HORMONE
RESEARCH IN
PÆDIATRICS

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HORMONE
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Plenary Lectures

PL1
Environmental Chemicals, Thyroid Hormone and Human Intelligence

Barbara Demeneix
Paris, France

Thyroid hormone is the only hormone for which all babies are screened at birth. This is because it has been known for decades that the consequences of thyroid hormone insufficiency during postnatal development, cretinism, are severe and irreversible. However, the last 15 years have witnessed major, and unexpected, insights how thyroid hormone acts during prenatal brain development across vertebrates. For instance, even mild maternal hypothyroidism or hyperthyroidism during early pregnancy are associated with IQ loss and modified brain structure in their children. Other recent insights include the tight control of tissue thyroid hormone levels by deiodinases and the existence of membrane thyroid hormone transporters (THTs). Mutations in THTs are associated with Allen Dudley Hernon syndrome, a severe form of intellectual and physical disability. In parallel to this increased understanding, we are witnessing an unprecedented increase in autism spectrum disorders (ASD) incidence, often correlated with IQ loss. Although, changes in diagnosis and awareness contribute to the ASD increase, many authors consider that environmental factors are implicated. Four arguments support this hypothesis. First, numerous chemicals are found routinely in human amniotic fluid including, pesticides, plasticizers (such as phthalates, BPA), nitrates, perchlorate, antimicrobials (such as Triclosan), flame-retardants, surfactants and mercury. Second, many chemical categories are demonstrated thyroid hormone disruptors. Third, prenatal exposure to many chemicals is significantly associated with IQ loss and/or increased ASD risk. Fourth, chemical production has risen exponentially in the last few decades, continually increasing exposure. I shall present data on how we exploit the evolutionary conservation of thyroid signalling to use transgenic Xenopus as a screening tool for environmental chemicals affecting thyroid hormone signalling and brain development. I shall also consider the evidence that interference with thyroid hormone orchestration of human brain development could be implicated in the observed increase in neurodevelopmental disease as well as in significant IQ loss at a population level, engendering enormous socio-economic costs.

PL2
Recent Advances in the Genetics of Adrenal Hyperfunction and Tumours

Jérôme Bertherat
Paris, France

There is a variety of unilateral adrenocortical tumors (ACT) and bilateral nodular adrenal hyperplasias that can be responsible for Cushing' syndrome. Before puberty the most frequent are adrenocortical cancer (ACC) or micronodular adrenocortical hyperplasia (MiAH). The most classic form of MiAH is primary pigmented nodular adrenocortical dysplasia (PPNAD), diagnosed in more than two-third of Carney Complex patients. In adults adrenocortical adenomas (ACA) and primary bilateral macro-nodular adrenal hyperplasia (PBMAH) along with ACC can causes various level of cortisol dysregulation, ranging from non secreting tumors to overt-Cushing. Recently, genomics led to spectacular and fast progress in the identification of genetic and epigenetic alterations of all type of ACT. Exome sequencing identified somatic activating mutations of the catalytic subunit of PKA (PRKACA) in ACA responsible for overt-Cushing. Combining pangenomic snp analysis and whole genome sequencing led to the identification of inactivating germline mutations of a new tumor suppressor gene, ARMC5, in PBMAH. The identification of ARMC5 as a gene frequently altered in adults with PBMAH revealed the hereditary nature of this disease. The use of combined genomics in ACC has shown alterations of key driver genes like CTNNB1 (β-catenin), TP53, ZNRF3, and demonstrated frequent epigenetic changes at 11p15 (IGF2 locus). With these progress the alterations of the cAMP and the Wnt/β-catenin signaling pathways are now clearly described. Interestingly, activation of the cAMP pathway lead to benign and small unilateral or bilateral tumors with a very high steroid synthesis capacity causing overt-Cushing. On the other hand activation of the Wnt/β-catenin signaling pathways seems to be mostly observed in more aggressive tumors with a lower secretion capacity. These progress offer not only new molecular tools for genetic predisposition screening and molecular classification of adrenal causes of cortisol excess, but also open new perspectives for therapeutic development.

PL3

Abstract unavailable.

PL4

"Genomic Imprinting and Evolution"

Robert Feil

Montpellier, France

Genomic imprinting in mammals is controlled by DNA methylation. This essential epigenetic phenomenon mediates the mono-allelic expression of about hundred autosomal protein-coding genes and hundreds of regulatory non-coding RNAs, such that these become expressed from one of the two parental alleles only. Although the first imprinted genes were discovered less than thirty years ago, given their key roles in fetal development, homeostasis and brain functions, these exceptional genes have been studied in great detail. For many, dosage is critical and environmentally-induced or stochastic perturbations cause disease. Evolutionarily, imprinting is a young phenomenon which arose at the time that placentation became more important for development with a growing dependence on maternal resources postnatally. Amongst the youngest, most recently evolved, imprinted genes many are imprinted in the placenta only, and different studies have linked their expression to fetal growth. The recent discovery of polymorphic imprinting in humans suggests that the evolutionary process is still ongoing. The underlying reasons are debated and different evolutionary theories have been proposed. Imprinting research evolves fast as well and has boosted our understanding of endocrine and other imprinting-related disorders. A challenge for the future will be to unravel the relative importance of genetic versus epigenetic alterations in the emergence of imprinted gene expression, and in its pathological perturbation in animals and humans.

PL5

Abstract unavailable.

PL6

Abstract unavailable.

Symposia

S1.1

Innovative Therapies in Bone and Mineral Metabolism: Anti FGF23 in X-linked Hypophosphatemia

Thomas Carpenter

CT, USA

Background: Hypophosphatemia due to excess urinary phosphate losses and rachitic bone disease occur in several related disorders. The most common form of the heritable hypophosphatemic disorders, X-linked hypophosphatemia (XLH), is due to loss-of-function mutations of the osteocyte/osteoblast protein, PHEX. Reduced abundance of phosphate transporters on the luminal surface of renal tubular cells in the syngeneic animal model of XLH, and inappropriately normal (or frankly low) circulating levels of 1,25 dihydroxyvitamin D (1,25D) are characteristic of the disease. Thus currently available therapies for XLH employ supplementation with phosphate and 1,25D. **Objective and hypotheses:** Current replacement with phosphate and 1,25D is cumbersome, and fraught with complications. As the excessive renal phosphate losses and reduced capacity to maintain normal circulating 1,25D levels appear to be direct effects of increased FGF23 activity, we hypothesized that inhibition of FGF23 would serve to ameliorate the primary renal abnormalities, and restore a milieu conducive to the restoration of mineralization. **Method:** This talk will review potential strategies to improve therapeutic outcomes for children and adults with XLH, focusing on several clinical studies using an anti-FGF23 inhibitory antibody (KRN23). **Results:** Administration of KRN23 every 2–4 weeks corrects serum phosphate and improved 1,25D in adults and children. Improved patient-reported outcomes have been documented in adults and radiographic improvement in rickets scores is evident in growing children. **Conclusion:** Patients affected with XLH would benefit from a more effective and better-tolerated therapy than the currently available approaches. Inhibition of FGF23 activity using an anti-FGF23 inhibitory antibody appears to be a safe and effective strategy to improve biochemical status, rickets, and well-being for patients with this disorder.

S1.2

"Denosumab as an Alternative to Bisphosphonates in Osteogenesis Imperfecta"

Eckhard Schoenau

Cologne, Germany

Osteogenesis imperfecta (OI) is a hereditary disease characterized by skeletal findings like increased fracture rate, deformed long bones and vertebral compression fractures. Non-skeletal findings include hypermobility of joint, hearing and dental impairments and weakness of collagen involving structures like vessels and valves. Therapy is based on an interdisciplinary approach including orthopaedic surgery to correct deformities, physiotherapy to increase musclefunction and pharmacological treatment. During the last two decades antiresorptive therapy with bisphosphonates are more and more frequently used to treat patients with moderate or severe types of OI. Bisphosphonates bind permanently to the bone and stay there for many years or decades. Bisphophonates are frequently used to treat osteoporosis in elderly but they are only approved for the treatment of OI in very few countries. When treating children special caution has to be given to long term side effects. In the treatment of osteoporosis concerns about impairments of bone remodelling after longtime bisphosphonate treatment have been raised regarding occurrence of pathological fractures (femur) and osteonecrosis of the jaw. Recently the RANKL-Antibody Denosumab has become available for the treatment of postmenopausal osteoporosis and is also approved in a few other oncological indications with increased bone resorption. A benefit of the antibody might be the direct interaction with the osteoclasts and a complete resorption after a few months. Denosumab has been used in very rare indications in children and has proven to be highly effective in reducing osteoclastic activity. In a growing skeleton it seems that the risk of a severe hypocalcemia after application is more prominent than in adults and calcium has to be monitored closely and substituted with high doses of oral calcium for a few weeks. A pilot trial of 1 year involving 10 severely affected OI children showed a higher increase of areal bone mineral density (aBMD) than it was achieved during the previous treatment with bisphosphonates. It has to be kept in mind that it is not clear which would be the best aBMD for OI patients. Special concerns have to be given to a rebound hyper-calcemia and -calciuria at the end of the treatment period which might cause nephrocalcinosis and calcification of vessels and has to be studied in detail in the future.

S1.3

Advances in Treatment of Achondroplasia

Laurence Legeai-Mallet

Paris, France

Skeletal development is a temporally-regulated non-linear process orchestrated by a complex genetic network that proceeds via two distinct ossification mechanisms, namely membranous and endochondral ossification. Genetic disorders of the skeletal system affect both bone and cartilage formation from early fetal development up to post-natal growth. Fibroblast growth factor receptor 3 (FGFR3) is an important regulator of bone formation. Achondroplasia is the most common form of dwarfism; it involved FGFR3 gene mutations, in which skull, appendicular and axial skeletons are affected. The understanding of disease mechanisms lead to targeted treatment. To date, the development of innovative therapies to treat achondroplasia is expanding. Several potential therapeutic strategies have emerged. Preclinical studies have been carried out: e.g. C-type natriuretic peptide analog (BMN111), intermittent PTH injections, soluble FGFR3 therapy, Meclozine, Statin and pan-FGFR tyrosine kinase inhibitor (NVP-BGJ398) treatments. Among the putative targets to antagonize FGFR3

signaling, CNP (or BMN111) is one of the most promising strategies. BMN111 acts as a key regulator of longitudinal bone growth by down-regulating the MAPK pathway, which is activated as a result of FGFR3 gain-of-function mutation. Today, BMN111 (vosoritide) is currently in clinical trial (phase 2) in pediatric patients with ACH. The first data show the improvement of the growth velocity in children with ACH and support the further development of vosoritide for the treatment of children with achondroplasia with open growth plates.

S2.1

Determination of Autosomal Monoallelic Expression in Thyroid Tissue Assessed by Whole-Exome and Bulk RNA Sequencing: A Role in Thyroid Dysgenesis, Autoimmunity and Cancer

Johnny Deladoey

Montréal, Canada

Background and hypotheses: Congenital hypothyroidism due to thyroid dysgenesis (CHTD) is a disorder with a prevalence of one in 4,000 live births, the cause of which remains unknown. The most common diagnostic category is thyroid ectopy, which occurs in up to 80% of CHTD cases. CHTD is predominantly not inherited and has a high discordance rate (>92%) between monozygotic (MZ) twins. The sporadic nature of CHTD might be explained by somatic events such as autosomal monoallelic expression (AME), given that genes expressed in a monoallelic way are more vulnerable to otherwise benign heterozygous genetic or epigenetic mutations. **Objective:** To search for complete (90%) AME in normal and dysgenetic thyroid tissues. **Method:** Aggregated analysis of whole-exome and bulk RNA sequencing performed on two ectopic thyroids, four normal thyroids and the human thyroid cell line Nthy-ori. **Results:** A median of 5,062 (range 2,081–5,270) genes per sample showed sufficient numbers of heterozygous SNPs to be informative. The median monoallelic expression represented 22 (range 16–32) of the informative genes for each thyroid sample. Examples of genes displaying AME are *FCGBP, ZNF331, USP10, BCLAF1* and some *HLA* genes; these genes are involved in epithelial-mesenchymal transition, cell migration, cancer and immunity. **Conclusion:** AME may account for the high discordance rate observed between MZ twins and for the sporadic nature of CHTD. Our findings have also implications for other pathologies including cancers and autoimmune disorders of the thyroid.

S2.2

Genetics of Thyroid Dysgenesis and Associated Malformations

Michel Polak

Paris, France

Thyroid dysgenesis (TD) is the most common cause of congenital hypothyroidism in iodine sufficient regions. TD includes a broad spectrum of developmental anomalies varying from absence of thyroid (athyreosis) to an abnormally located thyroid (ectopy), small (hypoplasia) or asymmetric thyroid. Thyroid dysgenesis is usually sporadic, but up to 2% of cases is familial. Genetics of TD is complex and advances in developmental biology over the past two decades revealed monogenetic forms of TD. But these monogenetic forms represent less than 10% in TD and to date the discordance between monozygotic twins remains unexplained. However, inheritance of TD is not based on a simple Mendelian pattern and additional genetic elements might contribute to the wide spectrum of observed phenotypes. Accumulating evidence supports the view that the genetics is complex, possibly on a polygenic/multifactorial or epigenetic basis. Developmental biology allowed the identification of candidate genes (thyroid transcription factors) and broadened the spectrum of associated malformations in Humans. Detailed phenotype of patients, up-to-date technologies (high-throughput sequencing), and relevant animal models are crucial to advance our knowledge of the mechanisms in normal and abnormal thyroid development. We will provide an update on known responsible genes, new genes discovered in our laboratory and underlying mechanisms of TD. Up-to-date technologies in genetics and biology will allow us to advance in our knowledge and elucidate the enigma of TD. Our work on TD is partly financed, by the Fondation Jérôme Lejeune for the study of thyroid dysgenesis of Down syndrome in murine models, by Merck Serono France, Sandoz SAS France, Electricité de France, Princess Grace de Monaco Foundation, by Fondation Maladies Rares and by a national clinical research grant "PHRC": ClinicalTrials.gov Identifier: NCT01916018.

S2.3

New Insights in Thyroid Development

Mikael Nilsson

Göteborg, Sweden

The mammalian thyroid gland stands out in comparison to other organs as it develops from no less than three independent anlagen that originate in anterior endoderm. The median or central anlage present in the pharyngeal floor gives rise to the thyroid bud or diverticulum that provides progenitors to the thyroxin-producing follicular cells. Bilaterally, the ultimobranchial bodies bud off from the inferior-most pharyngeal pouch. Until recently those structures were considered merely as vehicles that brought neuroendocrine C cells of neural crest origin to the embryonic thyroid; by genetic lineage tracing in mice this concept is now abandoned in favour of an endoderm origin of thyroid C cell precursors, thus indicting that both endocrine cell lineages of the thyroid are foregut derivatives. Defective development of the midline primordium produces a spectrum of anatomical malformations collectively referred to thyroid dysgenesis, the most common cause of congenital hypothyroidism in humans. Only few of those patients have a mutation in today known thyroid

developmental genes. The presentation will summarize the roles of established and newly discovered genes in thyroid morphogenesis before the pituitary gets control of the embryonic thyroid. A new concept of thyroid growth reminiscent of branching in e.g. lung development will be introduced. Deficient C cell development has no clinical phenotype, but transcription factors implicated in embryonic growth and migration of C cell precursors from endoderm may shed new light on the pathogenesis of medullary thyroid carcinoma in children with MEN2B, which will be discussed. Finally, in view of the possibility that the first somatic mutation in childhood papillary thyroid cancer may arise already in the foetus or infant, recent progress in tracing oncogenically mutant cells with a fluorescent transgene, with the purpose to investigate directly in the microscope putative interactions with bystander normal follicular cells before tumorigenesis gets started, will be presented.

S3.1

Sleep and Glycaemic Control in Children with Type 1 Diabetes

Karine Spiegel

Lyon, France

Rapidly accumulating epidemiologic and experimental evidence has indicated that insufficient sleep, such as commonly experienced in modern societies by all age groups, reduces insulin sensitivity and impairs glucose metabolism in healthy adults, and increases the risk of incident type 2 diabetes. Studies in type 1 or type 2 diabetic adults show a link between reduced sleep quality or duration and poor glyceamic control. While poor diabetes control may impair sleep due to nocturia, nocturnal hypoglycemia disrupting sleep and the need for night-time diabetes care, the fact that prospective studies show a relationship between insufficient sleep and the development or aggravation of existing type 1 or type 2 diabetes suggests the existence of an opposite direction of causality. Studies that examined the link between sleep and glyceamic control/glucose metabolism in pediatric populations are scarce. Nevertheless, similarly to adult studies, experimental and cohort studies have reported an association between short sleep and insulin resistance in healthy children/adolescents. No study used objective assessment of sleep to examine the link between habitual short/poor sleep and glyceamic control in type 1 diabetic children/adolescents. In this presentation, we will show preliminary results from an ongoing longitudinal study that uses both subjective and objective measures of sleep to delineate which sleep characteristics (quality, duration, regularity) best predicts glyceamic control in type 1 diabetic children and adolescents. The magnitude of the associations between sleep disturbances and glyceamic control in our sample suggests that intervention studies aiming to pay a sleep debt and/or improve sleep regularity may be clinically relevant.

S3.2

Optimising Nocturnal Glucose Control in Children with T1D: Therapeutic Implications

Thomas Danne

Hannover, Germany

Background: Nocturnal hypoglycemia is not regularly predictable on the basis of a bedtime BG level and can only be confirmed by BG tests at regular intervals during the night or continuous glucose monitoring (CGM). **Objective and hypotheses:** A bedtime snack containing carbohydrate as well as fat and protein may be useful in preventing nocturnal hypoglycemia, but this should not be at the expense of high overnight BG levels. In many individuals, a lowering of the insulin dose after intense exercise should be considered to prevent nocturnal hypoglycemia. Short- and long-acting insulin analogues and continuous insulin infusion therapy may further decrease risk for nocturnal hypoglycemia. **Method:** Availability of CGM results in real-time (RT-CGM) to the patient with diabetes and immediate corrections to keep glucose levels in range have been shown to improve day and nighttime glycemic control more effectively than 'blinded' collection of data analyzed by a health provider retrospectively. Flash Glucose Monitoring (FGM) is the newest method of glucose testing that is seen as a hybrid between meters and CGMs. **Results:** FGM does not have hypo- or hyperglycemia alarms and will only provide a trend graph if it has been swiped in the past eight hours. However, the IMPACT trial in adults with type 1 diabetes has revealed significantly lower rates of nocturnal hypoglycemia also with FGM. While RT-CGM is beneficial in both patients using multiple daily injections and insulin pump users, the latter combination is more effective for nocturnal glucose control, particularly when combined with low glucose suspension algorithms or predictive low glucose management. Recently the success of conventional Real-Time CGM has led to the development of hybrid and full closed-loop insulin delivery systems, which have now reached the stage of clinical trials in patients' homes. These trials repeatedly showed optimized nocturnal glucose control. A first commercial device may be available on the market as early as 2017. **Conclusion:** Diabetes technology offers novel opportunities to optimize nighttime glucose control and may eventually propel wide-spread adaptation and reimbursement of devices for insulin delivery and glucose monitoring.

S3.3

Optimizing Nocturnal Diabetes Control: Optimising Insulin Delivery with New Technology: But Where is the Evidence?

Roman Hovorka

Cambridge, UK

The use of insulin pumps is increasing particularly in the paediatric population with between 50% to 74% pump users below the age of 6 years. Real-time continuous glucose monitoring

enables greater understanding of glucose excursions, provides low and high glucose alarms, and facilitates more responsive insulin dose adjustments. An enhancement of the sensor-augmented insulin therapy pump is the low-glucose suspend (LGS) and predictive low glucose management (PLGM) features reducing the risk of hypoglycaemia in hypoglycaemia prone individuals. The LGS function allows insulin to be automatically suspended for up to two hours when sensor glucose falls below a present threshold. The hypoglycaemia-prediction algorithms and automatic pump suspension enable insulin delivery to be suspended when hypoglycaemia is predicted. The Artificial Pancreas (closed loop system) automatically delivers insulin according to real-time sensor glucose levels, below and above preset insulin amount, combining glucose sensor, insulin pump and a control algorithm, to achieve as much as possible functionality of a healthy pancreas. In youth, closed-loop prototypes have been tested extensively under controlled laboratory conditions demonstrating reduced risk nocturnal hypoglycaemia and increased time in target glucose range. The risk of hypoglycaemia may be further reduced with the use of bihormonal (also known as dual-hormone) closed-loop systems delivering subcutaneous glucagon when hypoglycaemia is observed or predicted. Pioneering home studies have been performed to demonstrate benefits during free living. Performance of closed-loop systems is damped by variable and relatively slow absorption of currently available rapid-acting insulin analogues, which delays onset and prolongs insulin action. This may attenuate daytime closed-loop performance due to rapid glycaemic fluctuations observed during meal-times and exercise, as reflected by relatively better closed-loop glycaemic performance overnight compared to daytime.

S4.1

Activating Mutations in STAT3 Leading to Early-Onset Multi-organ Autoimmune Disease

Megan Cooper

MO, USA

Background: Monogenic disorders of the immune system are increasingly recognized as a cause of early-onset immune dysregulation and autoimmunity. We recently identified 13 patients with a newly-described syndrome of early-onset polyautoimmunity, including endocrinopathies, and immune deficiency caused by gain-of-function (GOF) variants in the *STAT3* gene. *STAT3* is a highly conserved transcription factor that affects cytokine-induced changes in gene expression. Patients bearing germline, loss-of-function *STAT3* variants suffer from recurrent infections. Somatic, gain-of-function (GOF) mutations in *STAT3* are associated with cancers. The identification of early-onset autoimmunity caused by germline *STAT3* GOF variants thus represents a third category of disease caused by alterations in STAT3. **Objective and hypotheses:** The objectives of this talk are to discuss this recently identified syndrome of *STAT3* GOF including review of clinical and immunological features of this disorder, potential mechanisms of disease, and therapeutic strategies. **Method:** There have been more than 20 patients reported with autoimmunity associated with GOF STAT3. I will review the clinical features of these patients and recent work from our laboratory investigating the mechanism of immune dysregulation due to STAT3 GOF. **Results:** Patients with STAT3 GOF present at a young age (average 4 years), usually with autoimmunity of two or more organ systems. Cytopenias are the most common autoimmune disease, and others include type I DM (including neonatal onset), enteropathy, lung disease, thyroid disease, and arthritis. The majority of STAT3 GOF patients have short stature, for unclear reasons but possibly due to impaired STAT5b signaling. Analysis of T cell populations shows decreased peripheral blood regulatory T cells (Tregs). Recent studies from our laboratory suggest impaired Treg differentiation and enhanced Th17 differentiation directly caused by STAT3 GOF variants. Therapies have included immune suppression, stem cell transplantation, and anti-IL-6R. **Conclusion:** STAT3 GOF is a cause of early-onset autoimmunity. While the cause of immune dysregulation has not been fully elucidated, there are indications that dysregulation of T cell differentiation may contribute to disease.

S4.2

Abstract unavailable

S4.3

Type 1 Diabetes: Lessons from nPOD Pathology and Clinical Trials

Alberto Pugliese

Miami, Florida, USA

Type 1 diabetes (T1D) is considered chronic autoimmune disease in which autoreactive T-cells and inflammation cause severe loss of pancreatic beta cells. Insulitis, the pathologic hallmark of T1D, is an inflammatory lesion consisting of immune cell infiltrates around and within the islets. New research initiatives and methodologies are advancing our understanding of pancreas pathology. A major impetus to the field has been given by the institution of the JDRF nPOD (Network for the Pancreatic Organ donor with Diabetes, www.JDRFnPOD.org); nPOD recovers and provides pancreata from organ donors with T1D to the scientific community and facilitates collaborative studies about the pathogenesis and pathology of T1D. Studies by several nPOD investigators have revealed the predominant cellular types that infiltrate the islets, novel molecular aspects associated with insulitis, and the coexistence of additional pathological abnormalities. While insulitis is a critical element of T1D pathogenesis, it is present only in a modest proportion of islets at any given time, even at diagnosis, with overall limited relation to disease duration. Thus, the relative importance of insulitis as a determining factor of diabetes symptoms at diagnosis may be overestimated; at the same

time, growing evidence shows that beta cell loss at diagnosis is more modest than previously thought, and co-existing beta cell dysfunction may be a key contributor to insulin deficiency at diagnosis. This recognition has relevance for the design of clinical trials, as targeting the immune system only may have limited therapeutic efficacy. Combination therapies that promote both immunoregulation and address beta cell dysfunction should be more effective in treating this chronic disease process. It remains a major goal to clarify the relation of insulitis with the dynamics of beta cell loss and coexisting mechanisms of dysfunction, according to clinical stage; such improved understanding is key to design therapeutic strategies that target multiple pathogenic mechanisms.

S5.1

Wolfram Syndrome, a Prototype of ER Stress-Induced Beta Cell Death

Fumihiko Urano

MO, USA

Background: Endoplasmic reticulum (ER) participates in so many cellular tasks that trouble can ensue when it stops working properly, including β cell death in type 1 and type 2 diabetes mellitus. Despite the underlying importance of ER dysfunction in β cell death during the progression of diabetes, there is no effective treatment targeting the ER due to the complex etiologies of type 1 and type 2 diabetes. **Objective and hypotheses:** Our strategy for overcoming this challenge is to focus on genetic forms of diabetes in which mutations in single genes are involved in ER dysfunction and disease manifestations. **Method:** Wolfram syndrome is a rare autosomal recessive genetic disorder characterized by juvenile-onset diabetes, optic nerve atrophy, hearing loss, and neurodegeneration. The prevalence is estimated at 1:200,000-1:700,000. Caused by mutations in the *WFS1* gene, Wolfram syndrome is considered a prototype of human ER disease. Diabetes mellitus is typically the first manifestation, usually diagnosed around age 6. We have recently shown that ER calcium depletion, followed by subsequent increase in cytoplasmic calcium levels, is a common molecular pathway altered in β cell models of type 1 and type 2 diabetes, as well as Wolfram syndrome. **Results:** We have recently shown that ER calcium depletion, followed by subsequent increase in cytoplasmic calcium levels, is a common molecular pathway altered in β cell models of type 1 and type 2 diabetes, as well as Wolfram syndrome. **Conclusion:** In this lecture, I will articulate the role of ER stress in β cell dysfunction and death in Wolfram syndrome and its relevance to type 1 and type 2 diabetes, and discuss a therapeutic strategy targeting the ER for diabetes.

S5.2

Abstract unavailable

S5.3

Activation of HSP 72: A Therapeutic Target for Diseases Related to both ER Stress and Mitochondrial Dysfunction

Mark Febbraio

NSW, Australia

Over the past decade, work from our research group has demonstrated that over-expression or activation of the chaperone protein heat shock protein 72 (HSP72; the inducible form of the 70kDa family of heat shock proteins) in skeletal muscle reduces obesity-induced insulin resistance (for review see). These findings led to the development of the small molecule activator of HSP72, namely BGP-15 which, in pre-clinical studies, has proven to be effective in the treatment of several diseases including type 2 diabetes, atrial fibrillation and Duchenne Muscular Dystrophy. While we originally ascribed the mechanism of action of HSP72 activation to preventing inflammation and endoplasmic reticulum (ER) stress, we have recently shown that HSP72 is both necessary and sufficient to maintain mitochondrial structure and function in the context of obesity and insulin resistance. These recent results are most significant as they suggest that HSP72 may be a therapeutic target for not only T2D, but for conditions in which mitochondrial function is impaired. Recent work on the role of activating this pathway on both ER stress and mitochondrial structure and function and its relationship to cellular function will be discussed in this presentation.

S6.1

Long-term Consequences of Childhood Obesity: The Impact of Genes and Lifestyle

Paul Franks

Malmö, Sweden

In most complex traits, susceptibility to certain risk exposures and response to clinical interventions in is under genetic control, a concept broadly termed "gene-environment interaction". Although in animals and in plants there is evidence supporting this notion, in humans most evidence is confined to rare monogenic disorders. In complex diseases like type 2 diabetes and obesity, interactions between genetic and environmental risk factors are likely to begin very early in life, perhaps even pre-conception. Of the hundreds of published studies, several stand out as having been replicated across diverse settings, although most have not, and even those that are replicated often lack robust evidence of mechanisms or causality. My lecture will begin by overviewing the rationale and the approaches used to studies gene-lifestyle interactions. I will begin by focusing on early life risk factors and the likely mechanisms of interaction between genes and the early life environment. I will also overview some of the evidence for gene-lifestyle interactions in type 2 diabetes and obesity later in life. I will end by speculating on how research in this field might evolve in the next decade and how doing so might lead to better disease prevention and treatment.

S6.2

Early Childhood Life Style Intervention and Obesity Outcome

Claude Marcus

Stockholm, Sweden

Background: Treatment of childhood and adolescent obesity is rarely effective if "cure" i.e., BMI below the obesity range, is used as the definition of success. However, results of obesity treatment is much more effective if treatment is initiated in 6–7 years old children. It is therefore urgent to develop interventions for young children, both preventive and obesity treatment efforts. Results from such interventions as well as preliminary results from ongoing studies will be presented. **Results:** Population-based prevention studies for young children such as Idefics, Primrose and many others have shown limited results when weight has been the main outcome. Improved parental knowledge about eating habits has been reported and in some studies also short-term effects on weight development have been observed. Early STOPP (Stockholm Obesity Prevention Project) is an ongoing longitudinal randomized controlled study from 1–6 years of age where obese and overweight parents with 1 year old children are targeted. It is well known that their children have a 5–10 times higher risk to develop obesity early in life. Promising results from the first 2–3 years of the intervention based on MI delivered support regarding sleep, physical activity and eating habits provided by health coaches will be presented. It is also unclear if obesity treatment is effective in young children, 4–5 years old. Preliminary results from the More or Less study where parents to 4–5 years old children with obesity are randomized to either to a program focused on parental skills or to standard care will also be presented. **Conclusion:** Taken together, the effectiveness of published interventions is limited and we need to learn and accept from these studies what is ineffective so we don't repeatedly carry through the same ineffective studies only because we hope it will work – next time. However there are some promising interventions indicating that it is possible to reduce overweight and obesity at an early age.

S6.3

Childhood Obesity Prevention: What Do We Need and How Are We Doing? A European Perspective

Johannes Brug

Amsterdam, The Netherlands

The worldwide prevalence of overweight and obesity has been steadily increasing, also among children and adolescents, and has reached alarming pandemic proportions in Europe and elsewhere. Childhood overweight is a main predictor of adult overweight and obesity. Obesity treatment is largely ineffective, and a still stronger focus on primary prevention is needed. Such prevention should take a population and a life course approach and should focus on promoting healthy energy balance-related behaviors rather than weight management or weight loss. To encourage and facilitate healthful energy balance behavior, we need insight in the 'causes of the causes', i.e. in why children and their parents eat too much and move too little. Energy balance-related behaviors (sufficient healthy physical activity, healthy eating, and less sedentary time) are a result of personal motivations and abilities, and contextual or environmental opportunities. It is not personal determinants or environmental opportunities that make a difference; it is mediation and interaction between and across these 'causes of the causes' that drive healthful behaviors. To effectively encourage and facilitate healthful energy balance beahviors, health promotion efforts (to improve motivation and abilities), as well as health protection efforts (to make the healthy choice the default choice) are needed. Such an integrated approach needs to be supported by participation of the main stakeholders in all phases of intervention and policy development, implementation and evaluation. Such integrated prevention approaches have and are being developed and tested across Europe. In this presentation the rationale, data, results, ongoing efforts for cross-European research will be presented - such as the European Commission funded ENERGY (EuropeaN Energy-balance Research to prevent excessive weight Gain among Youth), and SPOTLIGHT (Sustainable prevention of obesity through integrated strategies) projects, as well as results from the European DEDIPAC (Determinants of DIet and Physical ACtivity knowledge hub) joint action.

S7.1

Abstract unavailable

S7.2

Abstract unavailable

S7.3

The Role of GPR101 in Human Growth

Constantine Stratakis, Fabio Faucz, Giampaolo Trivellin

Bethesda, USA

We recently showed that Xq26.3 microduplications are associated with early childhood-onset gigantism, a condition we named X-linked acrogigantism (X-LAG). Patients with X-LAG present with mixed GH/PRL secreting pituitary macroadenomas and/or hyperplasia. The original smallest region of overlap for the microduplications included 4 coding genes, of which only one, an orphan G protein-coupled receptor named *GPR101*, was highly expressed in tumors. A single patient with GPR101

microduplication *only* was recently reported: this proves that GPR101 overexpression alone may cause gigantism. GPR101 was found to be expressed at very low levels or was not expressed in almost all adult human tissues examined, with the exception of specific regions of the brain, including the nucleus accumbens. High expression of GPR101 was observed in the human fetal pituitary but not in adult pituitary tissue and in pituitary tumors other than those with Xq26.3 defect. In contrast to human tissues, adult pituitaries of both rhesus monkey and rat expressed GPR101. However, the pituitary cell type expressing this receptor differs: gonadotrophs in monkeys and somatotrophs in rats express GPR101. In the developing zebrafish embryo, GPR101 showed a bimodal expression pattern: expression levels progressively waning during the first cell divisions (presumably representing maternal transcripts) and then gradually rising with the appearance of the first somites. Beginning at 48 h post-fertilization a strong and brain-specific staining including part of the hypothalamus and pituitary was seen. These studies show that GPR101 is likely to be a significant regulator of growth; the brain is the major site of GPR101 expression across different species, although divergent species-specific expression patterns are evident, especially concerning the pituitary. Differences among species might reflect their different growth, development and maturation patterns. It is also interesting to note that the highest GPR101 expression levels in adult human tissues were observed in the nucleus accumbens, which plays an important role as the reward center, hinting that GPR101 might also be involved in the regulation of food seeking behaviors, in addition to growth and/or puberty.

S8.1
Novel Function of Pituitary Stem Cells during Organ Homeostasis

Cynthia Lilian Andoniadou

London, UK

Background: Using genetic lineage tracing in the mouse pituitary, we previously revealed that SOX2 positive cells can act as stem cells *in vivo* and contribute to all hormone-secreting cell types during postnatal life. However, SOX2-expressing stem cells are not the sole source of new endocrine cells, instead they complement contribution from more committed cell types during organ homeostasis. **Objective and hypotheses:** We seek to determine key signalling mechanisms required to regulate organ turnover, since their disruption can underlie disease states e.g. organ failure or the formation of tumours. The WNT signalling pathway plays critical roles in stem cell function of many organs and pathway elevation in pituitary stem cells leads to tumours. Our aim is to understand the function of the WNT pathway during normal pituitary physiology, specifically if it is required for proliferation and to identify sources of WNT signals. **Method:** By combining genetic and molecular approaches we are able to manipulate the WNT pathway in the pituitary and to label WNT-responsive cells and follow their fates. **Results:** We find that WNT-responsive cells contribute the major source of new cells to organ turnover. Unexpectedly, we uncover that SOX2-expressing stem cells secrete WNT ligands, thus acting as critical regulators of homeostasis in a paracrine manner. **Conclusion:** Pituitary stem cells contribute to the organ both directly through the generation of new cells, as well as indirectly through acting as essential niche cells promoting proliferation of more committed cell types. This represents a key step towards understanding the mechanisms controlling stimulation of new cell generation *in situ*, with an impact on future regenerative medicine approaches.

S8.2
Pluripotent Stem Cells in Endocrinology

Rudolph L. Leibel

USA

The ability to differentiate human embryonal stem cells (hESC) and induced pluripotent stem cells (hiPSC) into virtually any cell type has enabled the creation of cellular models of diseases for which human cells are not readily accessible. Using these strategies, we have examined the molecular pathogenesis of monogenic forms of diabetes such as Wolfram's syndrome and various MODYs using stem cell-derived insulin producing cells created from fibroblasts of patients with these disorders. Our recent development of a protocol for the generation of arcuate-type hypothalamic neurons from somatic cells of human subjects has enabled us to study the neurobiology of disorders such as Bardet-Biedl and Prader Willi syndromes, as well as disorders of proconvertase 1 activity. Using Crispr/Cas, we have both corrected beta cell and neuronal mutations in affected cell lines, and introduced mutations into unaffected cell lines. Such experiments allow the analysis of gene-gene interactions, the screening of molecules that may mitigate specific cellular phenotypes, and could ultimately provide transplantable cells for treatment of disease.

