testis parenchyma in the right adnex and adjacent cystic lesion 32×25×23 mm in size; solid soft tissue 17×9×11 mm in size that could be consistent with testis parenchyma in the left inguinal region and adjacent cystic lesion 38×20×18 mm in size'. The Sexual Orientation and Gender

Identity Committee decided on gonadectomy. Histopathological evaluation of the gonad revealed a Sertoli cell tumour. **Conclusion:** There are reports of a unilateral Sertoli-Leydig cell tumour in two AIS cases and a bilateral tumor in one AIS case in the literature. We discussed a rarely seen Sertoli cell tumor developing in a CAIS case with USG and MR findings.

P3-1000

Final Height of Children with SGA Treated with Biosynthetic GH: About a Series of 30 Children

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Background: Small gestational age (SGA) is defined by a small size and/or a birth weight < -2 DS/standards for the term of pregnancy. Most of these children catch up to their size in the first 2 years of life. Only 10% of them will stay with a size of < -2 DS. These children may benefit from treatment with GH, which improves their stature prognosis. **Objective and hypotheses:** Study the final height of children with IUGR have reached adulthood and treated by GHR. **Method:** 30 children with average age of 8.5 years for females and 9.5 for males at diagnosis were treated with GH (average dose of 0.045 mg/kg per day) to achieve the adulthood. These children were compared to a similar group of 36 children with the same disease and untreated. **Results:** The mean size at diagnosis was -3.5 DS/TC and -4.5 DS/M (Sempé). After treatment for 4 years (on average) adult height was -2 DS/TC and -3 DS/M in children against -2.9 DS in the non-treated group, the difference was significant ($P=0.005$). The height gain in adulthood with the GHr was 1.5 against 0.6 DS. DS in the non-treated group ($P=0.002$). The age at puberty similar in both groups was successful. **Conclusion:** Despite a delay in diagnosis and treatment initiation by GHr, results on final height are satisfactory. The effectiveness of the GHr in children with SGA is well established. Early introduction of treatment to éfficace dose allows normalisation of the size of children to adulthood. Puberty is not affected by the GH.

P3-1001

Anti-Müllerian Hormone is a Useful Marker of Gonadotoxicity in Girls Treated for Cancer: A Prospective Study

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Background: Gonadal dysfunction is one of the major endocrinological late effects among cancer survivors. Chemotherapeutic agents and radiation are so gonadotoxic that ovarian reserve diminishes. Measurement of anti-müllerian hormone (AMH) concentration is useful as a marker of ovarian reserve or gonadal deficiency in female childhood cancer survivors (CCSs), particularly among patients without high gonadotropin levels. **Objective and hypotheses:** The aim of the study was to investigate the variations of serum AMH levels in determining the acute and chronic effects of cancer therapy on the ovarian reserve. **Method:** We conducted a prospective, longitudinal study of AMH before and after different cancer therapy at a single hospital. The medical records of three included female patients with haematological disease were reviewed. **Results:** <Case 1> Myelodysplastic syndrome, Therapy: 10 years 0 months～, reduced intensity stem cell transplantation (SCT), Preparation: Fludarabine 30 mg/m^2 per day×5, L-PAM 90 mg/m^2 per day×2, Puberty: thelarche 11y1m, menarche 12 years 5 months, AMH (ng/ml): 1.48 (pre), <0.10 (post SCT 1–9 m), 0.9 (12 m), 0.34 (15 m), <0.1 (18–30 m). <Case 2> Acute lymphocytic leukaemia, Chemotherapy: 11 years 8 months～, Puberty: menarche 9 years, regular menstruation, AMH: 1.85 (pre), <0.10 (post 0 m), 1.46 (3 m), 0.6–0.7 (6–18 m), 1.24 (24 m). <Case 3> Acute myelocytic leukemia, Therapy: 13 years 11 months～ chemotherapy and myeloablative stem cell transplantation, Preparation: total body irradiation 2G years×6, L-PAM 90 mg/m^2 per day×2, Puberty: menarche 12 years,post-treatment amenorrhea, AMH:1.41 (pre), 0.88 (during therapy), <0.10 (post SCT 0-24 m). **Conclusion:** Different patterns of AMH during the recovery phase supported the significance of longitudinal study. AMH level after the treatments was low in patients with spontaneous puberty and with regular menstrual cycles, whereas gonadotropin were not increased. The time to measure AMH should not be just after the end of the therapy for the CCSs. This study may help to better understand the ovarian toxicity of cancer therapy and to predict the needs for hormone replacement therapy and fertility counselling in future.

P3-1002

Leydig-Cell Tumour, a Rare Cause of LH-Independent Sexual Precocity in Boys

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Background: Leydig-cell tumours in children are rare, comprising only 4 to 9% of all primary testis tumours in

prepubertal males. These boys present with isosexual precocious pseudopuberty characterized by increased testosterone and low gonadotropin levels. We describe two cases and will discuss differential diagnosis and pathogenesis. **Case 1:** C. was first referred at 8 years old for pubertal development with accelerated growth since 4 years of age. His voice has broken. Pubertal stage was A1P2G1, left testicular volume 4 ml, right 2 ml, penile length 60 mm. There was no acne, no gynecomastia, and no cafe-au-lait spots. Blood tests showed: low gonadotropin levels, FSH 0.74 UI/l, LH <0.07 UI/l, high testosterone level 1.1 ng/ml, total β-hCG level <2 UI/l. Scrotal ultrasound examination showed a left testicular solid tumour (size: 9*7 mm) with hypervascularisation. Tumor was surgically removed by enucleation without orchiectomy. Histological analysis supported the diagnosis of Leydig-cell adenoma. LH-receptor gene sequencing is ongoing in blood and tumour sample. **Case 2:** A. was first referred at 5 years old for premature pubic hair. Pubertal stage was A1P2G1, left testicular volume 4 ml, right 2 ml, and penile length 40 mm. There was no acne, no gynecomastia, and no cafe-au-lait spots. Blood tests showed: low gonadotropin levels, FSH 0.17 UI/l, LH 0.04 UI/l, high testosterone level 1.04 ng/ml, total β-hCG <2 UI/l. Scrotal ultrasound examination showed a left testicular solid tumour (size: 7*5 mm) with hypervascularisation. Tumour was surgically removed by enucleation without orchiectomy. Histological analysis supported the diagnosis of Leydig-cell adenoma. No abnormality in sequence of LH-receptor gene was found in blood or in tumour sample. **Conclusion:** Scrotal ultrasound examination should be performed in case of LH-independent sexual precocity in boys with testicular asymmetry in order to diagnose Leydig-cell adenoma. This tumour should be treated by enucleation without orchiectomy.

P3-1003

Antimullerian Hormone and Inhibin B Markers of the Ovarian Reserve After Ovariectomy

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Background: Ovarian reserve is defined as the functional potential of the ovary, which reflects the number and quality of the follicles left in the ovary at any given time. In literature there studies about the evaluation of ovarian reserve after ovariectomy for tumors and cysts, using serum markers, such as inhibin-B, and anti-Mullerian hormone (AMH), combined to ultrasonographic markers, in adult women but none in peri-pubertal girls. **Case presentation:** We report the case of a 10-years and 11-months old girl, who came to our attention to assess her pubertal development. At 2 weeks of life she underwent the removal of both the right ovary because of a neonatal torsion and a cyst of the left ovary, probably of therato-amartomatous origin. At our visit she had a height between the $+1$ and $+2$ S.D. and a weight between the M and $+1$ S.D. for sex and age, with a pubertal stage of P1, T1 and A1, according to Tanner. Bone age radiograph showed a bone age correspondent to her chronological age, using the standards of Greulich and Pyle. The abdomen ultrasound revealed the presence of a prepubertal uterus with no ovaries nearby. We performed the GnRh test, which revealed a hypergonadotropic hypogonadism (FSH and LH before the stimulus of 161 and 27.8 U/l and after the stimulus of 328 and of 176 U/l respectively, with no estradiol increase, 99.5 and 93.2 pmol/l before and after the GnRh test). To understand if she had a minimal ovarian function, we evaluated finally her AMH and Inibin B concentration: both hormone were very low (AMH <0.08 μg/l and Inibin B <2.6 ng/l), so we decide to begin estrogen, at a minimal dose of 25 mg, as replacing therapy. **Conclusion:** We suggest that AMH and Inhibin B, in association to the standard tests to study the pubertal development, could help in understanding the real ovarian reserve of pubertal girls after ovarian surgery, optimizing the Estrogen Replacement Treatment beginning.

P3-1004

Girl with Pendred's Syndrome, Breast and Ovary Cysts (Clinical Case)

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Background: Pendred's syndrome (Pendred's disease) is a genetic disorder leading to congenital bilateral sensorineural hearing loss and goitre with occasional hypothyroidism. Cause of Pendred's syndrome is mutations in the SLC26A4 gene. The SLC26A4 gene provides instructions for making a protein called pendrin. The pendrin transports negatively charged ions (chloride, iodide, and bicarbonate) into and out of cells. **Objective and hypotheses:** We describe a clinical case of Pendred's syndrome in girl, 16 years old. with breast and ovary cysts. **Method:** Total examination (including mammological and gynecological examination), hormonal analysis, thyroid, mammological and gynecological USE. **Results:** Physical development: height 157 sm, weight 59 kg, BMI 23.9 kg/m^2. Sex development: Tanner V. Deafness (congenital bilateral sensorineural hearing loss). Thyroid examination: palpable and visible struma, USE (goiter and colloid cysts). Gynecological examination: dysmenorrhea I, USE (follicular cyst in left ovary). Mammological examination: cyclic mastalgia, breasts symmetry, skin and nipples normal, bilateral palpable lumps in areola areas, USE (bilateral cysts in areola area). Hormonal analysis (follicular phase) ?SH 1.9 mUI/l, Anti-TPO 530 U/l (normal 0–30), LH 6.6 UI/l, FSH 7.7 UI/l, prolactin 559 mUI/l, cortisol 733 nmol/l. Treatment: hearing-aid, L-thyroxine, cycling Vitamins.

P3-1005

Incidence and Etiology of Hyperandrogenism in Children and Adolescent

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Background: The hyperandrogenism in the teenager is a frequent reason for consultation. It poses diagnostic problems and sometimes therapeutic ones. **Objective and hypotheses:** Search of the incidence and aetiology of hyperandrogenism in children and adolescent. **Method:** This is a retrospective study of patients hospitalized for exploration of hyperandrogenism. 14 patients was for collected, all underwent to a profound clinical examination, gonadal and adrenal balance (FSH, LH, E2, testosterone, 17OHP, Androstendione) and a pelvic ultrasound imaging. The assessment was completed according to the context of the patient. **Results:** The mean age of patients was 17 years, the beginning of the troubles was at the para-pubertal age (average age: 12 years). The delay in the consultation was due to a misunderstanding of the problem (*n*: 10) or the trivialisation of the late (*n*: 4). The reasons for consultation were: in 100% of cases hyperandrogenism, hyperandrogenism associated to menstrual disorders in 50%, primary amenorrhoea 7.14%, 35% of patients had PCOS (mean age 18 years) and 65% had an adrenal hyperplasia (CAH) has belatedly (mean age 17 years). The clinical status was characterised in the HCS by: severe hirsutism associated with signs of virilisation (clitoral hypertrophy). The cycle disorders were present in half of them; the spaniomenorhee was constant in the case of PCOS. Obesity was found in 70% of cases. Furthermore, note the absence of metabolic disorders. In the case of arrhenoblastoma, hyperandrogenism was moderate and there was a tumour syndrome. **Conclusion:** The hyperandrogenism child and adolescent require careful exploration. An accurate diagnosis must be made for the rapid initiation of effective treatment.

P3-1006

Early and Sever Manifestation of McCune-Albright Syndrome with GNAS Mutation in the Liver Tissue

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Background: McCune-albright syndrome is clasiically defined by the clinical triad of fibroud dysplasia of bone (FD), café-au-lait spots and precocious puberty. It is a rare disease with variable presentation caused by somatic (non-germline) gain of function mutation in GNAS gene. It can affects both endocrine and non-endocrine tissue. In addition to precocious puberty, other hyperfunctioning endocrinopathies may be involved including hyperthyroidism, growth excess, cushing syndrome and renal phosphate wasting. Skin and skeletal manifestation is the most non-endocrine pathology, but other tissues like gastrointestinal and hepatobiliary system has been also reported. **Objective and hypotheses:** To report a case with early and sever manifestation of McCune Albright syndrome where diagnosis was not a straightforward. **Method:** We report a 2 years old girl who was presented to medical attention at the age of 16 days with cholestatic jaundice with acholic stool and multiple hyperpigmented skin lesions involving right sided of the face, back, buttocks and thigh. She was found to have hyperthyroidism caused by hyperfunctioning nodule in the the left lobe of the thyroid gland, it was uncontrolled with medical treatment. At 4 months of age, she developed vaginal bleeding with high estradiol level and found to have large left ovarian cyst. It was recurrent and difficult to control. At 6 months of age, she developed hypoechoic lesion involving right lobe of the liver, these lesion was progressively worsening and required right lobectomy and lesion was confirmed histopathologically to be hepatic adenoma. She had multiple skeletal fracture involving right femur and clavicle which was a results of diffuse polyostotic fibroud dysplasia. Lastly, she shows an evidence of growth acceleration with advanced bone age which was a result of growth hormone excess with normal pituitary MRI (Picture and Tables will be provided). **Results:** GNAs mutation was negative in both peripheral blood and skin tissue samples. Heterozygous GNAS mutation with a change from Arginine (CGT) at codon 201 to Histidine (CAT) was identified in liver tissue sample. **Conclusion:** To our knowledge, such a sever neonatal form of McCune Albright syndrome is rarely reported in the literature. Non-endocrine manifestation has to be considered in the management of McCune Albright syndrome. GNAS mutation should be evaluated in the tissue affected if the blood and skin tests are negative.

P3-1007

Depth and Timing of Hypoglycaemia Achieved During Insulin Tolerance Test in Children

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Background: Achieving adequate hypoglycaemia during the insulin tolerance test (ITT) is important but excessive hypoglycaemia is undesirable. We aim to evaluate factor affecting insulin sensitivity and hypoglycaemia during ITT. **Patients and method:** 106 children (76 males) who had an ITT (Actrapid 0.1 units/kg) performed between 2009–2013 for evaluation of short stature, poor growth or re-assessment after completion of growth following rhGH therapy. Plasma glucose, cortisol and GH measurements at −30, 0, 15, 30, 60, 90,120 min were studied by a second order negative feedback mathemaciacl model to describe dynamic changes of production rates. The slope of the change in glucose clearance rate vs its concentration was defined as insulin sensitivity. Adequate hypoglycaemia was defined as glucose <2.2 mmol/l. **Results:** Median age of the group was 12.7 years

(range: 5.7–19.3), Ht S.D.s-2.8 (−4.2, 1.5), BMISDS −0.1 (−4.0, 4.4). 22 of the 106 (20.7%) did not achieve adequate hypoglycaemia based on measured plasma glucose. The nadir for measured plasma glucose occurred at 15 min (15, 30). However, simulated nadir glucose occurred at 11 min (8, 29) with simulated plasma glucose of 1.44 mmol/l (0.09, 4.75). Of the 22 who did not achieve adequate hypoglycaemia based on measured plasma glucose, 8 (36.4%) achieved adequate simulated hypoglycaemia at 13.5 min (11, 29). Nadir measured plasma glucose was highly associated with nadir simulated glucose ($r=0.96$, $P<0.0001$). In a multivariate model, there was a trend for children with GH deficiency to have greater insulin sensitivity (95% CI: 0.0–0.60). Age, gender, BMISDS, HtSDS, body surface area, puberty were not associated with insulin sensitivity. In multivariate analysis (age, gender, puberty, body surface area, baseline glucose),baseline glucose was the only significant independent factor associated with the extent ($P=0.009$, 95% CI=0.14–0.93)and timing of simulated nadir glucose ($P=0.005$, 95%CI=1.58–8.79) **Conclusion:** 20% of children who underwent ITT were classified as achieving inadequate hypoglycaemia based on plasma glucose. However, based on the simulation model, over one third of these children would have achieved adequate hypoglycaemia. Given that the identification of GH and cortisol deficiency on ITT critically depends on optimal hypoglycaemia, these results have important clinical implications.

P3-1008

Presenting Characteristics, Auxological, and Aetiologic Evaluation of 364 Patients with GH Deficiency

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Background: GH deficiency (GHD), can either be isolated (IGHD) or part of multiple pituitary hormone deficiency (MPHD), is a pituitary hormone disorder that manifests with short stature. **Objective and hypotheses:** To evaluate the presenting characteristics, auxological and etiologic factors of GHD in a large cohort from a single tertiary paediatric endocrine centre. **Methods:** Hospital files of patients followed with GHD deficiency at Diyarbakir Children's State Hospital, between the year 2010 and 2014, were reviewed. **Results:** The number of patients recruited was 364 ($n=221$; 60.7% male). The mean age of the diagnosis was 10.4±3.3 (range: 0.5–17.3). Patients with IGHD ($n=312$; 85.7%) constituted the largest group followed by patients with MPHD ($n=35$; 9.6%), and bioinactive GH ($n=15$; 4.1%). While female patients were presented earlier (mean age: 9.8±2.9) than males (mean age: 10.8±3.4) ($P=0.002$), the mean height-S.D.s at presentation was not statistically different (mean height-S.D.s was −2.8±1.1 and −2.7±1.1 respectively, $P=0.310$). There was no a statistically significant difference between the age of presentation of patients with IGHD and MPHD ($P=0.924$). However, compared to the patients with IGHD, patients with MPHD was shorter at the time of the diagnosis (mean height S.D.s was −3.5±1.6 and −2.5±1.0 respectively, $P<0.001$). In 28 out of 35 patients MPHD was idiopathic, whereas in seven patients craniopharyngioma was the underlying pathology. While in 336 out of 364 patients (92.3%) GHD was sporadic, 28 patients (7.7%) had familial GHD. Although presented younger, patients with familial GHD had lower height-S.D.s compared to the sporadic group (Mean age of the diagnosis was 8.6±3.9 vs 10.4±3.2; $P=0.027$ and mean height-SDS was −3.5±1.7 vs −2.7±1.0; $P<0.001$ respectively). **Conclusion:** In this male predominant large cohort of GHD patients, MPHD patients account for about 10% of patients. Except for earlier presentation of females, no phenotypical diversity was observed between the male and female patients. Patients with familial GHD were presented earlier and had a more severe clinical phenotype.

P3-1009

Nutritional Supplementation, Sleep Patterns and Growth in Short and Lean Prepubertal Children

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Background: GH secretion is affected by duration and quality of sleep. Studies examining the connection between sleep and linear growth have reported conflicting results. Recently, we reported that nutritional supplementation was effective in promoting growth in children. In the present study, we extended our evaluation of the nutritional supplement to assess the association between nutrition, sleep and growth. **Objective and hypotheses:** To examine whether nutritional supplementation affects sleep patterns and growth. **Method:** Study design: Prospective randomised, double-blinded, placebo-controlled study of nutritional supplementation at the Endocrinology Department of a tertiary Pediatric Medical Center of healthy, lean, short, pre-pubertal children. Outcome measures: Anthropometric measurements (Height-SDS, Weight-SDS and BMI-SDS), sleep pattern (sleep-schedule time questionnaire (SSTQ)) and nutritional intake (3-day food diaries), were assessed at entry and after 6 months intervention. **Results:** 164 healthy short and lean pre-pubertal children (127 boys, mean age 5.6±1.5 years) – 83 from the formula group and 81 from the placebo group – were recruited to the sleep assessment study. Baseline characteristics were similar in the formula and placebo groups. In the formula group 'good' consumers (intake of ≧50% of the recommended dose) had a shorter sleep latency ($P=0.046$) compared with 'poor'

consumers (intake of <50%). Children with 'fast' time to sleep (<15 min) improved significantly weight-SDS (0.25±0.34 vs 0.07±0.36, $P=0.044$), and tended to improve height-SDS (0.09±0.13 vs 0.03±0.13, $P=0.057$) as compared to 'slow' time to sleep. In the placebo group, differences in sleep latency and growth measurements were not found. Positive correlations were found between mean sleep duration and caloric intake/kg, protein/kg, carbohydrate/kg and fat/kg both, at baseline and after 6 months of intervention. **Conclusion:** Our data suggests that in short and lean pre-pubertal children nutritional supplementation is associated with improved sleep patterns. Yet to be elucidated are the mechanisms linking between nutritional intake, sleep patterns, and linear growth. **Conflict of interest:** M.YG., L.L., R.S., and M.P. together with Schneider Children's Medical Center of Israel, created NG Solutions a company aimed at distributing the study formula.

P3-1010

Disease-Specific Growth Charts of Marfan Syndrome in Korea

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Background: Patients with Marfan syndrome (MFS) presents with primary skeletal manifestations such as tall stature, chest wall abnormality, and scoliosis. And these primary skeletal manifestations affect the growth pattern in MFS. Therefore, it is not appropriate to use normal growth charts to evaluate the growth status of MFS. **Objective and hypotheses:** We aimed to develop disease-specific growth charts for Korean MFS patients and to use these growth charts for understanding the growth patterns in MFS and managing of patients with MFS. **Method:** Anthropometric data were available from 187 males and 152 females with MFS through a retrospective review of medical records. Disease-specific growth charts were generated and 3, 25, 50, 75, and 97 percentiles were calculated using the LMS (refers to λ, μ, and σ respectively) smoothing procedure for height and weight. Comparisons between MFS patients and the general population were performed using a one-sample *t*-test. **Results:** With regard to the height, the 50th percentile of MFS is above the normative 97th percentile in both genders. With regard to the weight, the 50 percentile of MFS is above the normative 75th percentile in male and between the normative 50th percentile and the 75th percentile in female. **Conclusion:** The disease-specific growth charts for Korean patients with MFS can be useful for monitoring growth patterns, planning the timing of growth-reductive therapy, predicting adult height and recording responses to growth-reductive therapy.

P3-1011

Targeted Birth Length and Parental Height Measurement in Babies with Birthweight ≤9th Centile; Improved Uptake During Second Study During 1 Calendar Year in a Single Newborn Unit

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Background: The contribution of intrauterine growth restriction (IUGR) and parental height (PH) to childhood short stature is difficult to determine in countries, including the UK, where birth length (BL) is not routinely measured, while accurate PH may become unavailable due to separation/divorce. A previous study (2008–2009) examined the feasibility of BL and PH measurement in the lightest 9% of babies born in a single maternity unit. Uptake was disappointing, with particularly limited success of PH capture after birth. **Objective and hypotheses:** To re-evaluate the feasibility of measuring BL and PH in light infants in a second study in the same maternity unit. **Method:** BL and PH measurement were offered for infants with birth weight (BW) ≤9th centile (UK 1990 reference data) from October 2013–2014. Infants were stratified based on BW and/or BL≤−2 S.D.s as: i) Light ii) Short or iii) Light+Short. Re-measurement at 2 years has been arranged for Short and Light+Short babies to evaluate catch-up growth. **Results:** BW was collated for 3484/3510 liveborn infants and was ≤9th centile in 416 (11.9%) infants of 28–41 weeks gestation. Consent to participate was obtained in 206 (50%) infants, refused in 127 (31%) and not requested by oversight in 78 (19%). BL was measured in 189 (92%) consented infants, of whom 14 (7%) were Light, 50 (26%) Short and 38 (20%) Light+Short. Both PH were measured in 175/206 (85%) infants. Follow-up at 2 years is planned for 88 infants of whom 85 (97%) have one or both PH measured or reported. **Conclusion:** This second study has demonstrated a high success rate for BL and PH measurement in consented babies, confirming that targeted measurement in the lightest 9% of babies is feasible. The problems encountered with obtaining consent could be obviated if measurement of light infants and follow up of short children were incorporated into standard practice.

P3-1012

Case Report of Wolf-Hirschhorn Syndrome by Chromosomal Microarray Analysis: Importance of the Molecular Investigation for the Aetiological Diagnosis of Short Stature

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Background: Growth is a complex process influenced by several genetic factors both pre and postnatal, in which 80% of the height variation is explained by genetic factors. Nevertheless, the standard medical evaluation of short stature (SS) relies upon physical examination and laboratory parameters and identifies a pathological cause of SS in 1–40% of individuals. Recent advances in genetic diagnosis are revolutionizing the clinician's ability to obtain a molecular diagnosis for patients with growth disorders. The Wolf-Hirschhorn syndrome (MIM194190) is a complex genetic disorder caused by loss of genomic material from the short arm of chromosome 4 (4p16.3 region), including LETM1 and WHSC1 genes. **Case presentation:** We report a female patient, 1 year old, presented with severe SS (−4.36 *z*-score), IUGR, neonatal jaundice, syndromic facies (microcephaly, prominent glabella, high arched eyebrow, broad nasal bridge and hypertelorism, short filtrum, mouth turned down, micrognathia, malformed ears), delayed psychomotor development, intra-atrial communication and seizures. She had a female karyotype, without any suggestion of chromosome alteration. We performed the chromosomal microarray analysis (CMA) on the proband and her parents. The array used was Affymetrix's GeneChip CytoScan HD SNP array. CMA detected four *de novo* genomic imbalances, corresponding to a 3.86 Mb microdeletion at 4p16.3, a 1.55 Mb microdeletion at 4p16.3, a 320 kbp microduplication at 5p13.2 and a 4.21 Mb microduplication at 9p24.3. The CMA showed that the microdeletion at 4 p was harbouring several genes, including *LETM1*, *WHSC1*, *WHSC2*, *MSX1* that have been described and related to the Wolf-Hirschhorn syndrome. **Conclusion:** These findings allowed identification of a genomic cause for the clinical features of the proband. Molecular diagnosis is important because it can end the diagnostic workup for the patient, it may alert the clinician to other medical comorbidities for which the patient is at risk, and it is extremely valuable for the genetic counselling.

P3-1013

Achondroplasia Reference as Background Matrix for Following Children with Extreme Short Stature

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Background: There is a shortage of clinically useful growth charts for following growth development in conditions with extreme short stature. At the same time, it is not possible to construct syndrome-specific growth charts for many of these conditions due to low prevalence and perhaps also often a great inter-individual variability of the growth defect within a certain syndrome. **Objective and hypotheses:** The aim of this project was to evaluate growth patterns of children with severe growth retardation using our newly constructed achondroplasia reference as a short stature reference. **Method:** Height and weight measurements from about 200 children and adolescents with defined skeletal dysplasia (e.g. spondyloepiphyseal dysplasia congenita (SEDC) and Kniest syndrome, acrodysostosis, spondylometaphyseal dysplasia, acromesomelic dysplasia) aged 0–20 years were expressed in S.D. score both relative to the WHO and the achondroplasia reference (Neumeyer *et al.*, unpublished). Syndrome-specific growth patterns were evaluated. **Results:** Height in several syndromes followed within the normal range (±2 S.D.) of the specific short stature standard. Height development in acromesomelic dysplasia Maroteaux for instance was identical to the achondroplasia mean; weight developed at −1 S.D. of the short stature reference. For other extreme conditions such as in Kniest syndrome, height pattern seemed better captured in the short stature reference compared to the WHO standard. **Conclusion:** The presented examples show clearly the value of expressing growth pattern in severe growth retardation in S.D.S-format. The results of this study could facilitate the adjustment of surveillance and follow-up programs and could be used in clinical centers following individuals with severe growth restriction irrespective of diagnosis. **Funding:** This work was supported by Stiftelsen Promobilia.

P3-1014

Altered Gene-Expression in Human Growth Plate Cartilage Tissue Exposed to Dexamethasone

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Background: Synthetic glucocorticoids (GCs) are widely used drugs but their suppression of growth in pediatric patients is a well-known problem. Different mechanisms have been suggested but we still do not know the sensitivity of human growth plate cartilage to GC treatment. Here in this study, we have investigated the direct effects of GC treatment on the expression of crucial genes in the growth plate, such as collagen-2A1, osterix (Osx), and transforming growth factor β1 (TGF-β). **Objective and hypotheses:** Our aim was to study the expression pattern of collagen-2A1, Osx and TGF-beta in human growth plate cartilage when exposed to GCs. **Method:** Biopsies of human growth plate cartilage from one boy (patient 1), pubertal stage GH; PH4 (Tanner), and one girl (patient 2), pubertal stage B2; PH2, were obtained at epiphyseal surgery. Sections of the cartilage were cultured and treated for 24 h with 10 uM dexamethasone, and snap-frozen in liquid nitrogen. RNA was extracted with Trizol® and qPCR was performed with primers for human collagen-2A1, Osx, and TGF β1. **Results:** In patient 1, we found that dexamethasone suppressed collagen-2A1 expression by 88%, compared to control. Interestingly, dexamethasone also

suppressed TGF-beta by 79%, compared to control. There was a slight increase in Osx expression in dexamethasone treated cartilage vs control. In patient 2, there were only marginally changes in the gene expressions between the control and GC-treated cartilage sections. **Conclusion:** These data from rare growth plate tissue obtained from paediatric patients suggest that GCs can directly sensitize human growth plate chondrocytes and differentially regulate genes involved in chondrogenesis. We also observed that the tissues from the two patients responded differently when challenged to GCs. More observations are needed to confirm these results, which'll help us to understand direct effects of GC therapy on bone growth.

P3-1015

Reversible GH Excess in Two Girls with Neurofibromatosis Type 1 and Optic Pathway Glioma

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Background: 12 cases of neurofibromatosis type 1 (NF-1) children with optic pathway glioma (OPG) and GH excess (GHE) are reported to-date. The aetiology of GHE is unknown. We describe two NF-1 girls and OPG with reversible GHE. The diagnosis of GHE was established from auxological data, high IGF1 and lack of GH suppression during an oral glucose tolerance test (OGTT). Our aim is to increase awareness of GHE in NF-1 children with OPG and help its management. **Case presentation:** Case1: A tall, obese and pre-pubertal 6.9 years girl with NF1 and treated OPG was found to have GHE. She started SSa and her growth decelerated and IGF1 normalised. At 7.8 years she developed central precocious puberty (CPP), which was suppressed with GnRHa. At 10.2 years she had acute pancreatitis and SSa was stopped. Off SSa, IGF1, GH profile and growth velocity remained normal. GnRHa was stopped at 13.5 years with menarche at 14.3. Final height was −0.6 S.D., BMI +1.8 S.D.. She developed type2 diabetes at 15.5 years. IGF1 remains normal 8.2 years after stopping SSa. Case 2: An obese, tall, 7.4 years girl with NF-1 treated for CPP with GnRHa after completing chemotherapy for OPG continued to grow at a faster rate despite clinical and biochemical pubertal suppression. IGF1 was high and GHE was proven on an OGTT. She started SSa at 8.9 years which normalized her growth rate and IGF1. Because of the clinical history of case1, at 12.8 years SSa was stopped and GHE reassessed. IGF1 remained normal with GH suppression on OGTT at 2.8 years follow-up. At 11 years GnRHa was stopped but subsequently she developed hypogonadotropic hypogonadism and started on HRT. She remained obese (BMI 2.6 S.D.), final height +0.9 S.D. **Conclusion:** GHE in NF-1 with OPG can be reversed and only short term SSa therapy might be needed, reducing patient discomfort/cost/potential side effects. The aetiology remains unknown but its course suggests a hypothalamic dysfunction.

P3-1016

Autosomal Recessive Omodysplasia: A Rare Cause of Disproportionate Short Stature

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Background: Autosomal recessive omodysplasia is considered a rare skeletal dysplasia characterized by severe micromelia with shortening and distal tapering of the humeri and femora. **Objective and hypothesis:** To report the prenatal findings of a patient with autosomal recessive omodysplasia, a rare condition characterized by disproportionate short stature. **Population and/or methods:** We performed a description of the case along with a literature review. **Results:** The pregnant woman presented 38 years and she was in her seventh pregnancy. She was initially assessed in fetal medicine at the hospital at 29 weeks and 6 days of gestation due to obstetric ultrasound showing short femur and humerus. The pregnancy was uneventful. Her husband presented 40 years of age and was healthy and non-consanguineous. Family history was positive for a maternal uncle with nanism. Foetal ultrasound performed at 29 weeks and 6 days of pregnancy showed reduced amniotic fluid and important rhizomelic shortening of the limbs. The humerus measured 1.8 cm and the femur 2.4 cm. The hands and feet, as well as the face and thorax seemed normal. Bone mineralization was also normal. At this point, achondroplasia/hypochondroplasia emerged as diagnostic hypotheses. GTG-Banding karyotype performed through cordocentesis revealed a normal chromosomal constitution (46, XY). Foetal echocardiography was also normal. The ultrasound performed at 35 weeks and 6 days of gestation revealed femur measuring 3.4 cm. The estimated foetal weight was 1.441 g. The patient was born through vaginal delivery, at 37 weeks and 4 days of gestation, weighing 2.320 grams, measuring 40 cm, with head circumference of 33 cm and Apgar scores of 9 at 1st min and ten at fifth. He presented micromelia with important rhizomelic shortening of the upper and lower limbs, normal thorax and some dysmorphia: nevus flammeus at nose and glabella, small mouth, micrognathia, small ears with overfolded helix, bilateral single palmar crease and cryptochid testis. These clinical data added to the radiological features (that included radial head dislocations) were consistent with the diagnosis of autosomal recessive omodysplasia. **Conclusions:** There are few reports in the literature of prenatal features of patients with this genetic condition. In prenatal, autosomal recessive omodysplasia has also been confused with other syndromes, as diastrophic dysplasia or even hypo/achondroplasia, due to the similarity of the findings. The definition of the diagnosis has important implications over the genetic counselling and patient management.

P3-1017

The Growth Characteristics of Patients with Noonan Syndrome, and First 2 Years Results of GH Treatment: A Nationwide Multicentre Study

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Introduction: Short stature is a common manifestation of Noonan syndrome (NS). GH deficiency, GH insensitivity, and neurosecretory dysfunction have been reported in the literature. The optimal GH treatment for NS is still controversial. In this study, we aimed to evaluate the growth characteristics in addition to clinical features of NS, and the growth response to GH treatment by using a nationwide registration system. **Material and methods:** Children and adolescents with clinical (according to van der Burgt criteria) and/or genetic diagnosis with NS were included to study. Laboratory assessment including standard GH stimulation tests result were evaluated. Height increment of patients with or without GH treatment were analysed after two years therapy. **Results:** A total of 99 patients with NS (68 males, 31 females) have been enrolled. On admission, the mean age of patients was 8.37 ± 4.2 years, height S.D.s was -3.03 ± 1.65, parentally adjusted height deficit was -2.25 ± 1.73, and 30% of them were pubertal. The percentage of frequently seen clinical findings in NS were 77% short stature, 58% cardiac abnormalities, 59% criptorchidism, 34% chest deformity, 30% neuromotor developmental problem, and 23% ophtalmological disorders. GH stimulation tests were performed on 63 patients, and 40 of them showed suboptimal GH response (<10 ng/ml). 36 patients received rhGH (mean dose: 0.25 ± 0.05 mg/kg per week). Height S.D.s increased from -3.69 to -2.85 after 2 years of therapy. Significant differences was observed according to nonGH-treated patients (*n*: 25) (*P*: 0.02) (Table). PTPN11 gene were analysed 45 of patients, and 29 of them (64%) had mutation. Height S.D.s at admission were similar in patients with or without PTPN11 gene mutation. **Conclusion:** In the 1st year GH therapy, increase in ΔHeight SDS is observed as a positive effect. However this effect of therapy waned at the second year. We suggest that growth therapy optimisation is needed for this NS patients.

P3-1018

Vitamin D in Short Children on GH Therapy: Effects of Vitamin D Status and Vitamin D Supplementation on Glucose Homeostasis

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Background: Glucose metabolism effects of vitamin D deficiency are debated. GH therapy is associated with increased insulin values and decreased insulin sensitivity. **Objective and hypotheses:** To investigate vitamin D status in short children treated with GH- to investigate if the known effects of GH therapy on glucose metabolism are modulated by vitamin D supplementation. **Method:** 41 children treated with GH for short stature where evaluated 6 months before and 6 months after receiving vitamin D 1000 UI/day (colecalciferolum). We analysed: 1. Vitamin D status; 2. Glucose homeostasis evaluated with: glucose, HbA1S, Insulin, HOMA index before starting vitamin D supplementation and 6 month after vitamin D administration. **Results:** Vitamin D level was below 30 ng/ ml in all the patients and bellow 10 ng/ml in 15% of the patients. Vitamin D supplementation with 1000 UI for 6 months increased vitamin D levels over 30 ng/ ml in 56% of the patients and over 10 ng/ml in all the patients. Vitamin D administration had a demonstrable influence on insulin secretion and insulin sensitivity: in vitamin D <10 ng /ml patients insulin correlated positively with vitamin D concentration. In vitamin D >30 ng/ml patients insulin concentration and HOMA index had a decreasing tendency which could be understood as an effect of lowering GH therapy induced hyperinsulinemia and insulin insensitivity and there metabolic consequences. There was no significant influence of vitamin D supplementation for six months on growth parameters. **Conclusion:** Conclusions: vitamin D evaluation and supplementation is needed in short patients on GH therapy for decreasing the glucose metabolism consequences of GH therapy and possibly in the long time for improving response to therapy.

P3-1019

Laron Syndrome Caused by a Large Deletion in GH Receptor Gene

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Background: Laron syndrome, which is characterised with GH insensitivity, is caused by mutations of GH receptor (GHR). GHR, consisting of nine exons, is located on 5th chromosome. Typical findings of this syndrome are immature facial appearance, prominent forehead and eyes, depressed nasal bridge, low IGF1 and IGFBP3 levels which do not increase with IGF-generation test. **Case report:** A 4-year and 3-month old boy was admitted because of growth retardation. The birth weight was 4 100 g and he was hospitalized for respiratory distress and jaundice in the neonatal period. He also had micropenis and cryptorchidism. Parents were non-consanguineous; however their roots were from the same village. Physical examination revealed midfacial hypoplasia, depressed nasal bridge, prominent forehead. The height was 77 cm ($<$3p, -6.3 S.D.s), the weight was 8.6 kg ($<$3p, -7.4 S.D.s), the head circumference was 45 cm ($<$3p), the left testis was 2 ml, the right testis was retractile and 1–2 ml in size and stretched penile length was 2.6 cm. Laboratory investigations showed that the electrolytes were normal, venous glucose level was 49 mg/dl, thyroid functions were normal, baseline GH level was 23.3 ng/ml, IGF1 was $<$25 ng/ml and IGFBP3 was $<$0.5 μg/ml. IGF1 and IGFBP3 levels were still undetectable after an IGF-generation test. The patient was diagnosed with GH insensitivity and treatment with Mecacermine was commenced. A large deletion in exon 4–10 was detected with genetic analyses. **Conclusion:** There are more than 200 patients with GH insensitivity. Most cases in the literature have mutations on exon 2–7. According to our knowledge our patient is the second case with this mutation. This case was reported since it is a very rare clinical condition.

P3-1020

GH Deficiency and Glucose 1 Transporter Deficiency Syndrome

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Background: GLUT1 deficiency syndrome (GLUT1DS) is a treatable epileptic encephalopathy resulting from impaired glucose transport into the brain. Clinical features comprise motor and mental developmental delay, seizures with infantile onset, deceleration of head growth often resulting in acquired microcephaly, and a movement disorder with ataxia, dystonia, and spasticity. While it is known that ketogenic diet may cause growth retardation, GH deficiency (GHD) may represent another possible cause of growth failure in children with GLUT1DS. **Case presentation:** We report a case of GHD in a 10-year-old Caucasian boy with GLUT1DS. The child was admitted for evaluation of growth failure. His target height was 181 cm ($+1$ S.D.s). He had mild facial dysmorphism (epicanthus, telecanthus, hypertelorism), his height was 123.8 cm (-2.56 S.D.s), his growth velocity was 2.1 cm/year in the previous year (-4.33 S.D.s). Two GH provocative tests (with arginine and clonidine) showed GH deficiency (GH peak: 9.4 ng/ml on the first test, 7.4 ng/ml on the second test), with IGF1 in the lower range (106 ng/mL, normal range: 88–452). The patient was started on GH replacement therapy at a dose of 26 μg/kg per day, with marked improvement of his growth velocity after just 3 months of therapy. After 6 months of therapy his height was 128.5 cm (-2.42 S.D.s) with a growth velocity of 19.2 cm/year ($+0.96$ S.D.s). The diagnosis of GHD was established before the diagnosis of GLUT1DS, excluding the confounding role of ketogenic diet. **Conclusion:** We speculate that GHD may represent a poorly recognised clinical feature of GLUT1DS and that under-diagnosis could derive from the fact that growth failure may be ascribed to ketogenic diet and therefore not further investigated.

P3-1021

Response to rhGH Treatment in Patients with Transient or Permanent GH Deficiency

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Background: GH (rhGH) treatment improves adult height in GH deficient (GHD) patients. However, there are differences in short and long term responses to treatment between children with permanent deficit (PDGH) and those who present a transient deficit (TDGH) when reassessed at final height (FH). **Objective and hypotheses:** To evaluate the response to rhGH treatment in patients with PDGH or TDGH one year after initiating treatment and at FH when treatment was suspended. **Method:** Descriptive, retrospective study including 89 patients diagnosed of GHD. Patients were treated with rhGH and followed-up to adult height. TDGH was defined as GH peak greater than 6 ng/ml on final reassessment. **Results:** 25/89 patients (28%) had PDGH. Their chronological age at diagnosis was 10.7 ± 2.9 years and height -2.46 ± 0.86 S.D. Age at diagnosis of TDGH group was 10.8 ± 2.7 years and height -2.24 ± 0.68 S.D.. GH peak value was 4.26 ± 2.78 and 6.2 ± 2.01 ng/ml for permanent and transient deficit, respectively. Genetic height and predicted adult height were higher in PDGH. Initial dose of rhGH was 0.030 ± 0.003 mg/kg per day for all patients. When considering on reassessment a height increase $> +0.3$ S.D., 56% of PDGH and 46% of TDGH had a good response to rhGH. When growth velocity (GV) $> +1$ S.D. was evaluated, 76% of patients in both groups had a good response. Increase of height and GV were higher in the group of PDGH: $+0.55 \pm 0.53$ and 4.33 ± 3.53 S.D. in this group vs $+0.36 \pm 0.47$ and $+2.95 \pm 2.54$ respectively, in TDGH. FH was -0.81 ± 0.87 S.D.

in PDGH patients and −0.95±0.83 S.D. in the TDGH group. Height recovery was greater in patients with DPGH. FH increase over target height was −0.19±1.15 S.D. for PDGH and −0.001±1.09 S.D. for TDGH patients. **Conclusion:** PDGH patients had a better response to rhGH than TDGH at 1st year of treatment and at adult height. FH was below their genetic height for all patients.

P3-1022

Postnatal Growth and Biochemical Markers of Late Preterm Infants: Prospective Birth Cohort

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Background: Late preterm birth (defined as infants born between 34 and 36 weeks of gestational age) is increasing worldwide. Their postnatal growth has not been fully investigated. **Objective and hypotheses:** To identify the characteristics of postnatal growth and biochemical markers in late preterm infants. **Method:** Among 2014 children in the birth cohort study conducted from 2010, 51 children were born late preterm with birth weight and height as AGA. 40 children matched in maternal age and other background, but born in term were selected as control group. We measured their height and weight from birth, 1, 3, 6, 9, 12 months and 2.3 years. Serum IGF1, Leptin, Adiponectin, and total cholesterol were measured at the age of 1 and 3. Maternal history during pregnancy, including weight gain and complications, was obtained from cohort database. Children's nutrition was surveyed by questionnaires. Statistical analysis was performed using Kruscal-Wallis test. **Results:** There was no significant difference in mother's condition during pregnancy and nutrition of the children within late preterm and term controls. At the age of 2, late preterm group had significantly higher BMI compared to controls. ($P=0.0238$, mean 16.36 kg/m^2 vs 15.71). At the age of 3, there was no statistically significant difference in BMI, although late preterm children showed a tendency of higher BMI (mean 16.36 vs 15.21). Height S.D. score, serum biochemical data didn't show significant difference between these two groups. **Conclusion:** This result suggests late preterm group may have higher risk in developing obesity later in life.

P3-1023

Alterations of SHOX and Its Enhancers as a Cause of Short Stature: Evolution of Our Cases

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Background: Heterozygous alterations of SHOX and its regulatory region PAR1 are identified in approximately 70% of Léri-Weill dyschondrosteosis and 2–5% of idiopathic short stature cases. Identification of a SHOX mutation enables GH treatment to be offered to the patient. **Objective:** To evaluate the clinical characteristics of seven patients with SHOX haploinsufficiency and their evolution. **Method:** Retrospective analysis of patients with a genetic study of SHOX and the regulatory regions. Analysis of medical records. **Results:** Seven patients: three girls, four boys. Average age at first visit 8.0 years (4.9–11.7). Referrals for short stature (seven). Personal history: SGA (two), preterm (one), obesity (one). Family history: short stature and alteration of body segments in parents (seven). Average target height −1.7 S.D.s (−1 to −2.1). Physical exam: mesomelic limb shortening (seven), Madelung deformity (two). Mean height at first consultation −2.75 S.D.s (−1.9 to −3.9). Radiological study: pathological in all patients. GH deficiency in three patients (two GH functional tests <10 ng/ml). GH treatment was initiated in four patients: mean inicial height −2.84 S.D.s (−2.1 to −4.1). Mean height after 1 year of treatment: −2.4 S.D.s (−1.75 to −3.28); mean increase 0.45 S.D.s (0.0 to 0.84); mean increase 7 cm/year (4–9.8). One patient, late onset: 12.3 years (bone age 13.0 and menarche a year earlier), increased 0.0 S.D.s and 4 cm in the 1st year. Mean height last consultation −2.36 S.D.s (−1.8 to −3.0). Genetic study: 3/7 presented with a heterozygous mutation, 1 stop mutation (c.79G>T (p.G27X)), two common 47.5 kb downstream enhancer deletions. Cosegregation of the mutation with the phenotype was confirmed when possible (two families). **Conclusion:** The study of short stature should include a comprehensive physical examination to analyse body segments and skeletal dysplasias, requesting radiological study where appropriate. An early genetic study based on clinical suspicion (physical exam and family history) leads to early treatment with better response.

P3-1024

Vitamin D Status in Pre-Pubertal Children with Isolated Idiopathic GH Deficiency: Effect of GH Therapy

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Background: Some studies suggested a correlation between vitamin D (VD) and the GH-IGF1 but few studies, and with controversial results, have prospectively analysed the vitamin D status in children before and after GH treatment. **Objective and hypothesis:** To assess VD status in pre-pubertal children with idiopathic GH deficiency (GHD); and to evaluate effect of GHD and GH treatment on VD levels. **Methods:** 50 pre-pubertal children with isolated idiopathic GHD were subjected to history, anthropometric assessment and measurement of 25 hydroxy vitamin D (25-OHD), serum calcium, phosphorous, alkaline phosphatase and parathyroid hormone at diagnosis and 1 year after GH therapy (0.025 mg/kg per day). Patients were compared to 50 age-, sex-, and pubertal stage-matched controls. VD deficiency was defined as a 25-OHD<20 ng/ml, VD insufficiency

as a 25-OHD between 20 and 30 ng/ml and VD sufficiency as a 25-OHD > 30 ng/ml. **Results:** 25-OHD levels were lower in cases than controls. Twenty GHD children (40%) were VD insufficient and 22 (44%) deficient; while 8 (16%) were VD sufficient at baseline. There was a positive correlation between 25OH-D and baseline GH levels ($r = +0.98$, $P < 0.0001$). After 12 months of GH therapy, 25OH-D increased (23.4 ± 12.4 ng/ml at baseline vs 34.5 ± 10.1 ng/ml after therapy; $P = 0.001$). Overall, 13 (26%) of children remained insufficient and 11 (22%) deficient, with an increase in prevalence of children with normal levels (26 (52%); $P = 0.001$). **Conclusions:** Hypovitaminosis D is prevalent in GHD children and significantly improved 12 months after GH therapy. VD should be assessed in GHD children both at diagnosis and during the follow-up. The relatively high prevalence of low VD levels remaining after 12 months of GH treatment, would suggest the idea that GHD children could also profit from VD supplementation.

P3-1025

New Point Mutation in Short Stature Homeobox Gene Leads to Phenotype of Lery-Weill Dyschondrosteosis

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Background: Short stature homeobox (SHOX)-related haploinsufficiency is associated with a wide clinical variability, all characterized by growth failure with or without mesomelia and/or Madelung deformity. In patients, the effect of GH therapy on final height is comparable to the effect that can be obtained in Turner syndrome. The majority of the patients with SHOX-related haploinsufficiency disorder have deletions of varying sizes in SHOX. Point mutations in SHOX account for 30% of the SHOX-related haploinsufficiency disorders[1]. **Case presentation:** An 11 year old girl of Moroccan descent, presented with non-familiar short stature. Her target height was 0 S.D. on the Dutch growth chart. Her height was −2.5 S.D. below target height (−2 S.D. for girls of Moroccan descent), sitting height/height ratio was +2 S.D. Clinical and radiological examination showed Madelung deformity of the wrists. Karyotyping showed 46, XX and Multiplex Ligation-dependent Probe Amplification (MLPA)-analysis of the *SHOX* gene identified no deletions. Because Lery-Weill dyschondrosteosis was clinically suspected, sequence analysis of the *SHOX* gene was requested. This identified heterozygosity for a *de novo* c.836T>G p.(Leu279Arg) unclassified, but likely pathogenic variant in the *SHOX* gene. GH therapy was initiated at the age of 13 years. **Conclusion:** We identified a new, likely pathogenic point mutation in the *SHOX* gene in a girl with a clinical phenotype of Lery-Weill dyschondrosteosis. Although point mutations make up one third of the SHOX-related haploinsufficiency disorders, standard analysis for point mutations after negative screening for deletions was not common practice in the Netherlands at the time we requested diagnostics. SHOX-related haploinsufficiency is an indication for GH therapy. Therefore, we recommend that sequence analysis or mutation scanning of the *SHOX* gene should always be performed in children with a clinical phenotype of SHOX-related haploinsufficiency, when deletion/duplication analysis of the *SHOX* gene does not confirm the diagnosis.

1. GeneReviews.org: SHOX-Related Haploinsufficiency Disorders, Last Update February 1, 2008

P3-1026

Fasting and Post-Meal Levels of Appetite Regulating Hormones, before and Following GH Treatment, in Children with Idiopathic Short Stature

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Background: Poor appetite is common in children with idiopathic short stature (ISS), and is usually improved with GH therapy. **Objective and hypotheses:** To investigate the effect of GH therapy on appetite regulating hormones following a standard meal test (SMT) and to examine the association between these changes and growth response, body composition and resting energy expenditure (REE). **Method:** Nine ISS pre-pubertal children underwent a SMT before and 4 months following initiation of GH. Leptin, ghrelin, GLP1 and insulin levels were measured; area under the curve (AUC) was calculated. Height, weight, body composition and REE were recorded at baseline and after 4 and 12 months. **Results:** Following 4 months of GH therapy, an improvement in appetite was reported and a significant increase in height-SDS ($P = 0.011$), weight-S.D.s ($P = 0.021$) and REE ($P = 0.025$) were observed. At 4 months, an increase in fasting insulin levels ($P = 0.043$), a decrease in fasting GLP1 levels ($P = 0.038$) and a decrease in fasting and meal's AUC ghrelin levels ($P = 0.051$) were observed, while leptin levels remained unchanged. The incremental response of ghrelin and GLP1 to SMT (ghrelin-continuous decrease, GLP-1 – initial rise and subsequent fall), were similar before and during GH treatment. Ghrelin levels before GH treatment were positively correlated with the changes in weight-S.D.s and REE (fasting: $r = 0.667$, $P = 0.05$ and $r = 0.866$, $P = 0.005$ respectively; AUC: $r = 0.788$, $P = 0.012$, $r = 0.847$, $P = 0.008$ respectively). Ghrelin AUC levels at 4 months, were positively correlated with the changes in Ht-S.D.s ($r = 0.741$, $P = 0.022$) and free-fat-mass ($r = 0.890$, $P = 0.001$) at 12 months of GH treatment. **Conclusion:** The significant reduction in ghrelin and GLP1 following GH treatment suggests a possible role for GH in appetite regulation. Fasting and meal-AUC levels of ghrelin may serve as biomarkers for predicting growth response to GH treatment. The mechanism linking GH with changes in appetite regulating hormones remain to be elucidated.

P3-1027

Impact of Using WHO vs National Growth Charts on the Clinical Performance of a Decision Rule for Growth Monitoring

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Background: Since the publication of international growth charts by the World Health Organization (WHO) in 2006, the use of national growth charts for growth monitoring (GM) has been questioned. **Objective and hypotheses:** To evaluate the potential impact of using WHO vs. national growth charts on the performance of a clinical decision rule for detecting children with one of the target conditions of GM: GH deficiency (GHD). **Method:** In a case-referent study, we applied the Grote clinical decision rule on growth data of 33 children with GHD related to pituitary-stalk interruption syndrome (cases), and 2 200 apparently healthy children followed longitudinally from birth (referents). The Grote clinical decision rule is mainly based on the following auxological criteria combined in various ways: standardised height, distance to standardised target height, absolute height deflection, and small for gestational age with no catch up after 3 years (Grote 2008). The sensitivities, specificities and theoretical improvement in time to diagnosis of the rule using French or WHO growth charts were calculated and compared using McNemar or Wilcoxon tests for matched pairs/series. **Results:** The application of the Grote clinical decision rule would have led to a higher sensitivity (78.8% vs 66.7%, $P=0.04$), and a lower specificity (98.3% vs 99.2%, $P<0.01$) with the WHO vs. French growth charts, respectively, with no statically significant theoretical improvement in time to diagnosis (9 months vs 4, $P=0.12$). **Conclusion:** The use of WHO growth charts to apply the Grote clinical decision rule for the early detection of GHD would have notable impacts on false-positive rate. Indeed, among the 2012 French birth cohort ($n=822\,000$), 14 220 vs 6 500 would have been inadequately referred using WHO vs. French growth charts respectively.

P3-1028

Comparison of the Performance of Algorithms Proposed to Standardize Growth Monitoring

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Background: In industrialised countries, the main goal of growth monitoring (GM) of apparently healthy children is the early detection of severe underlying conditions. However, empirical evidence suggests globally poor performances of GM, with important diagnosis delays for priority target conditions and many unnecessary referrals for diagnostic work-up for disease-free children. **Objective and hypotheses:** To evaluate and to compare the performance for early detection of GH deficiency (GHD) of seven algorithms proposed in the literature to standardize GM: the WHO criterion, the Coventry consensus, the Dutch consensus, GHRS criteria, the Grote clinical decision rule and Saari's clinical decision rules. **Method:** In a case-referent study, we applied the seven algorithms on growth data of 33 children with GHD related to pituitary-stalk interruption syndrome (cases), and 2 200 apparently healthy children followed longitudinally from birth (referents). The sensitivities, specificities and theoretical improvement in time to diagnosis of these rules using French growth charts were calculated, and highly specific ($>98\%$) rules were compared. **Results:** Sensitivities and specificities varied from 15 to 100% and 48 to 100% respectively. Among the two algorithms with a specificity $>98\%$, the Grote clinical decision rule had a higher sensitivity (67% vs 15%, $P<0.0001$) and offered a better theoretical improvement in time to diagnosis (4 months vs 0 months, $P<0.0001$) than the Coventry consensus respectively. **Conclusion:** Among algorithms proposed for GM, the Grote clinical decision (Grote 2008) had the best performance for early detection of GHD, using French growth charts. Its performance on other target conditions of GM and using WHO growth charts must be evaluated.

P3-1029

Evaluation of 207 Danish Girls with Constitutional Tall Stature: Diagnostic Characteristics and Effects of Oral Administration of 17-β Oestradiol

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Background: Tall stature may be associated with psychological distress in some girls, and height reduction by oestrogen therapy has been described, but remains controversial. Possible side effects of ethinyl oestradiol therapy need to be balanced

against a possible beneficial effect on adult height. In our centre natural 17-β oestradiol, which has a better safety profile, is used to reduce final height. **Objective and hypotheses:** To evaluate the phenotypic characteristics in a large cohort of 304 girls referred due to tall stature, and to evaluate the effect of oral 17-β Estradiol (E2) on final height. **Method:** A retrospective observational study of 304 tall statured girls referred between 1993 and 2013 in a single tertiary centre. We included 207 girls whom fulfilled the criteria height >2 S.D., after exclusions due to misclassification and overgrowth syndromes. Of these girls, 60 were treated with E2 for an average duration of 1.7 years (1.2–2.5) and 26 were followed until final height. Auxology, adult height prediction (AHP), reproductive hormones and attained final height were evaluated. **Results:** Chronological age and bone age were 11.6 years (7.95–13.4) and 11.8 years (8.9–13.3) respectively. Bone age delay at referral was significantly greater in the treated girls (0.26 years (-0.66–1.33)) compared to non-treated girls (-0.41 years (-1.2–0.23)), $P<0.05$. At referral, maternal height was higher in treated girls ($P<0.05$) but there were no significant differences in Height S.D.s, AHP, FSH, LH, E2 and IGF1 levels. Final height was reduced in 18/26 girls, from an average AHP of 184.5 cm (183.4–186.7) at baseline to 183.3 cm (181.7–186.3), $P<0.05$, $n=26$. CA, BA and IGF1 at baseline did not predict E2-induced height reduction. **Conclusion:** Treatment of constitutional tall stature (CTS) with 17-β oestradiol has moderate growth reducing effects, and cannot be recommended in general but should be reserved for selected cases.

P3-1030

Sitting Height/Height Ratio: An Indicator for Genetic Study of the SHOX Gene in Children with Disharmonic Short Stature – An In-House Analysis

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Background: Gene *SHOX* haploinsufficiency due to deletions or mutations in heterozygosis causes a wide spectrum of phenotypes ranging from very severe disharmonic short stature (S. Léri-Weil, S. Turner) to very mild forms with the appearance of idiopathic short stature (IST) of difficult clinical recognition. Auxological study directed at evaluating body disproportions such as the sitting height/height (SH/H) ratio in patients with IST has been postulated as useful for orienting the *SHOX* gene. **Objective and hypotheses:** To establish the prevalence of *SHOX* gene defects in children with disharmonic short stature evaluated by the (SH/H) ratio regardless of the presence of dysmorphic features and radiological anomalies. **Method:** Prospective study of 37 consecutive patients with height <-2 S.D. and (SH/H) ratio $>+2$ S.D.. All initially underwent genetic study using MPLA or CGH array. Sequencing of all exons of the *SHOX* gene and flanking intronic regions was carried out in patients without *SHOX* gene deletion or its regulating regions. **Results:** The following defects of the *SHOX* gene were located in eight patients (six girls; age range: 9.9 ± 3.3 years and height: -2.7 ± 0.9 S.D. Complete deletion: 2, complex reorganisation of the regulating region: 2, regulating region deletion: 1, duplication 0.56 Mb: 1, partial deletion: 1 and p.Ala267dup mutation in exon 5: 1. A further three patients were diagnosed of Turner syndrome (kariotypes: 46, X; 46, XX (65%)/45, X; 46, X,+mar). **Conclusion:** The frequency of *SHOX* gene defects in our cohort with disharmonic IST evaluated by the (SH/H) ratio was 29.7%. The (SH/H) ratio is a highly useful parameter for identifying patients with disharmonic IST and orienting *SHOX* gene study. A significant proportion of patients with disharmonic IST remain undiagnosed, which renders this an open field for clinical research.

P3-1031

Final Height in Survivors of Childhood Acute Leukaemia

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Background: Long-term survivors of childhood acute leukaemia can suffer from growth impairment. The purpose of this study was to evaluate longitudinal growth and final height of paediatric patients who were treated with acute leukaemia and factors that can cause growth impairment. **Methods:** Of 234 patients (133 males and 101 females) who were diagnosed as acute lymphoblastic leukaemia (ALL; $n=162$) or acute myeloblastic leukaemia (AML; $n=72$) before age 18 between June 1996 and June 2009, 112 patients (65 males and 47 females). The mean age at enrolment was 19.2 ± 2.6 years. Among them, 59 patients treated with chemotherapy only and 53 patients received hematopoietic stem cell transplantation (HSCT). We reviewed height S.D. scores from diagnosis to final height and risk factors such as sex, age at diagnosis, diagnosis, pubertal status at diagnosis, radiation and chronic graft-versus-host-disease (cGVHD) that can affect growth were evaluated. **Results:** The mean height S.D.s at diagnosis of 112 patients was 0.19 ± 1.11 and the mean final height S.D.s was -0.89 ± 1.31. The mean height S.D.s from the diagnosis to their final height were significantly decreased (Δheight S.D.s $=-1.08\pm1.12$, $P<0.001$). The height loss was more severe in the patients who received HSCT than the patients who received chemotherapy only (-0.81 ± 0.87 vs -1.38 ± 1.29, $P=0.008$). In chemotherapy only patients ($n=59$), the changes in height S.D.s from the diagnosis to final height were positively correlated with age at diagnosis ($r=0.117$, $P<0.001$) and negatively correlated with pubertal state at diagnosis ($r=-0.474$, $P=0.039$) and cranial irradiation ($r=-0.716$, $P=0.022$). In multiple regression analysis, younger age at diagnosis was the only significant risk factor of loss in final height in chemotherapy group ($P=0.008$). In HSCT patients ($n=53$), the differences of height S.D.s between at diagnosis and final height were showed positive correlation with age at diagnosis ($r=0.177$, $P<0.001$) and negative correlation with pubertal status at diagnosis ($r=-1.197$, $P=0.001$) and total body irradiation (TBI) for conditioning ($r=-1.192$, $P<0.001$). In multiple regression analysis, younger age at diagnosis was significant risk factors cause loss of final height in HSCT patients

($P=0.002$). **Conclusions:** The loss of final height in survivors of childhood acute leukaemia was significantly related with younger age at diagnosis.

P3-1032

Impact of Recombinant Human GH on Height in Children with Chronic Kidney Disease

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Background: Chronic kidney disease (CDK) is one of the most common indications for treatment with recombinant human GH (rhGH). **Objective and hypotheses:** The aim of our study was to investigate the effect of rhGH therapy in pediatric patients with different stages of CKD. **Method:** 49 children (35 boys and 14 girls) aged from 0–18 years (mean age 9.01 ± 4.28) with proven CKD and height retardation were treated with rhGH by a single subcutaneous injection every evening at dose of 9.4 mg/m^2/weekly and followed up for a period of 14 years (mean 3.48 years). The height measurements before and after treatment were analysed as S.D. score. **Results:** According to the classification of CKD the patients were divided into two groups – 33 had CKD stage 2–4, and 16 had CKD stage 5. At disease onset 69.40% of the children had severe growth retardation defined by height S.D.S < -1.88; 26.50% had moderate height retardation defined by height S.D.S between -1.88 and 1.00 and 4.10% had mild height retardation defined by height S.D.S > 1.00. The mean height S.D.S during the treatment period increased from -2.75 at baseline to -1.64 at treatment termination. The height S.D.S increased by 7.57% as measured at 12 month ($P=0.021$) and by 4.71% at 48 month of treatment ($P=0.013$). The reached height correlated to the disease stage at the baseline and the duration of the rhGH treatment. **Conclusion:** The early and continuous treatment with rhGH in children with CKD stage 2–5 increase the height velocity in this subgroup of pediatric patients and should be taken into account in the treatment program of CKD.

P3-1033

Birth Length and Metabolic Syndrome in Obese Children

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Background: Low birth weight is associated with cardiometabolic risk in adulthood. To date, there is no evidence of a relationship between birth length and metabolic risk. **Objective and hypotheses:** To evaluate the relationship between birth size and risk of metabolic syndrome (MetS) in obese children. **Method:** 41 obese children were studied (23 females/18 males, 13.2 ± 1.26 years). All patients underwent anthropometric, biochemical, hormonal evaluation and careful familial history. Body composition assessment was available in 30 subjects. MetS was defined according to The International Diabetes Federation criteria. Subjects were subdivided into two groups matched for age (± 0.5 year), gender and BMI (± 0.5), according to the presence of MetS (11 females/ nine males, 13.2 ± 1.84 years) or not (12 femess/ nine males, 13.1 ± 1.68 years). **Results:** Patients with MetS were significantly shorter at birth than patients without MetS (-0.7 ± 1.3 vs 1.13 ± 2.39 S.D.s, $P=0.032$). Whereas no difference in birth weight, current height, body composition were found. Familial history for obesity, type 2 diabetes and cardiovascular disease was not significantly different in the two groups. Birth length was inversely related to waist circumference height ratio ($r=-0.49$, $P=0.02$) and BMI ($r=-0.46$, $P=0.03$). Birth weight was inversely related to triglycerides ($r=-0.44$, $P<0.01$) and triglyceride HDL cholesterol ratio ($r=-0.44$, $P=0.005$). **Conclusion:** Our results suggest for the first time that birth length may be related to the risk of MetS in obese children independently of birth weight.