S8.3
Hubs in the Pancreas

David Hodson

Birmingham, UK

Background: The arrangement of beta cells within islets of Langerhans produces a gain-of-function in insulin release through the generation of rhythmic activity patterns. A privileged role for individual beta cells in orchestrating these responses has long-been suspected, but not directly examined. **Objective and hypotheses:** Identify and characterize a rare subpopulation of beta cells tasked with pacemaking insulin release. **Method:** Optogenetics, photopharmacology and photopainting approaches

were used to functionally interrogate and label single beta cells *in situ* within islets. **Results:** Specialized cells, termed hubs, possess lowered expression of beta cell identity markers (Pdx1, Nkx6.1, insulin etc) and are metabolically adapted, as evidenced by increased expression of glucokinase and elevated mitochondrial potential. Importantly, hubs are specifically targeted by proinflammatory and glucotoxic insults to induce widespread islet dysfunction. **Conclusion:** The islet is wired by hubs, whose failure may contribute to type 1 and type 2 diabetes. Importantly, the finding that the beta cell population is heterogeneous has clear repercussions for the *de novo* construction of islets from stem cells, as well as treatment of diabetes.

S9.1

Long-term Health in Congenital Adrenal Hyperplasia: Lessons from a National Study

Anna Nordenström

Stockholm, Sweden

Congenital adrenal hyperplasia (CAH) is lethal in its most severe forms if not treated with glucocorticoids. However, glucocorticoids may increase the cardiovascular and metabolic morbidity. The long term outcome in CAH was studied using the Swedish national CAH registry, 588 patients 335 females and 253 males, $>80\%$ with known severity of CAH; were compared with 100 controls per patient matched for sex, and year and place of birth. Information on mortalty, cause of death, morbidity, and psykosocial factors were derived through linkage of national population-based registers. Subgroup analyses were performed regarding sex, clinical severity (salt-wasting, simple virilising, non-classic), *CYP21A2* genotype (null, I2 splice, I172N, P30L) and before and after the introduction of neonatal screening. **Results:** The mean age of death was lower (41.2 ± 26.9 vs 47.7 ± 27.7 years ($P < 0.001$). The hazard ratio of death was 2.3 (1.2–4.3) in males and 3.5 (2.0–6.0) in females. The causes of death were adrenal crisis (42%), cardiovascular (32%), cancer (16%), and suicide (10%). Metabolic disorders (OR 3.9), and cardiovascular disease (OR 2.7) were increased. Both men and women had more disability pension (OR 1.5) and sick leave (OR 1.7). The men more often had long lasting employment (OR 3.1). Men were more often (OR 1.6) while women were less often married (OR 0.7). Patients had children less often (OR 0.3). Women with salt-wasting (SW) CAH had completed primary education less often (OR 0.3), this was not explained by neonatal salt-crisis or hypoglycemia since the men did not differ from controls. Men and women in the less severe I172N genotype group were more likely to have an academic education (OR 1.8) and SW women were more likely to have an income in the top 20 percentile (OR 2.0). Both males and females had an increased psychiatric morbidity. In particular, the risk of substance misuse was increased with OR 2.8 in females and 1.9 in males and appeared most common among the girls and women with the most severe null genotype (OR 5.5). The risk of stress and adjustment disorders was doubled (OR 2.1). **Conclusions:** CAH was associated with excess mortality due to adrenal crisis despite diagnosis and treatment. The salt-wasting phenotype seemed to have a worse outcome not only before the introduction of neonatal screening. Our studies show important outcome differences regarding education, employment, marriage and fertility depending on sex and severity of CAH. The mechanisms behind this and the increased risk for sick leave or disability pension in both men and women should be identified to improve medical and psychological care. Late diagnosis may explain some of the findings. Those born before the introduction of neonatal screening were more affected, which may be explained by the higher age.

S9.2

Recent Advances in CAH: New Approaches to Glucocorticoid Replacement

Richard Ross

Sheffield, UK

Adult CAH patients have poor health outcomes and these in part relate to the method of glucocorticoid replacement in children and adults. Life-saving glucocorticoid replacement was introduced in the 1950s and the majority of children are treated with immediate release hydrocortisone whereas adults are treated with a mixture of hydrocortisone, prednisolone, prednisone and dexamethasone from one to four times daily and in circadian and reverse circadian regimens. Despite these personalised glucocorticoid treatments adult patients remain shorter than the normal population, have an increase in obesity and osteoporosis and impaired fertility and QoL. There are two major challenges in glucocorticoid replacement for CAH patients; prescribing the correct dose and replicating the cortisol circadian rhythm. At the present time there are no paediatric dose specific formulations of glucocorticoids making it challenging to titrate therapy in neonates and infants. Cortisol has a distinct circadian rhythm with low levels at night, rising in the early hours of the morning, peaking on waking, and declining over the day to low levels in the evening. Loss of this diurnal rhythm in CAH results in an early morning rise in androgen levels which is not controlled with current therapy. New technologies are being developed that deliver more physiological glucocorticoid replacement including a paediatric dose specific formulation, Infacort, hydrocortisone by subcutaneous pump, and Chronocort a delayed and sustained absorption hydrocortisone formulation that replicates the overnight profile of cortisol. Infacort is a multi-particulate hydrocortisone formulation with taste masking provided in doses of 0.5, 1, 2 and 5 mg that is bioequivalent to currently available immediate release hydrocortisone. Subcutaneous hydrocortisone infusions using insulin technology have been demonstrated to improve control of CAH in small case series. Chronocort has been shown to improve androgen control of adult patients with CAH in a phase 2 clinical trial. Future work will focus on optimising glucocorticoid replacement in CAH patients from birth to old age and demonstrating these treatments improve health outcomes.

S9.3

Recent Advances in CAH: Treatments Saving GC Exposure

Richard Auchus

MI, USA

Background: Glucocorticoid therapy in 21-hydroxylase deficiency (congenital adrenal hyperplasia, CAH) both replaces the cortisol deficiency and reduces adrenal androgen production. Androgen control, however, often requires supraphysiologic and/or nocturnal glucocorticoid exposure. Chronic treatment in this manner contributes to long-term complications observed in CAH cohorts, including high rates of obesity, low bone density, glucose intolerance, skin fragility, and excess mortality. While cortisol replacement remains mandatory, alternative non-glucocorticoid agents to control androgen excess are desirable. **Objective and hypotheses:** We have explored 2 conceptually distinct approaches to lower adrenal androgen production in phase I trials: blockade of androgen synthesis and antagonism of corticotropin-releasing factor (CRF) action. **Method:** The first study included 6 women with classic CAH and serum androstenedione (AD) >1.5x the upper limit of normal (>12 nmol/l). These participants received 100 mg and 250 mg of the CYP17A1 (17-hydroxylase/17,20-lyase; P450c17 or P450 17A1) inhibitor abiraterone acetate (AA) for 6 consecutive days in sequential cycles of 100 or 250 mg/d. The second study employed a fixed-sequence single dose of 0, 300, or 600 mg of the CRF type 1 receptor antagonist NBI-77860 in 8 women with classic CAH. **Results:** In the AA study, mean first-morning AD for days 6 and 7 normalized in 5 of 6 participants at 250 mg/d. First-morning AD normalized in all participants on day 7 at 250 mg/d, and AD remained normal 2 to 8 h on day 6 at both doses. Testosterone (T) and its metabolites fell in parallel; hypertension and/or hypokalemia were not observed. In the NBI-77860 study, reductions of adrenocorticotropin and 17-hydroxyprogesterone were conclusively demonstrated in half of participants. Responses strongly correlated with drug exposure, providing evidence of target engagement. **Conclusion:** These studies demonstrate proof-of-concept for combination therapies using physiologic glucocorticoid dosing plus an agent to attenuate androgen production. Long-term studies of these and related drugs in children and adults with CAH are necessary to determine if these strategies are superior to conventional glucocorticoid therapy alone.

S10.1

Glucose Metabolism and Management in Premature Babies

Kathryn Beardsall

Cambridge, UK

Increasing numbers of infants are being born very preterm. These infants require intensive care and have a high risk of mortality and morbidity which has been associated with both hyperglycaemia and hypoglycaemia. In utero, glucose levels are normally maintained between 4–6 mmol/l, but infants born preterm are exposed to significant periods of both hyperglycaemia and hypoglycaemia. Early postnatal glucose control may be an important modifiable risk factor for clinical outcomes. However challenges remain in reducing hyperglycaemia without increasing hypoglycaemia. Many physiological parameters are monitored continuously to prevent wide fluctuations and the development of real time continuous glucose monitors provides the opportunity to monitor glucose levels in the same way. Managing glucose control in the preterm infant is also challenging due to the marked variability in insulin sensitivity between babies. The development of computer based algorithms, that can use the wealth of data obtained from the frequent glucose levels obtained by continuous glucose monitoring, could provide for individualized guidance on insulin treatment. We have used the combination of real time CGMs alongside a computer based algorithm to manage preterm infants: to reduce the prevalence of hyperglycaemia without increasing the risk of hypoglycaemia. This will help determine the impact of different strategies for nutritional management and glucose control, and what is 'optimal' glucose control. It will be important to address the potential impact not just on short term outcomes but on longer term health.

S10.2

The gonadotropic axis in premature babies

Leo Dunkel

London, UK

Background: The transient postnatal activation of the hypothalamic-pituitary-gonadal (HPG) axis, also called "mini-puberty," is a phenomenon during which gonadal hormone levels increase up to adult levels. **Results:** In boys gonadotropin and testosterone levels peak at one moths of age and are significantly higher in preterm than in full-term boys. Simultaneously, there is penile growth and the levels of prostate specific antigen increase, indicating increase in androgen effects. In preterm girls, FSH levels are extremely high after birth, but they decrease to similar levels as in full-term girls around the term age. Interestingly, when gonadotropin levels are assessed against postmenstrual age (i.e., age from the last menstruation of the mother) rather than chronological age (i.e., time from birth) the gonadotropin levels in premature infants actually decline to similar levels as in full-term infants at the same developmental stage suggesting that the duration of "minipuberty" is developmentally regulated. In girls, the decrease in FSH from its peak is associated with the maturation of antral follicles and increase of the follicle-derived AMH levels. Estradiol levels are higher in girls than in boys, but in girls the levels vary and do not display a similar uniform peak at one month as male testosterone levels. The growth of estrogen responsive target tissues (i.e., mammary glands and uterus) are maximally stimulated in full-term girls at birth by the high intrauterine estrogen whereas in preterm girls, the growth of the mammary

glands and the uterus are positively correlated with estradiol levels. **Conclusion:** The possible long-term significance of the observed differences in minipuberty between full-term and preterm infants requires further studies. These should include effects on reproductive development, childhood growth, bone mineralization, childhood psychosexual development, timing of puberty, sexual behaviour, and reproductive capacity in adulthood.

S10.3

The Mineralcorticoid System and its Implications for Neonatal Adaptation in Premature Babies

Laetitia Martinerie

Paris, France

Background and hypothesis: The neonatal period is characterized by high urinary sodium loss, most notably in preterm infants that questions the ability of the mineralocorticoid pathway to maintain sodium homeostasis. **Results:** We have demonstrated that neonatal sodium wasting is associated with a physiological renal aldosterone resistance in relation to a low renal mineralocorticoid receptor (MR) expression at birth in full-term infants, both in humans and mice, along with a down regulation of other mineralocorticoid signaling key-players. Moreover, very preterm infants present with defective aldosterone secretion while the kidney remains sensitive to aldosterone action owing to transient MR expression in the distal tubule during this period. Conversely, high circulating cortisol/corticosterone levels along with detectable renal glucocorticoid receptor are present at birth, consistent with functional glucocorticoid-signaling pathway both in preterm and full-term newborns. **Conclusion:** Thus, the neonatal period is characterized by defective mineralocorticoid signaling from two different mechanisms in preterm and full-term newborns, whereas renal glucocorticoid signaling is functional and very likely implicated in fetal programming. These results open new therapeutic possibilities for preterm infants in order to prevent from sodium wasting.

Novel Advances & Controversies in Paediatric Endocrinology

NA1.1

Abstract unavailable.

NA1.2

Intrauterine Imaging Strategies for Bone Disease

Yasemin Alanay

Istanbul, Turkey

Background: Fetal skeleton develops early in the fetal period. The appendicular and the axial skeleton undergo a programmed pattern of endochondral ossification, whereas the calvarium and portions of the clavicle and pubic bone ossify via membranous ossification. Disruption of the molecular mechanisms fine-tuning this process leads to osteo-chondrodysplasias (skeletal dysplasias) or dysostoses, namely genetic skeletal disorders. The 2015 revision of the Nosology and Classification of Genetic Skeletal Disorders provides a list of 436 disorders in 42 groups, and 364 related genes. **Objective and hypotheses:** Diagnosis of prenatal-onset genetic bone diseases mandates radiographic, clinical and molecular assessment. The combined use of these methods is essential for appropriate counselling of the parents. Information regarding the severity and natural history of an individual disorder is critical for the families and medical care providers. **Method:** In general, prenatal ultrasound (US) is currently the accepted modality for fetal assessment. Lethality should be determined based on US parameters and/or by molecular diagnosis. Those with a non-lethal condition may further be described as mild or severe. First trimester US, usually used for aneuploidy screening can identify severe, usually lethal skeletal dysplasias. Others are detected in the late second trimester, the remaining diagnosed in the third trimester or at birth. Imaging strategies have evolved in the last decade. Three-dimentional (3D) US is helpful in depicting and characterisation of the specific entity. Fetal magnetic resonance imaging (MRI) has also been documented to be useful for analysis of fetal spine and concurrent malformations. The most recent method is using 3D reconstructions of low dose computerized tomography images for prenatal evaluation. **Results:** The diagnosis of a genetic skeletal disorder is ideally made in the prenatal period to ensure accurate genetic counselling and provide a management plan before and after delivery. Imaging strategies are discussed with respect to possible outcome.

NA2.1

De.Coding Obesity – Control of Metabolism by the Noncoding Transcriptome

Jan-Wilhelm Kornfeld

Cologne, Germany

The pervasiveness of noncoding transcription has revolutionized our understanding of gene regulation. Although not yet fully catalogued in terms of numbers, mammalian genomes express a broad spectrum of, small and long, noncoding RNAs. Whereas small noncoding RNAs like microRNAs and their role in energy metabolism and glucose handling are rather well understood, we have little understanding concerning the metaboregulatory properties of those 10,000s of long noncoding RNAs (lncRNAs) encoded in mammalian genomes. To adress this, we applied deep next-generation sequencing to quantify the expression of lncRNAs in two mouse models of obesity and insulin resistance. Intruigingly, we observed the majority of hepatic lncRNAs being downregulated in obese animals, whereas fasting increased lncRNA expression. Using in silico motif enrichment and ChiP-Seq analyses in coding versus noncoding gene promoters, we observed that noncoding promoters are enriched for binding events of smallMafs, a repressive class of transcription factors. Crucially, hepatic overexpression of smallMafs mimicked the obesity-evoked downregulation of the noncoding transcriptome and caused disturbancies in hepatic lipid handling, whereas antisense-nucleotide-mediated depletion of small Mafs prevented diet-induced obesity. Collectively, we here identified a novel signaling circuit coupling obesity-evoked changes in signal transduction to global regulation of the Noncoding Transcriptome.

NA2.2

Abstract unavailable.

CON1.1

Abstract unavailable.

CON1.2
Surgical Management of DSD: New Insights

Sarah Creighton
London, UK

Traditional medical management of children born with atypical genitals includes genital surgery during early childhood. Young children cannot give informed consent and surgery is usually undertaken after a decision made by the multidisciplinary team with parental input. Long-term outcomes are uncertain and there is scanty research supporting the benefits of surgery on physical or mental well-being. Adult patients clearly describe the distress of multiple genital operations during childhood and repeated genital examinations. In addition small but increasing numbers of adolescents are now seeking to reassign gender and previous childhood genital surgery compromises this flexibility. However the impact on a family of a child with unexpectedly atypical genital anatomy should not be underestimated. Families find adjustment to the birth of such a child challenging and genital surgery is often the only or at least the main treatment option discussed. Many multidisciplinary teams are led by surgeons committed to genital surgery. In addition complex invasive surgery may be reimbursed at high tariffs for health care providers. Psychological support – although less costly – is often patchy or unavailable. Whilst parents may prefer to defer genital surgery until their child is old enough to take part in the decision making process, they may also feel ill-equipped to negotiate the undoubted challenges of childhood until that time. Credible non-surgical pathways with ongoing psychological support for the family currently do not exist. Current debate about the role of genital surgery is moving from clinical outcomes into the arena of human rights. It is probable that future decisions about normalising genital surgery will not remain in the hands of clinicians. Regardless of when this may happen, action must be taken now to develop and introduce non-surgical pathways as a matter of urgency. Parents need on-going support to acquire the skills and confidence to understand complex medical information, to be able to talk about genital differences and to de-medicalise sex and gender diversity. Without such support and given a choice between surgery and nothing, parents are still likely to choose genital surgery as the best – indeed perhaps the only – possible treatment option for their child.

CON1.3
Psychological Challenges

Franco D'Alberton
Bologna, Italy

The new care paradigm for DSD promoted by the Chicago Consensus of 2005 raised many psychological challenges, the most important being the way decisions regarding the sex of rearing and diagnosis communication are made. The traditional care paradigm, sustained by a binary sex categorization, suggested that for newborns, the decision about the sex of rearing should be made as soon as possible and no later than 18 months of life and that little should be said to the involved person in order to limit the potential effects of psychic trauma. New trends in DSD care are based on a more open conceptualization of gender, like in a bimodal continuum, where the subjective experience of the person and their full acknowledgement of their condition plays a major role. Moreover, experience has shown us that gender changes may happen in any stage of life. The decision about the sex of rearing of a newborn with a DSD challenges our knowledge, our ethical and moral certainties, our beliefs and personal opinions. Effective team work is necessary in order for individuals not to be overwhelmed by such a difficult process, maintaining the capacity to think together, thus avoiding shortcuts such as returning to previous ways of thinking. It is very important that healthcare operators work together, sharing their doubts, uncertainties and discussing the pros and cons of the possible choices in order to be able to help parents to cope with the new and unexpected situation. The aim of this close collaboration between specialists, beginning from birth or time of diagnosis, is to provide people living with DDS with the opportunity to live in an environment which is able to support the development of their personal, social and sexual identity as far as possible.

CON1.4
An Ethicist's Viewpoint

Clsssaudia Wiesemann
Göttingen, Germany

Decisions for children not able to consent must aim at promoting the well-being of the child and future adult and minimize physical and psychosocial risks. In atypical sex development, well-being is a complex category comprising physical and psychosocial health (present as well as long-term). The child has a right to a gendered identity, bodily integrity, fertility, quality of life including sexual life, and mental health. However, patient well-being is a normative concept and, depending on how it is interpreted, conflicts of interests may arise. Parents need psychosocial support to cope with the stress caused by their child's medical condition. The child should be encouraged to participate in decision-making as early as possible, dependent on the child's level of maturity and age. Children acquire decision-making competency between the ages of 10 and 14 and, if competent, must be addressed as relevant moral actors because of the highly personal nature of the issues at stake. In general, irreversible treatments with no direct health benefit should be postponed in order to leave options open for the future until the individual has capacity to consent.

Henning Anderson Award

HA1

KCNQ1 Mutations Cause Both Neonatal Diabetes and Hyperinsulinemic Hypoglycaemia of Infancy

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Background: Mutations in genes involved in insulin secretion or regulation of β cell identity cause both persistent neonatal diabetes (PND) and hyperinsulinemic hypoglycemia of infancy (HHI) pinpointing shared pathogenic mechanisms. *KCNQ1* encodes a potassium channel protein, $K_v7.1$, which is a voltage-gated potassium channel expressed in cardiac tissue, pancreas, inner ear neurons, and other tissues. Variants in or nearby to *KCNQ1* were linked to risk for both long QT syndrome (LQTS) and type 2 diabetes (T2D). **Patients and methods:** We performed exome sequencing in one child with PND and his consanguineous parents and subsequent sanger sequencing of *KCNQ1* in additional 90 children with diabetes or HHI of unknown origin. We detected overall three *KCNQ1* gene mutations in the child with PND (R397W, homozygous) and two children with HHI (G292D and splice-site mutation with complete deletion of E13, both heterozygous). Overexpressing these variants, we analysed insulin secretion and gene expression in a glucose-sensitive mouse β cell line. Moreover, we characterized morphological changes and gene expression in pancreas and islets of *Kcnq1* knock out versus wild type mice. **Results and discussion:** Overexpression of the KCNQ1-PND variant R397W in β cells suppressed, while that of the G292D-HHI and E13Del-HHI variants increased basal and glucose-stimulated insulin secretion; findings consistent with respective human phenotypes. Following overexpression of R397W, high MafB and Pax6 expression points to loss of β cell identity. Dedifferentiation or transdifferentiation of affected β cells are possible molecular mechanisms for diabetes and defective insulin secretion. In contrast, induction of Pdx1 by both HHI mutations (G292D & E13 del) suggests increase of β cell mass and insulin secretion. In *Kcnq1* KO mice, β cell mass was reduced by 35% and a consistent suppression of Pdx1, Foxa2, Arx1 and Irx1 indicates early disruption of both β and α cell differentiation. **Conclusion:** This is the first report on KCNQ1 mutations causing monogenic PND and HHI. Further deep investigation is necessary for better understanding of the molecular pathways linking these *KCNQ1* mutations to early-onset β cell dysfunction in humans.

HA2

BOREALIN Mutations in Thyroid Dysgenesis Reveal a New Function of this Protein in Cell Adhesion and Migration

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Background: Congenital hypothyroidism is primarily due to thyroid dysgenesis (TD). The genes implicated in TD, account for a small number of patients with monogenic forms, less than 5%. Borealin is a major component of the Chromosomal Passenger Complex, an essential regulator of mitosis. **Objective and hypotheses:** To understand the role of Borealin mutations found in patients with TD. **Method:** We performed whole exome sequencing (WES) in a consanguineous family with TD and subsequently sequenced a cohort of 136 probands with TD. We transfected Nthy ori 3.1 cells and human primary thyrocytes with vectors containing the Borealin-wt or the 3 mutants for functional study. Moreover, we performed transcriptome analysis in the thyroid tissue of a patient with a Borealin mutation. **Results:** We identified a homozygous missense mutation p.S148F in the *BOREALIN* gene (one daughter with ectopic thyroid and the other with hemiagenesis) by WES and two others heterozygous mutations by direct Sanger sequencing: p.R114W (thyroid ectopy) and p.L177W (athyreosis). No effect of the three Borealin mutations was shown on mitosis of Nthy cells. However, we found a significant decrease in migration and in the spreading

of Nthy transfected by mutants compared to Nthy-wt. We observed also a decrease expression of a set of genes involved in adhesion of human primary thyrocytes transfected with mutants compared to wt (*TLN1*, *ACTN1*, *ITGA3*, *CAV1*). These results were well correlated with the same genes expression pattern analyzed in the thyroid tissue of the patient with Borealin-p.R114W.

Conclusion: We identified a new gene, Borealin, involved in the adhesion and the migration of the thyrocytes. Heterozygous as well as homozygous mutations in certain domains of this gene are responsible for thyroid dysgenesis, opening new avenues in the genetics of TD in humans. Supported in part by a PHRC, ClinicalTrials.gov NCT01916018, Sandoz SAS, Merck.

Working Groups

WG1.1
Biological Determinants of Gender Identity

Stephen Rosenthal
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Background: Numerous studies from a variety of biomedical disciplines—genetic, endocrine, and neuroanatomical—have begun to shed light on the biological underpinnings of gender identity. Results of these studies support the concept that gender identity is not simply a psychosocial construct, but likely reflects a complex interplay of biological, environmental, and cultural factors. **Objective and hypotheses:** This review will highlight data from studies in genetics, a variety of DSDs, and neurobiology which support the concept that biology plays a role in gender identity development. **Method:** Literature review. **Results:** See "objectives", above.

WG1.2
The Brain as a Target for Sex Steroids: Recent Trends in Endocrine Neuroimaging

Sven Mueller
Ghent, Belgium

Background: Sex hormones organize brain structure and function, particularly early in life. Endocrine neuroimaging offers the opportunity to assess the impact of sex hormones but also genetic contributions on structural neuroanatomy and neurocognitive-affective function in disorders of sexual development (DSD). This may be particularly relevant from a psychopathological perspective of how such neural changes contribute to mood and anxiety disorders frequently observed in DSD. **Objective and hypotheses:** To review recent developments in pediatric endocrine neuroimaging, particularly DSD. **Method:** Drawing from examples of different neuroimaging approaches such as structural and functional MRI and DTI in DSD, this talk will aim to provide a brief overview of the emerging field of pediatric endocrine neuroimaging. Moreover, findings from a recent treatment study on baseline neural synchrony (resting-state MRI) will be presented. **Results:** The reviewed studies indicate functional and structural changes in medial temporal lobe and prefrontal cortex in DSD that can be linked to altered cognitive-affective processing. The resting-state study indicates some plasticity and sensitivity to sex steroids, even in adulthood, and a potential intermediate step between brain structural and functional changes with sex steroid exposure. **Conclusion:** Pediatric endocrine imaging offers exciting new avenues to understanding the neurobiological mechanisms underlying DSD but more collaborative efforts with increased samples and replications are needed.

WG1.3
Gender Dysphoria and DSD

Peggy Cohen-Kettenis
Amsterdam, The Netherlands

Background: Among individuals with DSD, some conditions are more prone to develop distress about ones assigned gender (gender dysphoria; GD) than others. For instance, the percentage of gender change and GD in female-raised persons with testosterone synthesis deficiencies is around 50%, whereas GD hardly seems to occur in complete androgen deficiency syndrome. Unfortunately in many studies information on GD and gender role changes often cannot easily be determined and clinically useful information, such as potential predictors of GD, is frequently absent. **Objective and hypotheses:** To describe psychosexual outcome and moderators of outcome in various DSD groups. We expect that GD is elevated as compared to the general population, that gender reassignments between 2 and 12 years predict GD, and that genital appearance at birth predicts GD. **Method:** The European multidisciplinary outcome study dsd-LIFE evaluated 1061 individuals with conditions covered by the umbrella term DSD such as XY conditions with gonadal dysgenesis, androgen action or synthesis defects, XX conditions with gonadal dysgenesis, congenital adrenal hyperplasia. The study was conducted in 6 European countries (France, Germany, The Netherlands, Poland, Sweden and the United Kingdom). Self-reported gender experience, social gender role and GD were measured. For GD, a modified version of the Utrecht Gender Dysphoria Scale was used. **Results:** We will report on psychosexual parameters, as measured by gender experience, social gender role and GD, as well as the potential role of early gender reassignments and genital ambiguity.

WG1.4
Health Care Situation of Persons with dsd: Results From the dsd-LIFE Study

Birgit Köhler
Berlin, Germany

Introduction: The umbrella term disorders of sex development (DSD) encompass a conglomerate of different genetic conditions affecting gonadal and adrenal function. Access to specialized health care and dissatisfaction with medical and psychosocial care is an issue for many adult patients. However, it is not evident which type of health care meets the needs of care seekers with DSD. **Patients and methods:** The European multidisciplinary outcome study dsd-LIFE evalutated 1061 individuals with conditions covered by the umbrella term DSD such as XY conditions with gonadal dysgenesis, androgen action or synthesis defects, XX conditions with gonadal dysgenesis, congenital adrenal hyperplasia, Klinefelter and Turner syndrome and individuals with 45,X0,/46,XY karyotypes. Health care and satisfaction with care was evaluated in these patients by CQ4-4, CHC-SUN and a condition-specific self-constructed questionnaire

considering psychological care and information management. The study was conducted in 6 European countries (France, Germany, the Netherlands, Poland, Sweden and the United Kingdom). **Results:** Access to specialized health care and satisfaction with care of this cohort will be presented. The influence of diagnosis, sociodemographic data, centre of care and contact to support groups will be presented.

WG1.5

DSD Nomenclature, a Report of the Patients Views in the dsd-LIFE Study

Ute Thyen

Lubeck, Germany

Background: A decade ago the ESPE/LWSPE "Consensus Group on management of intersex conditions" proposed the new term *Disorders of Sex Development* and its acronym *DSD* as an umbrella term for congenital conditions in which the development of chromosomal, gonadal, or anatomical sex is atypical. The Consensus Group intended to replace a potentially stigmatizing vocabulary; however, the new nomenclature attracted criticism. **Objective:** To determine the views and perspectives of individuals having medical conditions that might be classified as DSD regarding the terminology. **Method:** In 2012 the European research project "dsd-LIFE", funded from the European Union (FP 7) was initiated, implementing the term DSD in its project title. Recruitment took place in Poland, Sweden, Germany, France, United Kingdom and the Netherlands between 2014 and 2015. Inclusion criteria of the study followed a generic definition of DSD following the consensus statement. **Results:** In total 1040 individuals participated and 941 responded to the items in the questionnaire related to terminology, including 212 with CAH, 273 with Turner-Syndrom (TS), 188 with Klinefelter-Syndrome (KS), 206 with XY DSD and 62 with other conditions. 29% participants reported that they disagreed with the *Disorders of Sex Development*, ranging from 38% in CAH, 34% in TS, 32% in KS and 23% in XY-DSD and other conditions. **Discussion:** Following the consensus statement the new nomenclature was readily introduced in pediatric care. In the medical profession it appears to improve interprofessional communication. Different from other medical conditions, in DSD individuals so affected are highly sensitive concerning the issue of lebelling and prejudice as aspects of personal integrity and gender identity. Although we found a predominantly positive reception of the term DSD, health care professionals should openly discuss the issue of medical and non-medical terminology and may agree with the patient on a preferred diagnostic label. The label may depend on the context of communication, i.e. health care system, social and working environment, or family and friends.

WG1.6

Fertility in Persons with DSD, Results From the dsd-LIFE Study

Anna Nordenström

Berlin, Germany

Introduction: Disorders of sex development (DSD) describes conditions affecting gonadal and adrenal function and therefore to large extent affect fertility. In some cases the gonads have been removed due to risk of malignancy. Information to the patients about their fertility and treatment options have not been optimal in the past. **Objective:** To describe fertility outcome in the different diagnostic groups of DSD and to assess to what extent assisted reproductive techniques were used. In addition we wanted to study if information about fertility have been given and how it was perceived by the patients. **Methods:** 1061 individuals with conditions covered by the umbrella term DSD such as XY conditions with gonadal dysgenesis, androgen action or synthesis defects, XX conditions with gonadal dysgenesis, congenital adrenal hyperplasia, Klinefelter and Turner syndrome and individuals mixed gonadal dysgenesis. The study was conducted in 6 European countries (France, Germany, The Netherlands, Poland, Sweden and the United Kingdom). Information on partner, number of children, assisted reproduction or adoption and step children were collected. The patients were asked if they if they would have been interested in having children if assisted reproductive treatment had been available in the past or would be future. The patients were asked if they had received information about their fertility and to rate how satisfied they were with the information they had been given. **Results:** Results on fertility for the different patient groups will be reported, if patients had received information on their fertility options and how they perceived the information.

WG2.1

Abstract unavailable

WG2.2

Bariatric Surgery in Obese Adolescents

Jovanna Dahlgren

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Background: Childhood obesity is a serious medical condition where excess body fat negatively affects a child's health. Although prevention is the primary step, there will be obese adolescents who benefit from bariatric surgery. There are four bariatric methods

(all using laparoscopic technique): Adjustable Gastric Banding (AGB), Roux-en Y Gastric bypass (RYGB), sleeve gastrectomy and Bilio-Pancreatic Diversion (BPD). In Sweden we predominantly use RYGB as it improves eating behavior, leads to larger weight loss and preserves free fat mass (FFM) compared to other techniques. Today several bariatric surgery studies in adolescent populations (of whom few randomized) are published, but none has 5–10 year follow-up data. **Objective and hypotheses:** The objective was to review the literature of all those major studies that performed bariatric surgery in 13–18 year olds with morbid obesity. The hypothesis was that if surgery is performed during adolescent years, a better outcome in terms of weight and health-related quality of life would be obtained, whereas more doubtful effects may be found concerning compliance and bone mineral content due to physical immaturity. **Method:** A systematic search was performed in PubMed, EMBASE, PsychINFO, BNI, ProQuest, the Cochrane Library, and a number of HTA-databases. We identified one randomized controlled trial (RCT) and three cohort studies. Seventeen case series were included, of which six dealt with the comparison between adults and adolescents. **Results:** The only published RCT has demonstrated that laparoscopic gastric banding is effective in adolescents recruited directly from the community when compared to the best conventional therapy. In contrast, other studies have not been successful with gastric banding in adolescents. Data from the Adolescent Morbid Obesity Study from Sweden show a weight loss (35%) in the same magnitude as found in adults, with substantial improvement of quality of life, preserved FFM but loss of bone mineral density. From the Teen Longitudinal Assessment of Bariatric Surgery, a prospective multicenter observational cohort of 242 obese adolescents in US, we know there is a favourable short-term complication profile. **Conclusion:** There is a lack of RCTs and long-term data outcomes of bariatric surgery in obese adolescents versus adults.

WG2.3
Clinical Approach To Severe Early Onset Childhood Obesity

Gabriel Á. Martos-Moreno

Madrid, Spain

The increase in childhood obesity prevalence led to the establishment of a monographic obesity clinic since 2009 in our Department. To date, over 1600 patients have been visited, focusing on early onset severity and generating a valuable dataset on the characteristics of these patients ("The Madrid cohort"). This has allowed the performance of genomic and genetic studies, which have led to the demonstration of a genetic background, underlying the development of the disease in a number of these patients (also detailed in FC 4.1 in this meeting). On the other hand, we have been able to analize the clinical, anthropometrical and metabolic characteristics of 1300 children affected with non-syndromic nor genetic (thus, common or polygenic) obesity at diagnosis, as well as the singularities of their follow up. As a result, we will expose their growth, pubertal and skeletal maturation status at diagnosis, according to their sex, age and race, and how they evolve during their evolution; analyzing whether there are singularities in the timing and tempo of pubertal events. Metabolic comorbidities have been thoroughly investigated both, with the diagnostic procedures usually used in the clinic (including the detailed analysis of glycemia and insulinemia in the OGTT test in over 800 patients) as also from the new perspective offered by the "omic" sciences, showing the existence of early proteomic and metabolomic impairment in young obese children, particularly in the presence of insulin resistance. Finally, an overview of the main features of the clinical follow-up of these patiens (drop-out, reconsultation rates) as well as the success rate and later BMI and metabolic evolution will be displayed.

WG2.4
Tanycyte Transport of Leptin into the Hypothalamus: Implications in Leptin Resistance

Vincent Prevot

Lille, France

Background: The survival of an organism relies on its ability to promptly, effectively and reproducibly communicate with brain networks that control food intake and energy homeostasis. To achieve this, circulating factors of hunger and satiety reflecting nutrient availability must cross the blood-brain barrier (BBB) to reach effectors neurons. **Objective and hypotheses:** Here I will discuss the key role played in this process by a peculiar type of glial cells named tanycytes, which have their cell bodies lining the floor of the third ventricle and their endfeet contacting the pial surface of the brain. **Conclusion:** Recent studies indeed suggest that tanycytes, besides regulating hypothalamic BBB plasticity according to nutrient status, capture metabolic signals such as leptin from the bloodstream and transport them towards their cell body for release into the cerebrospinal fluid. Blockade of this conduit for peripheral metabolic factors into the brain of obese individuals is thought to contribute to the pathophysiology of central hormonal resistance.