P3-1034

Birth Characteristics Influence the Male to Female Diagnostic Prevalence of Idiopathic GH Deficiency

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Background: A greater number of male (M) vs female (F) patients are diagnosed with GH deficiency (GHD). M have larger birth weight (BW), length and head circumference (HC) compared to F; these characteristics could contribute to subtle cephalo-pelvic disproportion and mild head trauma possibly contributing to idiopathic GHD (IGHD) and multiple pituitary hormone deficiencies (MPHD). **Objective:** To determine birth characteristics including mode of delivery and MRI abnormalities that could influence the M to F preponderance in IGHD and in MPHD. **Method:** Patients with IGHD ($n=14853$) and MPHD ($n=5218$) with a stimulated peak GH <7 µg/l registered in Pfizer International Growth Database were studied. Wilcoxon rank sum test and ANOVA were used for analyses, with P-value <0.01 considered significant. **Results:** Data are shown as means; $^*= P<0.001$ in M vs F. **Conclusion:** Breech delivery was higher in MPHD compared to IGHD and higher in males with MPHD. More MRI abnormalities were reported in MPHD patients without gender difference. Further evaluation of the relationship between gender and diagnosis of pituitary hormone deficiencies is warranted. **Conflict of Interest:** C Camacho-Hubner and A

Table 1 (for abstract P3-1034).

Variable	IGHD (GH <7 μg/l)		MPHD	
	Male	Female	Male	Female
Max GH (μg/l)	4.3	4.3	4.3	4.5
Age (years)	10.3	9.5*	9.7	9.1*
Height (S.D.s)	−2.8	−3.2*	−3.3	−3.6*
GA (wks)	39.0	39.0	38.8	38.9
BW (S.D.s)	−0.7	−0.7	−0.6	−0.7
HC (S.D.s)	−0.2	−0.2	0.1	−0.1
Normal delivery (%)	77.8	78.7	68.5	74.8*
+MRI normal (%)	84.0	82.7	69.0	69.7
Breech (%)	3.5	2.9	15.3	6.7*

Lindberg are full time employees of Pfizer Inc. **Funding:** Pfizer International Growth Database is a static database sponsor by Pfizer Inc.

P3-1035

Two Cases with Decelerated Linear Growth, Normal GH – IGF1 Axis with an Exceptional Response to GH Therapy

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Introduction: Idiopathic short stature (ISS) describes short children with normal GH secretion. There is a lot of controversy about the outcome of treating ISS children with GH. Exceptional fast growth in response to GH therapy in these children enable scientist to delineate the different etiologies behind this broad term of ISS **Case report:** We are reporting two children aged 5 years and 9 years diagnosed with ISS. They presented with short stature with normal birth measurements and nutritional history. They did not have dysmorphic features, skeletal anomalies, goiter or dyspigmentation. The rest of the examination was unrevealing. They had normal CBC, liver and renal functions, sweat chloride, ESR and thyroid function. (Table 1) MRI showed normal pituitary gland. **Treatment and results:** A trial of GH therapy was started (0.035 mg/kg per day S.C. HS) with a follow-up every 6 months. Significant growth response to GH was noted exceeding the genetic background (mid-parental HT S.D.s) (table 1). **Conclusion:** Two short children presented with short stature, decelerated growth rate, normal GH response to provocation, one with low IGF1 and the other with normal IGF1 level. Both responded well to the GH therapy to surpass their mid-parental height S.D.s. Exceptional fast growth in response to GH therapy in these children should be reported to enable scientist to decide about the different outcome of treatment in these patients.

Table 1.

	Case 1	Case 2
Age	5	9
Bone age	4	8.5
GV S.D./year	−5	−1.1
IGF1 S.D.s	−1	−2
Peak GHST (ng/dl)	10	18.5
HT S.D. pre treatment	−1.84	−2.4
Estimated adult HT pre treatment	164 cm	144 cm
Duration of treatment with GH	7 years	3.5 years
HT S.D. post treatment	0.83	−1
Estimated adult HT post treatment	181 cm	156.5 cm
Mid parental HT S.D.s	−0.6	−2.37

P3-1036

Impact of GH Treatment in Children Final Height and Weight Status

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Background: GH revolutionised treatment of children with GH deficiency, conditioning an improvement in height outcome but also an increase of lean body mass and reduction of fat mass. **Objective and hypotheses:** The authors aimed to evaluate the growth and weight response in children with GH deficiency and identify potential factors affecting the outcome of these patients. **Method:** The growth and weight data of 58 children (33 boys and 25 girls) with GH deficiency, treated with 0.033 ± 0.004 mg/kg per day of GH, for 5.4 ± 3.1 years, were retrospectively analysed. 62.1% of the studied population had idiopathic GH deficiency (IGHD)

and 37.9% had organic GH deficiency (OGHD). Statistical analysis:SPSS (21). **Results:** At onset, chronological age was 11.6+2.3 years in children with IGHD and 10.6+4.2 years on those with OGHD. The S.D. score of growth velocity (GV) at 1st year was only negatively correlated to age at the onset of therapy ($r=-0.56$, $P=0.008$). 23 (39.7%) patients achieved the predicted *target height* based on mid-parental *height* (15 boys with 168±5 cm and eight girls with 155±2 cm). Final height S.D.s was positively correlated with initial height-S.D.s ($r=0.35$, $P=0.009$) and with target height-S.D.s ($r=0.44$, $P=0.001$). Final height-S.D.s was not significantly different between IGHD and OGHD (−1.6±0.8 vs −1.8±1.1, $P>0.05$). GH treatment was also associated with a slight increase of S.D.s-BMI, either in patients with OGHD (+0.21±0.96) or IGHD (+0.12±0.87). When S.D.s-BMI variation was analysed according to initial weight status, only underweight and normal weight children increased their BMI-S.D.s (0.70±1.5 and 0.15±0.87 respectively) whereas obese ones decreased their BMI-S.D.s (−0.07±0.55). **Conclusion:** More than one-third of the children with GH deficiency achieved a final height comparable to their genetic potential. The most significant determining factors were children's age (influencing GV during 1st year) and height at the onset of the treatment. Our study also confirmed that long term GH treatment contributes to normal weight status, particularly in children that are underweight or obese.

P3-1037

Expanding the Role of Nurses in Improving Patient Care and Clinical Outcomes in Growth Disorders

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Background: Despite having a significant impact on patient care and treatment success, nurses' roles and responsibilities in growth disorder (GD) treatment varies substantially between countries and should be optimised. **Objective and hypotheses:** To understand the critical role nurses play in patient clinical outcomes and how they can improve the patient management pathway. **Methods:** Nurses involved in the care of patients with GD from France, UK, Israel, USA and Japan convened at an advisory board in December 2014 to discuss their role at each stage of the patient management pathway and how unmet needs in GD could be addressed. **Results:** Nurses outlined three crucial stages of the patient management pathway where their role can help improve patient adherence and clinical outcomes. Stage 1: after confirmation of GD diagnosis by a physician, most nurses will discuss treatment options and implications with the patient and family, resulting in mutual treatment selection. Stage 2: educating the patient on selected treatment. Nurses will train the patient and family at home or in the clinic on the use of the device and initiate treatment. Stage 3: long-term follow-up is primarily by clinic visits, where nurses troubleshoot any problems raised by the patient or family regarding treatment, including growth expectations, side effects and adherence. A key unmet need in GD identified by the panel was for nurses to educate general practitioners, paediatricians, paediatric nurses, and school nurses in growth surveillance to improve awareness of GD, which could improve early referral of children to a paediatric endocrinologist. **Conclusion:** Nurses play an important role in the patient management journey. From their contribution to early diagnosis and referral through aiding in treatment selection, long-term management and adherence, nurses ensure success of the GD patient journey. Moreover, nurses can expand their role to educate healthcare practitioners and ultimately improve patient care. **Disclosures:** Authors did not receive payment for abstract development but attended a meeting sponsored by Novo Nordisk where discussions within this abstract took place: Galit Asher (Israel), Corinne Bertin (France), Nami Eguchi (Japan), Maryann Johnson (USA), Hiromi Komiyama (Japan), Peter Laing (UK), Sylvie Uhel-Dennie (France) and Amanda Whitehead (UK) also participated. **Conflict of interest:** Authors did not receive payment for abstract development but attended a meeting sponsored by Novo Nordisk where discussions within this abstract took place: Galit Asher (Israel), Corinne Bertin (France), Nami Eguchi (Japan), Maryann Johnson (USA). **Funding:** Abstract development was supported by Novo Nordisk, Zurich, Switzerland. Editorial assistance was provided by Dr Juliet Bell of apothecom scopemedical ltd, funded by Novo Nordisk.

P3-1038

Short Stature in a Rare 15q Duplication – is hGH Treatment Beneficial?

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Introduction: Distal chromosome 15 duplication is a very rare genetic disease, first described in 1974 by Fujimoto et al. The symptoms and physical findings include prenatal and/or postnatal growth retardation, mental retardation, poor speaking abilities, asymmetrical dysmorphic facial features, malformations of the fingers and/or toes and sometimes heart conditions. **Case report:** We report a case of a 2 years 5 months old girl, born with SGA (uterine growth delay with arterial pathology at 13 weeks of gestation, emergency caesarean section at 33w due to severe oligohydramnios–weight(W):1200 g, −2.8 S.D., height (H): 38 cm, −3.4 S.D., with developmental delay (didn't speak until 2 years of age, walked at 2 years and 1 month, limited understanding partially due to transmission deafness). She is the second child in a brotherhood of 2 (one brother, 4 years old, healthy), from apparently healthy nonconsanguineous parents (father H: 174 cm,

mother H: 160 cm) and with a parental aunt diagnosed with pituitary dwarfism (H: 109.5 cm −9.5 S.D., W: 23 kg −5.4 S.D., infanto senescent features, IGF1 < 25 ng/ml) and Turner syndrome (mosaicism) for which adult hGH replacement was proposed. Based on the child's development delay and clinical features (short stature, big forehead, small triangular facies, micrognathia, anterior fontanelle open, repetitive hypoglycaemic episodes) she was first diagnosed with Silver Russell syndrome, ruled out by molecular investigations and then on an extensive research she was later diagnosed with '*de novo*' interstitial chromosome 15 duplication q21.2 to q24.1 (not present in neither of her parents-FISH), which explains her phenotype. Evaluation at the Endocrinology Department of 'St. Spiridon' Hospital Iasi revealed H: 74 cm −5.38 S.D., W: 7000 g, delayed bone age ∼1 year 6 months, predicted size 160.5 cm. Given the SGA, bone age delay, genetic diagnosis and the small predicted height, treatment with hGH was assessed which ameliorated the growth rate (0.66 cm/month). **Conclusion:** We present an unique case of distal 15q duplication – mutations on this region are inducing extremely different phenotypes, depending on the precise location and the length of the mutation. In our case, treatment with hGH ameliorated growth velocity and prevented other hypoglycaemic episodes.

P3-1039

Sotos Syndrome: Why is Better an Early Diagnosis?

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Background: Sotos syndrome is characterized by overgrowth. The four mayor criteria for diagnosis are: overgrowth (accelerated bone age), macrocephaly, characteristic facial features and developmental delay. They can also present escoliosis, heart or genitourinary disease, seizures, hypotonia, cerebral malformations, feeding difficulties, hearing loss and a greater risk of tumours. **Case report:** A 10 months old girl was referred for overgrowth. BW and BL was over p99 since birth. Normal pregnancy with single umbilical artery. Caesarean section at term due to failure to progress. BW 4320 g ($P > 99$, 2.68 DE), transient respiratory distress and mild hipoglucemy in the first hours of life, required admission in neonatology unit. Normal metabolic screening. Breastfeeding 8 months. She was evaluated for congenital torticolis at 2 months of age, and at 7 months of age the neurosurgical team ordered a CT scan to study plagiocephaly and dolicocephaly, considered normal. Abdominal ultrasound (due to single umbilical artery) showed renal duplicity with ectasia and ovarian cysts (12–14 mm). 10 months old: BW 3.25 S.D., BL 3.65 S.D., HC 3.2 S.D.. Characteristic facial features, large hands and feet, large mandible, *hypertelorism* with *macrodolichocephaly* and a sacrococcygeal malformation. Normal Blood test and kariotype 46, XX. BA 18 m with CA 12 m, BA 5 years with CA 3.5 years old. 2 years old: Mild developmental delay, learning disabilities, problems with speech and language. Sacrococcigeal MRI no neurological malformations. Normal EEG. Brain MRI will have the results soon. Mutation in the *NSD1* gene in 5q35 (heterocigous change of C-T in the exón 4 p.Arg788Term). **Conclusion:** Mutations in the NSD1 gene are the primary cause of Sotos syndrome 90% of cases. An early diagnosis would help to avoid the use of x-ray (CT scan) or innecessary exams if it possible, and to focuses in associated complications. Early notification of special educational needs should be ensured.

P3-1040

Psychomotor Development in Children Born Small for Gestational Age During Early Infancy

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Background: Neurocognitive retardation is one of the most important consequences that small for gestational age (SGA) children may suffer although conflicting results have been published. **Objective and hypotheses:** The aim of this study was to study psychomotor development (PD) in children born SGA during the first two years of life in order to identify children at risk as early as possible. **Method:** 108 cases borh SGA have been studied between 3 months and 2 years of age. Girls: $n = 59$ (54.6%). 76 were born at term (six twins) and 32 were preterm (< 37 weeks). Catch up growth occurred in 65.3% of term and in 67.9% of preterm children. Mean gestational age was 37.5 weeks. Length was -2.7 ± 0.5 SDS, weight was -2.45 ± 0.8 SDS, and head circumference was -2.1 ± 1.1 SDS. SGA children suffering perinatal comorbidity with a known negative impact on PD were excluded in order to avoid confounding factors. PD was evaluated by the Brunet Lezine test in a cross-sectional and longitudinal study. Results were compared with normal controls and expressed in SDS. Patients and controls have been evaluated by the same psychologist. **Results:** Cross-sectional study. Mean developmental quotient (DQ) was -1.1 ± 1.2 SDS at a mean age of 10.4 ± 7.7 months of age ($n = 108$). DQ at different time points were as follows -1.4 ± 1.4 SDS at 3 months; -0.9 ± 1.1 SDS at 6 months; -1.1 ± 1.1 SDS at 9 months; -1.1 ± 1.1 SDS at 12 months; -1.0 ± 0.7 SDS at 18 months; and -1.0 ± 1.2 SDS at 24 months. When comparing with controls there were significant differences at 3, 6, 12, and 24 months of age. Mean DQ in SGA term children was -1.1 ± 1.2 SDS at a mean age of 9.8 ± 8 months and in preterm children was -1.3 ± 1.1 SDS at a mean age of 11.8 ± 7 months without showing significant difference between both groups. Longitudinal study. 30 SGA children had been followed longitudinally showing the following results: -1.3 ± 1.2 SDS at 4.2 ± 1.9 months; -0.7 ± 1.1 SDS at 7.3 ± 2.0 months; -0.9 ± 1.2 SDS at 10.6 ± 2.8 months; and -0.8 ± 1.2 SDS at 14.6 ± 4.1 months. **Conclusion:** A negative impact on psychomotor development in children born SGA has been observed early

after birth. During infancy psychomotor DQ is around – 1 SDS with 23% of children showing values ≤ 2 SDS at 10 months of age. Considering that confounding factors had been eliminated, SGA can be considered a condition that have an early negative impact on neurocognitive development and preventive measures should be taken.

P3-1041

Patient with Classic Phenotype of Hypochondroplasia and Deletion of the Gene *SHOX*

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Background: Hypochondroplasia is an osteochondrodysplasia inherited in an autosomal dominant pattern that results in a disproportionately short stature, characteristic facial features and skeletal alterations such as lordosis and *genu valgum*. Haploinsufficiency of the fibroblast growth factor receptor 3 gene (*FGFR3*) is responsible for 50–70% of the cases, but a negative result doesn't rule it out. **Case presentation:** We report an 11 years and 10 months old boy with family history of disproportionately short stature and personal background of small for gestational age (39 weeks, birth weight 2020 g (-3.2 S.D.), length 44.5 cm (-3.2 S.D.). He begins puberty at the age of 10. Physical examination: weight: 37.6 kg (-0.53 S.D.), height 133.5 cm (-2.1 S.D.), sitting height-to-standing height ratio (SH/S) 0.57 (>97), and Tanner IV (20–20 cc). Clinical features suggestive of hypochondroplasia with facial dysmorphia with frontal bossing, large hands with enlargement of interphalangeal joints, short and wide fingers, limited forearm supination and short limbs with rhizomelia, and significant muscle hypertrophy. Complementary examination: skeletal survey: rhizomelia, Madelung's deformity, and widened lumbar interpeduncular distance. Bone age: 14 years. Molecular genetic analysis of FGFR3: negative. HCG-ARRAY: 0.045 Mb deletion of the regulation region of the gene *SHOX*, found as well in the mother and the siblings. **Conclusion:** In patients with clinical features suggestive of hypochondroplasia and negative result in molecular genetic analysis of FGFR3, defects in the gene *SHOX* should be ruled out.

P3-1042

GH Treatment in Survivors of Paediatric Brain Tumors

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Background: Survival from brain tumors is increasing in children and these patients will likely have severely GH deficiency. **Objective and hypotheses:** To evaluate the effect of GH treatment (GHT) in children treated for brain tumor successfully. **Method:** Thirteen patients who received GHT after brain tumor treatment were evaluated retrospectively. Height SDS, annual growth rate SDS, height gain, and serum IGF1 levels were collected at baseline and at the time of evaluation. **Results:** Mean age of patients was 15.4 ± 4 (five females and eight males). Eight (61.5%) of the patients had medulloblastoma, 4 (30%) craniofarengeoma, and 1 (7.7%) pinealoma. Patients with medulloblastoma and pinealoma underwent chemotherapy and craniospinal radiotherapy post-operatively. One case with craniofarengeoma underwent cranial radiotherapy because of recurrence. At the time of diagnosis, 77% were pre-pubertal, 27% were pubertal and height SDS was -1.5 ± 1.7. Mean time to initiation of GHT and duration of GHT was 38.6 ± 15.5 and 33.5 ± 17 months respectively. Height SDS, growth velocity SDS and IGF1 SDS was -2.3 ± 1.6, -3.2 ± 2.4, and 1.8 ± 0.6 at baseline respectively. During GHT height SDS for the first, second and third year was -1.1 ± 1.2, -0.6 ± 1.3, and -0.9 ± 1.2. IGF SDS was between -0.2 and $+0.4$ SDS during treatment. Delta height SDS was $+1.1$ SD. Four patients reached final height during the time of evaluation and are receiving GHT in adult dose. Their final height were -1.2 ± 1.5 SDS. GHT was discontinued in 6 patients (recurrence: 2, final height access: 2, poor treatment adherence: 1, and non-responsive: 1). Recurrence was observed in two patients with pinealoma and medulloblastoma. **Conclusion:** Children with brain tumor after remission should be monitored for GH and other pituitary hormone deficiencies to increase final height.

P3-1043

GH Deficiency in a Patient with 4p16 Deletion: An Infrequent Association with Wolf–Hirschhorn Syndrome

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Background: Wolf–Hirschhorn syndrome (WHS) is caused by variably-sized deletion of chromosome 4 involving 4p16 whose typical craniofacial features are 'Greek warrior helmet appearance' of the nose, microcephaly and prominent grabella. Almost all patients show mental retardation and growth delay. **Case presentation:** We report on a patient carrying a 4p16 deletion and GH deficiency treated with recombinant human GH (rhGH). The patient is male, born at tem (birth weight 2810 g and length 50 cm) with normal perinatal events. His mother has type 1

diabetes mellitus on intensive insulin therapy. Developmental delay was evident since the first months of life. At the age of 5 years he referred to us due to short stature 87 cm (−4.99 SDS), delayed bone age 3 10/12 years and impaired growth velocity 3 cm/year. On physical examination he had generalized hypotony, dysmorphic features (microcephaly, hyperthelorism, prominent nasal bridge and glabella, epicanthus, micrognathia, and cleft palate) psychomotor development (IQ <30), and systolic murmur 3/6. Owing to growth retardation GH reserve was investigated by both L-DOPA and glucagon GH provocative tests (GH peak 6.29 and 8.06 ng/ml respectively). Both tests showed GH deficiency. He was on treatment with levothyroxine for 2 years. Thyroid ultrasound showed small shaped thyroid gland while heart and abdominal ultrasonographic evaluations were normal. Brain MRI showed small anterior pituitary gland. Conventional chromosome analysis of peripheral blood lymphocytes showed a karyotype 46,XY. Array CGH was performed showing deletion of chromosome 4 involving 4p16.3–p16.2, sized 4.7 Mb associated with WHS. RhGH treatment in a dose of 0.025 mg/kg per day was initiated. At the end of the first year of treatment, the patient's growth velocity reached 7.8 cm/year. **Conclusion:** We describe the second case of a boy with WHS and GH deficiency. Although WHS associated with GH deficiency is extremely rare it should be included in the workout as GH replacement therapy may promote patients' growth.

P3-1044

Value of Alkaline Phosphatase Assay in Short Stature Exploration

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Background: Short stature is a common reason for pediatric endocrinologist consultation, but in many cases, no cause can be identified. Childhood hypophosphatasia has widely variable clinical features from short stature to low bone mineral density with skeletal deformities, and the place of serum alkaline phosphatase (ALP) activity assay could be raised as etiological exploration is not consensual **Objective and hypotheses:** The aim of our study was to evaluate the ALP levels in a cohort of short stature children. **Method:** Children referred in our teaching hospital of Rouen for evaluation of short stature (height < −2 S.D., or decreased growth velocity >1 S.D.) from the 1st January 2010 to 31th December 2014 were included in the present retrospective study. Children were eligible when a GH stimulation test and an ALP assay were performed. Anamnestic, auxological, biological, and radiological data were collected. **Results:** 167 children (101 boys and 66 girls) were included at a mean age referral of 8.6 years old (0.5–18) with a mean height at −2.4 S.D. (−5 to 0.5). Whereas the majority of patients revealed normal ALP level, 12 showed low ALP levels (i.e. <120 U/ml) (67–119), among whom four had a somatotropin deficiency. None of them demonstrated radiological abnormalities or skeletal deformations. Seven among the 12 patients had a second ALP assay revealing for five of them normal ALP level, mostly concomitant with an acceleration of growth velocity. No controls were available up to now for the others children. **Conclusion:** Abnormal ALP activity was observed in 7.1% studied patients suggesting that hypophosphatasia could be a rare cause of short stature and that ALP assay need to be performed until further studies in larger population confirm this hypothesis.

P3-1045

Small for Gestational Age Incidence in One of the Regions of the Russian Federation

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Background: Intrauterine growth retardation (small for gestational age (SGA)) is connected with perinatal morbidity, neurological pathology and stature. **Objective and hypotheses:** The aim of our study is to estimate the incidence of SGA and its consequences in newborns and infants at the age 1. **Method:** The incidence of SGA among newborns in the Udmurt Republic (the region of the European part of the Russian Federation) has been studied. SGA has been diagnosed according to National standards: birth weight and/or length below the 10th percentile for gestational age. **Results:** 208 155 infants were born in the republic during the period of 2005–2014. High incidence of SGA (151.9±0.8/1000 newborns) has been observed, including in full-term newborns 153.7±0.7 and premature 122.6±3.0 ($P<0.001$). There is a trend towards a reduction in the incidence of SGA in recent years: within the period of 2005–2010 – 160.9±1.1; within the period of 2011–2014 – 140.2±1.2 ($P<0.001$). Clinical examination of 500 newborns has shown that SGA is connected with perinatal pathology of the nervous system (84.8±1.6%), perinatal infections (50.6±2.2%), and metabolic disorders (26.0±1.9%). SGA consequences in infants at the age of 1 are the low rates of physical development (22.8±1.9%). **Conclusion:** Our study indicates the high incidence of SGA that involves other medical problems.

P3-1046

Final Height in Patients with and without Pituitary Abnormalities Detected by MRI and/or CT Treated with GH

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Background: GH deficiency (GHD) occurs due to different aetiologies, morphological abnormalities in pituitary, or mutations leading the individual to lose the genetic growth potential. The pituitary dysfunction can be as GHD alone or associated with other hormones deficiencies. Patients with abnormalities in pituitary may present a greater height loss than others and couldn't reach the target height (TH) according to final height (FH). **Objectives:** To evaluate the FH of patients with pituitary dwarfism treated with GH. Correlate to the initial height, with FH and the TH of the patients. To compare the gain of height until FH in patients with and without pituitary abnormalities changes detected by MRI and/or CT treated with GH. **Materials and methods:** A quantitative longitudinal study was conducted through analysis of medical records of patients treated with GH, in the period 1993–2014 at a single service. Inclusion criteria for the study were patients who have reached FH. Initial H-SDS, FH-SDS, TH-SDS, and ΔH-SDS, were obtained and made comparison between patients who did and who did not pituitary abnormalities detected by MRI/CT. Comparisons between means and medians of the initial H-SDS, FH-SDS, and TH-SDS were made. **Results:** 34 patients was evaluated, 18 males. 25 without pituitary abnormalities. Highest prevalence of pituitary hypoplasia. There was a significant difference between initial H-SDS in patients with pituitary abnormalities compared in patients without pituitary abnormalities, but no difference were found in FH-SDS in these groups. Although ΔH-SDS in patients with pituitary abnormalities was biggest than the other group, no significant difference was found. All patients reached TH-SDS. **Conclusion:** H-SDS in patients with pituitary abnormalities were worse than without pituitary abnormalities at diagnoses. In both groups of patients, FH reached according TH.

P3-1047

Congenital Heart Disease and its Effects on Growth in Children

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Background: Children with congenital heart disease (CHD) are predisposed to growth failure, due to the decreased intake of nutrients and also due to the increased energy requirements. Growth failure represents a frequent cause of increase of both morbidity and mortality in children with CHD. **Objective and hypotheses:** Assessment of physical development in children with CHD and identification of significant factors that influence z scores. **Method:** We monitored the severity of the growth and development disorders in children with various types of CHD. We followed up the prevalence of growth failure in 117 children with CHD, aged 1 month and 10 years. In all cases we evaluated the demographic factors, clinical factors, socio-economic level, and the nutrition history. We performed anthropometry and then, calculated the z score for weight, height, and weight/height, using WHO-2007 reference values. **Results:** From a total of 117 children with congenital heart disease (72 boys and 45 girls), 39 children (33.3%) presented a normal z score, 78 children (66.6%) presented malnutrition: 20 children (25.6%) mild malnutrition ($-2 < z$ score < -1), 24 children (30.8%) moderate malnutrition ($-3 < z$ score < -2), and 34 children (43.6%) severe malnutrition (z score < -3). Weight-for-age z-score was ≤ -2 for 75 children (44.38%), weight-for-height was ≤ -2 for 48 children (28.4%), and height-for-age was ≤ -2 for 72 children (42.6%). Comparing z scores we have identified a significant difference ($P < 0.01$) between averages of height-for-age z-scores and statistically highly significant ($P < 0.001$) for weight-for-age z-scores between children born prematurely and eutrophic children. The presence of heart failure (HF) influenced negatively the physical development in children with CHD, $P = 0.0001$ in weight-for-age z-score and $P = 0.015$ in height-for-age z-score. Inappropriate food selection has been negatively correlated with physical development ($P < 0.05$, 95% CI). **Conclusion:** Children with CHD often present growth failure, therefore, is very important to monitor the nutritional status in these children, in order to prevent occurring and enhanced of deficits.

P3-1048

A Rare Cause of Short Stature: the Floating Harbor Syndrome

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Background: Short stature has several causes ranging from complex hormonal deficiencies mostly related to pituitary gland genetics, to idiopathic and environmental causes such as maternal smoking in pregnancy, etc. Floating harbor syndrome is a rare genetic disorder characterized by short stature, delayed bone age, mild to moderate mental retardation, retarded speech development, and typical facial dysmorphic features. The syndrome is caused by heterozygous mutations in exon 34 of the Snf2-related CREBBP activator protein (SRCAP) gene encoding the core catalytic component of the multiprotein chromatin-remodeling SRCAP complex. The encoded ATPase is necessary for the incorporation of the histone variant H2A.Z into nucleosomes.

It plays a key role in regulating cell growth and division, and is important for normal development. **Objective and hypotheses:** Identify the cause of short stature in a child with dysmorphic features and delayed speech development. **Method:** We report the case of 53-month-old boy with severe short stature (−3.5 SDS), associated with micropenis, speech delay, hearing impairment, and dysmorphic features compatible with floating harbor syndrome. He was term born with normal BW (3.220 kg), short BL (46 cm), and normal HC (36 cm). Family history was remarkable with two elder sisters aged 17 and 15 years who are short stature (145 cm). Endocrine screening revealed (peak GH: 12.60 mUI/l; IGF1: 86 ng/ml; and IGFBP3: 2640 ng/ml; normal urea and electrolytes, normal thyroid and liver function tests, LH: 0.3 UI/l; FSH: 0.5 UI/l; PRL: 10 ng/ml; cortisol: 298 nmo/l; fasting blood sugar: 4.47 mmol/l; and negative celiac screening, BA: 3 years and normal head MRI. **Results:** The SRCAP gene analysis by direct sequencing method was performed in all family members, but it revealed a previously described heterozygous mutations c.7303C>T (p.arg2435*) mutation in the *SRCAP* gene (*de novo*) only this patient. *SHOX* gene study was unremarkable. The child has been started on GH. **Conclusion:** Floating harbor syndrome is rare, characteristic features are particular and should lead to its diagnosis. GH therapy has proved beneficial in treated patients, regular screening for celiac disease is mandatory.

P3-1049

Correlations Between IGF1 Levels and Anthropometrical Parameters in Children Under GH Therapy

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Background: GH therapy is used to treat a series of growth disorders in childhood. No recent studies are available in our country regarding the influence of GH after more than 1 year of treatment in children with growth failure. **Objective and hypotheses:** The aim of our study is to evaluate the effects of GH treatment and to find out if there is any relationship between IGF1 increment and growth velocity (GV), weight, and BMI in children with growth failure caused by GH deficiency, Turner syndrome and those born small for gestational age. **Method:** Type of study: retrospective; target population: children 3–16 of age with short stature; sample: composed of 45 children (group 1) with short stature diagnosed in Mures County Hospital and treated 1 year with GH; 29 children (group 2) continued the treatment until 2 years. Variables: age, sex, height SDS (H-SDS), GV, weight, BMI, and IGF1 before, after 1 year, and after 2 years of treatment. Statistical analysis used Microsoft Office Excel. **Results:** In our study GH treatment increased the H-SDS (first group: from −3.18 to −2.64 S.D. and second group: from −3.13 to −2.15 S.D.) and IGF1 levels (first group from −1.69 to +0.14 S.D. and second group from −1.75 to +0.26 S.D.). GV in 1 year GGH therapy had a mean velocity of 8.41 cm/year while in the second year of treatment GV decreased to 7.02 cm/year. We also had a semnificative correlation between IGF1 increment and height and weight increade ($r=0.69$, $P<0.001$) but without a semnificative correlation between IGF1 and GV ($r=0.26$, $P=0.08$). **Conclusion:** Daily GH treatment in short children demonstrated increased GV and increased IGF1 levels with significant result on anthropometric parameters in the first year of treatment.

P3-1050

BMI and Total Cholesterol are Negative Predictors of Peak Stimulated GH in Han Children with Short Stature

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Background: BMI has a negative impact on spontaneous and stimulated GH secretion in children, but the impact of BMI and free fatty acids (FFA) on peak stimulated GH values in Han children with short stature is unknown. **Objective and hypotheses:** To assess the effects of BMI and FFA on peak GH values in Han children with short stature. **Method:** This was a retrospective, cross-sectional study. We used arginine–clonidine test to analyse the GH–IGF1 axis in 657 Han children aged 2–16 years with short stature. **Results:** BMI–SDS and total cholesterol (TC) were the only significant and negative predictors of peak GH (stepwise multiple regression; $P=0.000$; $P=0.004$). Increased BMI–SDS was associated with increased incidences of GHD and CGHD (χ^2; $P=0.000$; $P=0.000$), the incidence of CGHD increased sharply with a BMI–SDS >2. Significant differences in BMI–SDS; TC and triglyceride (TG) levels were found among the peak GH categories (ANOVA; $P=0.000$, $P=0.007$, and $P=0.001$). **Conclusion:** Our data confirm that BMI and TC have a negative impact on the peak GH response to arginine–clonidine testing, the effects are particularly strong in obese children.

P3-1051

A 4-Month-Old Boy with Beckwith Wiedemann Syndrome

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Background: Beckwith Wiedemann syndrome (BWS) is an overgrowth disorder with vari-able phenotype (hemihypertrophy, macroglossia, visceromegaly, malformations, and hypo-glycaemia

in 30–50%) and predisposition for tumors, during the second part of pregnancy and first few years of life. **Objective and hypotheses:** Molecular characterisation of a patient with BWS was perfor-med to ensure adequate clinical management. This analysis revealed the most common form of BWS due to loss of methylation in KvDMR1 in presence of a normal *H19*-DMR methylation. **Method:** We present a 4-month-old boy with overgrowth and longitudinal hemihypertrophy of tongue and left cheek delivered with Elective Section Cesarean (ELSC) due to fetal macrosomia. His birth weight was 4600 g (+3.0 SDS), 98.6th percentile and birth length 53 cm (+1.25 SDS), 90th percentile. The boy had 9.9 kg (+3.5 SDS) and height 68 cm (+2.3 SDS) at 4 months, both at 99th percentile. There was a difference of 1 cm circumference between his left and right leg, but not in their length or in arms. Diagnostic assessment was achieved according to clinical features, ultrasound survey, biochemical, and molecular analysis. **Results:** Performed tongue, cardiac, abdominal, and renal ultrasound scans (USS) showed: longitudinal left hemi-hypertrophy of tongue tissue, round heart shape with mild aortal valve stenosis, mild hypertrophy of liver and moderate hyper-trophy of kidnies, especially left one. A brain ultrasound was uneventful, but on MRI were prominent both frontoparietal subarachnoideals more than 5 mm. Karyotype was normal male, 46,XY. No evidence of clinical or biochemical parameters for hypoglycemia. Molecular analysis revealed hypomethylation of KvDRM1 (LIT1) in chromosome 11p15 region and normal methylation pattern for *H19* with estimated tumor risk of 1–5%. **Conclusion:** We present a patient with BWS phenotype associated with molecular confirmation of loss of function in specific gene in the imprinting cluster and low risk of embryonal tumors. The overall estimation will predict his clinical management.

P3-1052

MEGHA: Observational Study on Prescription of the GH Saizen in Adults in France

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Background: Final results from MEGHA study required by Health French Authorities (HAS). **Objective and hypotheses:** Objectives are to carry out longitudinal follow-up during maximum 5 years of AGHD patients treated with Saizen, with a description of prescription modalities, demographic and clinical characteristics, patient compliance, product safety, and quality of life. **Method:** MEGHA is a multicentric study, with prospective follow-up of patients every 6 months during the first year then every 12 months in the subsequent years. **Results:** 90 GH-deficient patients (45 women; 49 childhood acquired deficiency (CO-group), 41 adulthood (AO-group), 31, 8±13 years; 26.4 kg/m^2) were enrolled between December 2003 and October 2007. 94% of patients had at least one GH stimulation test. IGF1 was <-2 SDS in 62.5 and 41.7% of CO-group and AO-group patients. 95.6% of patients had at least one associated hypopituitary deficiency. Initial GH dose was between 0.15 and 0.3 mg/day for 51.4% of patients and <0.15 mg/day in 27.1% (median 0.24 mg/day). In 1 year after inclusion, IGF1 remains <-2 SDS for 48% of CO-group patients and 5% of AO-group. BMI, WHR, BP levels, lipids, and glycaemia were not significantly changed. The total mean treatment exposure was 39.8±22.7 months. 50% of patients discontinued their treatment at a median of 13 months after inclusion. An improved quality of life (PGWB questionnaire) was observed for the first 6 months with a subsequent stabilization particularly for AO-group. 13 patients had treatment-related adverse events (no serious AE) leading to treatment discontinu-ation in three patients. **Conclusion:** In the great majority, prescription recommendations for Saizen in adults are observed and the treatment is well tolerated. Beside GH dose adaptation to improve IGF1 treatment response, adherence is probably key. **Funding:** This work was sponsored by Merck Serono.

P3-1053

Comparative Study of Low-Dose GH Treatment in Children with Idiopathic Short Stature and GH Deficiency

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Background: Idiopathic short stature (ISS) is defined as short stature of unknown origin. It is apparently not associated with GH deficiency (GHD). High-dose GH treatment is considered to be more beneficial in children with ISS than in those with GHD. However, responses to GH in children with ISS are highly variable and dose-dependent, and the optimal treatment is controversial. **Aims:** To compare the effects of low-dose GH treatment in children with GHD vs ISS. **Methods:** This retrospective study was conducted at Ajou University Hospital, Korea. Patients diagnosed with GHD ($n=66$) or ISS ($n=35$) and subsequently treated with low-dose GH over a 2-year period (0.22 mg/kg per week, six times per week) were evaluated. We reviewed their auxological data, laboratory findings, and responses to GH and analysed the clinical factors associated with 1st year changes in the height SDS and growth velocity. **Results:** No differences were observed in the pretreatment height SDS, IGFBP3 SDS, mid-parental height, BMI, or bone age delay between the GHD and ISS groups. However, the ISS group had a higher IGF1 SDS and stimulated peak GH levels

than did the GHD group. Low-dose GH did not affect the growth velocity in the ISS group, although a significantly greater 1st-year Δ height SDS was observed in the ISS group than in the GHD group (0.82 ± 0.32 and 0.67 ± 0.31, respectively; $P < 0.05$). Age was negatively associated with first-year growth velocity and Δ height SDS in both groups. **Conclusions:** Low-dose GH was similarly effective between children with ISS and GHD. Early intervention with GH is the most appropriate therapeutic option to obtain optimal responses in both ISS and GHD.

P3-1054

To Investigate the Changes of Hormone Levels and Body Composition in Pubertal Children with Growth Retardation: a Clinical Controlled Study

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Background: Adolescent growth spurt is the fast and intense increase in the rate of growth in height and weight that occurs during the adolescent stage of the human life cycle. **Objective and hypotheses:** To investigate the changes of hormone levels and body composition in pubertal children with growth retardation. **Method:** A non-randomised clinical controlled study was conducted in 208 cases (males 122, 10–14 years and females 86, 8–13 years) with growth retardation who were divided into two groups. Pubertal group (Tanner stages II–IV) included 104 cases, while prepubertal group (Tanner stage I) included 104 cases with matched age and sex frequencies. All patients received the clinical evaluation of height, weight, and pubertal stage by pediatric endocrinologists. All of those patients underwent GH stimulation testing after overnight fast, with a combination of arginine and clonidine. And blood biochemistry, thyroid function, insulin, C-peptide, IGF1, and bone age were measured. The statistical analysis was performed using SPSS 19.0. Comparisons between two groups were performed using *t*-test. A P value < 0.05 was considered statistically significant. **Results:** Compare with the prepubertal group, the mean peak GH of pubertal group was increased slightly but insignificantly ($P = 0.821$), the level of IGF1 was increased significantly (1.48 times, $P = 0.000$), and height SDS of puberty group increased by 0.39 SDS ($P = 0.001$), while bone age increased by 1.3 years ($P = 0.000$). Levels of insulin, C-peptide, and blood glucose of pubertal group were in normal range and increased significantly ($P = 0.003$, $P = 0.003$, and $P = 0.014$). All of pubertal group had normal thyroid function, TSH level was increased slightly but insignificantly ($P = 0.625$), FT_4 level was decreased slightly but insignificantly ($P = 0.082$), while FT_3 level increased significantly ($P = 0.002$). Blood lipid level remained constant, but the BMI was increased ($P = 0.044$) in pubertal subjects. Furthermore, we divided our cases by sex, BMI of pubertal females increased significantly ($P = 0.007$), and BMI of males increased slightly and insignificantly ($P = 0.406$). TSH of puberty males decreased slightly and insignificantly ($P = 0.559$), and TSH of puberty females remained constant ($P = 0.973$). **Conclusion:** The reaction of GH–IGF1 axis in children with growth retardation was poor during puberty. The height increased in pubertal group slightly, while bone age increased significantly, and growth time reduced, for pubertal children with growth retardation, treatments are urgent.

P3-1055

The Effect of BMI in Reducing Risk of Refractory Seizure due to Probable Lipoid Tissue Factors

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Background: Refractory epilepsy (RE) is a neurological disease, which affect relatively 20–30% of epileptic patients. Although, previous studies noted obesity as the leading factor for maladaptive processes for exacerbating chronic diseases such as epilepsy, multiple sclerosis and Alzheimer's disease. On the other hand, enough endocrine products such as leptin by adipose tissue is effective in epilepsy. We aim to assess the effect of BMI in reducing risk of refractory seizure due to lipoid tissue factors. **Materials and methods:** This is a matched population-based cross-sectional case–control study which consisted of cases (patients with refractory epilepsy) and control (healthy children). Data were gathered by a form including demographic characteristics, types of epilepsies, predominant time of epilepsies, therapeutic approach, frequency of epilepsies, time of disease onset, and anthropometric indices. The same group of researchers measured anthropometric indices and transformed them into *Z*-scores. Data were reported by statistical tests in SPSS 19. **Results:** There was no significant difference between sex groups regarding anthropometric indices ($P > 0.05$) generalized and focal types of epilepsies were noted by 57.5 and 38.75% of patients respectively. Daytime epilepsies happened in 46.25% of patients and 33.75% noted no predominant time for epilepsies. Clinicians indicated poly-therapy for the majority of patients (92.5%) and 36–72 months were the most common onset times for epilepsies.(32.5%). Results showed that lower onset time indicated lower frequency of refractory epilepsies. Although, there was significant difference between *Z*-height and predominant time of epilepsies but, results showed no significant relation between types of epilepsies and frequency of epilepsies with anthropometric indices ($P > 0.05$). In multivariate regression analysis by backward LR, results noted *Z*-weight and birth weight as the predicting factors of refractory epilepsies. **Conclusion:** According to results, it seems that this effect may be because of leptin. Therefore, researchers recommend further investigations regarding this issue in children with epilepsy.

P3-1056

GH Treatment for Idiopathic Short Stature

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Background: The purpose of this study was to analyse characteristics and evaluate the effectiveness and safety of treatment with recombinant GH (rGH) in children with idiopathic short stature (ISS). **Method:** Patients ($n=54$) were evaluated prospectively. Treatment was received by 27 patients with ISS during 1 year. The administration was done by the accepted methodology. The effectiveness of treatment was evaluated based on change in growing speed, growth SDS and bone age maturation. **Results:** The mean age of children was 8.0 ± 2.7 ($3.0 \div 12.0$) years. Their height SDS were -2.9 ± 0.55 ($-4.8 \div -2.2$) and bone age delayed on 1.6 ± 1.2 ($0 \div 3.6$) years. Height velocity SDS were -1.54 ± 1.39 ($-4.92 \div 1.15$). SDS of IGF1 was -0.39 ± 0.3 ($-2.3 \div 1.5$). In this group were found that 22.2% patients had low level of IGF1. We also found that 16.7% of these patients had low level of IGFBP3. Analysed MRI investigation of brain we identified that 81.8% of this patients had normal brain MRI, hyphopisis hypoplasia had 13.7% of patients, in 4.5% cases we found the empty sella turcica. We also analysed the effectiveness and safety of treatment with rGH. There was an improvement in absolute growth at 6 as well as 12 months period of treatment ($P=0.02$; $P=0.03$).The same was found for growth SDS ($P=0.02$; $P=0.03$). Effectiveness of rGH therapy on bone age maturation also showed improvement among children ($P=0.01$; $P=0.02$). Concurrently, we have analysed the effectiveness of treatment on the following indicators: the level of IGF1 was increased ($P=0.03$; $P=0.03$). The same improvement was in IGFBP3 levels ($P=0.03$; $P=0.03$). **Conclusion:** It can be concluded that the treatment with rGH to patients with ISS is beneficial as it improves height. During the treatment there were no any changes in indicators of kidney's function, indicators of liver's function as well as the indicators of carbohydrate metabolism.

P3-1057

The Frequency Study and the Aetiological Profile of Short Stature in 2–15 Years Old Children Admitted in Endocrinology Clinic of 17 Shahrivar Hospital, Rasht, Between 2008 and 2013

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Background: Short stature is a common problem in children. This study aimed to determine the cause of short stature in children in Rasht is 2–15 years. **Methods:** This study was done on 148 children aged 2–15 years with short stature in 2008–2011 shorter 17 Shahrivar patients have been conducted. Demographic characteristics of children, child, and family history of the disease, blood tests, hormone stimulation test growth, physical examination, radiographs of the wrist were recorded for each child. Data were analysed using the software SPSS 19. **Results:** The study population included 64 females and 84 males, mean age of males and females, respectively, $8.07+4.12$ and $9.48+3.77$ years. 148 children, bone age, bone age vs chronological age in 26 cases and 122 cases of bone age less than chronological age. Short stature in children 53.4%, respectively, after which growth hormone deficiency vitamin D3 13.5%, temperament 7.4%, hypothyroidism, 7.4%, short of genetics 6.8%, and due to Turner syndrome 4.1%, which was statistically significant difference between the two sexes was found to cause short stature. People with hypothyroidism and GH deficiency, significantly lower mean bone age compared with those with constitutional short stature or genetics or a lack of vitamin D3. **Conclusion:** Based on the findings of this study have, the most common cause stunting of GH deficiency has been studied.

P3-1058

Cystic Encephalomalacia and Infantile Spasm as a Complication of Transient and Mild Hyperinsulinemic Hypoglycemia

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Background: Although it is known that hypoglycaemia could cause severe negative effects on brain development and also infantile spasm, it has not been reported that transient hyperinsulinaemic hypoglycaemia, which spontaneously improves over a short time, may cause infantile spasms. Infantile spasm is a disorder of early childhood typically seen in first year of life characterized by the occurrence of sudden, brief, generally bilateral and symetric motor spasms of muscles of the trunck, neck, and limbs. Infantile spasms are classified as idiopathic or symptomatic. The most common form – symptomatic infantile spasms – is due to prenatal, perinatal or postnatal insults. **Case presentation:** A 3140 g, full-term baby was admitted with poor sucking and feeding difficulty on the postnatal 2nd day. The patient was followed-up with the diagnosis of hyperinsulinaemic hypoglycaemia and intravenous glucose infusion (15 mg/kg per min) was administered, but due to the persistence of hypoglycaemia, diazoxide treatment was initiated. Hypoglycaemia was not observed under diazoxide treatment and the drug was gradually decreased; treatment was terminated on the 21st day. The patient was continuously normoglycaemic during follow-up and admitted with flexor spasms on the 45th day. A modified hypsarrhythmia pattern was detected in the electroencephalography. On cranial magnetic resonance imaging, diffuse cystic encephalomalacia areas

were observed in the temporoparietal white and gray matter. The convulsions were not completely controlled with ACTH and vigabatrin treatments, and topiramate and valproate were administered, by which convulsions were partially controlled. **Conclusion:** The present case report emphasized that even HH is short-term and transient; i) it could cause cerebral damage, ii) it could present as infantile spasms in the late period, and therefore, iii) long-term follow-up is important for these patients.

P3-1059

Hyperglycemia Preceded by Neonatal Hyperinsulinemic Hypoglycemia in Infants with Novel *HNF1A* Mutations

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Background: Neonatal hyperinsulinaemic hypoglycaemia (HH) has recently been recognized as a consequence of mutations in *HNF1A*, which also cause maturity-onset diabetes of the young (MODY) later in life. **Aims:** To report phenotypic and genetic investigations of two patients with functional characterisation of identified mutations in *HNF1A*. **Case reports:** Two unrelated patients presented with HH requiring i.v. glucose administration during the neonatal period. Patient 1 repeatedly developed hyperglycemia with ketonuria during acute respiratory infections in infancy. Fasting glycaemia of 7 mmol/l was observed in patient 2 at the age of 18 months. Positive family history of diabetes was reported in both families. **Methods:** DNA was analysed by directed sequencing. Thereafter, the pathogenic effect of the novel *HNF1A* mutations on normal HNF1A function was assessed by transcriptional activation assay in transfected HeLa cells, and DNA binding studies using *in vitro* expressed (TnT) proteins and analysed by electrophoretic mobility shift analysis. **Results:** Two novel mutations in the *HNF1A* gene were detected: patient 1 carried p.Leu254Gln and patient 2 p.Asn62fs. Both mutations segregated with β-cell defect within the families. Functional investigation of the p.Leu254Gln and p.Asn62fs mutation demonstrated severely reduced transcriptional activity (~20 and ~0% activity) compared to WT HNF1A (100% activity) respectively. Both of the *in vitro* expressed mutant proteins failed to bind to an HNF1A site in the rat albumin promoter. **Conclusion:** Complex characterisation of two patients suggests that the capacity of β-cells to respond to high demands on insulin secretion may be impaired due to mutations in *HNF1A* at an early age. Our clinical and functional analyses confirm the role of HNF1A in pathogenesis of HH and emphasize the importance of molecular genetic testing of the *HNF1A* gene in patients presented with hyperinsulinaemic hypoglycaemia. **Funding:** Internal Grant Agency of Czech Ministry of Health (NT11402).

P3-1060

Transient Congenital Hyperinsulinism and Renal Fanconi Syndrome

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Background: Congenital hyperinsulinism is the most common cause of persistent hypoglycaemia in early infancy. Mutations in the *HNF4A* gene lead to transient hyperinsulinism in early infancy and maturity-onset diabetes of youth (MODY1), later in life. Fanconi syndrome is a generalised dysfunction of the renal proximal tubule with a loss of glucose, amino acids, phosphate, low molecular weight proteins, bicarbonate and urate, causing growth failure and rickets in childhood. **Case reports:** Patient 1: full-term female infant with normal birth weight presented with recurrent neonatal hypoglycaemia and hypoglycaemic convulsions because of hyperinsulinism. Therapy with diazoxid was necessary for the first 6 months of life. At 3 years of age, an atypical renal Fanconi syndrome with bilateral nephrocalcinosis was diagnosed. The child had radiological and clinical signs of phosphopenic rickets. Therapy with calcitriol and cholecaliferol as well as supplementation with oral sodium phosphate led to regression of the rachitic malformation. Mutational analysis revealed a heterozygous HNF4A R76W (c.187C>Tp.R63W) mutation. Patient 2: pre-term, large-for-gestational age male infant presented with severe recurrent neonatal hypoglycaemia because of hyperinsulinism. Hypoglycaemia responded to diazoxid therapy. In addition, the child developed a Fanconi syndrome at 5 months of age. Radiological evidence was present for rickets. Therapy with calcitriol and supplementation with oral sodium phosphate and sodium bicarbonate was started. However, the patient failed to thrive and was below the 3rd percentile for both weight and length at 6 months of age. The result of mutational analysis will be presented. **Conclusion:** The clinical presentation of transient neonatal hyperinsulinism and renal Fanconi syndrome suggests the presence of an inactivating mutation in *HNF4A*. This disease entity seems to be a further differential diagnosis of congenital hyperinsulinism.

P3-1061

Clinical Characteristics and Molecular Analysis of Turkish Patients with Congenital Hyperinsulinism: a Single-Centre Experience with 15 Cases

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Objective: Congenital hyperinsulinism (CHI) is the most common cause of hypoglycaemia in children. Early identification and management is crucial to prevent irreversible brain damage. CHI has a heterogeneous clinical presentation, histology and molecular biology. We aim to discuss the clinical characteristics and genotype–phenotype correlations of Turkish CHI patients from a single centre. **Design and methods:** A total of 15 patients with CHI were recruited from one paediatric endocrine centre in Turkey. Patients with secondary hyperinsulinaemic hypoglycaemia (HH) due to IUGR, perinatal asphyxia, or maternal diabetes mellitus were excluded. All patients had normal acylcarnitine and urine organic acid profile. ABCC8 and KCNJ11 were sequenced in all patients and if no mutations were identified HADH sequencing was performed. **Results:** A genetic diagnosis was made in 9 (60%) patients (HADH $n=5$, ABCC8 $n=2$, and KCNJ11 $n=2$). Diazoxide unresponsiveness was observed in one patient with a *KCNJ11* mutation who was managed with subtotal pancreatectomy. Among the diazoxide-responsive patients ($n=14$), mutations were identified in eight cases (57%). Genotype–phenotype studies showed that *ABCC8* and *KCNJ11* mutations resulted in increased birth weight and *HADH* mutations were associated with liver dysfunction progressing from mild to severe disease. The clinical, biochemical and genetic characteristics of patients are summarised in Table 1. **Conclusions:** Our results are different from previous studies from Turkey which report recessive *ABCC8* and *KCNJ11* mutations as the most common cause of CHI. We identified mutations in three different genes in 57% of diazoxide-responsive patients which is a higher pick-up rate compared to other studies. Homozygous *HADH* mutations are a rare cause of CHI but in our cohort they accounted for 33% of cases. Hepatic dysfunction, cardiomyopathy or effects on skeletal muscle have not been reported in patients with HADH mutations to date. This work therefore extends the phenotype associated with these mutations.

P3-1062

Congenital Hyperinsulinaemic Hypoglycaemia of Infancy, Renal Fanconi Syndrome and Hepatopathy due to a Mutation in the *hnf4a* Gene

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Introduction: Congenital hyperinsulinaemic hypoglycaemia of infancy (CHHI) associates with mutations in known genes in approximately 60% of cases. CHHI and mutations in *HNF4A* gene are reported in 0.5–2.4% in large series. A case of CHHI with renal Fanconi syndrome (FS) and hepatopathy is presented. **Clinical description:** Male newborn, gestational age: 38 weeks, weight: 4250 g +2.7 S.D., length: 55 cm +3.29 S.D., developed hypoglycaemia during the first day of life. Laboratory tests on hypoglycaemia revealed high insulin and C-peptide (6.1 mU/l and 2.7 ng/ml respectively) with low β-hydroxybutyrate (10.2 mcmol/l). Glucose perfusions up to 17 mg/kg per min were needed. After CHHI diagnosis, diazoxide (8 mg/kg per day) was started normalizing glucose needs. Reduction of diazoxide was required because of hyperglycaemias and it was stopped at 3 months of age because of glycemias up to 300 mg/dl, later treatment involved adapted diet alone. Six months old: he had failure to thrive and later presented stunting and hepatomegaly, with persistent hypertransaminasemia and glucosuria. Viral and autoimmunity tests were negative. An increase of alkaline phosphatase (800–900 IU/l), low vitamin D and phosphate (3–3.2 mg/dl) were observed. At sixteen months he presented signs of rickets and FS was diagnosed. Genetic tests: positive *HNF4A* heterozygous mutation (exon 2, c.187C>T). Negative ABCC8 and KCNJ11. 28 months old: he is receiving treatment for the tubulopathy and recovering satisfactorily from his height and weight deficits. No relatives are phenotypically affected. **Discussion:** This mutation was first reported in 2010; it is linked to CHHI, FS and frequently, macrosomia and subsequent DM. Seven cases have been reported, only one had hypertransaminasemia and liver glycogen accumulation. No other mutations causing this phenotype have been described. **Conclusions:** Mutations in *HNF4A* must be suspected in patients with CHHI, macrosomia and diazoxide hyperresponse. During follow-up, awareness about the possibility of associated diseases is needed, like in this exceptional case.

P3-1063

Genotype–Phenotype Associations in 90 Children with Congenital Hyperinsulinism

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Background: Congenital hyperinsulinism (CHI) is a common cause of hypoglycaemia in neonates, infants and children. CHI is a heterogeneous disease in terms of clinical presentation, genetics and histology. **Objective and hypotheses:** The aim of this study was to describe the clinical characteristics, genotype–phenotype correlations and treatment outcome of Russian patients with CHI. **Method:** A total of 90 children with CHI were identified from 2009 till 2015 in Russia, of which 64 (71.1%) responded to the medical therapy (diazoxide and/or octreotide) and 26 (28.9%) were resistant and underwent subtotal or partial pancreatectomy. **Results:** Mutations in *ABCC8* and *KCNJ11* genes were found in

28/86 patients (32.5%); 3/86 patients (3.4%) were found to carry heterozygous GCK mutations; 3/86 (3.4%) – *GLUD1* mutations and one patient (1.1%) had *HADH* mutation. Among medically resistant cases, 17/26 patients (65.4%) had K_{ATP} genes mutations, of which nine were paternally inherited and represent focal HI, what was confirmed histologically and eight had diffuse disease (four heterozygous *de-novo* mutations and four homozygous and compound heterozygous mutations); one patient (3.8%) had severe *GCK* mutation; 8/26 patients had WT genes. Among medically responsive cases, 11/64 patients (17%) had mutations in K_{ATP} genes, interesting that two of them (both with heterozygous intronic mutations) spontaneously recovered during 6 months after diagnosis; 2/64 (3.1%) – in GCK, 3/64 (4.6%) – in GLUD1 and 1/64 (1.5%) – in *HADH* gene. Genotype–phenotype correlation revealed that mutations in K_{ATP} genes were associated with an increased birth weight and early age of presentation. Follow up studies showed high prevalence of severe developmental delay, cerebral palsy, and optic neuropathy (40, 26, and 7.5% respectively). **Conclusion:** A genetic cause was detected in 26 and 69%, of children with mild, and severe CHI, respectively, in Russia. Mutations in *ABCC8* and *KCNJ11* were found to be the most common cause and associated with severe course of the disease and poor neurologic outcome.

P3-1064

Comparison of Diagnosis Value of Glucometer with Laboratory Method in Neonatal Hypoglycaemia

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Background: Neonatal hypoglycaemia is an emergency condition requiring immediate treatment to prevent serious outcomes. Today blood glucose meter is a current methods for detecting blood glucose in health centre of our country. **Objective and hypotheses:** To determine the accuracy of blood glucose meter in comparison to laboratory method in detecting neonatal hypoglycaemia. **Method:** This cross-sectional study was conducted in the neonatal intensive care unit of Al Zahra Hospital from September 2013 to March 2014. In infants who had risk factors of hypoglycemia blood glucose were tested with blood glucose meter (ACCU CHEK – Performa), if the blood glucose was under 60 mg/dl, simultaneously the venous blood glucose values were done on (Selectra2) auto analyzer by glucose oxidase method. Sensitivity, specificity, and positive and negative predictive values of glucometer were determined. **Results:** A total of 200-paired samples were taken from 100 neonates. Hypoglycemia was detected in 65 cases (32.5%). Weak correlation was observed between result of glucometer and laboratory method ($r = 0.275$). Sensitivity, specificity, accuracy positive predictive value and a negative predictive value of glucometer were 45.45, 74.6, 65, 46.8, and 73.5% respectively in blood glucose < 45 mg/dl. **Conclusion:** According to the results obtained in this study glucometer has not sufficient diagnosis value to detect of neonatal hypoglycaemia. Blood glucose meter results should be confirmed with laboratory method.

P3-1065

Glycogen-Storage Disease Type VI in a Girl Presenting with Recurrent Ketotic Hypoglycaemia but No Hepatomegaly

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Background: Glycogen-storage disease type VI (GSD VI) is an autosomal recessive disorder due to deficiency of the liver isoform of phosphorylase resulting in abnormal accumulation of glycogen. Patients typically present in early childhood with growth retardation, hepatomegaly, hypoglycaemia and ketosis. Ketotic hypoglycaemia is a relatively common diagnosis (of exclusion) in children presenting with hypoglycaemia. **Case:** A 3-year-old girl presented with an episode of collapse and hypoglycaemia. She had an uneventful past medical history and was born at term to non-consanguineous Caucasian parents. She did not have any intercurrent illness. She had a normal examination with no dysmorphic features or hepatomegaly. The hypoglycaemia screen revealed appropriately suppressed insulin, low c-peptide and elevated free fatty acids and ketones, and normal cortisol suggesting a diagnosis of 'ketotic hypoglycaemia'. The plasma amino acids, ammonia, lactate, acylcarnitine profile and urine organic acids showed no abnormalities. She was noted to have short stature (height -2.5 SDS) and further endocrine evaluation revealed normal thyroid function, bone profile, prolactin, 46,XX karyotype, and low IGF1. The glucagon stimulation test revealed a suboptimal growth hormone response of 4.7 μg/l; hence she was commenced on GH. She continued to have symptomatic hypoglycaemic episodes and repeated hypoglycaemia screen demonstrated ketosis. In view of the persistent ketotic hypoglycaemic episodes, not necessarily triggered by intercurrent illness, further genetic analysis was undertaken using a targeted sequencing panel. This revealed a heterozygous *PYGL* mutation (c.1900G > C) suggesting a possible diagnosis of GSD VI. **Conclusion:** We report a case of GSD VI who presented with recurrent ketotic hypoglycaemia and did not have hepatomegaly on clinical examination. As ketotic hypoglycaemia is a diagnosis of exclusion, it is important to consider alternative diagnoses especially in the presence of recurrent hypoglycaemic episodes and short stature. Genetic evaluation may be warranted in selected cases of ketotic hypoglycaemia.

P3-1066

Congenital Hyperinsulinism in a Newborn with a Novel Paternally Inherited Heterozygous Mutation (p.E1517G) in the *ABCC8* Gene

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Background: Congenital hyperinsulinism (CHI), a clinically and genetically heterogeneous disease, is the most common cause of persistent hypoglycaemia in infancy. **Case presentation:** Here we describe an Egyptian male neonate first order of birth born to non-consanguineous healthy parents. At day 1 of age he presented with severe hypoglycemia and generalised seizures. At the time of hypoglycaemia (16 mg/dl) insulin and C-peptide levels were increased (insulin 72 (6–25 μIU/ml; C-peptide 7.8 (1.1–3.3 ng/ml), leading to the diagnosis of hyperinsulinaemic hypoglycaemia (HH). Serum GH, cortisol, ammonia, and lactate were normal. Patient was given glucose infusions and regular feeding hourly to maintain normoglycaemia. The patient was discharged and an out-patient follow-up was instituted without any treatment. However, recurrent episodes of hypoglycemia were noticed. Medications (hydrocortisone and nifedipine) had no substantial effect on glycemic profile. Another treatment was started on diazoxide 10 mg/kg per day with increasing dosage up to 25 mg/kg per day. This treatment was not effective and repeated episodes of hypoglycemia were observed two to three times a day. As parents refused surgery, Hydrochlorothiazide was added with substantial improvement of glycemic level. The child now is 1 year old growing well with no neurodevelopmental delay. Sequence analysis has identified a novel heterozygous missense mutation, p.E1517G (c.4550A > G) of the *ABCC8* gene inherited form the father. As the p.E1517G mutation has been paternally inherited a focal lesion is possible, no mutation was identified in the mother. **Conclusion:** Heterozygous paternally inherited *ABCC8* mutations can lead to CHI which was responsive to medical treatment alone.

P3-1067

Discontinuation of Diazoxide Therapy in Children with Hyperinsulinaemic Hypoglycaemia with no Identified Genetic Aetiology: a Long-term Follow-up Study

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Background: Congenital hyperinsulinism (CHI) is a cause of severe persistent hypoglycaemia in children. Diazoxide is the first line medical therapy for CHI; however diazoxide is usually ineffective in CHI with K_{ATP} channel gene mutations. Patients with no mutations in the K_{ATP} channel genes do respond to therapy with diazoxide. There are no previous studies assessing how long diazoxide therapy is needed in those patients with no genetic aetiology identified for the CHI. **Objective and hypotheses:** To describe the clinical, biochemical and genetics aspects of a cohort of CHI patients with no genetic aetiology identified and their duration of diazoxide therapy. **Method:** Retrospective review of diazoxide-responsive CHI patients admitted to Great Ormond Street Hospital. Data on gestation age, birth weight, maternal risks, age of diagnosis, biochemical and genetic studies on ABCC8 and KCNJ11 were obtained. Follow up data on glycaemic profile, fasting studies, dose of diazoxide and duration of therapy were recorded. **Results:** Ten children with diazoxide-responsive CHI and no known with genetic aetiology were identified. They were diagnosed between 9 days and 23 months old, with three presenting as neonates. Three were female and all were born at term with median birth weight of 3.793 kg (2.99–4.99 kg). There was no history of maternal gestational diabetes mellitus. All responded to diazoxide, with median maximum dose of 11.5 mg/kg per day (5–20). All were negative for *ABCC8* and *KCNJ11* mutations. In all patients diazoxide was stopped at a median age of 8.5 years (4–15); the median duration of diazoxide therapy was 7.25 years (2.9–14.6). Fasting studies done after stopping diazoxide showed resolution of CHI. **Conclusion:** CHI children with no known genetic aetiology may be able to come off diazoxide at some stage during follow up. These children need regular assessments for continuing diazoxide therapy. The molecular mechanism(s) that lead to the gradual improvement in CHI over time are not known.

P3-1068

Pancreatic Hormones in Children with Hyperinsulinaemic Hypoglycaemia

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Background: In congenital hyperinsulinism (CHI) there is dysregulation of insulin secretion that leads to hypoglycaemia. It is possible that other pancreatic hormones are also dysregulated in CHI. **Objectives:** i) To verify the utility of Luminex Multiplex to determine pancreatic hormones in the paediatric age. ii) To investigate the response of pancreatic hormones (insulin, C-peptide, glucagon, amylin and PP) to a fast in children with CHI due to different underlying mechanisms. **Patients and methods:** Plasma pancreatic hormones were collected in 12 children with CHI at a single centre in London (UK) at normoglycaemia and at hypoglycaemia (end of fast). The patients are five males and seven females with ages between 11 days of life

and 13 years. Their CHI is due to different aetiologies, histology types and with different response to treatments. Hormones were analysed using multiplexing manner (Luminex Multiplex assay) on 0.025 ml of plasma. **Results:** Insulin concentration (mean ± SDS) decreases from 909 ± 441 pg/ml in normoglucemia to 503 ± 306 pg/ml at hypoglucemia (*P* 0.004). Similarly, C-peptide descends from 1547 ± 1013 pg/ml to 806 ± 366 pg/ml at normoglycaemia and hypoglycaemia, respectively (*P* 0.005). The concentrations of glucagon at these two time points are 97 ± 239 and 103 ± 260 pg/ml (*P* 0.21). Amylin decreases from 35 ± 22 pg/ml to 21 ± 9 pg/ml (*P* 0.014) whilst PP remains almost unchanged: 84 ± 106 pg/ml at normoglycaemia and 86 ± 115 pg/ml at hypoglycaemia (*P* 0.65). **Conclusions:** This assay proves to be useful in determining pancreatic hormones in children. Glucagon's response to hypoglycaemia is impaired in children with CHI. This is the first study to look at amylin concentrations in CHI. Amylin decreases during hypoglycaemia so as to avoid it's anorectic effect, but interestingly PP's concentrations remain stable despite hypoglycaemia.

P3-1069

Experience Based on 193 ^{18}F-DOPA PET CTs in Patients with Congenital Hyperinsulinism: Pearls and Pitfalls in Imaging Diagnostics in Patients with CHI

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Background: In congenital hyperinsulinism (CHI) ^{18}F-DOPA PET CT plays an essential role in differentiating between focal and diffuse CHI forms and in the analysis of the localization of a potential focus before surgery. **Objective and hypotheses:** The aim of this retrospective analysis was the evaluation of the ^{18}F-DOPA PET CT efficacy in a large cohort of CHI patients. **Method:** In the last few years 193 ^{18}F-DOPA PET CTs were performed in our centre in CHI patients and we performed a retrospective analysis of specificity and sensitivity based on the results of the histological evaluation of the samples after surgery, clinical course of the patient and molecular genetic findings. **Results:** With one exception it was possible in all cases with the ^{18}F-DOPA PET CT to differentiate between focal and diffuse CHI forms in addition to molecular genetic results. However, in three cases the ^{18}F-DOPA PET CT failed to visualize the complete expansion of the affected region and the giant spreading of the focus was identified during surgery. Finally, in three cases the CHI patients received in addition to the ^{18}F-DOPA PET CT scan a DOTATOC PET CT. Thereby one focus was additionally identified, which would have been missed with the traditional approach using only the ^{18}F-DOPA PET CT. **Conclusion:** The imaging diagnostics is a critical step in the work up of patients with CHI. Being aware of the advantages and pitfalls of this method is an important step to improve the quality of the diagnostic and finally the therapeutic regime in patients with congenital hyperinsulinism.

P3-1070

Severe Neonatal Hypoglycemia in the Newborn Despite Prenatal Diagnosed Cerebral Midline Malformations: a Review of Three Cases

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Background: Brain abnormalities like cerebral midline malformations (CMM) can be detected by fetal sonography. CMM with neonatal hypopituitarism may cause severe hypoglycemia. **Case presentation:** We report about three cases of term eutrophic newborns, which all presented with severe neonatal hypoglycemia despite prenatally diagnosed CMM. All three patients were born vaginally and were immediately breastfed after normal postnatal adaptation. In the first case septooptic dysplasia was diagnosed prenatally. The newborn boy developed recurrent periods of shivering and eventually seizures within the first 8 h of life. Blood glucose was extremely low with 0.6 mmol/l (NR 3.5–5.5) and resulted in severe multicystic encephalopathy, epilepsy and severe developmental delay. Congenital hypopituitarism was confirmed via blood tests. In the second case an agenesia of the corpus callosum was known from prenatal diagnostics. After normal glucose tests at 1, 3 and 6 h after birth, the monitoring was stopped. At an age of 32 h the boy presented with a hypoglycemic seizure (glucose level 1.4 mmol/l). Follow-up revealed severe neonatal GH deficiency and a microdeletion syndrome 46,XY,del(18)(q21.2). In the third case prenatal diagnostics revealed an isolated absence of the septum pellucidum. Glucose measurements were normal for 4 h postnatally. Fourteen hours after birth the boy appeared pale, tachycardic and shivering. Glucose level was 1.6 mmol/l. Despite glucose infusion one further hypoglycemia occurred. Endocrine assessment revealed isolated GH deficiency. **Conclusion:** Prenatal diagnosis of cerebral midline defects should urge caring physicians to plan the delivery in centres with paediatric endocrine experience. Neonatal glucose monitoring should be performed not only within the first 4 h after birth but over a longer period of several days. Endocrine assessment is required within the first days in order to test for congenital hypopituitarism. Close collaboration between gynecologists, neonatologists and endocrinologists may prevent bad neurological outcome.

P3-1071

A Case of Mild Congenital Hyperinsulinaemia Presenting with Developmental Delay, Complicated by Diazoxide-induced Transient Neutropenia

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Background: Congenital hyperinsulinaemic hypoglycaemia (CHI) can cause various degrees of hypoglycaemia in infancy. In mild CHI, unnoticeable recurrent hypoglycaemia may cause deterioration of central neurological functions in patients. We report a case of mild CHI that presented with developmental delay without any previous hypoglycaemic events. **Case presentation:** An 18-month-old Japanese girl was admitted to our hospital with seizures and unconsciousness. Her blood glucose level measured at admission was 58 mg/dl. However, laboratory data collected the next day showed a blood glucose level of 40 mg/dl and a serum insulin level of 10.9 μU/ml. On the basis of these findings we made a diagnosis of CHI. The patient had never shown apparent hypoglycaemic events previously and had developed normally until 6 months of age, after which mild developmental delay was observed. She was administered diazoxide that was followed by severe neutropenia. A bone marrow aspiration performed 2 days after cessation of the drug showed a reduction in nucleated cell count and increased numbers of immature myeloid cells, indicating transient myeloid suppression. Because we were unable to control her blood glucose levels appropriately by meals or other supplemental diets, and octoreotide is not registered for treatment CHI in Japan, she was restarted on diazoxide with close monitoring. The patient has not developed neutropenia again and her metabolic status has been controlled successfully. **Conclusion:** In patients who develop gradual central neurological problems, recurrent blood glucose measurements should be recommended for the differential diagnosis of CHI. Neutropenia is a rare adverse effect of diazoxide. However, this may be transient and the drug should be reintroduced with close monitoring after recovery of the bone marrow.

P3-1072

Failure of Sirolimus Response on Three More Cases with a Diffuse Type of Congenital Hyperinsulinism

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Background: Congenital hyperinsulinism (CHI) represent a group of clinically and genetically heterogonous disorder that characterized by unregulated insulin secretion by B-cells. It is the most common cause of hypoglycaemia in the neonatal period. Infants with diffuse CHI have homozygous or compound heterozygous mutation in the KATP channel and the majority are unresponsive to standard medical therapy and eventually they need near total pancreatectomy. Recent data showed the efficacy of MTOR inhibitor in adult patients with insulinoma and neonate with sever diffuse CHI and were managed with Sirolimus therapy avoiding pancreatectomy. **Objective and hypotheses:** To test Sirolimus therapy response in three Saudi infants with sever CHI, confirmed mutation in KATP channel who failed medical therapy with Diazoxide and Octreotide treatment. **Method:** Three Saudi infants who presented in the neonatal period with sever non ketotic hypoglycaemia, biochemically confirmed CHI, all of them were on high glucose infusion rate, require high dose Diazoxide (20 mg/kg per day) and Octreotide (45 μg/kg per day) therapy were subjected to Sirolimus therapy trial, two patients had Sirolimus trial preoperatively and one post near total pancreatectomy with a dose range from 1.2 to 4.5 mg daily. **Results:** One case the genetic test confirmed mutation in exon 1 of KCNJ11 gene, the second case is the double cousin of case 1 and the, last case is having mutation in exon 7 of ABCC8 gene. all of them were still having recurrent hypoglycaemia hyperinsulimemia state despite the Sirolimus level reached the therapeutic level. **Conclusion:** Although treatment of CHI with Sirolimus in the previous trials were successful, our cases with homozygous mutation of KCNJ11 and ABCC8 mutations failed to response to Sirolimus trial and it should probably not be used as the first line of medication until further experience and better understanding of its relative risks and benefits.

P3-1073

Auxological Characteristics of Persistent Hyperinsulinemic Hypoglycemia at Birth

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Background: Most infants with persistent hyperinsulinaemic hypoglycaemia (PHH) are born large for gestational age (LGA) due to excessive anabolic effect of prenatal hyperinsulinism. However, other auxological characteristics than weight in infants with PHH have not been described well. **Objective:** The objective of this investigation was to characterize anthropometric parameters at birth (weight, length, and head circumference) in PHH compared with those in idiopathic LGA. **Method:** Clinical data in full term birth for PHH and idiopathic LGA were retrospectively collected at two institutions. We excluded infants of diabetic mothers or those with known overgrowth syndrome. Variables analysed included birth weight SDS, length SDS, and head circumference SDS. The variables between PHH and idiopathic LGA were compared using the Mann–Whitney *U* test. **Results:**

The present study included seven infants with PHH and 134 with idiopathic LGA. The birth weight SDS in PHH (median, 3.03; range, 1.46 to 3.67) were significantly greater than that in idiopathic LGA (1.75; 1.04 to 4.03) ($P=0.01$). The birth length SDS in PHH (1.45; 0.25 to 2.73) were significantly greater than that in idiopathic LGA (0.90, −2.19 to 3.19) ($P=0.02$). There was no significant difference in head circumference SDS between PHH (0.71; 0.19 to 1.70) and idiopathic LGA (1.14; −1.52 to 3.34). The difference between birth weight and head circumference SDS in PHH (median, 1.94; range, 0.33 to 3.14) were significantly greater than that in idiopathic LGA (0.64; −1.66 to 3.13) ($P=0.003$). The difference between birth length and head circumference SDS in PHH (median, 0.73; range, −0.06 to 1.83) were significantly greater than that in idiopathic LGA (−0.19; −2.61 to 2.04) ($P=0.01$). **Conclusion:** These data indicate excessive prenatal growth in weight and length for infants with PHH, but not in head circumference. Prenatal growth promoting effect of insulin may differ depending on body and brain.

P3-1074

Congenital Hyperinsulinism in Siblings: Case Report

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Background: Congenital hyperinsulinism (CHI) is the most common cause of hypoglycemia in childhood, and diagnosis and treatment of CHI is one of the most difficult aspects of modern endocrinology and diabetology. In half of infants suffering from congenital hyperinsulinism, which may require resection of pancreatic, potentially curable focal form can be found. Recently introduced diagnostic imaging using ^{18}F-DOPA-PET allows for differentiation as a diffuse and focal form and determines further treatment. Identification of the exact location of lesions is used in preoperative planning, which involves resection limited to the focus and as a result it leads to a reduction in postoperative complications. **Case report:** Case report of the two sisters, who were diagnosed with congenital focal form of hyperinsulinism and the impact of performed diagnostic test for the treatment and the occurrence of postoperative complications. Congenital hyperinsulinism in older sister was diagnosed when diagnostic imaging with ^{18}F-DOPA-PET was not yet available, which led to subtotal pancreatectomy and ultimately resulted in diabetes and pancreatic enzyme deficiency symptoms after operation. In the postoperative examination of the removed tissue a single focus of hyperinsulinism was found. In the second, younger sister during diagnosis it was possible to perform the study with ^{18}F-DOPA-PET, and there was identified an isolated focus of hyperinsulinism, which was resected during operation. In this patient none postoperative complications were observed and complete resolution of the symptoms of hypoglycemia. In both sisters genetic tests were performed for searching the reason of familial from of CHI. **Conclusions:** It is important to perform diagnostic imaging with ^{18}F-DOPA-PET in children with CHI before planning pancreatectomy in CHI.

P3-1075

Genetic Causes of Congenital Hyperinsulinism in Slovakia

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Background: Congenital hyperinsulinism (CHI) is the most common cause of the persistent hypoglycemia in children. Mutations in *KCNJ11* and *ABCC8* genes coding potassium channel subunits are responsible for a significant proportion of CHI patients. The type of mutation correlates with the type of B-cell hyperplasia (focal or diffuse), and determinates further diagnostics, treatment and prognosis of disorder. **Aims and objectives:** The aim of this study was to determine etiology of patients with severe hypoglycemia by DNA analysis, and choose appropriate therapeutic approach based on the result. **Methods:** During the period of 10 years (2005–2014) 14 patients with congenital hyperinsulinism were identified throughout Slovakia. In all of them the DNA analysis by Sanger sequencing of the genes *KCNJ11* and *ABCC8* was performed. **Results:** Five patients have been found with a mutation in one of the analyzed genes. Two patients had a diazoxide-resistant focal form of CHI caused by paternally inherited *ABCC8* mutations (p.Q444H and c.2694+1G>C, respectively). Subsequently, in both patients pancreatic surgery with the aim to reduce B-cell mass was carried out. In two patients sensitive to diazoxide two different mutations were identified (i.e. dominant p.V17A mutation of the *ABCC8* gene, and a novel *KCNJ11* mutation p.T180N, respectively). Combination of two recessive mutations in the *KCNJ11* gene (p.Q52*; p.R301G) was identified in a 4 months old boy with severe hypoglycemia resistant to diazoxide. Based on the results of DNA analysis we started treatment with octreotide, what in combination with frequent feedings through a gastrostomy led to normalization of glycaemia. **Conclusion:** DNA diagnostics allows identification of etiology in congenital hyperinsulinism. In case of channelopathies the type of mutation determinates the most appropriate therapeutic procedure (diazoxide in dominant mutations, surgery in focal forms, and somatostatin analogues in recessive mutations causing diazoxide resistant diffuse forms of CHI). **Funding:** This work was supported by the Slovak Research and Development Agency (APVV 0107-12).

P3-1076

Hyperinsulinism Secondary to Congenital Portosystemic Shunt in a Neonate

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Background: Hyperinsulinism is a common cause of persistent hypoglycaemia in infant. Insulin secretion from pancreatic β-cells is unregulated and inappropriate for the level of blood glucose, causing glucose into the insulin-sensitive tissues, such as the muscle, liver and adipose tissue, leading to hyperinsulinaemic hypoglycaemia. But congenital portosystemic shunt, a rare vascular malformation, can cause hyperinsulinaemic hypoglycaemia rarely because glucose from portal to systemic circulation causes early hyperglycaemia leading to exaggerated insulin secretion, leading to bypassing the hepatic metabolism directly entering into the systemic circulation, which results in hyperinsulinaemia, then in turn causes late hypoglycaemia. **Case:** We report a rare case of hyperinsulinaemic hypoglycaemia secondary to a congenital portosystemic shunt in a newborn. A 1-day-old female was referred our hospital for hypoglycaemia without response in i.v. 10% glucose infusion. She was born at 38 weeks via caesarean section and second child of healthy parents. Her birth weight was 3.3 kg. The patient developed dyspnea after birth, so applied oxygen and checked blood test. Blood glucose was 16 mg/dl. The evaluation of insulin/glucose ratio was performed – glucose 34 mg/dl (normal range: 60–108 mg/dl), insulin 67.43 μIU/ml (normal range: 12–25 μIU/ml), insulin/glucose ratio 1.98. Abdominal USG was performed to find pancreas anomaly, there were normal pancreas and intrahepatic portosystemic shunt. Liver dynamic CT showed intrahepatic portosystemic shunt – middle and left hepatic vein between left portal vein – and hypoplasia of right portal vein. The patient was treated with intravenous 10% glucose (glucose IR 17 mg/kg per min) and frequent oral feeding, hypoglycemia slightly improved. So with frequent feeding and glucose monitoring at home, we have plan to have surgical correction. **Discussion:** Even though rare, congenital portosystemic shunt can cause hyperinsulinism and hypoglycaemia in infant, so imaging study is needed about vasculature in liver with pancreas, avoiding unnecessary treatment, for example, diazoxide.

P3-1077

Clinical Presentation of a Patient with a Novel Homozygous Mutation in the TRPM6 Gene

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Background: Herediter hypomagnesemia with secondary hypocalcemia (HSH) is a rare autosomal recessive disease caused by mutations in the transient receptor potential melastatin 6 (TRPM6) gene. Affected individulals present at early infancy with severe hypocalcemia and hypomagnesemia which leads to tetany and seizures. **Objective and hypotheses:** In this report, we want to present the clinical features, treatment regimen, follow-up of a patient with a novel homozygous mutation in the TRPM6 gene. **Method:** Molecular analysis of *TRPM6* was performed by direct sequencing of the coding region and the intron/exon boundaries. **Results:** We report a 6-year-old Turkish girl who presented with seizure at two months of age secondary to hypomagnesemia. She had been on magnesium therapy since then. At the time of her first admission to our clinic, she was 3.6 years old, her weight was 14 kg (−0.94 SDS), height was 97.5 cm (−0.69 SDS), BMI was 14.7 (−0.54 SDS). Systemic evaluation was normal and there were no dysmorphic features. Family history was unremarkable regarding hypomagnesaemia. There was a consanguinity between parents. During her follow up, she had an age appropriate physical and neurological development under magnesium oxide therapy at a dosage of 26 mg/kg per day. A homozygous frame-shift mutation (c.3447delT->p.F1149fs) in the *TRPM6* gene was identified. **Conclusion:** We want to present the follow-up and importance of the treatment in HSH. Furthermore, we identified a novel mutation in the TRPM6 gene. We want to highlight the requirement of molecular study in the inbred or familial cases with hypomagnesemia.

P3-1078

Long Acting Somatostatin Analogues in the Management of Congenital Hyperinsulinism in Cases with Poor Compliance to Conventional Therapy

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Background: Congenital hyperinsulinism (CHI), is the most common cause of severe hypoglycaemia in neonates and infants. The cornerstone of medical therapy is diazoxide. Octreotide, a somatostatin analogue, is the second therapeutic option in diazoxide unresponsive cases. However, due to its short half-life and requirement of multiple daily doses, lack of compliance may cause recurring hypoglycaemia and related neurological deficits, particularly for the family with low socioeconomic status. Long acting somatostatin analogues that provide good glycaemic control by a monthly injection, might help in the management of CHI patients who have poor compliance with conventional medical therapy. Herein, we report the management of 5 patients with diazoxide unresponsive CHI who have poor compliance, using the long-acting somatostatin analogue, octreotideLAR (oLAR).

Patients: Patient details are summarised in Table 1. Patients 1, 2 (siblings) and 3 were diagnosed in the neonatal period and were diazoxide unresponsive but, octreotide responsive. All developed severe neurodevelopmental deficits and epilepsy due to recurring hypoglycaemic episodes as a result of the poor compliance. Patient 4 was the first cousin of patient 3 and had another sister with CHI due to identical mutation and severe mental-motor retardation. This patients was commenced oLAR at a younger age and had favorable blood measurements and neurological development. Patient 5 was also started on oLAR therapy at a younger age and had a good glycaemic control, consequently normal neurological development. In all five patients diazoxide and multidose octreotide was weanned off successfully. Furthermore, we have not observed any severe acute or long-term side effects requiring treatment withdrawal. **Conclusion:** Administration of long acting somatostatin analogs (every 28 days) resulted in better compliance and thereby prevented recurring hypoglycaemic episodes and related neurological deficits. In low scoieconomic class with anticipated poor compliance, long acting somatostatin analogs may potentially be the first option in the medical therapy of CHI.

P3-1079
Isolated Postprandial Hyperinsulinaemic Hypoglycaemia

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Background: Only a few case reports have described isolated postprandial hyperinsulinaemic hypoglycaemia (PPHH) in children. **Objectives:** To describe a single tertiary paediatric centre's experience in the management of isolated PPHH. **Patients and methods:** Six children (three females) were identified. A retrospective review of the clinical characteristics, diagnosis, management and follow-up of patients with PPHH was performed. Investigations included: 24 h glucose profile, continuous glucose monitoring system, diagnostic fast, prolonged oral glucose tolerance test (OGTT) and mixed meal (MM) test. Management options were: dietary intervention, diazoxide and acarbose. **Results:** At diagnosis ages were between 4.1 and 8.9 years and all children had auxology parameters within the normal range. All the patients showed a normal fasting tolerance but a prolonged OGTT demonstrated symptomatic hypoglycaemia (blood glucose <3.5 mmol/l) after 120 min with simultaneous detectable serum insulin concentrations. The mean follow-up was of 3.3 ± 3.1 years. Four patients were tried on acarbose, which had a positive glycaemic and symptom-control effect, but due to its side effects, only one patient remained on it on the long-term. One patient responded to diazoxide. The other patients were managed on frequent feeds but, even on this, prolonged OGTT/MM demonstrated persisting PPHH. On follow-up two patients spontaneously grew out of the condition. **Conclusions:** The identification of hypoglycaemia in PPHH requires a prolonged OGTT. Acarbose was beneficial in children with PPHH, although it was poorly tolerated. Hypoglycaemia persisted on prolonged OGTT in those patients managed exclusively on frequent feeds. The cause of the PPHH in these patients still needs to be elucidated.

P3-1080
Severe Congenital Hyperinsulinism in a Neonate Homozygous for Two Novel Missense Mutations in the *KCNJ11* Gene

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Table 1. Presenting age, genetics, treatment and follow up of patients (for abstract P3-1078).

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age of diagnosis (week)	1st week	1st week	1st week	2nd week	1st week
Age at oLAR therapy (year)	5.8	9.8	4.0	1.3	1.9
Mutation	Homozygous c.3512del (*ABCC8*)	Homozygous c.3512del (*ABCC8*)	Homozygous c.3554C>A (*ABCC8*)	Homozygous c.3554C>A (*ABCC8*)	NA
Octreotide dose (μg/kg per day)	10	5	13.3	20	10
Diazoxide dose (mg/kg per day)	10	10	7.5	15	15
OctreotideLAR (mg/28 day)	30	30	30	30	30
Baseline TFT's	Euthyroid	Euthyroid	Euthyroid	Euthyroid	Euthyroid
TFT's at follow up	Euthyroid	Euthyroid	Euthyroid	Euthyroid	Euthyroid
Linear growth	Normal	Normal	Normal	Normal	Normal
Baseline IGF1/IGFBP3 (μg/l)	108/3000	241/4030	53/3140	NA/4280	101/3020
IGF1/IGFBP3 follow-up (μg/l)	NA/NA	NA/NA	136/NA	NA/NA	167/4180
Gallbladder pathology	No	No	No	No	No
Side effect (other)	No	No	No	No	No

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Background: Congenital hyperinsulinism (CHI) is a heterogenous disorder characterized by hyperinsulinaemic hypoglycaemia, and may present in the neonatal period in severe forms of the disease. Molecular defects involving eight genes has been described so far. Herein we report a case of severe, diazoxide unresponsive CHI caused by two homozygous novel missense mutations in the *KCNJ11* gene. **Case report:** An 8-day old girl was referred for hyperinsulinaemic hypoglycaemia. She was the first child of first degree cousins. She had hypoglycemia on the first day of life. Unresolved repeated hypoglycaemia despite high glucose infusion rates (GIR) and an elevated insulin (47 μIU/ml) suggested CHI and the patient was started on diazoxide (15 mg/kg per day). She continued to have boutes of hypoglycaemia, considered to be diazoxide unresponsive and referred for pancreatectomy. Upon arrival she had hepatomegaly, also ASD, PDA, pulmonary hypertension as well as concentric left ventricular hypertrophy was discovered on ECHO. Blood glucose was kept in the normal range initially using diazoxide (15 mg/kg per day), hydrochlorothiazide (2 mg/kg per day), octreotide (20–40 μg/kg per day) and glucose infusion (10–12 mg/kg per min on 20th postnatal day, she developed heart failure and was digitalized, diazoxide was replaced with glucagon (20 μg/kg per day). On 22nd day of life PDA was ligated, and 36th day of life near total pancreatectomy was carried out. Following pancreatectomy hypoglycaemia recurred and she was put on octreotide. Pathology showed diffuse hyperplasia, hypertrophy and nucleomegaly in the islet cells. Molecular analysis revealed that the patient was homozygous for two novel missense mutations (p.R221H and p.Q299H) in the *KCNJ11* gene. Both parents were heterozygous for the same mutations. **Conclusion:** Pathology and molecular findings suggested autosomal recessive CHI. The arginine residue at codon 221 and the glutamine residue at codon 299 are conserved across species. It is therefore likely that one or both of these mutations are pathogenic.

P3-1081
Congenital Glucose–Galactose Malabsorption in a Male Infant

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Background: Congenital glucose–galactose malabsorbtion is a rare autosomal recessive disorder of intestinal transport of glucose and galactose. It is characterized by watery diarrhoea, dehydration, failure to thrive, or early death without appropriate dietary treatment. **Case presentation:** The patient was 15 days old when he was admitted to the hospital because of continued, severe, watery, acidic diarrhoea and hypernatremic dehydration. The abnormal stool looses were recorded within 4 days of birth. They were followed by abdominal distension, with no vomiting, and persistent, osmotic, watery diarrhoea for the next 2 months. Despite management with lactose-free semielemental formula, and periodic administration of total parenteral nutrition during hospitalization, severe malnutrition occurred. Further laboratory investigations revealed repeated low blood sugar levels, slight intermitent glycosuria, low stool Ph, and presence of reducing substances in the faeces. Oral glucose tolerance test showed flat blood glucose response. Diagnostic evaluation ruled out infectious aetiology of the diarrhoea, cystic fibrosis, familial chloride diarrhea, and lactose intolerance. The X-ray examination of the intestinal tract revealed no abnormality. The clinical history of the patient and performed laboratory investigations were strongly suggestive of congenital glucose–galactose malabsorption. Dramatic ceasure of the diarrhoea followed when the patient was treated with a commercial glucose and galactose-free formula – galctomine 19 (specialized fructose-based formula). **Conclusions:** All these findings and further successful, sustained weight gain, established the diagnosis of congenital glucose–galactose malabsorption in our patient. At the age of 12 years he had normal growth and neurological development.

P3-1082
HYNIC TOC: a New Radionuclide Material in the Evaluation of Persistent Hyperinsulinaemic Hypoglycaemia of Infancy: an Alternative to ^{18}F-DOPA?

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Background: Evaluation of persistent hyperinsulinaemic hypoglycaemia of infancy (PHHI) requires accurate anatomic diagnosis for appropriate medical/surgical management. ^{18}F-DOPA PET scan is used to localise the disease in pancreas, but is not available in many centres. **Objective and hypotheses:** We were highly restrained by the availability of investigations for evaluation of PHHI, especially ^{18}F-DOPA. To localise the disease process, we use genetic testing and response to therapy as a guide. So, we tried HYNIC TOC as a new material for PET scan and tried to correlate with the genetic results and patient's clinical course. **Method:** Neonate born LGA with birth weight 4.8 kg had hyperinsulinaemic hypoglycaemia (critical sample insulin-67.07 μU/ml). Workup done for other causes of hypoglycaemia were negative. Hypoglycaemia was persistent with high dextrose requirements and refractory to oral diazoxide therapy (upto 10 mg/kg per day). But he responded to octreotide s.c. injection at 5 μg/kg per day. His genetic work up was done at Exeter Labs, UK which showed compound heterozygous mutation in *ABCC8* gene (location exon 2 and intron 20; missense and aberrant splicing) inherited from both the parents. These clinical course and genetic reports suggested diffuse involvement of pancreas causing hyperinsulinism, but we were restrained by the non availability of ^{18}F-DOPA in India. So PET scanning was done using a new

radionuclide material called HYNIC TOC. **Results:** HYNIC TOC PET/SPECT scan showed diffuse uptake of radionuclide material in the pancreatic tissue suggesting diffuse nesidioblastosis. **Conclusion:** HYNIC TOC, used in the diagnosis of neuroendocrine tumours in adults widely can be tried in children with PHHI where ^{18}F-DOPA is not available, suggested by the correlation we found. Also, the properties like high *in vitro* and *in vivo* stability, rapid blood clearance, predominant renal excretion, improved image quality, lower radiation dose and EASY AVAILABILTY may make it an ideal material for this indication.

P3-1083

Cholestatic Hepatopathy and Hypoglycaemic Seizures as Primary Manifestation of Hypocortisolism in Infancy

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Background: Cholestatic hepatopathy is a rare but serious threat to neonates and young infants. Their immature hepatic excretory function predisposes for severe and rapidly progressive hepatic injury. Because of the wide range of possible etiologies, it is often difficult to make an accurate diagnosis. One rare endocrine cause can be primary or secondary hypocortisolism. **Case presentation:** i) A 7-week-old term-born female with cholestasis, elevated liver enzymes, fatigue and history of hypoglycaemic seizures was referred to our centre. Parents are consanguineous. Conjugated bilirubin was 9.6 mg/dl ($<$0.3), AST 884 U/l ($<$79), ALT 215 U/l ($<$48). ACTH was elevated ($>$2000 pg/ml) and serum cortisol was not detectable. Mutational analysis revealed a homozygous mutation in melanocortin 2 receptor-associated protein (MRAP) as cause of ACTH resistance due to defective receptor signalling. ii) A 2-day-old full-term girl presented due to hypoglycaemic seizures. She was treated with intravenous glucose. At this time only Gamma-GT was elevated to 300 U/l ($<$181). She was discharged 13 days later with normalized blood sugars. Two weeks later she developed cholestasis, anaemia and elevated liver enzymes: conjugated bilirubin was 5.35 mg/dl ($<$0.3), AST 797 U/l ($<$79), ALT 278 ($<$48). Basal cortisol levels were decreased (0.3 µg/dl) and ACTH and cortisol showed a diminished reaction on stimulation with CRH (ACTH max. 16.9 pg/ml and cortisol max 4.9 µg/dl). MRI revealed septo-optic pituitary dysplasia. In both cases hydrocortisone replacement led to complete normalization of liver enzymes and bilirubin. **Conclusion:** Since symptoms may be unspecific or very subtle, diagnosis of neonatal/infantile hypocorticsolism can easily be missed with significant delay in starting hormonal replacement therapy. Therefore, we strongly emphasize to analyse cortisol levels in the work-up of cholestasis in newborns and infants in particular in association with severe hypoglycaemia.

P3-1084

Plasma Kisspeptin Levels of Infants Breast Growth in Neonatal Period

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Background: The studies investigating kisspeptin levels in the neonatal period is very limited. **Objective and hypotheses:** This study was intended to investigate plasma kisspeptin hormone levels in newborns with or without breast growth. **Method:** This prospective study was performed to determine plasma hormone levels of kisspeptin in patients admitted to the Erzurum Ataturk University Faculty of Medicine Research and Educational Hospital Pediatric Endocrinology Policlinic in September 2013–March 2014. Forty infants aged 14–28 days (20 girls and 20 boys) were included as the study group and 40 healthy infants (20 girls and 20 boys) as the control group. Two-milliliter venous blood samples were placed in hemogram tubes with K_2EDTA. Plasmas were performed using the enzyme-immunoassay method. Kisspeptin levels were expressed as as ng/ml. **Results:** Mean plasma kisspeptin levels in the breast growth group was 0.55 ± 0.16 ng/ml and in the control group was 0.48 ± 0.1613 ng/ml. Plasma kisspeptin levels differed significantly between the two groups ($P=0.039$). Significant correlations were determined between plasma kisspeptin levels and LH levels ($P=0.05$, $r=0.312$). **Conclusion:** In this study, plasma kisspeptin levels were identified in newborns. Elevated kisspeptin in newborns breast growth shows that kisspeptin may be involved in the physiopathology of breast growth in newborns. **Funding:** Funded by the Scientific and Technological Research Council of Turkey (TÜBİTAK).

P3-1085

Circadian Variation in Cortisol Concentration in Mother's Milk

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Background: In mammals, maternal glucocorticoids are transmitted through breast milk, particularly under stressful circumstances. In humans, it is unclear whether milk cortisol levels are dependent on stressful perinatal circumstances, such as preterm birth. **Objective and hypotheses:** Our aim was to compare cortisol concentrations in breast milk of mothers of very preterm infants (GA $<$32 weeks) to breast milk cortisol concentrations of mothers of full-term infants (GA $\geq$37 weeks). We expected to find higher cortisol concentrations in preterm breast milk. **Methods:** Breast milk samples from five preterm mothers and five full-term mothers were obtained weekly in the

first month *postpartum*. After hexane extraction, cortisol concentrations were assessed by our extensively validated LC–MS/MS method. Longitudinal changes in cortisol concentrations, as well as the influence of time of collection, were analysed by generalised estimating equations. Results are shown as β (95% CI). **Results:** No significant difference in cortisol concentration was found between groups: −31.7 (−72.4; 9.1), $P=0.13$. Concentrations were dependent on the time of collection, with the highest cortisol level between 0600 and 1200 h: 48.6 (45.3; 51.8), $P<0.001$. **Conclusions:** We found no difference in cortisol level between preterm and full-term breast milk. Instead, our study provided evidence for diurnal rhythmicity in human milk cortisol concentration. To explore this further, we are now conducting a study in which healthy full-term mothers are requested to collect ten paired breast milk and saliva samples over 24 h. We hypothesise that cortisol concentrations in breast milk follow a diurnal rhythm, parallel to the salivary cortisol concentration.

P3-1086

Usefulness of ultrasonography for detecting adrenal haemorrhage in neonates with relative adrenal insufficiency

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Background: Relative adrenal insufficiency (RAI) may be associated with neonatal adrenal hemorrhage (AH). **Objective and hypotheses:** The purpose of this study was to investigate the usefulness of ultrasonography for detecting AH in steroid treated neonates with RAI. **Method:** A retrospective analysis of 52 corticosteroid-treated patients with RAI at a neonatal intensive care unit of a tertiary center from January 2006 to April 2014 was performed to assess for the prevalence of adrenal hemorrhage and to identify factors associated with RAI. In addition, 17 patients who had been diagnosed with AH from January 2000 to June 2014 were investigated retrospectively to examine the clinical characteristics of the patients. **Results:** The median gestational age of the 52 patients with RAI was 27 + 2 weeks and their median birth weight was 878 g. The basal cortisol levels before and after corticosteroid treatment were 6.2 and 8.0 μg/dl, respectively. Ultrasonography was performed for the 52 patients and none showed evidence of adrenal hemorrhage. For those 17 patients who had been diagnosed with AH, 15 were born full term while two were born premature. Four of the 17 patients were large for gestational age. The reasons for the initial abdominal ultrasonography were septicemia ($n=7$), sacral dimple and single umbilical artery ($n=1$), abnormal prenatal ultrasound with suspected adrenal mass ($n=7$), and acute scrotum ($n=1$). Sixteen patients had unilateral AH of which 14 were right sided. Only one patient with associated sepsis, jaundice, anemia, and thrombocytopenia had bilateral AH and also showed signs of adrenal insufficiency requiring steroid treatment. **Conclusion:** Abdominal ultrasonography is not necessary for the detection of adrenal hemorrhage in corticosteroid treated neonates. However, adrenal function and ultrasonographic evaluation may be required in those neonates with septicemia, severe anaemia, prolonged jaundice, and/or thrombocytopenia.

P3-1087

Differences in Leptin Levels Between Newborns with and without Intrauterine Growth Restriction Born in the Hospital Gineco Obstétrico 'Isidro Ayora' of Quito-Ecuador. Year 2013–2014

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Background: Obesity has increased drastically in the last few years. It's well known the connection between intrauterine growth restriction (IUGR) and the development of metabolic syndrome based on the thrifty phenotype. Some studies have proposed that a poor intrauterine environment could lead to the development of chronic conditions later in life, and its believed leptin is involved in this process. **Objective and hypotheses:** Establish the mean of leptin in the full term newborns born in the Hospital Gineco-Obstétrico 'Isidro Ayora' and the influence of intrauterine growth restriction in this mean. Leptin levels found in full term newborns born in the Hospital Gineco-Obstétrico 'Isidro Ayora' with IUGR are significantly lower than the levels found in newborns without IUGR. **Method:** Comparative cross-sectional study with 90 full term newborns randomly selected divided into two groups: Group A: 45 newborns without IUGR and Group B: 45 newborns with IUGR. All the newborns met the following criteria: normal singleton delivery, with Hispanic parents, and a 5 min APGAR score ≥ 7. We used cord blood to measure leptin concentrations with an ELISA method. **Results:** Serum leptin concentrations were significantly lower in IUGR newborns than in newborns without IUGR (3.06 ± 2.22 ng/ml vs 4.64 ± 2.69 ng/ml; $P=0.0032$). Serum leptin concentrations were higher in female than in male (5.06 ± 2.55 ng/ml vs 2.59 ± 1.93 ng/ml). Serum leptin levels were positively correlated with birth weight and gestational age. **Conclusion:** Lower serum leptin concentrations found in IUGR newborns will indicate that an alteration in the intrauterine environment will lead to change in endocrine axes and will result in excessive weight gain, fat storage, and insulin resistance. These levels are apparently lower in both groups compared to the levels found in Caucasian newborns.

P3-1088

Leptin and Neuropeptide Y Levels in Newborns

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Background: Several studies have investigated leptin and NPY levels in children, but the information for newborns in the literature is limited. **Objective and hypotheses:** The aim of this study was to determine leptin and neuropeptide Y (NPY) levels in between 14 and 28-days newborns. **Method:** This prospective study was performed in the Erzurum Atatürk University Medical Faculty Research Hospital Neonatal Clinic, Turkey, between July and December 2014. Sixty-two 14–28-day-old babies, 26 female and 36 male, were included in the study. Patient age, height and body weight were recorded. Feeding status was recorded. Babies were divided into two groups, those receiving breastfeeding only and those receiving breastfeeding and formula. Plasma leptin levels were measured by the enzyme amplified sensitivity immüno assay and plasma NPY levels were measured by the enzyme immüno assay method. Leptin and NPY levels were expressed as nanograms/milliliter. **Results:** In the 14–28 day-old-girls mean leptin level of was 4.25 ± 3.08 ng/ml and mean NPY level 24.79 ± 9.87 ng/ml. In the 14–28 day-old-boys mean leptin level of was 3.49 ± 2.52 ng/ml and mean NPY level 25.80 ± 9.58 ng/ml. No significant difference was also determined between leptin ($P=0.228$) or NPY ($P=0.144$) in terms of feeding status. No significant difference was observed between the sexes in terms of leptin or NPY levels (leptin $P=0.775$ and NPY $P=0.687$). **Conclusion:** There were no difference respect to feeding status and sex of leptin and NPY levels in the neonatal period.

P3-1089

Cord Blood and Maternal Serum IGF1,2, IGFBP3 Levels in Overweight Pregnants

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Background: Obesity or excess weight gain in pregnancy period cause increased insulin secretion even if glucose screening test is normal. The growth promoting effect of insulin may release somatotropic hormones, such as IGF1,2 and its binding proteins are involved in the regulation of foetal growth. **Objective and hypotheses:** In this study, we determined the changes of intrauterine growth factors (IGF1,2, and IGFBP3) in pregnants gained over weight during pregnancy period and evaluated its relation with birth weight. **Material and method:** The patient group was consisted of pregnant women ($n=75$) attending the Obstetric outpatient clinic. Patients had gained over weight during pregnancy period compared with normal weight gain pregnants ($n=46$). Insulin and c-peptide measured by ICMA, and IGF1,2, and IGFBP3 were analysed by ELISA. **Results:** Birth weight of newborns in the patient group (3.9 kg) were significantly high when compared with the control group (3.2 kg) ($P<0.05$). IGF2 and IGFBP3 levels were significantly high in patient group (maternal IGF2: 615 ng/ml, IGFBP3: 3395 ng/ml; cord IGF2: 476 ng/ml, IGFBP3: 1632 ng/ml) ($P<0.05$) when compared with controls. In the patient group maternal and cord IGF2 and HOMA-IR level were positively correlated with birth weight. **Conclusion:** To become overweight or obese in pregnancy period may be responsible increased foetal IGF2 level and nutrient flux due to hyperinsulinaemia can lead to increased birth weight.

P3-1090

Crystal Formation in the Meibomian Glands as Diagnostic Proof of Pseudohypoaldosteronism Type I

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Background: Pseudohypoaldosteronism type I (PHA1) is a rare disease of mineralocorticoid resistance (MR). Neonatal manifestation leads to life-threatening dehydration due to massive salt-loss, acidosis and frequently, failure to thrive. Two clinically and genetically distinct forms exist, namely systemic and renal PHA1 caused by mutations in the subunit genes (*SCNN1A*, *SCNN1B*, *SCNN1G*) of the epithelial sodium channel (ENaC) and mineralocorticoid receptor coding gene *NR3C2*. **Case presentation:** After an uneventful pregnancy, a eutrophic term male newborn presented poor feeding and some degree of respiratory distress within the first hours of life and was admitted to a neonatal unit. Family history was inconspicuous, as he was the second child of non-related Turkish and otherwise healthy parents. Antibiotic therapy to treat suspected neonatal infection was initiated immediately, as was additional intravenous fluid support, leading to apparent stabilisation. Unfortunately, on the 6th day of life his condition began to progressively deteriorate due to respiratory distress secondary to dehydration and severe electrolyte-imbalance as in neonatal manifestation of congenital adrenal hyperplasia with hyponatraemia, hyperkalaemia and metabolic acidosis. Medical therapy with a stress dose of hydrocortisone was attempted without convincing success. The boy was therefore referred to the neonatal ICU of our tertiary medical centre on his 7th day of life. Surprisingly, neonatal screening revealed normal 17-a-hydroxyprogesterone levels (17-a-OHP), but elevated plasma renin and aldosterone concentrations at the same time. Of note,

impressive salt-crystal formations on the eyelids were macroscopically visible on both sides! This is attributable to salt loss via the excretory meibomian glands, known to be specific clinical proof of a severe manifestation of systemic PHA1. Mutational analysis revealed a compound heterozygous *SCNN1B* mutation. **Conclusion:** This infant's clinical appearance provided impressive proof of primary PHA1. Life-saving specific therapy could be initiated in a timely manner.

P3-1091

Transient Neonatal Hypoparathyroidism Secondary to an Unknown Maternal Parathyroid Adenoma

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Background: Transient neonatal hypoparathyroidism (hPT) by inhibition of fetal parathyroid secondary to undiagnosed asymptomatic hyperparathyroidism (HPT) in the mother often debuts as late neonatal seizures. **Objective and hypotheses:** To emphasise the indication of maternal metabolic study (Cacium-Ca-, Phosphorus-P- and PTH) in addressing late neonatal hypocalcemia, especially in the case of late neonatal hypocalcemic seizures. **Method:** We report the case of a male new born, the result of pregnancy and childbirth without incident. Mother of 33, healthy, two episodes of renal colic. The new born presented on the 9th postnatal day partial seizures. In the metabolic screening, hypocalcemia 5.4 mg/dl and hypomagnesemia 1.2 mg/dl. Receive calcium gluconate infusion and magnesium. Seizures last for 24 h. Cranial ultrasound and EEG were normal. iPTH lower limits of normal (15 pg/ml). He received oral contributions of calcium, magnesium and cholecalciferol until complete metabolic normalization at the 4th month of life. In the extension study the mother showed calcemias between 10.2 and 10.5 mg/dl, P and Mg normal, elevated iPTH (between 95 and 113 pg/ml) and hypercalciuria. Parathyroid ultrasound and scintigraphy, evidenced left higher adenoma of 2.5 cm. Video-assisted parathyroidectomy is performed with subsequent analytical standardization. **Conclusion:** i) In a late neonatal hypocalcemia, the study of maternal calcium-phosphate metabolism is required since the mother HPT is usually asymptomatic in most cases. ii) The diagnosis of a maternal hypercalcemic HPT is simple, being more unusual the diagnosis of HPT with normal-slightly elevated Ca and normal P such as we present. Late neonatal seizures may be the first expression of an undiagnosed maternal parathyroid adenoma, so the study of an apparently healthy mother is a benefit for both. iii) The therapeutic approach of a transient neonatal hPT includes contributions of Ca and vitamin D and frequently Mg. The metabolic evolution is standardization in a few weeks.

P3-1092

Relations of Birth Chest Circumference to Blood Serum IGF1 in the Newborn Free of Life-threatening Disease: Possible Role of Birth Body Weight in Addition to Respiratory Supportive Treatment

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Background/objective and hypotheses: Chest circumference (CC) is related to intrauterine growth rate as well as to development-function of respiratory system. We evaluated the relevance of birth body weight (BW) in birth CC (BC) relations to blood serum IGF1 after control for preterm birth (PTB), oxygen (O_2) supplementation as $\%O_2$ in respiratory gases (O_2R) and assisted ventilation of any kind (AV) in the newborn (NWB) without life-threatening disease. **Method:** Data available in each NWB: i) gender (SEX), gestational age (GA, unit:complete week), BW (unit:gr), BC (unit:cm), presence/absence of BW $<$ 10th centile for GA (SGA) or of PTB defined as GA $\leq$ 36, and ii) same-day records of AV, O_2R, and IG1 RIA-measurements (unit:μM/dl) at one of the first 5 postnatal days (x), 5 days after x(y) and 10 days after x(z), of postnatal age (PNA;unit:day). NWBs with any among total parenteral nutrition, life-threatening disease, diabetes mellitus (DM), endocrine diagnosis out of DM, clinically relevant trunk trauma or DM in mother were excluded. 78 NWBs were included (male SEX,n,43; PTB,n,46; SGA,n,20; GA range = 28–42; BW range = 1200–4150; BC range = 22.0–39.0; presence of O_2R,n,x = 22,y = 11,z = 1; presence of AV,n,x = 8,y = 4,z = 1). Natural log-transformed IGF1 (IGF1-LN) resulted near-normally distributed. Multiple Linear Regression (MLR) was used (computations; male SEX, PTB, AV, condition present = 1, condition absent = 0). **Results:** MLRs with IGF1-LN as outcome showed a significant partial correlation (PC) coefficient (r) of BC PCs with IGF1-LN when including as predictors PNA, O_2R and AV chronologically corresponding to outcome, as well as SEX, PTB and BC (BC vs IGF1-LNx, r:0.37, P: 0.0012; BC vs IGF1-LNy, r: 0.40, P: 0.0005; BC vs IGF1-LNz, r: 0.29, P: 0.0142), while no significant r of BC PCs with IGF1-LN at x, y or z was observed in MLRs including i) IGF1-LN as outcome and ii), as predictors, PNA, O_2R and AV chronologically corresponding to outcome as well as SEX, PTB, BC and BW (R2 of MLR models, 0.27–0.54, significant in all cases). **Conclusion:** BW could be involved in BC relations to IGF1-LN not explained by SEX, PTB, PNA, O_2R and AV in not-life-threatened NWBs.

P3-1093

Relations of Birth Chest Circumference to Blood Serum IGFBP3 in the Newborn Free of Life-threatening Disease: Possible Role of Birth Body Weight Beyond Blood Serum IGF1 and Respiratory Supportive Treatment

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Background/objective and hypotheses: Chest circumference (CC) is related to intrauterine growth rate as well as to development-function of respiratory system. We evaluated the relevance of birth body weight (BW) and blood serum IGF1 (IG1) in birth CC (BC) relations to blood serum IGF-binding-protein-3 (IB3) after control for preterm birth (PTB), oxigen (O_2) supplementation as $\%O_2$ in respiratory gases (O_2R) and assisted ventilation of any kind (AV) in the newborn (NWB) without life-threatening disease. **Method:** Data available in each NWB: i) gender (SEX), gestational age (GA, unit:complete week), BW (unit:gr), BC (unit:cm), BW $<$ 10th centile for GA (SGA), PTB defined as GA $\leq$ 36 and, ii) same-day records of postnatal age (PNA;unit:day), O_2R, AV and IG1-IB3 RIA measurements (unit:μM/dl) at one of the first 5 postnatal days(x), 5 days after x(y) and 10 days after x(z). 78 NWBs without any among total parenteral nutrition, life-threatening disease, diabetes mellitus (DM), endocrine diagnosis out of DM, malformation, clinically relevant trunk trauma or DM in mother were included (male SEX,n,43; SGA,n,20; GA range = 28–42; BW range = 1200–4150;BC range = 22.0–39.0;PTB,n,46; presence of O_2R,n,x = 22,y = 11,z = 1; presence of AV,n,x = 8,y = 4,z = 1). Natural log-transformed IB3 (IB3-LN) resulted near-normally distributed. Multiple Linear Regression (MLR) was used (computations; male SEX, PTB, AV, condition present = 1, condition absent = 0). **Results:** MLRs with IB3-LN as outcome showed a significant partial correlation (PC) coefficient (r) of BC PCs with IB3-LN when including as predictors either i) PNA, O_2R and AV chronologically corresponding to outcome, and SEX, PTB and BC (BC vs. IB3-LNx, $r = 0.35$, $P = 0.0022$; BC vs IB3-LNy, $r = 0.47$; $P = 0.0000$; BC vs IB3-LNz, $r = 0.53$, $P = 0.0000$), or 2)PNA, O_2R, AV and IG1 chronologically corresponding to outcome and SEX, PTB and BC (BC vs. IB3-LNx, $r = 0.30$; $P = 0.0101$;BC vs. IB3-LNy, $r = 0.30$; $P = 0.0104$;BC vs. IB3-LNz, $r = 0.51$; $P = 0.0000$), while MLRs showed no significant r of BC PCs with outcome IB3-LN at x, y or z when including as predictors PNA, O_2R and AV chronologically corresponding to outcome, as well as SEX, PTB, BC and BW (R2 of MLR models, 0.38-0.66, significant in all cases). **Conclusion:** BW appeared more able than IG1 chronologically corresponding to IB3-LN in explaining BC relations to IB3-LN after control for SEX, PTB, PNA, O_2R and AV in not-life-threatened NWBs.

P3-1094

EPIPEG-PREMEB Proyect. Clinical Situation before 12 months go on a SGA Population

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Background: Cohort SGA in North of Spain – EPIPEG. **Objective and hypotheses:** Establish a SGA cohort for monitoring, assessment catch-up, and analysis of middle-environmental and social factors. **Method:** We study live births in singleton pregnancies in our hospital during 2012–2014, and are classified according age gestation (EG) and weight/height (Spanish growth 2008). Visits were made at 0, 3, 6, 9, 12 months, with measurements weight, height and perimeter. Blood samples are analyzed and be stored is obtained. **Results:** 80 PEG recruited in 18 months (♂44, 55%). Epidemiological data: average age 32.2 years mother brothers previous SGA 11/80 (14%); maternal smoking during pregnancy 32/80 (40%), 4 (3–15) cigarettes/day; worker during pregnancy 55/80 (68%), of which 80% with $>$ 3 h walking/day; drugs during pregnancy 24/80 (30%), 70% for asthma, 20% L-thyroxine and 10% other. Pathologies associated: 41/80 (53%) (gestosis, eclampsia, DM, thyroiditis, psychogenic stress). Childbirth: a term 52/80 (67%), eutocic 68/80 (85%). Facts children at birth: middle weight DS -2.6 (-3.5 to 2.0), average size DS -2.5 (-3.2 to 2.1), for sex and EG. Lactation exclusive breast: 60/80 (75%) during the 1st month of life. RN income or pathology in the 1st month of life 20/80 (25%). PEG cases that have reached 12 months of follow up 48 cases. Income over 12 months 2/48 (4%) (bronchitis). With 12 months of life have 7/48 cases (15%) did not catch up with adequate P and/or T $<$ P10, 28/48 cases (60%) catch up very fast with P and/or T $>$ P90. **Conclusion:** The age of the pregnant, their lifestyle (snuff, stress and work) and regular medications (asthma), is causing of SGA. These children seem to require greater use of artificial feeding, a higher rate of hospital admissions at birth than children with PAG, but later is not a disease risk population. However detected since 75% of the RN SGA present a metric inappropriate development with year of life, which may have future implications. **Funding:** Pfizer international research grants were used for starting this study and for buying clinical material and a personal computer.

P3-1095

McCune–Allbright Syndrome in a Male Newborn with Hyperthiroydism

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Introduction: McCune–Albright syndrome (MAS) is a rare disease defined by café-au-lait spots, gonadotropin-precocious puberty and fibrous dysplasia. It could be associated with others endocrinopathies: thyroid involvement as a common feature. The prevalence is very low, being outstanding the neonatal diagnosis, especially in males. **Case presentation:** A male term newborn with a café-au-lait extensive spot involving the back, arms, legs and scrotal area, was hospitalized in the neonatal unit at 12 h of life with respiratory distress, which disappears after 48 h. There were no family pathologic history, neither parent's blood relatives. On day of life (DOL) 5 he presented jaundice, acholia and chyluria, without hepatomegaly. Conjugated bilirrubin reached 15.95 mg/dl on DOL 17: total bilirubin was 20.2 mg/dl. Common causes of cholestasis were discharted. TSH was 0.1 μIU/l, thryroxine (T_4) 32.7 pg/ml and triiodothyronine (T_3) 6.44 pg/ml. Anti-thyroid antibodies were negatives. Thyroid sonography was normal. In DOL 12, he started respiratory distress and tachycardia. He initiated propranolol, lugol and methimazole. He developed dilated left cardiac cavities and slight pericardial effusion. Thyroid profile normalized in 30 days. Bilirubin decreased but GOT and GPT increased up to 280 and 499 U/l. Basal GH was 11.8 ng/ml. Cortisol, and growing factors were normal. Radiological image showed ground glass density, forming the pattern of polyostotic fibrous dysplasia. On DOL 45, he showed haematological profile of aplastic anaemia. Bone marrow exam indicated selective erythoblastopenia. The café-au-lait spot was biopsied, being compatible with the typical macule of MAS. Karyotype was normal. Results for genetic testing for the gene GNAS1 are still unknown. **Conclusions:** The diagnosis of MAS must be suspected in a newborn with fibrous displasia, café-au-lait macules and endocrinological disorders, despite the low incidence or male condition. Early treatment is essential; It's not enough to diagnose the entities which comprises, but the possible side effects of the drugs and their impact on children's development.

P3-1096

Role of Notch1-Dll4 Signalling Pathway in Mice Model of Oxygen-induced Retinopathy

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Background: Notch1-Delta-like ligand 4 (Dll4) signalling pathway has a biological effect of negative feedback regulation to VEGF in retinal vascular development process. There are few studies on the inhibition of Notch1-Dll4 signalling pathway in ROP and the regulatory pathway of VEGF. **Objective and hypotheses:** To investigate the role that Notch1-DLL4 signal pathway played in the oxygen-induced retinal neovascularization of mice by analyzing the expression of DLL4, VEGFR-1, and VEGFR-2 in retinal neovascularization. **Method:** Sixty 7-day-old mice were divided into oxygen-induced retinopathy group and control group. We took ten mice from each group at postnatal day 7 (p7), p12 and p17 respectively, and then used the retinas to extract RNA. We detected mRNA expression of DLL4, VEGFR-1 and VEGFR-2 by RT-PCR. **Results:** VEGFR-1 expression of retinopathy group was lower than the control group in p17. $P=0.022$). There was no statistically significant difference in VEGFR-2 expression between these two groups in each timing. $P>0.05$. DLL4 expression of retinopathy group became lower in p12 and p17. $P=0.022$). As time went on, the expression of VEGFR-1 and DLL4 protein decreased ($P<0.05$), and that of VEGFR-2 increased $P<0.05$) in retinopathy group. In control group, the expression of VEGFR-1 and DLL4 protein didn't change a lot from p7 to p17 ($P<0.05$), and that of VEGFR-2 increased $P=0.001$. It showed positive correlation between DLL4 and VEGFR-1, $r=0.905$, $P0.001$. **Conclusion:** Notch1-DLL4 signalling pathway may be involved in the regulation of VEGF in the process of retinal angiogenesis. The expression of DLL4 was inhibited in oxygen-induced retinopathy mice during the formation of neovascularization, so it failed to show negative feedback regulation to VEGF. DLL4 restrained the expression of VEGF by the up-regulation of VEGFR-1.

P3-1097

Experience in Insulin Pump Therapy in the Treatment of Neonatal Diabetes

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Background: Neonatal diabetes (ND) at first 6 months and its frequency is one in 500 000 newborns. There are some difficulties in its treatment, due to low demand and high sensitivity to insulin. **Case presentation:** We present the experience in insulin pump therapy treatment. A 13 days girl was taken to Regional Children's Clinical Hospital in Krasnodar. It was the child from the1st pregnancy with toxicosis in the one st trimester, threat of termination in the 2nd trimester and with the – FPI – in the 3d trimester. The child was born of 2150 g on the 36th week of pregnancy. Due to reduced response and inspection, weak physiological reflexes, sluggish sucking and the 27 mmol/l hyperglycemia on the 12th day it was decided to start with i.v. insulin to 0.05 UN/kg per h via infusion pump. Having the lability of the DM currents, the tendency of the problem of injection of small doses of insulin with syringe pens and inconvenience of constant intravenous infusion, the child was transferred to pump insulin delivery on its 53d-day of life. It was used the basal mode of

delivery of insulin for each feed at a dose of 0.05 UN within 1 h (0.002 UN/kg per h), due to the fact that modern pumps are not suitable for the introduction of low doses of insulin with the help of bolus scheme. Glycaemia with the intravenous insulin is 20,9-16,4-2,9-12,6-10,1-1,5-4,6-9,7 mmol/l, the dynamics of glycemia on the background of continuous s.c. administration of insulin is – 13,5- 16,5- 10,4-11,0-9,5-7,5-8,5-6,5-4,0 mmol/l. On hospitalizing it was HbA1c −5.5% (2.9–4.2% – norm); C-peptide <0.1 ng/ml (0.9–4.0 – norm), after 1 month C-peptide is 1.93 ng/ml. In the 4 weeks was noted digestive disorders (lactase deficiency) insufficiency of the exocrine functions of the pancreas, which was corrected substitution therapy of pancreatic enzymes and in taking gidrolizirovanny mixture. Putting on weight for 2 months was 1.5 kg, glycaemia, it was returned to normal on the 7th week of life. **Conclusion:** Insulin pump therapy effective in the treatment of neonatal diabetes.

P3-1098

Case Presentation; a Neonate Presenting to a District General Hospital with Isolated Cranial Diabetes Insipidus Evolving to Partial Hypopituitarism

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Background: Hypernatraemia in a neonate can be common, and is usually due to high rates of insensible water loss and high urine output and subsequent dehydration. This is commonly resolved with supplementation of feeds. **Case presentation:** We present a preterm baby born at 35 weeks gestation who was born in good condition, did not require ventilation or intensive care support. The only support required was for feeding and thermoregulation. In the second week of life was noted to have weight loss and hypernatraemia thought to be hypernatraemic dehydration, therefore feed volumes were increased by bottle and nasogastric tube. Despite feed supplementation hypernatraemia persisted. Further investigation with paired osmolalities was suggestive of diabetes insipidus. Test dose of desmopressin showed weight gain and normalisation of investigations. Initial further endocrine tests were normal and patient was discharged home on desmopressin. Regular follow-up showed reduced height velocity at 3 years of age. Endocrine testing was repeated and showed inadequate response to glucagon stimulation test, therefore partial hypopituitarism was diagnosed. The patient was regularly reviewed in the joint endocrine clinic by tertiary Paediatric Endocrinologist and a course of GH treatment was initiated. **Conclusion:** Hypernatraemic dehydration not responsive to rehydration should be further investigated and diabetes insipidus considered. This case illustrates the importance of continuous monitoring and regular endocrine evaluation in identifying development of additional pituitary dysfunction.

P3-1099

Isolated GH Deficiency (IGHD) Associated with 7q11.23 Duplication Syndrome: a Case Report

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Background: Congenital pituitary hormone deficiency is etiologically heterogeneous and occurs in 1:4000 live births. Of those, isolated GH deficiency (IGHD) is the most common, followed by combined pituitary hormone deficiency with or without extrapituitary anomalies. **Objective and hypotheses:** Description of a patient with IGHD, associated with multiple additional organ anomalies. **Method:** Case report, Sequencing of *HESX1, SOX2* and *SOX3*, aCGH array. **Results:** Boy, presented at age of 8.7 years with short stature (SDS_h −3.46). No available perinatal data. At examination: mild mental retardation, developmental delay, mutism, loss of hearing, cleft palate, partial IGHD (peak GH 4.1 mU/l), 4-years delayed BA, cryptorchidism, refractive anomalies – high degree of hypermetropia and astigmatism, congenital cataracta. Anterior pituitary hypoplasia (MRI). Institution of rhGH, initially with 0.05 U/kg per 24 h s.c. No additional pituitary hormone deficits could be established during follow up; spontaneous and fast progressing puberty was evident. A 3.297 Mb duplication 7(q11.23q11.23)(72366111-75663082)x3[hg19], containing 59 genes and 13 pseudogenes was found by aCGH after the negative screen for *HESX1, SOX2 and SOX3*. There is 87% match with the autosomal dominant 7q11.23 microduplication syndrome. The estimated prevalence is 1:12 000 live births. Symptoms include mild facial dysmorphic features, mental retardation, developmental and speech delay, language and hearing difficulties, short stature, cleft palate, cryptorchidism, ocular abnormalities which showed an overlap with our patient's phenotype. Up to now, none of the 7q11.23 patients are described to have hypopituitarism. **Conclusion:** Patients with complex hypopituitarism phenotype associated with extrapituitary anomalies should undergo screening of the whole genome. This approach may contribute to new etiological insights of hypopituitarism. The 7q11.23 microduplication syndrome is very rare, up to now there are about 50 patients described worldwide. To our knowledge this is the first patient with IGHD due to pituitary hypoplasia as part of the 7q11.23 microduplication syndrome. **Funding:** Medical University Sofia, Grant 'Mlad issledovatel' Nr. 41-D, contract Nr. 30-D.

P3-1100

Cushing Disease in a Patient with Beckwith–Wiedemann: an Unusual Association

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Background: Beckwith–Wiedemann syndrome (BWS) is an overgrowth syndrome with an increased risk of embryonic tumors during early childhood. About 80% of patients with BWS show a molecular defect in the 11p15 imprinted region. Loss of methylation at the imprinting control region 2 (ICR2) is the most frequent defect which leads to a loss of expression of the *CDKN1C* gene, increasing cell proliferation. These epigenetic defects occur mostly as a mosaic event. **Objective and hypotheses:** We describe the first case of Cushing disease secondary to an ACTH microadenoma of the pituitary in a patient with BWS. **Method:** Methylation status of the 11p15 region was assessed with the ASMM-MQ6PCR. **Results:** A 19-year-old female patient has been referred in an endocrinology reference centre for excessive weight gain, hirsutism and secondary amenorrhea. Furthermore, she presented hemihyperplasia, and macroglossia was noticed by the parents during the first years of age. Blood test showed persistant elevated levels of cortisol through the 24 h, with elevated free urinary cortisol, and inappropriate ACTH levels. Dynamic tests (dexamethasone suppression tests and stimulating tests) confirmed the ACTH dependant hypercortisolism. MRI showed a microadenoma of the pituitary. After surgery, the adenoma was positive for ACTH staining. Methylation analysis of the 11p15 region found a loss of methylation at ICR2 in a mosaic state in the leucocytes (methylation index (MI): 17%, normal values 48–53), and a total loss of methylation in the adenoma (MI: 1%). **Conclusion:** We report the first case of pituitary adenoma in a patient with BWS diagnosed at the adult age. We showed that the molecular defect was present in a higher proportion in the pituitary gland, which may have led to the adenoma. This report highlights the variable expressivity of BWS, and such a diagnosis should be evoked in case of a tumoural process with hemihyperplasia.