WG2.5
Palatability Can Drive Feeding Independent of AgRP Neurons

G.P. Raphaël

Paris, France

Feeding behavior is exquisitely regulated by homeostatic and hedonic neural substrates that integrate energy demand as well as the reinforcing and rewarding aspects of food. Understanding the net contribution of homeostatic and reward-driven feeding has become critical due to the ubiquitous source of energy-dense foods and the consequent obesity epidemic. Hypothalamic, agouti-related protein-secreting neurons (AgRP neurons) represent primary orexigenic drives of homeostatic feeding. Using a models

of neuronal inhibition or ablation we demonstrate that the feeding response to a fast, ghrelin or serotonin receptor agonist relies on AgRP neurons; however, when palatable food is provided, AgRP neurons are dispensable for an appropriate feeding response. In addition, AgRP-ablated mice present exacerbated stress-induced anorexia and palatable food intake—a hallmark of comfort feeding. These results demonstrate that hedonic circuitry can solely operate feeding and override the homeostatic circuitry especially in conditions where positive response to energy demands is chronically defective.

WG3.1

Spontaneous Fertility and Pregnancy Outcomes in Turner Syndrome

Sophie Christin-Maitre

Paris, France

Background: Turner syndrome (TS) occurs in 1/2000 newborn girls. Primary ovarian insufficiency (POI), due to an increased follicular apoptosis, is a classic feature of TS. It occurs in more than 95% of TS patients. Therefore, oocyte donation is often the only option for women desiring a pregnancy. **Objective and hypotheses:** Few studies have reported the outcome of spontaneous pregnancies (SP) in TS patients. **Method:** We evaluated the prevalence of SP in a large cohort of 480 French women with TS, recruited from Centres of Rare Diseases, all over France. **Results:** Twenty-seven patients (5.6%) had a total of 52 SP. The two predictive factors correlated with occurrence of a SP, were spontaneous menarche and mosaic karyotype. Miscarriage occurred in 16 pregnancies (30.8% versus 15% in the general French population ($P<0.01$)). The remaining pregnancy outcomes were: legal abortion ($n=2$), medical interruption ($n=3$), intrauterine fetal death ($n=1$) and delivery at term ($n=30$). Caesarean section rates were higher than in the general population, respectively 46.7% versus 21% ($P<0.001$). Pregnancy-induced hypertensive disorders (PHDs) occurred in 4 cases (13.3%), including 2 cases of mild preeclampsia (6.7%). Neither aortic root dilatation nor aortic dissection was observed. Two cases of TS were identified in the 17 daughters issued from this cohort. **Conclusion:** Our study suggests that pregnancy outcomes in SP are more favorable than those in TS after oocyte donation. Furthermore, it should help giving patients with TS, their families, pediatricians and physicians involved in reproduction, a better counseling concerning fertility. However, predictive markers of SP are still lacking. Finally, oocyte freezing in TS patients will be discussed. Adding SP and pregnancies after oocyte freezing, pregnancies issued from their own oocytes may be more common in TS patients, in the near future.

WG3.2

Skeletal Disproportion In Turner Syndrome

Jarod Sze Choong Wong

Glasgow, UK

Short stature and skeletal disproportion is recognised in individuals with Turner Syndrome, with several studies demonstrating disproportionately lower leg length compared to sitting height. The skeletal disproportion is thought to at least,in part, to be due to the short stature homeobox containing gene (SHOX) abnormality. Whilst all girls with short stature deserve investigation to rule out Turner Syndrome, the identification of a short pre-pubertal girl with disproportionately shorter legs should raise the index of suspicion further. The availability of reference data for sitting height/height ratio SDS may facilitate this as up to 60% of TS girls have a sitting height/height ratio SDS $> +2.0$. There is limited information on skeletal disproportion in adults with TS. Current evidence suggests that the disproportion still exists although may be less severe. The role of therapy with recombinant human growth hormone and oestrogen replacement on disproportion in Turner Syndrome is unclear. Finally, poor bone development leading to osteoporosis is a recognised complication of Turner Syndrome. It is unclear if girls with Turner Syndrome with greater degree of disproportion are at greater risk of osteoporosis, as a subset of girls with a more severe skeletal phenotype, and this deserve further studies.

WG3.3

The Added Value of Experience Based Coaching and the Outcomes for Women with Turner Syndrome in the Netherlands

Helen Mijnarends

Maastricht, The Netherlands

To support people with chronic diseases in labour, reïntegration or participation, the Dutch Centre of Chronic Illness and Work developed a certification programme for professional experienced based coaching for patient support organisations. This 8-month during programme combines professional aid and peer-support for a diversity of chronic diseases. Experience based coaching is innovative and can assist patients emotionally by supporting them with coping and accepting their limitations. In my presentation I will explain this method and emphasize the differences and advantages of experience based coaching in comparison with other professional coaches and counselors. Since the introduction of this programme in 2014, 4 women with Turner syndrome (TS) were certified in the Netherlands. These coaches supported about 50 women with TS (age 15–60 years). These women were referred for peer-coaching because they experienced difficulties at school, study or during their work. Most commonly, problems were due to a low self-esteem, uncertainty and pleasing-behavior. Self-acceptance, empowerment, assertiveness and self-management are therefore the keystones in our coaching. Our self-management-course is a major support for a lot of women with TS because of its targeted and actionable approach. Women with TS function at similar occupational levels in comparison with other women. However, they retire at earlier age and often have difficulties in keeping a positively challenging job. I supported about 10 adult women with TS who couldn't confirm to the job-requirements. I coached them in order to get

adjustments in tasks or to find another job which was more suitable. As a Turner-woman myself, I know the struggles and challenges we have to deal with in different phases of our lives. I can offer professional advice as well as trust and support. When I started this coaching (2 years ago) I had never thought it would give me so much pleasure and satisfaction.

WG3.4
Face Perception in Turner Syndrome (TS)

Vardit Gepstein

Haifa, Israel

Individuals with TS exhibit a distinct cognitive profile. They show deficits in visual-spatial and visual-motor skills, such as mental rotation, object assembly, design copying, visual memory and attention, deficits in arithmetic abilities, executive function, and some language aspects, such as verbal fluency. Other intellectual capacities, however, are preserved in TS, and in some domains, such as linguistic receptive and expressive abilities, performance is, at times, even superior than that of the general population. Individuals with TS also have poor psychosocial functioning. In childhood, girls with TS have difficulties in forming and maintaining relationships, and they are more socially isolated than controls. As adults they have problems with social and partner relationships, and decreased likelihood of independent living and professional achievements that are compatible with their education level. Several studies have found that women with TS are impaired, compared to normal peers, in tasks that examine Theory of Mind (ToM) - the ability to attribute mental states to the behaviour and intention of others. A recent study has examined social competence in young girls with TS. TS girls performed poorly on several measures of social competence, including social awareness, cognition and communication. They were also impaired in the autistic mannerisms scale which includes items such as restricted interests and stereotypic behaviour. One particular area of social functioning, which is the focus of our study, is the impairments of TS individuals in face and emotion perception, yet the face-specific configural and holistic processes that underlie intact face perception appear to function normally. In addition, TS women showed impairments in social cognition, especially when asked to express descriptions of mental states (mentalizing). It remains unknown how such cognitive patterns are dependent on TS-related genetic and hormonal factors.

WG3.5
Estradiol Supplementation in Turner Syndrome: An Update

Theo Sas

Rotterdam, The Netherlands

Background: Most Turner syndrome patients will need estrogen replacement therapy – first for induction of puberty and later for maintaining secondary sex characteristics, attaining peak bone mass, and normalizing uterine growth for possible pregnancy later. **Results:** An updated overview of the different estrogen replacement therapy regimen will be presented.

WG4.1
The Genetics of Overgrowth Syndromes

Katrina Tatton-Brown

London, UK

Human growth results from an increase in cell size, cell division and amount of interstitium and is determined by the complex interplay of genetic and environmental factors. Over the last 14 years our group has been studying growth through the genetic interrogation of rare individuals presenting with syndromic overgrowth defined as an increased height and/or head circumference, compared to the age-related peer group, in combination with an intellectual disability. In the years since the study's inception we have defined the molecular and phenotypic spectra associated with Sotos syndrome and, more recently using a trio based exome sequencing approach, have identified the overgrowth genes *EZH2* (Weaver syndrome); *DNMT3A* (DNMT3A overgrowth syndrome) and the *PP2A* subunit genes, *PPP2R5B/C/D*. It is noteworthy that many of the overgrowth gene family either encode members of the PI3K/mTOR growth regulatory pathway (*PTEN, PP2A* subunits, *PIK3CA, PIK3R2, AKT1*) or are components of the epigenetic arsenal determining chromatin modelling and gene expression (*NSD1, EZH2* and *DNMT3A*). In addition, somatic mutations affecting many of the overgrowth genes have also been implicated in the development of malignancies. However, to date only a minority of overgrowth syndromes have been associated with an increased tumour susceptibility. Further, longitudinal clinical studies are underway to clarify associated tumour susceptibilities and the range of medical complications associated with Sotos syndrome, Weaver syndrome, the DNMT3A overgrowth syndrome and the PP2A subunit gene conditions.

WG4.2
Hypercalcaemic Disorders in Children

Rajesh V. Thakker

Oxford, UK

Hypercalcaemic disorders in children may present with poor feeding, hypotonia, lethargy, dehydration, vomiting, polyuria, failure to thrive, seizures and hypertension. The causes of hypercalcaemia in children, which can be classified as parathyroid hormone (PTH)-dependent or PTH-independent, are similar to those occurring in adults except that primary hyperparathyroidism and malignancy which the most common causes in adults, and account for $>90\%$ of adult patients with hypercalcaemia, are rare in children. Moreover, genetic causes of hypercalcaemia, which

may be syndromic or non-syndromic, are common in children. Thus, genetic causes of hypercalcaemia in children include those associated with: elevated serum PTH, e.g., neonatal severe primary hyperparathyroidism (due to calcium-sensing receptor (CaSR) mutations), and the multiple endocrine neoplasia (MEN) types 1, 2/3, and 4 (MEN1-4) syndromes (due to mutations of the tumour suppressor gene, *MEN1*, that encodes menin, *RET* proto oncogene encoding a receptor tyrosine kinase, and cyclin-dependent kinase inhibitor 1B (*CDKN1B*), respectively); inappropriate serum PTH concentrations due to altered sensitivity of the CaSR and its signalling pathway e.g., familial hypocalciuric hypercalcaemia (FHH) types 1, 2 and 3 (FHH1-3) (due to mutations of CaSR, G-protein alpha 11 subunit, and adaptor protein 2 sigma subunit, respectively); and low serum PTH concentrations e.g., infantile hypercalcaemic (due to mutations of the vitamin D 24-hydroxylase (CYP24A1) gene), William's syndrome (due to a microdeletion of chromosome 7q11.23), Jansen's disease (due to activating mutations of the PTH receptor), and hypophosphatasia (due to mutations of tissue-non specific alkaline phosphate). Non-genetic (acquired) causes of hypercalcaemia in children include: vitamin D intoxication, vitamin A intoxication, subacute fat necrosis, granulomatous diseases (e.g., tuberculosis, sarcoidosis, cat-scratch fever), and inflammatory disorders (e.g., Crohn's disease). Advances in identifying the genetic causes that have resulted in increased understanding of the underlying biological pathways and improvements in diagnosis and treatments will be discussed.

WG4.3

Abstract unavailable

WG4.4

"A Clinical and Genetic Approach to Diagnosis and Treatment of Fractures in Infancy"

Oliver Semler

Cologne, Germany

Nearly 30% of children suffer a fracture during till the end of growth. Most of these fractures are accidental fractures and many are located at the forearm. Non accidental fractures can by caused due to an appropriate force (e.g. child abuse) or can be classified as pathological fractures which are often caused by benign tumours like bone cysts, non-ossifying fibroma or fibrous dysplasia. Most reasons for fractures can be detected by carefully recording the medical history of the patient and the family. In cases without a traumatic history or non-accidental injury additional laboratory tests to exclude metabolic reasons of decreased bone stability are necessary. Radiographs which have been taken of the fractured bone can also give some first impressions about bone structure, modelling of the bone and of the mineralization. After excluding systematic and metabolic reasons for a reduced bone mass, many different types of skeletal dysplasia can cause a reduced bone stability. The most frequent hereditary disease causing an increased fracture rate in children and adolescents is Osteogenesis imperfecta (OI) with an incidence of 1:20,000 births. Osteogenesis imperfecta is primarily a clinical diagnosis but during the last years the knowledge about the molecular reasons for impaired bone stability has increased tremendously. Most patients are affected by dominant mutations involving collagen production (*COL1A1/A2*) causing a reduced amount of bone matrix, which can additionally show an impaired bone mineralization. Besides these typically types of OI many different genes (most of them recessive ones) have been discovered to cause diseases belonging to the spectrum of "hereditary bone fragility syndromes". Some of these rare types can be differentiated by characteristic clinical findings, like the calcified membrane interossea at the forearm in OI type 5 or the combination of fractures and contractures in Bruck-Syndrom. Other types are characterized by increased bone mineral density (caused by mutations in BMP) or an increased amount of osteoid in bone biopsies like OI type 6. Not all different diseases can be diagnosed based on clinical findings and therefore genetic testing including bone panels or Exome Sequencing is frequently necessary to find the correct diagnosis which is important for treatment of patients and counselling of families.

WG4.5

FGF23, Klotho and PTH in the Regulation of Mineral Homeostasis

Thomas Carpenter

CT, USA

Background: The Fibroblast Growth Factors (FGFs) are a large family of proteins including paracrine, intracrine, and endocrine FGFs. Paracrine and endocrine FGFs interact with specific cell surface receptors (FGFRs) that, via intracellular tyrosine kinase activity, initiate a cascade of downstream intracellular events. Specificity of paracrine/autocrine FGF activity is provided locally by the local production of these FGFs and their cognate receptors. In contrast, endocrine FGFs, such as FGF23, generally require a coreceptor, alpha- or beta-klotho, to effectively bind to their respective target cells. Thus endocrine FGFs target activity to tissues that express klotho. The discovery of FGF23 and its unusual role has brought to attention a novel understanding of mammalian mineral homeostasis, and important clues to the mediation of disorders of hypo- and hyper-phosphatemia. **Conclusion:** FGF23, its receptor(s), Klotho, and vitamin D serve as part of an interconnected system for the multifaceted regulation of calcium and phosphate homeostasis. Such a system is advantageous for appropriate management of mineral needs in times of limited supply, overabundance, and for the changing needs of the vertebrate skeleton. Disruption of the system can lead

to a variety of disorders of bone and mineral metabolism, and pharmacologic targeting of the system should provide a productive strategy for the treatment of some of these disorders.

WG5.1

Abstract unavailable.

WG5.2

SWEET: Developing Centers of Excellence (CoR)

Thomas Danne

Hannover, Germany

Background: SWEET (www.sweet-project.eu) is a non-profit entity endorsed by ISPAD aiming to create an extensive network of certified CoRs for childhood diabetes in order to ensure high quality care. **Objective and hypotheses:** SWEET aims at an improved and more uniform care for people with diabetes through comparing processes and outcomes among participating members. The results of data analysis are conveyed to members through biannual benchmarking reports. In collaboration with NHS Diabetes, peer review visits to applying centers are organized so as to assess compliance with the SWEET quality criteria. Smaller centers can participate as collaborative centers. **Method:** Electronic documentation of at least 150 pediatric patients with diabetes annually, with subsequent upload of anonymized data to a common database is a main prerequisite. The SWEET dataset consists of 37 clearly definable items that reflect adherence to ISPAD's guidelines. Data can be uploaded either through the DPV software that is adapted for a multilingual group or in other electronic formats. **Results:** SWEET includes all forms of pediatric diabetes. Of the 29 centers collaborating in the subgroup of "Genetic disorders of glucose and insulin homeostasis" within the application for an European Reference Network for Rare Endocrine Diseases (Endo-ERN), 10 are also participating in SWEET. Currently 48 SWEET centers from 33 countries in 5 continents have contributed data for 28,667 patients. In 2015, 19.131 patients (51.6% males, median age 14.2 y, T1D: 96.0%, T2D: 1.1%, other forms: 2.9%) with 69,028 visits were recorded. Median HbA1c was 7.8% with 39.1%, 41.4%, and 19.4% of patients having HbA1c $< 7.5\%$, 7.5–9% and $> 9\%$, respectively. One third of all centers achieve a median HbA1c $< 7.5\%$. Regarding treatment modality, 41.2% of all patients were pump users. Data completeness rates have significantly improved over time. **Conclusion:** Benchmarking has highlighted the importance of complete and accurate data to achieve meaningful interpretation. Hopefully SWEET will therefore help to harmonize care to optimize outcomes of children with diabetes worldwide whatever the etiology of their diabetes is.

WG5.3

Use and Discontinuation of Continuous Subcutaneous Insulin Infusion and Continuous Glucose Monitoring in Paediatric Patients with Type 1 Diabetes: Rates and Causes

Shlomit Shalitin

Petah Tikva, Israel

Background: A large percentage of pediatric patients with type 1 diabetes (T1D) do not achieve their glycaemic targets. The most impactful benefit can be achieved by improving the implementation of novel technologies developed to manage diabetes. **Objective and hypotheses:** Two novel technologies were introduced to help patients with T1D achieve glycaemic control: continuous subcutaneous insulin infusion (CSII) and continuous glucose monitoring (CGM). They were expected to change dramatically the method of treatment and improve patient quality of life (QOL). The aim was to evaluate the rate of use and the rate and reasons for discontinuation of these technologies in paediatric patients. **Method:** We reviewed studies that included paediatric patients with T1D using CSII and CGM. **Results:** The number of children treated with CSII has increased in most diabetic centres. CSII was found to lead to better glycaemic control, better health-related QOL, and decreased hypoglycaemic risk. Overall, the rate of CSII discontinuation has been relatively low. Factors associated with CSII discontinuation were lower frequency of self-blood glucose measurements (SBGM), higher HbA1c levels, older age at the time of CSII initiation, female gender, and decreased compliance. CGM was found to improve glycaemic control, especially when used $> 70\%$ of the time. However, its rate of adoption has been relatively low. Its use was more likely in the presence of a higher frequency of SBGM, higher patient education, higher household income, and use of CSII. **Conclusion:** While the hope for the development of a fully automated artificial pancreas remains, it is crucial to formulate effective approaches to implement the currently available technological advances, and ensure that their use is sustained. Lack of a proper education, diminished motivation, and behavioural attitude can affect patient compliance. Long-term follow-up with intensifying education and behavioural therapy accompanied by adequate training and ongoing support might improve adherence and enhance treatment satisfaction, leading to better glycaemic control.

WG5.4

Use of Dual Hormone (Glucagon) v. Single Hormone (Insulin) in the Treatment of Diabetes with Close-loop System

Revital Nimri

Israel

Background: Blood glucose levels are physiologically controlled by insulin and counter-regulatory hormones, mainly

glucagon. Type 1 diabetes patients are deficient in insulin and some level also glucagon. Therefore, bi-hormonal closed-loop system seems to be the best way to control glycemia. **Objective and hypotheses:** There are two main approaches to add glucagon: (a) as safety measures for rescue in case of hypoglycemia (2) as a mean to optimize metabolic control. Glucagon has the potential to better control hypoglycemic events than insulin alone. **Method:** The advantages and disadvantages of bi-hormonal closed-loop system will be discussed. **Results:** Several studies that compared closed-loop system with single hormone (insulin) and bi-hormone (insulin and glucagon) may suggest an advantage of the bi-hormonal over single-hormone. Insulin activity has a relatively long duration; hence suspension of insulin delivery alone may not be sufficient to prevent hypoglycemia. The add-on of glucagon may reduce those "unavoidable" hypoglycemic events. This approach is beneficial mainly to those susceptible to hypoglycemia, i.e. young children, subjects with hypoglycemia unawareness or physically active. Glucagon can also be used to improve postprandial hyperglycemia, namely, insulin over-delivery for reducing prandial glucose excursion and then compensating with glucagon. Some may argue that bi-hormonal closed-loop system is more complex and expensive. Nevertheless, technology overcomes it by a combined pump infusion device and new formulation of stable glucagon. **Conclusion:** Addition of glucagon to insulin in closed-loop system is feasible, safe, well tolerated and may help to mitigate the risk of hypoglycemia, improve metabolic control as well as allow patients to be more spontaneous in their daily activities.

WG5.5
Use of Dual Hormone (Glucagone) vs Single Hormone (Insulin) in the Treatment of Diabetes with Closed-loop System

Tadej Battelino

Ljubljana, Slovenia

Dual hormone closed-loop insulin/glucagon delivery has been successfully used in in- and out-patient clinical setting with a reduction in hypoglycemia and improvement in time in range of glucose concentration. However, the main goal of the dual hormone closed-loop systems – complete prevention of hypoglycemia – has not been achieved. In the latest published studies with dual hormone closed-loop systems the amount of intervention with oral carbohydrates is still almost half of the amount in the control arm. Several physiologic and technical barriers preclude complete elimination of hypoglycemia with the dual closed-loop systems. The glucagon action is physiologically less potent at high insulin concentrations in the blood, which is exactly when its action is most needed in the dual hormone insulin delivery. Additionally, its subcutaneous application may not always be successful due to various technical reasons. Finally, partial protection from hypoglycemia with the use of dual hormone closed-loop systems may reduce the attentiveness of its users to the remaining alarms requiring rescue carbohydrate ingestions. On the other hand, an increasing amount of published data on single hormone closed loop systems demonstrates its safety and efficacy, and most importantly feasibility of its routine day-to-day use. Hybrid single hormone closed-loop systems seem more efficient in clinical studies as pre-meal boluses reduce post-prandial hyperglycemia. However, in every-day routine full single hormone closed-loop system may become the option of choice.

WG5.6
Prescribing Software for the Treatment of Diabetes

Moshe Phillip

Petah Tikva, Israel

Management of Type1 diabetes is a challenge for both patients and health-care providers. The majority of patients worldwide are not reaching the desired glycemic control. Barriers to good control include risk of hypoglycemia, glucose monitoring limitations, technologies of insulin administration, scarceness of diabetes experts their limited time required in order to give the appropriate level of personalized treatment and supervision during patients' visits. Other reasons are the patients' burden and emotional fatigue and their difficulty to keep up with the burden of the therapy over time. Technologies of data management and software tools may be of help patients and care-givers in tailoring the right solution. It puts the specific patient in the center of the treatment and empower the patient and the care-giver. Software prescribed to a specific patient should be personalized, targeted and suited for individual needs. Individual patient's information about the treatment, and the insulin glucose response data is largely available from pumps, sensors, glucose meters, fitness apps and devices, biometric devices, and a built-in food and medication database. The data can be collected seamlessly through applications or different platforms at the clinic and transformed into meaningful treatment recommendation via a software prescription, changing the way diabetes is treated and managed.

WG5.7
The Interaction Between Human and Technology in the Treatment of Diabetes

Katharine Barnard

Bournemouth, UK

Background: Research has demonstrated that technologies to support diabetes self-management for people living with diabetes can have positive effects on medical and quality of life outcomes. It also shows that there may be an additional burden of wearing and using these technologies. Both diabetes and its treatment can have significant deleterious effect on quality of life, thus it is crucial that the interaction between the technology and the user offers maximum benefit with minimum burden.

Objective and hypotheses: Dr Barnard's talk explores the rapidly changing world of diabetes technology and it's impact on the lives of people living with diabetes. She will discuss the role of healthcare professionals in supporting appropriate use of technology, both in terms of access and what "success" looks like to different key stakeholders. **Method:** An overview of recent technological developments including automated insulin delivery systems, continuous glucose monitoring and so-called smart meters. Specific focus on the benefits and burdens of technologies, in the context of everyday living, and how to effectively manage expectations to ensure optimal outcomes both bio-medically and psychosocially. **Results:** Delegates will be guided through the minefield that is diabetes technology, its uptake and continued successful use for people with diabetes.

WG6.1

Abstract unavailable.

WG6.2

Anorexia & Amenorrhea

Madhusmita Misra

Boston, USA

Background: Anorexia nervosa (AN) is a condition of severe malnutrition that impacts multiple endocrine axes, including the hypothalamic-pituitary-gonadal (HPG) axis. Although amenorrhea is no longer required for the diagnosis of AN (DSM-5), amenorrhea continues to be common in this disorder. **Objective and hypotheses:** This talk will review the prevalence and consequences of HPG axis suppression and amenorrhea in adolescents with AN. **Method:** Data for this talk come from observational and interventional studies examining the impact of AN and amenorrhea on bone, neurocognitive and emotional outcomes. **Results:** Amenorrhea in girls with AN is a consequence of low energy availability, which impacts several hormones that in turn have deleterious effects on the HPG axis. Hypogonadism and other endocrine alterations lead to low bone density and impaired bone accrual at a time when healthy adolescents are typically actively accruing bone. Thus, there is a high prevalence of fractures in AN. Weight gain and menses restoration are critical for improving bone density, and physiologic estrogen replacement has beneficial effects. Hypogonadism may also have an impact on cognitive and emotional outcomes, with physiologic estrogen replacement improving both. **Conclusion:** Hypogonadism in adolescents with AN contributes to low bone density and impaired cognitive and emotional outcomes that improve with restoration of estrogen status.

WG6.3

Physical Exercise & Amenorrhea

Neoklis Georgopoulos

Patras, Greece

Exercise-related reproductive dysfunction appears to be multifactorial in origin and remains a diagnosis of exclusion. The main factors etiologically correlated with menstrual disturbances in athletes are body composition, stress (physical exercise and psychological stress), energy balance (energy availability), diet, training methods (sports character) and reproductive maturity. Recent data highlight the endocrine role of the adipose tissue in the regulation of metabolism and reproduction, providing further elements on our current comprehension on the pathophysiology of exercise-induced reproductive dysfunction. The emerging role of adipose as an active endocrine organ has attracted the scientific concern and revealed a number of adipose-secreted factors (known as adipokines) involved in signaling and regulating homeostasis, energy balance, insulin action, reproductive function and inflammation process. Recent studies have implemented energy availability (defined as dietary energy input, minus exercise induced energy expenditure), rather than body weight or exercise stress, in the pathogenesis of reproductive dysfunction in female athletes. Clinical manifestations range from primary amenorrhea or delayed menarche to luteal phase deficiency, oligomenorrhea, anovulation and secondary amenorrhea. Amenorrhea constitutes the most serious clinical consequence involving skeleton and bone loss. Early diagnosis, thorough evaluation and individualized management (ranging from diet and exercise behavior adjustments to pharmacologic treatment) should be a priority, in order to preserve bone mass. Management strategies mainly include the use of oral contraceptives and hormone replacement therapy and a remodelling of energy balance with enhanced energy input and reduced energy output on a equilibrated daily training program.

WG6.4

Breast Cancer Risk in Adolescent Girls

Ellen Copson

Oxford, UK

Background: Less than 1% of breast cancer cases occur in women aged <25 years but young age at diagnosis is associated with an increased risk of recurrence and inferior survival compared to older patients. Breast tumours from young patients have an increased incidence of adverse pathological features; however it is not clear whether this fully explains poor outcomes. **Objective and hypotheses:** The Prospective Study of Outcomes in Sporadic and Hereditary Breast Cancer (POSH) was designed to investigate factors affecting prognosis of young breast cancer patients in the UK. I will present data from this study as well as a general overview of the epidemiology of breast cancer in young women. **Method:** Between 2000–2008, 2956 patients aged <41 years were recruited to the POSH observational study. Tumour pathology, disease stage, treatment received, overall survival (OS)

and distant disease-free interval (DDFI) were assessed. To date we have any analysed the effect of ethnicity, obesity and family history on the outcome of this cohort. **Results:** Median patient age was 36 years. Median tumour diameter was 22 mm, and 50% of patients had positive lymph nodes; 59% of tumours were grade 3, 33.7% were oestrogen receptor (ER) negative, and 24% were human epidermal growth factor receptor 2 (HER2) positive. Five-year OS was higher for patients with ER-positive than ER-negative tumours (85.0 vs 75.7%; $P < .001$), but by eight years, survival was almost equal. In multivariable analyses obesity and ethnicity were both significant independent predictors of OS and DDFI in ER-positive patients. A positive family history was not a significant independent risk factor for breast cancer outcome. **Conclusion:** Young onset breast cancer is associated with poor outcomes and new treatment approaches are required in younger women with this disease.

WG6.5
Benign Breast Conditions in Adolescent Girls

Philippe Touraine

Paris, France

Benign breast diseases (BBD) have always been neglected in comparison to cancer, despite the fact that there are many more patients with such diseases than patients presenting to a breast clinic for cancer, especially in young women. So far, BBD have been the subject of a relatively few isolated and unconnected studies, and earlier related work has often been ignored. This situation has led to a great deal of confusion, especially because different authors have their own nomenclature for benign lesions of the breast, and, unfortunately, a unique and unequivocal definition has not yet been commonly accepted. Hence, it is even more difficult to find in the literature data concerning the mechanisms involved in the development of such disorders, especially when it concerns rare BBD or in adolescents. Breast tissues are under a complex system of control by systemic factors, particularly hormones acting through their respective receptors, as well as a number of local factors. This network starts with the onset of puberty. This includes paracrine hormones, released by one type of cell to influence adjacent cells of similar or differing function; juxtacrine factors, situated on the surface of the producing cell to influence adjacent cells by direct contact; and autocrine hormones, which act on the same cell by intracellular or surface receptors. All of these hormones interact, as is true for systemic hormones, by influencing locally derived factors— cell adhesion-related proteins as well as autocrine and paracrine hormones—to produce signal pathways that finally result in cell regulation and stimulation. We recently identified in a population of women, including adolescents, with multiple breast fibroadenomas (MFA), a germline heterozygous variant in exon 6 of the human Prolactin Receptor gene (hPRLR), encoding Ile146 to Leu (I146L) substitution in the extracellular domain of the receptor. This sole substitution was sufficient to confer constitutive activity to the receptor variant, as reflected by PRL-independent activation of the PRLR/Stat5 cascade and proliferative and antiapoptotic effects in various cell lines. However, in a more recent study, we suggested that these $PRLR_{I146L}$ and $PRLR_{I176V}$ variants are not associated with breast cancer or MFA risk. However, one cannot exclude that low but sustained PRLR signaling may facilitate or contribute to pathological development driven by oncogenic pathways. The role of such variants in developing benign breast tumors will be discussed, especially in adolescents. Others benign breast diseases, in adolescents will be discussed in terms of diagnosis, management and therapeutic approaches.

WG7.1

Abstract unavailable.

WG7.2
The Activities of AdrenalNET and the Paedeatric Emergency Card for Europe

Johan Beun

The Netherlands

BijnierNET/AdrenalNET: AdrenalNET is the result of collaboration in the domain of adrenal gland disorders between healthcare providers, patients, nurses and informal carers. An extremely good modus of cooperation has developed between the endocrinologists at all the Dutch university medical centers and ten of the top teaching hospitals, the patient association (Adrenal Society NVACP) and the National Working Group of Endocrine Nurses (LWEV). **The mission:** AdrenalNET helps adrenal gland patients, carers and healthcare practitioners find reliable, accessible and understandable information (both scientific and general), and offers a secure platform for the exchange of information so that together they can improve the care provided - from the diagnosis itself to the scheduling of care - all with a view to reinforcing the patient's management of his or her own life. **Board:** The Board consists of representatives of the Dutch Adrenal Society NVACP, the Dutch Adrenal Fund, the University Medical Centers, the teaching hospitals, the LWEV and the Dutch College of General Practitioners (NHG). This broad-based involvement ensures that all aspects of caring for patients with adrenal gland disorders are represented. The Executive Board consists of two doctors (Ad Hermus of Radboud UMC and Anton Franken of Isala Hospital), two patients (one of whom is Alida Noordzij), and the coordinator, Johan Beun. **Task:** The activities of AdrenalNET focus primarily on three areas that are particularly important for people with an adrenal gland disorder, namely:

- Improving the quality of specialist-led chronic care
- Improving diagnosis
- Improving care in emergency situations.

WG7.3

Empowering Nurses as Scholars

Terri Lipman

PA, USA

Background: Nurses are expert in providing patient care and have numerous and varied clinical responsibilities. Nurse may feel unprepared for the pursuit of scholarly role-writing for publication/engaging in research/giving professional presentations may seem overwhelming. It is essential that nurses have the skills and are empowered to become scholars. **Objective and hypotheses:** The purpose of this systematic review was to explore the following questions: 1) What are the barriers nurses that impede nurses from pursuing a scholarly role? 2)What systems are needed to support nurses in a scholarly role? 3) How can nurses be empowered to be scholars? **Method:** A literature review was conducted to address the guiding questions. Inclusive criteria included articles that were (a) published between 2010–2015, (b) published in English, (c) relevant to the study questions. Search terms included, but were not limited to ("Nurses, Scholarship" [Mesh] OR "Nursing Scholarship" [Mesh] OR "Advanced Nursing Practice, Scholarship" [Mesh] AND "Nursing Empowerment". **Results:** An in-depth search in the PubMed data base yielded 879 articles. Articles not published in English or published more than 5 years ago were discarded. This narrowed the search to 335 articles. Those articles were reviewed. Ultimately 80 articles were read and analysed using a thematic approach. **Conclusion:** A variety of themes were identified related to empowering nurses as scholars that included the need for 1) mentorship, 2) funding, 3) protected time, 4) infrastructure, 5) guidance, 6) incentives and 6) inspiration.

WG7.4

Poster Review

Nicole Kirouac

Calgary, Canada

Background: Pediatric Endocrine Nurses are experts in caring for children with Endocrine conditions. Many nurses do not have the confidence, knowledge and technical skill set to produce poster presentations that allow them to share this expertise. **Objective and hypotheses:** This session will give Pediatric Endocrine Nurses an opportunity to hear how a poster presentation can be developed, from an idea to the final product. Nurses will feel empowered to take a question/observation and share it with others via a poster presentation. **Method:** Discuss the question/issue, data collection, analysis, literature review. **Results:** Review of a poster submitted for ESPE 2016 titled "A Nursing Perspective: Best practices for pubertal suppression for individuals with central precocious puberty and transgender". **Conclusion:** Nurses can develop posters for sharing information with others within their centres, conferences or internationally.

WG7.5

Abstract unavailable.

Free Communications

FC1.1

DNA Methylation of HSD3B2, NUR77 and RARβ Promoter Genes is Not Involved in functional Differentiation of Human Androgen-Producing Adrenocortical Cells

Maria Cecilia Alonso Burgos, Javier Goni, Nora Saraco, Natalia Perez Garrido, Marco A. Rivarola, Alicia Belgorosky, Maria Sonia Baquedano

Garrahan National Pediatric Hospital, CABA, Argentina

Background: RARβ cooperates with Nur77 to *in-vitro* regulate HSD3B2 transcription. NUR77 expression parallels HSD3B2 expression with a much lower level in androgen-producing adrenocortical tissues (childhood virilizing adrenocortical tumours (VAT), fetal zone (FeZ) and zona reticularis, ZR). RARβ is down-regulated in starved, hyperandrogenic H295R cells. However, the mechanisms regulating this expression pattern and the relevance of RARβ to human adrenal physiology are unknown. **Objective:** To evaluate developmental changes in DNA methylation of HSD3B2, NUR77 and RARβ genes in VAT and normal human adrenal tissues (HAT). **Method:** VAT ($n=11$, age 0.75–4.5 year) and HAT collected from 3postnatal groups: Gr1:< 3mo, $n=9$, FeZ involution; Gr2:3mo to 6 year, $n=9$, pre-adrenarche; and Gr3:>6 to 20 year, $n=8$, post-adrenarche, were evaluated. Total DNA and RNA from whole tissue and from laser capture microdissected zona fasciculata (ZF) and ZR in Gr3 were isolated. Total RARβ (RARβT) and RARβ2 expression were studied using qRT-PCR. Promoter methylation pattern were examined by bisulfite sequencing. **Results:** RARβT and RARβ2 mRNAs were similar among HAT from the 3 groups. RARβT mRNA was lower in VAT compared to age-matched group HAT ($P<0.05$). RARβ2 tended to be lower in VAT compared to HAT without statistical significance. RARβT and RARβ2 mRNA expression showed no significant difference between micro-dissected ZR and ZF. HSD3B2 NUR77 mRNAs were much lower in ZR cells ($P<0.05$) . In silico screened showed that NUR77 promoter was embedded within a CpG island but it remained completely unmethylated in HAT from the 3Grs and in VAT. No differences in adrenal zone-specific NUR77 methylation were observed. **Conclusion:** RARβ was not associated with ZR-specific down-regulation of HSD3B2 in postnatal human adrenocotical zonation. DNA methylation would not be involved in zone-specific and VAT downregulation of adrenal NUR77. Lack of CpG Island in HSD3B2 suggested that the known downregulation of HSD3B2 gene expression in human ZR would not be directly mediated by DNA methylation.