P3-1101

Baseline Characteristics, GH Response, and Long term Evolution in 67 Patients with Pituitary Stalk Interruption According to the Initial Presentation

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Background: Pituitary stalk interruption syndrome (PSIS) is a frequent cause of congenital hypopituitarism. Patients are initially referred for the evaluation of hypoglycemia during the neonatal period or growth retardation during infancy or childhood. PSIS are either associated with extra-pituitary malformations (EPM+) or isolated (EPM−). **Objective and hypotheses:** To compare baseline characteristics, GH response, and long term evolution in patients with PSIS according to the initial presentation. **Method:** 67 patients with PSIS followed at the Children's Hospital in Toulouse, France, between 1984 and 2014, were included. Data of different groups were compared: EPM− ($n=32$) vs EPM+ ($n=35$) patients, neonates referred for hypoglycemia ($n=10$) vs children referred for growth retardation ($n=44$). **Results:** All cases were sporadic with a male predominance (63%). Median age at diagnosis was 2.5 years (range 0–16.3 years). All patients had GH deficiency at diagnosis. Compared to children referred for growth retardation, neonates often displayed a hypogonadotropic hypogonadism (frequently associated with micropenis and cryptorchidism), multiple hormone deficiency, and absent anterior pituitary ($P=0.0180$, 0.0002, and 0.0017 respectively). Sixteen patients (36%) referred for growth retardation had neonatal hypopituitarism features. Compared to EPM− patients, EPM+ patients were diagnosed earlier (1.4 years vs 4.1 years, $P=0.0004$) and had more often multiple hormone deficiency (especially ACTH and TSH deficiencies) and absent pituitary stalk ($P=0.0151$ and 0.0310 respectively). Height gain after 2 years of GH treatment and adult height were similar in the four groups. **Conclusion:** PSIS patients diagnosed during neonatal period or with associated EPM (syndromic PSIS) have a more severe hormonal impairment and MRI abnormalities. GH response is similar in all groups.

P3-1102

Clinical Characteristics of Children with Congenital Combined GH Deficiency without Associated Syndrome in Belgium

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Background: Despite the fact that pituitary stalk interruption syndrome (PSIS) is a frequent finding in children with combined GH deficiency (CGHD), clinical data are still limited and the growth response to GH treatment has not been evaluated in comparison with CGDH with a normal stalk. **Objective and hypotheses:** To report the clinical and hormonal findings and evaluate the short term growth response to GH in Belgian children with congenital non-syndromatic form of CHGD presenting with and without PSIS at MRI. **Method:** Fifty-nine children with a congenital form of CGHD without additional cerebral anomalies, who were started on GH between January 1996 and December 2011, were retrieved from the national GH database. MRI,

hormonal and growth data in the first year of GH therapy were evaluated. **Results:** In 36 (61%) of the patients, PSIS was diagnosed on MRI. In patients with and without stalk involvement the median peak of GH levels after stimulation were similar (1.6 and 1.5 ng/ml respectively), while TSH deficiency was present in respectively 97 and 82% of cases, ACTH deficiency in 78 and 52% ($P=0.04$), and LH/FSH deficiency in 61 and 35% ($P=0.04$). Median age at start of GH was respectively 5.6 and 4.9 years. The mean height gain in the first year of GH treatment was 11.8 cm ($\pm$ 4.0 cm) or 1.2 SD ($\pm$0.77 SD) and 11.0 cm ($\pm$5.7 cm) or 0.77 SD ($\pm$1.0 SD), which remained non-significant after adjustment for age at start GH. **Conclusion:** Pituitary stalk anomalies are a frequent finding in patients with congenital non-syndromatic CGHD. Compared to congenital CGHD patients with a normal stalk, PSIS is associated with more frequent occurrence of ACTH and LH/FSH deficiencies, but a similar initial growth response to GH treatment. **Funding:** This work was supported by the BESPEED.

P3-1103
Pitfalls in Reporting of Paediatric Pituitary Scans

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Objective: MRI is the modality of choice to evaluate morphology of hypothalamic pituitary axis (HPA) and associated endocrinopathies. In the paediatric population it presents a diagnostic challenge because of small size and varied disease processes. We undertook a retrospective study to determine the pitfalls in reporting of pituitary imaging. **Methods:** Evaluation of pituitary MRI scans in 18 patients. We sought a second opinion from a paediatric neuro-radiologist and compared it with the local opinion of a general radiologist. We also evaluated the time delay, difference in diagnosis and the effect on the management. **Results:** Eighteen patients were recruited for the study, ten male, eight females with a mean age 7 years 10 months. The mean time between the scan and its first report was 12 days (range: 0–54); whilst the mean time between the scan and the second opinion was 53 days (2–183). 11 patients presented with varying endocrine pathology namely GH deficiency, precocious puberty, congenital hypothyroidism, premature thelarche and hypogonadotrophic hypogonadism. Seven patients with non-endocrine pathology were excluded from analysis. Specialist opinion on MRI was different from the initial report in nine out of 11 patients. Four diagnosed as pituitary microadenoma were either normal or incidental pars intermedia cyst. One diagnosed as hypothalamic hamartoma was an artefactual abnormality. One diagnosed as possible Langerhan cell histiocytosis with thickened infundibulum was considered a congenital malformation. Two scans reported as normal or possible bulky pituitary underwent rescanning for further information. One scan was amended with additional findings of thickening of skull bones, suggesting a different pathology. **Conclusions:** False positive results in paediatric pituitary scans can lead to parental anxiety and wrong management plans. Paediatric pituitary MRI should be reported by specialist paediatric neuroradiologists in conjunction with the clinical multi-disciplinary team.

P3-1104
Long term Follow-up of a Child Treated with CyberKnife Radiosurgery for ACTH-secreting Pituitary Adenoma after Bilateral Adrenalectomy

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Background: First line treatment for an ACTH-secreting pituitary adenoma is transsphenoidal resection (TSR) of the tumor. Treatment options for patients with recurrent or persistent disease after surgery include another TSR, medical management, bilateral adrenalectomy, radiosurgery, or a combination of these. Radiosurgery represents a potentially curative treatment option for patients with recurrent or persistent disease. **Case presentation:** A boy was diagnosed at 10 years of age with an ACTH-secreting pituitary adenoma on the basis of symptoms (poor growth velocity, excessive weight gain and headache), laboratory findings (alterations of cortisol and ACTH circadian rhythm, cortisol and ACTH levels unsuppressed by dexamethasone suppression test, elevated urinary cortisol levels) and MRI imaging (4 mm microadenoma). He underwent TSR, but after few months ACTH and cortisol levels remained persistently high. As repeated neuroimaging were unable to identify the presence of a pituitary adenoma in spite of the persistent cushinoid features, we gave up the program to perform a new TSR and at the age of 13 years patient instead underwent a bilateral adrenalectomy followed by substitutive hormonal treatment with glucocorticoid and mineralcorticoid. After 18 months he developed a Nelson syndrome, characterized by very high ACTH levels and evidence of a microadenoma at the MRI. A second TSR was performed, but ACTH levels were persistently high after surgery. Then we decided to treat the patient with radiosurgery. At the age of 16 years he underwent a single treatment with CyberKnife (dose 20 Gy). At the age of 22 years, after a 75 months follow-up period, patient is still in remission and does not exhibit other pituitary hormone deficiency. **Conclusion:** Radiosurgery is a potentially curative treatment option in patients with recurrent and persistent pituitary adenoma. CyberKnife is a relatively new technology, but represents a valuable alternative option to the well-known Gamma Knife, as demonstrated in our patient.

P3-1105
Off-label Use of Vaptans in Children with Severe Symptomatic Hyponatremia due to SIADH

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Background: Vaptans, vasopressin receptor 2 antagonist, are used in adults to treat hyponatremia associated with congestive

heart failure, cirrhosis, and the syndrome of inappropriate antidiuretic hormone (SIADH). To date, in paediatric patients with SIADH there are few data about use of vaptans, still considered off-label. **Case presentation 1:** A 9-yo female with surgically treated suprasellar astrocitoma developed chronic hyponatremia (121–128 mmol/l) in SIADH, although no symptoms were present until she had a grand mal seizure episode. As chronic hyponatremia became symptomatic we chose tolvaptan as treatment option in association to orally levetiracetam. Daily dosage was 4 mg, increased to 7.5 mg due to persistent hyponatremia. As expected, she had polydipsia and polyuria lasting for 4 weeks after tolvaptan introduction. Actually, after 15 months of treatment, serum natrium levels are quite normal (131–135 mmol/l), with no adverse effects nor seizure episodes, so levetiracetam treatment was stopped. **Case presentation 2:** A 7-yo boy affected by rapid-onset obesity, hypothalamic dysfunction, hypoventilation and autonomic dysregulation (ROHHAD) syndrome was treated with tolvaptan as he developed SIADH. When he had a severe seizure episode due to hyponatremia (118 mmol/l), he started treatment with orally valproic acid in association to tolvaptan at 5 mg daily dosage, increased progressively to 10 mg daily due to persistent hyponatremia. Actually after 2 years of treatment serum natrium levels range from 137 to 145 mmol/l with no adverse effects nor seizure episodes. **Conclusion:** Tolvaptan should be considered as treatment option for symptomatic chronic hyponatremia in paediatric age, due to hypothalamic diseases. More data are needed about effectiveness and safety and serum natrium levels should be carefully monitored. Aquaresis due to vaptans do not cause loss of electrolytes so no repletion is needed.

P3-1106

Acquired Long QT Syndrome in a 14-year-old Boy with Panhypopituitarism

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Background: Acquired QT prolongation can be caused by electrolyte abnormality, myocarditis, cerebrovascular disease, drug intoxication and hormonal disorders such as hypopituitarism, hypothyroidism, and adrenal insufficiency. **Case presentation:** We describe a 14-year-old boy with hypopituitarism after transsphenoidal surgery (TSS) due to suprasellar mass who manifested bradycardia and QT prolongation on electrocardiogram. This subject complained of blurred vision and bilateral temporal hemianopsia for 1 month. Brain magnetic resonance image (MRI) revealed 3 cm sized suprasellar mass and TSS was performed. Germinoma was confirmed by pathology, and he received scheduled chemotherapy including cytoxan. On physical examination, his height and body weight were 143.1 cm (−2.22 SDS) and 40.3 kg (−1.34 SDS). He grew only 10 cm for past 4 years and had no pubertal sign. His pubic hair was Tanner stage I and testicular volumes were <4 cc. As the subject showed polyuria and urine was not concentrated during chemotherapy, he started desmopressin 0.1 mg bid. Before cocktail test was done, his heart rate decreased to 35 beat/min and blood pressure was 90/60 mmHg during sleeping. His heart rate was not increasing and QT interval was prolonged to 580 ms on E.K.G, so 0.025 mg/kg per h of isoproterenol, beta agonist, was started. Thyroidal and pituitary function test performed at that time, resulting in panhypopituitarism. Thyroid stimulating hormone and free T_4 were 0.15 μIU/ml and 0.67 ng/dl, respectively. The stimulated ACTH was 35.2 pg/ml despite cortisol was 1 ng/dl. After hormone replacement including hydrocortisone 5 mg three times (10 mg/m^2 per day) and levothyroxine 50 μg/day, isoproterenol were tapered off for 5 days and QT interval was normalized. Ten days after multiple hormone replacement, hormone levels were also corrected well and his vital sign and E.K.G were also stable. **Conclusion:** This case highlights that hormonal disorders should be considered as a cause of arrhythmia or prolongation of QT intervals and this can be prevented and cured by appropriate hormone replacement therapy.

P3-1107

Between 3 to 4 Years after Severe Traumatism Brain Injury 22% at Least of Children and Adolescents do have Persistent Pituitary Dysfunction

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Background: Traumatic brain injury (TBI) is common in childhood but long-term endocrine consequences are yet to be documented by prospective data. **Objective and hypotheses:** We have previously demonstrated in prospective study that, 1 year after severe accidental TBI (ATBI) or inflicted TBI (ITBI), children and adolescents may present pituitary and growth hormone (GH) dysfunction. We present here the follow-up of this population to determine whether or not early GH dysfunction may be persistent. **Method:** Our initial study included 87 patients (0–15 years old). After 1 year post-TBI 27/87 had presented GH dysfunction (two stimulated GH peak <7 ng/ml); 5/27 had GH deficiency (GHD) (GH peak <5 ng/ml, IGF1 <−2DS). The patients with GH dysfunction were included in the present study; clinical evaluation and pituitary hormonal testing (basal levels and dynamic GH tests) were performed between 3 and 4 years after TBI. **Results:** 27 children were included (22 ATBI, 5 ITBI), 18 underwent hormonal investigations (16 ATBI, 2 ITBI), two declined study, three were

lost and four missed hormonal evaluation at that time. Among the 18 investigated patients, two GHD (14.7 and 6.4 years old) started GH treatment 14 and 18 months post-TBI respectively, seven had normal pituitary function (2/7 were GHD at 1 year post-TBI) and nine had low stimulated GH peak. Among these nine patients, four were overweight, two had normal IGF1 levels, and three had low IGF1 with conserved growth velocity (one developed thyreotropic deficiency 18 months post-TBI). The GH treated adolescent remained GHD at the end of treatment. One normal girl had precocious puberty. **Conclusion:** 6/27 included patients had persistent pituitary dysfunction (5/27 somatotropic dysfunction) of whom four needed treatment. These results lead us to recommend a prolonged endocrine follow-up of children who presented GH dysfunction 1 year post-TBI. **Funding:** Supported in part by Pfizer SAS.

P3-1108

Causes and Consequences of Thickened Pituitary Stalk Found by MRI in Children and Adolescents with Central Diabetes Insipidus

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Background: Magnetic resonance imaging (MRI) of the hypothalamic-pituitary area is extremely useful in the investigation of patients with central diabetes insipidus (CDI) due to infiltrative processes. **Objective:** We aimed to associate pituitary stalk thickness with the etiology of CDI and hormone deficiencies. **Method:** A retrospective single-center study of 15 patients (four boys and 11 girls) with CDI was performed and clinical-epidemiological data and MRI characteristics studied. Median age at diagnosis of CDI was 9.7 years (range 1.3–15.6). The pituitary stalk was measured at its transversal part. Thickened pituitary stalk (TPS) was considered as >3 mm, (mild 3.1–3.9 mm, moderate 4–6.5 mm and severe >6.5 mm). **Results:** At the first MRI evaluation, pituitary stalk enlargement in seven patients varied from 4 to 30 mm (mild $n=1$, moderate $n=1$ and severe $n=5$). A diagnosis of germinoma was made in five of them (PST severe). Of the eight patients without TPS, two were diagnosed with Langerhans' histiocytosis (LCH) and six of idiopathic CDI (ICDI). Follow-up MRI was performed in eight patients without etiological diagnosis. Stalk increase was demonstrated in four of them (moderate $n=3$, severe $n=1$) in median time interval of 2.98 years (range 2.08–11.24). They were diagnosed with germinoma ($n=3$) and idiopathic ($n=1$) CDI. Stalk morphology was heterogeneous in patients with germinoma (normal $=1$, uniform $=1$, pyramid $=2$, V-shaped $=2$, round $=2$), uniform in LHC, and normal in half of the patients with ICDI. Two patients had GH deficiency and eight patients had combined hormone pituitary deficiency (germinoma $=7$). Etiology of CDI was germinoma ($n=8$), LCH ($n=2$) and idiopathic ($n=5$). **Conclusions:** i) Germinoma is the most common cause of CDI in childhood and adolescence; ii) The greatest degree of pituitary stalk thickness is associated with combined hormone pituitary deficiency. **Funding:** CIBEROBN. Instituto de Salud Carlos III and Fundación Endocrinología y Nutrición. Madrid, Spain.

P3-1109

Acute Phase Proteins and Endocrine Dysfunction after Traumatic Brain Injury in Childhood

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Background: Endocrine impairments, such as diabetes insipidus (DI), growth hormone deficiency (GHD) and, to a lesser degree, thyroid or cortisol deficiencies, have been reported after traumatic brain injury (TBI) in adults and much less in children both at the acute post-traumatic phase and after a lag period of time. However, no prospective data exist on the endocrine and acute phase protein response to TBI in childhood. **Aim/objective:** To unravel possible endocrine impairment and acute phase protein response after TBI in children hospitalized in a single pediatric Neurosurgery department. **Methods:** Twenty-one children (11 girls), age range 1.3–12.6 years, with TBI were prospectively enrolled and studied at three phases: at the acute phase and at 6 and 12–18 months following the injury. Five out of the 21 patients dropped-out at 6 months and three more patients at 12–18 months. The endocrine and acute phase protein assessment was performed at all time-points. **Results:** At the acute phase, GHD, as assessed by low IGF-1 levels, was found in 24% of cases, DI in 19% and subclinical hypothyroidism in 5%. Permanent endocrine dysfunctions 12–18 months after TBI were hypothyroidism and DI in 15% and low IGF1 levels in 6%. Contrary to literature data, prolactin levels were normal during the 1st and 2nd phase, with an increase observed in 12% of the cases 12–18 months after TBI. Moreover, S100b, a biomarker of brain damage was increased in all children at all phases, indicating a persisting neuronal damage 12–18 months after TBI. All children demonstrated a good spontaneous recovery with no clinically relevant permanent neurological deficits. **Conclusions:** Our results reveal a significant percentage of endocrine dysfunction in children after TBI, both at the acute phase and long after the incident. A subclinical persistent neuronal damage observed in all children calls for long-term surveillance of children post TBI.

P3-1110

Two Cases of Combined Pituitary Hormone Deficiency Proven to have Mutations of *GLI2*

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Background: *GLI2* is a transcription factor in Sonic Hedgehog signaling and implicated in ventral forebrain and pituitary development. *GLI2* mutations were reported not only in patients with holoprosencephaly but also in patients with pituitary hormone deficiencies without holoprosencephaly. Other phenotypes of *GLI2* mutations are midline facial defects, cleft hands and feet, and polydactyly. We report two patients with combined pituitary hormone deficiency, carrying *GLI2* mutations. **Objective and hypotheses:** Reporting two cases of combined pituitary hormone deficiency proven to have novel mutations of *GLI2*. **Method:** Genomic DNA was extracted from the patients, and 11 genes related to congenital hypopituitalism were screened on Miseq next generation sequencer. **Case 1:** The patient was born full term by vaginal delivery without fetal distress. He had cleft lip and palate, micropenis, cryptorchidism, GH, TSH, ACTH, LH, FSH and antidiuretic hormone deficiencies. A brain MRI showed a pituitary aplasia and an ectopic posterior lobe. **Case 2:** The patient was born full term by vaginal delivery without fetal distress. He had micropenis, cryptorchidism, GH, TSH, ACTH, LH and FSH deficiencies. A brain MRI showed a pituitary hypoplasia and an ectopic posterior lobe. **Results:** We identified heterozygous *GLI2* mutations: c.3544 C>T, p.Gln1182*(Case1) and c.3076dupC, p.Ser1025fs(Case2). **Conclusion:** The phenotypes of *GLI2* mutations are variable. Case 1 is the first case who has antidiuretic hormone deficiency with an ectopic posterior lobe in patients carrying *GLI2* mutations. Like case 2, in patients with only pituitary hormone deficiency, *GLI2* mutations may be identified more than expected.

P3-1111

AVP-NPII Gene Mutations and Clinical Characteristics of the Patients with Autosomal Dominant Familial Central Diabetes Insipidus

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Background: Familial central diabetes insipidus (DI), usually an autosomal dominant disorder, is caused by mutations in arginine vasopressin–neurophysin II (AVP-NPII) gene that leads to aberrant preprohormone processing and gradual destruction of AVP-secreting cells. **Objective and hypotheses:** To determine clinical and molecular characteristics of patients with familial central DI from two different families. **Method:** The diagnosis of central DI was established by 24-h urine collection, water deprivation test, and desmopressin challenge. To confirm the diagnosis of familial central DI, the entire coding region of AVP-NPII gene was amplified and sequenced. A total of eight affected patients and three unaffected healthy relatives from two families were studied. **Results:** Genetic analysis revealed a previously reported heterozygous mutation (p.C98X) in family A, and a heterozygous novel mutation (p.G45C) in family B, both detected in exon 2 of AVP-NPII gene. When we compared the clinical characteristics of the two families, we noticed that as the age of onset of symptoms in family A ranges between 4 and 7 years, it was <1 year in family B. Additionally, pituitary bright spot was present in the affected siblings, but absent in their affected parents. **Conclusion:** Familial central DI is a progressive disease, and age of onset of symptoms can differ depending on the mutation. Bright spot on pituitary MRI might be present at onset, but become invisible over time. Genetic testing and appropriate counselling should be given in familial cases of central DI to ensure adequate treatment, and to avoid chronic water deprivation that might result in growth retardation in childhood. **Funding:** This research was funded by the Scientific and Technological Research Council of Turkey (SBAG Project No: 112S513).

P3-1112

A Boy with Combined Pituitary Hormone Deficiency and Agenesis of Right Internal Carotid Artery: A Rare Association or a Simple Coincidence?

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Background: Congenital combined pituitary hormone deficiency (CPHD) may be associated with pituitary/extra pituitary abnormalities. Well-known causes are mutations in pituitary transcription factor genes. Agenesis of internal carotid artery (ICA) is a rare vascular anomaly that has been associated with CPHD. **Case presentation:** The patient is a 2-year old male, born at term to non-consanguineous parents, birth wt 3.2 kg, length 47 cm, no gestational or perinatal complications. Shortly after birth he developed symptomatic episodes of hypoglycemia with capillary glucose between 33 and 39 mg/dl. Insulin was not measured. He was treated with IV glucose infusion (16 mg/kg per min) until oral intake increased and IVF could be discontinued. He was discharged on the 6th day with q3h-breastfeeding. On F/U he showed poor growth, dropping below the 3rd percentile for wt and length, and micropenis and cryptorchidism were noticed. Hormonal work up at 5 months revealed glucose 69 mg/dl, IGF1 <15 ng/ml (n.v.27-114), IGFBP3: 583 ng/ml (n.v.600-2900), LH

0.4 mIU/ml (n.v.3-22), testosterone 9 ng/dl (n.v.72-340), FT4 0.7 ng/ml (n.v.0.6-1.2), TSH 4.73 mIU/l (n.v.0.8-6.), cortisol 21.4 ug/dl. The diagnosis was CPHD (GH + gonadotrophin deficiency). A cranial/sellar MRI showed an empty sella, interrupted pituitary stalk and absence of the right ICA with a complex arterial anastomosis supplying the middle cerebral artery on the right side. At 9 months the patient was started on *rh*GH and growth velocity doubled. He reached the 10th pc after 14 months of treatment. **Conclusion:** CPHD and ICA are rare disorders individually and even rarer together. Underlying mechanisms for this combination are unclear and may involve a single molecular abnormality that could primarily cause ICA and secondarily affect the blood supply of the developing pituitary, or affect both vascular and pituitary development simultaneously. This eleventh case of CPHD + ICA here described, together with the other ten already described, may stimulate the molecular research for the cause of this new clinical entity.

P3-1113

A Rare case of Congenital Hyperinsulinism Associated with Hypopituitarism due to Pituitary Stalk Interruption Syndrome

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Introduction: Congenital hyperinsulinism (CHI) is a rare genetic disorder that is characterised by persistent hypoglycaemia in infants and children. We are reporting a rare case of diffuse CHI who was also found to have hypopituitarism and several other congenital anomalies. A similar association has not been reported in literature. **Case:** A female baby was born at 42 weeks gestation with a birth weight of 4.185 kg (1.72SDS). She suffered shoulder dystocia and was ventilated for 12 days. Her persistent hypotension, hyponatremia and hypoglycaemia triggered further investigations. She was noted to have low free T_4 (5.3 pmol/l), undetectable TSH (<0.03 μ/l) and plasma cortisol (<50 nmol/l). She was commenced on T_4 and hydrocortisone. Her glucose requirement remained high at 20 mg/kg per min and a hypoglycaemia screen revealed raised insulin (90 pmol/l) and suppressed free fatty acids and ketones during hypoglycaemia confirming CHI. The hypoglycaemia was initially managed with high concentration dextrose infusion and intravenous glucagon. She was subsequently started on Diazoxide but developed cardiac failure; therefore it was replaced by subcutaneous Octreotide injections. This was later discontinued due to liver dysfunction. Genetic analysis was negative for *ABCC8, KCNJ11* and *HNF4A* mutations and microarray was normal. She was also noted to have pulmonary stenosis requiring balloon dilatation, unilateral choroidal coloboma, and facial dysmorphic features including single median incisor. MRI brain showed hypoplastic anterior pituitary gland with absent posterior pituitary and 18F DOPA PET CT scan showed a diffuse pancreatic lesion. She is now 3 year old and managed with continuous gastrojejunostomy feeds, hydrocortisone, T_4 and growth hormone. **Conclusion:** We report a rare association of diffuse persistent CHI and hypopituitarism in a patient with several other associated anomalies with probably an unidentified genetic aetiology. The described case highlights the importance of maintaining a high degree of suspicion for alternative diagnoses in infants diagnosed with hypopituitarism but have persistent hypoglycaemia.

P3-1114

Management of Risperidone Induced Hyperprolactinemia in an Adolescent with Severe Autism

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Background: Risperidone is a second-generation antipsychotic medication, which inhibits dopamine and serotonin receptors. Around half of children and adolescents treated with risperidone develop hyperprolactinemia. Chronic hyperprolactinemia can lead to osteoporosis, cardiovascular disease and delayed growth and puberty. There is no available guidance on management of antipsychotic induced hyperprolactinemia in children. We describe the challenges in the management of a teenage girl with severe autism who had significant problems with symptomatic hyperprolactinemia secondary to risperidone therapy. **Case:** A 15-year-old girl with severe autism was referred for Endocrinology consultation due to problems related to galactorrhea secondary to hyperprolactinemia. She was on risperidone (0.5 mg twice daily) from 13 years of age for severe behavioural difficulties with outbursts of aggression. At 15 years of age, she presented with excessive weight gain, galactorrhea and secondary amenorrhoea. Endocrine work up revealed a normal thyroid function and a very high prolactin concentration of 3053 mU/l (normal: 0–500). Macroprolactin concentration was 8%. The MRI scan of the pituitary was normal. Cabergoline 125 microgram three times a week resulted in gradual resolution of the symptoms with fall in plasma prolactin concentration to 958 mU/l over a period of 12 months. Risperidone was subsequently weaned and stopped. Frequent blood sampling to monitor prolactin concentrations was extremely challenging due to her severe behavioural difficulties. It was only possible to obtain blood samples, during the times, when the patient was anaesthetised for medical procedures. **Conclusion:** Cabergoline can help ameliorate the symptomatic hyperprolactinaemia secondary to risperidone therapy in children. Frequent monitoring of serum prolactin concentration is a challenge in this group of patients due to the underlying nature of the condition. It is important to develop evidence-based guidelines for optimal management of hyperprolactinemia in children and young people on antipsychotic therapy.

P3-1115

Stevens Johnson Syndrome in a Case with Type 1 Diabetes Mellitus: Relation or Coincidence?

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Background: Stevens-Johnson Syndrome (SJS) is an acute life-threatening dermatosis characterized by conjunctivitis, oral ulcerations, fever and erythematous macules. The most important etiological factors are infections and drugs including anticonvulsants and nonsteroidal anti- inflammatories. **Objective and hypotheses:** Cases with both SJS and type 1 diabetes mellitus have been reported rarely in the literature. Herein, we report a diabetic case of recurrent SJS due to different causes. **Method:** A 10-year-old boy was admitted to our department with a 3-day history of fever, oral mucosal ulcerations and skin lesions. The patient was not under any treatment apart from insulin. He was diagnosed with type 1 diabetes 4 months ago. He has history of SJS with amoxicillin 3 years ago and clarithromycin 4 years ago. Physical examination revealed oral mucosal ulcerations, haemorrhagic crust on the lips, and bullose lesions on his thrunk and penis. Laboratory tests, including CBC, serum electrolytes, liver and renal function tests, urine analysis and sedimentation rate were within normal limits. Chest radiography was also normal. Mycoplasma PCR was negative **Results:** The patient was diagnosed with unknown origin SJS and treated with methylprednisolone. The lesions progressively resolved in 5 days and methylprednisolone therapy was terminated. **Conclusion:** Type 1 diabetes mellitus is an autoimmune disease and associated with other autoimmune disorders such as thyroiditis and cealiac disease. SJS also occurs due to immune system defects. SJS may be associated with type 1 diabetes. New reports are required to define whether this association is a possible link in pathogenesis or coincidence.

P3-1116

Hormone Disorder and Vitamin Deficiency in Attention Deficit Hyperactivity Disorder (adhd) and Autism Spectrum Disorders (ASD)

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Objective: To evaluate thyroid hormones and antibodies, vitamins B12 and D levels, ferritin levels, adrenal and gonadal steroid levels in children diagnosed with ADHD and ASD. **Material method:** Patients between the ages of 2–18 years followed-up with the diagnosis of ADHD and ASD in the Van region were included in this study. The weights and heights of the patients were recorded and then the blood samples were obtained between 0800 and 0900 h. in the morning due to the diurnal variation of the hormone. 27 cases compatible with the patient group in terms of age and gender and who did not have the diagnostic criteria of ADHD and ASD were taken as the control group. **Findings:** While there was no significant difference between the groups for thyroid hormone levels statistically, there was a significant difference in terms of vitamins B12 and D and ferritin statistically. While the highest ferritin and lowest vitamin M12 and vitamin D levels were found in the ASD group, the vitamin D level in the ADHD group was significantly lower than that of the controls, too. There was no statistically significant difference between the groups in terms of adrenal and gonadal hormone levels. **Conclusion:** Our study is unique in the literature in terms of including and evaluating ADHD and ASD and the risk factors vitamin B12, ferritin, vitamin D, adrenal androgens, celiac disease and subclinical hypothyroidism. Besides, with the current study, we want to screen the levels and importance of supplementation of vitamin B12 and D in ASD and ADHD group patients and to especially emphasize the informing of the population about vitamin B12 and D deficiency in terms of prevention of these diseases and necessity of stimulation of the health workers in order to take the measures such as diet relieving the deficiency and supplementation.

P3-1117

Two Novel Mutations in GLI2 Gene in Two Unrelated Argentinean Prepuberal Patients, One with Isolated Growth Hormone Deficiency, and Another with Multiple Pituitary Hormone Deficiency, Both with Developmental Defects in Posterior Pituitary Gland

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Background: Congenital growth hormone deficiency may be isolated (IGHD) or multiple pituitary hormone deficiency (MPHD). The Sonic Hedgehog signalling (SHH) pathway has an important role in the pituitary development and growth, acting early in ventral forebrain. The SHH signalling mediates its effects through three zinc fingers proteins (Gli1, Gli2 and Gli3), which lead to activation or repression of target genes. Several heterozygous GLI2 mutations have been reported in patients with IGHD or MPHD with or without other malformations, most often, ectopic posterior pituitary and postaxial polydactyly. **Aim:** To analyse the presence of GLI2 gene alterations in an IGHD 46,XX patient with cleft lip/palate and ectopic posterior pituitary lobe (P1) and in a MPHD 46,XY patient with absent posterior pituitary lobe (P2). **Methods:** Automated sequencing of GLI2 gene from gDNA of affected subjects and relatives. *In silico* tools were applied to identify the functional impact of newly found

variants (Polyphen2, SIFT, Mutation Taster). **Results:** P1 was found to be heterozygous for the novel p.Arg231Gln variation, while P2 was found to be heterozygous for the novel p.Arg226Leu variation, as well as homozygous for the already described p.Met1444Ile and p.Leu1445Phe variations. Both novel variations affect highly conserved amino acids of the Gli2 protein and were not found in the databases of NCBI and Ensembl Genome Browser. In silico tools suggest that these variations would be disease causing. **Conclusion:** We report two novel heterozygous missense mutations in the GLI2 gene that affect the repressor domain of the protein and two homozygous missense mutations in the activator domain of the protein. Our study suggests that GLI2 gene would be one of the candidate genes to analyse when developmental defects in posterior pituitary gland are present. The highly variable phenotype found suggests the presence of additional unknown factors that could contribute to the phenotypic variation observed in these patients.

P3-1118

Pituitary Stalk Interruption Syndrome Presenting with Normogonadotropic Amenorrhea and Hypoprolactinemia

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Introduction: Pituitary stalk interruption syndrome (PSIS) is a rare congenital abnormality of the pituitary gland. Perinatal injuries, defective organogenesis or rare mutations of HESX1, LHX4, OTX3 and SOX3 are proposed to be the cause of PSIS in familial cases. It is characterized by the triad of a very thin or interrupted pituitary stalk, an ectopic (or absent) posterior pituitary and hypoplasia or aplasia of the anterior pituitary. Typical features are tertiary hypothyroidism, hyperprolactinemia and other pituitary hormone deficiencies. **Objective and hypothesis:** To present the clinical and hormonal characteristics of a patient with PSIS who was referred for primary amenorrhea. **Results:** A 16-year-old female was referred for primary amenorrhea. She was born at term without a history of birth asphyxia. She had no chronic illness. Parents were not related and target height was 161 cm (0.17 SDS). There was no family member with delayed puberty or amenorrhea. On physical examination, height SDS was −1.49, weight SDS was 1.63, pubertal development was delayed (Tanner stage B2P3). Hormonal analysis revealed a normogonadotropic state with low E_2 levels, central hypothyroidisim, low IGF1 and persistently low prolactin levels. Pelvic ultrasonography revealed small ovaries and uterus for age. Karyotype was 46,XX. Pituitary MRI showed anterior pituitary hypoplasia, an ectopic posterior pituitary and absent pituitary stalk. According to the findings in MRI, the patient was diagnosed with PSIS. Results of GH provocation tests suggested GH deficiency, and a low dose ACTH stimulation test revealed a normal cortisol response. **Conclusion:** We present a case of a PSIS with normogonadotropic amenorrhea and low prolactin levels. Despite the fact that this is a rare disorder, which typically presents with hyperprolactinemia, it should always be kept in the differential diagnosis of a patient with normogonadotropic amenorrhea and/or hypoprolactinemia.

P3-1119

Paediatric CNS Germ Cell Tumours: Endocrine Outcome

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Background: In paediatric CNS tumours, germ cell neoplasms usually produce endocrine disorders helping an early diagnosis. **Objective and hypotheses:** To describe presenting symptoms in paediatric CNS germ cell tumours and endocrine abnormalities on follow-up. **Methods:** We reviewed the records of children and adolescents aged under 14 who were followed in our unit presenting a CNS germ cell tumour. Endocrine abnormalities at diagnosis and over the follow-up period were recorded. **Results:** We studied 11 patients (ten female), aged at diagnosis 7.0–12.0 years. Hypothalamic origin was the most frequent (10/11) and chorionic gonadotropin was secreted in five cases. Reasons of consultation were neuro-ophthalmic signs/symptoms in eight cases and endocrine complaints only in three. Endocrine disorders, not leading to consultate, were also the presenting symptoms in other six cases. Seven children referred diabetes insipidus beginning 2–5 years before tumour diagnosis. Anterior hypopituitarism developed in all the hypothalamic lesions immediately after starting oncologic treatment. **Conclusions:** The management of paediatric germ cell tumours involves a multidisciplinary effort. Endocrine disorders usually occurred long time before neurological and ophthalmological symptoms, so identifying them may help to earlier diagnosis. Hormonal evaluation is mandatory as well on follow-up.

P3-1120

Description of Patients Diagnosed with Central Diabetes Insipidus, 14 Year Experience at the National Children's Hospital, Costa Rica

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Background: Diabetes insipidus is a heterogeneous clinical syndrome involving an alteration in water balance. When caused by a deficiency in the production of antidiuretic hormone (ADH) it's called central diabetes insipidus (CDI). It is difficult to establish

the cause of CDI in a good proportion of patients and thus classified as idiopathic in 10.4–55.2%, according to various studies. There are no previous studies in our population. **Objective and hypotheses:** To describe the epidemiology of patients diagnosed with central diabetes insipidus (CDI) in the National Children's Hospital, from January 2000 to December 2013. Is thought to be a disease with a low incidence in our country. **Method:** A retrospective study based on the clinical records of patients with central diabetes insipidus. Were analysed a total of 30 patients, after exclusion of some records. Qualitative and quantitative analysis of variables, measures of central tendency were used (mean, median and frequencies). **Results:** Of the total of 30 patients, there was a sex distribuion of 17 males and 13 females, no statistical difference. The incidence of central diabetes insipidus was of 2.6 cases per 100 000 habitants. The mean age at presentation was 60 months (1–154 months). At diagnosis, 83% of patients reported polyuria and was documented hypernatremia in 100% of cases and hyperosmolarity in 83%. The most common cause of CDI was the immediate posoperative period of suprasellar tumours, in 11 of the 30 patients (36%), which the most frequent was craniopharyngioma (64% of the tumors and 50% of the total CDI). The other most common hormone deficiency added to the CDI was central hypothyroidism, in a total of 11 patients. **Conclusion:** The CDI in Costa Rica is rare problem occurring in childhood at a mean age of 5 years. The most common cause are suprasellar tumours, of which the most common is the craniopharyngioma.

P3-1121

Pegvisomant in Child Acromegaly

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Background: Acromegaly is a rare childhood disorder. The use of a growth hormone (GH) receptor antagonist, pegvisomant, has shown great results in adults with acromegaly. We describe results of pegvisomant therapy in two girls with invasive GH pituitary macroadenomas. **Case presentation:** Case 1: A somatotroph pituitary macroadenoma was diagnosed in a 8-year-old girl with progressive tall stature (height: 148 cm, $>+3$ S.D.; growth velocity (GV):11 cm/year), GH hypersecretion without suppression during oral glucose loading (nadir serum GH: 34 mU/l), high serum IGF1 (691 ng/ml) and prolactin (270 mUI/l) levels. Bone age was 10 years. Transphenoidal surgical tumor removal was incomplete. Histological examination showed a mixed GH and prolactin-secreting adenoma. Serum IGF1 and GH levels remain high after surgery and cabergoline treatment (819 ng/ml, 20 mUI/l). Pegvisomant in combination with cabergoline quickly led to IGF1 normalisation (115 ng/ml) and growth arrest (GV: 0 cm/7 months). Case 2: A 15-year-old girl presented with clinical and biochemical evidence of acromegaly: tall stature (182 cm, >3 S.D., no GV available), pubertal stage IV, bone age 13 years, high IGF1 and GH serum levels (776 ng/ml, 109 mUI/l). Pituitary MRI revealed a large and invasive mass. She was treated with a combination of oestrogen -to accelerate epiphyseal fusion-, somatostatin analogs and pegvisomant titrated up to 40 mg/day. Medical treatment failed to normalize IGF1 and halt growth (GV:2 cm/6 months) but major weight gain was noticed ($+14$ kg/6 months). Therefore the tumour was partially resected by a trans-sphenoidal surgical approach. Histological characterization confirmed the diagnosis of GH-secreting adenoma. Pegvisomant adjuvant therapy was resumed to improve IGF1 serum level control (571 ng/ml after surgery and nadir GH: 8.7 mU/l) and halt physical growth. **Conclusion:** In childhood acromegaly, pegvisomant appears to be effective in stunting growth and normalizing IGF1 only after pituitary tumor debulking.

P3-1122

Case Series; Central Diabetes Insipidus Presenting to a District General Hospital

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Background: In a paediatric setting polydipsia can be a commonly reported symptom which is usually innocent and habitual in nature. Diabetes Insipidus is a rare cause of pathological polydipsia. A high index of suspicion must be used in patients who exhibit other symptoms alongside polydipsia and investigations considered. **Case presentation:** We present three patients who have presented to a district general hospital within a short period of time with subsequent diagnoses of Central Diabetes Insipidus (DI). Case A; a 12 year old boy presented with polyuria, polydipsia and poor appetite. Endocrine workup (thyroid function tests, short synacthen test and renal ultrasound) was normal. MRI brain revealed absent posterior pituitary and the patient was diagnosed with isolated cranial DI. Case B; a 10 year old boy with a history of previous basal skull fracture following a road traffic accident, presented to the General Practitioner (GP) with secondary nocturnal enuresis. Medical treatment for nocturnal enuresis (desmopressin) started by the GP showed some initial improvement in symptoms, but when symptoms deteriorated and polydipsia developed he was referred for paediatric assessment. Endocrine workup confirmed partial cranial DI. Case C; an 11 year old boy who presented with polyuria, polydipsia and lethargy, initial endocrine workup showed absent posterior pituitary on MRI brain but was otherwise normal. Repeated testing at regular intervals revealed mildly abnormal thyroid function at 1 year, repeat MRI head was performed showing germ cell tumours requiring treatment with chemotherapy and radiotherapy. **Conclusion:** Cranial DI as a cause for polyuria and polydipsia remains a rare cause but continued neuro-endocrine surveillance is essential for potential identification of an underlying cause as demonstrated in our third case.

P3-1123

A 5-Year-Old Patient with Cushing's Disease

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Background: The overall incidence of Cushing's syndrome in children is ~0.2–0.5 new cases per million people per year. Cushing's disease is more infrequent under 7-year-old children. The typical symptoms are not often observed in childhood. Therefore, the early diagnosis is difficult, when pituitary tumour is not detected by pituitary MRI. **Objective and hypotheses:** A 5-year-old boy was referred to our hospital by a decrease in growth velocity with obesity (Ht: 102.4 cm (−1.3S.D.), Wt: 24.4 kg (+2.1S.D.)). He has moon face, buffalo hump, hypertension, peripheral edema, and pigmentation. **Method:** His 24-h urinary free cortisol was 76.2 μg/day, and 61.7 μg/day (referral range: <70 μg/m^2) and basal ACTH level was 61.5 pg/ml (referral range: <10 pg/ml). In addition to his clinical symptoms, Cushing's syndrome was suspected due to incomplete suppression of plasma cortisol levels with a low-dose overnight dexamethasone suppression test (DEX: 20 μg/kg, ACTH: 21.2 pg/ml, cortisol: 21.2 μg/dl). In the high-dose dexamethasone suppression test (DEX: 120 μg/kg), the cortisol level was suppressed (ACTH: 2.5 pg/ml, cortisol: 1.3 μg/dl). Despite of the results of endocrine test, enhanced pituitary MRI was no findings of adenoma. Then, we performed a selective sinus sampling test to confirm the oversecretion of ACTH from pituitary gland. He had 10.5-to-1 central (left inferior petrosal sinus)-to-peripheral gradient at baseline and 42.4-to-1 central-to-peripheral gradient after stimulation with CRH injection (CRH: 1.5 μg/kg) during the sinus sampling. Finally, he was diagnosed with Cushing's disease. **Results:** Routine pituitary imaging was reported to detect ACTH-secreting tumours in ~50%. Bilateral inferior petrosal sinus sampling should be considered in patients suspected of having Cushing's features for earlier diagnosis and treatment. **Conclusion:** We diagnosed 5-year-old patient with Cushing's disease. This case was not detected with pituitary findings by MRI, but we must perform a selective sinus sampling test to diagnose Cushing's disease even under 7-year-old.

P3-1124

Sequelae in Giant Prolactinoma in a Teenage Boy

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Background: Macroprolactinomas are rare during childhood. Hypopituitarism is a common feature and recovery of pituitary function was reported following cabergoline therapy. **Objective:** We present a case of 13 year-old boy with macroprolactinoma who responded to cabergoline therapy with a complete regression of the tumor with a partial empty sella. **Results:** He complained of a decreased of right vision since 1 year. Evaluation of anterior pituitary function showed an elevated serum prolactin (15.900 mU/l n.v. 56–278 mU/l), normal cortisol, thyroid function and low insulin-like growth factor 1 (IGF1). Magnetic resonance imaging (MRI) of the brain revealed a 63×59×56 mm sellar mass with predominant suprasellar extension compressing the optic chiasma with right temporal lobe and posterior cranial fossa extension. Cabergoline was initiated initially at 1 mg/week and then at 2 mg/week with a normalization of the vision and a progressive regression of the tumor size. During the year after the diagnosis he presented an important reduction of growth velocity (−2.46 ds) with persistent low IGF1 and a delayed puberty. An arginine-LHRH-TRH test was done and revealed a deficit of growth hormone (GH) with low values of gonadotropins. Then he started a growth homone replacement therapy that it was stopped after 5 years when an arginine retest revealed an adeguate hormone production (GH peak >3 ng/ml) for bone age (Greulich pyle 18 years). In suspicion of an hypogonadotropic hypogonadism to induce pubertal development he received three injection of intramuscular testosteron with subsequent normal testosteron level and adequate pubertal progression. On the last control the endocrine function was all within normal limits and MRI revealed a partial empty sella with a residual thin adenohypophysis. **Conclusion:** Cabergoline is recommended as first-line therapy for prolactinoma for excellent safety profile. However the optimal withdrawal strategy and the accurate recurrence rate associated with cabergoline withdrawal remains uncertain recurrence rate associated with cabergoline withdrawal remains uncertain.

P3-1125

Combined Pituitary Hormone Deficiency

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Background: Combined pituitary hormone deficiency (CPHD) may be congenital or acquired disorder, which affects more than one hormonal axis. Congenital hipopituitarism includes heterogenic group of disturbances. It may be result of mutations or deletions in genes for signaling and transcription factors responsible for pituitary development. The disorder might affect one or multiple family members. The age of appearance and intensity of the first hormone deficiency symptoms may depend on type of mutation. Some particular mutations may result in specific phenotype, form syndromes or show characteristic abnormalities in neuroimaging. We present group of 25 patients with combined pituitary hormone deficiency. In some of the patients delivery complications, neonatal adverse events such as hypoglycemia or intrahepatic cholestasis appeared, in others later on in childhood CPHD manifested as growth or puberty retardation. The symptoms observed in the youngest patients are non characteristic for hipopituitarism, what is the cause of difficulties and delayed diagnosis in this group. CPHD should be

considered in neonates/infants presenting hypoglycemia, cholestasis, severe distress in course of infection, thermoregulation disturbances and dimorphic features. **Objective and hypotheses:** Characterisation of CPHD patients' group and determination of genetic cause of CPHD. **Method:** Assessment of pituitary imaging, hormonal function and molecular analysis of genes for transcription factors PROP 1 and OTX 2. **Results:** Patients with CPHD are heterogeneous group. Mutations in gene encoding PROP 1 were found in five of 21 analyzed patients. The analysis of OTX 2 gene was negative in the patient with CPHD and microphthalmia. **Conclusion:** The variety of phenotypes and symptoms' intensity poses serious problem for indication of the one characteristic genetic mutation. Defect in PROP 1 gene constitutes only part of possible genetic causes responsible for CPHD. Determining of specific gene mutations at early diagnostic stage enables to establish proper prognosis and adjust the optimal treatment.

P3-1126

Outstanding Growth Response to Growth Hormone Replacement Therapy in 3 Different Cases of Growth Hormone Deficiency

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Background: Growth response in growth hormone deficient children during growth hormone (GH) replacement therapy rarely fulfil our projections and patient's expectations. We here report 3 cases with outstanding growth response. **Case reports:** First patient was diagnosed as gluten enteropathy in early childhood, but the diet did not improve his growth. At age of 7 years the diagnosis of isolated growth hormone deficiency (GHD) was established and GH substitution therapy introduced. Next 2 years his growth velocity increased to 10 cm/year. Routine head MRI revealed hypothalamic tumour. Severe growth failure in 8-years-old boy with history of purulent meningitis in toddler period and head trauma at age of six. MRI discovered congenital pituitary abnormality (pituitary hypoplasia and ectopic posterior pituitary). Combined substitution therapy improved his height from −3S.D. to +0.67 S.D. An Empty Sella Syndrome was diagnosed in short obese boy with delayed puberty. At diagnosis his height of 148.8 cm was −1.88 S.D. (P3). During 4 years of combined therapy he achieved height of 184 cm (P90), +1.28 S.D. **Conclusion:** Mechanisms of excellent growth response in these GH deficient children certainly include 'growth because of insulin', concomitant hypogonadism, but somatostatin deficiency may also be considered. **Funding:** Supported by a grant from the Ministry of Science of Republic of Serbia, No 41018.

P3-1127

Pituitary Stalk Interruption Syndrome: A Case of an Infant

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Background: Pituitary Stalk Interruption Syndrome (PSIS) is a rare congenital abnormality of the pituitary that is responsible for anterior pituitary deficiency. It is characterized by a classic triad of interrupted pituitary stalk, absent or ectopic posterior pituitary, and anterior pituitary hypoplasia or aplasia. Hypothalamic hypothyroidism, hyperprolactinemia and deficiency of anterior pituitary hormones are typical characteristics. Clinical presentation varies according to age of diagnosis, patients usually complaints of short strature and delayed puberty. **Results:** (Case presentation) A 5.5 months old boy applied with a complaint of micropenis. He was born in term from a healthy 27 years old mother, via C/S due to head/pelvis unsuitability with a birth weight of 3300 g, had been followed up for hypoglicemia and jaundice in newborn period and had no known disorder. In his family history, there was no similar disorder or consanguinity between parents. On physical exam: weight: 7740 g (25–50p)(−0.39 S.D.), height: 67.5 cm (25–50p)(−0.22 S.D.), puberty Tanner stage-1, stretched penis lenght:2.5 cm (<10p). There was no dysmorphic finding, other system examinations were normal and neuromotor development was appropriate to his age. In his laboratory exams: TSH:8.96 μIU/ml, fT_4:0.7 ng/dl, fT_3:3.45 pg/ml, LH:1.5 mIU/ml, FSH:0.9 mIU/ml, T.testosteron:2.5 ng/dl, prolactin:49.01 ng/ml, cortisol:1.57 μg/dl, ACTH:11.5 pg/ml, IGF1 <25 ng/ml, IGFBP-3:1.13 μg/ml, urine density:1025. Low dose ACTH stimulating test indicated central adrenal insufficiency, TRH test indicated hypothalamic hypothyroidism and LHRH stimulation leaded to prepubertal LH response. Pituitary gland MRI showed normal pituitary height, absence of pituitary stalk and ectopic neurohypophysis, Cranial MRI was normal. In the 4 months follow up period of the patient who received hydrocortison, Na-L-thyroxin and local dihydrotestorteron treatment, growth rate is normal according to his age and planned to perform growth hormone stimulating tests when his growth slows. **Conclusion:** The early diagnosis of anterior pituitary deficiency is important to avoid from possible mortality and morbidity. This case who is diagnosed as PSIS in infant period will be presented to emphasize the importance of early diagnose and treatment in deficiency of multipl pituitary hormones as well.

P3-1128

Congenital Adiptical Diabetes Insipidus: A Clinical Case

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Background: Congenital adiptical diabetes insipidus is rare condition in infancy. Immediate diagnosis and treatment is required to ensure normal development. **Case report:** A boy, from the 2nd pregnancy, 1st term delivery was born with weight 4480 g. Bottle feeding from the 1st months. Weight at 1st months – 4500 g, at 2nd – 5000 g. Until the first 2 months mother complained on child's apathia, feeding problems, vomiting, weight stagnation. At 2 months of age all these symptoms increased. A child was consulted by surgeon and neurologist no problems were found. A boy was dehydrated, and sent to the intensive care department of University hospital (Minsk), than to the endocrinological department. Pathological laboratory findings: Na 151–170 (norm 132–145 mmol/l), K – 3.4–5.1 (3.1–5.1 mmol/l), heamoglobin – 87–119, ph 7.34–7.44 (7.35–7.45), ABE (−3.5)−3.8 ((−2)−3) mmol/l), SBE (−1.9)−3.9 ((−1.5)−3 mmol/l), pO2 58.1–80.7 (65–95 mmHg), pCO2 – 34–44.2 (35–45 mmHg) urine density 1001–1003. Hormonal assay: TSH 1.9 (norm: 0.3–4 IU/ml), free T_4 – 17 (11–23 nmol/ml), cortisole 486–1367 (170–720 nmol/ml), aldosterone 1344 (<1900 ng/ml). On the neurosonography little brain vessel cyst was found without any hemodynamic changes. The urine volume was increased (4 ml/kg per h). Congenital diabetes insipidus adiptical variant was diagnosed. The boy was giving desmopressine 0.3 mg/daily, feeding with low levels of Na, but his condition was not still stable, so, hypothyazide 25 mg/daily was added. At the age of 4 months mother came to the endocrinologist and complained on apathia, vomiting. Height 63 cm, weight 6630 g., blood pressure 120/60, urine density 1006–1007, Na 142 mmol/l, K 4.6 mmol/l. Brain MRI with contrast showed middle periventricular oedema. Enalapril 5 mg/daily and metoclopramide 10 mg/daily (continuing vomiting) were added to the treatment. Symptomatic arterial hypertension was added to the diagnosis. **Conclusion:** Reported case of congenital adiptical diabetes insipidus in infancy is rare and such cases in Belarus are limited.

P3-1129

Thickened Pituitary Stalk with Central Diabetes Insipidus: What Diagnosis?

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Background: Central diabetes insipidus (DIC) is usually the final result of lesions affecting the hypothalamic–neurohypophysal system, for the children, Germinoma is the main reason. The MRI aspect is often limited to thickness pituitary stalk with loss of hyperintensity of the neurohypophysis. **Objective and hypotheses:** Thickening of pituitary stalk is suggestive of germinoma, the clinical picture is dominated by a DIC (90%), associated to hypopituitarism (60%), his natural history is unpredictable, he should always be considered. The diagnosis is easy if the ßhCG rate is high, or if there is a pineal localization, but in most cases, these tests are normal and the MRI does not differentiate germinoma from other causes thickening pituitary stalk (histiocytosis, sarcoidosis or lymphocytic hypophysitis. **Method:** A 15 years old boy, referred to our clinic for his growing delay and polyuria – polydipsia syndrome appeared 6 months earlier (estimated 5 l/day). Physical exam: weight = P3, size <P3, Tanner step I. He shows signs of growth hormone and corticotropin deficiencies. No intracranial tumour syndrome. **Results:** Hormonal test: DIC with hypocortisolism, hypogonadism and growth hormone deficiency. i) Pituitary MRI: pituitary salk enlargement (6 mm), loss of T1 hyperintensity of the posterior pituitary. ii) Biologic and morphologic analysis discards a secreting germinoma, histiocytosis X and sarcoidosis assumption. **Conclusion:** MRI report is the diagnosis key of isolated large pituitary stalk, with other clinical clues; but still a long monitoring each 3–6 months, without histological evidence, can be suggested;Checking for Germinoma or histiocytosis existence, especially in child case. There are no good imaging predictors for hypopituitarism, making clinical and hormonal evaluation of all patients with pituitary stalk lesion crucial.

P3-1130

Clinical Features and Pubertal Timing in Girls with Premature Adrenarche

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Background: Premature adrenarche is defined as the development of axillary and/or pubic hair in association of the DHEA-S concentrations >108.4 nmol/l (40 μg/dl) before the age of eight in girls. **Objective and hypotheses:** This retrospective study aimed to investigate the clinical presentation, metabolic status, growth velocity and pubertal timing of girls with premature adrenarche. **Method:** Medical records of 117 patients were investigated. Pubertal onset was regarded as breast enlargement (Tanner stage-2) and/or elevation of baseline LH level to 1 mIU/ml or stimulated LH to 5 mIU/ml. **Results:** Mean adrenarche age of 117 girls was 6.96±0.82 years. The complaint was pubic hair in 105 (%89.7), axillary hair in 63 (%53.8), adult type axillary odour in 31 (%26.5) patients. Prematurity (<37th week) was present in 17 (%14.5) patients while low birth weight (SGA) was present in 9 (%7.6). Hypertension was the most common (%62.6) finding in family history. Eighty-two patients had normal body mass index, while 17 (%14.7) had obesity, 15 (%12.9) had overweight and only two had under-nutrition. Mean DHEA-S level was 95.02 μg/dl and it was negatively correlated with birth weight and gestational age. Growth velocity, bone age, volumes of ovaries and uterus were positively correlated with height SDS, weight SDS and testosterone levels, indicating the effects of oestrogen which is produced by the aromatization of androgens. Puberty was started in 37 girls, mean age of pubertal timing was 8.28±0.95 and a

significant decrease was found when compared with mean age in healthy population. Treatment with GnRH-analogue was needed in ten (%8.4) patients. **Conclusion:** Pubertal timing was diminished in girls with premature adrenarche, suggesting the necessity of following patients in terms of puberty precocious and rapidly progressive puberty. Monitoring the growth and pubertal signs are important especially in premature and SGA children.

P3-1131

Growth Outcomes in Childhood Craniopharyngioma: A Longitudinal Assessment of 21 Cases at a Single Centre

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Background: Craniopharyngiomas are rare suprasellar tumours with good survival but high endocrine morbidity. The commonest endocrinopathy is GHd which can precede diagnosis. Later obesity (BMI $>+2$SDS) may be treatment or tumour related. **Objective and hypotheses:** To evaluate endocrinopathy, height, weight and BMI outcomes after a conservative surgical treatment strategy with pre-treatment pituitary provocation tests for children diagnosed between 2009 and 2014. **Method:** Retrospective longitudinal review of 21 patient electronic case notes (14M, 7F) diagnosed at median age of 7.8 (range 1.9–17.18) years and followed up for 3.15 (0.52–5.37) years. We calculated SDS for Mid-parental height (MPH), height, weight and BMI and noted endocrinopathy at diagnosis and latest follow up. We used the Paris classification to grade the degree (0–2) of hypothalamic involvement and analysed paired data with non-parametric statistics. **Results:** The current prevalence of endocrinopathies follows the hierarchy of GHd (100%), TSHd (80.9%), Gnd (66.7%), ACTHd (66.7%), DI (47.6%) and obesity (28.5%). At diagnosis, 9 (42.9%) patients had pre-existing GHd (peak 1.40 ($<$0.1–3.30)) and Grade 0 ($n=2$), 1 ($n=1$) or 2($n=6$) tumour. The remaining 12 (57.1%) patients with Grade 1 ($n=2$) or 2 ($n=10$) tumours developed GHd 0.15 (0.01–1.81) years after treatment (peak 1.00 (0.2–6.60)). Overall increments in height, weight and BMI SDS occurred with GH replacement. This was significant for weight ($P=0.023$). Six patients became obese (1 Grade 1, 5 Grade 2), five of whom did not have GHd at diagnosis. Children with GHd at presentation remain significantly shorter than those without ($P=0.031$) and are also below MPHSDS ($P=0.043$). During GH therapy 5 (20%) patients with Grade 2 tumours required delayed radiation to residual for relapse. **Conclusion:** Prospective dynamic GH assessment identifies a highly susceptible cohort for GHd and obesity, especially those with Grade 2 tumours. Prompt diagnosis and GH treatment in conjunction with a conservative treatment strategy, improves auxology outcomes with likely benefits on long term health.

P3-1132

Effects of GnRH Agonists and Antagonists on Danazol-Induced Precocious Puberty Rat

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Background: GnRH agonists are a common treatment modality for patients with central precocious puberty. **Objective and hypotheses:** Danazol-induced precocious puberty rats were used as an animal model to compare the effects of GnRH analogues and to assess combinations of treatment with agonistic and antagonistic GnRH analogues. **Method:** A 5-day-old female Sprague–Dawley rats were subcutaneously injected with a single dose of 300 μg danazol. After vaginal opening, the rats were injected daily for 5 days with a combination of GnRH agonists (triptorelin) and antagonists (cetrorelix acetate). Serum levels of LH and FSH were obtained on days 2, 5, and 15 of treatment. **Results:** Rats treated with danazol showed significant advancement in vaginal opening compared with WT rats ($P=0.000$ respectively). LH and FSH inhibition was strongest after 2-day treatment with antagonist alone (LH 1.07 ± 0.04 ng/ml vs 1.25 ± 0.08 ng/ml in controls, $P=0.004$ and FSH 0.39 ± 0.03 ng/ml vs 0.55 ± 0.09 ng/ml in controls, $P=0.006$). Antagonist for 2-day followed with combined agonist/antagonist had the second lowest levels of LH and FSH, though not statistically significant (after 5-day treatment, LH 1.09 ± 0.05 ng/ml vs 1.17 ± 0.04 ng/ml in controls, $P=0.33$ and FSH 0.46 ± 0.04 ng/ml vs 0.47 ± 0.07 ng/ml in controls, $P=0.7$). Agonist only group showed significant increase of LH and FSH after 5-day of treatment (LH 2.27 ± 0.08 ng/ml vs 1.17 ± 0.04 ng/ml in controls, $P<0.0001$ and FSH 2.91 ± 0.65 ng/ml vs 0.47 ± 0.07 ng/ml in controls, $P=0.0008$). **Conclusion:** Combination of GnRH agonist with antagonist, and especially treatment with antagonist alone seems to suppress gonadotropin levels most sufficiently. The danazol treated rat model proved to be a model of true precocious puberty; further related studies involving this animal model should be considered.

P3-1133

Clinical Characteristics of Girls with Atypical Precocious Puberty

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Background: Precocious puberty, pubertal development in girls before 8 years, has considerable biological, psychosocial, and long-term health implications. It is classically ascribed to the premature activation of the hypothalamic-pituitary–gonadal axis, and hence an LH response >5 U/l in the LHRH test. Whilst this group of patients is well understood, there is a paucity of literature characterising patients who show pubertal development not driven by LH, atypical precocious puberty. It has been hypothesised that

obesity and endocrine disruptors may play a role. **Objective and hypotheses:** i) To identify the number of girls in our unit with signs of early puberty and a non-LH predominant (LH <5 U/l) response in the LHRH test and ii) to compare their clinical characteristics to those with an LH predominant (LH >5 U/l) response in the LHRH test. **Method:** 148 girls had an LHRH test between 2004 and 2014. Tanner staging, symptoms and signs of puberty, LHRH test results, bone age, height, weight and BMI were collected retrospectively. Patients with an organic cause for precocious puberty and premature thelarche (B2-5, and P1 or bone age advancement <1 year) were excluded. **Results:** We identified 19 patients with an LH predominant response and 20 patients with a non-LH predominant response. Age at first symptom (breast or pubic hair development) and age at evaluation were not significantly different. Also, there was no significant difference in Tanner staging at presentation, bone age advancement or height SDS between the groups. However, the non-LH predominant group had significantly higher weight SDS ($P=0.025$) and BMI–SDS ($P=0.019$). **Conclusion:** Girls with atypical precocious puberty have similar levels of pubertal development and bone age advancement as their peers with classical precocious puberty. Their increased BMI supports the hypothesis that obesity may result in precocious puberty due to reduced SHBG and increased aromatase activity leading to increased oestrogen bioavailability.

P3-1134

Paraphilic Compulsion Secondary to Dopamine Replacement Therapy and Successful Treatment with GnRH Analogues

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Background: Hypersexualized behaviour in the paediatric population is a rare phenomenon. The aetiology of paraphilia is not completely understood, but some studies suggest imbalance of the dopamine serotonin system. Paraphilia has also been described as a side-effect of treatment with monoaminooxidase inhibitors (MAOI) and dopamine agonists. Most of the currently used pharmacologic treatments of the paraphilias have serotonin and testosterone/dihydrotestosterone as their targets and treatment options such as selective serotonin reuptake inhibitors (SSRI) and GnRH analogues have been described. **Case report:** We report the case of a 16-year-old boy with background of aromatic L-amino acid decarboxylase (AADC) deficiency, a rare inherited neurometabolic disorder, and autism. AADC is a pyridoxal 5′-phosphate enzyme responsible for the production of the neurotransmitters dopamine and serotonin and is predominantly found in neural and kidney and liver tissue. Its deficiency clinically presents with prominent extrapyramidal and autonomic features and CSF monoamine deficiency with increased 3-*O*-methyldopa. Management options include use of MAOI and dopamine agonists (DA). Our patient had been on long-term treatment with tranylcypromine (MAOI) and rotigotine (DA) and developed secondary paraphilia and aggressive behaviour causing severe distress for himself, his parents and carers. After multidisciplinary discussion treatment with GnRH analogues was initiated. This led to persistent resolution of the hypersexualized behaviour and aggressiveness. **Conclusion:** This is the first case to describe successful treatment of paraphilia with GnRH analogues in children. It is also the first case to describe paraphilia secondary to MAOI and dopamine-agonists in paediatric patients with AADC deficiency.

P3-1135

Cardiovascular Disease Risk Factors in Girls with Isolated Premature Pubarche

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Background: Premature pubarche is the appearance of pubic hair before 8 years in girls and 9 years in boys, being more frequent in girls. Current literature demonstrates associations between premature pubarche and metabolic and cardiovascular diseases. **Objective and hypotheses:** To evaluate the frequency of cardiovascular disease risk factors in girls with isolated premature pubarche (IPP). **Method:** Observational study using data from medical records of 41 girls with IPP aged 2–19 years attended at the Paediatric Outpatients Clinic of the University of Blumenau between 1999 and 2013. Excess weight (overweight and obesity according WHO criteria), blood pressure, low birth weight (<2.500 g), bone age (Greylich and Pyle), dyslipidaemia (total cholesterol >150 mg/dl or LDL-c >100 mg/dl or HDL-c <45 mg/dl or TGL >100 mg/dl), basal blood androgens levels (17-OH-progesterone, androstenedione, DHEA-S, and total testosterone), hyperinsulinism (basal insulin >15 mUI/l) and insulin resistance (HOMAR-IR >3.16) were analysed. The appearance of pubarche before 8 years without breast development was considered IPP. In the presence of advanced bone age (>1 year) and elevated basal blood androgens levels an adrenal stimulation test with exogenous ACTH was performed to ruled out congenital adrenal hyperplasia. **Results:** The mean age at the first medical evaluation was 7.8 ± 1.4 years. Excess weight was present in 42.1% (26.3% overweight and 15.8% obesity), elevated blood pressure in 17.3% and dyslipidaemia in 45.8%. Hyperinsulinism and insulin resistance were not observed. Nevertheless, the group with excess weight showed fasting insulin levels higher than excess weight group (7.3 ± 4.2 vs 4.3 ± 2.8; $P<0.05$). Bone age was advanced in 81.8%. Basal blood levels of 17-OH-progesterone, androstenedione, DHEA-S, and total testosterone were elevated in 48.6, 35.1, 32.4, and 37.2% respectively. Low birth weight ocurred in 13.1%. **Conclusions:** Excess weight and dyslipidaemia were the most frequent cardiovascular disease risk factors observed. Almost 50% of the girls presented these clinical conditions.

P3-1136

Menstruation Pattern in Idiopathic Central Precocious Puberty Girls after Discontinuing GnRH Agonist Therapy

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Background: GnRH agonist (GnRHa) has been used in treatment of idiopathic central precocious puberty (ICPP) girls for more than 20 years. However, the menstruation pattern after discontinuation of treatment has been rarely reported. **Objective and hypotheses:** To evaluate menstrual patterns in ICPP girls after discontinuing GnRHa therapy. **Method:** Menstrual diary was recorded for 3 consecutive months by ICPP girls after discontinuation of treatment and normal healthy girl was a control group. **Results:** Sixty-two ICPP girls were treated with GnRHa 3.75 mg s.c. injection every 4 weeks at a mean age of 7.9 ± 1.5 years. The duration of treatment was 2.3 ± 1.6 years. Menstruation developed at14.0 ± 6.0 months after discontinuing GnRH a therapy at a mean age of 11.8 ± 1.5 years. Normal healthy girls had a mean menarcheal age of 11.3 ± 2.0 years. The percentage of subjects with irregular menstrual pattern was significantly higher in ICPP girls than the control group (67.9% vs 23.4%, $P < 0.001$) during the first gynaecological year but this was not different in the second gynaecological year (30.4% vs 27.8%). Final BMI SDS in ICPP girls was significantly higher than that of control (0.84 ± 1.35 vs 0.2 ± 1.48, $P < 0.001$) but not reach over weight criteria. **Conclusion:** Irregular menstrual patterns in ICPP girls previously treated with GnRH agonist therapy are observed only during the first gynaecological year.

P3-1137

Age of Menarche and Near Final Height after Long-Term Use of GNRH Agonist or Combined with GH in Idiopathic Central Precocious Girls

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Background: The use of GnRHa in central precocious puberty is known to slow puberty progression, subsequently prevent early menarche, and attenuate the height loss by advanced skeletal maturation. But enhancing the final height was so controversial that an additional approach has been used. **Objective and hypotheses:** To investigate the age of menarche, and the height outcomes in central precocious girls treated with GnRHa ($n = 61$) or combined GH ($n = 24$). **Method:** GnRHa was started at 8.1 ± 0.7 years for 2.1 ± 1.0 years. GH was used for subjects with short predicted adult height (PAH) for 2.1 ± 1.1 years. **Results:** Menarche occurred at 11.6 ± 0.8 years after 15.7 ± 6.4 months of GnRHa discontinuation. PAH increased significantly from 152.0 ± 7.2 to 158.8 ± 5.6 cm during treatment, and near final height (NFH) was 159.7 ± 4.8 cm, taller than mid-parental height of 157.8 ± 3.4 cm. The combined treatment group showed greater height increment during treatment. Younger age, taller height at the start of treatment, taller parental height, and longer duration of treatment were the factors influencing NFH. **Conclusion:** Long-term GnRHa treatment in central precocious girls could improve NFH, and delay menarche to become close to those of the general population. If combined GH is used in precocious girls with short mid-parental height, it would improve NFH to become similar to the general population. **Funding:** This work was supported by a research grant from Chungbuk National University in 2013.

P3-1138

Psychosocial Changes after GnRH Agonist Treatment in Girls with Idiopathic Central Precocious Puberty

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Background: In precocious puberty, girls experienced secondary sexual development earlier psychologically as well as physically. Self-stress due to a different body shape from the peer group, psychological concerns due to discrepancies between physical and chronological age, and long-term behavioural problems could occur. **Objective and hypotheses:** The aim of this study was to evaluate psychosocial changes in girls with precocious puberty between before and after treatment. **Method:** The girls with idiopathic central precocious puberty whose parents completed the Korean-Child Behavior Checklist (K-CBCL; $n = 66$) and Children's Depression Inventory (CDI); $n = 61$) were enrolled in this study. K-CBCL and CDI were checked at diagnosis and 1 year after treatment with GnRH agonist. *T* score was used in K-CBCL for statistical analysis. **Results:** In K-CBCL, *T* score of problem behaviour total score was significantly lower at 1 year after treatment than at diagnosis ($P = 0.000$). *T* scores of anxiety/depression, atrophy/depression, aggressive behaviour, social immaturity, and other problem were significantly lower, respectively. *T* scores of affective problems, anxiety problems, and oppositional defiant problems were significantly lower. *T* score of post-traumatic stress problems was significantly lower. *T* score of academic performance was significantly higher. In CDI, score was significantly lower at 1 year after treatment than before treatment. **Conclusion:** In idiopathic central precocious puberty, psychosocial problems as well as physical changes may be improved by suppression of sex steroids after treatment with GnRH agonist.

P3-1139

Multicentre Study of Early Screening and Prevention of Prader–Willi Syndrome

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Background: The current diagnostic criteria for Prader–Willi syndrome (PWS) although widely accepted, is challenging to be implemented in Chinese population. **Objective and hypotheses:** The present study collected PWS cases from 12 centres across China. By analysing the clinical manifestation during early infancy, we aimed to provide data for clinical characteristics, screening strategy and effect of GH treatment in Chinese PWS patients. **Method:** We screened 63 suspected PWS cases in 12 centres from May 2012 to August 2013 using MS-PCR. Patients diagnosed by MS-PCR further underwent analysis by MS-MPLA and STR to identify PWS genetic markers. Data on patients' history, clinical manifestation, anthropometrics and clinical biochemistry test before/after GH treatment were collected for analysis. **Results:** Among our enrolled subjects, 16 were confirmed by MS-PCR. Further analysis using MS-MLPA and STR analysis showed that 13 were associated with paternal deletion while the rest three were maternal uniparental disomy (mUPD). Among the 16 diagnosed PWS, 13 were delivered at full term, one were preterm birth, two postterms, four delivered vaginally, and 12 delivered by caesarean section. Fetal distress was diagnosed in ten cases while abnormal foetal position found in five cases. All patients had reduced foetal movement, hypotonia and infant feeding difficulties. Characteristic facial appearance was found in six cases when 13 showed hypogonadism, eight had hypopigmentation. There were four patients received rhGH treatment. When we found patients treated with GH had improved physical development, no difference was found in thyroid function, plasma IGF1 levels, fasting blood glucose, fasting insulin levels, and blood lipid levels. **Conclusion:** PWS might account for 25% of infants with idiopathic hypotonia and infant feeding difficulties. Screening using MS-PCR in suspected cases is critical to identify PWS patients. Hypogonadism and hypopigmentation are important clues for diagnosis. GH treatment during infancy can improve physical development in PWS patients, however how to improve cognitive development and function of endocrine system in PWS patients requires future studies.

P3-1140

A Novel *GLUT1* Mutation in a Patient with Apparently Normal Cerebrospinal Fluid Glucose Level

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Background: Glucose is the main energy source for the brain's cells. Glucose transporter 1 (GLUT1), encoded by the *SLC2A1* gene, is a membrane protein that plays an essential role in the transport of glucose across the blood-brain barrier. A mutation in *GLUT1*, so-called GLUT1 deficiency syndrome (GLUT1 DS; OMIM #606777), results in low levels of glucose in the cerebrospinal fluid despite normoglycaemia. GLUT1 deficiency causes a series of symptoms that may differ considerably from one patient to another. **Case presentation:** We describe a 17-year-old boy with GLUT1 DS, who was found to have a novel mutation, c.1167C > A (p.Phe389Leu), as the cause of infantile-onset myoclonic seizures. Both serum and cerebrospinal fluid (CSF) glucose concentrations were normal (blood glucose, 93 mg/dl; CSF glucose, 47 mg/dl; and CSF to blood glucose ratio, 0.50). **Conclusion:** Our patient helps to clarify the phenotype of GLUT1 deficiency more clearly and reveals a new pathogenic mutation.

P3-1141

Does Treatment with GnRH Analogues Affect BMI in Children with Precocious or Early Puberty?

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Background: Treatment of precocious puberty with GnRH analogues is well established. But there are concerns about weight gain in patients on this treatment. There have been conflicting reports about the effect of GnRH analogues on weight. **Objective and hypotheses:** To assess the change in BMI in children treated with GnRH analogues within a UK Endocrine Service and to analyse the patient/parent experience of the treatment. **Method:** A retrospective study along with a questionnaire survey of patient/parent experience of the treatment was conducted. Data were collected from patients with precocious puberty on GnRH analogues for at least two years. Baseline BMI was compared with BMI at 2-years of treatment. An anonymised questionnaire survey assessed patient's experience of treatment, associated side effects and overall satisfaction of the services. **Results:** Ten percent of children were overweight (BMI–SDS between 2 and 3) prior to treatment, while 21% were overweight at 2-years of treatment ($n = 19$). BMI–SDS showed an increasing trend (0.78–0.91) but was not statistically significant ($P = 0.379$). 92% of patients were either satisfied or very satisfied with the service. 70% of patients did not report any side effects ($n = 14$). 30% of patients perceived weight gain which resulted in low self-esteem. **Conclusion:** Our study showed an increasing trend in the BMI of children treated with GnRH analogues for precocious/early puberty though this was not statistically significant. This is in agreement with the recent joint consensus statement (2009) by the European Society of Paediatric Endocrinology (ESPE) and Lawson Wilkins Paediatric Endocrine Society (LWES) on GnRH analogues. Along with the joint consensus statement, this study on a UK regional patient population will enable us to give more reassurance to our patients.

P3-1142

Qualitative Assessment of Precocious Puberty-Related UCC (User Created Contents) on YouTube

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Background: Precocious puberty is one of the fastest-growing paediatric diseases in South Korea. As the UCC (User Created Contents) has provided lots of medical information, it becomes an easy and important source of medical information. **Objective and hypotheses:** This study aimed to investigate and to evaluate the quality and scientific accuracy of precocious puberty-related UCC on Youtube. **Method:** The key words 'precocious puberty', 'pre-cocious puberty', 'precocious-puberty', 'pre-cocious-puberty', 'early puberty', 'early-puberty', 'sexual precocity', 'sexual-precocity', or 'precocity' were searched into YouTube from June to July 2014. More than 1500 UCC matched the keyword. The 51 UCC were identified, excluding UCC that were duplicate, inaccessible, irrelevant, related to other disease, shorter than 1 min, and in foreign language other than Korean. According to information provider, it was classified as medical, oriental, commercial and others. We evaluated the quality with the DISCERN instrument ranging from 15 to 75, and giving a scientific accuracy with information score (IS) ranging from 0 to 60. **Results:** The 51 UCC were analysed according to the information provider as medical ($n=17$), oriental ($n=17$), commercial and others ($n=17$). The overall quality score of medical UCC (score: 3.4) was significantly higher than that of oriental, commercial and others UCC (score: 2.8 and 2.3 respectively) ($P<0.001$). Assessing the scientific accuracy, the mean information score of medical (score: 30.7) was almost double the overall average (score: 17.2) and significantly higher than that of oriental, commercial and others UCC (score: 15.9, and 5.1 respectively) ($P<0.001$). Mean length of oriental UCC was the longest ($P<0.001$), however, hits was the lowest among them ($P=0.088$). **Conclusion:** The quality and accuracy of precocious puberty-related health information on UCC were variable and not all of them were reliable. Overall quality of UCC regarding precocious puberty was moderate. Only medical UCC has provided scientifically accurate information compared to oriental, commercial and others UCC. As UCC becomes a popular source of health information, it is important to provide reliable information as well as scientifically accurate information.

P3-1143

Premature Adrenarche is Associated to Precocious Thelarche but not to Precocious Gonadarche or Pubarche in Chilean Adolescents

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Background: Premature adrenarche (PA) has been associated to increased metabolic risk. Areas of controversy regarding associated co-morbidities are precocious pubarche, PCOS and lower birth weight, which may depend on ethnic background. **Objective and hypotheses:** To describe the risk of precocious thelarche (PT, <8 years), pubarche (PP, <8 years F, <9 years M) and gonadarche (PG, <9 years) in children with premature adrenarche. **Method:** A longitudinal Chilean cohort ($\sim$20% indigenous/Mapuche origin) the Growth and Obesity Cohort Study (GOCS, $n=1052$, 49.9%F) followed from 2006 (born in 2002), PA defined by DHEAS (RIA) >75th percentile for each gender (45.1 M, 42.0 F µg/dl at age 6.8 ± 0.6 years) and annual clinical examination including Tanner and pubarche assessment. Logistic regression models adjusted by age and BMI assessed the relation between DHEAS and premature thelarche, gonadarche and pubarche. **Results:** At age of DHEAS determination, overweight/obesity (O/OW) was present in 43.6% M, 42.2% F. We found a 18.2% of PT, 8.8% PG and 15.2% (M) and 1.3% (F) PP; any precocious event were observed in 20.9% of M, and 19.2% of girls. In Girls with PA, we observed a 2.5 OR of PT ($P<0.001$), but they did not have an increased risk of PP. In boys with PA, a 1.3 OR of PG (ns), and PP was less frequent in those with PA (10% vs 18%, $P<0.001$) but difference was no longer significant after adjustment. The OR (only adjusted by age) between PA and PT, PG and PP was not different in obese or non-obese children. **Conclusion:** In Chilean adolescents, precocious events of pubertal development were, in line with worldwide secular trend of earlier sexual maturations. PA was only associated with PT continuous follow-up of this cohort is a unique opportunity to address prospectively the interrelationships of PA, early growth, adiposity as determinants of gonadarche, pubertal rate and sequence progression and ovarian function. **Funding:** FONDECYT 1140447 and 1120326.

P3-1144

Central Precocious Puberty in Cerebral Palsy

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Background: Children affected by cerebral palsy (CP) could experience central precocious puberty (CPP) 20 times more than general population. Nevertheless, the treatment is challenging. **Objective and hypotheses:** To compare CPP features and the effects of gonadotropin-releasing hormone agonist therapy (GnRHa) in children with CP and in controls. **Method:** The study involved 16 children with CPP and CP (median age (range)

at diagnosis of CPP: 7.2 years (2.7–8.9); two males) (group A) and 11 children with CPP but no CP (7.4 years (5.2–7.9); no males) (group B). Auxological, biochemical and instrumental data were collected at diagnosis of CPP and at two follow-up visits. **Results:** At diagnosis of CPP, height-SDS-adjusted-for-target-height (H-TH) was lower in A than B (-0.15 ± 1.78 vs 1.56 ± 1.38, P 0.03), while BMI-SDS (0.24 ± 1.15 vs 0.45 ± 0.82, P 0.30) and the discrepancy between chronological and bone ages (1.25 ± 1.01 vs 1.74 ± 1.57 years, P 0.50) did not differ between groups. Basal LH (3.15 ± 2.44 vs. 0.49 ± 0.50 mUI/ml, P 0.009), estradiol levels (29.51 ± 19.12 vs 12.65 ± 6.94 pg/ml, P 0.001) and median ovarian volume (3.37 ± 1.04 vs 1.92 ± 0.75 ml, P 0.006) were significantly higher in A than in B. GnRHa was effective in both groups decreasing gonadotropins, estradiol and signs of pubertal progression. However, it affected differently growth: at second follow-up visit, H-TH (-1.43 ± 1.43 vs 1.48 ± 1.42, P 0.003) and Δ H-SDS (-1.20 ± 1.31 vs 0.21 ± 0.33, P 0.017) were lower in A than B. **Conclusion:** CPP in CP seems to progress rapidly supporting the hypothesis of a more intense activation of hypothalamic–pituitary–gonadal axis. We demonstrated that growth failure could partially mislead the diagnosis of CPP in CP and seemed to worsen during follow-up despite GnRHa. The complex management of these patients should be considered when a decision to treat has to be performed. Parents should be adequately supported in order to ensure the best therapeutic choice for each case.

P3-1145

Changes in BMI During GNRH Agonist Treatment in Girls with Idiopathic Central Precocious Puberty and Early Puberty

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Background: GNRH agonist (GnRHa) has been widely used for decades to treat in patients with central precocious puberty (CPP). There are severe studies concerning changes in body composition in CPP patients following GnRHa treatment, but the results are inconsistent. **Objective and hypotheses:** The aim of this study was to investigate the change of BMI in children treated with GnRHa for 2 years. Also, the present study was performed to assess whether BMI affects treatment outcomes. **Method:** This study included 383 girls (214 CPP and 169 early puberty girls) were treated with depot leuprolide acetate monthly for at least 2 years. We analyzed the changes in BMI SDS. Furthermore, a single LH obtained 30 min after depot leuprolide acetate administration every 6 months to evaluate adequate hypothalamic–pituitary–gonadal axis suppression. **Results:** Before the initiation of therapy, the girls with CPP had a mean BMI SDS for chronological age of 0.39 ± 0.87. After 2 years of the treatment, mean BMI SDS was significantly increased (0.51 ± 0.85, $P < 0.001$). The frequency of overweight and obese patients increased from 22.4% to 27.4%. Single LH levels of 30 min after leuprolide injection at 2 years of treatment were not significantly different among normal weight, overweight, and obese subjects (0.32 ± 1.83, 0.17 ± 0.21, 0.12 ± 0.09 IU/l, respectively, $P = 0.646$ for all comparisons). **Conclusion:** The BMI SDS for chronological age was significantly increased during treatment. Adequate education concerning lifestyle and diet during GnRHa treatment is needed.

P3-1146

An Elevated Tumour Marker and Adrenarche in a Child Using Lavender Oil: A Case Report

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Background: 'D' was a 7 year old Caucasian female who presented with a history of adult-type body odour starting at age 3 years. At age 6y 9m her bone age was 7y 10m. She had had a sharp increase in her weight in the past 2 years and her PCP noticed pubic hair growth. Her very anxious single mother was convinced she had a serious illness that needed immediate intervention. **Case presentation:** At presentation, D had Tanner 2 pubic hair and Tanner one breast development. BMI was >99%. Her complexion was clear. Her work-up showed no history of exogenous androgen exposure, but her mother was applying non-diluted lavender essential oil to her feet several times a day to help eliminate odour. Labs showed normal gonadotropin levels, thyroid, kidney and liver function. Her HCG tumour marker was 15 mlU/ml (normal <1). This lab was repeated with a result of 16.1 mlU/ml, then re-run using heterophile blocking reagent which was also elevated. Mother was advised to discontinue using any type of oil or other remedies of any kind throughout the duration of her testing. Abdominal ultrasound and brain MRI revealed no abnormal findings. Two weeks after the initial work-up, her HCG tumour marker was <0.6 mlU/ml. **Conclusion:** Many patients are using complementary and alternative methods (CAM) of healing. A recent NIH study suggests that use of lavender oil may cause gynecomastia in males. There is no evidence suggesting lavender oil causes precocious puberty in females, yet a concerning lab finding returned to normal after our patient stopped using it. Although the research science is not available for many of the remedies being use, this case highlights the importance of exploring use of CAM methods during a work-up for endocrine issues. Parents should be cautioned accordingly.

P3-1147

Persistent Isolated Cyclical Vaginal Bleeding (Premature Menarche) not Associated with GnRH Pubertal Response or Endometrial Echo Should be Considered for Examination Under General Anaesthesia

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Background: Isolated prepubertal menarche is described in the absence of any other signs of precocious sexual development. This condition remains unclear in its aetiology and there is currently no consensus on investigations to be undertaken. **Objective and hypotheses:** The objective of our study is to evaluate the following factors associated with persistent isolated cyclical vaginal bleeding: clinical presentation, gonadotrophin-releasing hormone (GnRH) stimulation test, genital examination under anaesthetic (EUA) and pelvic ultrasound findings. **Method:** We describe a retrospective case series of 14 girls with isolated prepubertal menarche from two centres between January 2007 and December 2014. All girls presented with persistent cyclical vaginal bleeding without signs of precocious sexual development. **Results:** At presentation, mean age was 7.4 years (range 5.0–9.67), mean BMI was 19.6 (range 14.6–29.3), mean height SDS was 0.33 ± 1.35 and mean weight SDS was 1.01 ± 1.75. Vaginal bleeding was reported to be cyclical ranging from 1 week to 3 monthly, lasting 1 to 4 days in duration. Bleeding was reported to have persisted between 6 and 18 months in all girls. GnRH stimulation test was performed in all girls. Mean LH peak was 3.1 U/l (range 0.3–14), mean peak LH/FSH ratio was 0.23 (range 0.07–0.66) and oestradiol levels were < 100 pmol/l in all girls. Pelvic ultrasound showed prepubertal uterus with no identifiable endometrial echo in all girls. Bone age showed no advancement in all girls. EUA was performed in eight girls. EUA was normal in seven girls and one girl had a 1.5 cm foreign body found. The girl with the foreign body presented with cyclical vaginal spotting weekly for 6 months prior to the EUA. **Conclusion:** Persistent isolated cyclical vaginal bleeding was not associated with identifiable endometrial echo on pelvic ultrasound, GnRH pubertal response or elevated oestradiol levels. Low oestradiol levels may result in an increased sensitivity of the endometrium resulting in vaginal bleeding. EUA should be considered in persistent isolated cyclical vaginal bleeding to exclude other causes such as foreign body.

P3-1148

Endocrine Dysfunction in Hypothalamic Hamartoma Depends on Presentation (Endocrine or Epileptogenic), Radiological Characteristics and Surgery

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Background: Hypothalamic hamartomas(HH)-rare heterotopic congenital malformations (incidence 1:200 000)-present with central precocious puberty (CPP) or gelastic seizures (GS) but their natural history and best treatment strategy are unknown. Given their proximity to the hypothalamus–pituitary axis, wider endocrine dysfunction may be expected. **Objective and hypotheses:** To describe clinical features and any evolving endocrinopathies in HH patients, by presentation (CPP or GS), radiological characteristics and any surgical treatment imposed. **Method:** Retrospective-longitudinal review of case notes of children with HH seen at our centre between 1.1.1991 and 31.12.2014. **Results:** Over a 14 year period, 34 children (21M:13F) aged 3.97 (± 3.5 SD) years were diagnosed with HH and followed for 5.9 (± 4.3 SD) years. Fourteen (41.2%) patients each, presented with either GS or CPP and a further 6 (17.6%) were identified incidentally (MRI). Patients presenting with GS tended to be older (4.9 years) than those with CPP (3.1 years) or incidental HH (3.7 years) and all (100%) had sessile hamartomas. By contrast, most HH in CPP (79%) and incidental (83%) groups were pedunculated. 28.6% (4/14) patients with GS developed CPP 3.16 (± 2.8 SD) years later at 4.5 (± 3.8 SD) years old (in three after surgery). Similarly, 28.6% (4/14) CPP patients were diagnosed with GS (2/4 sessile) 0.57 (± 0.41 SD) years later. 32.3% (11/34) patients (ten presenting with GS and one with CPP), all with refractory GS, underwent surgery 3.3 years (± 2.6) from diagnosis. At last assessment, half of presenting GS patients had pituitary deficits compared with none of CPP and just 16.6% of incidental. No patient had ACTH or Gonadotropin Deficiency and only 4 (all post-operative) had Central Diabetes Insipidus (CDI), 3 with additional GH deficiency (GHd) and TSH deficiency (TSHd). Obesity (BMI > + 2 SD) rates were high, especially in those presenting with CPP (60%) and GS (46%) (vs 20% incidental). **Conclusion:** CPP HH (especially if sessile) require routine neurology referral (to exclude occult GS). GS HH require routine endocrine review, especially if surgery contemplated. Routine dynamic pituitary testing (including LHRH) of all HH patients may unmask undiagnosed GHd (or CPP), whilst prompt GH replacement may reduce currently high obesity rates.

P3-1149

Idiopathic Central Precocious Puberty – Treatment Criteria

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Background: Central precocious puberty is due to premature activation of the hypothalamo–pituitary–ovarian axis. In girls it is idiopathic in up to 95%. Children with clinical rapid progression are treated with prolonged activity GnRH agonist. **Objective and hypotheses:** Characterise cases of idiopathic central precocious puberty (ICPP) followed at our hospital comparing the group treated with GnRH agonist (group A) with the group not treated (group B) at 6–12 months of follow-up. **Method:** Retrospective study including children ICPP diagnosed between January/2006 and January/2014, with minimum 6 months' follow-up. Data collected: age, auxologic data and Tanner stage, at admission and along follow-up; target family height (TFH), parental pubertal age, growth velocity (GV), hormonal levels, bone age, predicted adult height (PAH), and treatment. Statistical analysis with SPSS21th ($P<0.05$). **Results:** We included 42 children with ICPP, without treatment criteria at first visit. All were females, with a mean follow-up time of 11months. Clinical progression was slow in 17 children (group A) and rapid in 25 children (group B). Group B was treated with LHRH, started 12,8 months after the first visit. TFH was 158.3 ± 1.3 cm in group A and 159.3 ± 1.1 cm in group B ($P=$NS). Mothers' menarche age was under 10 year in 12.5% in group A and 32% in group B. At first visit, there was no significant difference in both groups in analysed variables. At about 12 months of follow-up, group B had significantly higher GV (8.8 ± 1.9 vs 6.8 ± 2.3; $P=0.004$), FSH (3.3 ± 1.6 vs 1.8 ± 1.0 UI/ml; $P=0.001$), IGF1 (410 ± 125 vs 331 ± 116 ng/ml; $P=0.05$) and IGF1 SDS (2.5 ± 1.4 vs 1.3 ± 1.1; $P=0.005$) than group A. Comparing data from first visit to 12 months follow-up visit, there was significant difference only for group B. This had a significantly increase of height-sds ($P<0.0001$), LH ($P=0.004$), FSH ($P=0.006$), IGF1 ($P=0.003$), bone age ($P<0.0001$) and a significantly decrease in PAH ($P=0.019$). **Conclusion:** Our data confirmed the need to monitor puberty evolution along time, including height, growth velocity, bone age, gonadotropic hormones and IGF1. Children with rapid progressive puberty should be treated in order to avoid compromising final adult height.

P3-1150

Physiological Dose Reverse Rhythm Testosterone Treatment Abolishes the Development of Permanent Gynaecomastia in Adolescent Boys with 47,XXY Klinefelter Syndrome

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Background: Gynaecomastia (GM) is common in boys with Klinefelter syndrome (KS) during adolescence due to the higher diurnal oestradiol–testosterone ratio in early-to-mid puberty. The physiological mid-late pubertal rise in testosterone (T) causes the GM to disappear in chromosomally normal boys, but GM persists in boys with KS if this rise in T is blunted. **Aims and objectives:** We aimed to examine the effect of routine T supplementation in boys with KS ascertained antenatally or clinically on the development and persistence of GM. **Methods:** The presence of GM was routinely ascertained in consecutively referred KS boys to a specialist multidisciplinary clinic. 29 boys were over 11 year. Once puberty had started and GM identified and recorded using Tanner breast staging and measurement of cross sectional breast disc diameter, either oral T undecanoate (TU – Restandol) 40 mg or transdermal T (Tostran) 20 mg was commenced each morning. T was administered in the morning, in reverse rhythm, in order to counterbalance the physiological decline of T concentrations in the afternoon/evening which is known to be more marked in boys with KS. **Results:** 8/29 boys developed GM. Two did not adhere to treatment and the GM persisted. In the other six, GM stages B2-B3 with breast discs diameter range 1–3 cm appeared at mean age 12.8 year (range 11.4–14.2 year) and at puberty stages G2–G3. Only one had a high BMI (+3 SD). GM resolved completely within a mean of 1.1 year on treatment (range 0.2–1.9 year). Physiological T replacement was continued. Transient recurrence in 1/6 boys was ablated with a physiological TU dose increase. No major adverse effects were noted. **Conclusion:** Reverse rhythm T, using a morning administration regimen started at the onset of GM and then given continuously in physiological dose increments, abolishes the development of permanent GM in adolescent boys with KS.

P3-1151

Urinary Bisphenol A and Its Relation with Kisspeptin in Girls with Idiopathic Central Puberty Precocious and Premature Telarche

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Background: Endocrine disruptors cause harmful effects to human body through various exposure routes. These chemicals mainly appear to interfere with the endocrine or hormone systems. Bisphenol A (BPA) is known as an endocrine disruptor with an estrogenic effect and it is supposed that it may have a role on development of precocious puberty (PP). Kisspeptin, a hypothalamic peptide, is a neuromodulator of GnRH and it has a big role on regulation of the onset of puberty. **Objective and hypotheses:** In this study we investigated the BPA levels in girls with PP and premature telarche (PT) and its relation with kisspeptin levels. **Method:** Twenty-eight girls with PP, 28 girls with PT and 22 prepubertal girls as a control group were enrolled to the study. Urinary BPA and serum kisspeptin levels were compared in groups. Bivariate correlations were performed to evaluate the relation of BPA with kisspeptin and estradiol. **Results:** There was no statistical difference between groups regarding BPA levels. Serum kisspeptin levels were higher than control group

(306.56 (23.69–926.15) vs 157.62 (22.54–650.41) p:0,031). There were no correlations between BPA and kisspeptin levels (r:0.185, p:0.102) and between BPA and estradiol (r:0.115, p: 0.331). **Conclusion:** The relation of BPA levels with PP or PT and especially correlation with kisspeptin levels could not be demonstrated in our study. The kisspeptin levels were highest in PP group, This difference was not statistically significant between PP and PT groups whereas it was significant between PP and control groups. **Funding:** This work was supported by the Bezmialem Vakif University Research Council (grant numbers 2013,0132)

P3-1152

Prevalence of Parental Consanguinity in Children with Precocious Puberty and Kisspeptin Gene Polymorphisms

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Background: Precocious puberty (PP) is one of its variations which defines as appearance of physical signs of sexual development in a child prior to the earliest accepted age of sexual maturation, 7 years in girls and 9 years in boy. The exact mechanisms and genetic background of ICPP are not well understood. It is suggested that the kisspeptin neuropeptide, encoded by the KISS1 gene, could have role in this regard. **Objective and hypotheses:** Considering the higher rate of parental consanguinity among Iranian population and its possible role in the occurrence of PP, the aim of current study was to determine the mutation of kisspeptine gene (KISS1) among a group of patients with PP and role of parental consanguinity in this regard. **Method:** In this case control study, a group of children with diagnosed PP and a group of healthy children were selected. Genomic DNA was extracted from peripheral blood of selected population. Occurrence of any mutation or polymorphism in KISS1gene was investigated. The rate of parental consanguinity was determined in patients with and without KISS1gene polymorphism/mutation. **Results:** In these study 33 patients with idiopathic PP and 30 control age and sex matched children were studied. Genetic analysis indicated that there was not any polymorphism or mutation in studied participants of control group. Among patients with PP, four SNPs within the promoter and coding regions of KISS1 gene were determined in nine patients (five boys and four girls). There was not any case of familiar PP as well as any case with parental consanguinity among patients with detected polymorphism. **Conclusion:** The findings of current study identified one novel polymorphism and three reported polymorphism in KISS1gene among patients with PP in Iran. Considering that parental consanguinity was not associated with reported polymorphism of KISS1gene, further epigenetic studies are recommended.

P3-1153

Effects of Nutrition and Vitamin D Deficiency on Central Puberty Precocious

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Background: Puberty is a dynamic period of physical growth. Genetic factors, increasing prevalence of adiposity, environmental factors and the widespread presence of endocrine-disrupting chemicals are suspected to contribute to the trend of earlier pubertal onset. **Method:** The study group consists of 32 girls diagnosed with central puberty precocious. The eating habits and physical activity status were evaluated with a detailed questionnaire. Daily calorie and nutrients intake were calculated according to the three-day dietary records. Anthropometric measurements, bioelectrical impedance analysis and biochemical findings were compared with the age matched control group. **Results:** All patients admitted with breast enlargement before 8 years and diagnosed by a GnRH test. The birth weight was significantly lower than the control group ($P<0.05$). Duration of breast feeding, beginning of supplementary food, ingestion of vitamin or mineral supplements, usage of feeding bottles and pacifiers were not significantly different between groups. Feeding with formula was more frequent in the study group; however it was not statistically different. Mean calorie and macronutrients intake was not different, as well as physical activity status. The possibility of puberty precocious was found as 3.5 fold increased in patients who consume yogurt <2 times a week, 9.7 fold increased in patients who consume salami every day or more than once a week and 3.4 fold increased in patients who consume chicken together with its skin. Serum Vitamin D levels were significantly low in the study group ($P<0.01$). **Conclusion:** Recent studies have shown that the age of menarche is decreasing across the world and they also draw attention to the environmental factors. Our study showed that the some nutritional factors are important and level of 25OHD was significantly lower in girls with central puberty precocious, supporting the results of recent studies in the literature.

P3-1154

The Relationships between Serum Vitamin D Level and Precocious Puberty in Korean Girls

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Background: The recent articles showed a kind of associations of the serum vitamin D levels and chronic diseases, for example, autoimmune diseases, vascular disorders, as well as malignancies. Also vitamin D deficiency impacts normal growth and maximal bone mineral accretion in puberty. Of pediatric population in Korea, the prevalence of cases of vitamin D deficiency and precocious puberty were continuously increasing nowadays. **Objective and hypotheses:** We investigated whether there is the relationship of vitamin D level and precocious puberty or not, in accordance to increasing cases in Korea. **Method:** In this cross-sectional study, we enrolled total 135 girls composed of 84 Korean girls with central precocious puberty and 51 control girls. The serum 25-hydroxyvitaminD (25OHD) levels of all subjects were measured by radioimmunoassay. The anthropometric data and bone age were recorded. The definitions of the vitamin D status according to their 25OHD serum levels were as follows: deficient for patients with levels <20 ng/ml, insufficient for levels of at least 20 but <30 ng/ml, and normal for levels $\geqq 30$ ng/ml. The data of precocious puberty group and control group were compared using the Student t-test, and χ^2 test. The odds ratio of central precocious puberty depending on vitamin D levels were investigated by binary logistic regression. Statistical significance was defined as $P<0.05$. **Results:** Their mean ages were 7.7 ± 1.2 year (central precocious group) and 8.96 ± 1.8 year (control group). The prevalence of vitamin D deficiency in all subjects was 62.2% (97 out of 135), that of vitamin D insufficiency was 37.8% (38 out of 135). There was a statistically significant difference in mean serum 25OHD level between the central precocious puberty group and control group (16.9 ± 4.7 ng/ml vs 19.18 ng/ml, $P<0.05$). Seventy eight percent of CPP girls (66 out of 84) have revealed vitamin D deficiency, and 21.4% (18 out of 84) were vitamin D insufficient. In the control group, 60% (31/51) had vitamin D deficiency and 39% (20/51) were vitamin D insufficient. After χ^2 test, there was a statistically significant difference in both groups ($P<0.05$). Vitamin D deficient girls had a significantly higher odds ratio (OR, 2.36; 95% CI, 1.09–5.09, $P=0.028$). **Conclusion:** This study indicated that vitamin D deficiency is more prevalent in girls with central precocious puberty than normal control girls with same ages. So, vitamin D-deficient state might influence sexual maturation and hormone metabolism. Because vitamin D-deficient effect on pubertal progression is not known, further studies about the mechanism of vitamin D deficiency on the onset of precocious puberty would be needed.

P3-1155

Familial Precocious Puberty: Clinical Characteristics and GnRH Agonist Response

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Background: Familial precocious puberty is defined by the existence of more than one affected member either in the proband generation or in the pedigree. Recently, several gene mutation cause familial CPP is elucidated, gain of function mutations in KISS1 and KISS1R, loss of function mutations in the MKRN3, the feature of familial precocious puberty is not fully understood. **Objective:** To investigate the clinical characteristics of familial precocious puberty (FPP) and the response of GnRH agonist treatment compared to sporadic precocious puberty (SPP). **Method:** This study was conducted retrospectively. 62 sibling pateints with familial precocious puberty and 60 patients with sporadic precocious puberty was included. We reviewed their auxological data, family history and laboratory finding and also analyzed the response of GnRH agonist treatment and change of predicted adult height. **Results:** The onset of precocious puberty was not available. Baseline characteristics including age, bone age, height SDS, the bone age advancement, BMI, Tanner stage, LH peak on GnRH stimulation test and PAH revealed no significant difference between familial CPP and sporadic CPP. Target height, paternal height and maternal age at menarche were lower in FPP group than SPP group (158.58 ± 3.33 and 160.12 ± 3.44 (cm), 170.88 ± 4.50 and 173.10 ± 5.32 (cm), 12.60 ± 1.329 and 13.19 ± 1.02 (year) respectively, $P<0.05$). PAH after GnRH agonist was greater in familial CPP group than sporadic group (165.21 ± 5.29 and 162.28 ± 4.80 (cm), $P<0.05$). **Conclusion:** Familial precocious puberty was characterised by significantly lower target height, paternal height and maternal age at menarche than sporadic precocious puberty. GnRH agonist treatment can improve the growth outcome of FPP. Detailed family history, close follow up of growth and pubertal changes in the younger siblings is necessary.

P3-1156

Eating Disorders in Greek Adolescents: Frequency and Characteristics

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Background: Eating disorders constitute serious mental disorders, characterized by a wide range of dysfunctional behaviors related to food. The term mainly includes anorexia nervosa, bulimia nervosa and binge eating disorder, and is closely related to onset during puberty. The study herein, presents the preliminary results of a school-based intervention trial regarding body weight disorders among Greek adolescents. **Aims and objectives:** To explore the prevalence of eating disorders in a sample of 399 Greek adolescents (41.6% boys) aged 14.43 ± 3.42

year-old. **Methods:** All participants answered in privacy the questionnaire of eating habits, EAT-26. After calculation of the questionnaire scores, adolescents presenting score >20 were identified as individuals with serious indications/signs of eating disorders. **Results:** Median score of EAT-26 questionnaire was nine with interquartile range (IQR) (5–14). After grouping the sample by gender, boys presented a median score of 7 (IQR: 4–10.25) while girls one of 10 (IQR: 5–16). The score of EAT-26 in the subgroup of girls was significantly higher compared with that of boys ($P<0.001$). In the total sample, 39 adolescents (30 girls) were detected to present serious indications/signs of eating disorder (9.77%). Signs of serious eating disorder were significantly more prevalent in girls than in boys ($P=0.013$). **Conclusions:** Almost one out of ten adolescents presents signs of serious eating disorder, which require integrated diagnostic-psychiatric investigation and treatment. Girls present significantly greater prevalence of eating disorders. Early diagnosis and treatment constitute the necessary strategy for preserving mental health in the adolescent population. **Funding:** Integrated System for Promotion and Education of Health of the Municipality of Ampelokipoi-Menemeni to combat obesity and eating disorders in adolescents ESPA European Community fund.

P3-1157

Assessment of Endocrine Function in Egyptian Adolescent B-Thalassemia Major Patients

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Objective: To evaluate the endocrine function among Egyptian adolescent thalassemic patients. **Patients and methods:** 54 patients and 28 age-matched normal controls was included. Anthropometric measurements, clinical pubertal assessment were done for all patients. Oral glucose tolerance test (OGTT) was done to all patients and controls with measuring serum insulin level at 0.120 minutes. Insulin sensitivity and release index were calculated. 32 patients had short stature and arrested or failure of puberty. Thyroid profile, insulin-like growth factor-1 (IGF1) and GH provocation by two tests and GnRH stimulation test was carried out. **Results:** Among the 32 patients, 12 (40%) patients had sub-clinical hypothyroidism and 10 (33.3%) had growth hormone deficiency (GHD). Failure of puberty was confirmed in 71.4% of boys and 33.3% of girls, while arrested puberty was observed in 28.6% of boys and 66.7% of girls. All girls had amenorrhea, primary amenorrhea in 88.9% and secondary amenorrhea in 11.1%. Among the 54 patients, thirteen patients (24.1%) were diagnosed to have abnormal glucose tolerance (AGT); either diabetes in 6 (11.1%) cases or impaired GT(IGT) in 7 (13%) cases. Patients with AGT had significant higher mean postprandial insulin, fasting insulin resistance index (FIRI) and HOMA insulin resistance (IR) and significant lower mean HOMA if compared to the cases with normal GT (NGT). **Conclusion:** GHD is an etiological factor in short stature thalassaemic. Delayed puberty is either due to failure of gonads or failure of the whole hypothalamic pituitary gonadal axis. Abnormal glucose tolerance is common which could be attributed to early impaired beta-cell function, along with increasing insulin resistance.

P3-1158

Evaluation of the Effect of Two Different GnRH-Agonist Therapies on the Anthropometric Measurements in Girls with Idiopathic Central Precocious Puberty

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Background: The GnRH-agonists are the drugs of choice for therapy of idiopathic-CPP. To assess two different GnRH-agonist (Leuprolide acetate: LA vs Triptorelin depot: TD) treatment effects on anthropometric measurements. **Patients and methods:** 74 girls with ICPP (mean age 33.8 ± 8 years) were enrolled the study. Complaints had been begun before 8 years old. 50 girls underwent GnRH stimulation test. 58 girls with ICPP were followed up 18 months. Children were treated with LA (*n*:42) or TD (*n*:32) 3.75 mg/q4wk. The dose had to be increased 7.5-mg/q4 wk in 15 patients. Hormonal data, and height, weight, BMI and growth velocity (GV) of patient were recorded before (PRE) and 6 months interval, during the therapy. **Results:** At the admission thelarche was a major complaint (60/74) and nine girls had menarche. Bone age (LA:10.4 ± 1.9 years vs TD: 9.1 ± 1.8 years) and peak LH (LA: 14.8 (19.37) IU/ml vs TD: 8.56 (8.2) IU/ml) was significantly different in both groups. Left ovarian volumes (LA:2.0 (2.92) ml vs TD: 1.71 (1.81), *P*:0.03) were significantly different in both groups. Although there were no differences GV at 6th, 12th and 18th months between in LA and TD groups, first 6th months GV was significantly lower from GV at 12th months of the therapy in both groups (Figure 1). Differences in BMI at PRE-BMI, BMI-6th, BMI-12th and BMI-18th were significantly lower in TD group than LA group (Figure 2). GnRHa dose was significantly correlated with BMI during therapy (at 6th ($P<0.0001$), 12th ($P=0.005$) and 18th ($P=0.001$)) in LA group compared to TD group. **Conclusions:** GV in girls with ICPP decreased with GnRHa treatment. Dose-dependent increase in BMI was observed during treatment in girls treated with LA. Clinicians should be alert of obesity risk in children treated with GnRHa.

P3-1159

Testotoxicosis: Be Careful to Predict the Final Height!

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Background: Familial male-limited precocious puberty, known as testotoxicosis, is an autosomal dominant disease that leads to the activation of luteinizing hormone receptor. It presents with progressive virilization, advanced bone age and linear growth acceleration and may lead to loss in predicted adult height. We report the case of a patient diagnosed with testotoxicosis at two years of age. **Case presentation:** Two-year-old boy with penis enlargement and pubic hair. On physical examination, muscle hypertrophy, Tanner G3P2, 10 cm penis, 94 cm tall (Z-score +2.25). Lab work-up: total testosterone 734.5 ng/dl, bone age seven years. He was treated with ketoconazole, spironolactone, cyproterone acetate and anastrozole, with partial response, although maintaining high concentrations of testosterone, progress of bone age and of growth velocity, and growth of the right testicle. At age four, scrotum US showed testicular microlithiasis on the right side; on biopsy, there was intense focal proliferation of Leydig cells without atypia and indefinite limits. He was submitted to right orchiectomy associated with treatment with leuprolide acetate (due to secondary gonadotropin-dependent precocious puberty – GDPP), with stabilization of bone age. At age 16, his height was160 cm, within the family target. **Discussion:** The treatment of testotoxicosis aims to stop the progression of puberty and avoid the loss of the final height. Despite the therapeutic difficulty, the patient reached the familial target height. The presence of microlithiasis raised the suspicion of a testicular tumor, not confirmed, with subsequent orchiectomy. The induction of a GDPP demanded blocking with leuprolide acetate, which may have contributed to a favorable outcome in adult height.

P3-1160

Central Precocious Puberty Presented due to Late Started Treatment for Familial Testotoxicosis

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Background: Peripheral precocious puberty (GnRH independed): precocious development of secondary sexual characteristics may also be caused by mechanisms that do not involve activation of pulsatile GnRH secretion. Familial male-limited precocious puberty, also known testotoxicosis is a rare dominant form of gonadotropin independent precocity caused by constitutively activating mutations of the human LH choriogonadotropin receptor (LHCGR). If do not treat with appropriate drugs such as aromatase inhibitors, anti androgens, ketoconazole spironolacton etc. High testosterone levels can cause to central precocious puberty. We presented here a boy have testotoxicosis but late started treatment and therefore induced central precocity. **Case:** A boy 8.5 year old admitted for pubic and axillary hair started after 4 year. He have two healthy sisters and no consanguinity between mother and father's. In physical examination height 141 cm (>97per, +2.5 SD), weight 35 kg (>97p) BMI 17.6 kg/m^2 (50–75per), pubic and axillary hair tanner stage IV, penil length 12 cm(>97per, >+2.5 SD) testes volume bilaterally 10 ml was found. Laboratory analysis LH< 0.1 mIU/ml, FSH 0.2 mIU/ml, testosterone 650 ng/dl, alpha-fetoprotein 0.9 IU/ml, HCG 0.1 IU/ml, DHEA-SO4 75 µg/dl, ACTH 30 U/l, bone age 13 year, bone age/chronological age: 1.73. Geneticalley evaluation showed LHCGR gene p.T577I (c.1730C>T) heterozygot mutation. After a month of treatment initiation with bicalutamide 50 mg/day and letrozole 2.5 mg/day LH 2.2 FSH 6.8 testosterone 580 ng/dl was found. Triptorelin 7.5 mg/monthly added to treatment. After 6 month of treatment initiation LH: 0.48 mIU/ml, FSH: 0.4 mIU/ml testosterone 115 ng/dl. Bone age13.5 year and advancement stopped. **Conclusion:** Testotoxicosis is a rare dominant form of gonadotropin independent precocity. Bicalutamide and letrozole can be used safety and effectively. It should be noted if treatment for peripheral precocious puberty do not started early high testosterone levels can lead to central precocity.

P3-1161

A Practical and Integrative Approach to Differential Diagnosis Between Precocious Puberty and Premature Telarch: Newly Proposed Clinical and Laboratory Finding-Based Diagnostic Scoring in Precocious Puberty and Premature Telarch

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Background: Accurate and differential diagnosis of preococious puberty (PP) have some important challenges. Many parameters have used to diagnose pubertal diseases so far. However LH-RH stimulation test is considered as a gold standard procedure, ıt has some difficulties in practise. **Objective:** We aimed to set a newly proposed clinical and laboratory finding-based diagnostic scoring in the differential diagnosis of preoccious puberty and premature telarch (PT). **Method:** In this study, a total of 267 patients (164 PP; 103 PT) were enrolled in Paediatric Endocrinology Department of Medical Faculty of Gaziantep University. We accepted following including criteria: At least one of secondary sex characteristics is T2 or P2 according to Tanner scoring. We used basal LH 0.31 or peak LH of at least 5 IU/l and/or stimulated LH/FSH ratio of at least 0.31 as cutoff

Table 1. Cut off levels for PP and PT.

Variables (%)	Cut off	PP (*n*:164)	PT (*n*:103)
Age at diagnosis (year)	>6.5	142 (86.6)	44 (42.7)
	≤6.5	22 (13.4)	59 (57.3)
BA-CA (year)	>1.1	116 (70.7)	14 (13.6)
	≤1.1	48 (29.3)	89 (86.4)
Estrogen	>12	87 (53.0)	6 (5.8)
	≤12	77 (47)	97 (94.2)
Uterine length (mm)	>32	132 (80.5)	28 (27.2)
	≤32	32 (19.5)	75 (72.8)
Ovarian volume (cm^3)	>1.09	126 (76.8)	27 (26.2)
	≤1.09	38 (23.2)	76 (73.8)
PLH	>4.37	109 (79.6)	19 (26)
	≤4.37	28 (20.4)	

Significant at $P<0.05$. Nagelkerke $R^2=0.77$. Cox & Snell $R^2=0.56$.

criteria for pubertal response during GnRH testing. We accepted following findings as pubertal signs: i) uterine length is 35 mm or longer; ii) ovarian volume is 1 ml or larger size; iii) bone age is more advanced than chronological age by 1 years or older; iv) oestradiol level is higher than 10 pg/ml. **Findings:** We determined among all parameters what we can use in clinical scoring. (Nagelkerke) These parameters: i) age at diagnosis ii) BA-CA(year) iii) Estradiol level iv) uterine length (mm) v) Ovarian volume(cm^3) vi) peak LH level. We determined scoring every single parameters and established two different scoring model: i) Model 1 (without LH-RH stimulation test); ii) Model 2 (including peak LH level). We have designed the total score respectively as 12 and 15 points in Models 1 and 2. For diagnosis of precocious puberty, we accepted above five points (>5 points) in Model 1 and above seven points (>7 points) in Model 2 (Table 2). The specificity of both models were statistically significant. Model 1(%88.4); model 2(%91.4). **Conclusion:** Clinical and laboratory finding-based practical and integrative diagnostic scoring in the differential diagnosis of preoccious puberty) and premature telarch can be more logical and reasonable approach. We propose a newly scoring system which is used onset age, bone age-choronological age,uterine length, ovarian volume, estradiol in differential diagnosis of PP and PT. The newly proposed scoring system which allows to diagnose PP and PT without LH-RH stimulation test. This scoring model both eliminates disadvantages and provides applicaple to every society, standard and measurable approach.

P3-1162
Delayed Puberty in Girl: Clinical and Aetiologic Study

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Background: Delayed puberty in girls is evoked at the absence of breast development after the age of 13 years. It is relatively rare and must look contrary to the boy an organic cause. **Objective and hypotheses:** Search the frequency and aetiology of delayed puberty in girls. **Method:** This is a retrospective study of patients consulting for delayed puberty and collected in 5 years. The of patients was compared to the number of delayed puberty observed in boys. All patients underwent a complete clinical examination, a gonadal balance (FSH, LH, E2) and a radiological assessment (wrist and the left hand X-ray, pelvic ultrasound). A complementary paraclinical exploration was carried out depending on the etiological context (karyotype, ovarian or adrenal androgens exploration, hypophysiogramm, MRI HH.). All patients were followed and reassessed every six months. **Results:** 60 cases have been reported vs 110 in boys. The average age in the consultation was 15.8 years (14–20). Etiological exploration revealed an organic cause in 2/3 of cases: turner syndrome35%, Idiopathic hypogonadotropic hypogonadism 15%, Kalmann syndrome 10%, autoimmune oophoritis 3% hypogonadotropic hypogonadism post radiotherapy 3%, PCOS2%. In 32% of cases, it was a simple delayed puberty. **Conclusion:** In accordance with the literature, delayed puberty in girls is twice less than boys. It is usually organic, and must be explored early. In all cases, early and prolonged management is essential to ensure optimal growth and pubertal development and normal reproductive function.

P3-1163
Pubertal Development Anticipation

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Table 2. Scores for every single parameters (for abstract P3-1161).

	Model 1: Nagelkerke $R^2=0.77$				Model 2: Nagelkerke: $R^2=0.81$			
Variables *n* (%)	β	Rounded score	Adjusted OR (95% Cl)	*P*	β		Adjusted OR lower	*P*
Age at diagnosis	3.02	3	20.4 (5.87-70.90)	0.001*	3.32	3	27.68 (5.87–141.93)	0.001*
BA-CA	2.15	2	8.61 (3.34-22.22)	0.001*	2.68	2.5	14.63 (95.87–70.90)	0.001*
Estrogen	3.63	3.5	37.64 (9.33-151.90)	0.001*	2.74	2.5	15.60 (2.83-85.800)	0.002*
Uterine length	1.89	2	6.65 (2.75–16.12)	0.001*	1.60	1.5	4.95 (1.61–13.17)	0.005*
Overian volume	1.54	1.5	4.64 (1.89–11.35)	0.001*	2.35	2	10.52 (2.97–37.27)	0.001*
pLH	–	–	–		3.51	3.5	33.52 (8.20–136.89)	0.001*
		Total = 12				Total = 15		

Background: Pubertal timing is influenced by a complex interaction among genetic, nutritional, environmental and socio-economic factors. Over the past 30 years a trend in pubertal timing anticipation has been demonstrated. Environmental factors involved in this phenomenon are mainly represented by endocrine disruptors compounds (EDCs), such as pesticides, industrial compounds and persistent organic pollutants, estrogens and phytoestrogens. **Objective and hypotheses:** We report our experience with patients referred to our Unit for evaluation of pubertal development anticipation. **Method:** Over the last 4 years 82 patients, 76 females and six males, aged between 4.5 and 11.0 years were referred to our pediatric endocrinology department for pubertal development evaluation. Work-up included auxological evaluation, measurement of FSH, LH, prolactin, testosterone, estradiol, FT_4, TSH, beta-HCG, alpha-fetoprotein in addition to bone age and pelvic ultrasound in females. MRI of the hypothalamic-pituitary region to rule out organic causes of precocious pubertal development and GnRH stimulation tests were performed in those patients who presented clinical and laboratory features consistent with precocious pubertal development. **Results:** Out of 82 patients, 48 (42 females and six males) were diagnosed with precocious pubertal development: 20 patients with central precocious puberty (three secondary and 17 idiopathic), 12 with precocious pubarche, 12 with precocious thelarche, and four patients with thelarche variant. Patients (two adopted males) with central precocious puberty received treatment with GnRH analogue. All patients on treatment showed slowing of both pubertal progression and bone maturation. No adverse events were observed. **Conclusion:** Our experience, even if carried out on a small number of patients, is in agreement with the growing evidence of pubertal maturation occurring at earlier ages. A key role is probably played by EDCs, more often widely used in everyday life. Many authors are suggesting to redefine the ages for early maturation, since the entire distribution of pubertal timing has shifted to a younger age.

P3-1164

The Relationship between Xenoestrogens Exposure and Early Puberty among Young Females Living in Jeddah, Saudi Arabia

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Background: Xenoestrogens are artificial oestrogen compounds, found in our environment throughout various chemical products, and claimed to affect the process of early puberty among young females. **Objective and hypotheses:** To investigate the relationship between exposure to xenoestrogen products and early pubertal sex development. **Method:** Cross-sectional study conducted in Jeddah, Saudi Arabia in July 2014 ($n = 568$), pubertal staging was done using the Tanner staging, data collected through a questionnaire. Data analysis done by Pearson's Correlation Coefficient. **Results:** A significant relation between the usage of children toys and the age of breast (P value $= 0.040$) and pubic hair development (P value $= 0.028$). Usage of plastic bottles showed a significant relation with early pubic hair development (P value $= 0.048$). An inverse effect on pubertal signs. Which means the more frequent they use them the earlier they get their puberty. **Conclusion:** This study confirmed the association between using xenoestrogen products and early puberty in young females. Therefore, we advise to decrease the use of products that contain xenoestrogens in our daily life.

P3-1165

One Year Follow-Up of Asymptomatic Precocious Puberty; Clinical and Laboratory Characteristics

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Background: Children with bone-age advancement without any pubertal sign (asymptomatic precocious puberty, asmyptomatic PP) were reported (CW Ko,et al, at the Annual Meeting of ESPE, 2012 and 2013). **Objective and hypotheses:** In our follow-up study, some more children with asmyptomatic PP were enrolled additionally. We analysed their clinical and laboratory characteristics at the time of diagnosis, and they were followed-up prospectively to see their clinical and laboratory changes during 12 months. **Method:** Among children who visited to predict their final adult heights between July 2007 and May 2014, children with significant bone-age advancement (>1 year) without any pubertal sign under the age of 8 years in girls and 9 years in boys were enrolled. Their clinical and laboratory data including GnRH stimulation were analysed at the time of diagnosis. In order to see their start of pubertal signs and changes of laboratory characteristics including GnRH stimulation test, 48 and 33 children with asymptomatic PP were followed-up at 6 and 12 months later, respectively. **Results:** Fifty-five children with asympomatic PP were enrolled. Male:female ratio was 1:2.2. Positive value (peak LH >5 IU/l) of GnRH stimulation test was found in 23 out of 55 children (42%). Positive results of GnRH stimulation test were significantly more common in boys than in girls, 67 and 30%, respectively ($P < 0.05$). Positive results of GnRH test were observed 80 and 90%, at 6 mo and 12 mo follow-ups, respectively, in boys. In girls, the frequency of positive GnRH test at 12 mo follow-up was not increased compared to 'at the time of diagnosis', 25 and 23.6%, respectively. Pubertal signs appeared in 24 (50%) out of 48 patients, 80 and 35%, in boys and girls, respectively. Pubertal signs appeared more common in boys than in girls during 6 mo ($P < 0.05$). **Conclusion:** Boys with bone-age advancement without any pubertal sign should be closely followed-up. Long-term observatory study is necessary in terms of need for GnRHa treatment and final height.

P3-1166

Functional MRI of a Female Teenager of Prada-Willi Syndrome Complicated with Mosaic Turner Syndrome

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Background: A patient with both Prader-Willi syndrome and mosaic Turner syndrome is extremely rare. We performed fMRI and euglycaemic-hyperinsulinaemic clamp test for her. **Case presentation:** A 17-yr-old girl was diagnosed as Prader-Willi syndrome by her clinical investigations including poor feeding in infancy, hyperphagia, developmental delay, mental disorders, behavior problems, thin upper lip, almond-shaped eyes, acromicria and genital hypoplasia. Maternal uniparental disomy of chromosome 15 was determined by MLPA. Chromosomal analysis showed her Karotype was mosaic 46,XX [26]/45,X [4]. Euglycaemic-hyperinsulinaemic clamp test revealed that M-value was 1.76 mg/Kg per min. Her fasting leptin level was 3.63 ng/ml, while 2 h-post leptin level was 1.94 ng/ml. serum E_2 was 28.00 pg/ml and T 0.32 ng/ml,while FSH was 5.34 IU/l and LH 0.45 IU/l. Functional MRI did not show any high activity for thalamus. **Conclusion:** Patient with both Prader-Willi syndrome and mosaic Turner syndrome has typical clinical presentations of Prader-Willi syndrome, lower insulin sensitivity and normal activity of thalamus when examined by functional MRI.

P3-1167

In a Severe Precocious Puberty Case Who Treated with Frequent Leuprolid Acetate Injections, a Rare Adverse Effect: Sterile Abscess

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Introduction: GnRH analogues common used in precocious puberty are highly effective agents. The drug dose and injection frequency should be designed for each case. However these agents are common well tolerated, some rare adverse effects may be occur. We present a case of frequent leuprolid acetate injections-related sterile abscess. **Case:** The case was 16-month-old boy. He had rapid growth, big penis, and excessive pubic hair. These symptoms have appeared since last year. Both height and weight were over 97th percentiles. His stretched penil length was 7 cm and bilateral testicular volume were 6 ml. Bone age was 3 years old. Hormone tests: basal FSH: 11.2 mIU/ml, LH: 6.7 mUI/ml, and testesterone: 43 pg/ml. Pituitary MR had no abnormal findings. We diagnosed central precocious puberty. Then, we started leuprolid acetate (Lucrin 3.75®) injections once every 4 months. But we didn't observe response to treatment. We had to give injections respectively once every 3 weeks and once every 2 weeks. We managed to suppress gonadotropin secretion. After four weeks, sterile abscesses appeared in his arm and leg. Abscesses were drained by surgeons. We replaced leuprolid acetate to triptorelin acetate (Decapeptyl 3.75®). We gave injections once in 10 days. **Conclusion:** During the precocious treatment, the rare adverse effects like sterile abscess may occur and they shouldn't be ignored by clinicians. Severe precocious puberty case can be treated with more frequent injections and higher doses.

P3-1168

Endocrinopathies in a 17-Year-Old Girl with Diamond–Blackfan Anemia and Transfusion-Associated Iron Overload

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Background: Diamond–Blackfan anemia (DBA) is an inherited bone marrow failure syndrome, which presents with anemia in early infancy. Survival depends on blood transfusions, which in consequence lead to iron overload (IOL). The most common complications of IOL are hepatic cirrhosis, endocrinopathies and cardiomyopathy. **Results:** We present the case of 17 years old girl with DBA and IOL-associated endocrinopathies. Her treatment consists of multiple blood transfusions and corticosteroids. Iron chelation therapy with deferasirox and desferrioxamine was started at 10 years (irregularly). At first examination in our clinic at age 15 the girl was severely growth retarded (-4.20 SDS, bone age $=15$ years, serum IGF1 level were within normal ranges for age) and had excess weight (1.10 SDS BMD). Serum ferritin (SF) level was in the range of 1785–4277 ng/ml (IOL–SF $>$ 1000 ng/ml). At age of 15 the girl was diagnosed with hypogonadotropic hypogonadism (there was no response FSH/LH to LHRH stimulation; AMH, marker for ovarian reserve, was normal), impaired glucose tolerance (75 g oral OGTT was performed), insulin resistance (ISI Matsuda $=2.5$ ($n>2,6$) and HOMA-IR $=4.6$ ($n<3.2$)), second hyperparathyroidism, osteoporosis (BMD of the lumbar spine was examined, Z-score $=-2.7$ S.D.). Basal adrenal and thyroid function were normal. We used (MRI) to measure pituitary iron concentration and volume. The pituitary height and volume were significantly decreased: $V=64$–68 mm^3 (n 305 ± 86 mm^3). Results of pituitary MRI (T2*) were in the range of 6.9–7.1 ms ($n>20$ ms). **Conclusion:** In conclusion, we have demonstrated that endocrinopathies are extremely frequent in patients with IOL. Hypogonadism is the most common morbidity in patients with transfusion-dependent anemias. Pituitary iron overload and volume loss are independently predictive of hypogonadism. MRI can be used as a non-invasive tool to recognize pituitary IOL and identification of proper chelation therapy for the prevention of irreversible pituitary tissue damage. Our observations emphasize the importance of periodic, meticulous evaluation of the endocrine function of patients with transfusion-associated IOL.

P3-1169

Large Goitre in a Patient with Congenital Hypothyroidism

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Background: Congenital goitre presenting in the newborn period is very rare. Here we present a case of congenital hypothyroidism with a large goitre, leading to trachea compression symptoms. Hormone replacement therapy was started leading to normal levels of TSH, FT_4, and thyroid volume. In face of maternal normal thyroid levels, dyshormonogenesis considered to be the most probable cause of hypothyroidism. **Case presentation:** A male full term newborn to non-consanguineous healthy parents. Neck mass was first diagnosed by ultrasound at 33 weeks of gestation. The boy incubated soon after birth due to breathing abnormalities and asphyxia, which were caused by trachea compression. He was diagnosed with congenital goitre and thyroid deficiency at day 1 of life (goitre volume 55 ml, TSH levels >75 mIU/l, and FT_4 levels <4.5 pmol/l). In addition, he was found to have trial septal defect and cardiomegaly. Therapy with levothyroxine started on day 2 of life at the initial dosage of 15 mg/kg per day, what lead to immediate reduction of the goitre volume and possibility of extubation. Normalisation of TSH and FT_4 levels achieved at 29 days of life. Goitre volume decreased down to 13 ml by the 29th day of life. Patient's DNA was analysed for a wide genetic panel, including *NKX2-1, UBR1, GLIS3, AITD3, TRH, SLC26A4, SECISBP2, DUOXA2, THRB, IYD, SLC5A5, DUOX2, TRHR, TSHR, DUOX1, THRA, SLC16A2, TPO, TSHB, FOXE1, PAX8, GNAS*, and *NKX2-5* genes, by using massive parallel sequencing, no mutations were found. **Conclusion:** Congenital hypothyroid goitre can grow huge volume. In our case, it led to trachea compression and need for mechanical ventilation. Even though we were not able to find mutations in genes, known to be involved in thyroid formation, we suspect dyshormonogenesis as the most possible cause of goitre development. Additional genetics studies should be performed in attempt to disclose other possible mechanisms.