FC1.2

Transcriptomic Analysis in Healthy Subjects with Differences in Tissue Sensitivity to Glucocorticoids Identifies Novel Disease-associated Genes

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Background: Glucocorticoids exert profound immune-modulating effects and regulate the expression of genes involved in cell cycle progression and apoptosis. Synthetic glucocorticoids are the most potent agents used in the treatment of inflammatory, autoimmune and lymphoproliferative disorders. Considerable variation in response to therapeutic doses of glucocorticoids exists among individuals, as evidenced by differences both in disease response and in the incidence of glucocorticoid side-effects. **Objective and hypotheses:** To identify novel glucocorticoid (GC) sensitivity-determining genes using genome-wide expression profiling in healthy volunteers. **Methods and Results:** One hundred healthy adults were given 0.25 mg of Dexamethasone at midnight, and serum cortisol concentrations were determined at 08:00 h the following morning. Accordingly, subjects were polarized into the 10% most GC sensitive ($n=10$) and 10% most GC-resistant ($n=10$). Sequencing of the human glucocorticoid receptor (NR3C1) gene in the 20 subjects revealed no mutations or polymorphisms. RNA sequencing identified 133 upregulated and 49 downregulated genes involved in immune response and NF-κB cascade in the GC-resistant versus the GC-sensitive group. Several Systemic Lupus Erythematosus-associated genes were more active in the GC-sensitive group, while multiple targets of NR3C1 gene were positively regulated in the GC-resistant group. Cluster analysis in the expression profile of the 20 subjects revealed clear differences between the two groups with 3 GC-sensitive and 3 GC-resistant individuals. Differential expression analysis revealed upregulation of 900 and downregulation of 1100 additional genes. Alzheimer disease-amyloid secretase pathway, dopamine receptor-mediated signaling pathway and telomere maintenance were novel signaling pathways more active in the GC-sensitive subjects. Key molecules associated with neurological diseases, such as Synuclein A in Parkinson's disease, were upregulated in the GC-sensitive group. Finally, the NR3C2 gene was more active in the GC-resistant group. **Conclusion:** Differences in tissue sensitivity to glucocorticoids among healthy adults are associated with differential expression of genes related to autoimmune and neurological disorders.

FC1.3

Steroidogenesis in the Human Fetal Adrenals at the End of the First Trimester

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Background: Steroid hormones produced by the human fetal adrenals (HFA) are suggested to regulate intrauterine homeostasis and the maturation of certain fetal organs necessary for extrauterine life. Appropriate development and hormonal function of the HFA therefore are critical for normal fetal maturation and survival. Little is known about the possible relationship between the expression of steroidogenic enzymes and corresponding transcription factors in the HFA *in vivo* at the end of first trimester due to limited access to material at that fetal age. **Objective and hypotheses:** The aim of the study was to investigate steroidogenesis in human fetal adrenocortical cells (HFACs) *in vitro* and to explore the ontogenetic expression profiles of steroidogenic enzymes and transcription factors in the HFA during the first trimester *in vivo*. **Method:** Steroids produced by intact and ACTH-stimulated HFACs were analyzed by gas and liquid chromatography/mass spectrometry (GC-MS/MS and LC-MS/MS). Expression steroidogenic enzymes and transcription factors were explored by qPCR and automated Western blotting in the HFA at gestational week (GW) 9–12. **Results:** ACTH-stimulated HFACs produced steroids of the Δ5pathway and had no potential to synthesize potent androgens at GW9-12. The HFA expressed high protein levels of CYP17A1 and CYP11B1 at GW11-12 and GW10-11, respectively, which were correlated with elevated expression of SF-1 and GATA-6. However, HSD3B2 peaked at GW10 but significantly decreased at GW11. **Conclusion:** Our findings indicate that the HFACs are responsive to ACTH stimulation but have no potential to produce potent androgens at GW9-12. The onset of HFA steroidogenesis is a complex coordinated process that is tightly regulated by cooperative action of relevant transcription factors.

FC1.4

Identification of Novel Central Nervous System Imaging Biomarkers Associated with Cognitive Abnormalities in Patients with Congenital Adrenal Hyperplasia

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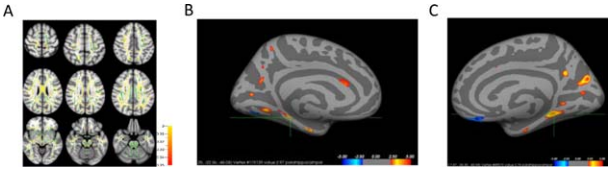
Background: Management of patients with CAH remains challenging. There is increasing evidence to suggest that failure to optimize treatment during childhood not only affects final height but also leads to psychological and psychiatric problems. Previous qualitative structural T2-weighted MRI studies have identified white matter hyper-intensities in up to 46% of CAH patients. The nature and functional relevance of these abnormalities remains unknown. **Objective and hypotheses:** We aimed to identify novel MRI brain biomarkers of CAH and to examine their association with cognitive abnormalities. **Method:** All participants completed subtests of the Cambridge Neuropsychological Test Automated Battery and underwent brain volumetric, magnetic resonance spectroscopy and diffusion tensor imaging. Freesurfer (neural volumes and cortical thickness), TARQUIN (metabolites) and Tract Based Spatial Statistics (fractional anisotropy) were used to process the neuroimaging data. *T*-tests were performed to compare significance between groups, adjusted for multiple comparisons. Partial correlations were performed to assess the relationship between MRI markers and neuropsychological measures. **Results:** Seventeen females with 21-hydroxylase deficiency and 18 age-matched healthy females were recruited (32.7 and 28.6 years, $P=0.25$). Patients with CAH had significantly lower episodic memory, learning and spatial working memory ($P<0.001$) scores. Patients with CAH had significant reductions in total brain volume ($P=0.02$), corpus callosum volume ($P=0.03$), hippocampal N-Acetyl Aspartate ($P=0.03$) and choline ($P=0.002$), brain fractional anisotropy (Figure A, $P<0.01$) and parahippocampal cortical thickness (B, left, C, right, $P<0.05$). There were significant relationships between; corpus callosum volume and spatial working memory ($P=0.001$), parahippocampal thickness, episodic and working memory ($P<0.05$), hippocampal choline and rapid visual information processing ($P<0.02$). **Conclusion:** For the first time we have identified central nervous system imaging biomarkers of clinically significant cognitive abnormalities in patients with CAH. Further studies are required to determine the age of onset of these abnormalities and to develop preventative strategies.



FC1.5

AAV Gene Therapy of 21-Hydroxylase Deficiency (21OHD) in Cyp21$^{-/-}$ mice

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Background: Despite current treatment, girls and women with severe forms of 21OHD are exposed lifelong to a chronic excess of androgens and the secondary effects of suppressive corticoids, which make gene therapy (GT) an option to be explored. **Objective:** To evaluate the effect of human CYP21 gene transfer mediated by adeno-associated virus (AAV) in a *Cyp21*$^{-/-}$ mouse model. **Methods:** 17 adult *Cyp21*$^{-/-}$ mice received two doses of AAVrh10- CYP21 vector. Wild type (WT) mice ($n=9$) and control untreated *Cyp21*$^{-/-}$ mice ($n=7$) were injected with a control vector. Weight and progesterone were measured for 15 weeks. At this date, vector copy number (VCN), qRTPCR of steroidogenic enzyme mRNAs and immunohistochemistry of adrenal cortexwere studied. **Results:** GT of *Cyp21*$^{-/-}$ mice resulted in a progressive and stable decrease of urinary progesterone, which became 19.5 ± 6 ng/mg creatinine (vs 56 ± 15 before treatment). For comparison, urinary progesterone is 7.5 ± 3 in WT. Weight increased from 14.5 ± 2 g to 25.5 ± 1 g in males (normal 30) and from 16 ± 1 g to 22.5 ± 1.5 g for females (normal 25). Mean VCN was 0.1–0.15 per cell depending on vector dose. Immunohistochemistry showed CYP21 expression in both zona glomerulosa and fasciculata. Correction of hyperexpressed *Star, Cyp17a1, Cyp11b2, Mc2r* and PRKAR1A/R2A/Ca/Cb was observed in adrenals and of hyperexpressed renin in kidney. **Conclusion:** Systemic GT at the studied doses allowed a near-complete correction of the Cyp21$^{-/-}$ phenotype. Studies in large animals are underway.

FC1.6

A Novel Syndrome of IUGR, Congenital Adrenal and Gonadal Insufficiency, Severe Infections, Thrombocytopenia and Monosomy 7 is Caused by SAMD9 Mutations

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Background: The association of intrauterine growth restriction (IUGR), adrenal insufficiency and gonadal dysgenesis is well recognised. Some children have been reported to develop monosomy 7 and myelodysplasia. However, the genetic basis of this condition was poorly understood. **Objective and hypotheses:** Our aim was to investigate the genetic basis of eight children with IUGR, adrenal insufficiency and gonadal failure and additional features including severe infections and high mortality in the first 2 years of life. **Methods:** A combination of whole exome sequencing and targeted Haloplex array analysis was undertaken in the eight children. All had a 46,XY karyotype, IUGR, adrenal insufficiency and testicular dysfunction, and female external genitalia in 6 out of 8 patients. Expression studies were done using qRTPCR and immunohistochemistry (IHC). Genetic studies included array CGH, single-nucleotide primer extension assays, subcloning and sequencing of PCR-amplified DNA. Functional analysis of the mutants was performed with proliferation assays, EM and confocal imaging studies in patient derived cells. **Results:** Heterozygous mutations in sterile alpha motif-containing protein, SAMD9 (OMIM 610456, chr 7q21.2), were found in *all* cases. These changes were *all de novo* (7/8 children tested), affected highly conserved regions and were not in control DNA ($>100{,}000$ alleles). With qRTPCR and IHC of human fetal and adult tissues, SAMD9 was most highly expressed in the fetal adrenal gland, with high expression also in the colon, thymus, bone marrow, liver and testis correlating well with patient phenotypes. Cell profileration was reduced consistent with gain of function changes in a growth suppressor. Five patients had partial or complete monosomy 7 in their bone marrow or blood and four had mosaic somatic second hit mutations disrupting the SAMD9 gene. By analysing serial samples, we were able to show that the monosomy 7 was an acquired phenomenon leading to loss of the mutated allele and thereby partially rescuing the life-threatening phenotype. **Conclusion:** This novel rare congenital disease provides evidence that secondary somatic events can partially rescue lethal developmental defects. The life of affected patients can potentially be saved by bone marrow transplantation, if mutations are detected early.

FC2.1

Characterization of GNAS miRNAs Targets: Trying to Better Understand the Pathophysiology of Pseudohypoparathyroidism 1B (PHP1B)

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Background: Patients affected with PHP1B are characterized by resistance to PTH which binds to the PTH receptor and activate the cAMP/Gsa signaling pathway. Gsa is encoded by *GNAS*, a locus subjected to genomic imprinting. PHP1B patients present with abnormal methylation at the maternal *A/B* promoter and, in some cases, at the other promoters (*XLas*, *GNAS-AS1* and *NESP55*) of the *GNAS* locus, likely leading to a decreased expression of Gsa. Clinical features of PHP1B are not fully explained by the cAMP/Gsa signaling defect. From the 3' UTR of the *GNAS-AS1* transcript, arise 3 miRNAs: hsa-miR-296-5p, hsa-mir-296-3p and hsa-mir-298-5p.

Objectives: Demonstrate that the GNAS-miRs are imprinted. Characterize their expression in controls and PHP1B patients and identify their targets. **Methods:** Analysis of the *GNAS* miRNAS imprinting through pyrosequencing and qPCR. *In silico* characterization of *GNAS* miRNAs putative targets. Identification of targets of the GNAS-miRNAs through the overexpression of the 296-3p miRNA in HEK293 cells. **Results:** 1- the GNAS-miRNAs display an imprinting expression pattern (in fibroblasts of one matUPD20 patient, down expression by 400 and 3.5 fold of the 296-5p miRNA ($P=0.0015$) and the 296-3p miRNA ($P=0.0289$), respectively). 2-Targets of the 3 miRNAs were characterized in silico using mirbase and subsequently classified in three groups: cAMP signaling, calcium signaling and growth. 3- In HEK cells, overexpression of the 296-3p miRNA leads to a significant decrease in the expression of AKAP6 and PRKAG1 by 35% ($P=0.000085$) and 44% ($P=0.000023$), respectively. In leukocytes of one patUPD20 patient, we found a significant decrease in AKAP6 ($P=0.0015$) and a non significant decrease in PRKAG1 expression, respectively. Both factors are involved in cAMP signaling. **Conclusion:** The GNAS-296-5p-miRNA and the GNAS-296-3p-miRNA are imprinted and target factors involved in cAMP signaling independently from Gsa. Additional studies are necessary to decipher the precise role of the GNAS-miRNAs on the PHP1B phenotype.

FC2.2

From Pseudohypoparathyroidism to Inactivating PTH/PTHrP Signaling Disorder (iPPSD), a Novel Classification Proposed by the European EuroPHP-Network

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Background: Disorders related to an impairment in parathyroid hormone (PTH) signaling pathway are historically classified under the term pseudohypoparathyroidism (PHP), that now encompasses rare, related but highly heterogeneous diseases with demonstrated (epi)genetic causes. The actual classification is based on the presence or absence of specific clinical and biochemical signs together with an *in vivo* response to exogenous PTH and an *in vitro* assay of Gsα protein activity. However, this classification does not take into consideration other related diseases like acrodysostosis (ACRDYS) or Progressive Osseous Heteroplasia (POH), as well as recent associations to phenotypes and genetic/epigenetic background of the different subtypes. **Objective and hypotheses:** The EuroPHP network met on three different occasions with the major goal of developing a new classification that encompasses all disorders with an impairment in PTH and/or PTHrP cAMP-mediated pathway. **Method:** An extensive review of the literature was performed. Several meetings were organized to discuss about a new, more effective and accurate way to describe disorders related to abnormalities of the PTH signaling pathway. This led to the realization of a novel terminology and classification of these disorders. **Results:** After a selection of major and minor criteria to consider for the diagnosis of these disorders, we proposed to group them under the term of "inactivating PTH/PTHrP signaling disorders", abbreviated as iPPSD. This terminology: i) defines the common mechanism responsible for all diseases, ii) does not require a confirmed genetic defect, iii) avoids ambiguous terms like "pseudo", iiii) eliminates the clinical or molecular overlap between diseases. **Conclusion:** We believe that the use of this nomenclature and classification will facilitate the development of rationale and comprehensive international guidelines for the diagnosis and treatment of iPPSDs.

FC2.3

The Impact of Intragastric Balloon Placement Suppported by a Lifestyle Intervention Programme on Cortical and Trabecular Microstructure and Strength in Severely Obese Adolescents

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Background: The effect of profound weight loss following obesity surgery on skeletal microarchitecture and strength in adolescents has not been studied. Obese children are at an increased risk of fracture and childhood obesity leads to reconfiguration of trabecular bone without augmenting bone strength. **Objective and hypotheses:** To examine the impact of weight loss following 6 months treatment with an intragastric balloon supported by a lifestyle intervention programme on cortical and trabecular bone microstructure and bone strength in obese adolescents. **Method:** We recruited 11 adolescents aged 13.8 to 16.8 years, BMI >3.5 S.D., Tanner stage 4/5 to undergo intragastric bariatric balloon placement. Serial distal radial and

tibial high resolution pQCT (peripheral quantitative computed tomography) imaging, subtotal body and lumbar spine (LS:L1 to L4) DXA was performed at baseline and 6 months. HRpQCT measures of microstructural properties included trabecular number (Tb.N, 1/mm), trabecular thickness (Tb.Th, mm), trabecular separation (Tb.Sp, mm), and cortical thickness (Ct.Th, mm). Biomechanical parameters were defined by miocrofinite element analysis. Results are expressed as (mean difference, 95% CI, significance (p)). **Results:** Weight SDS and BMI SDS decreased significantly (-0.38 (-0.62, -0.13) and -0.27 (-0.44, -0.10) respectively, $P=0.005$). Total body bone mineral content (BMC), LS BMC and LS bone area all demonstrated age appropriate increases following the balloon. Cortical BMD (14.0 mg/cm^3 (8.2, 19.7), $P<0.001$) and cortical perimeter size (4.0 mm (0.5, 7.5), $P=0.029$) increased at the radius. Cortical area (2.4 mm^2 (0.1, 4.7), $P=0.042$), cortical BMD (11.1 mg/cm^3 (4.1, 18.0), $P=0.006$) and cortical thickness (0.02 mm (0.001, 0.04), $P=0.042$) increased at the tibia. Paradoxically, total bone area at the radius diminished (-6.1 mm^2 ($-8.9.-3.2$), $P=0.001$). Bone stiffness and estimated ultimate failure load did not significantly change following surgery. **Conclusion:** There was no evidence of skeletal deterioration following intragastric balloon insertion despite a reduction in BMI SDS. Total body and regional bone accretion continued with the greatest gains in cortical bone. In the short term, balloon bariatric surgery does not cause bone loss in adolescence.

FC2.4

In vitro Evidence that Growth Plate Chondrocytes Differentiate into Perichondrial Cells

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Background: During early bone formation, mesenchymal stem-cells condense and differentiate into collagen type 2-expressing chondrocytes which form the cartilaginous bone anlagen. This anlage becomes enclosed by the perichondrium. The perichondrium consists of two layers, the inner cambium layer containing chondrocyte- and osteo-precursor cells and the outer fibrous layer important for mechanical and structural support. While the regulation of the growth plate is increasingly well understood, little is known about the regulative capacity of perichondrium on the growth plate, as well as in bone growth. **Aim:** To explore the cellular origins of perichondrium. **Methods:** Perichondrium-specific markers were identified by microarray and real-time PCR analysis of microdissected growth plate and perichondrial tissues. High-density chondrocyte pellets were produced by isolating chondrocytes from epiphyseal cartilage. During the dissection, the perichondrium was carefully removed and its absence was confirmed by histological examination and by real-time PCR for perichondrium markers. Differentiation of pellet cultures was studied using real-time PCR and *in situ* hybridization for chondrocyte and perichondrium markers. **Results:** Cultured chondrocyte pellets developed a surrounding perichondrium-like tissue by day 21 of culture. This surrounding tissue did not express chondrocyte markers, collagen 2 or 10, as assessed by *in situ* hybridization. Instead, perichondrium markers Periostin (Postn), Roundabout 2 (Robo2), Dickkopf 3 (Dkk3), Pleiotrophin (Ptn), Protein Tyrosine Phosphatase Receptor Type Z 1 (Ptprz1), Cadherin 2 (Cdh2), and L-galectin (Lgals) were upregulated during the formation of the perichondrium-like tissue by real-time PCR and *in situ* hybridization. Interestingly, only molecular markers for the cambium (Dkk3 and Lgals) and not the fibrous layer (Collagen 14) were upregulated in cultured chondrocyte pellets. **Conclusions:** These findings support previous cell-lineage tracing studies suggesting that the perichondrium is formed from chondrocytes in the periphery of the bone anlagen. In addition, the results suggest that epiphyseal chondrocytes of postnatal animals are not terminally differentiated, but still retain the potential to transdifferentiate into perichondrial cells. In addition, this study presents evidence that not only epiphyseal cartilage, but also bone tissue and perichondrium are made up from collagen 2 expressing cells.

FC2.5

Determination of the Minimal Clinically Important Difference in the Six-Minute Walk Test for Patients with Hypophosphatasia

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Background: Hypophosphatasia (HPP) is a rare, inherited, metabolic disease caused by loss-of-function mutation(s) in the gene encoding tissue nonspecific alkaline phosphatase (TNSALP). Poor skeletal mineralisation, muscle weakness, pain, and accompanying complications characteristic of HPP result in impaired physical function, decreasing ability to perform daily activities, and quality of life. Improvement in physical function is a treatment target, yet established physical activity measures have not been validated in patients with HPP. The 6-Minute Walk Test (6MWT) is an accepted measure of physical activity reflective of daily functioning for children with other chronic diseases. **Objective/Hypotheses:** Determine concurrent validity and minimal clinically important difference (MCID) for the 6MWT for patients with HPP. **Methods:** Data were from a Phase II trial of asfotase alfa, a replacement TNSALP, for children with HPP (ENB-006-09/ENB-008-10). MCID was estimated as per McDonald et al. 2013 using baseline/screening data, and standard error of measurement (SEM) and one-third standard deviation (1/3SD) distribution-based approaches. Clinical relevance was assessed via Pearson correlations between 6MWT and measures of skeletal disease (Radiographic Global Impression of Change [RGI-C] scale, Rickets Severity Scale [RSS]), and activities of daily living (parent-reported Childhood Health Assessment Questionnaire [CHAQ] Disability Index, Pediatric Outcomes Data Collection Instrument [PODCI]). **Results:** MCID for patients with HPP was estimated at 20.2 meters (SEM) and 30.2 meters (1/3SD). Correlation analysis (127 datapoints) indicated significant ($P<0.001$), moderate-to-strong linear relationships between distance walked (percent predicted for age, gender, height) and RSS ($r=-0.73$), CHAQ Disability Index ($r=-0.57$), and PODCI subscales, including Global Function ($r=0.76$), Transfer/Basic Mobility ($r=0.69$), and Sports/Physical Functioning ($r=0.78$). Changes in 6MWT and RGI-C scores demonstrated weaker correlation ($r=0.32$; 68 datapoints; $P<0.01$). **Conclusions:** The 6MWT is a valid, clinically relevant measure of disability and treatment outcomes for patients with HPP. A change

of 20–30 meters represents a clinically meaningful difference in functional abilities in this population.

FC2.6

Effect of KRN23, a Fully Human Anti-FGF23 Monoclonal Antibody, on Rickets in Children with X-linked Hypophosphatemia (XLH): 40-week Interim Results from a Randomized, Open-label Phase 2 Study

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Background: In XLH, high circulating FGF23 causes hypophosphatemia, rickets, and short stature. **Objective and hypotheses:** To evaluate KRN23 effects on serum phosphate (Pi) level and rickets severity in XLH children in a Phase 2 study. **Method:** 52 XLH children (ages 5–12 years, ≤Tanner 2) received KRN23 subcutaneously biweekly (Q2W) or monthly (Q4W). Serum Pi was measured at 2-week intervals. KRN23 dose was titrated (maximum 2 mg/kg) targeting age-appropriate serum Pi concentrations. Rickets severity was assessed by the Thacher Rickets Severity Score (RSS) and Radiographic Global Impression of Change (RGI-C; −3=worsening; +3=complete healing). **Results:** The first 36 subjects had a mean 6.6 years of standard-of-care treatment before washout. KRN23 increased serum Pi from baseline in all subjects to near normal levels (mean increase 0.30 mmol/l at 38 weeks; $P<0.001$) and was more stable with Q2W dosing; hyperphosphatemia did not occur. KRN23 significantly improved RSS with greater improvements seen with Q2W dosing (44% reduction; $P=0.0126$) and particularly in higher-severity subjects (baseline RSS ≥1.5) (59% reduction; $P<0.0001$). Q2W dosing improved RGI-C by +1.6 ($P<0.0001$) with higher-severity subjects showing substantial healing (+2.0; $P<0.0001$). Most treatment-related adverse events (AE) were mild; transient injection site reactions occurred most frequently (39%). One child experienced a serious AE (fever/muscle pain) that improved and the child continues in the trial. No clinically meaningful changes occurred in serum/urine calcium, serum iPTH, or renal ultrasound. **Conclusion:** KRN23 improved phosphorus homeostasis and rickets in children with XLH.

FC3.1

The MAPK Effector BRAF is Essential for the Integrity of Hypothalamic-Pituitary Development and Deregulation of this Pathway Causes Congenital Hypopituitarism

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Background: BRAF is a component of the *RAS/MAPK* signalling pathway; germline mutations in components of this pathway are associated with congenital abnormalities such as Cardio-Facio-Cutaneous (CFC), Noonan and Costello Syndromes. These syndromes, known as RASopathies, are characterised by variably penetrant central nervous system, cardiac and facial abnormalities. Importantly, short stature and delayed puberty have been associated with these syndromes, as have features of septo-optic dysplasia (SOD). Although a BRAF mutation, p.V600E, has been associated with papillary craniopharyngiomas, a direct causative role for this *MAPK* effector in hypothalamo-pituitary (HP) axis development has not been reported. **Objective and hypotheses:** We hypothesised that *BRAF* is essential for the integrity of HP-axis development and that *BRAF* mutations are causative of congenital hypopituitarism. We aimed to understand the direct role of MAPK pathways in HP-axis development. **Methods:** We expressed mutated $BRAF^{V600E}$ in a tissue-specific manner in the pituitary and hypothalamus in mice. By genetically targeting these tissues, we can identify the direct consequence of MAPK over-activation in HP-axis development. Additionally, BRAF was sequenced in patients with clinical features of CFC

Table 1. (for abstract FC2.6)

		All Patients			Patients with Baseline RSS ≥1.5	
		Baseline	Wk 40		Baseline	Wk 40
Mean Total RSS	All (N=36)	1.4	1.0*	All (N=18)	2.3	1.2*
	Q2W (N=18)	1.5	0.9*	Q2W (N=9)	2.4	1.0*
	Q4W (N=18)	1.3	1.1	Q4W (N=9)	2.2	1.4*
Mean RGI-C	All (N=36)		+1.4*	All (N=18)		+1.9*
	Q2W (N=18)		+1.6*	Q2W (N=9)		+2.0*
	Q4W (N=18)		+1.2*	Q4W (N=9)		+1.7*

*P<0.05, comparing Wk 40 to baseline.

and congenital hypopituitarism/SOD. **Results:** Tissue specific transgene activation of $BRAF^{V600E/+}$ allele in murine HP-axis resulted in severe pituitary hyperplasia and failure of terminally differentiated cell-types leading to dwarfism. This phenotype indicates for the first time a direct and critical role for BRAF in HP-axis development leading to congenital hypopituitarism, which resembles the human phenotypes observed in association with *BRAF* mutations. Four genetic variants in BRAF were identified in the patients. **Conclusion:** Our data, together with the functional characterisation of 4 novel genetic variants identified in unrelated children with CFC/congenital hypopituitarism/SOD, reveal a previously unreported role of BRAF in pituitary development leading to endocrine deficits. Our data link mutations in the MAPK pathway present in CFC and other RASopathies with HP-axis developmental abnormalities, leading to endocrinopathies.

FC3.2

Spectrum of LHX4 Mutations in a Cohort of 510 Patients with Hypopituitarism

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Background: Mutations in the gene encoding LHX4, a homeodomain-containing factor with two LIM domains, are responsible for dominant hypopituitarisms with incomplete penetrance and variable expressivity. To date, only 14 unambiguous LHX4 mutations have been reported. Among those cases, 12 had an absent or ectopic posterior pituitary (EPP) and/or an abnormal sella turcica. **Objective and hypotheses:** To i) assess the contribution of LHX4 in combined pituitary hormone deficits, and ii) assess the functional consequences of the identified variants and the role of LHX4 LIM domains. **Method:** We screened a group of 510 independent patients presenting with various pituitary hormone deficits associated with an EPP and/or sella turcica anomalies. The functional consequences of the variants identified and LIM1- or LIM2-defective variants were assessed by luciferase assay, immunocytofluorescence and co-immunoprecipitation studies. **Results:** LHX4 heterozygous variations were identified: 4 truncating mutations [p.(Tyr131*), p.(Arg48Thrfs*104), c.607-1G>C, c.606+1G>T], 3 LIM1 missense variants [p.Lys40Asn, p.Ala65Val, p.Arg71Lys] and 3 missense variations located in the homeodomain area [p.Thr163Pro, p.Arg221Gln, p.Arg235Gln]. Truncating mutations (p.(Tyr131*) and p.(Arg48Thrfs*104)) and the homeodomain missense variant p.Thr163Pro were unable to transactivate POU1F1, GH and PRL proximal promoters. Putative truncated proteins displayed a cytoplasmic localisation; however the corresponding transcripts are likely to be subjected to mRNA decay. All missense variants were found to be expressed in the nucleus. Interaction studies between LHX4 and different protein partners did not unveil any loss of interaction for the missense variants located in the LIM1 domain. Deletion of the LIM1 domain altered LHX4 transactivation capacity, whereas a LIM2-domain deletion abolished LHX4 interaction with ISL2 and LDB1. **Conclusion:** This study, performed in the largest cohort of patients so far screened for LHX4 mutations, shows that this gene is responsible for at most 1% (5/510 independent probands) of hypopituitarisms. This work also highlights the respective roles of LIM1 and LIM2 domains.

FC3.3

Contribution of GLI2 Mutations to Pituitary Deficits and Delineation of the Associated Phenotypic Spectrum

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Background: GLI2 is a zinc-finger transcription factor of the SHH signaling pathway, expressed during ventral forebrain and pituitary development. *GLI2* mutations account for microforms of dominant holoprosencephaly. So far, only 15 unambiguous mutations were found in hypopituitarism –essentially combined pituitary hormone deficiency (CPHD)– frequently associated with holoprosencephaly-like malformations and/or polydactyly.

Objective and hypotheses: To i) assess the prevalence of *GLI2* mutations in patients with CPHD, isolated GH deficiency (IGHD) or isolated diabetes insipidus, associated with a personal or family history of midline defects and/or polydactyly/syndactyly, ii) provide a most complete description of *GLI2*-associated phenotypes. **Method:** Sequencing of *GLI2* coding exons in 206 independent probands. **Results:** Twenty rare heterozygous variations (allele frequency <0.05 in ExAC) were identified in 23 probands. Nine are non-ambiguously deleterious: 3 nonsense mutations [p.(Arg264*), p.(Tyr893*) and p.(Gln1145*)], 5 frameshifts [p.(Asp129Glyfs*159), p.(Gly198Argfs*153), p.(Leu788-Argfs*16), p.(His959Profs*72) and p.(*1587Tyrext*46)] and 1 missense variation in the first zinc finger (p.Tyr435Cys). Five missense variations [p.Pro63Leu, p.Arg473His, p.Ser831del, p.Ser941Arg and p.Arg1382His], located in functional domains, are probably deleterious (charge/steric change and involvement of residues invariant throughout evolution). Six other missense variations [p.Ala117Thr, p.Gly619Ser, p.Arg720His, p.Ala1077Val, p.Pro1228Leu, p.Asp1435Glu] would require functional studies. The 14 patients with a deleterious/probably deleterious mutation had IGHD ($n=8$) or CPHD ($n=6$). The extra-pituitary defects were: bilateral cleft lip/palate ($n=3$), unique central median incisor ($n=2$), choanal atresia/hypoplasia ($n=3$), corpus callosum anomaly ($n=2$), polydactyly ($n=2$), 2–3 foot syndactyly ($n=3$) and septum pellucidum agenesis ($n=1$). Among the seven relatives carrying a deleterious mutation, one had isolated polydactyly, and six were asymptomatic, thereby underlining the difficult aspects of genetic counseling. **Conclusion:** In this large series of patients with hypopituitarism and a personal or family history of midline defects and/or digit anomalies, *GLI2* mutations, which are associated with a wide range of extra-pituitary defects, are responsible for at least 7% (14/206) of independent cases.

FC3.4

A Novel Mutation in Eukaryotic Translation Initiation Factor 2 Subunit 3 (*EIF2S3*) is Associated with X-Linked Hypopituitarism and Glucose Dysregulation

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Background: A mutation in *EIF2S3* (NM_001415; Xp22.11) was previously associated with microcephaly and developmental delay in a single pedigree. *EIF2S3* encodes the eukaryotic translation initiation factor 2 subunit 3 (eIF2γ), the largest of three EIF2 subunits. EIF2 initiates protein synthesis by forming a ternary complex with GTP and initiator methionyl-tRNA which then binds to the 40S ribosomal subunit, enabling scanning of mRNA from the 5′ end to identify the AUG start codon. Mutations in *EIF2S3* have not previously been associated with hypopituitarism. **Objective and hypotheses:** To identify the molecular basis for X-linked hypopituitarism by performing X chromosome exome sequencing, expression studies and functional analysis of novel variants. **Patients:** Three males (twin brothers and their maternal cousin) presented with hyperinsulinaemic hypoglycaemia, GH and TSH deficiencies, and anterior pituitary hypoplasia. All three males were treated with rhGH, thyroxine and diazoxide. The latter was stopped in the twins at 7 years, one of whom later manifested glucose dysregulation [2 hr blood glucose (BG) 8.4 mmol/L, insulin 22 mU/L on OGTT; late hypoglycaemia with BG 2.7 mmol/L, insulin 5.5 mU/L 5hrs post-glucose load]. His brother demonstrated late hypoglycaemia (BG 2.7 mmol/L, insulin 4.8 mU/L). The mothers (sisters) had resolved secondary amenorrhoea. Candidate gene screening for hypopituitarism and hyperinsulinism was negative. **Methods and results:** We identified a novel hemizygous *EIF2S3* variant (c.1294C$>$T, p.P432S) in the three males (mothers heterozygous; absent in the ExAc control database) . *EIF2S3* was strongly expressed in the human embryonic ventral diencephalon, Rathke's pouch, the anterior/posterior pituitary, and pancreatic islets of Langerhan. We have generated a human *EIF2S3*-knockout pancreatic (1.1B4) cell line, using lentiviral shRNA cassettes. Preliminary data show higher caspase activity with increased apoptosis in *EIF2S3*-knockout cells. **Conclusion:** We report a novel *EIF2S3* mutation associated with X-linked hypopituitarism and glucose dysregulation. Preliminary data suggest critical roles for *EIF2S3* in both human pituitary development and insulin secretion.

FC3.5

Septo-optic Dysplasia Spectrum: Pubertal Features of a Large Cohort of Children and Adolescents with Septo-optic Dysplasia, Congenital Hypopituitarism and Optic Nerve Hypoplasia from a Single Centre

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Background: Children with septo-optic dysplasia (SOD) and related disorders can present with either hypogonadotropic hypogonadism or precocious puberty. This phenotypic variability remains unexplained. **Objective and hypotheses:** To compare pubertal characteristics of SOD with isolated congenital hypopituitarism (CPHD) and optic nerve hypoplasia (ONH). **Method:** Retrospective longitudinal data collection from 259 patients with: SOD ($n=171$), CPHD ($n=53$) or ONH ($n=35$). **Results:** In males, under-virilized external genitalia were observed at birth in 70% CPHD, 43% SOD, and 14% ONH ($P=0.005$). Of males with under-virilized external genitalia, 39% SOD and 100% CPHD were diagnosed with probable GnRH deficiency ($P=0.002$). Compared with SOD, CPHD had lower testosterone responses to 3 days ($P=0.015$) and 3 weeks ($P=0.056$) of HCG, and lower LH ($P<0.0001$) and FSH ($P<0.0001$) concentrations on GnRH testing. Spontaneous onset of puberty was observed in 93% ONH ($n=14$), 82% SOD ($n=66$) and 45% CPHD ($n=15$) ($P<0.001$) and occurred at similar ages in the three groups. A likely diagnosis of GnRH deficiency was made in 28% ($n=72$) SOD and 75% ($n=24$) CPHD ($P=0.0001$). Sex steroid treatment was required in 8% SOD ($n=95$) and 32% CPHD ($n=28$) ($P<0.002$) to start

(7 SOD and 7 CPHD) or progress (1 SOD, 2 CPHD) through puberty. 12% of SOD ($n=98$) and 12% of ONH ($n=25$) needed treatment for cessation of early/precocious puberty. Premature thelarche occurred in 2 ONH and 5 SOD, premature menarche in 2 SOD and premature adrenarche in 4 SOD and 3 ONH. **Conclusion:** Our data demonstrate, particularly in males, a more frequent and severe impairment of GnRH function in CPHD as compared to SOD/ONH in whom GnRH function is often retained with early/precocious puberty and adrenarche. These data suggest that distinct genetic and/or environmental insults at different stages of brain development may dictate the variability of phenotype observed.