P3-1170

Topical Iodine Induced Thyrotoxicosis in a Newborn with Giant Omphalocele

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Background: Thyrotoxicosis in neonates is a life-threatening condition that can be associated with lasting neurologic problems. Most cases are seen in neonates born to mothers with Graves' disease in which thyroid stimulating immunoglobulin (TSI) is transferred to the foetus and results in hyperthyroidism. Hypothyroidism due to topical iodine use has been reported in neonates, but thyrotoxicosis has never been described in this age, while in adults is a known entity. We hereby describe a first case of topical iodine induced thyrotoxicosis in a new-born with giant omphalocele. **Case presentation:** A female baby born at 34 weeks of gestation with multiple congenital abnormalities, including a giant omphalocele, persistent ductus arteriosus, and thoracolumbar scoliosis. In preparation for surgery omphalocele was covered with daily betadine dressings containing potassium iodide (KI). On day 3rd of life, evaluation of thyroid revealed suppressed TSH at 0.59 mcIU/ml (NL 0.73–4.60 mcIU/ml) and elevated free thyroxine (FT_4) at 5.63 ng/dl (NL 0.58–1.64 ng/dl) that subsequently lead to symptomatic hyperthyroidism with tachycardia and hypertension. Maternal history was negative for thyroid disease and thyroid antibodies were negative. Therefore we presumed that hyperthyroidism was secondary to KI dressing. On day 5th of life the KI dressing was changed to SilvaDene (iodine free) dressing, and propranolol 0.01 mg/kg per dose was started to treat hypertension and tachycardia. Serial daily thyroid tests were monitored. Thyroid status gradually improved with complete resolution in 8 days after removal of KI dressing (FT_4 1.26 ng/dl, TSH 2.21 mcIU/ml, and FT_3 2.34 pg/ml). Propranolol discontinued. **Conclusion:** Hypothyroidism due to topical iodine use in omphalocele has been described in new-borns. Novel insight: to our knowledge, this is the first case of topical iodine induced neonatal thyrotoxicosis. This case demonstrates the critical need to monitor thyroid status in new-borns treated with topical iodine, in order to identify thyroid abnormalities and to consider alternative methods.

P3-1171

A Familial Case of Congenital Hypothyroidism due to a Mutation in the Thyroglobulin Gene Detected by Next Generation Sequencing

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Background: Congenital hypothyroidism (CH) is a heterogeneous disorder. While the great majority of cases are considered sporadic, the use of next generation sequencing (NGS) may bring significant advances in elucidating the underlying molecular mechanisms. **Case presentation:** We selected a family with three children affected by CH with gland *in situ* and diagnosed at neonatal screening: the index patient, his sister and his brother. Data at diagnosis and follow-up are listed in the Table 1. They present an important familiarity for thyroid diseases. The mother and her sister have a multinodular goiter in euthyroidism without anti-thyroid antibodies; the mother's thyroglobulin (TG) level is 126 ng/ml (range 0–60 ng/ml). In addition, the maternal grandfather developed a multinodular goiter with a Plummer adenoma

Table 1. (for abstract P3-1171)

Patient	I spot TSH (mcIU/ml)	Serum TSH (mcIU/ml)	Serum FT_4 (ng/dl)	Thyroglobulin (ng/ml)	US	L-thyroxine therapy at diagnosis	Re-evaluation	Range of TSH values without therapy (mcIU/ml)
Index patient (2013)	10.01	16.9–11.07	1.2–1.07	189 (0.2–55)	Normal	No	No	5.6–11.7
Sister (2005)	12.5	42.8	1.15	148 (0.2–55)	Normal	Yes	Stopped L-T_4	7.32–14.71
Brother (2002)	10.7	19.51	1.1	34.8 (1–75)	Normal	Yes	Stopped L-T_4	6.39–10.25

requiring thyroidectomy. All family members have an adequate dietary iodine intake. NGS analysis revealed a heterozygous missense mutation (p.P118L) in the TG gene of the three siblings and of their mother. The other analyzed genes (*NKX2-1, PAX8, FOXE1, GLIS3, DUOX2, DUOXA2, SLC26A4, TPO, TSHR*, and *JAG1*) resulted WT. **Conclusions:** According to the identification of the genetic variant in TG with a strong positive family history for multinodular goiter, an adequate ultrasound follow-up and a tailored therapeutic strategy are needed. Indeed, these patients could benefit from hormone replacement therapy with levothyroxine, even in case of a mild increase in TSH concentrations, in order to avoid thyroid surgery in the future.

P3-1172
Central Hypothyroidism and GH Deficiency in a Boy with Williams–Beuren Syndrome

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Background: Thyroid disorders (subclinical hypothyroidism and structural abnormalities) are common in Williams syndrome (WS) patients. **Objective and hypotheses:** Central hypothyroidism and GH deficiency (GHD) in a WS patient are discussed. **Method:** Case report and literature review. **Results:** A 5-month-old male was admitted to our hospital because of growth failure since the 3rd month, mild dysmorphisms, micropenis. He was a second-born at term from non-consanguineous parents. During pregnancy the mother has been treated with levothyroxine for a Hashimoto's thyroiditis. After birth, the baby presented normal adaptation parameters, weight 2880 g (3rd–10th), length 48 cm (3rd–10th), and head circumference 33 cm (3rd–10th); later mild jaundice, without history of hypoglycaemia or calcium disorders was reported. No thyroid dysfunction was detected by screening test. At admission, weight was 5670 g (<3rd), length 63 cm (3rd), and head circumference 40 cm (<3rd); no neurological abnormalities or heart murmurs were noted. Main signs observed at the dysmorphological evaluation were: fullness of the peri-orbital structures, epicanthal folds, full cheeks, small upturned nose with long philtrum and down-turned corners of the mouth, micropenis. Blood tests revealed a central hypothyroidism (FT_4 0.72 ng/dl and TSH 3.53 mcIU/ml) associated to a GHD documented by two stimulation tests (peak of GH: 1.89 and 1.76 ng/ml), IGF1 6.8 ng/ml. Remaining pituitary gland function and structure (MRI) was normal. Echocardiogram resulted unremarkable. Levothyroxine was started (upto 2 μg/kg per day) with a prompt normalization of FT_4. hGH therapy was also initiated at a dose of 0.15 mg/kg per week with a growth improvement. Genetic tests (FISH) revealed a 7q11.23 microdeletion, confirming the suspected diagnosis of WS. Array-CGH is now ongoing to define the extension of the deletion and to understand if the involvement of other genomic regions, contiguous to the WS critical region or not, can contribute to this endocrinological picture. **Conclusion:** In addition to the peripheral forms, also a central hypothyroidism can be found in WS patients. Our patient also showed a GHD, that is rarely reported in WS.

P3-1173
Avoidable Thiamazole-Induced Omphalomesenteric Duct Remnants: 20-Year Retrospective Study in Our Hospital

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Background: Although thiamazole (MMI) is the first-line treatment for non-pregnant women with Graves' disease, the teratogenic effects of this drug have been confirmed. Surgical anomalies known as 'major MMI-related anomalies' include omphalomesenteric duct remnants. This is a common difficulty when attempting to clarify whether there is any association between infrequent surgical anomalies and MMI exposure using data derived from women with Graves' disease. So, it is necessary to investigate whether the incidence of infrequent surgical anomalies is associated with MMI exposure. Since our hospital is a specialized children's facility, we are able to accumulate a large database of surgical diseases. Consequently, we could review the incidence of infrequent MMI-related surgical anomalies. **Objective and hypotheses:** The objective of this study was to elucidate

the association between MMI exposure during pregnancy and major MMI-related surgical anomalies. **Method:** We reviewed 76 cases that attended our hospital over a 20-year period from 1991 to 2010. These cases received surgical treatment for omphalomesenteric duct remnants, omphalocele, or esophageal atresia. Based on the medical records of these patients, we investigated whether the incidence of these three anomalies was associated with exposure to MMI during pregnancy. **Results:** Having excluded patients with chromosomal aberrations, we were left with a total of 68 cases. Of these, 12 had omphalomesenteric duct remnants, 14 had omphalocele, and 46 had esophageal atresia. The following result show the ratio of each anomaly for which MMI exposure caused. For omphalomesenteric duct remnants, five out of 12 were exposed to MMI; for omphalocele, two out of 14 were exposed, and for esophageal atresia, only one out of 46 was exposed. There was a significant difference in the ratio between omphalomesenteric duct remnants and esophageal atresia. **Conclusion:** Based on medical records, we investigated whether there had been a history of MMI exposure during pregnancy among those patients presenting with major MMI-related surgical anomalies. From these data, we concluded that omphalomesenteric duct remnants were strongly associated with MMI exposure.

P3-1174

The Impact on Families of Receiving a Diagnosis of Congenital Hypothyroidism

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Background: Congenital hypothyroidism (CHT) may be viewed as a relatively easy condition to diagnose and treat. However, for the parents who are contacted with the neonatal screening results the news can be devastating, and the quality of information provided can be very variable. **Objective and hypotheses:** We aimed to explore the experience of parents at the time of diagnosis, and ascertain how we could improve this. **Methods:** In association with the British Thyroid Foundation, our regional service organised a family education day, followed by a nationwide web-based questionnaire to ascertain the views of families regarding their experiences. Questions included how and by whom the diagnosis was made, when treatment was initiated and what information they were given at that time. **Results:** One hundred people responded to the questionnaire. Seventy percent said they were first given the diagnosis by a doctor, and 70% were seen at the local hospital on the same or next day, although 18% were seen later than 4 days after diagnosis. Seventy percent felt that the doctor clearly explained the diagnosis and its implications, 38% were given comprehensive written information and 4% were given information about support groups. Ninety-three percent of families would have valued being put in touch with other parents of children with CHT. Common responses to free text questions were feelings of isolation, shock and fear for the future, and a lack of information and coordinated follow up. Positive points included receiving reassurance about the long-term outlook and spending time with a knowledgeable professional. **Conclusion:** Whilst we inform our patients and families about rare and complex medical diagnoses, perhaps we underestimate the need for equivalent input into what we may consider to be a relatively simple condition. We clearly need to provide more written information and support to our patients with CHT at the time of diagnosis.

P3-1175

Final Height in Italian Patients with Congenital Hypothyroidism Detected by Neonatal Screening: An Observational Study Over 20 Years

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Background: Linear growth in patients with congenital hypothyroidism (CH) born in 1970s and 1980s is reported normal. **Objective and hypotheses:** To evaluate whether the earlier diagnosis and the higher L-T_4 starting dose lead to an improvement in growth and pubertal outcome over the last two decades. **Method:** Two-hundred and fifteen patients with permanent CH born in 1980s and 1990s (age at diagnosis 25.1 ± 10.5 days, starting treatment 8.8 ± 2.9 (g/kg per day) were followed up until final height (FH, growth velocity <1 cm/year) was attained. **Results:** Height at puberty onset -0.1 ± 1.0 SDS, height gain during puberty -0.1 ± 0.8 SDS. Height at puberty onset was significantly higher than target height (TH; $P<0.001$). The puberty onset was within the normal limits for age in 212 (98.6%) patients. FH (-0.1 ± 1.0 SDS) was not different as compared to height at puberty onset but higher than TH (-0.8 ± 1.0 SDS, $P<0.001$). FH was significantly correlated with TH ($r^2=0.564$, $P<0.001$) and height at puberty onset ($r^2=0.685$, $P<0.001$), but not with age at diagnosis or the starting L-T_4/kg per day dose. The curve fitting analysis showed that over the two decades the age at diagnosis progressively decreased ($r^2=0.083$, $P<0.001$), while the TH and the starting L-T_4/kg per day progressively increased ($r^2=0.200$, $P<0.001$ and $r^2=0.033$, $P=0.007$ respectively). FH was not affected by the birthdate, the age at diagnosis, nor the starting L-T_4 replacement dose. **Conclusion:** Age at puberty onset was normal, as well as FH which was significantly higher than TH. The age at diagnosis did not play any role on FH. Despite the large improvement in the screening strategy and the treatment approach FH did not improve in patients born in 1980s and 1990s. The findings of

this study are in keeping with the described secular trend in height. The early diagnosis and the treatment strategy do not seem to affect the FH.

P3-1176

Graves' Disease in Childhood and Adolescence: Clinical Manifestations, Adverse Effects, and Predictive Factors for Response to Antithyroid Drugs

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Background: Antithyroid drugs (ATD) are recommended as the initial treatment in Graves disease in childhood and adolescence. Identification of predictive factors might lead to improve patient management by facilitating the identification of patients requiring long-term ATD or early alternative therapy. **Objective and hypotheses:** To assess the prevalence of signs and symptoms of hyperthyroidism in childhood and adolescence, to evaluate the rates of adverse events after medical treatment and to determine prognostic factors for the response to pharmacological treatment. **Method:** We performed a retrospective, descriptive study. We evaluated 157 patients, mean age of 10.78 ± 3.17 years, who were seen between September 2005 and May 2012 at Hospital J. P. Garrahan. **Results:** The most common symptoms were: tremor (79%), weight loss (70%), tachycardia (70%), attention deficit (49%), and exophthalmos (44.6%), goiter more than three times the normal size defined by palpation (35%), diarrhea (21%), fever (10.8%), and menstrual irregularities (28%). Three to five symptoms were simultaneously found in 64% of cases. At least one associated disorder was found in 29%, being the most frequent, Down syndrome (12.7%). Adverse effects generated by antithyroid medication were observed in 29 patients (18.5%). Hepatitis was seen in 8.3%, hematological disorders in 7%, and arthritis in 6.4%. Only five of 29 cases (18.5%) had more than one adverse effect. Overall, 69% (n: 109) did not respond to drug treatment over a time lapse of 4 years after the first visit. Logistic regression model of factors for poor response to medical treatment were as follows: Age at diagnosis <10 years ($P<0{,}01$), a large goiter ($P<0{,}01$), and high initial T_3 (>6.8 ng/ml), fT_4 (>5.24 ng/dl), and TBII ($>70.5\%$) levels ($P<0.0001$). **Conclusion:** In young patients with a large goiter and high serum T_3 and TBII levels, early alternative therapy instead of ATD should be considered.

P3-1177

The Correlation between TSH Levels and BMI Percentiles in Hypothyroid Children Who are Chemically Euthyroid on Levothyroxine Treatment

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Background: Prior research has shown a correlation between TSH levels and BMI in euthyroid subjects. Whether this relation can be applied to hypothyroid chemically euthyroid children has yet to be determined. **Objective and hypotheses:** To determine if there is a correlation between TSH levels and BMI percentiles in hypothyroid children who are chemically euthyroid on levothyroxine. **Method:** Retrospective chart review of patients from Rush University Medical Center and Stroger Hospital (Chicago, IL, USA) from 2008 to 2014. 154 children aged (6 months and 21 years) with a diagnosis of primary hypothyroidism that were on levothyroxine therapy for at least 6 months and chemically euthyroid were included. Normal TSH levels were divided into three groups: T1 (0.34–1.5 mIU/l), T2 (1.6–2.5 mIU/l), and T3 (2.6–5.6 mIU/l). Data was analysed by cross tabulation (χ^2). **Results:** A total 154 patients (mean age ± S.D.: 12.69 ± 6.84 years, median age = 14.88, 68% females and 32% males) were evaluated. These included 24.7% obese children (BMI percentile $>95\%$), 20.7% overweight (BMI >85–95%), and 54.5% healthy weight (BMI $<85\%$). There was a significant positive correlation between TSH and BMI percentiles ($r=0.283$, P value <0.001). The percentage of hypothyroid children who were chemically euthyroid with healthy BMI percentiles in TSH group T1 was 40.5%, while 29.8% in both TSH group T2 and TSH group T3 respectively. The percentage of hypothyroid children with obesity was 18.1% in TSH group T1 and 60.5% in TSH group T3. Pearson's χ^2 P value = 0.013. **Conclusion:** In hypothyroid children who are chemically euthyroid, there is a positive correlation between higher TSH levels (within the normal range) and elevated BMI percentiles. Our results indicate that keeping the TSH levels into the lower third (0.34–1.5 mIU/l) of the normal range may result in a healthier BMI.

P3-1178

Short Stature with Lipodystrophy: Reminder of a Forgotten Syndrome

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Background: The combination of various severe manifestations of hypothyroidism with pseudo muscular hypertrophy is called Kocher Debre Semelaigne syndrome (KDS). KDS is very rare in countries where newborn screening for hypothyroidism is in place. Most of the reports of KDS have come from India and developing countries with only a single report from Europe over last five decades. We present a 7-year-old boy from UK who had short stature and apparent partial lipodystrophy. **Case presentation:** A 7-year-old Caucasian boy was referred with possible partial lipodystrophy. His past history included bilateral uveitis diagnosed at 7 months. On examination, he had a sallow complexion, slightly dry skin and marked loss of fat with athletic physique and prominent musculature in lower limbs. His facial

appearance was sallow with sparse eyebrows and chubby cheeks. He had protruding abdomen with small umbilical hernia and hepatomegaly. His height SDS was −2.07. Investigations demonstrated TSH >100 mU/l, free T_4 1.2 pmol/l, ALT levels of 175 U/l with normal IGF1 levels, lipids, OGTT, coeliac screen, and leptin levels. Bone age was markedly delayed (2 years and 8 months at 7 years). Anti-TPO antibodies were positive. USG of thyroid was normal and USG of liver suggested fat accumulation. He was started on Levothyroxine replacement. His thyroid function, ALT levels, hepatomegaly, growth, delayed bone age, complexion, and facial appearance have improved gradually over time (current height SDS −1.5). The fat loss and pseudomuscular hypertrophy is improving more slowly. **Conclusion:** Long standing untreated hypothyroidism can cause severe fat loss associated with other systemic effects. Although KDS is very rare in the developed world with newborn screening in place, it can still occur with unrecognised autoimmune hypothyroidism. Recognition of this condition is important to facilitate prompt treatment and to prevent further unnecessary investigation.

P3-1179

Plasma Visfatin Level and Its Association with Apolipoproteins A1 and B in Hypothyroid Children

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Background and aim: Hypothyroidism could be accountable for cardiovascular diseases; hence, necessity of novel biomarkers being capable to predict patient's status is indispensable. The aim of this study was to appraise alteration of plasma visfatin levels (as a newly discovered proteins) and its association with lipid profiles of hypothyroid patients. **Materials and methods:** In this cross-sectional, descriptive, and analytical study, 30 children being 3–18 years with levels of serum TSH ≥6.4 mIU/l were enrolled. Initially T_4, T_3, TSH, anti-thyroid peroxidase (anti-TPO), anti-thyroglobolin (anti TG), visfatin, triglyceride, cholesterol, LDL, HDL, apolipoprotein A1 (ApoA1), and ApoB as well as BMI of every subject were determined and they were assigned either in overt or subclinical cohorts; afterwards, appropriate doses of levothyroxine were administered. Three months later, all of the above-mentioned criteria (except for anti-TPO and anti-TG) were assessed. **Results:** Mean age of the patients, which included 16 females and 14 males, was 10.2±5.2 years, while subclinical cases exceeded overt hypothyroid patients (24 and six cases respectively). Anti-TPO subjects surpassed and anti TG ones (11 and eight individuals respectively). Patient's treatment led to significant decrease of plasma visfatin, ApoB, TG, cholesterol, and LDL ($P<0.05$). Alternatively, HDL and ApoA1 increased as a result of our treatment ($P<0.05$); however, BMI remained unchanged. Not only before our treatment, but also after this procedure, plasma visfatin variations did not correlated with patient's lipid profile ($P>0.05$). **Discussion and conclusion:** This study showed that plasma visfatin could be suggested as a predictive risk factor of cardiovascular diseases in hypothyroid patients.

P3-1180

Outcome of Thyrotoxicosis in Childhood and Adolescence in a Geographically Define Area; a 24-Year Experience

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Background: Paediatric thyrotoxicosis is both rarer and more severe than in adulthood, rendering management difficult, and often unsatisfactory. **Objective:** To review outcome in a geographically defined area between 1989 and 2013; hence to develop an algorithm for improved clinical care. **Method:** Retrospective case note review plus questionnaire to family doctor requesting update. Graves' disease (GD) was defined as positive TSH-R-ab (TRAB+ve)±exophthalmos; Hashimoto's (HT) as positive TPO-ab but negative TRAB+no eye signs. Treatment with antithyroid drugs (ATD) carbimazole (CBZ)±propythiouracil (PTU), total or subtotal thyroidectomy or radioiodine (RI) was recorded. Syndromic disorders (including Down's) were excluded. **Results:** 67 patients (59F:8M) were identified,median (range) age at diagnosis 10.4 (2.9–15.8) years (diabetes mellitus in three) GD in 47, HT in 13, data insufficient in seven. Median (range) duration of ATD was 4.5 (0.3–16.2) years and was initially with dose titration in 46 patients and block and replace in 21. No deaths or liver disease occurred but 16 patients changed from CBZ to PTU due to rash/neutropenia. Of 35 patients who stopped ATD for possible remission after 4.5 (1.5–8.6) years, 17 remitted (eight GD:nine HT), six within and 11 after 3 years of treatment while 13 relapsed (12 GD:one HT); outcome unknown in five. RI 500 (250–500) MBq was given to 18 patients after 5.37 (0.7–12.3) years of ATD for relapse (5), poor control/compliance (10), or electively (3) with subsequent hypothyroidism in all except one girl aged 10 years who showed persisting hyperthyroidism requiring ATD. Surgery was performed in 15 patients aged 11.64 (6–21) years for

relapse with ATD (3), poor control/compliance (9), elective Rx(3), followed by hypothyroidism (7), relapse requiring RI (1), return to ATD (2), euthyroid (2), and unknown (3). One patient developed hypoparathyroidism after surgery. **Conclusion:** HT is more likely to remit with ATD than GD. Time to remission with GD is variable with no evidence to support trying patients off treatment after an arbitrary interval (e.g. 3 years). We recommend i) rigorous patient education; ii) ascertainment of TPO and TRAB status at diagnosis; iii) dose titration rather than block and replace to permit continuous evaluation of thyroid status and possible remission; and iv) recourse to second line treatment (RI or total thyroidectomy) sooner rather than later when adherence to ATD becomes a struggle for the family.

P3-1181

Early Discrimination between Transient and Permanent Congenital Hypothyroidism in Children with Eutopic Gland

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Background: Congenital hypothyroidism (CH) is a common condition that occurs in ~1:3000–4000 live births and is one of the most common preventable cause of mental retardation with an early diagnosis and prompt pharmacological treatment. Neonatal screening has abolished this disease but 10% of children originally diagnosed with CH will have a transient form of the disorder and this percentage is increased during the last years due to a lowering of cut-off. **Aim:** The schedules for re-evaluation of patients are different and factors useful to distinguish between transient and permanent CH are not well established. We enrolled 64 patients with a positive neonatal screening and eutopic thyroid gland that were re-evaluated at the age of three years, resulting to be affected both by permanent and transient CH. We aimed to identify factors useful to distinguish early between the two groups (A, transitory and B, permanent). **Results:** None of the patients in group A (46 patients) required an increase of L-T_4 dose during the first three years of life but L-T_4 dose was increased in 16/18 patients (88.8%) in group B ($P<0.0001$). Mean L-T_4/kg body weight was significantly different between groups A and B at 1, 2, and 3 years of age respectively (2.3 ± 0.8 μg/kg per day vs 3.8 ± 1.0 μg/kg per day; 1.9 ± 0.5 μg/kg per day vs 3.6 ± 1.1 μg/kg per day; and 1.4 ± 0.5 μg/kg per day vs 3.1 ± 1.0 μg/kg per day, $P<0.0001$). The results of ROC curve analysis suggested that: i) L-T_4 requirements >4.9 μg/kg per day at 12 months or >4.27 μg/kg per day at 24 months are highly suggestive of permanent CH; ii) L-T_4 requirements <1.7 μg/kg per day at 12 months or <1.45 μg/kg per day at 24 months are highly suggestive of transient CH. **Conclusion:** The analysis of L-T_4 requirements during the 1st years of life might allow an early discrimination between transient and permanent CH in eutopic patients.

P3-1182

The Role of Early Thyroid Imaging in Children with Congenital Hypothyroidism

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Background: Congenital hypothyroidism (CH) occurs in 1:3000–1:4000 newborns. The majority of newborns with CH are detected by routine screening programs and treatment is promptly initiated following confirmatory thyroid function testing. Although early imaging studies do not influence the treatment decision or management, they establish the underlying diagnosis and may distinguish between permanent and transient CH. **Objective:** To assess the role of early thyroid imaging in predicting the course and management of CH. **Methods:** A retrospective study of full-term healthy CH infants diagnosed between 2000 and 2012 and followed for at least 3 years in our institution. Patients were categorized into three groups based on their thyroid imaging and CH outcome: agenesis/ectopic, eutopic-permanent, and eutopic-transient. **Results:** Of the 142 infants who underwent imaging studies (scan 116 and ultrasonography 26), agenesis/ectopic thyroid was found in 58 (41%), and eutopic thyroid in 84 (59%) including hypoplasia in 32 (22.5%) and normal-sized gland with increased or normal uptake in 52 (36.5%). Imaging findings were comparable in the eutopic-permanent and the eutopic-transient groups ($P=0.55$). At initial evaluation, TSH levels were higher and FT_4 levels lower in the agenesis/ectopic vs eutopic-permanent and eutopic-transient groups (71.5 ± 11.2 mU/l vs 49.1 ± 27.9 mU/l and 42.5 ± 29.1 mU/l; 6.8 ± 4.9 pmo/l vs 11.4 ± 6.4 and 12.5 ± 5.1 pmo/l, respectively, $P<0.001$ for both parameters). Since the 3rd month of follow-up thyroxin requirements were significantly higher in the agenesis/ectopic compared to the eutopic-permanent group ($P<0.001$); since the 6th month they were significantly higher in the eutopic-permanent compared to the eutopic-transient group ($P<0.01$). Predictive factors for permanent CH were initial TSH >63.5 ($P<0.001$) and thyroxine dose >1.4 μg/kg per day at age >6 months ($P<0.01$). **Conclusions:** Transient and permanent CH are distinct in TSH levels at diagnosis and thyroxin requirements throughout follow-up. Early thyroid imaging does not distinguish between permanent and transient CH and can be postponed and preformed according to clinical judgment or needs.

P3-1183

Effect of Marijuana Use on Thyroid Function and Autoimmunity

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Background: Cannabis use has been legalised in four states in USA. However, endocrine effects of marijuana use are largely unknown. Published experiments on animals have suggested that acute cannabis exposure may lead to suppressed thyroid function, but human studies are limited. Of interest, some studies have shown that cannabis has immunomodulatory effects. **Objective and hypotheses:** We carried out a cross sectional analysis of data by National Health and Nutrition Examination Survey (NHANES) conducted 2009–2012 by CDC to assess the relationship between marijuana use and thyroid function, and the prevalence of thyroiditis between recent and nonuser/past users. **Method:** We included 1715 adults ages 17–45 years who responded to questions related to marijuana use and also had lab results related to thyroid function. Questions were self-administered using the ACASI system, assessing life time marijuana use, timing and frequency of use. We categorized subjects into two groups of i) recent marijuana users (used within 30 days) and ii) past users (older than 30 days) or non-users. Spearman correlations and χ^2 tests were used to look at associations between marijuana use and either thyroid function (TSH, total and free T_3, and total and free T_4) or positivity for thyroglobulin antibody (TBGA) and thyroperoxidase antibody (TPOA). **Results:** Total of 53% of the subjects reported lifetime cannabis use with 18% reporting recent use in the last 30 days. There were weak but statistically significant inverse correlations between recent marijuana use and thyroid antibody levels: TPOA ($r=-0.07$, $P=0.003$), TBGA ($r=-0.05$, $P=0.02$), while free T_3 showed a significant positive correlation ($r=0.05$, $P=0.04$). Based on the NHANES cut off of 4 IU/ml for positive TBGA, recent marijuana users showed a significantly lower rate of positive TBGA (2.8% vs 6.1%). **Conclusion:** Recent marijuana users have a lower prevalence of thyroid autoimmunity. This suggests that marijuana may have immunomodulatory effects. Large prospective studies are needed to confirm this finding.

P3-1184

Paediatric Thyroid Disease: About a Series of 48 Cases

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Background: The thyroid disorders in children and adolescents are varied. They are dominated by frequent malignant tumour lesions and goitres represented by Graves' disease and Hashimoto's thyroiditis in adolescence. They are characterized by several clinical forms. **Objective and hypotheses:** To study the clinical and aetiological characteristics of thyroid disease in children and adolescents. **Method:** This is a retrospective descriptive study of 48 observations of thyroid diseases in children and adolescents collected over a 10-year period (2005–2015). **Results:** Average age of our patients was 12.96 years (2–16), the prevalence is feminine with three 8G/10B familial predisposition was found IN 46.6% (*n*: 20). We observed 15 cases of hypothyroidism (eight congenital and seven autoimmune), 13 cases of hyperthyroidism (Graves' disease 100%) 12 cases of euthyroid goitre and six cases of thyroid nodule. Four of them were related neoplastic: differentiated thyroid cancer diagnosed at an advanced stage in 50% cases (T4 M1N1). **Conclusion:** Hypothyroidism can be congenital or acquired. It must be recognized and treated precociously to avoid deleterious effect on psychomotor development and growth. Hyperthyroidism in children is dominated by Graves' disease. The diagnosis is easy, the main difficulty is regarding patient care due to frequent relapses. In front of a thyroid nodule, the obsession is thyroid cancer that is characterized by a significant aggressiveness and poor prognosis. Cytology and clinical and morphological monitoring are essential. Despite the correction of iodine deficiency in our country, the prevalence of simple goitre remains high.

P3-1185

Neonatal Hyperthyroidism with Craniolacunia

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Background: Overt neonatal hyperthyroidism is estimated to occur in 1–2% of offspring of pregnant women with Graves' disease. Preterm delivery, enhancement of bone include advanced bone age, craniosynostosis, and microcephaly may be present. Ventriculomegaly and hydrocephalus may present rarely, and just three cases were reported previously. Craniosynostosis is a risk factor for delayed cerebral development, hydrocephalus, and psychomotor retardation. Craniolacunia (Lacnar skull deformity) is an abnormality of the calvarial bones of the skull, which develops during fetal life and is present at birth. It is almost always associated with meningocele, and rarely with craniosynostosis, Arnold-Chiari malformation, and Klippel-Feil syndrome. However craniolacunia with neonatal hyperthyroidism has not previously been reported. **Objective and hypotheses:** This is the first report of two cases with neonatal hyperthyroidism due to maternal Graves' disease associated with craniolacunia, although neither of them had craniosynostosis. **Results:** Case 1: a male infant was delivered at 35 weeks' gestation to a 27-year-old mother with Graves' disease. His mother had been treated with thiamazole (MMI) and levothyroxine from 25 weeks gestation because TRAb was >30 IU/l (normal, <2). He had a goitre, exophthalmos, irritability, dyspnoea, hepatosplenomegaly, thymic enlargement, thrombocytopenia, hydrocephalus with aqueductal stenosis, and craniolacunia. TSH <0.005 μIU/ml, FT_3 29.79 pg/ml, and FT_4 >7.8 ng/dl at 3 days old. Case 2: a female infant was delivered at

33 weeks' gestation and affected with ventricular septal defect. Her mother had pedal oedema and hypertension from 24 weeks gestation and was diagnosed as having Graves' disease on the first *postpartum* day (TRAb 23.5%; normal, $<15\%$). At 5 days old, she presented with irritability due to hyperthyroidism which abated spontaneously. She had craniolacunia. **Conclusion:** This is the first report of two cases with craniolacunia associated with neonatal hyperthyroidism due to maternal Graves' disease, although neither of them had craniosynostosis.

P3-1186

Is Transient Hypothyroidism in Preterm Infants True?

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Background: A second screening for congenital hypothyroidism between the 2nd and the 4th weeks of life in preterm infants is recommended in order to avoid false negative on the first screening. The incidence of transient hypothyroidism in this population is high. **Objective and hypotheses:** i) Analyse the utility of the second screening in our population of preterm infants. ii) Follow-up of those preterm infants with hypothyroidism. **Method:** Prospective study of 434 premature infants with a gestational age <32 weeks and/or BW 1500 g (220 females) born between January 2003 and December 2013 with a negative first screening, were included. TSH and free T_4 by chemiluminescence assay (Siemmens) were determined between the 2nd and 4th postnatal weeks. SPSS14 were used for statistical analysis. **Results:** 14 patients (3.2%) were diagnosed with hypothyroidism, 12 of them with a BW <1000 g. Gestational age (weeks) (S.D.): 27.4 (1.7); sex (F/M): 10/4; weight (g) 891 (215); multiple pregnancy: 5/14; SGA (one karyotype) two (47,XXY); and family history of hypothyroidism: 2; blood samples collection (days): 25 (15). Preterm infants with TSH 80.9 μU/ml (range: 12.9–312) and free T_4 0.79 ng/dl (0.30) started treatment with L-T_4 at an age of 32.58 (13.9) days of life, at initial dose of 10.98 μg/kg per day (3.1) for 34.8 (5.9) months. All thyroid ultrasound demonstrated eutopic thyroid. At reevaluation ten of 14 patients (four continues treatment) showed: 20% permanent hypothyroidism (thyroid scintigraphy in a male demostrated hypocaptation on the left lobe) ; 20% hyperthyrotropinemia; and 60% TSH <5 μU/ml, suggesting transient hypothyroidism. However, follow-up of the patients with transient hyperthyroidism and two patients with normal function after discontinuation of treatment, develop permanent hypothyroidism. Studies on exon 10 of the TSH receptor gene performed in some patients were normal. **Conclusions:** Our data emphasises the importance of follow-up thyroid function in preterm infants. Female and multiple pregnancy are factors associated with high risk of hypothyroidism. Long-term follow-up is indicated in these patients that require treatment in order to determine the definitive diagnosis.

P3-1187

The Benefits of Preterm Neonate Development by Early Replacement Therapy with Levothyroxine: Longitudinal Prospective Study

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Background: In premature neonates hypothyroidism or thyroid sick syndrome is frequently diagnosed, which is a result of the immaturity of the gland itself and the hypothalamic–pituitary–thyroid axis. The necessity of rapid adaptation to extrauterine life, generation of high thermal energy, and accelerated development of the central nervous system is the cause of the increased demand for thyroid hormone. **Objective and hypotheses:** The aim of our study is to determine the benefits of early levothyroxine (L-T_4) substitution therapy in premature neonates and to determine the optimal dose of the drug. The prospective, longitudinal studies were conducted during 7 years in 134 premature neonates with low and very low body weight by delivery. **Method:** The 82 children with a reduced fT_4 level received L-T_4 therapy at the doses of 5–7 μg/kg BW/day, since the 2nd week of life. The control group comprised 52 children with normal TSH, in whom the level of thyroid hormones were determined 4 weeks and later after birth; afterwards, they received L-T_4 therapy. The physical and mental development were compared. The mental development and IQ was assessed in the Wechsler Intelligence Scale for Children in the 7th year of life. **Results:** The preterm born neonates were observed to have a more rapid body weight gain in the first period of life after administration of L-T_4. In this group, all infants acquired the motor functions statistically significantly earlier in comparison to the infants from group with delayed treatment. In the 7th year of life, the IQs were significantly higher (103.6 ± 20.1) in group 1 treated since the 2nd week of life in comparison to group 2 (83.3 ± 21.3). **Conclusion:** The early replacement therapy with L-T_4 in doses 5–7 μg/kg BW/day initiated in the 2nd week of life may improve physical development in the newborn period and long-term mental development in preterm-born children.

P3-1188

Intrathyroidal Ectopic Thymic Tissue Mimicking a Thyroid Nodule: A Report of Three Paediatric Cases

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Background: Intrathyroidal ectopic thymic tissue is one of the rarest congenital abnormalities. Ectopic thymus tissue can be detected in various locations from the mouth or the base of the

skull to the superior mediasteneum. We report here three cases of intrathyroidal ectopic thymus tissue who presented as thyroid nodules in different ages. **Cases:** Case 1: a 10-year-old girl had a guatr and her thyroid function tests were normal. Thyroid US showed a hypoechoic calcified nodule (10×4 mm) in the right lobe. There was no regional lymphadenopaty. Fine-needle aspiration biopsy was recommended (FNAB), but the parents preferred to excision of the nodule. Right lobectomy was performed and pathologycal examination showed an ectopic intrathyroidal thymus tissue. Case 2: a 7-month-old baby was referred to our clinic because of thyroid nodules which were detected incidentally. She was euthyroid. Thyroid US was repeated and showed a hypoechoic nodule (7×5×9 mm) with multiple hyperechoic areas in the left lobe and a similar hypoechoic nodule in the right lobe which were reported as ectopic thymic tissues. FNAB was not done because it was an invasive diagnostic procedure. During 1 year follow-up, nodular enlargement was not seen. Case 3: a 4-month-old baby was referred to our clinic because of suspected thyroid nodule which was detected during neck US for torticollis. His thyroid function tests was normal and repeated thyroid US showed an intrathyroidal ectopic thymic tissue. There was no nodular enlargement during 18-month follow-up. **Conclusions:** Ultrasonographic findings are tipic for thymic tissue. The increasing use of thyroid US may result in an increased detection of intrathyroidal thymic inclusions that should be considered in the differential diagnosis of thyroid nodules in children and adolescents. If US results are inconclusive and further evaluation is needed, a biopsy may be useful for confirmative diagnosis.

P3-1189

Simultaneous Occurrence of Thyroid Storm, Diabetic Ketoacidosis, and Multiple Cerebral Infarction in a 16-Year-Old Girl

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Background: Diabetic ketoacidosis is one of the precipitating factors that can evoke a thyroid storm. Thyroid storm may cause cerebral ischemia in moyamoya disease, which coexist in the patient with Graves' disease. **Case presentation:** A 16-year-old girl complaining of dizziness and palpitation visited emergency room, and was diagnosed with diabetic ketoacidosis (DKA) combined by hyperthyroidism. Thyroid storm occurred in 6 h after the start of DKA management. Burch and Wartofsky score was 65 points. Right hemiplegia developed during the thyroid storm and brain MR diffusion weighted images revealed multiple acute infarcts on the both hemispheres. MR angiography showed stenosis of both distal internal carotid arteries and both M1 portions of the middle cerebral arteries, consistent with moyamoya disease. After the acute management for the thyroid storm with methimazole, Lugol's solution, and hydrocortisone, her neurologic symptoms were completely recovered in 1 month and free T_4 level was normalized in 2 months. **Conclusion:** Thyroid storm may trigger cerebral ischemia in moyamoya disease and lead to rapid progression of the cerebrovascular occlusive disease. As the simultaneous occurrence of diabetic ketoacidosis, thyroid storm, and cerebrovascular accident in moyamoya disease highly elevates morbidity and mortality, prompt recognition, and management are critical to save life.

P3-1190

Two Patients with Allen–Herndon–Dudley Syndrome: a Novel Mutation on *MCT8* Gene

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Background: Monocarboxylate transporter 8 (MCT8) is a specific transporter of triiodothyronine (T_3). *MCT8* gene mutations cause a rare X-linked disorder known as Allan–Herndon–Dudley syndrome, characterized by thyroid dysfunction (high T_3, low T_4, and normal/high TSH) and psychomotor retardation. **Case report:** A 4-year- and 9-month-old boy, who was already having L-T_4 treatment for hypothyroidism was admitted to our coutpatient clinic. He was also under supervision of paediatric neurology because of congenital hydrocephaly, cerebral palsy and epilepsy. Neuromotor development was severely retarded and complete blindness was present. The parents were non-consanguineous, his uncle and cousin also had similar neuromotor deficits and epilepsy. Physical examination revealed severe hypertonia of limbs and exaggerated deep tendon reflexes. The weight was 18.7 kg (50 p), the height was 106 cm (10–25 p), the head circumference was 47 cm (3–10 p, −1.29 SDS), thyroid gland was non-palpable and unilateral cryptorchidism was present. Thyroid hormone levels, under 100 µg/day L-T_4 treatment, were as follows: fT_3: 5.76 pg/ml (1.7–3.71), fT_4: 0.62 ng/dl (0.8–2.2), and TSH: 0.8 mUI/l (0.4–4). Thyroid hormones of his 2-year- and 9-month-old male cousin were as follows: fT_3: 5.41 pg/ml (1.7–3.71), fT_4: 0.7 ng/dl (0.89–1.76), and TSH: 5.5 mUI/l (0.4–4). Allan–Herndon–Dudley syndrome was confirmed by a deletion of 1683rd nucleotide of exon 6 of *MCT8* gene. **Conclusion:** In case of low fT_4 levels in association with severe neurologic findings, MCT8 deficiency should be considered and fT_3 measurement should be performed.

P3-1191

Audit of Thyroid Carcinoma in Children, Adolescents, and Adults

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Background: Thyroid carcinoma is the most common endocrine malignancy and most common secondary malignancy for childhood cancer survivors. Radiation exposure has been clearly linked to risk. Thyroid nodules in children have a high risk for malignancy, whether arising spontaneously or after radiation. Reported incidence of thyroid carcinoma after radiation is 20 times the population risk, partly due to improved long-term childhood cancer survival and more active surveillance. Despite metastatic disease being common, survival rate is high. **Objective and hypotheses:** To review a series of patients with thyroid carcinoma seen over 25 years. **Method:** Retrospective case note review of all thyroid carcinoma diagnosed from 1989 to 2014 in children, adolescents and those adults who had a history of childhood radiation exposure. **Results:** Forty-six patients were identified. Thirty-nine (84.8%) had papillary thyroid carcinoma, 5 (10.9%) follicular carcinoma, and 2 (4.3%) medullary thyroid carcinoma (MEN2B). Thirty-three had childhood radiation exposure (17 females) with thyroid malignancy occurring 6–37 years later. Thyroid cancer prior to 16 years was seen in 10 (21.7%) without radiation exposure. Smallest nodule size was 4 mm. A patient with multiple nodules 7–8 mm had multifocal papillary carcinoma with invasion into adjacent skeletal muscle and blood vessel. Total thyroidectomy was performed for all. Central node clearance with first surgery commenced in 2005, after several late metastases occurred. Diagnostic rTSH stimulated ^{123}I scan was performed for all, with ablative ^{131}I if any uptake was seen. Fourteen patients had metastases: to lymph nodes (14), lungs (3), skeletal muscle (2), and bone (1). Twenty-four (52.2%) had ^{131}I four requiring multiple courses. Forty-four are alive and tumour free. For medullary carcinoma, one continues treatment and one died. **Conclusions:** Ultrasound screening is required for early diagnosis as small nodule size is not predictive of benign histology or absence of metastases. Central node clearance provides better outcome. Despite metastatic disease at presentation in some, prognosis is favourable.

P3-1192

The Comparing of Thyroid Volumes between Healthy and Obese Children in Respect of Anthropometric, Biochemical, and Metabolic Parameters

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Objective: There have no been studies enough about thyroid volumes of obese and adolescent children. In this study, we purposed comparing of thyroid volumes in respect of anthropometric, biochemical, metabolic parameters in following groups: Overweight, obese, morbid obese, and healthy children. **Method:** Two groups were compared: The first group consisted of 190 children whose BMIs are above the 85th percentile. The second group was 90 children with normal weights. Anthropometric parameters of all children were noted. The following tests were performed in all children: fasting blood glucose, uric acid, total cholesterol, HDL, triglycerides, AST, ALT, TSH, free T_4, free T_3, thyroglobulin, anti-thyroglobulin, anti-thyroid peroxidase, insulin, ACTH, cortisol, IGF1, IGFBP3, urine iodine, and HOMA-IR. All children thyroid volumes were measured with thyroid ultrasound. SSPE for Windows version programme was used for statistical analysis. $P<0.05$ values were considered statistically significant. **Findings:** In two groups between morbid obese and control grups, there was statistically significant difference both anthropometric parameters and some tests that include uric acid, triglycerides, ALT, free T_3, and insulin. There was correlation between fatty liver and metabolic syndrome,insulin resistance. High ALT level may use as a marker to determine fatty liver. In over 12-year-old children with morbid obese, thyroid volumes are larger than healthy children's. However there was apositive correlation between thyroid volume and IGF1 level; we didn't find statistically significant difference in respect of IGF1/IGFBP3 rates in any groups. **Result:** In this study, we found that thyroid volumes of morbid obese children larger than healthy children's. This finding can contribute to literature. We also consider that not only IGF1 can cause enlargement in the size of thyroid volume, but also insulin may play important role.

Table 1. Thyroid volumes are in the groups.

Thyroid volume(total) (cm^3)	***n***	**Average**	**S.D.**	***P***
Morbid obese	145	6.612	4.440	0.603
Obese	19	6.811	2.988	
Overweight	26	6.369	3.971	
Control	99	5.968	3.079	
Total	289	6.383	3.886	

P3-1193

NKX2-1 p.Asp266Argfs142X *De Novo* Mutation in a Girl with Congenital Hypothyroidism (CH): Phenotypic Description

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Background: *Ttf1*$^{-/-}$ mice had complete absence of follicular and parafollicular cells, agenesis of lung parenchyma, ventral forebrain, and pituitary. Congenital hypothyroidism (CH) patients with chromosomal deletions encompassing the TTF1 locus and point mutations in the *TTF1* gene confirmed its implication in the phenotype: CH with a thyroid gland in place, associated with respiratory distress syndrome, neonatal hypotonia followed by choreoathetosis or ataxia. **Objective and hypotheses:** Description of the phenotype in a patient from the Bulgarian thyroid screening cohort. **Method:** Case report and direct sequencing of *NKX2-1*. **Results:** A term female newborn was detected by the

neonatal TSH screening (Table 1). Initial L-T_4 dosage: 12 µg/kg per day at day 53. Family history – unremarkable. Despite normal TSH and (f)T_4 under substitution she developed progressive hypotonia from early infancy, developmental delay, catch down of linear growth (SDS_h −3.6 at 2 years), mild bone age retardation during adrenarche. Until the age of six frequent respiratory infections (asthma, CF, and chronic pneumonias were excluded). After start of walking, movement affection resembles choreoathetosis. At reevaluation permanent CH due to hemiagenesia (right lobe) and a hypoplastic left lobe. Until 13 years she was euthyroid, attended a public school, the neurologic and lung involvement did not progress. Some behavior problems became much more important with age. According to the triad of thyroid, neurological and respiratory involvement the family was sequenced for *NKX2-1* after informed consent. A small deletion c.796delGA leading at protein level to Asp266ArgfsX142 in the NK2-specific domain in exon 3 was found only in the patient. **Conclusion:** Monogenic CH is heterogeneous and belongs to rare diseases. Hypotonia despite sufficient L-T4 treatment is an early sign which can guide to the suspicion of underlying *NKX2-1* mutations in primary CH.

Table 1.

Age (days)	**NTSH** (mU/l)	**TSH** (mU/l)	**T_4** (nmol/l)
3	31.4		
35	77.3		
53	97.8	145	77.9
2.5 years	76.3	137	57

P3-1194

Development and Risk Factors of Thyroid Dysfunction in Patients with Positive TPO Antibodies

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Background: Autoimmune thyroid disease (AITD) is the most common thyroid disorder in the paediatric age range. However, the development of thyroid dysfunction in biochemically euthyroid children with positive TPOAbs and associated risk factors is unclear. **Objective and hypotheses:** To evaluate the evolution of children with positive TPOAbs and normal thyroid function and identify predictive factors for the development of thyroid dysfunction. **Method:** A retrospective study analysing a database of 250 children with positive TPOAbs in 2010 and the development of thyroid dysfunction and levothyroxine treatment over 5 years. Clinical features and risk factors for hypothyroidism were recorded. **Results:** In 2010, 250 patients had TPOAbs analysed with 46 (18.4%) positive, median age 11 years, 147 (58.8%) non-diabetic children. Of the positive children, 32 (69.5%) were associated with normal thyroid function. We excluded 12 children (ten: on levothyroxine treatment and two: no further bloods test done). Among those with normal thyroid function (18 (90%) females, 10 (50%) diabetics, and 4 (20%) goitre), four developed hypothyroidism within a median 2.45 years (1.96–3.68) from initial testing, with 80% remaining euthyroid over 5 years. The median follow-up time of the children who remain euthyroid was 4.19 years (1.13–4.67) and the median time for the hypothyroid ones was 4.09 years (3.94–4.29). No differences in age or gender were seen. Children who remain euthyroid are more like to have lower TPOAbs levels, with an absence of goitre. **Conclusion:** Paediatric patients with increased TPOAbs need careful monitoring because no clear criteria exist to predict the development of thyroid dysfunction. Hypothyroidism developed in 20% of our children with positive antibodies within 4 years and it seems to be more prevalent in those with a higher level of antibodies together with the presence of goitre, but more studies are needed with greater subjects.

P3-1195

The Evaluation of CD8+CD122+T Cells in Children with Autoimmune Thyroiditis

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Background: The basic subset of T cells playing a major role in the pathogenesis of Hashimoto's thyroiditis are CD8+T cells. The mechanism of disease initiation is dysfunction of natural Tregs leading to breakdown of the self-tolerance. The best known subset of natural Tregs are CD4+Foxp3+T, but CD8+T cells expressing CD122 were also recognized as functional Treg cells. **Objective and hypotheses:** The aimof the study was to evaluate the contribution of CD8+CD122+T cells in the whole amount of CD8+T cells in children with autoimmune thyroiditis. **Method:** 59 children were examined: 35 with chronic autoimmune thyroiditis type Hashimoto (AIT), mean age 11.37±3.6 years; range: 4.5–17.5 years and 24 healthy children as controls. PBMCs were stained with MABs according to manufacturer instructions (Becton Dickinson): anti-CD8 FITC, anti-CD122 PE and isotypic controls were included. The samples were evaluated using flow cytometer FACS Canto II (Becton Dickinson). The results were presented as percentage of CD8+, $CD8^{bright}$, and $CD8^{dim}$ expressed CD122 antigen. TSH, thyroid hormones, and thyroid antibodies were evaluated by MEIA, Abbott. Statistical analysis was performed using Mann–Whitney *U* test and the correlation tests. **Results:** In children with AIT the percentage of CD8+ CD122+ was significantly higher than in control group, especially in the $CD8^{dim}$ CD122+ subset. In children with AIT any significant correlations between the subsets of CD8+CD122+T cells and hormonal or antibodies status were not found. **Conclusion:** In children with AIT is observed an increased contribution of $CD8^{dim}$CD122+T cells in the whole amount of CD8+T cells subset.

P3-1196

Hoffmann Syndrome in a Boy with Severe Acquired Primary Hypothyroidism

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Background: Hoffmann syndrome is a specific and rare form of hypothyroid myopathy in adults characterized by presence of muscle stiffness, proximal weakness and pseudohypertrophy. When this occurs in a cretin child it is known as Kocher–Debré–Sémélaigne syndrome. Patients with more severe or longstanding untreated hypothyroidism are more likely to develop clinically significant muscle disease. Serum muscle enzyme levels as CK, myoglobin and lactate dehydrogenase are frequently elevated. Although this increase is usually mild (CK <1000 IU/l), reports of rhabdomyolysis do exist in the literature. **Case presentation:** A 9-year-old boy presented with hoarse voice, pallor, weakness, and tiredness of 6 months duration. He associated poor height gain in the last year and muscular hypertrophy in the last months. He maintained adequate school performance without other associated symptoms. Physical examination revealed short stature (height 121.6 cm, -2.4 S.D.; BMI 18.6 kg/m^2, 0.2 S.D.), bradycardia (47 b.p.m.), palpebral edema, generalized muscular hypertrophy with proximal limb weakness and dry skin, without goiter. Laboratory studies showed a severe primary hypothyroidism: TSH 894.84 mU/ml (0.57–5.92), free T_4 0.036 ng/dl (0.72–2.0), and positive thyroid autoimmunity (anti-TPO antibodies >600 IU/ml and anti-TG antibodies >4000 IU/ml). He also presented elevated CK 3172 U/l (1–175), cholesterol 265 mg/dl, LDL 155 mg/dl, ALT 76.2 U/l (5–26), AST 123.6 U/l (5–37), and LDH 411 U/l (120–300). The ultrasound demonstrated a heterogeneous and enlarged thyroid gland. With these findings the patient was started on levothyroxine 2.7 μg/kg per day. **Conclusion:** We expose a case of Hoffmann syndrome in a child, presented with typical symptoms of muscular pseudohypertrophy caused by long-standing untreated hypothyroidism. This clinical picture has been very rarely reported in children. Although thyroid hormone deficiency is the underlying etiology of acquired myopathies in a small proportion of cases, all patients with an acquired myopathy and pseudohypertrophy should be screened to rule out hypothyroidism.

P3-1197

Congenital Hypothyroidism Incidence and Dysgenesis or Dyshormonogenesis Prevalence in a Large Infants Cohort from South of France

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Background: Congenital hypothyroidism (CH) is the most frequent endocrine disease in infants with prevalence ratio in the range of 1:2000–1:4000 new-borns. The disorder can be permanent (CHP) or transient (CHT). CH can be classified into two main groups: Dysgenesis, which accounts classically for 80–85% of cases and dyshormonogenesis for remaining 15–20%. From the last decade, studies described a upward trend for CH prevalence and changes in groups' proportions. **Objective:** To determine the updating prevalence of CH, CHP, CHT, dysgenesis, and dyshormonogenesis in infants confirmed with CH after newborn screening in a large French region (Midi-Pyrénées 31 000 births/year). **Method:** Dysgenesis and dyshormonogenesis were defined as proposed in ESPE consensus and based on neonatal thyroid ultrasonography, thyroglobulin level, and scintigraphy. CHP categorised dysgenesis or dyshormonogenesis as infants with L-T_4 replacement necessary after 3 years of life and CHT when L-T_4 replacement is stopped between 1 and 3 years of life, with normal thyroid lab tests, ultrasonography, and scintigraphy with perchlorate discharge test. **Results:** Between November 2002 and October 2011, 100 new-borns were confirmed with HC after TSH screening (62% females), Incidence is 1:2828 new-borns. Repartition was 51 dysgenesis (61% ectopy, 35% athyreosis, and 4% hypoplasia) and 49 eutopic gland (20 CHP and 29 CHT). Incidence for CHP (after 3 years) was 1:3983 infants. Congenital malformations in the whole group were found in 11% of neonates but none in the dysgenesis group. In the CHP group with dyshormonogenesis, molecular genetic studies identified seven genes mutations (NIS, three thyroglobulin, two TPO, and GNAS). In the CHT group, interestingly 1/3 of new-borns were premature babies and 2/3 were admitted in neonatal unit. Investigations confirmed the use of iodized antiseptic in these situations (for caesarean, neonatal surgery, or umbilical venous catheter). **Conclusion:** We found in our large French region a CH incidence as closed to 1:3000 new-borns, similar to French CH incidence. We confirmed the trend to an increased proportion of eutopic gland compared to dysgenesis. When regarding only CHP, this proportion also remains higher to the one classically described.

P3-1198

Thyroid Function in a Large Group of Obese Children: Causes and Consequences

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Background: Mild TSH elevations are frequently observed in obese patients, in the absence of any detectable thyroid disease. **Aims and objective:** To evaluate possible causes for the raised TSH levels and to verify possible biochemical and clinical consequences of this condition. **Methods:** We evaluated 779 (325 males/454 females) obese children, chronological age

14.38±2.56 (range 5.25 to 18.50), height SDS 0.27±1.04 (range −3.49 to 4.35), BMI–SDS 2.94±0.59 (range 1.6 to 4.62). After an overnight fast, they were admitted to the ward, for auxological evaluation, assessment of body composition by bioelectrical impedance analysis and energy expenditure by indirect calorimetry. A blood sample was obtained for the determination of thyroid function (fT_4, TSH, TPOAbs, and TGAbs), inflammation markers (total WBC and the subtypes, C-reactive protein), metabolic parameters (AST, ALT and yGT, glycaemia, insulin, total-, HDL- and LDL-cholesterol, triglycerides). An OGTT was performed for the assessment of glucose tolerance and for the calculation of the disposition index (ODI). The patients were then subdivided in two groups according to a TSH value above (group 1) or below (group 2) 4.5 mU/l. **Results:** Group 1 showed significantly higher values of AST (24.8±12.2 S.D. vs 22.5±9.6 S.D.; $P<0.05$), total cholesterol (170.3±28.7 vs 163.3±32.9; $P<0.05$), azotemia (28.9±5.3 vs 27.1±5.4; $P=0$) and alkaline phosphatase (168.6±89.7 vs 149.3±87.2; $P<0.05$). Multiple regression analysis showed that TSH serum levels was negatively affected by age ($P<0.05$) and positively by BMI–SDS ($P<0.001$) and total lymphocytes count ($P<0.01$). Because of the cardiovascular implications we also checked the determinants of cholesterol serum levels: AST ($P<0.01$) and TSH ($P<0.05$) were involved; however the model explained only 2% of the probability. **Discussion:** Fat excess and the consequent inflammatory status seem to be the main determinants of TSH elevation, probably through a negative influence on inflammatory cytokines on the TSH receptor. The raised TSH is a poor predictor of serum cholesterol levels.

P3-1199

Thyroid Nodules in Children and Adolescents

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Background: The presence of a thyroid nodule (TN) is a rare clinical condition during childhood and adolescence. In children, classically was considered malignant and total thyroidectomy was recommended whenever a TN was detected or in the case of cold nodules. There are not long time series in children, but recent clinical guidelines recommend an initial management as in adults. **Objective and hypotheses:** Review TN in children in our area. **Method:** Retrospective study (1999–2014) of TN >1 cm in children (0–15 years) in our area (138 000 pediatric population). **Results:** We found 15 TN, determining an incidence of 0.7/100 000 per year. Diagnostic was done by palpation in 40%. Mean age was 12.6 years and 80% were girls. Thyroiditis was associated in a 26.7%. Radiation history was related in a 13.3% and a 46% had familiar history of non-malignant thyroid disease. Thyroid function was normal in all cases. Long diameter in US was 2.6±1.6 cm. Only in six cases scintingraphy was performed, being three cold nodules. Fine needle aspiration biopsy (FNAB) and/or guided aspiration biopsy (GAB) was done in all nodules. Five of them were considered 'non benign' and surgery was indicated. Malignant diagnostic in macroscopic study was confirmed in four TN. **Conclusion:** TN >1 cm is a rare and a serious clinical condition in children. In this study, 26.6% of TN were malignant. In children, as in adults, we consider the use of PAAF and/or GAB always necessary to a correct management of TN.

Table 1. (for abstract P3-1199)

	US (cm)	Scint	PAAF	GAB	Surgery	Diagnostic	Follow-up
Case 1	7.5	No	Papillary	No	Total	C. papillary	NR
Case 2	5	Cold	Follicular	No	Total	C. follicular	NR
Case 3	3	Cold	No	Follicular	Hemi	A. follicular	Benign
Case 4	2.5	Hot	Follicular	Benign	Total	C. papillary	NR
Case 5	2	No	No	Papillary	Total	C. papillary	NR

NR, no recurrence; C, cancer; A, adenoma.

P3-1200

Trisomy 21 and Thyroid Dysfunction: About 50 Paediatric Cases

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Background: Trisomy 21 is a chromosomal abnormality that predisposes to autoimmune diseases. Among them the thyroid dysfunction is frequently observed. **Objective and hypotheses:** Study the various thyroid diseases in trisomy 21 patients and their therapeutic management. **Method:** This is a retrospective study of 50 cases of Down syndrome children with thyroid disease, collected over a period of 9 years (2006–2015). All children underwent a complete physical examination, a thyroid balance (FT_4 and FT_3 or -TSH TPO and anti us- AC or TSI) and a cervical ultrasound. **Results:** There are 34 boys and 16 girls. The mean age of diagnosis of thyroid dysfunction was 4 years (20 months–15 years). It was hypothyroidism in 46 cases and hyperthyroidism in

four cases. The discovery of hypothyroidism was made on the occasion of a systematic review in 36 cases before signs of hypothyroidism in ten cases. Hypothyroidism was compensated in 78% with an average rate of 17 pmol/l FT_4 and TSH 8.5 μUI/ml. The anti-thyroid peroxidase antibodies were positive in half the cases with aspect of thyroiditis at cervical ultrasound. Treatment with L-thyroxine quickly led to the normalization of TSH. Hyperthyroidism was discovered following a tachycardia and eye signs. Hormonal balance showed low TSH (<0.01 μUI/ml) and high FT_4 (mean 40 pmol/l). Cervical ultrasound revealed a thyroiditis aspect with anti TPO AC positive. There was not visceral or metabolic complications. The initiation of treatment with antithyroid drug led to a definite hypothyroidism. **Conclusion:** Thyroid disease is common in children with Down syndrome 21. Hypothyroidism is more common. a systematic monitoring of thyroid function is necessary.

P3-1201

NKX2-1 (TTF-1) Germline Mutations are not a Frequent Cause of Congenital Hypothyroidism due to Dysgenesis

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Background: Mexico is globally ranked as one of the countries with the highest incidence of congenital hypothyroidism. There are few studies that have searched for germinal mutations of candidate genes, such as *NKX2-1*, in patients with congenital hypothyroidism. **Objective and hypotheses:** i) To search for *NKX2-1* mutations in blood samples of patients with confirmatory diagnosis of congenital hypothyroidism (CH) due to thyroid dysgenesis (TD). ii) To describe their clinical findings and to identify cases of minimal gene expression or no penetrance by the clinical and molecular study of first degree relatives of patients with an identified *NKX2-1* mutation. Hypothesis: *NKX2-1* mutations may cause CH due to TD in Mexican population. **Method:** This study has an observational, descriptive, transversal and ambispective design. We included 34 Mexican patients in which *NKX2-1* mutations were searched by PCT, single-strand conformation polymorphism (SSCP) and Sanger automated sequencing of the three coding exons. **Results:** In the 34 patients included there was a female gender predominance (3.8:1). Most of our patients had ectopic thyroid ($n=19$). We found an abnormal migration pattern in exon 1 by SSCP in five of our patients, but we discharged any mutation by exon sequencing. In all of our patients the analysed sequence of *NKX2-1* gene was normal, no mutations or polymorphisms were found. **Conclusion:** In this study the high predominance of CH in Mexican population is not explained by mutations or polymorphisms in *NKX2-1* gene, so further studies are needed to analyse other genes involved in thyroid development, such as *NKX2-5* and *FOXE-1* to determine their role as a cause or influencing factor of CH due to TD in our population.

P3-1202

A Curious Case of Thyrotoxic Crisis and Lower Extremity Weakness in a 15 year-Old Female with Graves' Disease

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Background: Thyrotoxic crisis is a rare, emergent complication of paediatric hyperthyroidism. A rare neurological manifestation of thyrotoxicosis is thyroid myopathy. **Objective and hypotheses:** We report the case of a female teenager who presented to the Emergency Department with thyrotoxic crisis and lower extremity weakness. Our objective is to discuss the course of thyrotoxic crisis and review potential rare neurological manifestations of thyrotoxicosis and their non-thyroid differential. **Method:** History: this 15 year-old African American female was diagnosed with Graves' disease at age 14 and had a history of poor methimazole compliance and previous thyrotoxic crisis complicated by mild pulmonary hypertension. History also included asthma and chronic lower extremity weakness of uncertain aetiology. 5 days prior to admission, she developed fever and congestion and progressed to shortness of breath, sweating, dizziness, palpitations, weight loss, abdominal pain, vomiting, and diarrhoea. Exam: Her exam showed tachycardia (170 bpm), hypertension (147/81 mmHg), mild symmetric exophthalmos, a diffuse non-tender goitre (transverse diameter 6 cm bilaterally) with thyroid bruit, hyperdynamic precordium, and 3+ DTRs in legs. Despite professed lower extremity weakness, neurological examination revealed muscular deconditioning but normal lower extremity tone, strength, and gait. Work-up: Laboratory workup showed TSH <0.01 mIU/l (0.5–4.8), FT_4 >7.77 ng/ml (0.93–1.6), FT_4 by dialysis 15 ng/dl (0.8–1.7), T_3 471 ng/dl (80–185), T_4 23.6 μg/dl (4.9–13), and TrAB 34 IU/l (0–1.75). EKG showed sinus tachycardia with a normal ECHO. Clinical management: She received loading doses of propylthiouracil (PTU) 500 mg and hydrocortisone (HC) 300 mg and scheduled PTU 200 mg, atenolol 25 mg, potassium iodide 250 mg, and HC 100 mg. **Results:** Clinical symptoms improved over 2 days. TFTs decreased to FT_4 6.63 ng/dl and T_3 123 ng/dl 5 days later after increase in PTU dose, and she was switched to methimazole (MMI). Final labs showed FT_4 1.53 ng/dl, T_3 203 ng/dl, and T_4 7.6 μg/dl. Lumbar spine imaging and rheumatologic workup were negative. Her severe reported weakness was absent on neurological examination and was deemed to be consistent with conversion disorder with weakness, attributed in part to a conflictive maternal relationship, rather than thyrotoxic myopathy. She was discharged to an inpatient rehabilitation facility on MMI 20 mg daily and atenolol with plan for thyroidectomy. **Conclusion:** Our patient presented with thyrotoxic crisis, which was attributed to a combination of Graves' disease, MMI noncompliance, and stress. Her course included prolonged elevated thyroid hormone levels, possibly due to early escape from the Wolff-Chaikoff effect. Thyrotoxic myopathy is a rare cause of muscle weakness in hyperthyroid patients and should be considered in the differential diagnosis for all thyrotoxic patients complaining of muscular weakness; however, in this case, the aetiology of the weakness was cognitive rather than neurological. Finally, few cases of thyrotoxic crisis have been described in children and adolescents. As in adults, prompt diagnosis and management may prevent cardiovascular collapse and CNS dysfunction, but early escape from Wolff-Chaikoff effect may make treatment more complex.

P3-1203

Newborns of Mothers with Graves' Disease: Survey of 14 Years

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Background: Graves' disease (GD) is the most common cause of hyperthyroidism in fertile woman and can cause fetal and neonatal hyper or hypothyroidism. It is associated with transplacental transfer of maternal thyrotropin receptor antibodies (TRAb). **Objective and hypotheses:** The main objective of this study was to characterize the neonates born to women with GD followed in a pediatric endocrinology reference unit. **Method:** A retrospective chart review was done of neonates born to mothers with GD in the last 14 years. The parameters analysed were: maternal thyroid function and treatment during or before pregnancy, sex, gestational age, birth weight, newborn thyroid function and treatment. **Results:** Twenty RN neonates (55% female) were included, of 18 mothers with GD. Median gestational age was 37.7 ($\pm$1.2) weeks, with three pre-terms (35 and 36 weeks), 35% of first gestations. Mean birth weight was 2778.5 g ($\pm$437.6), with one born small for gestational age. One pregnancy was complicated by pre-eclampsia and in two fetus ultrasound changes were found (fetal goiter, oligohydramnios and intrauterine growth restriction). GD was diagnosed 3.1 years ($\pm$2.4, $n=16$) before the childbirth. Four mothers were submitted to ablative treatment with radioiodine. TRAb were elevated in the third trimester (>1 IU/l; maximum: 40 IU/l) in five pregnancies, four of which were treated with antithyroid drugs (ATD). Three newborns presented with hyper and four with hypothyroidism, whose mothers presented with elevated TRAb late in pregnancy. Half of the hypothyroid newborns were treated with thyroxine. There was only one baby with overt hyperthyroidism that was treated with methimazole for 4 months. **Conclusion:** There were an elevated number of newborns of GD mothers with abnormal thyroid function tests, mostly in uncontrolled mothers during pregnancy (all with elevated TRAb). We recommend an optimal follow up of these mothers and the establishment an adequate management protocol for the neonates.

P3-1204

Use of Liothyronine in a Case of Consumptive Hypothyroidism Caused by Hepatic Hemangiomas

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Background: Diffuse or multifocal infantile hepatic hemangiomas cause consumptive hypothyroidism due to overexpression of type 3 deiodinase in the endothelium of vascular tumor. Because type 3 deiodinase converts of T_4 to reverse T_3 and of T_3 toT_2, a use of levothyroxine alone may not maintain normal levels both fT_3 and fT_4. T_3 therapy in this order has scarcely been reported. We here present a Japanese case with multifocal infantile hemangiomas, whose fT_3 and fT_4 levels were low and normal respectively. The low level of fT_3 improved with liothyronine alone. **Case report:** He was referred to our hospital because of jaundice at the age of 2 months. He showed no signs of hypothyroidism except jaundice. On physical examination, the liver was palpable 3 cm below the right costal margin. Abdominal ultrasonography showed multifocal hemangiomas in both lobes of the liver. Blood tests at this time were as follows: serum total bilirubin 6.4 mg/dl, serum direct bilirubin 0.2 mg/dl, TSH 17.7 μU/ml, fT_3 1.96 pg/dl, fT_4 1.48 ng/dl. We diagnosed him as having hypothyroidism due to hepatic hemangiomas. Propranolol (2 mg/kg per day) and liothyronine (0.1 μg/kg per day) were started. We used liothyronine alone for hypothyroidism because only fT_3 was decreased. The thyroid hormone requirement was gradually reduced and the treatment was discontinued at the age of 5 months. At the age of 8 months, His growth and neurological development were normal for age and he was euthyroid. **Conclusion:** A use of liothyronine alone can be useful in some patients with hypothyroidism caused by infantile hepatic hemangiomas, especially when their fT_3 level is low, compared to fT_4 level.

P3-1205

Subclinical Hypothyroidism in Children and Adolescents – A 5-year Single-center Follow-up Study

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Background: Most experts agree that subclinical hypothyroidism (SH) represents early, mild thyroid failure, however there are controversies about the evolution of SH over time. **Objective and hypotheses:** The aim of the study was to analyse the dynamics of thyroid dysfunction in children initially referred as patients with SH. **Method:** During the period January 2010 – January 2015, 258 unselected consecutive SH patients (140 girls), who met the criteria of SH: serum TSH concentration above the upper limit of the reference range with fT_3 and fT_4 concentration within their reference range, were studied in one clinical center. Thyroid examination (clinical and ultrasound), laboratory tests (TSH, fT_4, fT_3, anti-TPO, anti-TG Ab) were carried out at least once in each patient. Those individuals on pharmacological intervention that might interfere with natural evolution of SH (amiodarone, antiepileptic agents, glucocorticoids) were excluded. **Results:** The mean age at SH diagnosis was 7.30 years (S.D. 5.44, medium 7.09 years; range: 0.0–17.86 years). SH girls were older than boys but not significantly (7.66$\pm$5.51 v 6.89$\pm$5.34; $P=$NS). In 25 (9.7%) patients there was positive family history. On the basis of follow-up study it was found that out of 258 SH patients, 23 (8.9%) had positive thyroid autoantibodies and Hashimoto

thyroiditis was diagnosed. Eleven (4.3%) patients developed hypothyroidism, but only in two of them TSH levels were below 10 mU/l initially. **Conclusion:** Our data confirmed that only a small percentage of children with SH can proceed to overt hypothyroidism.

P3-1206

The Difference between Cord and Filter Paper TSH Level in Congenital Hypothyroidism Screening Programme

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Background: Neonatal thyroid screening is considered one of the best cost-effective tool to prevent mental retardation in population. Different strategies are suggested for thyroid hormone estimation in the sample obtained at birth using cord blood or later in neonatal period. In King Abdulaziz Medical City, cord TSH is the screening tool to detect congenital hypothyroidism cases with a cut off value of 30 MIU/l considered positive result. In 2011, newborn screening programme was started and TSH in heel prick with a cut-off value of 20 uU/l was part of the programme. **Objective and hypotheses:** The aim of this study is to compare the sensitivity and specificity of cord blood TSH and heel stick TSH in detecting congenital hypothyroidism. **Method:** All deliveries conducted at King Abdulaziz Medical City in Riyadh region KSA during the period from May 2011 to May 2013 were included in this study. Both cord blood and heel stick samples for TSH were collected from each delivery for screening. **Results:** A total of 17729 neonates were screened, of those seven were diagnosed to have congenital hypothyroidism. All of the cases were detected by both cord and heel stick TSH level. 305 neonates had positive heel-stick TSH result (sensitivity 100% and specificity 98.32%), 88 neonates had positive cord TSH result (sensitivity 100% and specificity 99.55%). **Conclusion:** Both cord and heel-stick TSH detects all the cases of congenital hypothyroidism. Cord TSH is superior than heel stick as false positive rate was around three times higher in heel stick compared with cord TSH.

P3-1207

Neonatal Hyperthyrotropinaemia – Watchful Waiting vs Treatment: Experiences from a Tertiary Centre

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Background: Neonatal hyperthyrotropinaemia (HT) is defined by elevated TSH and normal fT_4. HT is an increasingly common diagnosis and may be transient or permanent. There is a often a diagnostic dilemma whether to treat to prevent subclincal hypothyroidism or to wait thereby avoiding the risks of iatrogenic hyperthyroidism. **Objective and hypotheses:** To examine a large population of infants referred to a tertiary centre over one year and determine prevalence, sex distribution and natural course of neonatal HT. In our study HT resolved in 76% of infants. We recommend watchful waiting with thyroid function tests repeated every 2 weeks. **Method:** A 1 year retrospective study was conducted at Great Ormond Street Hospital between 2012–2013. Neonates with an abnormal screening test and a raised TSH (6–20 mU/l) and a normal fT_4 on confirmatory tests were included.149 babies were referred to the hospital with abnormal newborn screening tests. 123 had congenital hypothyroidism, 26 had neonatal hyperthyrotopinaemia. TFT's were tested every 2 weeks in neonates with HT. Information was provided to parents about the importance of testing. Thyroid antibodies were evaluated in all babies with HT and were found to be negative. Thyroid scan was done when TSH was more than 15 mU/l and showed evidence of dyshormonogenesis in one. All babies were born at term. There was a male predominance (17/26). HT resolved in 8 weeks in 17 babies and in 12 weeks in three babies. six babies were started on thyroxine. **Results and conclusion:** A diagnosis of HT was made in 17% of babies evaluated for an abnormal screening test in this study. In most cases HT appears to be transient, resolving in 76%.In the event of TSH rising above 20 mU/l, TSH remaining static or TSH and fT_4 decreasing correspondingly we started treatment (24%).We recommend watchful waiting in neonatal HT.

P3-1208

Congenital Central Hypothyroidism due to a Homozygous Mutation in the *TSHB* Gene – Just Think about It!

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Background: Congenital primary hypothyreoidism occurs in about 1 of 3 600 life births and is usually detected with newborn screening. Early levothyroxine treatment is the prerequisite for normal psychomotor development of affected children. However, patients suffering from congenital central hypothyroidism are missed by the screening procedure, which may lead to delayed diagnosis and therapy. In very rare cases central hypothyroidism is caused by isolated TSH deficiency due to mutations in the TSHB gene. **Case presentation:** A 1.5 year old boy of non-consanguineous parents presented at the age of 5 months because of feeding problems and weight loss. On admission he was in poor condition and suffered from a severe RSV infection requiring artificial ventilation. He had pale skin, umbilical hernia, short stature and marked developmental delay. The boy had already been hospitalized twice because of icterus prolongatus, meteorism and feeding problems, unfortunately without recognition of the

severe hypothyroidism. A very low TSH (0.17 mU/l) in combination with unmeasurable fT_4 and T_3 led to the suspicion of isolated TSH deficiency. Sequencing revealed a homozygous mutation c.373delT; p.Cys125Valfs*10 in the *TSHB* gene. Interestingly, this particular mutation (formerly named C105V or 313ΔT) has already been described as a homozygous mutation in a couple of German families without obvious consanguinity, indicating a founder mutation. Levothyroxine treatment was immediately started. At age 14 months Bayley scales of infant development revealed a developmental age of 9–10 months, absent speech but fortunately no hearing deficit. **Conclusion:** Central hypothyroidism is still a clinical challenge, as it is not detected in newborn screening. Paediatric endocrinologists should therefore advice their paediatric colleagues about this syndrome and its clinical picture. *TSHB* gene mutations should be considered in cases with very low TSH with preservation of other pituitary axes and normal pituitary MRI.

P3-1209

A Case of Acute Suppurative Thyroiditis with Piriform Sinus Fistula Treated with Chemocauterization Using Trichloroacetic Acid

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Case presentation: A 23 months-old girl visited the hospital because of fever and left neck mass. She was diagnosed as acute suppurative thyroiditis with piriform sinus fistula. Thyroid sonography showed perithyroidal abscess formation and thyroid scan showed decreased uptake of Tc-99 m pertechnate of both thyroid glands. Magnetic resonance imaging of neck suggested infected 3rd and 4th branchial cyst. And there was tiny fistula between thyroid and piriform sinus on barium esophagogram. Streptococcus gordonii was isolated on needle aspiration culture. **Conclusion:** We report a case of acute suppurative thyroiditis associated piriform sinus fistula, she was treated with chemocauterization using trichloroacetic acid and antibiotics.

P3-1210

Thyroid Dysfunction in Children with Trisomy 21: When Subclinical Hypothyroidism should be Treated?

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Background: Thyroid dysfunction is well-established feature in children with Down syndrome (DS). There are several reasons for both clinical (CH) or subclinical (SH) hypothyroidism in these children- thyroid dysgenesis and dyshormonogenesis early in life, thyroid insensitivity to TSH; or autoimmune disease during school age. **Objective and hypotheses:** Evaluation of thyroid function in children with DS. **Method:** Thyroid function from 80 children with DS was evaluated. The cohort was divided according age and type of thyroid dysfunction. TSH and T_4 were taken in all, while ultrasonographic evaluation was made if elevated TSH was found. Various developmental tests according age were made in all; re-evaluation was made in the group of SH or when starting the therapy with L-thyroxine. **Results:** Impaired thyroid function was found in 25% of patients, from which 3 (3.7%) had congenital hypothyroidism detected on neonatal screening, the remaining 7 (8.7%) developed CH within the first 2 years. SH was noticed in 10 (12.5%) respectively. There was dysgenetic thyroid (hypoplastic, ectopic or unilobulated) in 30% of hypothyroid children. The children with SH were followed up for at least 3 years, of which 4 had improved thyroid function, and in six elevation of TSH and decrease of fT_4 occur where therapy was given. In latter group developmental tests worsen at least 6 months before elevation of TSH; after establishing the therapy they showed better results. According age, there were two peaks of onset of hypothyroidism- one in 2^{nd} year -mostly children with thyroid dysgenesis, and one in 13^{th} year of age, where thyroid antibodies were negative in majority of cases. **Conclusion:** Thyroid dysgenesis seems to have major role in developing clinical hypothyroidism in children with DS at birth or early childhood. Frequent follow up of thyroid parameters, ultrasonographic finding and developmental tests are needed in order to begin with therapy on-time.

P3-1211

Rectal Diluted Levothyroxine for the Treatment of Neonatal Hypothyroidism: An Alternative Route of Administration

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Background: Most individuals with neonatal hypothyroidism present clinically asymptomatic or with few symptoms. Early treatment with oral levothyroxine prevents complications related to this disorder. We report a case of a male infant with Short Bowel syndrome (SBS) and congenital hypothyroidism (CH) treated with rectal levothyroxine. **Case and presentations:** A male patient with previous gastroschisis underwent multiple surgical approaches for small bowel resection and developed SBS. We suspected of CH when he was 4 months old because of jaundice (direct bilirubin up to 59 mg/dl), the absence of evacuation, oral diet intolerance and intestinal dysmotility. The diagnosis was confirmed after a TSH = 34.45 μIU/mL and a fT_4 = 0.64 ng/dl. As fasting was necessary because of SBS, we started rectal diluted levothyroxine. After 4 weeks, the patient had spontaneous bowell movements, improvement of jaundice, and direct bilirubin of

4.62 mg/dl, $fT_4 = 1.34$ ng/dl and TSH = 0.75 mIU/l. **Conclusion:** In the present case the patient was on fasting because of SBS. An alternative route for drug administration was warranted. We empirically prescribed rectal diluted levothyroxine because intravenous and suppository levothyroxine were not available. This method proved to be safe and effective on improving the patient clinical status besides normalizing fT_4 and TSH.

P3-1212

Goitre in Childhood and Adolescence; Clinical Course and Associated Factors for Thyroid Autoimmunity or Isolated Nonautoimmune Hyperthyrotropinemia

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Background: Simple goitre (SG) and autoimmune thyroid disease (AITD) are the two most common causes of goiter in children. **Objective and hypotheses:** The prevalence of thyroid dysfunction, AITD, and SG at the time of goiter diagnosis was investigated. The natural course of SG was studied and factors related to the development of AITD and/or thyroid dysfunction were analysed. **Method:** A retrospective review of 1,225 patients (1071 females, 5.0–17.9 years) initially diagnosed with goiter was performed. Anthropometrics, pubertal status, goitre grade, and family history of thyroid disease were investigated. SG was defined as a euthyroid goitre without pathologic cause after exclusion of AITD or isolated nonautoimmune hyperthyrotropinemia (iso-NAHT). **Results:** At initial diagnosis, 29% of children showed thyroid dysfunction and/or AITD (euthyroid AITD (8.1%), hyper or hypothyroid AITD (14.2%), and iso-NAHT (6.7%)). Despite being initially euthyroid, the AITD group had a higher risk of subsequent medication when compared to the SG group (19.2% vs 0.8%, $P < 0.001$). Hashimoto's thyroiditis (HT) and iso-NAHT developed in 18.5% and 13.7% of those initially diagnosed with SG after 1.8 ± 1.1 and 1.5 ± 1.2 and years respectively. Compared to the persistent SG group, the HT group showed proportionally greater family history (50.0% vs 28.0%, $P = 0.005$) and increasing size of goiter (15.2% vs 5.4%, $P = 0.024$). The iso-NAHT group had higher baseline thyrotropin levels (2.9 ± 0.9 vs 2.0 ± 0.8, $P < 0.001$) , greater proportion of patients with increasing goitre size (18.2% vs 5.4%, $P = 0.01$) and overweight or obese (35.3% vs 18.1%, $P = 0.026$) patients. **Conclusion:** Thyroid dysfunction and/or AITD were detected in one-third of children at initial diagnosis of goiter. Judging from higher risk of subsequent medication in euthyroid AITD patients, thyroid autoimmunity should be checked at diagnosis and during follow-up. During follow-up of SG, thyroid dysfunction or AITD can develop in one-third of patients, especially in those with family history of thyroid disease or increasing goitre size.

P3-1213

Hyperthyroidism in Children and Adolescents: Causes, When and How to Treat – A Tunisian Experience

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Background: Hyperthyroidism is considered to be rare in children; its clinical profile is different and the most cause is Grave's disease (GD). **Objective and hypotheses:** To evaluate clinical features and evolution of childhood hyperthyroidism. **Method:** Longitudinal retrospective study of children diagnosed with hyperthyroidism in an endocrinology unit in a children hospital in Tunisia. **Results:** Seven cases of hyperthyroidism were identified from 2000 to 2015 with a sex-ratio of five girls for two boys. The patients' average age at diagnosis was 6.3 years (7 days–10 years). Appearing symptoms were dominated by goiter in six cases, tachycardia in five cases, exophtalmia in four cases and loss of weight in two cases. In the laboratory evaluation, we highlight: TSH suppression in six/seven patients, raised fT_4 in all patients; Trab were elevated in three cases, elevated titles of antiperoxidase were found in three cases. In the imaging evaluation, the thyroid gland was homogenous and diffusely enlarged in three cases, normal in one case and multinodular in two cases. Causes of hyperthyroidism were dominated by Grave's disease in 5 children associated with Down Syndrom in one case and with coeliac disease in another one. Other causes were thyroïditis (one case) and a rare case of resistance to the thyroid hormones confirmed by molecular biology. All the patients except the one with resistance to the thyroid hormones received a drug therapy. The remission was obtained under carbimazole in two patients. Other patients have been treated for more than 2 years. Additional treatment with β-blockers have been used in 3 patients. No iodine or surgical treatment have been made. The patient with resistance to thyroid hormones do not receive any treatment. **Conclusion:** Grave' disease is the most common cause of hyperthyroidism in children. Nevertheless, we shouldn't forget more rare aetiologies. Treatment is based on antithyroid drugs (ATD) with a low remission rate. The use of scores for identification of predictive factors of the risk of relapse after ATD treatment will lead to improvements in patient management.

P3-1214

Massive Pericardial Effusion and Short Stature Caused by Autoimmune Hypothyroidism in 9-Years-Old Dyspneic Girl

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Background: Massive pericardial effusion is uncommon complication of acquired hypothyroidism in children, and prompt drainage should be performed for impending tamponade. Thyroxine supplementation improves all clinical signs except profound growth failure, resulting poor catch-up growth. **Case presentation:** 9 years 11month old girl was brought to emergency room with sudden worsening dyspnea for 1 day. Previously healthy girl showed weight increase of 10 kg during recent 1 year, and hypercholesterolemia was found during school health exam. She looked short and chubby with height 120 cm (<3rd percentile), weight 30 kg (25^{th} percentile) and BMI 20.8 (90∼95 percentile). Her vital was as follows; respiration 22/min, pulse 65/min, BP 105/57 mmHg. She was prepubertal without goiter. Chest radiogram showed cardiomegaly, EKG was low-voltage. Echocardiogram showed massive effusion with fluctuating mitral inflow, reflecting impending tamponade. Effusion was drained by closed pericardiostomy. The effusion was exudate containing protein 5.6 g/dl, glucose 79 mg/dl, WBC 80/uL (mononuclear cell 90%) and LDH 460 IU/l. Bacterial and viral studies were all negative. Serum total cholesterol was 526 mg/dl with LDL-cholesterol 476 mg/dl. TFT showed hypothyroid with TSH >50 uU/ml, fT_4 0.27 ng/dL. Thyroid autoantibodies were positive with anti-thyroglobulin Ab 154 IU/ml, anti-peroxydase Ab 282 IU/ml and TSH receptor Ab > 40 U/l. Thyroid scan revealed nearly non-visualization of left lobe. Thyroxine was replaced with no recurrence of pericardial effusion. During 1^{st} year of thyroxine therapy, growth velocity (GV) was 11.1 cm/year and height-S.D.s increased from −2.61 to −1.65 with rapid bone age (BA) progression (9.0–10.5 years). GV during next 6 months was decreased to 7.8 cm/yearr, but BA progressed rapidly to 11.5 years. Due to the anxiety of poor catch-up growth, growth hormone was tried for 6 months, resulting increased GV of 12.6 cm/year, and height-S.D.s of −1.10 at the end of 2^{nd} yearsr treatment. **Conclusion:** Primary hypothyroidism should be included in the etiologic evaluation of massive pericardial effusion, especially associated with relative bradycardia. Additional growth promoting therapy should be considered for incomplete catch-up growth in prolonged hypothyroidism during thyroxine supplementation.

P3-1215

Prevalence of Goitre and Thyroid Nodule and Analysis of the Association between Anthropometric Measurements and Thyroid Volume in Children

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Objective: To determine the prevalences of goitre and thyroid nodule, and to analyse the associations among age, gender, anthropometrics and thyroid volume in school children. **Materials and method:** Schools governed by Ministry of Education in Van province were included into the study. Sonographic evaluations of thyroid glands were performed in children aged 6–17 years, and weight, height, waist circumference, hip circumference, and skinfold thickness were measured in subjects. **Results:** Overall, 2 284 school children were included to the study. Median age was 11.08 years in participants. When the association between age and goitre prevalence was analysed according to World Health Organization parameters, it was found that 10.2% of children and adolescents had goitre and 0.8% of these had a nodule. These ratios were 9.4 and 1% among girls whereas 11.3 and 0.7% in boys respectively. **Conclusion:** It was seen that iodine deficiency is still endemic in Van province. In addition, to best of our knowledge, this is the first study showing the relationship between triceps skinfold thickness and thyroid volume.

P3-1216

Hyperfunctioning Thyroid Nodule in an Adolescent

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Background: In adults, autonomously functioning thyroid nodule (AFTN) rarely require cytologic evaluation and hyperthyroidism is often treated with radiojod (131J). In children and adolescents with AFTNs thyroid carcinoma was identified in about 10%. **Results:** An 17-year-old adolescent presented with symptoms of hyperthyroidsm. She suffered from agitation and headache. Thyroid function tests revaled a suppressed TSH (0.10 mIU/ml (reference range 0.51–4.3)), fT_3 elevated with 4.9 ng/l (reference range 2.3–4.2) and normal fT_4 11.8 ng/l (reference range 8.9–17.6). Her height was 163 cm (−0.8 S.D.), her weight 64 kg, BMI 24.3 kg/m^2 (+1.0 S.D.). Blood pressure was 125/76 and heart rate 80. She had a visible swelling of the left lobe of her thyroid with a palpable compact nodule. No lymph nodes were palpabel. Further clinical examination was without pathological findings. No change in her weight or bowel habits was noted. Her medical history was unremarkable, no history of radiation exposure. TSH-receptor-antibodies were negativ, Calzitonin was not elevated (1.58 ng/l (reference range 5.17–9.82)). Thyroglobulin was elevated with 725 µg/l (reference range: 3.5–77). The thyroid ultrasonography showed a large hypoechoic tumour with cystic transformation 3.6×2.3×1.7 cm in the left lobe. Treatment was started with carbimazole 10 mg/day. Hemithyroidectomy was perfomed and histopathologic analysis revealed a benign follicular adenoma, diameter 3.1 cm. **Conclusion:** We describe an adolescent with a hyperfunctioning thyroid nodule due to a follicular adenoma. Hemithyroidectomy was performed because of the visible nodule and the nodule size. Presence of a palpable nodule and large nodule size are associated with an increased risk for malignancy. Detection of an AFTN in children and adolescents does not rule out the possibility of thyroid cancer. Surgery may serve as therapy and diagnostic tool.

P3-1217

Subclinical Hypothyroidism in Children and Adolescents: About a Study of 25 Cases

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Background: The hypothyroidism is defined by an elevated TSH with normal fT_4 and the absence of symptoms of hormonal deficiency. In children and adolescents, it is mainly due to chronic thyroiditis or radiotherapy for cervical cancer. **Objective and hypotheses:** Assess clinical, etiological and evolutionary characteristics of subclinical hypothyroidism in children and adolescents. **Method:** This is a retrospective and prospective study of 25 cases of children and adolescents with subclinical hypothyroidism. All patients underwent a clinical examination, hormonal assment: FT4, TSHus, AC anti TPO, cervical ultrasound and lipid exploration Clinical and laboratory tests were performed annually. **Results:** The average age is 8 years (six–ten) in children (eight girls, five boys) and 14.5 years among adolescents (seven girls and six boys).The reason for consultation was -In children: stature delay (50%) and goitre (50%). In Teenagers: Goitre (40%), signs of hypothyroidism (20%), a systematic exploration (40%); 60% of patients had a goitre with positivity for anti TPO AC. Patients without goitre had no markers of autoimmunity. The clinical exam was normally except for a stature delay in 30% and asthenia in 10%. The lipid profile was normal in all cases. The mean TSH was 8.8 µ/l (4.5–10). Etiological, it was a Hashimoto thyroiditis in 60% of cases and a post radiotherapy hypothyroidism in 15% of cases. No etiology was found in the other cases. Monitoring patients revealed after a mean follow of 6yrs the transition to frank hypothyroidism in 30% of cases, normalising hormone function in 40% of cases and stabilization in the remaining cases. **Conclusion:** Subclinical hypothyroidism is a rare disease in the child and adolescent. Its development is characterised in most cases by a normalisation of TSH or its stability. In a few cases a frank hypothyroidism appears.

P3-1218

Effects of Subclinically Hypothyroidism on Haemorheological Parameters in Paediatric Population

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Objective: Subclinical hypothyroidism (SH) prevalence in the paediatric population is reported between 1.7 and 9.5%. Results of the adult studies on SH showed that long term SH had negative effects on atherosclerosis, dyslipidaemia, insulin resistance and cognitive functions. The decision about treatment of SH in paediatric patients is still a matter of debate. None of the consensus statements published about the management of SH addressed the issue of SH in the paediatric population. Haemorheology, a branch of biorheology focuses specifically on blood and its interactions in both macro- and microcirculation under the influence of the applied constraints. Blood flow, RBC deformability and aggregation are main components of haemorheology. Effects of hypothyroid on haemorheology of patients had widely attracted the attention of researchers during last decade. The present study has been planned with the purpose to determine the effects of subclinically hypothyroidism on haemorheological parameters. **Method:** 53 children with SH and 31 euthyroid healthy children (control group) were enrolled in the study. The groups had similar age, gender, puberty and BMI. Patients with obesity, chronic illness and other endocrine disorders were excluded. Venous blood samples were drawn after 8 hours of fasting and haemorheological parameters were carried out within 3 h after blood collection. **Results:** The haemorheological parameters of SH group and healthy group shown in Table 1 and Table 2. These results indicate that haemorheological parameters are changing in children with SH. **Conclusions:** The results of this study showed that SH is associated with haemorheological changes in children.

P3-1219

Unilateral Graves' Disease in an Adolescent: Case Report

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Background: Graves' disease is a rare autoimmune thyroid disease that characterized by hyperthyroidism, diffuse goitre and ophthalmopathy. It generally involved both lobes of the thyroid, unilateral involvement was rare. **Case report:** A 18 year old girl presented with weakness, alopecia, menstruel irregularity. In physical examination moist skin, increased pulse rate (116/min) and enlargement of the right lobe of the thyroid was determined. Her blood pressure was 130/88 mmHg, weight was 60 kg (0.39 S.D.s), height was 158.5 cm (−0.71 S.D.s), BMI was 23.88 (0.70 S.D.s).No eye signs were detected. Thyroid function tests were TSH 0.19 mU/l, fT_4 2.08 ng/dl, fT_3 5.43 pg/ml, thyroid microsomal antibody 724 mU/l, thyroglobulin antibody 468 mU/l, TSH receptor antibody was elevated.Other laboratory investigation was normal. Tc99m pertechnetate scintigraphy revealed that uptake of the radioisotope was increased in the right lobe of the thyroid gland. In ultrasonography a non-nodular, enlarged, and

heterogeneous right lobe was shown. The left lobe of the thyroid was shown as normal size in ultrasonography and supressed in scintigraphy. Unilateral Graves disease was considered. Methimazole and propranolol were started. **Conclusion:** To our knowledge unilateral involvement of the thyroid gland is a rare presentation of Graves' disease. Functional or structural differences of the two lobes may be responsible. We reported a case of Graves' disease presenting with unilateral involvement of the thyroid gland.

P3-1220

Transient Hyperthyroidism Associated with a Thyroid Nodule

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Introduction: Developing an acute onset thyroid nodule is rare in children and usually associates with infectious or neoplastic disease; when linked to hyperthyroidism, the most likely diagnosis is toxic adenoma. **Clinical description:** 9-year-old boy with no relevant medical history was seen at the emergency department for acute cervical pain and tumor involving the left thyroid lobe with no inflammatory signs or history of trauma. Physical examination revealed no fever, normal BP and no exophthalmos. A nodule without clearly defined borders could be palpated. No lymphadenopathies were detected. Additional Examinations: Neck ultrasound: Well-defined heterogenic nodule measuring 3.3×2.5×2.4 cm involving the left thyroid lobe, with no Doppler signal, and probable hematic content. Analgesic and antibiotic treatment was initiated owing a suspected spontaneous hemorrhage. Over 72 h, the patient developed nervousness, insomnia and palpitations with no evident change in the nodule's external appearance. HR: 90 bpm, BP 110/70 (95 p). Normal CBC and general biochemistry. Thyroid function: TSH 0.019 mU/l (0.64–6.27), fT_3 9.81 pg/ml (2.3–4.2), fT_4 2.44 ng/dl (0.8–1.76), thyroglobulin: 3241 pg/ml (0–55). Treatment was started with beta-blockers. Pertechnetate scintigraphy: low thyroid uptake, almost abolished in the involved region. FNA: scant non-diagnostic cellular material. Thyroid function 15 days after presentation: TSH 0.016 mU/l, fT_3 4.82 pg/ml, fT_4 1.32 ng/dl, thyroglobulin: 857 pg/ml. Gradual reduction in US measured nodule size also showing contents changing from anechoic to hypoechoic, favoring a hematic nature. One month post-presentation thyroid function had normalized: TSH: 2.2 mU/l, fT_3: 3.51 pg/ml, fT_4: 0.95 ng/dl, thyroglobulin: 90.1 pg/ml. Owing a persistence of the nodule, a hemithyroidectomy was indicated. Histopathology: hyperplastic residual nodule with widespread signs of previous hemorrhage. **Comments:** Although transient hyperthyroidism is very rare in children, it has been described in early stages of Hashimoto's thyroiditis and in intoxications with exogenous thyroid hormones. The release of thyroid hormones due to spontaneous hemorrhage appears to have caused the transient hyperthyroidism in our patient.

P3-1221

Hyalinizing Trabecular Tumour of Thyroid Gland in 17-Year-Old Boy – Case Report

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Background: Hyalinizing trabecular tumour is a rare, begin thyroid neoplasm, which shares some histologic features with thyroid papillary carcinoma or medullary carcinoma. Sometimes it is misdiagnosed as papillary carcinoma on fine-needle aspiration cytology (FNAC). The aetiology of hyalinizing trabecular tumour is unknown. The tumour may arise in a background of chronic lymphocytic thyroiditis, multinodular goitre, or after radiation exposure. Hyalinizing trabecular adenoma (HTA) is predominantly diagnosed in middle-aged women. In children it is casuistic **Case presentation:** We present the case of 17-year-old boy, who was diagnosed in our Outpatient Clinic of Endocrinology due to an asymptomatic left neck mass suggestive of a thyroid tumour. Clinical examination confirmed the diagnosis of the nodule within the left lobe of thyroid gland, without lymph nodes metastases. Serum thyroid hormones and thyroid antibodies were in normal range. An ultrasound of the neck confirmed the presence of solid nodule measuring 38.7×24.5×28.7 mm and mixed blood flow (with predominance of peripheral flow) within nodular change. In elastography this nodule was tough (typical for malignancy) with elasticity index ROI1/ROI2 = 5. A papillary thyroid carcinoma (PTC) was diagnosed by FNAC. Total thyroidectomy was performed, with hypothyroidism as a post-surgical result. Immunohistochemistry was positive for thyroglobulin but negative for calcitonin, eliminating the possibility of medullary carcinoma. The cells of tumour had a Ki-67 reactivity at the cell membrane and cytoplasm, characteristic of hyalinizing trabecular tumour. There was no area of focal capsular invasion. A final pathological diagnosis of hyalinizing trabecular adenoma was reported. The patient's treatment with an ablative dose of radioactive iodine was redundant. Now he is euthyroid with thyroid replacement and has no evidence of recurrence at 6 months of follow-up. **Conclusion:** In conclusion, distinction of hyalinizing trabecular adenoma from thyroid papillary carcinoma in cytologic specimen is very difficult. Diagnosis of a thyroid tumour determinate appropriate management.

P3-1222

Seven Cases with Williams Beuren Syndrome: Endocrine Evaluation and Long-Term Follow-Up

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Objectives: Hypercalcaemia, hypothyroidism, and early puberty are the most common endocrine disorders defined in Williams-Beuren syndrome (WBS). Here, endocrine evaluation and long-term follow-up of seven patients with WBS are given. **Methods:** Data were obtained from patient's medical records. WBS was diagnosed by demonstration of the deletion on chromosome 7 by using FISH method (7q11.23). OGTT were performed in four patients. Thyroid ultrasonography was performed. LT_4 was started in patients with hypothyroidism and WBS. **Results:** Six patients were male. Age at diagnosis WBS was 1.04 (3.47) a decimal-year. They all had mild hypercalcemia (9.9–11.1 mg/dl). Three of them had overt hypothyroidism while subclinical hypothyroidism were detected in three patients ((0.66 (5.77) decimal-year). At the diagnosis, serum TSH was 10.5 ± 6.3 μIU/ml and fT_4 was 0.9 ± 0.1 ng/dl. LT_4 was started at 5 ± 3.9 μg/kg. Four patients had thyroid hypoplasia and thyroid agenesis had one. GH deficiency was determined in one patient. Height S.D.S was -3.26 at the age of 34/12 decimal-years when hGH was initiated and increased to -1.45 at the age of 6.08 decimal-years. Age of onset of puberty in three patients was early according to healthy peer. IGT was detected in three pubertal patients and metformin was started. Follow-up duration was 5.7 ± 2.1 years. Mean GV was 12.9 ± 7.2 cm and 7.6 ± 2 cm at the end of 1st and 2nd years of the therapy respectively. At the last visit, LT_4 dose was 2.9 ± 1 μg/kg. All patients had neurodevelopment retardation and were continuing to special education. **Conclusion:** Untreated hypothyroidism also causes mental and motor retardation particularly in infancy period in WBS. IGT could be detected in patients with WBS even if adolescence.

P3-1223

Clinical Course in a Girl with hTPO Mutation R161I in Exon 5: 18 Years of Follow-Up

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Background: Of the several genetic defects responsible for thyroid dyshormonogenesis, mutations in TPO gene are the most prevalent causes of inherited defects in CH. Prevalent mutations are in exons 8–11 (catalytic site). **Case presentation:** Girl, born at term (s.c) picked up by TSH screening and start of LT_4 treatment at d14 with 14 μg/kg per day (table 1), clinical signs: no goiter, hypotonia, dry skin, posterior fontanel >5 mm, obstipation, delayed bone age (32–33 gw), feeding difficulties. Euthyroidism achieved at d 27, good adherence with the therapy during entire follow up (frequent thyroid ultrasound, TSH, fT_4, auxology, bone age). Normal physical growth and development according to the genetic potential. Mental development: normal, high academic achievements. Candidate for hTPO molecular genetic studies based on permanent severe CH, orthotopic thyroid and high thyroglobulin levels. An uncommon homozygous mutation in exon 5, R161I was determined by dHPLC after reevaluation. Twice (at 9 and 12 years) a significant thyroid enlargement along with TSH elevation (12–20 mU/l) and low-normal fT_4 (9.6–12.4 pmol/l) was evident. Bone age variations – 1 years ahead of the chronological during puberty. **Conclusion:** An earlier molecular genetic analysis would have prevented the reevaluation; in order to prevent thyroid enlargement a more frequent TSH monitoring is indicated, especially in puberty. The increased risk for thyroid cancer should be kept in mind.

Table 1.

Age	NTSH mu/l	TSH mU/l	T_4 nmol/l	Tg ng/ml
4 days	297			
14 days	681	1120	<25	547
2 years 3 months	300	463	<25	211.6

P3-1224

Transient Polyarthritis with Carbimazole Treatment

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Background: Antithyroid drugs such as carbimazole form the mainstay of medical management of hyperthyroidism in children. Parents are always warned about agranulocytosis, which is a rare side effect of these drugs. Development of arthralgia after starting antithyroid medication can be a disabling side effect and needs to be distinguished from the more serious antineutrophil cytoplasmic antibody (ANCA) positive vasculitis. **Objective and hypotheses:** Here we report a 10 years old patient who developed significant joint pains after commencing carbimazole. **Method:** Case presentation: A 10 years old girl with background of asthma presented with complaints of weight loss and tremors. Her thyroid function tests showed hyperthyroid picture with suppressed TSH and elevated fT_4 measurements. She was started on carbimazole at a starting dose of 10 mg BD. Within 10 days of treatment she started experiencing significant multiple joint pains making her wheelchair-bound. This did not settle with use of non steroidal anti-inflammatory drugs. Her auto-antibody screen, including ANCA was negative. Her symptoms settled down within 4 weeks of stopping Carbimazole. Her hyperthyroidism is currently being managed using propylthiouracil and she is waiting to undergo definitive treatment. **Conclusion:** Development of arthralgia on antithyroid medication should warrant immediate investigation to rule out ANCA positive vasculitis. Symptoms of transient migratory polyarthritis or antithyroid arthritis syndrome usually subside on discontinuation of treatment. More definitive treatment options should be discussed with family while maintaining the patient on alternative antithyroid medication as a temporary measure.

P3-1225

Thyroid Functional Autonomy in Adolescents with Nodular Goiter

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Background and aims: To explore the functional autonomy in adolescents with nodular goitre. **Materials and methods:** We have examined 66 patients with nodular goiter from iodine deficient region. There were 48 girls (mean age 14.91 ± 1.78 years) and 18 boys (mean age 14.46 ± 2.75 years) among them. Uninodular goitre was diagnosed in 43 patients, 23 patients had multinodular goitre. The survey included thyroid scintigraphy 99mTc and assessment of the functional state of the pituitary-thyroid system: TSH, fT_4, fT_3. Reference values of TSH were detected as 0.4–4.3 mkEd/ml, fT_4 9–20 pmol/l, and fT_3 4.4–9.3 pmol/l. **Results:** Based on the results of scintigraphy of thyroid gland 'hot' nodules were diagnosed in 31 of 66 (47%) adolescents. 'Hot' nodules met with equal frequency in girls (27 of 48) and boys (four out of 18, $P = 0.129$) with nodular thyroid disease. There were 14 of 43 (33%), 12 girls/two boys with 'hot' nodules among patients with uninodular goitre, and 17 of 23 (74%) of patients (15 girls/two boys) in cases of multinodular goiter. Among patients with 'hot' nodules the ten (32%) adolescents had thyrotoxicosis. The number of nodules didn't influence on functional state of the thyroid gland ($P = 0.075$). So, thyrotoxicosis was found in eight (57%) patients (seven girls/one boy) with 'hot' uninodular goitre. Half of them produced symptomatic thyrotoxicosis (the mean values of TSH 0.24 ± 0.44 mkED/ml, fT_3 13.44 ± 2.01 pmol/l, fT_4 22.4 ± 2.67 pmol/l) and half–subclinical (the mean values of TSH 0.059 ± 0.1 mkED/ml, fT_3 4.77 ± 0.95 pmol/l, fT_4 13.26 ± 2.1 pmol/l). Among patients with multinodular goiter with 'hot' nodules, two of them (12%) had subclinical thyrotoxicosis (average values of TSH 0.2 ± 0.27 mkEd/ml, fT_3 4.34 ± 1.02 pmol/l, fT_4 11.85 ± 0.64 pmol/l). **Conclusion:** The results of the study have shown that every second adolescent with nodular thyroid disease from iodine deficient region has a 'hot' nodule, more than that, each third of them produces decompensation of autonomous thyroid function. That underlines the role of scintigraphy in adolescents with nodular thyroid disease.

P3-1226

A Rare Adverse Effect of Radioactive Iodine Therapy in a Child with Graves' Disease

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Background: Radioactive iodine (RAI) therapy has become the preferred treatment for Graves' disease in children. Its use has found favour due to the risk of adverse effects in medical management and the invasiveness of thyroidectomy. Side effects of RAI in adults are well-documented and include dry mouth, sore throat, and neck pain. With its relatively recent application to paediatric patients, there is not a complete understanding of adverse effects in the paediatric population. Previous studies have demonstrated that RAI uptake occurs in the sinuses and some adults have reported nasal symptoms following RAI. **Objective and hypotheses:** To report a case of clinical sinusitis due to RAI therapy in a child. **Method and results:** Patient is a 13.5 year old Caucasian female with a history of Gilbert's disease who underwent RAI therapy for Graves' disease. She received 20.9 mCi I-131. 8 days after RAI treatment, she developed symptoms of facial pain with a sensation of forehead burning. She did not have neck pain or sore throat at that time. Despite analgesics, rest and cold compresses, her complaints persisted. 13 days post RAI therapy; patient was diagnosed clinically with sinusitis secondary to RAI treatment. This patient was started on a trial of oral pseudoephedrine and her symptoms improved within 24 h. Upon review, patient had a history of chronic sinusitis preceding RAI therapy. However it had been well-controlled with nasal fluticasone at the time of RAI treatment. **Conclusion:** This patient endured prolonged discomfort and anxiety due to the under recognized adverse effect of RAI therapy. Studies have shown that even with diagnostic scintigraphy using 5 mCi, the nose is a common site of RAI accumulation. With smaller nasal passages, children may be at an even higher risk for this particular side effect. As we start treating younger patients with RAI, it is important to be aware of all potential side effects. To the best of our knowledge, this is the first report of this particular complication in a paediatric patient. Given the common nature of clinical sinusitis in the paediatric population and the increasing use of RAI to treat Graves' disease, clinicians must be alert to this adverse effect in order to treat appropriately and avoid unnecessary radiographic studies.

P3-1227

A 7 Month-Old Male Infant with Spontaneous Transient Graves' Thyrotoxicosis

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Background: Graves' disease (GD) is most prevalent autoimmune disorder in adult. The annual incidence in adult woman is approximately 0.5 in 1 000, and in adult men is one tenth as common as in women. GD is rare in children, with an annual incidence of 0.8 in 100 000, and with six times more common in girls, thus, GD in boys is very rare. An annual incidence of GD under 10 year-old is extremely rare. Spontaneous transient thyrotoxicosis with pregnancy is sometimes happened in 2–3% of all pregnant women. On the other hands, two adult cases of spontaneous transient Graves' thyrotoxicosis without pregnancy were reported. **Case:** A Japanese 7 month-old male infant was examined in developmental delay and poor weight gain by paediatric neurologist. Blood tests were performed, then TSH level was < 0.01 μU/ml (reference value; 0.62–8.05 μU/ml), fT_4 level was 2.14 pg/ml (reference value: 0.48–2.34 pg/ml). The paediatric

neurologist diagnosed him with hyperthyroidism, and reffered to our hospital at 8 month-old. Blood tests were performed. TSH level was <0.05 μU/ml, fT_4 level was 1.60 pg/mL, and fT_3 level was 5.2 pg/ml (reference value: 0.88–1.56 pg/ml), total cholesterol level was 112 mg/dl (reference value:128–219 mg/dl), thyroglobulin level was 73.6 ng/ml (reference value; 0.0–32.7 ng/ml), thyrotropin receptor antibody (TRAb) 3.9 IU/l (reference value: <1 IU/l), thyroid stimulating antibody (TSAb) 123% (reference value; $<180\%$), anti thyroglobulin antibody (TgAb) 5.8 IU/ml (reference value; <9 IU/ml), thyroid peroxidase antibody (TPOAb) <0.1 IU/ml (reference value; <5 IU/ml). However, He was non-condition, and fT_4 level was decreased after first our examination for 1 month, and blood flow of thyroid gland in an ultrasound did not increase and technetium uptake of thyroid gland in scintigraphy was relatively increased compared to intake of salivary gland. Therefore, we decided to carry out progress observation under no treating. After 1 month, TSH level was 0.274 μU/ml, fT_4 level was 1.15 pg/ml, giving that became a normal range. fT_4 did not go up for 8 months after that and condition did not appear without treatment. We diagnosed spontaneous transient Graves' thyrotoxicosis. **Conclusion:** 7 month-old male infant with spontaneous transient Graves' thyrotoxicosis is very rare case and show that follow-up is possible without treatment.

P3-1228

Sex and Age Differences in the Incidence of Thyroid Disease in Children with Obesity

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Background: Obesity in adults is closely associated with an increased prevalence of thyroid gland (TG) pathology, but thyropathy formation issues among children are not sufficiently studied. **Objective and hypotheses:** To determine the prevalence and structure of TG pathology in children with obesity by gender and degree of puberty. **Method:** In 121 patients 6–16 years old with obesity a thyropathy detection was conducted (diffuse nontoxic goiter (DNG), autoimmune thyroiditis (AIT)), based on a comprehensive study (ultrasound (US) study, determination of thyroid hormones level and thyroid antibody level in relation to TG tissue). Patients were grouped by gender (51 girl and 70 boys) and age according to the stage of puberty (1 g – pre-puberty, 2 g – early puberty, 3 g – puberty). **Results:** Thyropathy most common in children with obesity, as well as in general children population is DNG (66.1%), prevalence of which is independent of gender. AIT was diagnosed in 8.3% of children with girls' percentage being more significant (13.7%) than that of boys (4.28%). According to the US study results the following pathological changes in TG structure were discovered: lower echogenicity – in 50.4% echostructure heterogeneity – in 33.8%, capsule sealing – in 28.0%. These changes were found in children with increased TG volume, as well as in children with normal TG volume, absence of antithyroid antibodies and normal TSH levels – in 14.9%. The DNG was the most common pathology in every age group, but it's prevalence was the most significant in early puberty group (72.1% in 2 g against 65.2% in 1 g and 56.1% in 3 g, $P<0.05$). AIT in children with obesity was only found in early pubertal age, with gradual increase in prevalence of this thyropathy during puberty (9.3% in 2 g, 14.6% in 3 g, $P<0.05$) and girls' percentage being more significant than that of boys (13.6 and 4.7% respectively in 2 g, 21.4 and 3.7% in 3 g, $P<0.05$). **Conclusion:** In most children with obesity, even those in prepubertal age, thyroid pathology is present, and its prevalence depends on patients' sex and stage of puberty.

P3-1229

Euthyroid Sick Syndrome in Children Presenting with Diabetic Ketoacidosis

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Background: Euthyroid sick syndrome (ESS), also known as non-thyroidal illness or low T_3 syndrome, is defined as low T_3, low/normal T_4 and inability of rise in TSH due to extrathyroidal diseases. Any condition resulting stress such as infectious diseases, sepsis, metabolic disorders and severe malnutrition can associate to ESS. Patients presented with type 1 diabetes mellitus (T1DM) are usually being screened for other autoimmune diseases including autoimmune thyroiditis from the blood samples collected at presentation. **Objective and hypotheses:** Diabetic ketoacidosis (DKA) is characterised with metabolic decompensation that produces a profound stress. The aim of the present study is to evaluate the development of ESS in patients with T1DM who presented with DKA. **Methods:** Patients presented with T1DM at the Diyarbakir Children's State Hospital Paediatric Endocrinology Clinic between the years 2011-2013 were included. Thyroid function test (TFT), blood gases analysis, leukocyte count and C-reactive protein (CRP) level were measured at the time of the presentation. **Results:** Study included 83 patients (47 females) with T1DM. The mean age of the diagnosis was 8.8 ± 4.2 years (range: 0.5–17 years). Number of patients who had DKA at presentation was 54 (65.1%). In total 38 out of 83 (45.8%) patients had ESS. The frequency of ESS in patients with DKA ($n=32/54$; %59.3) was higher than those of patients without DKA ($n=6/29$; %20.7) ($P<0.0001$). The frequency of ESS in the patients with elevated CRP (46.1%) was not statistically different from those of patients with normal CRP (43.9%) ($P=0.887$). In all patients who had ESS at presentation, TFT's recovered to normal range during follow up with no need of thyroid hormone replacement.

Conclusion: ESS was more prevalent in patients who presented with DKA. Of which all became euthyroid with no need of treatment. Having or not having infection at presentation has not statistically significant impact on the development of ESS. These results suggested postponing the evaluation TFT's till recovery of DKA.

P3-1230

The Role of Thyroid Fine-Needle Aspiration Cytology in the Treatment and Follow-Up of Thyroid Nodules in the Paediatric Population

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Background: Although thyroid nodules are rare in children compared to adults, the risk of malignacy is higher. Thyroid fine-needle aspiration (FNA) is a reliable diagnostic method used in the prediction of malignancy in the evaluation of thyroid nodules together with clinical and ultrasonographic findings. **Objective and hypotheses:** To compare clinical, ultrasonographic, cytological and histopathological findings in patients who underwent FNA. **Method:** The study included 80 (52 females, 28 males) patients who underwent FNA ($n=107$), for thyroid nodules at presentation or at follow-up. Clinical, ultrasonographic, cytological findings of patients were evaluated retrospectively. **Results:** Mean age of the patients was 13.7 ± 2.8 years during FNA. Autoimmune thyroiditis was present in 32.5% ($n=26$) and history of radiotherapy to the head or neck in 10% ($n=8$) The cytological diagnoses of patients included inadequate or hemorrhagic in 10% ($n=8$), benign in 42.5% ($n=34$), atypia or follicular lesion of undetermined significance (AUS/FLUS) in 15% ($n=12$) suspicion of follicular neoplasia (FN) in 7.5% ($n=6$), suspicion of malignancy (SM), in 8.8% ($n=7$) malignant in 16.3% (n: 13). There were no significant correlations between cytological findings and age, gender, erythrocyte sedimentation rate, thyroid hormones, thyroid autoantibodies and ultrasonographic findings of the thyroid nodules. 37 patients underwent thyroidectomy. The results of histopathological examination indicated 83.8% as malignant, 16.2% as benign. 25% of benign lesions according to cytological diagnosis was malignant, but all of malignant lesions were found malignant. Histopathologic examination was indicated as malignant in 25% of patients with benign FNA cytopathology, in 100% of AUS/FLUS, in 75% of FN, in 85.7% of SM. Allpatients who received radiotherapy had malignancy. In our study, the sensitivity of FNA was 80%, specificity 100%, positive predictive value 100%, negative predictive value 75%, and diagnostic value was 87.5%. **Conclusion:** FNA results were highly compatible with thyroid histopathological examination. There were no clinical or sonographic findings that were related with thyroid cytopathological and histopathological examination.

P3-1231

Angioneurotic Oedema with Antithyroid Drugs in Thyroid Storm: What is the Best Therapeutic Option

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Background: Graves disease is the most common cause of hyperthyroidism in children. The frequency of the disease increases with age, peaking during adolescence.Thyroid storm is a rare but critical, ilness that can lead to multiorgan failure and carries a high death rate. Antithyroid drugs are usually recommended as the initial treatment and are generally well tolerated. Although current treatment options include radioactive iodine, but long term complications of thyroid irradiation is not well known. Near total or total thyroidectomy is an acceptable form of therapy too. Reactions to antithyroid drug medication makes the decision harder for choosing the suitable therapeutic option. **Case:** A 10 years old girl administrated to our outpatient clinic with palpitation, tremor, anxiety, sleepless, weight loss and fatigue. She was administered to another center with thyroid storm and diagnosed as Graves disease. The antithyroid drug therapy (methimazole and propranalol) was initiated to patient but she had angioneurotic edema. Following either propranalol or methimazole administration alone resulted with angioneurotic edema. In this situation the patient was reffered to our clinic for radioactive iodine ablation therapy. Physical examination and laboratory findings were given at Table 1. Under this circumstances thyroid ablation with ^{131}I seems to be a good solution but her iodine turnover was very high (4^{th} h: 62.4%; 24^{th} h 54.6%) and so the response will be poor and needs to be administered with higher recurent doses. Plasmapheresis could be another option in preparation for total thyroidectomy but it was risky.High dose oral glucucorticoid and antihistaminic therapy combined with propranolol was administered before surgery. Her thyroid hormone levels were decreased %70 in a week and total thyroidectomy was performed without any complication Postoperation period LT_4 therapy was initiated. **Conclusion:** In conclusion inorder to underline allergical reactions of antithyroid therapy, we wanted to remined oral steroid therapy benefits combined with surgery.

Table 1. Physical examination and laboratory findings. (for abstract P3-1231)

Laboratory findings	Our patient initial values	After high dose oral glucucorticoid and antihistaminic therapy values	Postoperative values
Physical examination	Height: 137.3 cm (HSDS: −1.3) Weight: 29.5 (BMI: 15.7) Heart rate: 125/min Goiter and tremor		Height: 139 cm (HSDS: −1,2) Weight: 31 (BMI: 16.06) Heart rate: 75/min
fT_3	36.31 pmol/l (3.8–6 pmol/l)	6,02 pmol/L	3,8 pmol/L
FT_4	71.5 pmol/l (7–16 pmol/l)	21.96 pmol/l	15.36 pmol/l
TSH	0.02 mcIU/ml (0.34–5.6 mcIU/ml)		
TRAb	405 U/l (0–9 U/l)		
Thyroglobulin Ab	311.1 IU/ml (negative)		
TPO Ab	221.4 IU/ml (negative)		
Hemogram	Hemoglobin:14,5 g/dl Leucocyte: 7400/mm^3 Platelet: 319 000/mm^3		Hemoglobin: 14.6 g/dl Leucocyte: 23 200/mm^3 Platelet: 277 000/mm^3
Liver functions	AST: 18 U/l (<41) ALT: 17 U/l (<34)		
Thyroid Color Doppler Ultrasonography	Thyroid volume: 14.1 ml (> +2 S.D.) Parenchyma in heterogeneous appearance, increased thyroid blood flow	Thyroid volume: 12.36 ml (> +2 S.D.) Parenchyma in heterogeneous appearance	
Thyroid Scintigraphy	Thyroid uptake above the normal limit (4^{th} h: 62.4%; 24^{th} h 54.6%)		

P3-1232

Malabsorption of Levothyroxine in a Child Affected by Short Bowel Syndrome

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Background: Hypothyroidism is a common problem during childhood generally due to autoimmune thyroid disease. It can also occur in case of severe loss of serum proteins, as well as in the case presented. The most accepted practice in the treatment of hypothyroidism consists in the oral administration of LT_4. Many conditions may affect the absorption of LT_4. **Case presentation:** We report an original case of LT_4 malabsorption in a 6-years old child affected by congenital multiple jejunal atresias. He presented TSH 30 μUI/ml (0.6–6.3) and fT_4 0.71 ng/dl (0.7–1.8), TGAb 34.5 U/ml (0–40) and TPOAb 20.8 U/ml (0–60), so we started LT_4 tablet 25 μg/day (2.5 μg/kg per day). The US showed a normal gland. After 1 month of treatment, TSH was 80 μUI/ml and fT_4 0.7 ng/dl, consequently the dosage was increased to 25 μg 5 days per week and 50 μg twice (4 μg/kg per day). Although the dosage was high, after one month TSH increased >150 μUI/ml and fT_4 was 0.2 ng/dl. Poor compliance could be ruled out. A severe malabsorption of oral LT_4 was hypothesized. The LT_4 oral solution, available in Italy, has a more rapid absorption than tablets in studies done in adult populations and this characteristics would have been an advantage in our patient, so we decided to switch to the treatment with LT_4 oral solution at the same dosage. After 4–6 months of treatment with LT_4 oral solution the values of TSH and fT_4 were within the normal range. **Conclusion:** Short bowel syndrome is the most common cause of intestinal failure in children and causes altered absorption of many drugs. In this case we observed how the TSH value decreased only after the switch from the LT_4 tablets to the LT_4 oral solution. The most important advantage of LT_4 oral solution consists of a faster absorption, which is very crucial in a population of patients having a limited absorption of drugs. We can certainly highlight the implications of the liquid formulation of LT_4, a novel and useful formulation in cases where the absorption of drugs is clearly hindered.

P3-1233

Growth Curves for Turkish Girls with Turner Syndrome: Results of the Turkish Turner Syndrome Study Group

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Background: Children with Turner syndrome (TS) have a specific growth pattern that is quite different from that of healthy children. Many countries have population specific growth charts for TS. **Objective and hypotheses:** Considering national and ethnic differences, we undertook this multicentered collaborative study to construct growth charts and reference values for height, weight, and BMI from birth to adulthood for spontaneous growth of Turkish girls with TS. **Method:** Cross-sectional height and weight data of 842 patients with TS, younger than 18 years of age and before starting any therapy were evaluated. Data were processed to calculate 3th, 10th, 25th, 50th, 75th, 90th, and 97th percentile values for defined ages and to construct growth curves for height for age, weight-for-age and BMI-for-age for girls with TS. **Results:** The growth pattern of TS girls in this series resembled the growth pattern of TS girls in other reports but there were differences in height between our series and the others. Mean birth length values were shorter than that of the normal population and deteriorated by age. While height was under −2 S.D. at 3–4 years of age, it gradually worsened and reached approximately −4 S.D. at about 12 years of age with lack of pubertal peak. The increase in BMI in TS girls especially between 2 and 6 years of age was noteworthy. **Conclusion:** This study provide disease-specific growth charts for Turkish girls with TS. These disease specific national growth charts will improve the evaluation and management of growth promoting therapeutic agents in TS.

P3-1234

Cardiovascular Assessment in Turner Syndrome: Current Practice in the United Kingdom

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Background: In 2007, the Turner syndrome (TS) Consensus Study Group developed an international guideline for clinical care of girls and women with TS. Given emerging concerns of long term cardiovascular complications, the consensus recommends that cardiac MRI should be performed when girls are old enough to tolerate the procedure or at the time of transition and to be repeated at least every 5–10 years. **Method:** We conducted a survey of cardiovascular (CVS) assessment in girls and women with TS in all tertiary paediatric endocrinology centres and all adult centres with dedicated TS clinical service in the UK. **Results:** An online survey was sent to 49 consultants (20 paediatric, 29 adult). There were 26/49 (53%) responders.13/26 (50%) provided care in childhood. At diagnosis of TS, echo (9/12,75%) or echo & MRI (3/12,25%) were performed. In adolescence, echo (6/13, 46%) or MRI (3/13, 23%) were performed for CVS re-evaluation. However, 4/13 (31%) were not re-evaluated in paediatric care. Median age of re-evaluation was 16 years (range 10–16) or at the time of transition. In adulthood, echo & MRI (10/13, 77%), MRI (2/13, 15%) and echo (1/13) were performed respectively at frequency of 5 years or less. Aortic sized index was provided in imaging reports of 5/10 (50%) and 13/13 of paediatric and adult responders respectively. Blood pressure was measured in the paediatric clinic: annually 3/12 (25%), 6 monthly 6/12 (50%) and 3–4 monthly 3/12 (25%), whereas this was measured in the adult clinic: annually 10/13 (77%), 6 monthly 2/13 (15%) and at every clinic 1/13. Cardiovascular risk is discussed by the primary treating paediatrician in 7/11 (64%) and by the primary treating adult physician in 12/13 (92%). Written information on cardiovascular risks is provided in 3/10 (30%) and 2/12 (17%) of paediatric and adult clinics respectively. In high risk patients, a recommendation to carry medical bracelet/card is provided by 2/10 (20%) and 2/12 (17%) of paediatric and adult clinics respectively. **Conclusion:** Despite the existing consensus, this survey, of clinicians providing care to individuals with TS in the UK, demonstrates wide variation in cardiovascular assessment especially in adolescence. This variability may relate to access to local expertise and specialist investigations. Uncertainties surrounding the value of investigations to clinical outcome of aortic dissection especially in childhood may also be a factor.

P3-1235

Turner Syndrome in Iceland 1968–2012: Congenital Anomalies and Clinical Outcomes

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Background: In 1968 a cytogenetics laboratory was established at the University Hospital, Reykjavik and has since then served as the only chromosomal laboratory for all hospitals and physicians in Iceland. Our current aim was to study the physical features, congenital anomalies and various clinical outcomes in Icelandic females, diagnosed with Turner syndrome (TS) for the period of 1968–2012. **Method:** Data was obtained from hospital records, from all pediatric endocrinologists in Iceland and the cytogenetics laboratory making this a nationwide retrospective population study. **Results:** A total of 51 females were diagnosed

with TS during the 45 year period with an average yearly incidence of one per 2 585 liveborn females. Average birthweight was 3 028 g. Clinical features were webbed neck (47%), shield chest (45%), low hairline (45%), cubitus valgus (27%), hyperconvex nails (25%) and short fingers (25%). Pedal hydrops was seen in 25% of cases at birth. 16% had bicuspid aortic valve, 12% coarctation of the aorta and 14% had horseshoe kidney. The most common late complication was recurrent acute otitis media (55%), followed by high blood pressure (29%) and various thyroid problems in 24% of cases. Three girls (7%) were diagnosed with type 2 diabetes and one girl had idiopathic thrombocytopenic purpura (ITP). 24 girls received GH treatment. 18 have completed treatment. Average final hight of girls who started GH before 1992 was 147.9 cm (−3.2 S.D.), but for girls started on GH after 1992, 156.5 cm (−1.8 S.D.). Eight girls had signs of spontaneous puberty but only one completed pubertal development resulting in unaided pregnancy. **Conclusion:** The clinical features and the most common clinical complications are similar to what has been described in the other nordic countries. Improvement in GH treatment and sex hormone replacement has resulted in improved height during the last two decades.

P3-1236

A Comparison of Efficacies between rhGH and rhGH Combined with Stanozolol Therapies in Growth of the Girls with Turner Syndrome

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Objective and hypotheses: To compare the different efficacies between recombinant human GH (rhGH) alone and rhGH combined with low does stanozolol on improving growth of the girls with Turner syndrome (TS). **Method:** TS girls were divided into two groups. Group 1 (15 cases) received rhGH therapy, aged (13.09±2.70) years, bone age (11.00±1.01) years, height was (131.46±8.22) cm. Group 2 (22 cases) received low does stanozolol combined with rhGH therapy, aged (13.37±2.09) years, bone age was (11.04±0.86) years, height was (129.21±8.19) cm. Treatment periods were one year. Growth velocity (GV), height S.D. score (HtSDS), ΔHtSDS, the change of bone age over the change of chronologic age (ΔBA/ΔCA) for both groups were measured or calculated. **Results:** The GV was (6.33±1.44) cm/a and (8.13±1.87) cm/a for group 1 and 2 respectively, HtSDS change from (−3.44±1.02) to (−3.06±1.09) and (−4.21±1.19) to (−3.43±1.06), and ΔBA/ΔCA was (0.63±0.40) and (0.77±0.56) for group 1 and 2 respectively. The GV and change of HtSDS for group 2 were significantly better than group 1 ($P<0.05$). The GV was negative correlation with the age. **Conclusion:** Comparing to the therapy with rhGH alone, combined therapy with rhGH and low dose stanazolol has advantage on improving GV without accelerating bone maturation among the girls with TS.