FC3.6

Pegvisomant is More Effective in Stunting Growth than Somatostatin Analogs in Childhood Acromegaly/Gigantism

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Background: We describe our experience in medical therapy for invasive somatotroph pituitary macroadenomas in 8 children or adolescents presenting with acromegaly/gigantism, in terms of growth and IGF-I levels control. **Patients:** Eight children, aged 5 to 17 years (median 12.4 years), presented with growth hormone (GH) hypersecretion related to somatotroph pituitary macroadenomas with cavernous sinus invasion in 6/8. Genetic testing revealed AIP mutation in only 3 out of 8. **Results:** Two children with hyperprolactinemia received cabergoline in addition to other therapies. In 4/8, transphenoidal surgery was performed as first-line treatment but was incomplete in all cases. Three of them were then treated with somatostatin analogs (SA) that were ineffective on growth and unable to normalize IGF-I levels. So, 2 children underwent pituitary radiation therapy and in the 3rd the adjunction of pegvisomant therapy to SA allowed normalization of IGF-I levels. The 4th child, aged 8 years, was treated with pegvisomant alone after surgery: this quickly led to a dramatic reduction in IGF-I levels (from 558 to 115 ng/ml) and growth arrest (<2 cm/year). She then entered puberty spontaneously and, since 2 years, titration of pegvisomant allows to perfectly control her growth velocity. Four children were treated medically as first-line therapy, three with SA and one with SA and pegvisomant. SA alone were ineffective in normalizing IGF-I levels and growth velocity in all three children. Surgical tumor debulking followed by re-initiation of SA allowed normalization of GH secretion and growth arrest in one of them. The two others received pegvisomant in combination with SA that allowed normalization of IGF-I levels and growth arrest only in one. In the other, growth arrest was only achieved after surgical debulking of the tumor. The patient who received a first-line combination of SA and pegvisomant, experienced a rapid normalization of IGF-I levels and tumor size decreased. **Conclusion:** In childhood acromegaly, pegvisomant alone or in combination with SA appears to be more effective in stunting growth than SA alone. In case of invasive macroadenoma in children, in the absence of visual impairment, surgical debulking can be delayed and a combination therapy with pegvisomant and SA may be a good option as first-line therapy.

FC4.1

Contribution of Rare CNVs and Point Mutations to the Etiology of Severe Early-onset Obesity

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Background: Studies aimed at elucidating the pathophysiology of obesity consistently describe it as a highly heterogeneous disorder at both clinical and molecular level. Despite rare monogenic forms and several regions of susceptibility have been defined, the genetic causes underlying the disease remain largely unknown. **Objective and hypotheses:** We aimed to identify novel genetic abnormalities in a cohort of Spanish children with severe non-syndromic early-onset obesity (EOO). **Method:** We obtained molecular karyotypes of 157 children with EOO. Large and rare CNVs were validated and segregated in the family. Results were replicated by MLPA in 323 EOO children and 480 controls. Additionally, 26 candidate genes (CNV-related or previously associated with EOO) were studied in both cohorts (480 subjects in each) by Next Generation Sequencing (NGS) using a pooled DNA strategy. **Results:** A higher burden of duplication-type CNVs was detected in EOO patients versus controls (OR $=1.85$, P-value $=0.008$). Likely pathogenic CNVs included duplications of glutamate receptors (*GRIK1*, *GRM7*), the X-linked gastrin-releasing peptide receptor (*GRPR*) and the *NPY* genes. By NGS focusing the analysis on rare variants, we identified a missense mutation in *NPY,* a nonsense mutation in *GRIK1,* and 5 missense mutations in *GRPR* in EOO cases, but no mutations in controls. In addition, a significantly higher burden of point mutations was also identified in candidate genes, remarkably *MC4R, SIM1, FTO, BDNF NEGR1, PPARG* and *MC3R*; we identified 30 rare variants in patients and 5 in controls ($P=0.0001$). The difference in the incidence of probable pathogenic variants (15 in patients vs 1 in controls) was also significant ($P=0.0005$). **Conclusion:** Genetic variants highly contributing to the phenotype were identified in up to 12% of patients. Our data reinforce the role of the proopiomelanocortin pathway in the pathophysiology of EOO and bring to light genes that may carry highly penetrant obesogenic allele variants, like *PPARG*, *BDNF, NPY or GRPR*.

FC4.2

Immune-Fat-Bone Axis in Obese Children: The Role of LIGHT

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Background: Obesity during childhood has been demonstrated to exert profound and lasting effects on bone strength and fracture risk. Furthermore, obesity is characterized by chronic inflammation and oxidative stress, with an increase in the mediators of innate immunity. It has been found that skeletal homeostasis is influenced by immune cells. LIGHT (lymphotoxin-like inducible protein that competes with glycoprotein D for herpesvirus entry on T cells) is emerging among cytokines produced by immune cells, also involved in inflammation and bone disease. It is a member of the tumor necrosis factor (TNF) family, primarily expressed on immune cells, which has a role in adipogenesis and osteoclastogenesis. **Objective and hypotheses:** We aimed to analyze whether LIGHT has a role in the bone fragility associated to childhood obesity. **Method:** LIGHT levels has been measured in the sera from 10 obese children (aged 10-8 $\pm$ 2.56 yrs) and 10 sex and age matched controls. Its expression has been evaluated by flow cytometry in circulating cells from patients and controls. PBMCs were cultured in presence/absence of neutralizing anti-LIGHT antibody. Mature multinucleated osteoclasts (OCs) were identified as TRAP+ cells. Bone status was assessed by QUS through BTT-Z-score and Ad-Sos-Z-score evaluation. **Results:** Higher serum levels of LIGHT were measured in obese children compared to controls (520 $\pm$ 265 ng/ml vs 240 $\pm$ 156, $P < 0.01$ ng/ml). In the same patients, elevated expression of LIGHT on monocytes was found. In culture spontaneously OC formation occurred, without the addition of exogenous growth factors. Interestingly, this spontaneous OC formation is inhibited *in vitro* by anti-LIGHT neutralizing antibody. Additionally, obese children had significantly reduced QUS parameters compared to the controls ($P < 0.01$). Interestingly, we found that BTT-Z-score inversely correlated with LIGHT serum levels ($r = -0.750$; $P = 0.03$). **Conclusion:** LIGHT could represent a key molecule linking inflammation-fat-bone in obese children.

FC4.3

Expression of Type 1 Insulin-like Growth Factor Receptor (IGF-1R) in Liver of Obese Children with Non-alcoholic Fatty Liver Disease (NAFLD)

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Background: Type 1 insulin-like growth factor receptor (IGF-1R) is the product of a single-copy gene located on chromosome 15 and is ubiquitously expressed in humans. Increased hepatic IGF-1R gene expression is found in hepatocellular carcinoma and in chronic hepatitis C, making parenchymal and non-parenchymal cells more susceptible to the mitogenic effects of IGF-1. **Objective and hypotheses:** As we have previously demonstrated that IGF-1 and IGF-2 circulating levels are rearranged in relation with the severity of liver damage in obese children with NAFLD, our aim was to investigate the hepatic expression of IGF-1R in the same group of patients. **Method:** In this preliminary study, immunohistochemistry and immunofluorescence were applied for analysing the expression of IGF-1R in 12 children with NAFLD. Three liver samples from healthy subjects were used as reference for tissue expression of IGF-1R. Expression data were correlated with severity of disease and with the expression of various liver cell markers. **Results:** Tissue expression of IGF-1R in liver samples from children with NAFLD is highly variable and expressed in both parenchymal and non-parenchymal cells. IGF-1R expression is strongly correlated with the severity of inflammation and fibrosis, decreasing in parallel to NAFLD activity score and increasing in patients with moderate to severe degree of fibrosis. Finally, the IGF-1R expression correlated with the number of hepatic stellate cells. **Conclusion:** Our preliminary data suggest that IGF-1R expression in liver is strongly related with the severity of fibrosis, suggesting, for the first time, that IGF-1R may play a role in the regulation of hepatic regeneration induced by liver fibrosis in obese children with NAFLD.

FC4.4

The Role of Apoptotic Marker Apo-1/Fas in the Metabolism and Endothelial Function of Healthy Children

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Background: Apoptosis is a programmed sequence of events towards cell death. Blood vessels employ apoptosis for remodeling during development and to maintain homeostasis during adulthood. The atherosclerotic process begins in early childhood and is correlated with obesity and metabolic disorders. **Objective and hypotheses:** To investigate the correlation of apoptotic marker Apo-1/Fas with children's biochemical and anthropometric characteristics. **Method:** About 165 students participated in our research, 6–18 years old, living in Peloponnese, Greece. Anthropometric, biochemical and immune-assays analyses for endothelial markers (CRP, I-CAM, Endothelin-1) and apoptotic markers (Apo-1/Fas) were performed.

Results: In group A ($\leq$9 years old), 51.8% of children had BMI%$>$85, 70.6% had WC%$>$85 and 23.5% were predisposed for Metabolic Syndrome(MetSyn). In group B ($>$9 years old), 35.4% of children had BMI%$>$85, 72.2% had WC%$>$85 and 31.6% were predisposed for MetSyn. Apo-1/Fas was negatively correlated with age ($P=0.008$) and predisposition for MetSyn ($P=0.019$). In group A, Apo-1/Fas was negatively correlated with fasting glucose ($P=0.015$), γGT($P=0.010$), cholesterol/LDL ratio ($P=0.004$), triglycerides/HDL ratio ($P=0.046$) and positively correlated with HDL ($P=0.047$). In group B, Apo-1/Fas was negatively correlated with fasting glucose ($P=0.012$), iron ($P=0.040$), cholesterol/LDL ratio ($P=0.003$) and triglycerides/HDL ratio ($P=0.038$) but positively correlated with CRP ($P<0.001$), I-CAM ($P=0.001$) and Endothelin-1 ($P=0.037$). ROC analysis showed that high values of age, BMI%, waist and blood pressure, indicate MetSyn predisposition, while decreased APO-1/Fas values indicate no predisposition for MetSyn. Multiple logistic regression showed that systolic blood pressure and Apo-1/Fas are independent prognostic factors for MetSyn. **Conclusion:** The role of Fas-mediated apoptosis in atherogenesis is complex and controversial. In adults, Apo-1/Fas is associated with adiposity and lipid metabolism. In our research, in young children Apo-1/Fas seems to exert a protective role maybe through down-regulating inflammation and the progression of artherosclerosis. On the other hand, in older children Apo-1/Fas expression is positively related to endothelial dysfunction markers. More studies are necessary to clarify the role of Apo-1/Fas in metabolic disorders in childhood.

FC4.5

Novel Association between the Non-synonymous A803G Polymorphism of the *N-acetyltransferase 2* Gene and Impaired Glucose Homeostasis in Obese Children and Adolescents

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Background: The N-acetyltransferase 2 (*NAT2*) A803G polymorphism leading to substitution of lysine to arginine at residue 268 and codifying for a cytosolic enzyme catalysing acetyl-CoA-dependent N- and O-acetylation reactions, has been associated with decreased insulin sensitivity in a large adult population with the A allele associated with insulin resistance (IR)-related traits. **Objective and hypotheses:** We screened for this polymorphism, for the first time in literature, a population of obese children and adolescents and evaluated its association with anthropometrical and metabolic parameters. **Method:** Seven hundred and forty-eight obese children and adolescents were enrolled. Anthropometrical and laboratory data were collected. IR was assessed using the homeostasis model assessment. All the patients underwent to an oral glucose tolerance test. Glycaemia at 60 to evaluate a possible exaggerated plasma glucose excursion at 1 h (1HPG) and at 120 minutes to evaluate a possible impaired glucose tolerance (IGT) were considered. Patients were genotyped for the *NAT2* A803G polymorphism. **Results:** The prevalence of both IGT and elevated-1HPG was higher in children carrying the A803 allele ($P=0.02$ and $P=0.03$, respectively). No differences among the *NAT2* A803G genotypes for the other parameters were shown. Children homozygous for the A allele presented an odds ratio (OR), to show IGT of 4.9 (95% C.I. 1.3–18.5, $P=0.01$). Children both homozygous and heterozygous for the A allele had an higher risk to show elevated-1HPG (OR of 2.7 (95% C.I. 1.43–1.6, $P=0.005$) and OR=2.3 (95% C.I. 1.2–4.1, $P=0.005$ respectively)) compared to patients homozygous for the *NAT2* 803G allele. **Conclusion:** *NAT2* A803 allele seems to play a role in worsening the destiny of obese children carrying it, predisposing them to elevated-1HPG and IGT and then to a possible future type 2 diabetes mellitus.

FC4.6

The Rise and Fall of the Swedish Childhood Obesity Epidemic – The BEST Cohort

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Background: Childhood obesity increases the risk for adult obesity and cardio metabolic disease. **Objective and hypotheses:** The aim with the present study was to investigate longitudinal changes of childhood body mass index (BMI), overweight, and obesity in boys born 1946 until present time, using the population-based BMI Epidemiology STudy (BEST) cohort in Gothenburg, Sweden. **Method:** We collected detailed growth data (height and weight) from archived school health records for boys born every five years between 1946 and 2006 ($n=1{,}584$ for reference birth cohort 1946, $n=425$ for each birth cohort 1951–2006, total $n=6{,}684$). BMI at eight years of age was calculated for all included individuals. **Results:** Childhood BMI at eight years of age increased 0.18 kg/m^2 (95% confidence interval 0.16; 0.20) per decade increase in birth year during 1946–2006. The increase was statistically significant from birth year 1971, peaked 1991, and after birth year 1991, an apparent reduction was seen. Next, we aimed to thoroughly explore the trend after birth year 1991 and therefore expanded birth cohorts 1991 ($n=1{,}566$), 2001 ($n=6{,}478$), and 2006 ($n=6{,}515$). Importantly, a significant decrease in mean BMI ($P<0.01$), overweight prevalence ($P<0.01$), and obesity prevalence ($P<0.05$) was seen after 1991. In boys categorized to Sweden as country of birth, a substantial reduction in overweight (-28.6%, $P<0.001$) and obesity (-44.3%, $P<0.001$) prevalence was observed between birth year 1991 and birth year 2006. **Conclusion:** Using the unique population-based BEST cohort, we provide clear evidence of a childhood obesity epidemic that increased statistically significant from birth year 1971, peaked birth year 1991, and declined afterwards. This is the first long-term study describing both the rise and the recent fall of childhood obesity. As childhood obesity is strongly associated with subsequent adult obesity, we propose that a similar reduction in adult obesity prevalence might be expected during the coming decades.

FC5.1

The Anti-diabetic Drug, Metformin, Suppresses Adipogenesis through both AMP-activated Protein Kinase (AMPK)-dependent and AMPK-independent Mechanisms

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Background and aim: Metformin is widely used in Type 2 diabetes, with increasing reports of a potential bone protective role. We investigated the role of AMPK in mediating the effects of metformin on mesenchymal stem cell (MSC) differentiation to either osteoblasts or adipocytes. **Methods:** Confluent mouse MSCs (C3H10T1/2), wild type (WT) and AMPK knockout (KO) mouse embryo fibroblasts (MEFs) were treated with metformin(500 μM), AMPK-activator A769662(100 μM), AMPK-inhibitor Compound C(1 μM/10 μM) and p70S6K-inhibitor rapamycin(10 μM), in both control and adipogenic-inducing environment (pioglitazone;10 μM). Nuclear extracts were prepared and separated by SDS-PAGE and immunoblotted with primary antibodies to the adipogenic markers; peroxisome proliferator-activated receptor gamma (PPAR?) and CCAAT-enhancer binding protein (C/EBPβ), the osteogenic marker; Runt-related transcription factor 2 (Runx2), the AMPK activity marker; phosphorylated-ACC (P-ACC(Ser79)) and the marker of mTOR signalling; phosphorylated-p70s6k (P-p70s6k(Thr389)). PPARγ and Runx2 activities were determined using Luciferase reporter assays and adipogenesis was quantified histochemically with Oil Red O. **Results:** MSCs treated with pioglitazone demonstrated a marked adipogenic phenotype, whilst both metformin and A769662 impaired adipogenesis. Pioglitazone induced increase in PPARγ expression ($P<0.05$), whilst metformin ($P<0.05$) and A796662 ($P<0.05$) suppressed this to basal levels. Runx2 activity, but not protein levels, was increased by metformin ($P<0.001$) and A769662 ($P<0.001$). As expected, A769662 promoted phosphorylation of ACC, but not so with metformin. Instead, metformin suppressed the phosphorylation of p70s6k ($P<0.01$), as did A769662 ($P<0.001$) and rapamycin ($P<0.001$). Luciferase assays confirmed the reciprocal action of metformin on adipogenesis and osteogenesis, namely suppression of PPARγ activity ($P<0.001$) and induction of Runx2 activity ($P<0.001$). Pioglitazone-treated WT MEFs, but not AMPK KO-MEFs, exhibited adipogenesis suggesting a basal AMPK requirement for adipogenesis. Both metformin and A769662 (both $P<0.05$) significantly induced phosphorylation of ACC, indicating an AMPK-dependent mechanism in MEFs. **Conclusions:** Metformin suppresses adipogenesis of C3H10T1/2 cells through the reciprocal regulation of PPARγ and Runx2, involving a novel AMPK-independent mechanism of action on MSC differentiation, through suppression of p70S6K. However, metformin can inhibit adipogenesis through AMPK-dependent or -independent mechanisms, depending on the cellular context.

FC5.2

Diabetes and Insulin Injection Modalities: Effects on Hepatic Expression and Activity of 11β-Hydroxysteroid Dehydrogenase Type 1 in Juvenile Diabetic Rats

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Background and hypotheses: Recent results showing elevated tetrahydrocortisol/tetrahydrocorticosterone ratio (THFs/THE) in morning urines of diabetic children compared to controls suggest an increased nocturnal activity of 11 β-hydroxysteroid dehydrogenase type 1 (11β-HSD1). We made the hypothesis that a reduced inhibition of hepatic 11β-HSD1 activity by exogenous insulin, due to its subcutaneous (SC) administration and absence of first hepatic passage, could explain these observations. **Objective:** Our main objective was to compare 11β-HSD1 activity and expression in the liver of young diabetic rats, treated either by subcutaneous (SC) or intraperitoneal (IP) insulin. Our hypothesis was that hepatic 11β-HSD1 is less inhibited by SC insulin than by IP insulin. **Method:** We formed 4 groups of juvenile Wistar rats: 12 controls, 36 streptozotocin-induced diabetic rats among them 12 were not treated (NT), 12 were treated with SC insulin and 12 with IP insulin. We measured 11β-HSD1 expression and activity in the liver at 7 weeks of life. **Results:** Hepatic gene expression and activity of 11β-HSD1 were increased in the untreated diabetic group compared to controls. Although diabetes was controlled equally whatever the route of insulin administration, 11β-HSD1 gene expression and activity were only decreased in the IP group. **Conclusion:** Ours results support that hepatic first pass is needed for 11β-HSD1 hepatic inhibition.

FC5.3

Glibentek, a New Suspension of Glibenclamide for Patients with Neonatal Diabetes, is as Effective and more Convenient than Crushed Tablets

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Background: Glibenclamide has proven to be efficient for patients with neonatal diabetes owing to potassium channel mutations. Anyway its pharmaceutical form is not suitable for young children or infants. The tablets dosage is too high for most infants and must be crushed and diluted before administration. We developed a suspension of glibenclamide (EMA Orphean drug designation january 2016) fitting recommendations of drug administration to allow a precise dosage and designed to be more practical for patients and their families. **Objective and hypotheses:** To determine if a suspension of glibenclamide is more suitable and as efficient as tablets in children with neonatal diabetes. **Method:** Patients where switched from crushed tablets to suspension during 3 months. Acceptability and efficiency were measured (self administrated questionnaires, hedonic scales and HbA1C) and compared to tablets ones. Adverse events were recorded. **Results:** 10 patients (6 boys) with KCNJ11 mutation, median age 2.7 years (0.3–16.2), median duration of glibenclamide therapy 2.3 years (0.01–11.3). Switch from glibenclamide tablets to glibentek didn't affect metabolic control (Median change in HbA1C: −0.35%, −1.3 to 0). Median dosage was 0.25 mg/k/day (0.075–0.77) before the switch and 0.12 mg/kg/day (0.06–0.56) 3 months after. 100% of parents were satisfied with the suspension (vs 50% for tablets). 60% reported administration difficulties with the tablets but none with the suspension. Infants and young children were more satisfied by the suspension than teenagers that could swallow the whole tablet. Safety record was excellent: no severe hypoglycaemia, sporadic abominal pains in one patient, transient rise in hepatic transaminases in another. Parents from infants and young children ($n=5$) preferred keeping the suspension than going back to tablets. **Conclusion:** Glibenclamide suspension is as effective as tablets and more practical for infants and young children with neonatal diabetes. (ClinicalTrial.gov NCT02375828).

FC5.4
Persistent Beneficial Metabolic Effect after Five Years in a Cohort of 28 Subjects with Neonatal Diabetes owing to Potassium Channel Mutation and Transferred from Insulin to Sulfonylureas

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Background: Sulfonylureas (SU) have proven to be effective in patients with monogenic diabetes owing to potassium channel mutation. They allow the discontinuation of insulin and a good metabolic control. Long-term data arguing for a persistent beneficial effect of SU are missing. **Objective and hypotheses:** SU provide a good metabolic control maintained over time in patients with neonatal diabetes. **Method:** From a French cohort of 34 patients (GENEODIA study – French Neonatal Glibenclamide Study Group), we selected patients transferred successfully (no insulin during the 12 months after the switch) for more than five years (before 2010). Data recorded retrospectively: safety, diabetes complication, SU dosage and HbA1C before switch and at last follow-up visit. **Results:** About 28 patients were eligible (18 boys – 24 KCNJ11 mutations – 4 ABCC8 mutations). Complete data before switch were available for 24 patients and after switch for 17 patients. Median time till SU start was 9.32 years (5.8–12.15) and median follow-up time 6.6 years (1.4–11.5 years). Median age at transfer from insulin to SU was 4.9 years (0.23–36.5). Median HbA1C before transfer was 7.4% (5.3–10.3) and 6.1% (5.1–8.1%) at last visit. Median change was −1.4% (−4 to +0.3%), $P<0.001$. Median glibenclamide dosage was 0.16 mg/kg/day (0.025–0.66) at last visit. Safety was good; no episodes of renal or hepatic failure and no development of retinopathy or nephropathy were reported. Insulin was re introduced permanently in 1 patient (3 years after SU transfer) and transiently in another (1 year after transfer and during 4 years). **Conclusion:** While prescribed off label, SU display a beneficial metabolic effect maintained over time with an extremely good safety profile in patients with neonatal diabetes owing to potassium channel mutation.

FC5.5
DPP-4 Inhibitor is an Alternative Effective Treatment in a Common Cause of Anti-GAD Negative "Type 1 Diabetes" - A Founder CISD2 Mutation

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Background: Wolfram syndrome type 2 (WFS2) characterized by childhood GI ulcers/ bleeding, diabetes, and neurodegeneration

with optic atrophy and hearing loss was recently elucidated as caused by CISD2/NAF-1 gene mutation. NAF-1 suppression in cells results in intra-mitochondrial accumulation of iron, increased ROS generation and consequently increased cellular apoptosis. So far only two mutations in four families were reported. **Objective:** Elucidate the clinical and the molecular genetic characteristics of anti-Gad negative "type 1 diabetes" in patients from seven unrelated Palestinian consanguineous families. **Patients and methods:** About 13 patients from seven different families were treated with insulin following juvenile onset diabetes. The finding of negative anti-GAD antibodies together with personal or sibling history of pediatric upper GI bleeding/ulcer lead into further investigation of mild (ignored) visual/acoustic symptoms. Consequently we sequenced the CISD2 gene and offered a therapeutic trial with DPP-4 inhibitor. **Results:** The homozygous IVS1+6G>C, p.E37Q CISD2 gene mutation resulting in skipping of the 2nd out of three exons of the CISD2 gene was identified in all of the cohort patients. Studying eight microsatellite markers flanking the CISD2 gene indicated a founder effect in at least six unrelated families. Restriction enzyme analysis of 200 healthy control alleles showed a surprising high carrier rate of 1/40-2.5%. Given the known protective effect of GLP-1 against ER stress-mediated cell death, using an agent combining Metformin and the DPP-4 inhibitor Sitagliptin enabled successful weaning from insulin while achieving a good glycemic control in our 2 first patients. **Conclusion:** Early manifestation of GI symptoms in anti-GAD negative "type 1 diabetes" should lead to suspect the relatively common diagnosis of WFS2 caused by a founder CISD2 mutation. Insulin may be switched to incretin based oral therapy. Further mechanistic studies with direct therapeutic consequences are underway to enable a definitive and effective therapy for the degenerative pathophysiology in WFS2.

FC5.6

Impact of Continuous Subcutaneous Insulin Infusion versus Multiple Daily Injections on Bone Health in Children and Adolescents with Type 1 Diabetes

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Background: Type 1 diabetes (T1DM) is associated with low bone mineral density (BMD) and bone alterations, probably due to lack of insulin and chronic hyperglycemia. Sclerostin and Dickkopfs-1 (DKK-1) are Wnt signaling inhibitors involved in bone remodelling. **Objective and hypotheses:** To assess serum levels of DKK-1 and sclerostin in T1DM children and adolescents on continuous subcutaneous insulin infusion (CSII) or multiple daily therapy (MDI). We hypothesized the involvement of these Wnt signaling inhibitors in the altered bone remodeling associated to diabetes. **Method:** One hundred T1DM patients (44 males, 11.58±4.58 yr), T1DM duration 4.21±3.06 yr, and 70 sex and age-matched controls were enrolled. Sixty five patients received CSII and thirty-five MDI. Serum DKK1 and sclerostin were measured by ELISA. BMD was measured by Quantitative ultrasonography (QUS). **Results:** The average of BMD Z-scores was within the normal range in patients, but reduced respect to controls. Significant increased serum levels of DKK-1 (3593±1172 vs 2660±664 pg/ml, $P<0.006$) and sclerostin (29.45±12.32 vs 22.53±8.29 $P<0.001$) were found in diabetics respect to controls. In particular, DKK-1 and sclerostin levels were higher in patients on MDI than ones on CSII (3744±1266 vs 2962±986, $P<0.001$; 30.25±13.10 vs 23.63±8.75, $P=0.02$). Glycaemic control was improved in CSII patients compared to MDI ones (glucose 195 vs 141 mg/dL, $P<0.001$; HbA1c% 8.35±0.98 vs 7.66±0.66, $P<0.001$). This improvement was also associated to a significant higher BMI-SDS (0.47±1.03 vs −0.28±0.92, $P<0.002$) and BMD (BTT-Z-score: 0.44±0.85 vs −0.34±1.21, $P<0.02$) in CSII compared to MDI patients. **Conclusion:** Our study highlighted: 1. the high levels of DKK-1 and sclerostin in T1DM children, and their relationship with altered bone remodelling and glycaemic control; 2. the effect of CSII on the improvement of glycaemic control and bone health in T1DM children.

FC6.1

Ghrelin-Reactive Autoantibodies are Elevated in Children with Prader-Willi Syndrome Compared to Unaffected Sibling Controls

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Background: Prader-Willi Syndrome (PWS) is a complex genetic disorder characterised by developmental and growth abnormalities, insatiable appetite, and excessive eating (hyperphagia). Hyperphagia is thought to be driven by supraphysiological levels of the appetite stimulating hormone ghrelin; however, the underlying causes of hyperghrelinaemia in PWS are currently unknown. Recently, ghrelin-reactive autoantibodies (isotype IgG) were identified in non-genetic obesity and were found to reversibly bind circulating ghrelin and, acting as carrier proteins, protect ghrelin from degradation thereby potentiating its orexigenic effects. **Objectives:** This project aimed to measure ghrelin-reactive autoantibodies in children with PWS. We hypothesised that patients possess higher levels of ghrelin-reactive autoantibodies compared to their unaffected sibling controls. We also tested whether the inactive ghrelin isoform, unacylated ghrelin (UAG), outcompetes ghrelin and sequesters autoantibodies *ex vivo*. **Methods:** Blood

samples were taken from patients and controls after an overnight fast and 10, 20, 30, 60 and 120 minutes after a standardised mixed meal. Plasma was extracted and ghrelin-reactive autoantibodies were measured using ELISA. To test specificity of the ELISA and to determine if the autoantibodies bind to UAG, the samples were also pre-absorbed with exogenous ghrelin and UAG (10^{-6} M) prior to being subjected to separate ELISAs. **Results:** We have demonstrated that children with PWS have significantly higher levels of plasma ghrelin-reactive autoantibodies compared to controls after an overnight fast ($P<0.0001$, unpaired t test). Food intake did not affect autoantibody levels in patients or controls. Both ghrelin and UAG pre-absorbed controls showed significant reduction of ghrelin-reactive autoantibody detection in the PWS and control groups ($P<0.001$, unpaired t test), suggesting that the autoantibodies complex with both isoforms. **Conclusions:** Increased levels of ghrelin-reactive autoantibodies in children with PWS may contribute to the hyperghrelinaemia and hyperphagia that characterises PWS. Targeting these autoantibodies may be a future therapeutic avenue for this incurable condition.

FC6.2

Whole Exome Sequencing Identifies *EPHB4* and *Plk3R6* as Causes of Generalized Lymphatic Anomaly

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Background: Generalized lymphatic anomaly (GLA) is a rare congenital disorder characterized by aggressive proliferation of dilated lymphatic vessels. The etiology of GLA is poorly understood. **Objective and hypotheses:** To identify the underlying genetic basis for GLA. **Method:** Exome sequencing (ES) was performed in two families, including a multigenerational family (family-1) with six affected members. RNA-seq was performed on skin biopsies obtained from the lead proband in family-1. To understand the roles of the mutated genes, *EPHB4* and *PIK3R6* in vascular morphogenesis, we generated two zebrafish models of *EPHB4* and *PIK3R6* deficiency, respectively. **Results:** ES analysis followed by Sanger sequencing in family-1 revealed that 6 affected individuals were heterozygous for an *EPHB4* mutation (c.2334+1G>C), a gene previously implicated in a biological pathway related to venous and lymphatic cell fate determination. The mutation was absent in seven unaffected family members. RNA-seq demonstrated that the *EPHB4* splice-altering mutation creates a cryptic splice donor that causes the retention of the intervening 12 bp of the intron. For family-2, ES revealed a homozygous variant, c.1393-7C>T, in *PIK3R6* in the proband with both parents being heterozygous. PIK3R6 is a regulatory subunit of PI3K complex. Zebrafish knockdown of either *EPHB4* or *PIK3R6* resulted in vessel misbranching and deformities in the lymphatic vessel development (Figure 1), indicative of possibly differentiation defects both in blood and lymphatic vessels and mimicking the presentations of the GLA patients. Western blot analysis using zebrafish lysates, which contained vascular abnormality, confirmed that reduced EPHB4 signalling resulted in downstream mTORC1 overactivation. Strikingly, drugs that inhibit mTOR signalling were able to rescue this misbranching phenotype. **Conclusion:** We report two novel genes that converge on the same physiological PI3K/AKT/mTOR pathway that underlies GLA, presenting a potential avenue for therapeutic intervention for GLA patients.

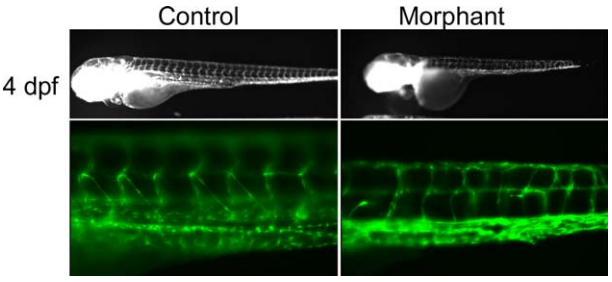

Figure 1 Zebrafish knockdown results in lymphatic developmental defects.

FC6.3

Oxytocin Improves Social and Food-Related Behavior in Young Children with Prader-Willi Syndrome: A Randomized, Double-Blind, Controlled Crossover Trial

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Background: Prader-Willi syndrome (PWS) is known for hyperphagia with impaired satiety and a specific behavioral phenotype with stubbornness, manipulative and controlling behavior and obsessive-compulsive features. PWS is associated with hypothalamic and oxytocinergic dysfunction. In humans without PWS, intranasal oxytocin administration had positive effects on social behavior and weight balance. **Objective and hypotheses:** To evaluate the effects of intranasal oxytocin compared to placebo administration on social behavior and hyperphagia in children with PWS. **Design:** Randomized, double-blind, placebo-controlled, cross-over study in a PWS Reference center. **Method:** Cross-over intervention with intranasal oxytocin and placebo administration, both during 4 weeks, in 25 children with PWS (aged 6 to 14 years). **Results:** In the total group, no significant effects of oxytocin on social behavior or hyperphagia

were found, but in the 17 children younger than 11 years, parents reported significantly less anger ($P=0.001$), sadness ($P=0.005$), conflicts ($P=0.010$) and food-related behavior ($P=0.011$), and improvement of social behavior ($P=0.018$) during oxytocin treatment compared with placebo. In the 8 children older than 11 years, the items happiness ($P=0.039$), anger ($P=0.042$) and sadness ($P=0.042$) were negatively influenced by oxytocin treatment compared to placebo. There were no side effects or adverse events. **Conclusion:** This randomized, double-blind, placebo-controlled study shows that intranasal oxytocin administration has beneficial effects on social behavior and food-related behavior in children with PWS younger than 11 years of age, but not in those older than 11 years of age.

FC6.4

Chromosome 14 Imprinted Region *DLK1/GTL2* Disruption: An Alternative Molecular Etiology for Silver-Russell Syndrome

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Background: Silver-Russell syndrome (SRS) is a clinically and genetically heterogeneous disorder, which remains a clinical diagnosis. The Netchine-Harbison clinical scoring system (NH-CSS), recently adopted by the first international consensus on SRS, defines SRS with at least 4 of the 6 following criteria: born SGA, postnatal growth retardation, relative macrocephaly at birth, prominent forehead, body asymmetry and early feeding difficulties. It is related to 11p15 ICR1 loss of methylation (LOM) in about 50% of patients and to maternal uniparental disomy of chromosome 7 in 10%. The molecular etiology remains unknown in about 40%. **Objective:** To clinically characterise a series of patients with molecular anomalies at the imprinted region 14q32 *DLK1/GTL2* and to establish their NH-CSS. **Method:** We analysed retrospectively a cohort of 24 patients: 16 with 14q32 *DLK1/GTL2* LOM; 7 with maternal uniparental disomy of chromosome 14 and 1 with a paternal deletion. **Results:** 75% of patients presented a NH-SCC $\geq$ 4/6, confirming a clinical diagnosis of SRS. Mean birth length, weight and head circumference were -2.5 SDS, -2.3 SDS and -1.4 SDS respectively. The mean height at 2 years was -2.0 SDS. Prominent forehead was identified in all patients, relative macrocephaly in 54% and body asymmetry in 33%. Early feeding difficulties were noted in 79% and the mean body mass index at 2 years was -1.5 SDS. Additional clinical signs included small hands (74%), small feet (59%), motor delay (62%), speech delay (53%) down turned mouth (75%), low set posteriorly rotated ears (60%). Patients who were at least 8 years old presented early (73%) or precocious (27%) puberty, after a period of BMI increase. Many patients presented an exaggerated adrenarche (high DHEAS levels for age) and 44% presented adrenarche before puberty. **Conclusion:** The majority of patients with 14q32 *DLK1/GTL2* disruption fulfilled the clinical criteria for SRS. The clinical overlap with patients with 11p15 ICR1 LOM remains to be explained in terms of molecular mechanisms.

FC6.5

Pathogenic Copy Number Variants are Frequently Identified in Children with Short Stature of Unknown Etiology

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Background: The etiology of short stature is heterogeneous, often encompassing complex genetic disorders of difficult diagnosis. Analysis of chromosomic copy number variants (CNVs) has been demonstrating the important role of these genomic imbalances in population diversity and human disease. **Objective and hypotheses:** To analyze the frequency and describe novel submicroscopic chromosomal CNVs in a group of patients with short stature of unknown cause. **Method:** We evaluated new 49 patients with short stature associated to other physical or developmental defects (dysmorphic features and/or intellectual disability), but without criteria for the diagnosis of known syndromes. All patients had normal G-banded karyotyping. Array-based comparative genomic hybridization (aCGH) or single nucleotide polymorphism array (aSNP) were performed with DNA from all patients. Detected CNVs were compared with CNV data from healthy control individuals and common copy number polymorphisms were excluded. **Results:** We found 11 CNVs and 2 uniparental disomies in 12/49 patients (24%). According to established criteria for assessment of CNV pathogenicity, at least 7 CNVs in 6 patients were considered pathogenic as well as one maternal uniparental disomy (14%). In 3 patients we found deletions affecting the IGF1R gene (including a child born appropriate for gestational age), 2 patients with deletions consistent with Miller-Dieker lissencephaly syndrome (deletion involving 17p13.3) and a maternal uniparental disomy of chromosome 14 (Temple syndrome). Another patient has an interstitial de novo duplication of 7p14.3p12.1 (31.828.208-53.625.890) involving 125 genes, including IGFBP3 and GRB10. Taking together all previously published results and the present one, the frequency of pathogenic CNVs in children with short stature of unknown etiology is 13% (95% CI:10–16%, $n=498$). **Conclusion:** Pathogenic NVs were common in the selected patients, suggesting that CNVs might contribute as a genetic cause of short stature. Genome-wide copy number analysis should be used as a diagnostic tool for evaluation of short stature.

FC6.6

Social Cognition Skills and Face Perception in Turner Syndrome (TS)

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Background: Patients with TS frequently demonstrate impairments in social cognition difficulties, visual-spatial processing, face and emotion perception. **Objective and hypotheses:** We examined face perception in the context of perceptual visual dysfunctions and social cognition skills in TS. **Method:** 26 young women with TS on estrogen replacement therapy, and 26 control participants. They were tested on various cognitive and psychological tests to assess general visual-spatial perception, face and emotion perception by Benton Facial Recognition Test, social cognition skills through emotion perception and Theory of Mind (ToM; false belief and recognition of faux pas tasks) and IQ (subtests from the WAIS-III). **Results:** The group did not differ on verbal IQ ($P=.78$). Women with TS showed difficulties in performance IQ (Block Design subtest; $P<0.05$), and facial expression processing ($P<0.005$): they were less accurate than controls in perception for fear ($P < .05$) sad ($P=.052$) and disgust expressions, yet they exhibited normal face-specific processes (configural and holistic processing). Their social cognition capacities were largely intact, including auditory perception of surprise, anger and fear, and in False Belief Task (first-, second-order), Question Type (belief, reality, memory and reference) and faux pas stories. Describing scenes of animation, women with TS gave more interaction descriptions ($P<.01$), while control women gave more mentalizing descriptions than TS ($P<.01$). TS' face perception impairments were related to their deficits in visual processing ($P<0.01$) but not to social cognition difficulties. **Conclusion:** Our results do not support the claim that the impairment in face processing, observed in TS, is related to difficulties in social cognition. Their social cognition is compromised to some degree; yet, their relative verbal strength may compensate them wherever they can use their verbal capacities. The results suggest that face perception difficulties in TS stem from visual impairments and may not be specific to faces.

FC7.1

Early Loss of Germ Cells in Testis of Androgen Insensitivity Syndrome Patients

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Background: In Androgen insensitivity syndrome (AIS) is a hereditary disease in which AR mutations in 46,XY patients present with partial (PAIS) or complete (CAIS) defects in virilisation. **Objective and hypotheses:** The aim was to analyze the effect of lack of androgen action in germ cell (GC) health and survival along postnatal development, previous to Sertoli cell (SC) pubertal maturation. **Method:** The histological features and quantity of GC in testes of AIS patients were compared to controls (C). Fourteen gonads of 10 AIS patients (median age 9.55, range 1.8–23 y) were studied. Three prepubetal (PP) and 4 pubertal (PUB) were CAIS and 3 PP were PAIS. Clinical diagnosis was confirmed by hormonal and molecular studies. Testes of C were collected at necropsy or biopsy from 11 PP and 4 PUB patients without endocrine disorders. A written consent was obtained. The Ethical Committee approved the study. GCs were identified using anti MAGE-A4 antibody. **Results:** PP AIS testes showed abundant gonocytes, huge GCs, calcifications, thickened basal membrane and/or fibrous interstitium. In PUB AIS testes signs of dysgenesis as Leydig cell hyperplasia, PP-like seminiferous cords with vacuolated SCs, scarce or none GCs and absence of meiotic spermatocytes were found. PPC and PUBC showed normal testicular parenchyma according to age. MAGE-A4 expression correlates with the presence of GC. AIS testes show a drastically loss of GC after 4.4 y ($r=0.558$, $P=0.038$). As the staining decreases, foci of positive cords were found. No difference between PAIS and CAIS was observed. In contrast, C shows an increase of MAGE-A4 expression as a function of age ($r=0.595$, $P=0.019$) and the staining pattern was homogeneous. **Conclusion:** Disturbed androgen action delayed the GC maturation rate during fetal and early postnatal life. Our results demonstrated that in an androgen deprived niche, GC number rapidly declined during childhood.

FC7.2

Serum Irisin Concentrations in Lean Adolescents with Polycystic Ovary Syndrome

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Background: The myokine irisin, is associated with the metabolic and hormonal dysregulation of polycystic ovary syndrome (PCOS) in adult women. Recent studies have shown that circulating irisin levels increase in adult women with PCOS. **Objective and hypotheses:** The purpose of this study was to determine serum concentrations of irisin in lean adolescents with PCOS and healthy controls and to evaluate correlations with clinical, sonographic and hormonal parameters. **Method:** Lean adolescents aged 13–21 years with PCOS diagnosed according to the Rotterdam criteria, were eligible to enter the study. Exclusion criteria included severe chronic disease, chronic medication or contraceptive use. Anthropometric parameters (weight, height), ovarian volume and serum levels of FSH, LH, estradiol, testosterone, free-testosterone, Δ4-androstenedione, dehydroepiandrosterone sulfate (DHEAS), 17-hydroxyprogesterone and sex hormone-binding globulin (SHBG) were measured and body

mass index (BMI), Ferriman-Gallwey (FG) score and Free Androgen Index (FAI) were calculated for each participant. Serum irisin concentrations were measured by ELISA (AdipoGen; assay range 0.001 μg/ml–5 μg/ml). **Results:** A total of forty adolescents (median age 17 years, range 13.1–21 years; median BMI 20.7 kg/m^2, range 17.7–22.5 kg/m^2); 23 PCOS patients and 17 age- and BMI-matched controls, were enrolled in the study. Compared with the control group, PCOS patients had significantly increased mean ovarian volume, FG Score, LH, estradiol, testosterone, free-testosterone, Δ4-androstenedione, DHEAS, 17-OHProgesterone and FAI while SHBG was significantly decreased. Serum irisin concentrations in PCOS patients (mean ± S.D.; 1.71 ± 1.03 μg/ml) were significantly elevated ($P = 0.007$) when compared to the control group (mean ± S.D.; 1.04 ± 0.35 μg/ml) ($P < 0.001$). Serum irisin was positively correlated (spearman's rho correlation) with height ($r_s = 0.558$, $P < 0.001$) and free-testosterone ($r_s = 0.681$, $P < 0.001$). **Conclusion:** Elevated serum irisin concentrations in lean PCOS adolescents were associated with excess of free-testosterone levels, that represent a core feature of the syndrome.

FC7.3

Estrogen Insensitivity due to a Novel ESR1 Mutation in a Consanguineous Family from Algeria

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Background: Estrogen insensitivity syndrome is a form of functional estrogen deficiency which is caused by a defect in the estrogen receptor type α (ESR1). As a result of the receptor mutation, estrogens cannot be recognized and hence initiate their biological action on pubertal growth, skeletal maturation, and accrual of bone mass. A mutation in the gene encoding ESR1 has been described in only 2 cases (one man and one woman). We now describe the first family with ESR1 mutation to be identified in Algeria in whom both male and female offspring were affected. **Family study:** Our index patient is a 21-year-old female, one of four children (three sisters and a brother) born to parents who are second cousins. She presented aged 16 years with absent breast development, primary amenorrhea and hirsutism. Clinical assessment showed height (Ht) 170 cm (+1.09 SDS), weight (Wt) 70 kg (+1.45 SDS), Tanner stage B1A3P5, acne and severe hirsutism (Ferriman-Gallwey score 22). Bone age was 11 years. Laboratory studies revealed serum oestradiol 9526 pmol/l (*N* 110 – 280 pmol/l) , elevated gonadotrophins - FSH 15 IU/L (*N* 2–11), LH 18 IU/l (*N* 2 – 9) with normal 46,XX karyotype, and multicystic ovaries on pelvic ultrasound. Genetic studies showed a c.1181G > A mutation in the fifth coding exon of ESR1, causing an arginine to histidine substitution at residue 394 (Arg 394His) of the ESR1 ligand-binding domain. Family screening revealed that both parents and one healthy sister are heterozygous for the mutation while an older sister aged 25 years and a brother aged 18 years are homozygotes. Similar to the index case they have pubertal delay with hypergonadotrophic hypogonadism. The brother's Ht is 165 cm (−1.65 SDS), Wt 73 kg (+0.56 SDS), and he has bilateral cryptorchidism, Tanner stage G1A1P1, with LH: 13 and FSH:55 IU/l, serum AMH 0.6 ng/ml (*N* 1.5–51) and Inhibin B: 5 pg/ml ($N > 100$). The older sister had hirsutism and primary amenorrhea, Ht:156 cm (−1.29 SDS), Wt:67 kg (+0.95 SDS), Tanner stage B1A3P5, LH: 21 IU/l, FSH: 20 IU/l. E2: 9476 pmol/l **Conclusion:** This family, the first to demonstrate clinical features of complete estrogen insensitivity in both male and female sexes, illustrates the range of pathology in estrogen resistance, and the challenge in terms of finding therapeutic solutions.

FC7.4

Disruption of Long-Range Transcriptional Regulation of Genes Known to be Associated with DSD

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Background: Early genetic diagnosis in patients with disorders of sex development (DSDs) can facilitate clinical management, predict recurrence risks, and augment general knowledge. Novel techniques such as SNP microarrays, GWAS, and exome sequencing have identified mutations in the coding regions of genes linked to DSDs. In some instances, variants in non-coding regions have been associated with 46,XY gonadal dysgenesis, e.g. deletions upstream of *SOX9 (*PLoS One 2011; 6: e17793). Much less is known about chromosomal rearrangements affecting regulatory genome sequences and gene expression of other genes implicated in DSD. **Objective and hypotheses:** To identify genomic copy number variants (CNVs) in non-coding regions that regulate gene expression associated with DSD. **Method:** We utilized a whole genome array comparative hybridization (aCGH) to identify CNVs in patients with DSD. Fluorescence *in situ* hybridization (FISH) analysis and direct sequence analysis of the breakpoints were performed to characterize CNVs and their possible effects on the genomic regulatory landscape. **Results:** Here, we present two patients with novel, de novo CNVs affecting the regulatory elements in the vicinity of the *SOX8* and *NR0B1* (*DAX1*) genes. Patient CHP-P46, a 46,XY phenotypic female who presented with skeletal anomalies and anemia, was found to have an 854 kb triplication involving evolutionary conserved enhancers upstream of *SOX8*. Genetic studies in CHP-P24, a 46,XX phenotypic male negative for *SRY* gene, detected an 80 kb deletion encompassing the *NR0B1* gene as well as downstream enhancer and insulator sequences. **Conclusion:** Genetic variants in non-coding sequences that disrupt long-distance transcriptional regulation of known DSD-causing genes were detected. The consequences of such genomic rearrangements on gene regulation need to be clarified. Analysis of such genomic alterations provides an invaluable opportunity to elucidate the role of sequence-conserved elements in gene regulation. Our findings reveal another level of complexity underlying the molecular mechanisms of DSD.

FC7.5

Targeted Exome Sequencing for Genetic Diagnosis of Patients with Disorders of Sex Development

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Patients with Disorders of sex development (DSD) can present with a large phenotypic spectrum and caused by a number of different genetic defects. Therefore, it is difficult to reach a specific diagnosis using traditional approaches including biochemical analysis and single gene sequencing in a number of patients with DSD. Recently, next-generation sequencing technologies have revolutionized the identification of causative genes with diseases with genetic heterogeneity using massive parallel sequencing of multiple samples simultaneously. **Objective and hypotheses:** This study was performed to investigate the genetic etiology of DSD patients using targeted exome sequencing of 67 known human DSD associated genes. **Method:** This study included 39 patients with 46,XY DSD and eight patients with 46,XX DSD. Exomes were captured using SureSelect kit (Agilent Technologies) and sequenced on the Miseq platform (Illumina, Inc.), which includes 2914 probes targeting a 152.953 kbp region spanning 67 genes. Mean coverage was over 150X for each sample, and approximately 99.46% of the targeted bases were read. We classified variants into five main categories (pathogenic, likely pathogenic, uncertain significance, likely benign, and benign) according to the American College of Medical Genetics and Genomics guidelines. **Results:** We identified known pathogenic mutations or deletion in 11 (23.4%) in the *AR*, *CYP17A1*, *POR*, and *DMRT1*/2 genes. Novel variants were identified in 10 patients (21.3%) in the *AR*, *ATRX*, *CHD7*, *FGFR1*, *MAP3K1*, *NR5A1*, *PROP1*, and *WWOX* genes. Of these, three patients harbored pathogenic or likely pathogenic variants, while the remaining 6 patients had variants of uncertain significance. **Conclusion:** Whole exome sequencing is expensive and laborious. Thus, targeted strategies provide efficient methods for identification of the genetic causes in DSD patients. This approach allows for early diagnosis of a genetic cause, which could influence clinical management and genetic counseling. In vitro analysis is needed to verify functional implications of the novel variants.

FC7.6

Whole-Exome Sequencing Reveals RAD51B Variant in Two Sisters with Primary Ovarian Failure

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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 Next-Generation Sequencing (NGS). **Method:** We studied seven familial cases (14 affected women) all of them with primary amenorrhea. DNA of two affected daughters and their sister, who parents are second cousins, was analyzed using Whole-Exome sequencing. Exons and splice sites were captured with the Agilent SureSelectXT Human Exon V5 Kit, and 2×100 bp paired-end WES was performed on an Illumina HiSDefault 2500. The mean coverage of the captured regions was $>$ 100x in all samples. The raw data was aligned to the reference genome (hg19 assembly) with BWA. Variant calling was performed with Freebayes and annotated with ANNOVAR. Sanger Sequencing was used to confirm Exome Sequencing variants and to evaluate 235 fertile women controls for putative identified damaging variants. **Results:** One novel homozygous frameshift variant (c.88delT:p.F30fs) in *RAD51B*, the gene encoding DNA Repair Protein RAD51 Homolog B, which is expressed in ovarian tissue, was identified in two affected women using Exome Sequencing. The unaffected sister was heterozygous for this variant. Additionally, the c.88delT:p.F30fs *RAD51B* variant is not present in 1000 Genomes, ESP6500 and ExAC databases as well as in the 235 fertile Brazilian women used as a normal control. **Conclusion:** Our findings indicate a novel homozygous frameshift variant in *RAD51B* associated with primary ovarian failure in two sisters. These results suggest *RAD51B* as a new candidate gene in the etiology of primary ovarian failure.

FC8.1

Transcriptomics and Machine Learning Methods Accurately Predict Diagnosis and Severity of Childhood Growth Hormone Deficiency

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Background: The diagnosis of Growth Hormone Deficiency (GHD) involves the use of GH stimulation tests that require day case admission, multiple blood sampling and are associated with significant adverse effects. **Aim:** To assess the utility of gene

expression (GE) profiling and candidate SNP analysis for the diagnosis of and classification of GHD. **Method:** Pre-pubertal treatment-naïve children with GHD (n = 98) were enrolled from the PREDICT study and controls ($n = 26$) acquired from online datasets. Whole blood gene expression (GE), determined with Affymetrix HU133v2.0 microarrays, was correlated with peak GH using rank regression and a Random Forest algorithm tested for prediction of the presence of GHD and in classification into severe (peak GH < 4 μg/L) and non-severe (peak ≥ 4 μg/L). For GHD severity classification data on age, gender, baseline IGF-I and IGFBP-3 levels was added to the Random Forest model along with SNP genotype for 97 growth-related candidate genes. Performance was assessed using Area under the Receiver Operating Characteristic Curve (AUC-ROC). A biological network of the GE related to peak GH levels was generated and cluster hierarchy assessed. **Results:** Rank regression identified 347 probesets representing 271 genes where expression correlated with peak GH concentrations: (R + 0.28, $P < 0.01$). These 347 probesets gave an AUC of 0.98 (sensitivity 100%, specificity 96%) for predicting GHD status versus controls, while using only the top 10 probesets ranked by network centrality gave an AUC of 0.94. Random Forest analysis was also able to accurately predict GHD severity with an AUC of 0.93 using transcriptomic data, not improved with addition of demographic, biochemical or SNP genotype data. **Conclusion:** GE profiling differentiates normal subjects from those with GHD and accurately predicts GHD severity. It may therefore be a useful tool to aid in the diagnosis of GHD, potentially replacing two GH stimulation tests with a single blood sample.

FC8.2

Whole Exome Sequencing can Identify Defects not Detected by Candidate Gene Sequencing in Patients with Short Stature and Features of Growth Hormone Insensitivity (GHI)

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Background: GH insensitivity (GHI) encompasses growth failure, low serum IGF-1 and normal/elevated serum growth hormone (GH) (basal level > 5 μg/L and/or peak on provocation testing > 10 μg/L). In a significant number of children the molecular cause is unknown. **Objective:** To investigate the genetic etiology of GHI in a cohort of children by candidate gene (CGS) and whole exome (WES) sequencing. **Methods:** About 109 patients (61 M, median age 6.5 yr [range 0.4–17.0]) with a phenotype consistent with GHI (mean height SDS −4.8; mean IGF-1 SDS −2.7) were accepted for genetic investigation since 2008. CGS was undertaken for *GH-IGF1* axis [*GHR, STAT5B, IGFALS, IGF1*] and 3M [*CUL7, CCDC8, OBSL1*] genes and WES was performed in unsolved cases (to date, 53 patients). A bioinformatic pipeline was developed to interrogate the WES data and identify potential causative genetic variants. **Results:** CGS identified homozygous mutations in the following genes in 36 patients: *GHR* [26], *IGFALS* [3], *OBSL1* [6] and *CUL7* [1]. WES identified changes in 13 patients: compound heterozygous *IGFALS* [1], homozygous *GHR* [5], heterozygous *PTPN11* [2], homozygous *CCDC8* [3], homozygous *CUL7* [1], and heterozygous *SOS1* [1]. 14 of these genetic variants are novel. In two subjects who were small for gestational age (birth weight SDS −2.3 and −1.8) hypomethylation in the imprinting control region 11p15 or mUPD7 was demonstrated confirming Silver Russell Syndrome (SRS). Mining the WES data of patients without a genetic diagnosis identified 24 candidate genes having deleterious variants in more than one GHI patient. **Conclusions:** A genetic diagnosis was obtained in 51 (47%) patients. These included 14 novel variants. Importantly, WES identified 13 mutations in known genes, which had not been detected on CGS. Diagnoses with phenotypes overlapping with GHI included SRS, 3M and Noonan syndrome. Variants in novel genes with potential impact on growth have been identified and are under further investigation.

FC8.3

PAPP-A2 Gene Mutation Effects on Glucose Metabolism and Bone Mineral Density and Response to Therapy with Recombinant Human IGF-I

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Background: PAPP-A2 (pregnancy-associated plasma protein A2) deficiency, caused by homozygous mutations in the PAPP-A2 gene results in a novel syndrome of significant growth failure. PAPP-A2 cleaves IGF binding proteins 3 and 5, thereby freeing IGF-I from its ternary complex and allowing it to become biologically active. We recently reported the first two families with PAPP-A2 mutations. Response to recombinant human IGF-I

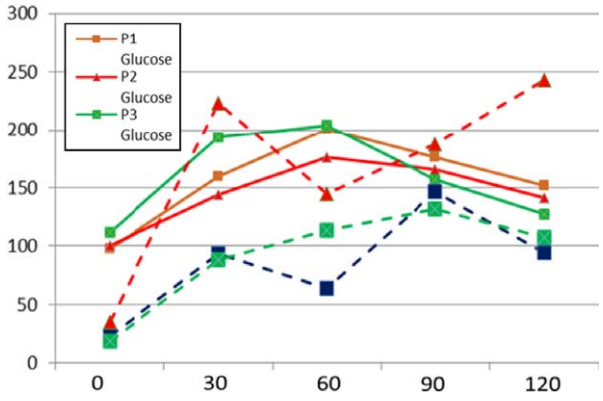

Table 1. (for abstract FC8.3)

Patient (Age)	Height (SD)	*Z*-score adjusted for height			
		Whole Body BMC	Spine BMD	Hip BMD	Forearm BMD
P1 (19)	138.1 cm (−3.8)	−0.99	−0.98	−0.24	−0.04
P2 (14)	141.9 cm (−2.9)	−2.08	−1.41	−1.94	−3.07
P3 (10)	121.0 cm (−3.0)	−1.28	−0.12	−0.54	−0.54

(rhIGF-1) in these patients is unknown. **Objective and hypotheses:** This study aimed to describe additional phenotypic features of patients with PAPP-A2 deficiency including glucose handling and bone mineral density (BMD) as well as to determine response to IGF-I therapy. **Method:** Three siblings with a homozygous missense mutation in *PAPPA2* (Ala1033Val) participated. Oral glucose tolerance tests, DXA, and renal/spleen ultrasonography were performed in the three patients. The two youngest boys, age ten and fourteen, were started on treatment with rhIGF-I. **Results:** The two elder siblings had elevated fasting glucose and impaired glucose tolerance with marked hyperinsulinemia. The youngest brother showed signs of insulin resistance (Figure). Hemoglobin A1c was normal in all three siblings. Bone densitometry showed that patients with PAPP-A2 gene mutation have mildly decreased size-corrected BMD (Table). Renal and spleen size was normal. On day 51 after initiation of therapy with rhIGF-I one of the patients developed severe headache and was diagnosed with pseudotumor cerebri. Therapy discontinuation resulted in resolution of symptoms. Treatment is ongoing in the younger sibling. **Conclusion:** PAPP-A2-deficient patients have abnormal glucose handling and insulin resistance which are likely related to elevated growth hormone and decreased free IGF-1 levels. These patients were also found to have mildly decreased size-corrected BMD. Increased intracranial pressure developed early on during rhIGF-I therapy in one of the patients. Nine month response to therapy of the younger patient will be presented at ESPE 2016 meeting.

FC8.4

Genetic Insights from Children with Idiopathic Short Stature in the EPIGROW Study

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Background: EPIGROW was a prospective European epidemio-genetic study in children with idiopathic short stature (ISS). **Objectives:** To identify (1) differences in frequencies of single nucleotide polymorphisms (SNPs) in growth related genes between ISS children and controls, and (2) associations between growth characteristics, IGF status and SNPs in these genes. **Methods:** Sequence data from EPIGROW was used to determine the difference in frequencies of SNPs/Indels in each of the 232 candidate genes between patients and controls. SNP/indel frequency was assessed for carriage of homozygous + heterozygous variants v wild type. To assess the genotype/phenotype relationships in the cases, we used PLINK, a whole genome association analysis toolset based on haplotype, a minimum allele frequency >2%, genotype present in >75% cases and a Hardy Weinberg equilibrium of 0.01. A Benjamini Hochberg corrected P value ≤ 0.05 was considered significant. **Results:** About 30 genes were identified where SNP carriage frequencies were different ($P \leq 0.05$). In ISS SNP frequencies were increased in 12 genes and decreased in 18. These included *IGFALS*(↓), *HRAS*(↑), *STAT5b*(↓) and *FANCA*(↓) which are associated with short stature conditions, *MAP2K1*(↑) and *A2M*(↓) associated with growth pathways and *SDR16C5*(↑) associated with adult height. In PLINK analyses, one SNP in *A2M* (Chr 12: 9154319, $P=0.02$) was associated with sitting height (SD score in those carrying a variant was −4.0 v −2.6 in wt), one SNP in *DNM3* (Chr1: 170643255, $P=0.05$) with head circumference and one SNP in *TP63* (Chr3: 191073565, $P=0.05$) associated with IGF-I levels. **Conclusion:** A number of genes, including those known to cause short stature, carry different frequencies of variants in ISS compared to controls, while specific SNPs are related to phenotype. Notably, the *A2M* gene (alpha-2-macroglobulin, a protease inhibitor and cytokine transporter) was identified in both analyses, and could have a role in causing short stature.

FC8.5

Longitudinal Study on Body Composition, Insulin Sensitivity and β-cell Function in SGA Adults from Stop of Long-term GH Treatment until 5 Years after Stop

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Background: GH treatment results in a decrease in fat mass (FM) and insulin sensitivity (Si), and an increase in lean body mass

(LBM). Only limited data are available on the longitudinal changes after discontinuation of GH treatment in SGA adults, aged 21 years. **Objective and hypotheses:** To assess longitudinal changes in body composition (BC) and glucose homeostasis after stop of GH treatment in SGA adults. **Method:** 197 previously GH-treated SGA adults were longitudinally followed after stop of GH treatment; at adult height, and 6 months, 2 yrs and 5 yrs thereafter. Data at 5 yrs after GH were compared to untreated adults born SGA with short stature (SGA-S) or spontaneous catch-up growth (SGA-CU), and adults born AGA. BC was determined by DXA scans and Si, acute insulin response (AIR) and β-cell function (DI) were assessed by frequently sampled intravenous glucose tolerance tests. **Results:** FM, trunk fat and limb fat increased steadily from stop of GH until 6 months, 2 yrs and 5 yrs thereafter ($P<0.001$). During 6 months after GH, LBM decreased ($P<0.001$), Si increased ($P<0.001$), AIR decreased ($P<0.001$) and DI increased ($P=0.032$) but all remained unchanged thereafter. At the age of 21 years, 5yrs after stop of GH, FM, Si and AIR were similar, LBM lower and DI higher in previously GH-treated SGA adults compared to age-matched SGA-S, SGA-CU and AGA adults. **Conclusion:** After GH treatment, body composition and glucose homeostasis changed, reflecting the loss of GH properties. FM steadily increased until 5 yrs after GH. GH-induced changes in Si and DI were fully reversed within 6 months after GH and remained similar during 5 yrs. At the age of 21 yrs, 5 yrs after GH, body composition and glucose homeostasis of previously GH-treated SGA adults were comparable to SGA-S, SGA-CU and AGA adults. Since the increase in FM is potentially unfavourable when persisting over time, further longitudinal evaluation of metabolic parameters is warranted.

FC8.6

Birth Characteristics Explain One Third of Expected Deaths in rhGH-treated Patients Diagnosed with IGHD, ISS & SGA

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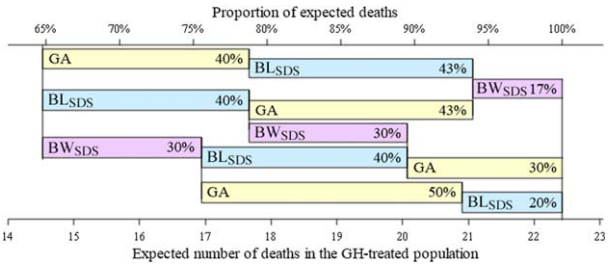

Background: That mortality is not increased in rhGH-treated patients when adjusting for birth characteristics was recently published (1). When applying a developed mortality model of the general population, the observed and expected deaths in rhGH-treated IGHD, ISS and SGA patients ($n=3847$) where 21 and 21.99, respectively. The model includes gender, age, calendar year, gestational age (GA), birth length$_{SDS}$ (BL_{SDS}), birth weight$_{SDS}$ (BW_{SDS}) and congenital malformations. When the model only adjusted for gender, age and calendar year (as for traditional SMR) the number of expected deaths was 14.68. **Objective and hypotheses:** How much of the expected deaths in rhGH-treated patients can be explained by the different birth characteristics. **Method:** Multiple stepwise regressions of the Poisson mortality model was performed, evaluating the results of different combinations of GA, BL_{SDS} and BW_{SDS} in addition to gender, age and calendar year with interactions between variables included as in the published model (1). Malformations were not included in these models causing the exact numbers to differ slightly (<2%) from previous calculations (1). **Results:** As much as 35% of the expected number of deaths (7.9/22.4) can be explained by different combinations of GA, BL_{SDS} and BW_{SDS} as visualized in the figure below. Depending on the order the variables are included, the number of deaths explained by GA became 30,40,43,50%; explained by BL_{SDS} became 20,40,43%; and explained by BW_{SDS} became 17,30% (see figure). **Conclusion:** As much as 35% of expected deaths among GH-treated children can be explained by various combinations of birth characteristics; GA, BL_{SDS} and $BW_{SDS;}$ valuable information when validating the Swedish mortality model in countries missing information. **References:** 1) Albertsson-Wikland, K et al. JCEM 2016:101. doi: 10.1210/jc.2015-3951

FC9.1

Next Generation Sequencing for the Diagnosis of Monogenic Diabetes in Switzerland

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Background: Monogenic diabetes (MD) remains undiagnosed in more than 90% of the cases. However, precise, quick and cost-effective diagnosis is important to choose an adequate

treatment and to avoid long-term complications. **Objective and hypotheses:** To develop and validate a diagnostic tool to improve diagnosis rate of MD in Switzerland, as well as to open new research directions. **Method:** Targeted next-generation sequencing (NGS) of 323 known or potential diabetes genes using the Haloplex technology on patients with neonatal diabetes (ND), anti-antibody negative type 1 (T1DM) and type 2 diabetes (T2DM) diagnosed before the age of 45 years without metabolic features. **Results:** In this ongoing study, 178 probands have been analyzed. A single mutation/variant was found in 41.6%, while two or more mutations/variants were found in 41.5% of the probands. 16.9% of the patients showed no anomaly. For the whole cohort, excluding ND, glucokinase (*GCK*) mutations were most frequent (19.6%), followed by *HNF1A* (5.6%) mutations and mean age at diagnosis was 27.7 years. For childhood onset diabetes (>6 months to $<$ 18 years), *GCK* mutations were found in 16.9% and *HNF1A* mutations in 10.2% of the probands. Mean age at diagnosis was 11.2 years. **Conclusion:** Using NGS in a selected population, we found a mutation or gene variant in 83.1% of the cases. Most patients were found to have *GCK* mutations. 7.9% of the probands had either *HNF1A* or *HNF4A* mutations for which oral antidiabetic drugs can replace insulin. These results highlight the importance of genetic analysis in patients with antibody-negative T1DM, ND or atypical T2DM. The identification of previously unknown variants in genes involved in beta-cell development or function opens the possibility to improve current knowledge about beta-cell physiology.

FC9.2

NBAS Mutations, a New Monogenic Cause of DISOPHAL, a New Syndrome with Type 1 Diabetes (T1D)

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Background: While non-autoimmune T1D is rare in late childhood, few monogenic causes have yet been identified. **Objective:** 1) to identify the genetic basis of the yet unreported disease phenotype associating late childhood antibody-negative T1D, short stature, optic atrophy (OA), Pelger-Huët anomaly (PHA) of leukocytes and recurrent liver cytolysis: the "DISOPHAL" syndrome; 2) to attract comparable cases for further genetic investigation. **Method:** Whole-exome sequencing combined with genetic mapping of disease loci. **Results:** Compound heterozygous mutations of neuroblastoma amplified sequence (NBAS) were found in three siblings of the same African family who had late childhood antibody-negative insulin-requiring T1D associated with dwarfism, OA, PHA and recurrent episodes of liver cytolysis. **Conclusion:** NBAS is a new gene associated with non-autoimmune T1D. NBAS mutations have been reported before in non-diabetic patients with dwarfism, OA and PHA ("SOPH" syndrome) or a separate disorder of recurrent liver failure ("RALF" syndrome). NBAS mutations can induce a wide and heterogeneous clinical spectrum, which showed its complete form in our patients.

FC9.3

Gastrointestinal Dysmotility and Pancreatic Exocrine Insufficiency as Newly Recognised Possible Features in Two Siblings with Donohue Syndrome

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Background: Donohue syndrome is a rare congenital syndrome of insulin-resistance and abnormal glucose homeostasis, caused by mutations in the insulin receptor (INSR) gene. It is characterized by specific phenotypic and clinical features and the diagnosis is based on clinical, biochemical and genetic criteria. **Case reports:** We report two siblings with Donohue syndrome with typical dysmorphic features and multiple clinical and biochemical characteristics. Genetic analysis detected a homozygous sequence variant in exon 4 of the INSR gene in both patients, predicted to result in an abnormal INSR protein, p.(Gly365Trp). Both patients presented with intra-uterine growth restriction, failure to thrive during the neonatal and infantile period, fasting hyperinsulinaemic hypoglycaemia and episodic post-prandial hyperglycaemia. Less common clinical features were also present, such as atrial septal defect (ASD) with left to right shunt and heart dilatation, abnormal clotting and liver function tests, and nephrocalcinosis. Of unknown cause were clinical signs, such as respiratory distress with prolonged oxygen requirement, intermittent fever and muscular hypotonia (case 2). Interestingly, two previously unrecognised possible manifestations of the syndrome were also identified: gastrointestinal dysmotility (case 1), that resulted in the patient's death at the age of 10 months, and pancreatic exocrine insufficiency (case 2). **Conclusion:** The co-existence of all the above clinical features makes these cases extremely rare. Gastrointestinal dysmotility should always be considered a potentially fatal feature in patients with Donohue syndrome, due to the complexity of the possible co-morbidities. In addition, our clinical experience for the first time suggests that exocrine pancreatic insufficiency may offer a possible explanation for the growth retardation seen in the syndrome. Our finding that replacement with pancreatic enzymes improved weight gain (case 2), indicates that failure to thrive may be treatable, hence we recommend that all patients with syndromes of insulin resistance should be investigated for exocrine pancreatic insufficiency.

FC9.4

The Protective Effects of Adenovirus-mediated IL-10 Gene and Anti-CD20 Monoclonal Antibody on the Pancreatic β Cells of NOD Mice in the Early Stage of Natural T1D Onset

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Background: Type 1 diabetes (T1D) is an autoimmune disease (AID) whose primary features include progressive pancreatic β cell damage and absolute insufficient endogenous insulin secretion. Recent studies have shown that a Th1/Th2 cell subset unbalance and excessively activated B lymphocytes are important pathogenic mechanisms. **Objective and hypotheses:** To investigate the protective effects of Adenovirus-mediated IL-10 gene and anti-CD20 monoclonal antibody (mAbs) on the pancreatic β cells in nonobese diabetes (NOD) mice with type 1 diabetes mellitus (T1D) at early stage. **Method:** 35 female NOD mice at onset of diabetes and aged 17–20 weeks old were randomly divided into 5 groups. Mouse 1, 2, 3, 4 and 5 groups were intravenously injected 500 ug of anti-CD20 mAbs, 500 ug of anti-CD20 mAbs combined with 100 ul of Ad-IL-10, 100 ul of Ad-IL-10, 100 ul of Ad-GFP, 100 ul of normal saline respectively. All mice were monitored for blood glycose everyday, and sacrificed 9 weeks after injection. Their serum levels of C-peptide were measured and the degree of insulitis were observed. Apoptosis related gene and protein were detected. **Results:** (1) The blood glucose level of mice in group 2 was reduced, $P<0.05$. (2) A majority of the insulitis was grade 0–1 in group 2, and grade 2–3 in group 5. (3) The apoptosis rate of pancreatic β cells was significantly lower in group 2 than that in the group 3, 4, 5, $P<0.05$. (4) Immunohistochemistry indicated that IL-10 could be highly expressed locally in the pancreatic islets. (5) The results of qPCR and western blot showed that combined intervention exerted protective effects on pancreatic β cells through activating Bcl-2 anti-apoptosis pathway, inhibiting the expression of TNF-α and Fas, and blocking caspase-8–caspase-3 as well as caspase-9–caspase-3 apoptosis pathways. **Conclusion:** Combined intervention could reduce the apoptosis of pancreatic β cells of NOD mice in the early stage of T1D, and had certain protective effects on the residual pancreatic β cell function.