P3-1237

Clinical Features and Genetic Considerations of Turner Syndrome: A Review of Our Cases

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Background: Turner syndrome (TS) involves a partial or complete loss of an X chromosome. TS patients have an increased susceptibility to various disorders. **Objective and hypotheses:** To describe the clinical presentation, genotype and follow-up of TS patients controlled in the Pediatric endocrinology department of our hospital. **Method:** Retrospective study of patients diagnosed with TS at the 'Navarra Hospital' between 1980–2014. Review of medical records. **Results:** 33 patients, actual mean age: 22.2 years (6–47), age at diagnosis: 7±3.8 years. The main reason for consultation was short stature (78%). 90% received GH treatment, at a mean age of 8.7 years. Genetic analysis: monosomy XO ($n=9$), isochromosomes ($n=10$), mosaic XX/XO ($n=5$), complex mosaicism 45X, 46XX, 47XXX ($n=5$), mosaic ring X ($n=2$), mosaic XX/XY ($n=1$) and complex reorganizations ($n=1$). Associated pathology: 30% heart disease (mainly bicuspid aortic valve, one case death by dissecting aneurysm); 27% recurrent otitis, 18% hearing loss, 24% kidney abnormalities, 35% thyroid disorder, 15% dyslipemia, 15% hypertransaminemia, 12% psychological disorders, 6% altered carbohydrate metabolism, 6% obesity and 3% HBP. Currently, 21 patients are over 18 years old: mean final stature: 149.4±5.1 cm, spontaneous puberty 43% (5 requested preconception advice, three IVF was done, resulting in 5 pregnancies, one patient had two spontaneous pregnancies). As for the medical follow-up: 75% are checked in gynecology, 60% in endocrinology, 20% otolaryngology, 10% mental health, 5% cardiology. 89% have done blood test in the past 2 years, 36% echocardiography in the past 5 years and 26% bone densitometry in the past 5 years. **Conclusion:** The chief complaint that led to the diagnosis of TS was short stature. Genetic analysis reveals a variety of karyotypes, highlighting the presence of monosomy XO and isochromosomes. Is imperative an adequate multidisciplinary follow-up in adults units, to ensure proper screening and management of major complications.

P3-1238

Growth Characteristics of Patient with Turner Syndrome Different Age and Karyotypes by the Ukrainian National Register

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Background: Turner syndrome (TS) is the most well-known and common chromosomal disorder accompanied by delayed

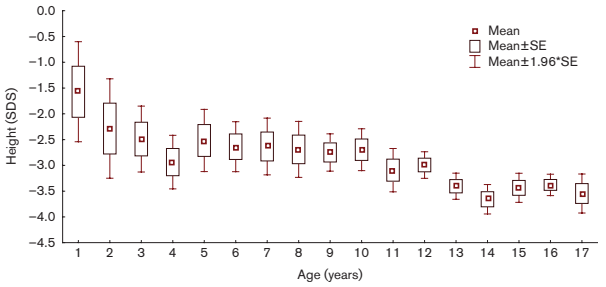

Figure 1 Degree of growth retardation at girls with TS.

growth. According to the Ukrainian national register (UNR) of children with dwarfism the growth retardation is common for all girls with TS. **Objective and hypotheses:** The aim of the study was to determine the growth parameters of TS girls different age and karyotype, before GH treatment. **Method:** According to the UNR it was provided a retrospective analysis in 2005–2014 years of growth parameters at 502 girls with TS aged 1–17 years old before GH treatment. **Results:** Growth delay in untreated girls with TS progresses with age: from −1.6±1.3 S.D. (children aged 1 years old) to −3.5±1.2 S.D. (age >17 years old). There was no significant difference in growth in TS girls with different karyotype (monosomy X, mosaicism and structural abnormalities of chromosome X) (*P*(0.05). Average height in patients with 45,X was 126.7±18.5 cm (−3.2±1.1 S.D.), with mosaicism −127.7± 17.8 cm (−2.8±1.1 S.D.), with structural anomalies chromosome X −125.5±17.0 cm (−3.3±0.9 S.D.). **Conclusion:** There is no difference in degree of growth retardation at TS girls with different karyotype. Growth delayed in TS girls is noticeable from the first year of life, increases with age, and is a greatest in the pubertal age. The mean growth delay in TS girls is −3.1±1.1 S.D. and is greatest in the age of 14 years.

P3-1239

Nationwide Study of Turner Syndrome in Ukraine

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Background: Turner syndrome (TS) is one of the most common genetic disorders associated with abnormalities of chromosome X that occurs in different populations with a frequency of 25–210 per 100 000 female live births. **Objective and hypotheses::** The aim of this study was to investigate the prevalence of TS in ukrainian children, as well as frequency variations of karyotype and age of primary diagnosis of TS. **Method:** We analysed the database of the Ukrainian Registry of children with dwarfism (2005–2014 years old), that include 453 girls with TS 11 month-18.2 years old. **Results:** The prevalence of TS in Ukraine is 77.5 per 100 000 female live newborns. Each year diagnosed 17–25 new cases of TS. Mean age of diagnosis – 9.4± 4.9 years old. Age of primary diagnosis of TS was lowest in children with karyotype 45, X0 – 9.1±5.2 years old, in children with mosaicism – 9.5±4.4 years old and it was highest in patients with structural abnormalities of chromosome X – 10.4±3.9 years old In 1.6% girls diagnosis was established in the 1st year of life, 3.6% – aged 1–4 years, 9.4% – aged 4–8 years old, 18.9% – in 8–12 years old and 66.5% – in 12–17 years old. Most of girls with TS (58.3%) had karyotype 45, X; mosaicism (45, X/46, XX) – 23.4%; mosaicism with polisomy X chromosome (45, X/47, XXX) – 1.4%, structural abnormalities of chromosome X – 16.9%, including 46, Xi (Xq) – 4.8%; 45, X/46, Xi (Xq) – 6.3%; 45, X/46, X+mar – 3.1%, 46, X, del (X)(Xq) – 1.9% and 45, X/46, X, del – in 0.8% of patients. **Conclusion:** In Ukraine the highest incidence of primary diagnosis of TS is in age after 12 years old and in girls with karyotype 45, X. The largest proportion of patients with TS has a karyotype with monosomy X.

P3-1240

Patients with Turner's Syndrome Should Have Ophthalmological Examination before Commencing Recombinant GH Treatment

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Introduction: Turner's syndrome (TS) is caused by an abnormality of one of the X chromosomes. Short stature or slow growth is one of the first manifestations of TS and it is recommended that GH therapy should be initiated as soon as it becomes apparent that affected girls are not growing normally to optimise final adult height. Idiopathic intracranial hypertension (IIH) is a well-known side effect of GH therapy, and it has also been reported in girls with TS with or without GH therapy. **Case:** A patient with TS aged 3.55 years, height 83 cm (−4.04 SDS) started treatment with GH (Norditropin SimpleXx) 0.5 mg subcutaneously (43 μg/kg per day). Within 2 weeks of the start of treatment she presented to the Emergency Department with headache and vomiting. Ophthalmological review revealed that she had bilateral papilloedema. A lumbar puncture (LP) was performed under general anaesthesia. The opening pressure was 24.5 cm H_2O. GH was stopped, however, she continued to have intermittent headaches but with no vomiting. Neurological examination remained normal. After 3 months; she presented with worsening headache and vomiting. At this time the opening pressure on LP was 33 cm H_2O. She started treatment with acetazolamide with good effect: Opening pressure after 1 week treatment, 24 cm H_2O. **Conclusion:** We concluded this patient may have had pre-existing, asymptomatic IIH that became symptomatic when she started GH therapy as IIH worsening despite stopping the GH therapy. We therefore recommend that all patients with TS should have detailed ophthalmological examination to rule out papilloedema before starting GH therapy.

P3-1241

Renal Problems in Early Adult Patients with Turner Syndrome

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Introduction: The prevalence of renal anomalies in Turner syndrome (TS) has been reported to vary from 30 to 70%. However, the influence of renal anomalies on renal function and morbidity have been less well investigated. We evaluate the status of renal function and the presence of urinary abnormalities in early adult TS patients. **Patients and method:** Sixty-three girls with TS, who are attending Pediatric Endocrine Clinics in Busan Paik Hospital, were studied. The mean age of the patients at last follow-up was 23.64±4.51 years and at diagnosis was 10.49±4.04 years. The mean duration of follow-up was 6.09±4.12 years. KUB sonography was performed in all TS patients and some of them also had IVP, renal DMSA scan, and renal CT. Renal function test with R-UA were examined in every visiting times. **Results:** Of the 63 patients, the karyotype showed 45,X in 32 (50.8%) patients, mosaicism in 22 (34.9%) and structural aberration in 9 (14.3%). Renal anomalies were observed in 20 of the 63 TS (31.7%). Of the 32 TS patients with 45,X karyotype, 13 (40.6%) had renal anomalies, while these were found in 7 (22.6%) of 31 TS patients with mosaicism/structural aberration. But there is no significant statistical differences between two karyotype groups. The renal anomalies included ten cases of horseshoe kidney, one case of renal agenesis, eight cases of abnormal renal collecting system, and one case of malrotation. At last follow-up time, the mean serum level of BUN and Cr level were 9.72±2.60 and 0.64±0.11 respectively. Hematuria was observed in 7 (11.1%) TS patients. Among them three TS patients have renal anomalies. One TS patient suffer from nephrotic syndrome for 2.5 years. **Conclusion:** The prevalence of renal anomalies in Korean TS patients was 31.7% and there is no significant differences between two different karyotypes. At last follow-up, all TS patients have normal renal function. Hematuria was observed 11% of TS patients. Although associated renal anomalies may not influence renal function in early adult, careful attention should be necessary in TS patients with hematuria to prevent progressing renal problems.

P3-1242

To Predict Ovarian Function is a Single Determination of AMH Useful in Patients with Turner Syndrome?

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Background: Different studies have underlined the role of anti-Müllerian hormone (AMH) and inhibin B as markers of the ovarian function in paediatric and adolescent patients with Turner syndrome (TS). **Objective and hypotheses:** Our study aims to verify the role of AMH in a cohort of patients affected by TS. **Method:** We analysed 23 TS patients, aged 2–34 years, describing their auxological parameters and the pubertal development, and evaluating their hormonal (AMH, FSH, LH, estradiol, and inhibin B) levels. **Results:** Twenty-one out of 23 (91.3%) were treated with GH. AMH resulted measurable only in two patients of 23 (8.7%), whereas inhibin B was measurable in 13 of 23 (56.5%) patients. Our results were highly heterogeneous. In particular, there are predictive factors neither for the response to GH treatment nor by the puberty. In fact, a good response of GH treatment both as final height and in relation to ΔTH (final height- mid-parental height) was independent from karyotype, from hormonal levels and from spontaneous puberty development. In addition, a karyotype 45X0 was not predictive of worst height gain or of not spontaneous pubertal development. **Conclusion:** There is not a predictive factor that allows to know in advance the evolution of puberty in patients with TS. A single determination of AMH is not informative; only repeated evaluations of this ovarian marker in childhood and adolescence may be useful to predict a spontaneous beginning of puberty and to suggest a possible fertility.

P3-1243

Anthropometric Findings from Birth to Adulthood in Turkish Girls with Turner Syndrome and Association with Karyotpye Distribution

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Background: Turner syndrome (TS) can manifest with various clinical features depending on the karyotype and the genetic background of affected subjects. **Objective and hypotheses:** The aim of this study was to evaluate growth parameters from birth to adulthood in girls with TS in a cross-

sectional study. **Method:** A total of 842 patients, with an age of diagnosis ranging from birth to 18 years followed-up between 1984 and 2014, from 35 different centers were included in this study. Patients who used growth hormone injections, estrogen or oxandrolone were excluded. **Results:** Fifty-one (8.8%) patients were born before 37 weeks. In this cohort small for gestational age was 33% and almost all of them were born termly. Mean birth length was 1.3 cm shorter and mean birth weight was 0.36 kg lower than normal population. At the mean of age of presentation was 10.1±4.4 years, mean height, weight, and BMI–SDS were −3.1±1.7, −1.4±1.5, and 0.4±1.7 respectively. There was no karyotype association with respect to birth length and weight or height and weight at presentation. Mid-parental height was the only parameter that that had an effect on the prediction of height of children with TS. **Conclusion:** There was no effect of karyotype in height of girls with TS however weight was heavier in 46,X,i(Xq) and 45,X/46,X,i(Xq) karyotype groups.

P3-1244

GH Therapy in Turner Syndrome

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Background: Turner syndrome (TS) is one of the most common causes of short stature in females. Adult height of patients with TS is 20 cm shorter than in general population. GH therapy improves height outcome in girls with TS; results depend on age at diagnosis, duration of therapy, and doses of GH. **Objective:** To evaluate growth and safety during the first 4 years of GH treatment in patients with TS. **Method:** Eight prepubertal girls with TS were included mean age of 11.54 years. They were treated with a mean dose of GH = 0.037 mg/kg per day and followed for at least 4 years (mean 5.2 years. **Results:** The mean height SDS increased from −3.61 at baseline to −1.37 at 4 years. Main gain over 4 years was 23.55 cm. The mean weight SDS increased from −1.28 at baseline to −0.68 at 4 years. Bone age was delayed at diagnosis by a mean value of 1.17 years and after 4 years the delay decreased to 0.22 years (Table 1). **Safety profile:** There were no cases of diabetes mellitus, impaired glucose tolerance or malignancies; four patients had transient increase in fasting glucose (>100 and <126 mg/dl); two patients developed hypothyroidism and were treated with levothyroxine. **Conclusions:** GH treatment is associated with highly significant changes in growth. In our study height velocity was maximum (8.53 cm/year) in the 1st year of GH treament; the improvements in growth declined in the second (6.85 cm/year), 3rd year (4.11 cm/year), and 4th year (4.05 cm/year). GH therapy had a favourable safety profile. Delayed diagnosis of TS has a negative impact on growth outcomes.

P3-1245

A Rare Variant of Turner Syndrome: First Clinical Report from Kuwait

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Background: Turner syndrome (TS) is characterised cytogenetically by X chromosome monosomy, the presence of an abnormal X chromosome, or mosaicism of a 45,X or have an abnormal sex chromosome rearrangement. Girls with variant TS show no features, fewer or milder features of TS. **Objective and hypotheses:** We are reporting on a clinical report of a girl with a rare variant of TS (46,X,i(X) (q10)). **Method:** This is a case report of a 12-year-old Kuwaiti girl who was referred for assessment of the short stature and hypothyroidism for which she has been already started on GH and thyroid replacement therapy. **Results:** The girl's height was at −4 S.D. Chromosomal analyses were revealed 46,X,i(X) (q10). Thyroid function test was normal on treatment with negative anti-TPO antibodies. Ultrasound of the abdomen and pelvis showed small uterus for her age and non-visualized ovaries with no renal anomalies. Echocardiography was normal. Genetic counselling was done for her and her family. She is currently under treatment with growth hormone and thyroid replacement with appropriate doses for her diagnosis. **Conclusion:** Our case demonstrated features similar to those in girls with this rare form of TS. However, our patient did not have oedema, cardiac or renal anomalies. This case demonstrates the importance of doing karyotype in such girl even without overt clinical features of TS to diagnose TS and its complications.

Table 1. (for abstract P3-1244)

Parameter	Baseline	1 year	2 years	3 years	4 years
Age (years)	11.54	12.54	13.54	14.54	15.54
Bone age (years)	10.37	10.95	12.48	14.05	15.32
Height SDS	−3.61	−3.05	−2.48	−1.92	−1.37
Height velocity (cm/year)	–	8.53	6.85	4.11	4.05
Weight SDS	−1.28	−1.08	−0.86	−0.80	−0.68

P3-1246

Turner Syndrome with Breast Development: Case Report

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Introduction: Turner syndrome (TS) is caused by monosomy or structural abnormalities of the X chromosome, with a prevalence of out 1/2500 females live birth. Most important clinical features of TS are short stature and gonadal failure. Approximately one third of girls with TS may undergo spontaneous puberty. Here we report a case of a variant TS with breast development. **Case report:** A 9-year-old girl was referred to our paediatric endocrinology outpatient clinic with complaints of short stature and breast budding. She was born at 35+2 weeks with a birth weight of 1930 g (10th percentile) and a length of 41.5 cm (10th percentile). There was no family history of genetic or congenital disorders. On personal past history, the patient had been treated as transient tachypnea of newborn at first day after birth. And she was diagnosed as Kawasaki disease and Brown syndrome at March 2012, at other hospital and followed up echocardiogram every years. Her height on referral was 122.4 cm, which placed her in the 10th percentile on a Korean standard growth chart and at the 90th percentile on a TS growth chart; her weight was 30.5 kg (70th percentile). The mid-parental height was 164.5 cm (75th percentile). A physical examination revealed a Tanner stage III for breast development and Tanner stage I for pubic hair development, Her bone age was 11 years. Chromosome analysis revealed a 46,x,der(x)t(x;x)(p11.21;q11.2). The size and shape of the heart were normal on echocardiography and a kidney ultrasound was normal. Pelvic ultrasound can evaluate her prepubertal uterus, sized 40×5×9 mm, but ovaries can't be evaluated due to poor visualisation, so follow up evaluation must be considered. Thyroid function tests of the patient was normal. A GnRH agonist stimulation test demonstrated a basal LH level of under 0.1 mIU/ml with a peak level of 4.8 mIU/ml at 45 min and a basal FSH level of 8.5 mIU/ml with a peak level of 49.9 mIU/ml at 90 min. A serum oestradiol was under 5.0 pg/ml, and serum levels of IGF1 and IGFBP3 were within normal limits. These findings were not consistent with precocious puberty but LH peak was nearly up to the level of precocious puberty. The patient was treated with GH. And it can be helpful for her growth and emotional support. **Conclusion:** Our case highlights the possibility of precocious puberty as an atypical clinical feature of TS. We emphasis on careful assessment on unusual growth pattern in any child, even though other underlying conditions.

P3-1247

The Association between Selected Endocrinopathies and Central Arterial Pressure in Children and Adolescents

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Background: Many endocrinopathies are associated with cardiovascular abnormalities. Central blood pressure (CAP), reflecting the condition of blood vessels, may be useful in monitoring of patients with endocrinopathies. **Objective and hypotheses:** To evaluate parameters of CAP in patients with selected endocrinopathies. **Method:** The study group comprised 122 patients (58 girls and 64 boys) with endocrinopathies: GH deficiency before GH therapy (group 1; $n=28$), undergoing GH therapy (group 2; $n=24$), diabetes mellitus (DM) lasting for ≤ 5 years (group 3; $n=15$), DM lasting for >5 years (group 4; $n=11$), treated hyperthyroidism (group 5; $n=14$), treated hypothyroidism (group 6; $n=13$), and obesity (group 7; $n=17$). The control group consisted of 29 patients (16 girls and 13 boys) with no cardiac irregularities or endocrinopathies. Three measurements of CAP were performed using Central Blood Pressure Meter (cBP01) and mean values were calculated. Statistical analysis was performed using Statistica 10.0. **Results:** Patients with untreated GH deficiency had significantly lower CAP than the control group (90.2 mmHg vs 99.8 mmHg; $P<0.001$), lower amplification index (1.55 vs 1.67; $P=0.046$), and higher augmentation index (0.66 vs 0.61; $P=0.02$). Both indices normalised after GH therapy. CAP, however, remained lower than in control group (93.24 mmHg vs 99.8 mmHg; $P=0.04$). Group 3 had significantly lower systolic blood pressure (111.26 mmHg vs 119.49 mmHg; $P=0.04$) and central pulse pressure (27.04 mmHg vs 31.43 mmHg; $P=0.049$) than control group. No such differences were observed in groups 4, 5, and 6. Values of CAP (114.68 mmHg vs 99.8 mmHg; $P<0.001$) and central pulse pressure (36.52 mmHg vs 31.43 mmHg; $P=0.03$), as well as peripheral arterial pressures, were significantly higher in obese patients than in control group. **Conclusion:** Endocrinopathies in children are associated with cardiovascular immaturity, expressed by lower values of central arterial pressure indices. Proper treatment of underlying diseases leads to normalisation of studied parameters. Obesity predisposes to higher risk of cardiovascular incidents.

P3-1248

The Development of a Publication Presentation Workshop: Enhancing the Publication of African Paediatric Endocrinological Research

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Background: There is much activity in Africa in Paediatric Endocrinology. The international societies, ESPE, and ISPAD helped significantly in the development of paediatric endocrinology training. Considerable research is being done at the PETCA in Kenya, PETWCA in Lagos and elsewhere, but too few of the studies are published. Owing to the pressure of clinical work in Africa most endocrinologists have difficulty in completing their

research. **Objective and hypotheses:** To devise a mechanism to increase the chances of the publication of African Paediatric Endocrinology studies. **Method:** Presenters of high-quality research projects which were at an advanced stage produced a structured abstract for selection for the Publication Presentation Workshop at the ASPAE 2015 Congress. Presenters of the selected projects were to prepare an oral presentation of 20 min to be presented at the Congress, as well as a draft article. These will be submitted to the editor of the Journal of Endocrinology, Metabolism and Diabetes of South Africa (JEMDSA), Prof. W Mollentze, who had agreed to be part of the workshop. After the presentation, two discussants per paper will discuss ways in which to improve it. **Results:** Seven research projects were considered to be of sufficient quality. They concerned topics such as diabetes mellitus, puberty, obesity, vitamin D deficiency, and the knowledge of health care workers. Contributors came from Cameroon, Nigeria, Uganda, and Zanzibar. The ASPAE 2015 Congress takes place in the first week of May. It is expected that the presenters will excel, that the discussants will contribute immensely to the improvement of the studies, and that the incentive of publication in an accredited journal will yield a completion rate of more than 50%. **Conclusion:** This is a wonderful opportunity for people in underresourced areas to publish their research. The offer of Prof. Mollentze and JEMDSA is unique and highly commendable.

P3-1249

Telomere Length in Young Adults Born Preterm and the Risk for Cardiovascular Disease; Support for Accelerated Biological Ageing in Subjects Born Preterm

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Background: Subjects born preterm have an increased risk for ageing-associated diseases such as cardiovascular disease (CVD) in later life but the underlying cause is largely unknown. Telomere length (TL) is a usable index for ageing, with shorter TL indicating older biological age. Furthermore, short TL is associated with CVD. **Objective and hypotheses:** To investigate TL in subjects born preterm compared to term and to assess if TL is associated with risk factors for CVD. **Method:** We measured mean leucocyte TL using quantitative PCR in 470 young adults. We analysed the influence of multiple variables on TL in a linear multiple regression analysis and compared TL between subjects born preterm ($n=186$) and term ($n=284$). Furthermore, we analysed the correlation between TL and risk factors for CVD (i.e. body composition, blood pressure, lipid levels, insulin sensitivity, and the inflammatory biomarker C-reactive protein). **Results:** Gestational age was positively associated with TL ($P=0.02$). Subjects born preterm had significantly shorter TL (mean TL = 3.12) than subjects born term (mean TL = 3.25) ($P=0.003$), comparable with a difference of ~180 bp (Brouilette *et al.*, *Lancet*, 2007). Significance of this difference increased after correction for gender and size at birth ($P=0.001$). TL was not associated with risk factors for CVD. **Conclusion:** Young adults born preterm have shorter TL than young adults born term, indicating a difference in biological age of ~5–12 years at the same calendar age. This supports the association between ageing-associated diseases and preterm birth. TL was not associated with risk factors for CVD, suggesting that TL is an independent biomarker in the correlation between preterm birth and CVD. Since the prevalence of preterm birth and survival is rapidly increasing, our results are of clinical relevance for an increasing number of subjects worldwide.

P3-1250

A Survival Analysis Approach to Assess the Association between Maternal Prepregnancy Overweight and Childhood Overweight: Results of the Ulm Birth Cohort Study (UBCS)

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Background: It has been suggested that maternal prepregnancy overweight has an effect on childhood overweight. **Objective:** We aimed to use a survival analysis approach to investigate the association between maternal prepregnancy overweight and childhood overweight in the prospective Ulm Birth Cohort Study (UBCS). **Design:** At baseline $n=1086$ mothers and their newborns agreed to participate in the UBCS. Weight and height values of the children were obtained at birth, 6 months, 1, 2, 3, 4, 5, and 6 years of age. Overweight in childhood was calculated using the $\geq 90^{th}$ age- and sex-specific percentiles of the German reference data. Missing BMI values were multiple imputed ($n=5$). Maternal prepregnancy weight status was obtained from maternal record of prenatal care (normal weight: BMI <24.9 kg/m^2 and overweight: BMI ≥ 25 kg/m^2). In the survival analysis we analyzed the data of $n=1026$ children and their mothers with complete baseline variables (age at delivery, migration background, school education, week of gestation, maternal smoking during pregnancy, number of parity and intention to breastfed the child). **Methods:** We performed a survival analysis using the Kaplan–Meier method. We calculated the hazard ratio (HR) of the effect of maternal prepregnancy overweight on childhood overweight using the Cox proportional hazard model after adjustment for covariates. **Results:** 20.9% of the children became overweight between birth

and 6 years of age. The time-to-event curve for offsprings of prepregnancy normal weight mothers was slightly higher compared to the curve for offsprings of prepregnancy overweight mothers. Compared to offsprings of prepregnancy normal weight mothers, offsprings of prepregnancy overweight mothers had a significantly elevated risk for overweight in childhood (HR: 1.60; 95% CI: 1.31–1.89), even after adjusting for baseline covariates (HR: 1.51; 95% CI: 1.21–1.82). **Conclusion:** These results suggest that maternal prepregnancy overweight may be a significant factor in the association between fetal environment and post-delivery development of overweight. **Funding:** The UBCS was supported by grants of the German Research Council (BR 1704/3-1, BR 1704/3) and of the German Federal Ministry for Education and Research (BMBF, project funding reference number: 01GI0851).

P3-1251

Sexually Dimorphic Methylation of SF-1 in Rat Placenta after Gestational Exposure to BPA

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Background: Gestational exposure to endocrine disrupting chemicals (EDCs) can impact the control of sexual differentiation by altering the hormonal environment of the foetus. Prenatal exposure to BPA, for instance could lead to disorders of sexual development. At the interface between the mother and the foetus, the placenta plays a key role in foetal programming and responds to environmental stressors in a sex specific manner. Epigenetics has appeared to be a key mechanism for regulation of gene expression in response to early life environment. **Aims and hypothesis:** We hypothesised that epigenetic modifications at the level of the placenta could be involved in the potential adverse effects of BPA on sexual differentiation and development. We aimed at studying the modifications of DNA methylation in male and female placenta after gestational exposure to BPA. **Methods:** Pregnant rats were exposed orally to BPA (10 mg/kg per day) from gestational day 6 (GD6) to GD18. Placenta obtained by caesarean section were harvested at GD19. Male and female placentas were identified using classical PCR for *SRY* expression. Genome-wide DNA micro-array analysis was performed to identify genes with increased methylation following gestational exposure to BPA. **Results:** Genome-wide analysis showed that four genes exhibited significant hypermethylation in the female placenta after BPA exposure. In particular, SF-1 was hypermethylated after BPA exposure in female but not male placenta and we are currently validating the hypermethylation of the SF-1 promoter using methylation specific PCR after bisulfite treatment. **Conclusion:** In conclusion, prenatal exposure to a high dose of BPA leads to changes in placental DNA methylation pattern of specific genes in a sexually dimorphic manner. SF-1, a key regulator of sexual development appears to be a good placental epigenetic biomarker of gestational exposure to BPA and could mediate the adverse effects of BPA on the reproductive system.

P3-1252

Abstract withdrawn.

P3-1253

Newborns with Longest Telomeres are Big at Birth and Have Most Lean Mass: Not Most Fat: in Late Infancy

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Background: Telomere length at birth is a major determinant of telomere length at later ages, up into senescence. However, the prenatal setting of telomere length is poorly understood. Individuals born large are at lower risk for later-life disorders, such as diabetes, than those born small, a feature of their longer health span being a higher lean mass that provides more muscle strength and is already present in infancy. **Objective and hypotheses:** To assess leukocyte telomere length (LTL) in small-, appropriate-, or large-for-gestational-age (SGA, AGA, and LGA) infants. To correlate LTL at birth with body composition at age 12 months. LTL will differ between AGA, SGA, and LGA subgroups. **Method:** At birth, we studied LTL (by real-time PCR, using RNAseP as a single copy gene) in 103 SGA, AGA, and LGA infants born after an uneventful, term, singleton pregnancy. All infants were breastfed for $\geq$4 months. At age 12 months, body composition was assessed by absorptiometry. **Results:** Telomere lengths were on average 25% shorter in SGA and 22% longer in LGA than in AGA newborns. Birthweights increased with telomere length. Notably, the infants with highest birthweights did not necessarily have long telomeres, but those with longest telomeres were consistently born LGA, whereas none of those with shortest telomeres was born LGA. Lean mass in late infancy – not fat mass – increased with telomere length at birth. **Conclusion:** Newborns with longest telomeres are big at birth and have most lean mass – not most fat – in late infancy.

P3-1254

Untargeted Plasma Metabolomics in Prepubertal ICSI and Naturally Conceived Children Unravels Gender: Dimorphic Metabolic Trajectories After ICSI

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Background: ICSI is an assisted reproduction technique (ART) mainly used to overcome male infertility. Nowadays, ICSI is employed frequently due to its high success rate, despite it being highly invasive (i.e. epigenetic risk). Recent studies in ART offspring show a higher incidence of cardio-metabolic risk than in naturally-conceived (NC) controls. Thus, in our prior untargeted metabolomic study between ICSI and NC prepubertal girls, we demonstrated insulin resistance in the former. **Aims and objectives:** Untargeted plasma metabolomic analysis of ICSI and NC prepubertal boys was performed to detect possible gender-dimorphic metabolic differences with respect to the girl study group. **Methods:** Blood plasma samples of strictly matched ICSI and NC boys were analysed by gas chromatography–mass spectrometry (GC–MS) metabolomics. Both metabolomic and biochemical data were analysed using multivariate statistics and compared with the corresponding results of the girl ICSI and NC groups. The results were visualized on a reconstructed inter-organ metabolic network. **Results:** Combining metabolomic and biochemical measurements differentiated the ICSI and NC groups in both genders, with this difference being more prominent in the girls. However, the discriminatory metabolites were gender-specific. Whereas in both sexes a significantly higher concentration in insulin resistance associated metabolites was observed in the ICSI group, in the ICSI boys the largest difference relatively to the NC group was the significantly smaller concentration of the aromatic amino acids, potentially correlated with brain and liver abnormalities. **Conclusions:** Our results suggest an increased risk for metabolic disorders as a result of ICSI in both boys and girls. By providing a high resolution perspective of the metabolic state in pre-pubertal children, metabolomics might help develop gender-specific tests and treatments. **Funding:** Hellenic Endocrine Society.

P3-1255

Analysis of Gene Methylation Difference and Evaluation the Effect of GH in Silver–Russell Syndrome

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Background: Nearly half of SRS epigenetic etiology is unknown. Effect of GH in SRS is not exact. **Objective:** To determine novel gene or imprinted gene associated with pathogenicity of Silver–Russell syndrome (SRS) through detection genome-wide methylation differences. To observe GH efficacy in SRS and the relationship between GH and epigenetic changes. **Method:** To detect genome-wide methylation site through the Illumina 450K methylation chip in seven SRS and five controls matched age. Other ten cases of SRS were analyzed GH efficacy. **Results:** Imprinted gene *OSBPL5* has the most significant methylation difference site in case group and normal control group ($P=0.023$, $\beta=-0.243$). And the gene is located on 11p15–45 UTR, it is quite possible pathogenic. Five important genes were found might related with SRS: TGFβ3, GAP43, HSF1, NOTCH4, and MYH14. Ten SRS with GH treatment, the average follow-up period was 13.2 months. The average GH dosages was 0.15 IU/kg per day. Growth velocity (GV) was 9.53 + 3.918 cm/year. which was higher than normal children's GV (5 cm/year), $P=0.005$. Five out of ten cases did epigenetic detection. One patient was matUPD (7) positive and his GV was 11.13 cm/year. Two patients were 11p15 ICR1 hypomethylation and their GV were 8 and 9.141 cm/year respectively. The other two cases were not found in epigenetic changes, whose GV were 14.4 and 9.54 cm/year. **Conclusion:** The imprinted gene *OSBPL5* is quite possible pathogenicity of SRS. Other five important genes: *TGFβ3, HSF1, GAP43, NOTCH4*, and *MYH14* may be related to SRS. This group of SRS have good GH efficacy. One case of UPD (7) mat was higher GV than two patients who were 11p15 ICR1 hypomethylation. **Funding:** This work was supported by the Basic-Clinical Research Fund of Capital Medical University (grant number 14JL75).

LBP-1256

Higher Expression of the Oncogene YAP1, a Wnt/β-Catenin Target, is associated with Poor Outcome in Pediatric Patients with Adrenocortical Tumors

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Background: overexpression of the oncogene Yes-associated protein 1 (YAP1), a Hippo pathway target, associates with increased cell proliferation in some human cancers. There is not data on adrenocortical tumors (ACT). YAP1 is a potential target of Wnt/β-catenin pathway, which plays an important role in ACTs. **Objective and hypotheses:** to evaluate the role of YAP1 and its interaction with the Wnt/β-catenin pathway in ACT. **Method:** Association between YAP1 mRNA and protein expression and clinical, biochemical, pathological and patient's outcome data was evaluated in 42 pediatric patients with ACT (81% females; median age: 31 months (5–185)). The expression data was compared to 21 normal pediatric adrenal cortices and 32 normal fetal adrenal cortices. In addition, *in vitro* experiments blocking the TCF/β-catenin complex with PNU-74654 in H295 adrenal tumor cells analyzed the interaction between YAP1 and the Wnt/β-catenin pathway, which is activated in H295 cells due to presence of the p.Ser45Pro β-catenin mutation. *YAP1* expression was evaluated by qPCR, Immunohistochemistry (IHC) and western blot. **Results:** IHC showed high nuclear expression of YAP1 in fetal adrenals but not in postnatal normal adrenals. YAP1 nuclear accumulation was observed in 97% of the tumor samples. Overall, no differential *YAP1* mRNA expression was found between control adrenals and ACTs. However, higher *YAP1* mRNA expression in ACTs was significantly associated with death ($P=0.02$) and recurrence/metastasis ($P=0.002$). Kaplan–Meier curve and log-rank test showed that higher *YAP1* expression was associated with lower survival ($P=0.02$). Bayesian linear regression also showed higher *YAP1* mRNA expression in patients with recurrence/metastasis (5.02; 95% CI: 2.09–7.94), death (5.09; 95% CI: 2.09–8.16) and advanced tumor stage (4.63; 95% CI: 0.61–8.64). In vitro data showed that in adrenal cells, YAP1 is also a Wnt/β-catenin target gene. The inhibition of the Wnt/β-catenin signaling diminished YAP1 protein expression by 44, 58, and 81% after 48 h with 50, 100, and 200 μM PNU-74654 respectively. **Conclusion:** Higher expression of the oncogene YAP1 appears to be a marker of poor prognosis and lower survival rates in pediatric patients with ACT. These original data highlight YAP1 as a potential target to treat patients with invasive or recurrent adrenal tumors.

LBP-1257

Prepubertal and Pubertal Predictors of Semen Quality in a Prospective Cohort Study of Russian Young Men: Focus on Endocrine-Disrupting Chemicals

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Background: We are not aware of other longitudinal cohort studies of boys with prepubertal assessment of exposure to endocrine-disrupting chemicals (EDCs) and annual long term follow-up of growth and puberty to evaluate semen quality. **Objective:** To describe semen quality and explore associations of prepubertal serum concentrations of organochlorine compounds and pubertal measures with semen parameters in an ongoing longitudinal cohort study of Russian boys. **Design/methods:** From 2003 to 2005, 516 prepubertal 8–9 year old boys were enrolled (86% of all eligible Chapaevsk boys, Russia) and underwent annual growth and sexual development assessments for ten years, including Tanner staging and measurement of testicular volume. Serum dioxins were measured by the U.S.CDC in baseline samples. At age 18, the 133 young men collected up to two semen samples ($n=256$) one week apart with 54% participation among those eligible. Semen samples were analyzed for volume, sperm concentration and motility by one technician (LS) according to the NAFA-ESHRE manual. Linear mixed models with random intercepts were used to examine the relation between quartiles of serum concentrations of dioxins with semen parameters. Models were adjusted for BMI, season, and abstinence time. **Results:** Men had a median sperm concentration and motility of 51.8 mill/ml and 64% respectively. Higher prepubertal serum TCDD levels (median of 2.9 pg TEQ/g lipid) were associated with lower semen parameters. The adjusted difference (95% CI) in percent change in sperm concentration, total sperm count, and total motile sperm count between the lowest and highest quartile was −39.7% (−60.5, −8.9), −32.9% (−59.5, 10.9), and −36.4% (−63.8, 11.6) respectively. Data are being analyzed for pubertal predictors of semen quality.

Conclusions: This is one of the first prospectively designed studies to follow a large cohort of boys annually from prepuberty until adulthood and collect semen samples. Higher serum dioxins at 8–9 years are associated with lower semen parameters at age 18 years indicating that the prepubertal period is a sensitive window of exposure to EDCs for sperm quality.

LBP-1258

A Distinct Population of Islet Cells Defines Diffuse Congenital Hyperinsulinism in Infancy but not Other Forms of the Disease

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Background/hypothesis: Congenital hyperinsulinism in infancy (CHI) mainly arises from mutations in ATP-sensitive potassium channel genes. However, the expression pattern of defects can be markedly diverse. In diffuse CHI (CHI-D) all islet cells express gene defects, whereas patients with focal CHI (CHI-F) only express defects in a localised region of islet cells due to loss of a maternally-imprinted locus. Here, we examined the properties of a novel population of CHI islet cells with enlarged nuclei. **Methods:** Tissue was obtained from patients with CHI-D ($n=9$), CHI-F ($n=5$), and age-matched controls ($n=8$, 2 days–36 months of age). High-content analysis of histological sections and serial block face-scanning electron microscopy were used to quantify nuclear enlargement and determined the extent of nucleomegaly. **Results:** Islet cells with nucleomegaly have; i) an average area of $100.1 \pm 3.8\ \mu m^2$ ($n=105$), which was 4.3- and 5.3-fold larger than nuclei in endocrine ($n=173$) and exocrine cells ($n=115$) respectively; ii) an increased nuclear volume from $157.33 \pm 9\ \mu m^3$ ($n=22$) to $\sim 420\ \mu m^3$; and iii) an endocrine phenotype as they stained positive for the neuroendocrine cell marker chromogranin ($n=398/405$ cells). The incidence of islet cell nucleomegaly was 6.4- and 8.4-fold greater in CHI-D ($0.67 \pm 0.11\%$ of islet cells, $n=40\ 320$) than in age-matched controls and CHI-F, respectively. Overall, $70.5 \pm 6\%$ of CHI-D islets contained at least one enlarged nuclei and $45.4 \pm 7\%$ of islets ($n=179$) were found to have more than one affected cell. As nuclear enlargement might be as a consequence of chromatin decondensation, we examined the correlation of Ki67 staining (as a marker of proliferation) with nucleomegaly. In controls (53%, $n=16/30$) and CHI-F (67%, $n=22/33$) nucleomegaly was positively-associated with proliferation, whereas only 9% of cells with nucleomegaly in CHI-D islets were Ki67 positive ($n=27/291$). **Summary:** These findings suggest that nucleomegaly is pathognomonic with CHI-D and unrelated to cell proliferation in CHI-D islets.

LBP-1259

Adrenal Steroid Precursors Accumulating in Congenital Adrenal Hyperplasia lead to Transactivation of the Glucocorticoid Receptor

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Background: Congenital adrenal hyperplasia (CAH) patients are clinically often less severely affected by cortisol deficiency than anticipated from their enzymatic defect. **Objective and hypotheses:** We hypothesize that adrenal steroid hormone precursors that accumulate in untreated or poorly controlled CAH have glucocorticoid activity and partially compensate for cortisol deficiency. We aimed to determine the *in vitro* binding, translocation and transactivation potential of the steroid hormone precursors 21-deoxycortisol, 17-hydroxyprogesterone, progesterone, and androstenedione on the human glucocorticoid receptor (hGR). **Method:** Competitive binding assays were performed in HeLa cells. Nuclear translocation of the hGR was studied by transfection of COS-7 cells with a GFP-tagged hGR and fluorescence microscopy. Transactivation assays were performed in COS-7 cells and repeated in HEK 293 cells using a dual luciferase assay after co-transfection of the cells with the hGR and luciferase reporter vectors. **Results:** 21-Deoxycortisol, 17-hydroxyprogesterone, and progesterone are able to bind to the hGR with binding affinities of 24–43% compared to cortisol. Androstenedione has a low binding affinity. Incubation with 21-deoxycortisol led to complete nuclear translocation of the hGR, whereas treatment with 17-hydroxyprogesterone or progesterone resulted in partial nuclear translocation. 21-Deoxycortisol transactivated the hGR with an EC50 approximately sixfold the EC50 of cortisol. 17-Hydroxyprogesterone and progesterone transactivated the hGR with EC50s of more than 100 times the EC50 of cortisol. No hGR transactivation was detected after incubation with androstenedione. **Conclusion:** 21-Deoxycortisol, 17-hydroxyprogesterone, and progesterone are able to bind, translocate and transactivate the hGR *in vitro* and thus may have glucocorticoid activity. Mainly 21-deoxycortisol might have a clinically relevant agonistic effect on the hGR and could potentially partially compensate the cortisol deficiency in CAH patients.

LBP-1260

Decreased *AMY1* Gene Copy Number is Associated with Increased Obesity Risk in a Population of Caucasian School Children

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Background: Genome-wide association studies have identified more than 60 SNPs associated with BMI. Additional genetic variants, such as copy number variations (CNV), have also been implicated in the pathogenesis of obesity. Recently, the highly polymorphic CNV in the salivary amylase (*AMY1*) gene has been associated with obesity risk in adults. **Objective and hypothesis:** To assess the potential association between *AMY1* copy number and BMI in a population of Caucasian school children. **Methods:** 748 children (356 boys, mean age ($\pm$S.D.): 8.4$\pm$1.4 years) underwent anthropometric assessments (height, weight, and BMI) and collection of salivary samples for DNA extraction. *AMY1* copies were evaluated by quantitative PCR. **Results:** In the whole study population median *AMY1* copies was 8 (range 2–27). A progressive decrease in BMI *z*-score was found across *AMY1* quartiles (Q): Q1–Q4, 0.64$\pm$1.04 vs 0.33$\pm$1.09 vs 0.56$\pm$1.01 vs 0.45$\pm$1.12, $P=0.03$. *Post-hoc* analysis revealed a significant difference in BMI *z*-score between *AMY1* Q1 and Q2 ($P=0.028$). After dividing the study population in BMI *z*-score deciles, *AMY1* copy number was lower in children in the top decile (BMI *z*-score >1.8, $n=74$) than in the lower deciles: (BMI *z*-score <1.8, $n=674$): 8 vs 9, $P=0.019$. In addition, all children with >17 *AMY1* copies had a BMI *z*-score in the lower deciles of the population distribution. In a logistic regression model, a significant and inverse association was found between *AMY1* copies and BMI *z*-score in the top decile: 0.911 (95% CI: 0.842–0.985). **Conclusions:** In this first pediatric-only, population-based study, a higher *AMY1* copy number emerged to be protective against obesity. These data confirm previous findings from adult studies and support a potential role of a higher expression of the salivary amylase, implicated in the first step of starch digestion, in protecting from excess weight gain. This finding could be of particular relevance for populations, such as ours, with a high dietary starch intake.

LBP-1261

POLR3H Variant is Associated with Primary Ovarian Failure in Two Families

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Background: Primary ovarian failure (POF) is a major cause of female infertility. POF is characterized by amenorrhea, hypoestrogenism, and elevated gonadotrophin levels. In POF disorder, several genetic alterations have been described, however in most of the patients the etiology of this disorder remains unknown. **Objective and hypotheses:** To identify new genes implicated in the development of POF using whole-exome sequencing (WES). **Method:** Four subjects with FOP of two families were studied. In family 1, DNA of two affected daughters and their mother were available. In the second family two affected sisters, their parents, and one unaffected sister were analyzed. Family 2 is consanguineous (parents are second cousins), suggesting a recessive mode of inheritance. Exons and splice sites were captured with the Agilent SureSelectXT Human Exon V5 Kit and 2$\times$100 bp paired-end. WES was performed on an Illumina HiSeq2500. The mean coverage of the captured regions was $>50\times$ in all samples. WES was performed in all described members and genetic variant was confirmed with Sanger sequencing. **Results:** One novel homozygous missense variant (c.149A$>$G) in *POLR3H*, the gene encoding polymerase (RNA) III (DNA directed) polypeptide H, was identified in all four affected women from both families. The parents were heterozygous for this variant and the unaffected sister did not carry the variant, consistent with perfect segregation with autosomal recessive mode of inheritance. *POLR3H* variant is not present the publicly available databases 1000Genomes, 6500ESP, and ExAC. Finally, the c.149A$>$G variant is predicted to be deleterious according to *in silico* analysis. **Conclusion:** Our findings identified a previoulsy undescribed homozygous variant in *POLR3H* associated with primary ovarian failure in two unrelated families. These results suggest the involvement of *POLR3H* gene in the etiology of primary ovarian failure.

LBP-1262

The Existence of an Androgen Responsive Transcriptome in the Peripheral Blood of Boys Extends the Utility of the HCG Stimulation Test

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Background: The hCG stimulation test is a valuable method for assessing androgen production but there is a need to explore its

utility in assessing androgen responsiveness and long-term prognosis. **Objective and hypothesis:** Our aim was to explore the effect of hCG stimulation on the peripheral transcriptome in boys undergoing investigation for DSD. **Method:** Thirteen boys undergoing investigation for 46,XY DSD received i.m. hCG 1500 U on 3 consecutive days and had blood sampling on D0 and D3. Testosterone was measured and phenotype recorded. RNA was extracted from peripheral blood mononuclear cells on the Qiacube using RNA Blood Mini Kit with an incorporated DNase step. Microarray hybridisation was performed on 13 paired samples using the Affymetrix Human Transcript Array (HTA) 2.0. Gene expression fold change was calculated and corrected for those boys who did not have a testosterone rise. **Results:** Median age (range) at test was 0.83 years (0.18–11.23) with a median external masculinisation score of 9 (6–11). Three boys had isolated proximal hypospadias, six had bilateral undescended testes, and four had a combination of hypospadias, impalpable testes or micropenis. Median pre and post hCG testosterone were <0.5 nmol/l (<0.5–6) and 7.9 nmol/l (<0.5–31.5) respectively. Median fold change of testosterone was 6.8 (1–26.6) and 3 (23%) boys did not demonstrate a testosterone rise (non-responders). Median AMH in the responders was 688 pmol/l (24, 1628) and in the non-responders was <4 pmol/l (<4256). 8 (80%) of the responders and 2 (66%) of the non-responders had *AR* mutation analysis performed and had no variant detected. When corrected for gene expression changes in the non-responders, all ten of the responders demonstrated a 20% or greater increase in the expression of piR-37150, a non-coding piwi-interacting RNA. 8 (80%), 6 (60%), and 4 (40%) of the responders demonstrated a 30, 40, and 50% rise respectively in a total of five piRNAs. **Conclusion:** The identification of a dynamic peripheral transcriptome that is associated with an androgen response following hCG stimulation extends the potential value of this clinical test. The role of piRNAs as a diagnostic and prognostic marker of gonadal function needs further investigation.

LBP-1263

Late Surgical Correction of Hypospadias Increases the Risk of Complication: a 501 Consecutive Patients Series

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Background: The surgical reconstruction of hypospadias is usually performed during the first 2 years of life but little objective data is available to determine its optimal timing. Whereas the no-early surgery option in DSD management is rising, the results of late genital surgery should be evaluated before advocating this attitude. **Objective and hypotheses:** To evaluate the outcome of hypospadias surgery according to age and to determine if some complications are age-related. **Method:** Monocentric retrospective study including 501 hypospadiac boys undergoing primary repair. Hypospadias was glandular or penile anterior in 63% ($n=298$), midpenile in 19.5% ($n=91$), penile posterior in 8% ($n=38$), and perineoscrotal in 8% ($n=38$). Fistulae, stenosis, dehiscence, hematoma, healing troubles, infection, postoperative detrusor-sphincter dyssynergia, and curvature recurrence were noted. 37 patients were lost to follow-up. Univariate and multivariate logistic regressions were performed. **Results:** The age range was 1–16 years. The overall rate of re-intervention was 22%. The rate of complication was significantly increased after 24 months of age (39% vs 26%, OR = 2.24, $P=0.0007$). Postoperative detrusor-sphincter dyssynergia was more frequent when surgery was performed close to the age of toilet-training (2–3 years) (13% vs 1.3%, $P=0.003$). Healing troubles were particularly frequent in peri-pubertal patients (14% above 10 years). Recurrence of curvature was more frequent after 8 years (2.3% vs 6.8%, OR = 3, $P=0.056$). Beside age, the severity of hypospadias (perineo-scrotal) was also associated with an increased risk of complication (61% vs 31%, $P=0.0006$). **Conclusion:** Late surgery may be detrimental for patients. Factors related to age may influence the rate of complication. Above 2 years, urethral surgery may interfere with the normal toilet-training process inducing urinary functional troubles. During puberty, endogenous testosterone may alter healing. Even if no specific data exist for severe hypospadias, it may be prudent to continue to advocate for early surgery in DSD patients.

LBP-1264

Family History of Genital Malformation is Under-Estimated in Children with Isolated Hypospadias: A Clinical Report of 105 Families

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Background: Severe forms of 46,XY DSD with uncertain sex may have a family history (FH) in ~15–20% of cases. On the other side of the DSD spectrum, data regarding isolated hypospadias is sparse and a FH of genital malformation is thought to be less frequent. **Objective and hypotheses:** The aims of the study were i) to determine the frequency of genital abnormalities in families of

isolated hypospadiac boys, ii) to determine whether there is a particular phenotype, and iii) to evaluate the prevalence of genetic defects in familial cases. **Method:** Prospective inclusion of hypospadiac boys screened for FH with a standardized questionnaire. Extensive clinical description, family tree, DNA sampling and sequencing of androgen receptor, 5α-reductase and *SF1* genes were performed. **Results:** Out of a series of 395 boys with hypospadias, 105 had a FH of genital malformation (hypospadias $n=88$ and cryptorchidism $n=17$). FH was thus more frequent than expected (26.6%). The familial cases were mainly unique (80%, multiple in 20%). Familial hypospadias were more frequently related to the paternal side (53.4% of cases) including the father himself (29.5%), the paternal uncles and/or cousins. Prematurity, use of ART, other congenital abnormalities and postnatal growth retardation were not more frequent in familial hypospadias. The severity of phenotype and ethnicity were not significantly different either. Intrauterine growth retardation tended to be less frequent in familial forms ($P=0.07$). Mutations of *AR* and *SF1* were more frequent in familial hypospadias ($n=5$, 5.68% vs 1.60%, $P=0.046$) (for AR: P392S, Q798E, A475V, P392S; for SF1: D275N). **Conclusion:** FH is more frequent in hypospadiac boys than previously reported. It involves more than a quarter of cases. Even isolated and minor hypospadias justify a full interrogation on FH. Detecting these familial forms may justify an etiologic work-up to find out the causative mutation, to improve the follow-up of these patients and to help the familial counseling.

LBP-1265

Profiling of a Novel NSIAD-Causing Mutation of Vasopressin Receptor 2 and its Differential Effect on Receptor Trafficking Compared to Previously Identified Mutations

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Background: Nephrogenic syndrome of inappropriate antidiuresis (NSIAD) results from gain-of-function mutations in the *AVPR2* gene coding for vasopressin receptor 2 (V2R). In contrast, nephrogenic diabetes insipidus (NDI) is caused by loss-of-function mutations in *AVPR2*. Here we describe and functionally characterize a novel mutation located in the seventh transmembrane domain of V2R. This mutation was identified in a boy suffering from water-induced hyponatremic seizures at the age of 5.8 years. **Objective and hypotheses:** The objective of this study was to profile a novel mutation of V2R found in a boy exhibiting symptoms of NSIAD, with the hypothesis that it was disease-causing. A further objective was to apply a cutting-edge biophysical approach to compare the real-time intracellular trafficking profile of this mutant receptor compared with a number of other NSIAD- and NDI-associated mutant receptors. **Method:** cAMP and inositol phosphate signalling were assessed using homogeneous time-resolved fluorescence (HTRF) assays. Arrestin recruitment and proximity to cellular compartment markers was assessed using bioluminescence resonance energy transfer (BRET) in real-time, with live HEK293FT cells transiently transfected with appropriate cDNA constructs. **Results:** The novel mutation resulted in substantial constitutive cAMP signalling. Furthermore, the trafficking profile differed from that observed with other mutant receptors. **Conclusion:** The observed constitutive cAMP signalling is consistent with the NSIAD phenotype, indicating that this is indeed a novel NSIAD-causing mutation. Moreover, NSIAD and NDI can be caused by mutations that have a variety of effects on V2R function.

LBP-1266

Determining the Effects of Race, Skin Colour, and Genotype on the Response to Vitamin D Therapy

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Background: Over-dosing and under-dosing of vitamin D in children and young people appears to be common, based on our audit of current practice. The contribution of ethnicity, skin colour, and vitamin D binding protein (VDBP) genotype has not been fully explored during vitamin D treatment. **Objective:** To investigate how ethnicity/skin colour and genetic variation affect the response to 150 000 units of vitamin D administered to young adults of White Caucasian and South or East Asian origin. **Method:** Prospective single centre clinical trial. Sixty healthy males aged 18–25 years, White Caucasian ($n=30$) and South or East Asian ($n=30$) were recruited. Fasting i) blood samples for total 25-hydroxyvitamin D (25OHD), VDBP (Genways polyclonal assay), VDBP genotype, bone biochemistry, albumin, PINP and CTX, calculated free, and bioavailable 25OHD and ii) urine for calcium to creatinine ratio were examined before and after an administration of single dose of 150 000 IU of vitamin D3. Anthropometry, skin colour grading and vitamin D and calcium intake assessment were undertaken. **Results:** All subjects achieved a ≥ 25 nmol/l increment in 25OHD level following vitamin D administration. Asians had significantly lower serum 25OHD and VDBP levels at baseline but similar estimated free and bioavailable 25OHD to whites. VDBP levels remained significantly lower in Asians post administration with no difference in total or free/bioavailable 25OHD compared to whites. No hypercalcaemia/hypercalciuria observed in any subject. Skin colour, race and VDBP genotype did not influence variation in treatment response. **Conclusion:** Our results show that a single dose of vitamin D is sufficient and safe to increase the 25OHD level to >50 nmol/l irrespective of, and unaffected by, skin colour, ethnicity, and genotype.

Table 1. (for abstract LBP-1266).

	Serum total 25OHD (nmol/l)	Serum VDBP (umol/l)	Calculated free 25OHD (nmol/l)	Calculated Bio25OHD (nmol/l)	PTH (ng/l)	PINP (ng/ml)	CTX (ng/ml)
Baseline							
Whites	34.06 (12.30)	6.59 (3.03)	0.014 (0.008)	0.015 (0.007)	44.60 (14.24)	107.2 (40.90)	0.82 (0.26)
Asians	26.34 (13.72)	4.73 (2.27)	0.012 (0.007)	0.020 (0.010)	69.83 (38.62)	82.0 (36.72)	0.68 (0.21)
P value	0.04*	0.01*	0.37	0.26	0.002*	0.002*	0.02*
Post dosing							
Whites	90.79 (16.71)	6.495 (2.83)	0.037 (0.018)	0.015 (0.007)	49.37 (20.28)	113.83 (46.5)	0.78 (0.24)
Asians	82.79 (14.04)	4.64 (2.15)	0.04 (0.02)	0.020 (0.011)	65.16 (32.77)	92.3 (40.2)	0.64 (0.22)
P value	0.17	0.008*	0.47	0.16	0.007*	0.025*	0.02*

*P value <0.05.

LBP-1267

Safety and Efficacy of Long-Acting GH (VRS-317) in Children with GHD: Effects of Dose Change in the Second Treatment Year

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Background: VRS-317, a novel fusion protein of rhGH exhibiting delayed clearance, serum half-life generally >100 h, and potential for once monthly dosing, was previously evaluated in a 6-month phase 1b/2a study of weekly, twice monthly or monthly dosing (5.0 mg/kg per month) in prepubertal GHD children ($n=64$). **Objective and hypotheses:** We evaluated whether increased VRS-317 dose from 12 to 18 months can offset the decrease in height velocities commonly seen during the 2nd year of daily rhGH treatment. **Method:** In an ongoing long-term safety extension study, 63 subjects received an increased dose of VRS-317 (3.5 mg/kg, twice monthly). Peak IGF1 SDS and mean height velocities were compared before and after increased dose. **Results:** 56 subjects completed 18 months of treatment. Mean age at Month 18 was 9.28 years; all but two subjects remain prepubertal. Increasing the twice monthly dose from 2.5 to 3.5 mg/kg increased mean peak IGF1 SDS from -0.30 ± 1.2 to 0.32 ± 1.6 (paired *t*-test, $P=0.007$); the number of peak IGF1 SDS >2.0 was limited to three values total for all subjects. Increased dosing appeared to stabilize height velocity: during the initial 12 months of treatment, mean height velocity was 7.9 ± 2.1 and 8.5 ± 2.1 cm/year for 5 mg/kg monthly and 2.5 mg/kg twice monthly dosing, respectively, compared with 8.1 ± 2.4 and 8.3 ± 1.8 cm/year (annualized), respectively, after 18 months (3.5 mg/kg twice monthly). Only mild and transient drug-related AEs were observed (n = 9 patients after 12 months; $n=7$ patients after 18 months). No new or unexpected AEs occurred. Injection site discomfort decreased with time on treatment, with only four subjects reporting discomfort after 18 months. **Conclusion:** Increasing VRS-317 dose at the start of the 2nd year of treatment to 3.5 mg/kg twice monthly (phase 3 dose) led to in an increase in mean peak IGF1 SDS and stabilization of mean height velocity, without changing the safety profile.

LBP-1268

Genetic Causes of Disproportional Short Stature Identified by Whole Exome Sequencing

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Background: Disproportional short stature (DSS) is the most frequent clinical presentation of skeletal dysplasias, which are a heterogeneous group of more than 450 disorders of bone. Skeletal survey is important to establish the diagnosis and to guide the genetic test, but has several limitations, especially in mild and atypical cases. **Objective and hypotheses:** To identify the genetic aetiology of DSS by exome sequencing. **Method:** Whole exome sequencing was performed in six patients with disproportional short stature without a definitive classification into a skeletal dysplasia category, and their affected ($n=6$) and unaffected ($n=5$) available relatives. All pedigrees suggested an autosomal dominant pattern of inheritance. Exons and splice sites were captured with the Agilent SureSelect XT, and were sequenced on an Illumina HiSeq. **Results:** The mean coverage of the captured regions was $170\times$. Our analysis focused on functional variants absent in controls that segregate in the families. We identified a causative variant predicted as pathogenic in three patients. Case 1 with

height SDS of −2.0 has a novel heterozygous mutation in *NPR2* gene (c.2905G>C/p.V969L). Heterozygous mutations in NPR2 are a cause of short stature without a distinct phenotype. Case 2 (height SDS of −4.5) has a heterozygous mutation in *FBN1* gene (c.5183C>T/p.A1728V). Mutations in *FBN1* were associates with gelophysic and acromicric dysplasia, but this patient lacks some of the cardinal features of these conditions. Case 3 with a height SDS of −2.5 and bilateral osteonecrosis of the femoral epiphysis has a heterozygous mutation in *COL2A1* gene (c.1852G>A/p.G618S). Mutations in *COL2A1* cause several skeletal disorders with highly variable phenotype. **Conclusion:** We identified three heterozygous mutations in three different genes that explain the disproportional short stature phenotype observed in our patients. Because of the mild and unspecific phenotype, only a genomic approach allowed the identification of the etiology of short stature in these patients.

LBP-1269

Reduced Humanin Levels in Children with Type 1 Diabetes Mellitus

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Background: Recent studies in multiple models of type 1 diabetes mellitus (T1DM) have demonstrated the role of mitochondrial abnormalities in the pathogenesis of this disease and its complications. Humanin is a potent cyto-protective and 'metaboloprotective' molecule *in vitro* and *in vivo*, including the protection of β cells from apoptosis, improvements in insulin secretion and action, and both prevention and treatment of diabetes in the NOD mouse model, by ameliorating various aspects of the pathogenesis of the disease. **Objective and hypotheses:** We hypothesized that humanin levels are decreased in patients with T1DM and may be related to duration or severity of disease and evaluated humanin levels in T1DM and matched controls as a function of HbA1c and microalbuminuria. **Method:** Subjects with T1DM and age- and sex-matched controls were recruited from the diabetes clinic of the IDIMI-HCSBA, Santiago de Chile. A complete physical exam including Tanner staging exam was performed. Early morning a blood sample was obtained for determination of HbA1c and humanin levels (in house ELISA, previously published). **Results:** T1DM ($n=154$) and controls ($n=76$), age 3–19 years old (T1DM mean 12.9, controls mean 10.8), males 57% in DM1 vs 47% in controls. New onset (<2 years) of diabetes in 32.4% of T1D ($n=50$). T1DM and controls were divided according to Tanner stages (1–5). Humanin levels are lower in T1DM compared to controls (974.6±498.3 in T1DM vs 1241.2±782.4 in controls, $P=0.0019$). This difference is observed only in girls (T1DM 1327.4±714.8 vs controls 1997.4±481, $P<0.01$). Humanin levels are lower in Tanner I and III inT1DM compared with controls ($P<0.05$). Humanin levels increased throughout puberty in controls children, but not in T1D adolescents. No association was observed between duration of T1D, albuminuria, or HbA1c. **Conclusion:** T1DM patients exhibit lower humanin levels, an observation that is especially pronounced in females and early Tanner stages. There is no correlation between the degree of metabolic control or disease duration and humanin levels. Future studies will address the impact of humanin levels on pathophysiology and metabolic control of diabetes.

LBP-1270

Long-Term Safety and Effectiveness of Daily and Weekly GH Treatment in Pediatric Patients

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Background: Daily GH has been used to treat growth disorders in children for a long time. The weekly sustained-release GH formulation has been approved for treatment in GH deficiency (GHD). It provides a practical strategy for improving adherence. However, there is still a lack of sufficient clinical research data of weekly GH. **Objective and hypotheses:** To evaluate the long-term safety and effectiveness of two formulations of daily (Eutropin injection) and weekly (EutropinPlus injection) GH in Korean pediatric patients. **Method:** A multi-center, cohort, long-term, prospective, and retrospective study. Statistical analysis has been conducted annually using a pre-defined method. The interim analysis was conducted in all patients who were enrolled from Jan 2012 to Feb 2015. **Results:** Among the 1287 enrolled patients, a total of 758 patients with GHD were analysed to compare the safety between daily ($n=537$) and weekly ($n=221$). Baseline demographics were similar between groups. 299 patients were analysed for effectiveness during the 2 years of GH treatment in GHD (daily ($n=208$) and weekly ($n=91$)). Height SDS at baseline was −2.41 in the daily and −2.54 in the weekly. Change in height SDS from baseline to 2 years was 3.11 in the daily and 2.88 in the weekly. Height velocity during the 1st and 2nd year was 9.03 and 8.23 cm/year in the daily, respectively and was 8.95 and 8.20 cm/year in the weekly respectively. Height SDS and velocity were not statistically different between groups. Adverse events (AEs) were reported in 14.7% of daily and 9.5% of weekly. The incidence of adverse drug reactions was 3.2% in the daily and 2.7% in the weekly. Mild to moderate AEs were most commonly reported. **Conclusion:** Growth response of weekly GH is comparable to daily GH in GHD. Also, both daily and weekly GH formulations were safe and well-tolerated.

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