FC9.5

Evaluation of a Novel Method to Detect Residual ß-Cell Function by Dried Blood Spots in Children and Adolescents with a Recent Diagnosis of Type 1 Diabetes

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Background: The majority of drug developments in type 1 diabetes (T1D) are aimed at preventing decline of beta cell function (BCF), as this has been associated with better glycaemic control and fewer long-term complications. Traditionally, BCF is evaluated by the C-peptide response to the labour-intensive mixed-meal-tolerance-test (MMTT), but there's a need for a more practical alternative. We developed a new method to measure C-peptide in 'dried blood spots' (DBS). **Objective:** To explore the use of a novel method to detect residual BCF in children recently diagnosed with T1D. **Method:** 26 T1D-subjects aged 6.9–16.5 years (10M;16F) had a MMTT within 6 months of diagnosis and 12 months after diagnosis with paired sampling of venous and DBS C-peptide at 0 and 90 minutes, and a urine sample for C-peptide/creatinine-ratio. In between MMTT's, weekly DBS C-peptide measurements before and after a standard breakfast were collected at home. **Results:** DBS and plasma C-peptide levels correlated well ($n=85$ paired measurements; $r=0.95$; $P<0.001$). All but 2 subjects had detectable fasting and postprandial DBS C-peptide throughout the study. Median fasting DBS C-peptide levels (range) at 6, 9 and 12 mo from diagnosis were 308 (<50–834), 210(<50–1299) and 272(<50–967) pmol/l, respectively. In multiple regression models with time and glucose as covariates of 21 cases with a median (range) of 24(8–29) home DBS measurements, fasting and post-prandial DBS C-peptide were negatively affected by time in 67 and 71%, and positively affected by glucose levels in 67 and 43%, respectively. A significant interaction between fasting or post-prandial glucose and time was identified in 19 and 5% of cases, respectively, indicating that glucose responsiveness decreased over time. The decline in fasting DBS C-peptide correlated well with that identified by the MMTT ($r=0.80$; $P=0.002$) and the urine C-peptide/creatinine ratio ($r=0.77$; $P=0.004$). **Conclusion:** DBS C-peptide measurement can be a useful tool in evaluating BCF in T1D intervention studies.

FC9.6

Circulating Angiopoietin-2 Levels in Young Patients with Type 1 Diabetes Mellitus: A Link between Inflammation, Micro-Vascular Complications and Subclinical Atherosclerosis

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Background: Angiopoietin-2 is a growth factor involved in the pathophysiology of different vascular and inflammatory diseases such as arteriosclerosis. Carotid or aortic scans provide non-invasive screening tools for assessment of preclinical atherosclerosis in high-risk children. **Aim:** We assessed serum angiopoietin-2 in children and adolescents with type 1 diabetes

mellitus as a potential marker for diabetic vascular complications in relation to glycemic control, inflammation and vascular structure. **Methods:** Sixty patients with type 1 diabetes were divided into 2 groups according to the presence of micro-vascular complications and compared with 30 healthy controls. High-sensitivity C-reactive protein (hs-CRP), hemoglobin A1c (HbA1c), urinary albumin creatinine ratio, serum angiopoietin-2 levels, carotid and aortic intima media thickness (CIMT and AIMT) were measured. **Results:** CIMT, AIMT and serum angiopoietin-2 levels were significantly increased in patients with and without micro-vascular complications compared with controls and the highest levels were in patients with complications ($P<0.001$). Serum angiopoietin-2 was higher in patients with microalbuminuria than normoalbuminuric group ($P<0.001$). The cutoff value of serum angiopoietin-2 at 900 pg/ml could differentiate patients with and without micro-vascular complications with a sensitivity of 92.3% and specificity of 100%. The cutoff values for CIMT and AIMT to detect micro-vascular complications were determined. Multiple regression analysis showed that fasting blood glucose, HbA1c, hs-CRP, CIMT and AIMT were independently related to angiopoietin-2. **Conclusion:** The relation between angiopoietin-2 and assessed parameters of vascular structure in type 1 diabetes reflects a state of subclinical atherosclerosis and highlights the role of disturbed angiogenesis and vascular inflammation in the occurrence of diabetic complications.

FC10.1

CYP11B1 Deficiency in Very Preterms: Evidence for an Adrenal Cortex Zone-Specific and Developmental-Dependent Maturation

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Background: Unlike term neonates, known to exhibit a physiological pseudohypoaldosteronism, very preterms (VPT) display a high sodium waste at birth with partial aldosterone deficiency. This context, combined with a low aldosterone/renin ratio is highly suggestive of a defect in mineralocorticoid biosynthesis. **Objectives and hypotheses:** To investigate mineralocorticoid and glucocorticoid pathways in newborns, and to clarify the impact of prematurity upon steroid biosynthesis at birth and during early post-natal development. **Methods:** Steroidomic profiles were assessed in umbilical cord blood samples originating from 152 neonates divided into three groups: $<$ 33 gestational weeks (GW), group 1 (46 patients), 33–37 GW, group 2 (67 patients) and $\geq$ 37 GW, group 3 (39 patients). Fifteen circulating corticosteroids (hormones, precursors and metabolites) were measured on $<$250 µl samples using a LC-MS/MS method. **Results:** An aldosterone secretion deficiency at birth was demonstrated in VPT (376 ± 137 vs 721 ± 404 pg/ml (mean$\pm$ S.D.) in group 1 and 3, respectively, $P<0.0001$). Likewise, aldosterone precursor levels were also decreased in VPT. A global defect in glucocorticoid secretion was also detected in VPT: cortisol (F, 16.3 ± 21.2 vs 46.9 ± 28.8 ng/ml, $P<0.0001$), as well as its precursors 11-deoxycortisol (S) and 17-hydroxyprogesterone. The activity of each biosynthesis step was evaluated by a product/substrate ratio as an index of enzymatic activity. Low corticosterone/11-deoxycorticosterone (B/DOC) and F/S ratios were consistent with a partial CYP11B1 deficiency while other product/substrate ratios were normal. Surprisingly, analyses of blood samples at 3 days of life revealed that partial CYP11B1 deficiency as estimated from B/DOC ratio was fully restored in VPT whereas F/S ratio remains altered suggesting a distinct and developmental enzymatic maturation in *zona glomerulosa* vs *fasciculata*. **Conclusion:** We identify a transient global steroid deficiency at birth in VPT, related to an unrecognized partial CYP11B1 deficiency. We also provide evidence for a zone-dependent CYP11B1 maturation during the first days of life, opening new therapeutic interventions.

FC10.2

Liver UPR and Metabolic Consequences in an Animal Model of Intrauterine Growth Retardation (IUGR)

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Background: Endoplasmic reticulum (ER) is the site where proteins are folded in the cell. Metabolic stress alters ER homeostasis and activates the unfolded protein response (UPR), which contributes to the development of insulin resistance and metabolic syndrome. **Objective and hypotheses:** To longitudinally evaluate liver UPR and its functional consequences in an animal model of IUGR followed from birth to adulthood. **Method:** On day 19 of gestation, Sprague-Dawley pregnant rats underwent ligation of both uterine arteries. The offspring was

either weighed and killed at 8 h after delivery or followed up to 105 d. Glucose and insulin concentrations were measured. Glucose tolerance test was performed at 105 d. The expression of genes that regulate liver UPR and their metabolic targets were investigated in 11 SHAM and 10 IUGR male rats at 105 d. **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 and 105 days. In the liver of IUGR male rats a significant reduction of insulin receptor, Akt and pAKT protein levels was observed ($P<0.05$). The liver expression of XBP1s mRNA was reduced ($P<0.01$) whereas the expression of PERK and Asns was increased ($P<0.05$). Western blot analysis confirmed UPR activation of IRE1a, PERK and ATF6 branches. A significant correlation between Xbp1s and pAkt levels was found ($P<0.01$). No significant differences were observed in gene expression of Pck1 and G6pc (gluconeogenesis related genes) and Acc2, Dgat2 and Scd1 (lipogenesis related genes). Histological examination of liver tissues showed focal steatosis in IUGR male rats. **Conclusion:** The offspring of mothers exposed to uteroplacental insufficiency show hepatic UPR activation. In parallel with IRE1alpha, ATF6 and PERK branch activation an impairment of glucose tolerance and focal hepatic steatosis were observed. These findings suggest that hepatic ER stress/UPR signalling may play a role in the long-term metabolic risk associated with IUGR.

FC10.3

Pharmacokinetics of Long Acting Somatostatin Analogue (Lanreotide) Therapy in Hyperinsulinaemic Hypoglycaemia (HH) and Understanding its Molecular Action via Somatostatin Receptors by Immunohistochemistry

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Background: Diazoxide and octreotide are first and second-line of treatment for HH respectively. Long-acting somatostatin analogue (Lanreotide, LA) has been used in adults with neuroendocrine conditions through its effect on somatostatin receptors 2 (SSTR2) and 5 (SSTR5). **Objective and hypotheses:** (i) To evaluate the efficacy, safety and pharmacokinetics of LA therapy in children with HH. (ii) To determine somatostatin receptor expression on pancreatic alpha, beta and delta cells of HH patients on LA therapy. **Method:** Children were started on 30 mg LA administered every 4-weekly. Plasma LA concentrations were collected in both groups (those on diazoxide and octreotide) and measured by radioimmunoassay (>3 years of age). The samples were collected at times 0, +1, +2, +4, +24 and +96 hours post 1st dose, before each dose for 6 months and then at 12 months of treatment. Children >3 years of age had paediatric quality of life (PedsQL) assessment and continuous glucose monitoring (CGMS) pre and 1-year post-LA. Formalin fixed pancreatic tissue sections were studied on those children who had pancreatectomy prior to starting LA therapy for immunohistochemistry. **Results:** 31 children were commenced on LA. Pharmacokinetic data on 21 children showed that LA concentrations significantly peak after 2–4 hours of administration. After the first dose of LA, there was a strong correlation ($r=0.836$, $P<0.001$) between the LA concentration and blood glucose. There was no significant difference in LA concentrations between two groups (diazoxide and octreotide) at each time period. Blood glucose concentrations <3.5 mmol/l were significantly reduced 1-year post-LA compared with pre-LA ($P=0.004$). The quality of life improved in health, emotion, social, school and psychosocial functioning 1 year post commencing LA. SSTR2 and SSTR5 expression was greater in diffuse and normal compared to focal pancreatic tissue. **Conclusion:** We observed significant benefits in terms of frequency of hypoglycaemia and quality of life one year after starting LA therapy. Immunohistochemistry suggest that diffuse disease is more likely to respond to LA than focal disease.

FC10.4

In Utero and Postnatal Consequences of Psychological Maternal Stress have Different Effects On Longevity: Studies in World War 1 Orphans

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Background: Early life stress (ELS) are known to have a deleterious impact on health, but their potential long-term consequences on mortality remain to be assessed. World War 1 (WW1) has caused major stress and bereavement to millions of European mothers. **Objectives and hypotheses:** To compare the effects of a maternal stress occurring during intra uterine or in postnatal life upon long-term mortality. **Patients:** Thanks to recently digitized databases and a unique French legislation put in place during WW1, we studied the adult mortality of French individuals born 1914–1916 whose father was severely injured or killed during WW1, a major psychological stress for the mother. Vital information and socio-demographic characteristics were extracted from civil registers for children who were granted the legal status of "Pupille de la Nation" and born between August 1st 1914 and December 31st 1916 in 11 boroughs of Paris ($n=4\,170$). A database comprising 1.4 million deceased French military was

used to discriminate between orphans and injured soldiers' children and retrieve vital information on orphans' fathers. Controls were drawn from the same civil registers. The life expectancy remaining at l_{min} = 30.7 years (e_{lmin}) of Pupilles was then compared to that of controls. **Results:** The life expectancy remaining at l_{min} = 30.7 years (e_{lmin}) of Pupilles was then compared to that of controls. With adjustment for several covariates, e_{lmin} for Pupilles was ~1 y below that of controls. The strongest effect was found for orphans who lost their father *in utero*. The difference in life expectancy between orphans and controls was found to decrease linearly with age, remaining close to 0 after age 65. **Conclusion:** These results suggest that psychological maternal stress is transmitted to child. Timing of ELS is crucial, but ELS contributes only moderately to health disparities at older ages.

FC10.5

Effects of Developmental Bisphenol A Exposure on Spermatozoal microRNA Expression

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Background: Bisphenol A (BPA), a ubiquitous endocrine-disrupting chemical, has been shown to exert transgenerational effects on adiposity, metabolism, and reproductive outcomes in rodents, indicating epigenetic inheritance. Recent studies of other environmental insults (stress and high-fat diet) have demonstrated a mechanistic role for spermatozoal microRNAs in the transgenerational transmission of acquired paternal traits. **Objective and hypotheses:** To assess the effects of developmental (gestational/lactational) BPA exposure on spermatozoal microRNA expression, with the hypothesis that BPA alters microRNA expression in a dose-dependent manner. **Method:** F0 female C57BL/6J mice exposed to vehicle (0.5% ethanol; VEH), low-dose BPA (0.4 mg/kg per day; LD), or high-dose BPA (8 mg/kg per day; HD) via their drinking water were mated with vehicle-exposed males to generate F1 offspring. Offspring were weaned to unadulterated water at 3 weeks of age. At 11 weeks of age, motile spermatozoa were isolated from males (n = 10 F1-VEH, n = 9 F1-LD, n = 8 F1-HD) and pooled in pairs/one trio to determine microRNA expression patterns by deep sequencing. **Results:** Median (IQR) post-weaning maternal serum BPA levels were 3.0 (2.6–21.0) μg/l for VEH, 40.2 (15.8–73.0) μg/l for LD, and 637.4 (356.7–4527.5) μg/l for HD. Deep sequencing analyses revealed that three microRNAs were upregulated and seven microRNAs downregulated in F1-LD spermatozoa compared to F1-VEH spermatozoa, including three downregulated microRNAs previously shown to be upregulated by early-life traumatic stress (miR-100-5p, miR-183-5p, and miR-191-5p). However, no microRNAs were differentially expressed between F1-VEH and F1-HD spermatozoa. Significant ($P \leq 0.001$) non-monotonic effects of BPA exposure were also observed for serum triglyceride level, inguinal fat-pad mass, and anogenital distance (all lowest in F1-LD mice), as well as liver mass (highest in F1-LD mice). **Conclusion:** These findings provide novel evidence that developmental BPA exposure at levels comparable to those observed in humans affects spermatozoal microRNA expression. Further work is required to determine whether this effect contributes to epigenetic intergenerational/transgenerational inheritance.

FC10.6

Developmental Programming of Somatic Growth, Behavior and the Endocannabinoid System (ECS) by Variation of Early Postnatal Nutrition in a Cross-Fostering Mouse Model

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Background: Nutrient deprivation during early development has been associated with the predisposition to metabolic disorders in numerous epidemiological studies. Experiments with rodents also indicate a developmental plasticity of neuropsychological characteristics following alterations of early postnatal nutrition. **Objective:** Considering its interaction with metabolism and regulation of appetite and behavior, the endocannabinoid system (ECS) may represent a promising target of early developmental programming. **Method:** By using a cross-fostering strategy with variation of the litter size, early postnatal nutrition of CB6F1-hybrid mice was controlled during the lactation period (3, 6, or 10 animals per mother). After weaning, all pups received standard chow ad libitum. mRNA expression analyses (fat, liver, hypothalamus) were performed at age 50 days. In addition, we investigated locomotor activity and social behavior in standardized settings. **Results:** Body growth was permanently altered, with differences for length, weight, BMI and visceral fat mass persisting beyond age 100 days according to early postnatal nutrition. This was paralleled by differences of hepatic IGF-I expression ($3 > 6 > 10$, $P < 0.01$). Furthermore, distinct expression patterns for ECS key enzymes were observed in fat and liver. EC-synthetizing

enzymes in adipose tissue tended to be higher expressed in formerly overfed mice (DAGLα $P<0.05$; NAPE-PLD $P=0.05$). Concordant expression patterns ($3>6>10$) were observed for EC-degrading enzymes FAAH ($P<0.05$, liver) and MGL ($P<0.05$, fat; $P<0.01$, liver). In the arcuate nucleus, formerly underfed mice tended to express more EC-receptor transcripts (CB1R $P<0.05$; CB2R $P=0.08$) than overfed animals. Open-field social behavior testing revealed significant differences, with formerly underfed mice turning out to be the most sociable animals ($10>6>3$, $P<0.01$). Locomotor activity was not different. **Conclusion:** Our data indicate a developmental plasticity of growth, behavior and the ECS, with measurable impact of early postnatal over- and undernutrition. Developmental programming of the ECS in metabolically active tissues may play a role in the formation of the adult cardiometabolic risk profile following perinatal malnutrition in humans.

FC11.1

Mutations in TBL1X as a Novel Cause of Familial Central Hypothyroidism

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Background: Congenital central hypothyroidism (CeH) may occur isolated, or in combination with other pituitary hormone deficiencies. Although a third causative gene for CeH was recently reported (*IGSF1*), the aetiology of isolated CeH has remained unexplained in most cases. **Objective and hypotheses:** We hypothesized that in three relatives with unexplained isolated CeH a mutation in another gene might be responsible for the phenotype. **Method:** Using X-exome sequencing, we identified a missense mutation in the Transducin β-like protein 1, X-linked (*TBL1X*) gene. Other pathogenic mutations were excluded with whole exome sequencing. The TBL1X protein is part of the thyroid hormone receptor corepressor complex. Sanger sequencing of this gene in unrelated cases of unexplained isolated CeH revealed five additional missense mutations. We performed clinical and biochemical characterization of the probands and relatives with a mutation identified by family screening. We investigated the functional consequences of the mutations in vitro, and used qPCR and immunostaining to study TBL1X expression in post-mortem human hypothalamus and pituitary tissue. **Results:** All probands ($n=8$, 6 males) had CeH with plasma free thyroxine (FT4) concentrations below the reference interval accompanied by thyrotropin concentrations within the reference interval. Family screening identified mutations in nine females and two males, all with FT4 concentrations in the lower half of the reference interval. Eleven out of 15 evaluated individuals with a mutation had hearing loss. The TBL1X mutations were located in the highly conserved WD40-repeat domain of the protein and influenced its expression and thermal stability, but not the ability to bind other corepressor complex proteins. TBL1X mRNA and protein were expressed in the human hypothalamus (particularly in the paraventricular nucleus) and pituitary. **Conclusion:** Mutations in TBL1X are associated with a novel syndrome of familial isolated CeH and hearing loss, presumably resulting from impaired function of the nuclear NCoR/SMRT corepressor complex.

FC11.2

Overexpression of DYRK1A Located in the Down Syndrome Critical Region, Leads to Primary Hypothyroidism in Down Syndrome through Interaction with FOXE1

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Background: Down Syndrome (DS) patients have a higher incidence of primary hypothyroidism. We previously demonstrated that transgenic mice overexpressing Dyrk1A had developmental (larger primary thyroids at E15.5 stage of development), morphological (disorganized follicles) and functional (significant lower plasma T4) impairments similar to DS thyroidal impairments (Endocrinology 2015). *DYRK1A*, localized in the DS critical region on chromosome 21, is therefore the candidate gene for thyroid dysgenesis in DS. **Objective and hypotheses:** We investigated the molecular mechanism involved. Our hypothesis is that Dyrk1A directly interacts with the molecules involved in thyroid development. **Method:** We performed western blots from embryonic wild type and transgenic Dyrk1a+/++ thyroids at E13.5, E15.5 and E17.5 with anti-Pax8 and anti-Foxe1 antibodies. The thyroidal human immortalized cells NThy.Ori were transfected with pGFP, pGFP-Dyrk1a, pFlag, pFlagFoxe1 and pFlag-Foxe1+pGFP-Dyrk1a. Immunoprecipitation from transfected cells were performed with anti-Flag antibody and immunoblots with anti-Dyrk1A antibody. Expression of *NKX2-1, FOXE1, PAX8, THYROGLOBULIN (TG)* and *SODIUM IODIDE SYMPORTER (NIS)* was studied by q-RTPCR in NThy.Ori and primary human thyrocytes transfected the same way. **Results:** We found an increased signal of FOXE1 blot in Dyrk1a+/++ embryonic thyroids at E15.5, suggesting a direct effect of Dyrk1a on Foxe1. Immunoprecipitation revealed an interaction between GFP-DYRK1A and Flag-FOXE1 proteins. We found a significant overexpression of *FOXE1* (1.4 fold expression, $P=0.002$), *TG* (3.2 fold expression, $P=0.002$) and *NIS* (10 fold expression, $P=0.02$) in cells transfected with pGFP-Dyrk1a, but no significant differences in *NKX2*−1 and *PAX8* expression. Similar results were confirmed in primary human thyrocytes. **Conclusion:** Overexpression of DYRK1A in embryonic thyroids leads to

FOXE1 overexpression. We found a direct interaction between DYRK1A and FOXE1 by immunoprecipitationin a human thyroidal cell line, which can explain an overexpression of *FOXE1* and secondarily to *THYROGLOBULIN* and *NIS* overexpression. Therefore, we can conclude that primary hypothyroidism in Down syndrome could be explained by this interaction.

FC11.3

Genetic Heterogeneity Revealed by WES in a Cohort of Patients with Brain-Lung-Thyroid Syndrome

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Background: Brain-Lung-Thyroid (BLT) syndrome (OMIM# 610978) is characterized by congenital hypothyroidism (CH), infant respiratory distress syndrome (IRDS), and benign hereditary chorea and is caused by thyroid transcription factor 1 (*NKX2-1/TTF1*) haploinsufficiency. The phenotype can be partial or complete and there is a large phenotypic variability. **Objectives and hypotheses:** Identify new genes in a selected group of patients presenting thyroid, brain and/or lung dysfunction, but without *NKX2-1* abnormalities. **Methods:** From a well-characterised cohort of patients *(Carré et al, Hum Mol Genet 2009)* with thyroid disorders associated with brain and/or lung symptoms, we selected 8 patients negative for *NKX2-1* mutations. Array Comparative Genomic Hybridization (aCGH) and multiplex ligation-dependent probe amplification (MLPA) analysis were performed to detect any DNA copy number variations (CNV) and *NKX2-1* deletion respectively. Whole exome sequencing was performed using the kit Agilent SureSelectXT Human All Exon V6 on Illumina HiSeq 2500 HT, with a trio analysis (proband and parents) strategy. **Results:** The complete triad was present in two patients. Thyroid disorders presented as CH ($n=7$) or subclinical hypothyroidism ($n=1$) and concerned gland *in situ* ($n=3$) and athyreosis ($n=5$). The majority of patients had neurological impairment (6/8 patients, 75%), mainly as ataxia ($n=3$) and neonatal hypotonia ($n=2$). Developmental delay was the major finding in one patient. Lung disease as IRDS was present in four patients. No CNVs were identified in chromosome 14 and close to region 14q13. MLPA did not reveal any anomaly. WES has already been realised in five trios ($n=15$) and two index cases and revealed new candidate genes involved in the pathogenesis of the disease. **Conclusion:** In this well-described cohort on clinical and molecular level, WES allowed to identify candidate genes. Genetic heterogeneity was demonstrated with several genes explaining the clinical phenotype and expanding our knowledge about the syndrome.

FC11.4

Decreased Proportions of CD4+IL17+/CD4+CD25+CD127− and CD4+IL17+/CD4+CD25+CD127-FoxP3+T Cells in Children with Autoimmune Thyroid Diseases

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Background: Until now, altered balance of Th1 and Th2 immune cells has been postulated to play an important role in the pathogenesis of autoimmune thyroid diseases (AITD). However, recent studies on thyroid diseases have suggested a new role for Th17 cells that have been classified as a new lineage, distinct from Th1, Th2 and Treg cells. Despite wide interest, the role of Th17 cells in the pathogenesis of inflammatory and autoimmune diseases is still debated. **Objective and hypotheses:** The aim of the study was to estimate the proportions of Th17/Treg T cells in peripheral blood from patients with Graves' disease (GD) ($n=29$, mean age 15.4 ± 5.1y), Hashimoto's thyroiditis (HT) ($n=39$, mean age 15.2 ± 4.1y) and in healthy controls ($n=49$, mean age 14.8 ± 3y). **Method:** Polychromatic flow cytometry and several fluorochrome-conjugated monoclonal antibodies were applied to delineate Th17 and Treg cells. **Results:** The analysis of Th17/Treg T cell proportions in peripheral blood from patients with Graves' disease revealed significantly lower ratios of CD4+IL17+/CD4+CD25+CD127− ($P<0.0021$) and CD4+IL17+/CD4+CD25+CD127-FoxP3+ ($P<0.0031$) than in the control group. In addition, in the case of HT we observed a significant decrease in the ratios of CD4+IL17+/CD4+CD25+CD127− ($P<0.0001$) and CD4+IL17+/CD4+CD25+CD127-FoxP3+ ($P<0.0001$) T cells in comparison to healthy children. In patients with untreated GD, a statistically significant positive correlation was found between the proportions of CD4+IL17+/CD4+CD25+CD127−, CD4+IL17+/CD4+CD25+CD127-FoxP3+T cells and the TRAbs ($R=0.71$, $P<0.029$; $R=0.72$, $P<0.026$, respectively) and a positive correlation was noted between the percentage of CD4+CD-IL-17+T cells and the level of TSAbs ($R=0.66$, $P<0.037$). **Conclusion:** We conclude that the changes in the proportion of Th17/Treg T cells in peripheral blood and their significant relationship with the level of anti-thyroid antibodies indicate an involvement of these cells in the pathogenesis of AITD.

FC11.5

Pediatric Reference Values of Thyrotropin (TSH) should be Personalized According to Child Characteristics

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Background: Primary care pediatricians (PCPs) use thyroid function tests (TFT) as screening tests in children and adolescents with various health complaints. Thus, it is crucial to evaluate the results according to appropriate cut-offs individualized to the child characteristics. Such references values, which are missing in the pediatric age group, are needed for proper evaluation of the thyroid functions. **Objective and hypotheses:** To determine normal TSH levels in a large cohort of healthy children individualized according to their age, sex, BMI and ethnicity. **Method:** Data was collected from the database of Clalit Health Medical Organization (CHMO) ensuring more than 1.3 million children. 75,857 children aged 5 to 18 years without previous thyroid disease or treatment, who had TFT evaluation during 2012–2014 were included in the study. Data evaluated included: age, gender, TSH, FT4 and FT3 levels, BMI SDS (according to WHO norms), ethnicity and dispensed medications. **Results:** TSH levels were significantly higher in boys compared to girls: median 2.21 mIU/L (normal range 0.83–5.25) vs 2.11 mIU/L (0.89–5.29), $P<0.0001$. TSH levels were found to vary significantly according to ethnicity; TSH Ievels in the Jewish population were significantly lower compared to the Israeli Arab population: median 2.14 mIU/L (0.85–5.14) vs 2.22 mIU/L (0.84–5.85), $P<0.0001$. BMI was found to significantly effect TSH levels with levels increasing as weight diverge from the normal range; median levels were 2.13 mIU/L (normal range 0.74–5.13), 2.04 mIU/L (0.79–5.05), 2.14 mIU/L (0.88–5.45), 2.37 (0.95–5.74) for children defined as underweight, normal weight, overweight and obese respectively. Age did not significantly affect TSH distribution. **Conclusion:** Our results in this uniquely large cohort show that the normal range of TSH in children is affected by gender, weight and ethnicity. Reference values should be thus individualized and modified accordingly. Such modifications will improve future clinical decision-making and treatment.

FC11.6

Too many TFTs? A Change in Neonatal Thyroid Function Testing in a Peripheral Hospital in Ireland

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Background: Thyroid disorders in the neonatal period can have serious consequences for growth and development. Neonatal bloodspot screening identifies congenital hypothyroidism. Current guidelines both internationally and in tertiary centres in Ireland have moved towards checking thyroid function tests (TFTs) solely in infants of mothers with hyperthyroidism and those identified on neonatal bloodspot screening. The practice in OLOLH, Ireland was that all infants of mothers with any form of thyroid disease had TFTs checked on day 14. **Objective and hypotheses:** We hypothesised that a new evidence based algorithm and guideline for management of neonates born to mothers with thyroid disease would reduce unnecessary TFT testing. **Method:** We performed a 12 month retrospective audit of neonates who had TFTs on DOL 14 performed. We then developed a new evidence based algorithm to identify neonates who required TFT testing. We then audited four months of TFT testing post algorithm implementation. **Results:** In the initial 12 months audited, 84 neonates were deemed to require TFT testing on DOL14. 78 attended and 6 were lost to follow up. Four of the 84 were picked up on bloodspot screening. 72 TFTs were normal, three normalised on repeat and three were persistently abnormal. All three of these had been identified on neonatal bloodspot screening. As per our new evidence based guideline only 16 of these 84 babies would have required bloods on day 14- 4 from bloodspot screening and 12 due to maternal hyperthyroidism. Re-audit post implementation of the new algorithm revealed only four infants had TFT testing in 4 months, which we extrapulated to approx 12/year- an 81% reduction in TFT sampling, excluding those identified from bloodspot screening. **Conclusion:** By implementing a new evidence based guideline and algorithm we have successfully reduced unnecessary TFT testing on neonates.

FC12.1

Rabconnectin3-α is Indispensable for the Activation and Maturation of the GnRH Neuronal Network

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Background: Acquisition and maintenance of fertility in mammals rely on the function of Gonadotropin Releasing Hormone (GnRH) neurons. During the juvenile period, GnRH neurons undergo morphological maturation, which involves changes in synaptic inputs and neuropeptide activation from afferent neurons. The functional importance of this maturation could be a pre-requisite for puberty onset. However, the mechanisms behind these dynamic changes have yet to be identified. **Objective and hypotheses:** Previously, we found that the neuronal knock-down of *Dmxl2*, encoding for the synaptic protein rabconnectin3-α (rbcn3-α), reproduced in mice (*nes::cre;Dmxl2*$^{loxp/wt}$) the GnRH deficiency found in *DMXL2* mutated patients. Here, we aimed to clarify if the GnRH deficiency observed in *nes::cre;Dmxl2*$^{loxp/wt}$ mice was due to abnormal GnRH

neuronal maturation. **Method:** Kp-10 and E2 injections combined with cre-dependent adenoviral filling of GnRH neurons *in vivo* in *nes::cre;Dmxl2*$^{loxp/wt}$ *and GnRH::Cre;Dmxl2* knock out mice were used to assess GnRH neuron number, morphology, and activation. **Results:** Male *nes::cre;Dmxl2*$^{loxp/wt}$ mice fail to respond to the GnRH secretagogue, kisspeptin(Kp-10). In adulthood, GnRH neurons display a majority of immature GnRH neuron morphology in both males and female *nes::cre;Dmxl2*$^{loxp/wt}$ mice. In addition, female *nes::cre;Dmxl2*$^{loxp/wt}$ mice exhibit an abnormal ovulatory circadian timed LH surge and unable to elicit E_2 positive feedback. Important, immature GnRH morphologies in *nes::cre;Dmxl2*$^{loxp/wt}$ mice were unresponsive to Kp-10 and E_2 treatments, but not in *GnRH::Cre;Dmxl2* KO mice. **Conclusion:** This study reveals that rbcn3-α is required for the maturation and activation of GnRH neurons by afferent neurons. This is a new mechanism of normosmic hypogonadotropic hypogonadism.

FC12.2

LGR4 and *EAP1* Mutations are Implicated in the Phenotype of Self-limited Delayed Puberty

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Background: Aberrations in the timing of puberty may result in significant adverse health outcomes, including cancers, cardiovascular and neurological pathologies. Self-limited delayed puberty (DP) (i.e. constitutional delay of puberty) runs in families with either autosomal dominant or complex inheritance patterns in $>70\%$ of families, indicating a strong genetic basis of the trait. However, only a few genes have been identified underlying DP so far. **Objective and hypotheses:** We hypothesize that genes causing DP are amenable to discovery through exome sequencing of our large cohort with familial DP. **Methods and results:** Whole exome sequencing was performed on DNA from 111 individuals of 18 multi-generational families affected with DP. After filtering we identified three rare, potentially pathogenic missense variants in *LGR4* (16 individuals in four families) and one in-frame deletion and one rare missense variant in *EAP1* in two families (five affected individuals) that all segregated with the DP trait. *In vitro* analysis on *LGR4* and *EAP1* revealed specific expression in mice olfactory epithelium at different embryonic stages and in the peripubertal mice hypothalamus, respectively. The pathogenicity of each of variant is under investigation. *LGR4* variants have been produced by site directed mutagenesis and expressed in eukaryotic cell through transfection. Intracellular trafficking, ligand binding and signal transduction through Wnt-signalling are being investigated. **Conclusion:** The preliminary results suggest a causal role for *LGR4* and *EAP1* in delayed puberty. Embryonic expression points to a role for *LGR4* in GnRH neuronal migration. *EAP1* may act upstream of GnRH to influence pubertal timing.

FC12.3

Inactivating Mutations in *CCDC141* Causing Idiopathic Hypogonadotrophic Hypogonadism/ Kallmann Syndrome

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Background: GnRH neurons originate outside the CNS in the olfactory placode and migrate into the central nervous system, becoming integral components of the hypothalamic-pituitary–gonadal axis (HPG). **Objective and hypotheses:** We hypothesize that gene(s), whose products are important for pubertal development can be identified via autozygosity mapping together with whole exome sequencing in patients with idiopathic hypogonadotrophic hypogonadism (IHH)/Kallmann Syndrome (KS). **Method:** We studied a cohort IHH/KS cases. **Results:** Our studies revealed three independent families in which IHH/KS is associated with inactivating CCDC141 variants. **Conclusion:** These results indicate that CCDC141 is required for successful migration of GnRH neurons to their final destination in the hypothalamus, and thus establishment of the central part of HPG axis.

FC12.4

Idiopathic Hypogonadotrophic Hypogonadism Caused by Inactivating Mutations in *SRA1*

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Background: What initiates pubertal process in humans and other mammals has remained elusive. **Objective and hypotheses:** We hypothesize that gene(s), whose products trigger the GnRH pulse generator to restart ticking at the usual time of puberty, can be identified via autozygosity mapping together with whole exome sequencing in patients with idiopathic hypogonadotrophic hypogonadism (IHH). **Method:** We studied a cohort IHH cases. Functional implications of variants were tested by a luciferase reporter assay in HeLa cells. **Results:** Our studies revealed three independent families in which IHH is associated with inactivating SRA1 variants. Functional studies with a mutant SRA1 construct showed a reduced co-activation of ligand dependent activity of the estrogen receptor alpha. **Conclusion:** SRA1 acts as a protein as well as a noncoding functional RNA product. These products function as co-regulators of nuclear receptors including sex steroid receptors as well as SF-1 and LRH-1, the master regulators of steroidogenesis. Our findings strongly suggest that SRA1 gene function is required for initiation of puberty in humans. Furthermore, SRA1 with its alternative products and functionality may provide a potential explanation for versatility, and complexity of puberty.

FC12.5

Abnormal Corticospinal Tract Decussation in Kallmann Syndrome due to ANOS1 (KAL1) Mutations: An Explanation of the Mirror Movements Frequently Observed in These Patients

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Background: Mirror movements (MM) are frequently associated to Kallmann syndrome (KS). They are mainly observed in patients with ANOS1 (KAL1) mutations. MM have never been reported in ANOS1 mutated females. A defect in the contralateral inhibition of the pyramidal tract has been proposed as the mechanism of MM in KS but never demonstrated. **Objective and hypotheses:** To investigate the molecular mechanism of a familial case of gonadotropic deficiency in which 11 males had KS whereas females were diagnosed with MM (family 1). To test the hypothesis that MM in KS may be due to an abnormal development of the pyramidal tracts. **Method:** Patients with KS were investigated for ANOS1 mutations. The pyramidal tracts were analysed by imaging (diffusion tensor imaging tractography) in an adult with ANOS1 mutation and by neuropathology in a mutated foetus. **Results:** A complex rearrangement in ANOS1 was found in male and female members of family 1 (C2067_2070AGGA>TCCT; p.Glu642Alafs21), one nonsense mutation in an adult (c.773G>A; p.Trp258X) and one mutation in a foetus (c.769C>T; p.Arg257X) who had been medically terminated for bilateral renal agenesis with cleft lip and palate. The tractography showed a lack of decussation of the pyramidal tracts in the adult proband. Pathology examination of the foetus revealed hypoplastic and abnormally shaped corticospinal tracts in the pons and medulla. **Conclusion:** We show clinical, imaging technique and anatomical evidence of MM in KS caused by ANOS1 mutation. Congenital MM may be transmitted as a dominant trait in ANOS1 mutated patients. ANOSMIN is involved in guidance and development of corticospinal axons, as already known for olfactory axons.

FC12.6

Pubertal Onset in Boys is Influenced by BMI and Genetic Variation of *Fshb* and *Fshr*: A Study in Two Population-Based Cohorts of Different Genetic Ancestry

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Background: Age at onset of puberty exhibits a remarkable variation mirroring nutritional, environmental, socioeconomic and genetic factors. While large genome-wide association studies identified more than hundred genetic loci associated with age at menarche in girls, knowledge on loci associated with age at pubertal onset in boys is sparse. *FSHB/FSHR* genetic variants have been shown to affect pubertal timing in girls and reproductive parameters in men. **Objective and hypotheses:** To investigate the effect of *FSHB* c.-211G>T, *FSHR* c.-29G>A, *FSHR* c.2039G>A and BMI on pubertal timing in two independent cohorts of healthy peripubertal boys. **Method:** 1130 healthy Danish (longitudinal and cross-sectional data) and 424 Chilean (longitudinal data) boys underwent blood sampling and clinical examinations including orchidometry. Testicular volume $\geq$4 ml was considered as marker of puberty. Cohorts were standardized on WHO BMI *z*-scores. **Results:** Age at pubertal onset, BMI and genotype frequencies differed significantly between cohorts. Age at pubertal onset was: Denmark 11.67 (11.59–11.76) years; Chile 11.00 (10.83–11.16) years [mean (95% CI)] ($P<0.001$). BMI *z*-score was 0.16 ($\pm$0.97) and 1.12 ($\pm$1.20) [mean ($\pm$SD)] ($P<0.001$), respectively. All genotype frequencies differed significantly between cohorts ($P<0.001$, chi-squared test). Age at pubertal onset was associated with 1) BMI *z*-score in both cohorts

(beta = −0.35 years in both cohorts, $P < 0.001$) 2) *FSHB* c.-211G>T (Denmark: beta = 0.16, $P = 0.03$; Chile: beta = 0.39, $P = 0.04$; corrected for BMI *z*-score). In a combined genetic model, *FSHR* c.-29G>A further modified this effect (Denmark: beta = 0.11, $P = 0.01$; Chile: beta = 0.22, $P = 0.02$; corrected for BMI *z*-score): boys with a genetic constellation resulting in weak FSH signalling (*FSHB* c.-211GT/TT + *FSHR* c.-29AA) entered puberty 8 (Denmark) and 11 months (Chile) later than boys with the most active FSH signalling (*FSHB* c.-211GG + *FSHR* c.-29GG/GA), respectively. **Conclusion:** Genetic variation of *FSHB, FSHR* and BMI affects age at male pubertal onset. The association was observed in two independent cohorts of varying genotype distribution and BMI.

FC13.1

Quantitative Proteomic of Rat Livers Shows a Major Reprogramming of Mitochondrial Enzymes in Food-Restriction and Increased Stress Hallmarks in Ad Libitum Feeding

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Background: Studies in young mammals on the qualitative and quantitative molecular effects of food restriction (RES) and re-feeding, leading to catch up growth (CU) are scarce. Whereas RES may lead to growth and developmental deficits in children, it is a proven treatment to prolong life in all animals checked. **Objective and hypotheses:** We used MS analysis to understand how RES might lead to growth attenuation and prolonged life span and identify the major qualitative and quantitative changes in liver proteins. **Method:** We used quantitative MS proteomic analysis of whole rat livers. **Results:** Over 1900 common proteins were significantly quantified in livers of ad libitum, RES- and re-fed rats, which summed up into 95% of the total protein mass of the cells. In RES livers, a strong increase of mitochondrial catabolic enzymes was observed, alongside a decrease of cytosolic molecular chaperones, which are hallmarks of cellular stress. Following a single day of *ad libitum* re-feeding, the significant differences of protein levels in RES were nearly fully reversed. **Conclusion:** The quantitative and qualitative protein values suggested that RES is not a stressful condition, as it necessitated only minimal levels of HSP-chaperones to maintain an optimal quali'ty of protein folding, thereby providing most advantageous conditions for an extended life span. In contrast, the protein profile of the *ad libitum* regimen was that of a chronic stressful condition necessitating constant high levels of HSP-chaperones to maintain protein homeostasis. The data thus suggests that the *Ad libitum* regimen brings a continuous strain on the protein quality control machineries of the cell, which may decrease the time of onset of aging and shorten life span.

FC13.2

Measurement of Immunofunctional Leptin to Detect Patients with Functional Leptin Deficiency

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Background: Recently, patients with severe obesity have been described due to functional leptin deficiency. This new entity is characterized by high immunoreactive levels of circulating leptin (Lep), but a reduced bioactivity of the hormone due to defective receptor binding (N Engl J Med 2015;372:48–54). Since these patients can be successfully treated with human recombinant leptin (metreleptin), a diagnostic tool to detect functional leptin deficiency is needed. **Aim:** We hypothesize that the measurement of immunofunctional leptin (bioLEP) by a new analytical approach is appropriate to estimate bioactivity of leptin. **Methods:** Microtiterplates were coated with the recombinant extracellular domain of the human leptin receptor. Added serum leptin molecules bound to the immobilized receptor and were detected by a highly specific polyclonal, biotin-conjugated antibody and a streptavidin-peroxidase conjugate. **Results:** The analytical range of the bioLEP assay was 1–120 ng/ml with intra and interassay coefficients of variation below 10%. Recovery of leptin international standard (NIBSC 97/594) or metreleptin was 102 and 109%, respectively. Physiological concentrations of soluble leptin receptor up to 100 ng/ml did not interfere with bioLEP measurement. In a clinical cohort ($n = 444$; age: 3–70 years, BMI-SDS: −2.1–5.3) with total Lep levels of 1.0–117.2 ng/ml, mean ± SD for the ratio of bioLEP/Lep was 1.07 ± 0.13 (range 0.75 to 1.66). Serum samples of patients with non-functional leptin due to homozygous amino acid exchanges like p.D100Y or p.N103K revealed high Lep levels but non-detectable levels of bioLEP. Upon treatment of these patients with metreleptin, Lep levels decreased while levels of bioLEP increased continuously. Individuals heterozygous for p.D100Y or p.N103K had ratios of bioLEP/Lep of 0.5 (0.42–0.67) making them clearly distinguishable from individuals homozygous for the wild type sequence. **Conclusion:** The bioLEP assay is able to detect only those leptin molecules capable of binding to the extracellular domain of the leptin receptor. Accordingly, this assay is a reliable method to identify patients with reduced leptin bioactivity resulting from either homozygous or heterozygous mutations in the LEP gene.

FC13.3

Hypothalamic Gliosis in Obese Children and Adolescents

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Background: Obesity is a persistent disorder that almost universally recurs following treatment, suggesting a disruption on central nervous system control over energy homeostasis. Recent literature suggests that hypothalamic inflammation may have an important role on obesity pathogenesis. This inflammatory reaction, which histologically appears as a reactive gliosis, may be detected using magnetic resonance imaging (MRI), and has just been shown in rodent models and adults. **Objective and hypotheses:** To test for hypothalamic gliosis in obese children and adolescents using quantitative MRI. **Method:** Eleven obese and 9 lean children and adolescents underwent fasting blood draws, body composition analysis by DXA, and brain MRI scans to measure T2 relaxation time using a multi-echo T2 sequence. **Results:** Participants' mean age was 13.4±2.4 year. Obese children had higher mean BMI z-score (2.1±0.3 vs −0.3±0.9, $P<0.001$), plasma leptin levels (33.4±15.4 vs 4.9±5.6 pg/ml, $P<0.001$) and pro-inflammatory cytokines (TNF-α: 2.0±0.7 vs 1.2±0.6 pg/ml, $P=0.02$; IL-6: 2.9±1.7 vs 1.0±0.5 pg/ml, $P=0.004$) and lower adiponectin levels (4.4±1.7 vs 6.8±1.5 ng/mL, $P=0.005$). The groups did not differ in age ($P=0.41$), sex and pubertal status proportions ($chi^2=0.20$, $P=0.66$; $chi^2=0.80$, $P=0.37$, respectively) or in mean fasting insulin concentrations (obese 6.2±3.1 vs lean 6.4±1.6 mcU/ml, $P=0.35$). Obese subjects had longer T2 relaxation times in the Medial Basal Hypothalamus (MBH) when compared to lean group (105.9±4.2 vs 99.5±4.3 ms), consistent with gliosis. Moreover, there was a highly significant group*region interaction ($P=0.0016$), demonstrating that signs of gliosis were specific to the MBH as compared to control brain regions. Longer T2 relaxation times were correlated with higher visceral body fat percentage ($R^2=0.35$, $P=0.01$) and android fat percentage ($R^2=0.46$, $P=0.003$), but not fasting insulin concentrations ($R^2=0.02$, $P=0.6$). **Conclusion:** Obese children have signs of hypothalamic gliosis that, when present, is associated with body fat distribution signifying high metabolic risk. The presence of MBH gliosis in an obese pediatric population raises concern that hypothalamic inflammation plays a role in childhood obesity and is prior to the development of insulin resistance.

FC13.4

Efficacy and Safety of Duodenal-Jejunal Bypass Liner in Morbidly Obese Adolescents-1 Year Experience

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Background: The duodenal-jejunal bypass liner (DJBL) is an endoscopically placed and removable bariatric device associated with weight loss and metabolic improvements in adults. **Objective and hypotheses:** To determined efficacy and safety of DJBL up to 1 year in morbidly obese adolescents. **Method:** About 14 obese adolescents with prediabetes or type 2 diabetes (10 female, mean (SD) age 17.7 (1.1) years) underwent endoscopic placement of DJBL under general anesthesia. Inclusion and exclusion criteria are described in detail at www.ClinicalTrials.gov (NCT02183935). Subjects were examined at months 1, 3, 6, 9 and 12 following DJBL placement. **Results:** Relevant weight loss and improved glucose and cholesterol metabolism were determined. None of the devices needed to be explanted and there were no serious device related side effects. Decrease in iron levels without a relevant effect on erythropoesis was however determined. Of importance no changes in B12 and folic acid levels were determined (DNS). A decrease in Se, Zn, vitamins A, D3 and E was also determined (DNS). **Conclusion:** This is the first report on the use of endoscopically placed and removable DJBL in adolescents for up to 1 year. Relevant weight loss, metabolic improvements

	Baseline ($n=14$)	6 months ($n=10$)	12 months ($n=6$)
BMI (kg/m^2)	42,5 (4,1)	37.6 (3.7)*	38.2 (5.3)*
BMI SDS	3.74 (.32)	3.25 (.37)*	3.26 (.54)*
Waist circumference (cm)	127 (12)	116 (11)	116 (13)*
Systolic pressure (mmHG)	124 (12)	116 (10)	117 (14)*
Cholesterol (mmol/l)	4.6 (.9)	3.7 (.5)*	3.7 (.7)*
Triglycerides (mmol/l)	2.1 (1.0)	1.2 (.4)*	1.2 (.3)*
WBISI	1.8 (07)	2.8 (1.4)*	3.3 (1.1)*
HOMA-IR	5.5 (2.1)	3.8 (1.5)*	2.8 (.8)*
A1c (%)	5.3 (.5)	5.2 (.3)	5.0 (.3)
Fe	14.3 (5.5)	8.1 (2.4)*	8.8 (3.2)*
Ferritin	82 (55)	25 (10)*	38 (28)*
Hemoglobine	144 (12)	131 (10)*	138 (15)
Ht	0.41 (0.03)	0.39 (0.03)	0.40 (0.03)
MCV	82 (3)	82 (4)	82 (3)

Difference between means (SD) was determined by ANOVA and Dunnett's postHoc test. *$P<0.05$ when compared to baseline.

and no serious side effects of DJBL were determined. However monitoring of vitamins and trace elements status, especially iron is needed in these subjects.

FC13.5

Effects of AZP-531, a First-in-Class Unacylated Ghrelin Analog, on Food-Related Behaviour in Prader-Willi Patients: A Multi-Center, Randomized, Placebo-Controlled Study

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Background: Prader-Willi syndrome (PWS) is a rare genetic disorder characterized by hyperphagia and abnormal behaviours towards food for both of which no approved treatment is available. Elevated plasma acylated ghrelin (AG) documented at all ages in PWS suggest that the ghrelin system may contribute to the pathophysiology of hyperphagia. Administration of unacylated ghrelin and 8-amino acid analog AZP-531 prevents AG-induced food consumption in animals and improves glucose control and decreases weight in animal models and in Phase 1 clinical trials. **Objective and hypotheses:** To evaluate the safety, tolerability and effects of AZP-531 on food-related behavior in patients with PWS. **Method:** About 47 male and female patients with PWS and evidence of hyperphagia (mean age: 26.8 ± 6.7 yrs, range: [13–46 yrs], mean BMI: 38.00 ± 12.01 kg/m^2, range: [20.6–67.4 kg/m^2]) were randomly assigned to receive sc AZP-531 (3 mg or 4 mg) or placebo once daily for 14 days. Study assessments were performed on Day -1 (baseline), Day 1 and Day 14. **Results:** AZP-531 was well tolerated. A significant improvement in food-related behavior, as assessed by the Hyperphagia questionnaire, was noted in AZP-531 patients on Day 14 ($P < 0.05$ vs placebo) with particular improvement in the severity score ($P < 0.05$ vs placebo). Findings were supported by reduction in appetite feelings following breakfast. Body weight did not change after treatment with AZP-531 for 2 weeks in this highly variable population at baseline but waist circumference decreased ($P < 0.05$ vs baseline) and glucose control tended to improve with a greater effects in patients with higher fasting or post-prandrial glucose levels at baseline. **Conclusion:** AZP-531 may be a new treatment strategy for PWS. Data support further investigation to assess long-term safety and efficacy on food-related behaviour and metabolic parameters.

FC13.6

Treatment for Early Onset and Extreme Obesity in Two POMC Deficient Patients: Successful Weight Loss with the Melanocortin-4 Receptor Agonist Setmelanotide

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Background: POMC deficiency is an extremely rare monogenetic obesity syndrome generally characterized by early onset hyperphagia, red hair and adrenal insufficiency. So far treatment of obesity and hyperphagia with MSH substitution failed, either due to ineffectiveness or side effects of available MC4R agonists. **Objective and hypotheses:** We hypothesized that the new MC-4R agonist setmelanotide might be a treatment option in POMC deficient patients. **Method:** A Phase 2, non-randomized, open label pilot study with the new MC4R agonist setmelanotide was conducted in two POMC deficient adult patients (EudraCT No. 2014-002392-28; clinicaltrials.gov identifier No. NCT02507492). Setmelanotide was injected subcutaneously once per day with a single dose of 0.5 up to 1.5 mg. **Results:** Treatment resulted in 51 kg body weight loss after 42 weeks in patient 1 (32.9% of initial body weight) and 20.5 kg after three months in patient 2 (13.4% of the initial body weight). During a short, 3-week off-treatment phase patient 1 suffered from an immediate recurrence of hyperphagia and weight regain. Parallel to the weight loss, in both patients hyperinsulinemia improved significantly and led to a normalization of the initial insulin resistance. No serious adverse events were observed during the study period and setmelanotide treatment did not elicit the cardiovascular adverse effects described earlier with other MC4R agonists. **Conclusion:** This is the first report showing successful treatment of extreme obesity in POMC deficient patients. We propose that weight loss by setmelanotide is the result of substitution at the hypothalamic weight regulatory POMC pathway, for the missing POMC derivative MSH thus restoring MC4R activation. We conclude that other syndromes of MSH deficient obesity including Leptin receptor defects and PCSK1 deficiency might also benefit from treatment with setmelanotide.

FC14.1

Clinical Characterization of Children with Autosomal Dominant Short Stature due to Aggrecan Mutations Broadens the Phenotypic Spectrum

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Background: Heterozygous mutations in the Aggrecan gene (*ACAN*) cause autosomal dominant short stature with bone age (BA) acceleration, and premature growth cessation. **Objective and methods:** To characterize the phenotypic spectrum, associated conditions and describe response to growth-promoting therapies, detailed clinical evaluation of 73 mutation positive individuals from 16 families different families with heterozygous ACAN mutations was performed. **Results:** Adult individuals have mildly disproportionate short stature (average SDS height −2,8, range −0.9 to −4.5) with sitting height indices at the upper part of the normal range or slightly elevated (SDS average: 2.0, range: 0.4–3.8) and histories of early growth cessation and/or lack of pubertal growth spurt. Growth of upper extremities is often less affected with arm spans greater than height (arm span – height: median 5 cm, range −5 to +13.3). The condition is associated with early-onset osteoarthritis (nine families) and degenerative disc disease (six families). Before puberty, height is less affected and often in the lower part of the normal range (average height SDS: −2.1). In contrast to most children with short stature, many children with *ACAN* mutations have an advanced bone age (BA – CA, median: +1.3; range +0 to +3.8yr) reflecting a reduction in the remaining growth potential. Twelve patients have been treated with GH. In addition, three girls and one boy have received GnRH analog and two boys letrozole in order to slow down bone age advancement and increase final height. **Conclusion:** Heterozygous *ACAN* mutations result in a phenotypic spectrum ranging from mild and proportionate short stature to a distinct skeletal dysplasia with disproportionate short stature and brachydactyly. Several of the mutations also cause articular/intervertebral disc cartilage dysfunction leading to early-onset osteoarthritis and degenerative disc disease requiring intervention. Careful monitoring of patients with *ACAN* mutations will reveal the full spectrum of this condition and may identify important genotype-phenotype correlations.

FC14.2

CG Methylation at the IGF1 P2 Promoter is a Major Epigenetic Determinant of Postnatal, Not Foetal Growth

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Background: The height of children has a Gaussian distribution. Genetics explain an important part of individual variability, but no single genomic variant accounts for more than 0.3% of height variance. At the interface of genetics and environment, epigenetics is expected to contribute to phenotypic variability. IGF1 is an attractive locus to test this hypothesis. **Objectives:** To quantify the effect of CG methylation of IGF1 promoters on height. **Patients:** a) 216 children of various heights b) 94 children with idiopathic short stature (ISS) c) 46 children with intra-uterine growth retardation (IUGR) d) 12 children undergoing surgical procedures for independent reasons. All were studied before puberty. **Methods:** CG methylation of IGF1 promoters P1 and P2 was measured using bisulfite-PCR-pyrosequencing. IGF1 gene expression was measured in various tissues with qPCR. **Results:** Methylation was 50% lower in liver and growth plates, indicating that P2 is a tissue-differentially methylated region (t-DMR). Methylation showed an inverse correlation with P2 transcriptional activity in mononuclear blood cells and in transfection experiments. P2 methylation showed a strong inverse association with IGF1 and growth: methylation contributed 13% to height variance and 10% to circulating IGF1 variance. P2 methylation was higher in ISS than in children of normal stature, notably at CG-137 (P 9.10^{-5}), but showed no difference between IUGR and children of normal birth size. **Conclusion:** The observed association of IGF1 P2 methylation with gene expression supports true biological causality. Epigenetics at the IGF1 locus is a major determinant of postnatal, not fœtal, growth.

FC14.3

CG at the Methylation IGF1 Locus is an Epigenetic Predictor of GH Sensitivity

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Background: The growth and IGF1 responses to GH treatment show a large variation across children with idiopathic short stature (ISS). Compliance and GH regimens are important determinants. The d3 variant of the GH receptor (GHR) is a significant genetic predictor. The role of individual epigenetics had not been studied. The IGF1 locus is an attractive candidate where CG methylation could influence GH action. **Objectives:** To study GH effects on a) IGF1 gene expression in mononuclear blood cells

(PBMC) in children with ISS b) IGF1 increase during a generation test (ght) c) IGF1 response to GH treatment (GHT) d) growth response to GT. **Patients:** 75 ISS children underwent an IGF1 ght; 145 ISS children were studied during GHT. All children were pre-pubertal. **Methods:** CG methylation of the two IGF1 promoters (P1 and P2) quantified by bisulfite-PCR-pyrosequencing. **Results:** CG methylation of the P2 promoter (not P1) had a strong consistent effect on the whole spectrum of GH responses: a) inverse correlation with IGF1 transcripts in PBMC b) inverse correlation with IGF1 increase during ght c) inverse correlation with IGF1 increase and d) growth increase during GHT. P2 methylation contributed a large fraction to the variance in response to ght and GHT: the greater the methylation, the lower the response. **Conclusion:** Individual variation of CG methylation at the IGF1 locus is an important predictor of acute and chronic responses to GH administration. Our observation provides a first example of pharmaco-epigenetics in endocrinology. It also reveals a source of physiological variation in individual GH sensitivity.

FC14.4

Preferential Paternal Transmission of the T Allele for the rs1802710 Polymorphism In Dlk1 Gene as a Pre- and Postnatal Growth Regulator

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Background: *DLK1* or *PREF1* is an imprinted gene highly expressed from the paternal allele in embryonic tissues and placenta. It has been recently implicated in adipose tissue expansion and diabetes development. The human rs1802710 polymorphism (SNP) in *DLK1* gene has been associated with early-onset extreme obesity but its role determining growth is unknown. **Objective and hypotheses:** To study the preferential paternal transmission of rs1802710 SNP T allele in *DLK1* gene and its association with pre and postnatal growth as well as maternal metabolism during pregnancy. **Method:** We genotyped the rs1802710 SNP in *DLK1* gene in blood from 217 trios (apparently healthy mother-father-newborn trios; 651 samples) by means of real-time PCR. Fasting serum C-peptide and lipids were assessed in pregnant mothers during the second trimester. At birth, placentas and newborns were weighed and length and head circumference were measured in all infants. Additionally, fetal ultrasound measurements were recorded during pregnancy as well as weight and length of the infants during the first year of life. **Results:** The T allele of rs1802710 SNP in *DLK1* gene transmitted from the father ($n=43$ vs $n=63$ for the C allele and $n=111$ for heterozygotes) was related to a greater increase in fetal femur length ($P=0.025$) and both higher birth length ($P=0.031$) and head circumference ($P=0.007$). Moreover, these infants showed a greater weight gain at 4 ($P=0.014$), 6 ($P=0.001$) and 12 ($P=0.023$) months of life. Mothers, in turn, had higher C-peptide levels during pregnancy ($P=0.03$). These associations remained significant after correcting for confounding variables in multivariate analysis. **Conclusion:** These results suggest that the transmission of the rs1802710 SNP in *DLK1* gene may be a mechanism by which fathers can influence fetal and postnatal growth as well as maternal metabolism during pregnancy.

FC14.5

Preferential Transmission of the Paternal C Allele of the rs9373409 Polymorphism in *plagl1* Gene as a Regulator of Fetal Growth and Maternal Metabolism

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Background: The phenotypic effects of single nucleotide polymorphisms (SNPs) may depend on their parental origin. *PLAGL1* is an imprinted gene expressed from the paternal allele in placenta that is associated with fetal growth, transient neonatal diabetes mellitus and postnatal growth disorders. The mechanisms whereby *PLAG1* regulates fetal growth are, however, unknown. **Objective and hypotheses:** To study if the preferential paternal transmission of rs9373409 SNP alleles in *PLAGL1* relates to fetal growth and maternal metabolism during pregnancy. **Method:** We examined parent-to-offspring transmission of rs9373409 SNP alleles in *PLAGL1* by means of real time PCR in leukocytes of 217 trios (apparently healthy mother-father-newborn trios; 651 samples). HOMA-IR, IGF-I and lipids were assessed in fasting serum samples of mothers during the second trimester of pregnancy. At birth, placentas and newborns were weighed and length and head circumference were measured in all infants. Finally, abdominal fat was measured by ultrasound one month after birth in the infants. **Results:** The transmission of the paternal C allele of rs9373409 SNP in *PLAGL1* gene ($n=95$ vs $n=58$ for the T allele and $n=64$ for heterozygotes) was associated with a higher birth weight ($P=0.017$), length ($P=0.050$) and head circumference ($P=0.033$) and increased abdominal fat ($P=0.015$) at one month of life. Mothers of infants receiving the C allele from the father exhibited a less favorable metabolic profile, showing increased HOMA-IR ($P=0.023$) and higher circulating IGF-I concentrations ($P=0.003$). All these associations remained significant after correcting for confounding variables such as: gestational age, gender, maternal age, maternal BMI and parity. **Conclusion:** The transmission from the parent of the C allele of rs9373409 SNP in *PLAGL1* may adversely affect maternal metabolism during gestation to promote fetal growth.

FC14.6

In vitro and *in vivo* Evidence for a Growth Inhibitory Role of the Transcription Factor *ZBTB38* Throughout Pre- and Post-Natal Life

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Background: Single nucleotide polymorphisms (SNPs) within the promotor and 5'UTR of the transcriptional factor, ZBTB38, are associated with adult height and idiopathic short stature although their precise auxological effects have not previously been described. In addition, the molecular mechanisms through which ZBTB38 affects growth have not been fully elucidated but potential downstream mediators are suggested to include MCM10 or IGF2. **Objectives: 1.** To describe the auxology of two independent cohorts of children genotyped for *ZBTB38* SNPs rs6764769 (G/A) and rs724016 (A/G) **2.** Explore the effects of *ZBTB38* expression on childhood growth, cell growth as well as *MCM10* and *IGF2* transcription. **Methods:** The EPIGROW ($n=261$) and Manchester Growth Study ($n=93$) were genotyped via sequencing (Next Generation/Sanger sequencing) and detailed auxology collected. *ZBTB38* knockdown was achieved in a SiHa cell line via siRNA transfection with transcription of *MCM10* and *IGF2* assessed by qPCR and cell growth by WST-8 assay. Age related childhood gene expression in PBMCs from normal control children was derived from data from multiple GEO datasets. **Results:** Carriage of GG genotype was associated with reduced birth length SDS (both SNPs, $P=0.001$) and birth weight (g) (rs724016, $P=0.01$) but there was no effect on childhood BMI, head circumference or response to GH therapy (defined as 1st year ΔHt SDS). *ZBTB38* expression in PBMCs was inversely related to growth rate throughout childhood and adolescence. The *in vitro* *ZBTB38* knockdown demonstrated increased cell growth ($P=0.001$) at 72 hours post-transfection with no change in *MCM10* or *IGF2* expression. **Conclusion:** The knockdown studies link reduced *ZBTB38* expression to increased growth independent of *IGF2* or *MCM10* expression. *ZBTB38* expression affects both pre- and post-natal growth and, given the location of the SNPs, it is likely that they mediate their effects via altering *ZBTB38* expression.

FC15.1

NR5A1 is a novel disease gene for 46,XX testicular and ovotesticular disorders of development

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Background: While many causes of 46,XY disorders of sex development (DSD) have been elucidated, the mechanisms leading to 46,XX testicular or ovotesticular DSD are poorly understood. It has been hypothesized that both conditions may represent a phenotypic spectrum and that they might be caused by (different) mutations in the same genes. **Methods:** Whole exome sequencing was used to identify the molecular cause in ten unrelated patients with 46,XX (ovo)testicular DSD. Transcriptional activation of the variant of interest was assessed using luciferase assays and RNA-seq was performed on patient-derived lymphocytes. Immunohistochemistry was done on gonadal specimens for markers of gonadal development. **Results:** We identified a novel heterozygous *NR5A1* variant c.274C>T p.(Arg92Trp) in three unrelated 46,XX (ovo)testicular DSD cases. This variant is absent in genomic databases and is predicted to be deleterious. The Arg92 residue is conserved up to zebrafish and located in the RGGR motif in the loop before the C-terminus helix in the conserved Ftz-F1 box. This domain was previously reported to be important for DNA binding specificity and stability. Structural remodeling indeed shows that Trp cannot be introduced without steric clashes. Immunohistochemistry confirmed SRY-independent SOX9 expression and absent FOXL2 in testicular parts of XX gonads and vice versa in ovarian regions. No consistent changes in transcriptional activation were seen. RNA-seq showed upregulation of *MAMLD1*, a direct target of NR5A1, that has already been associated with hypospadias and 46,XY DSD. **Conclusions:** Previously, loss-of-function mutations in *NR5A1* were found in a spectrum of male undervirilization and premature ovarian insufficiency in 46,XX females. Here, a novel *NR5A1* mutation was found in three unrelated cases with 46,XX testicular or ovotesticular DSD, an ultra-rare condition. We hypothesize that this variant results in upregulation of specific target genes, thereby triggering testicular differentiation in 46,XX individuals. We propose *NR5A1* mutation p.(Arg92Trp) as a new cause for 46,XX (ovo)testicular DSD.

FC15.2

Mutations in SGPL1, the Gene Encoding Sphingosine-1-Phosphate Lyase, Cause a Novel Form of Primary Adrenal Insufficiency with Steroid Resistant Nephrotic Syndrome

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Background: Primary adrenal insufficiency (PAI) is most commonly congenital in children. PAI is genetically heterogeneous with some gene defects causing syndromic disease. A third of patients have no genetic diagnosis meaning their prognosis is uncertain. We recently investigated families with a novel combination of PAI and steroid resistant nephrotic syndrome. **Objective and hypotheses:** To discover the genetic defect underlying this syndrome. **Method:** Whole exome sequencing (WES) was performed in two families with Sanger sequencing of *SGPL1* to confirm segregation and screen further families. **Results:** By WES and Sanger sequencing three different mutations in *SGPL1* were identified in four families. All mutations were homozygous in affected individuals and heterozygous in their asymptomatic parents. Kindred 1, three patients had a novel missense mutation [c.665G > A; p.R222Q], the index case presented with PAI (8 m), developed focal segmental glomerulosclerosis (FSGS) at 2.5y and received a kidney transplant aged 5y. A younger sibling with similar clinical history (not sequenced) died (4y) whilst an older sibling (8y) and a cousin (3y) have only PAI. Kindred 2, a child presenting with PAI had the p.R222Q mutation and at age 3.7y has no renal phenotype. Kindred 3, a female baby presenting with PAI (6 m) had a novel in-frame deletion, [c.1633_1635delTTC; p.F545del] and developed FSGS (5y) on follow-up, additional features included ichthyosis and neurological symptoms. Kindred 4, two affected siblings manifesting PAI and nephrotic syndrome (< 1yr) had a canonical splice site change, [c.261 + 1G > A; p.?], the male sibling additionally presented with micropenis, unilateral cryptorchidism, ichthyosis and developed neurological symptoms. **Conclusion:** We have identified a novel, potentially progressive, disorder incorporating PAI and nephrotic syndrome amongst other features. This novel syndrome highlights the importance of the sphingolipid metabolic pathway in adrenal function. A genetic diagnosis for patients with this form of PAI is important for correct treatment, genetic counselling and screening for co-morbidities.

FC15.3

Contribution of Next Generation Sequencing Approach for Management of Congenital Hypothyroidism with Eutopic Thyroid Gland

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Background: Congenital hypothyroidism (CH) is referred to dyshormonogenesis for 15 to 30%. Homozygous mutations associated have been demonstrated in DUOX2, TPO, TG, SLC5A5 (NIS), SLC26A4 (Pendred), DUOXA2, and IYD (DEHAL1) genes. **Objective and hypotheses:** Previous studies focusing on one or few thyroid-specific genes have proved not to be comprehensive enough for understanding physiopathological mechanisms of HC with dyshormonogenesis. Emerging diagnostic tools as next generation sequencing (NGS) led to efficiently study some targeted genes involved in a specific disease. **Method:** Using this approach, we have studied DNA samples from 30 newborns HC and eutopic gland for 18 candidate genes (CDS and UTR) to explore the causative genes for thyroid dyshormonogenesis. **Results:** Among the 30 infants, 16 (55%) presented mutation in one or more genes of the thyroid hormone synthesis axis. For 9 infants we have identified homozygous or composite heterozygous mutation for TG, DUOX2, TPO or SLC5A5 genes whereas 5 presented heterozygous mutations in two different genes of the thyroid hormonogenesis pathway, TG and DUOX2 or TG and TPO. In 2 cases, heterozygous mutation in the TG gene was the unique anomaly identified in the hormone synthesis pathway but related to disturbed hormonal balance. Exploring the thyroid hormone synthesis pathway by NGS has revealed that 7/16 newborns (43%) presented composite heterozygous or heterozygous mutation in two genes involved in the hormone synthesis process. Thyroglobulin is the high –frequency mutated gene in our population. In all cases the correlation between biological and imaging studies and molecular status was examined. **Conclusion:** The systematic exploration of genes involved in the thyroid hormone synthesis by NGS in HC with eutopic gland showed high level diagnostic relevance. Furthermore significant percentage of them occurs when two steps in the hormone synthesis process are impaired. Heterozygous composite mutations could be related to the phenotypic heterogeneity observed for HC with dyshormonogenesis.

FC15.4

Vitamin D-Dependent Rickets Type 1 Caused by Mutations in CYP27B1 Affecting Protein Interactions with Adrenodoxin

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Background: CYP27B1 converts 25-hydroxyvitamin D_3 to active 1,25-dihydroxyvitamin D_3, playing a vital role in calcium homeostasis and bone growth. Vitamin D-dependent rickets type 1 (VDDR-1) is a rare autosomal recessive disorder caused by mutations in CYP27B1. **Objective and hypotheses:** Enzymatic and structural analysis of mutations in a patient with calcipenic rickets. **Method:** Two siblings presented with calcipenic rickets and inappropriately normal 1.25-dihydroxyvitamin D_3 levels. CYP27B1 gene analysis showed compound heterozygous mutations confirming VDDR-1. We studied wild type CYP27B1 and mutations H441Y and R459L by computational homology modeling, molecular dynamics simulations and functional studies using a luciferase assay. The patient was successfully treated with calcitriol. **Results:** Mitochondrial cytochrome P450s require adrenodoxin (FDX1) and adrenodoxin reductase. We created models of CYP27B1-FDX1 complex which revealed negative effects of mutations H441Y and R459L. Upon structural analysis, near-identical folds, protein contact areas, and orientations of heme/iron-sulfur cluster suggested that both mutations destabilize the CYP27B1-FDX1 complex by negating directional interactions with adrenodoxin. This system is highly sensitive to small local changes modulating the binding/unbinding of adrenodoxin, and electron-transporting efficiency changes with mutations at the surface. Functional assays confirmed this hypothesis and showed severe loss of activity of CYP27B1 by both mutations. **Conclusion:** This is the first report of mutations in CYP27B1 causing VDDR-1 by affecting protein-protein interactions with FDX1 that results in reduced CYP27B1 activities. Detailed characterization of mutations in CYP27B1 is required for understanding the novel molecular mechanisms causing VDDR-1.

FC15.5

Effect of Conjugated Linoleic Acid and Metformin on Insulin Sensitivity, Measured by Euglycemic-Hyperinsulinemic Clamp Technique, in Children with obesity: A Randomized, Double-Blinded, Placebo-Controlled Trial

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Background: Insulin resistance precedes metabolic syndrome abnormalities, and may promote cardiovascular disease and type 2 diabetes in obese children. Lifestyle modification programs have been proposed as the gold standard of care in these individuals. However, results have been discouraging and the use of adjuvant strategies has been necessary. Metformin has beneficial effects on weight reduction, favoring a decrease in body mass index (BMI) and insulin resistance in obese non-diabetic individuals. Furthermore, several studies have acknowledged the beneficial effects of CLA isomers on body composition, insulin sensitivity and lipid metabolism in experimental animals and humans. **Objective and hypotheses:** Evaluate metformin and Conjugated Linoleic Acid (CLA) effects on insulin sensitivity, measured by the gold standard Euglycemic-Hyperinsulinemic Clamp Technique, in obese Mexican children. We hypothesized that Metformin and CLA would exceed lifestyle intervention benefit with an effect size of at least 30% over the main outcome M-value insulin sensitivity compared to placebo treated patients **Method:** A randomized, double-blinded 16-weeks placebo-controlled clinical trial was conducted. Obese children and adolescents were randomly assigned to receive either metformin (1 g), CLA (3 g) or placebo. (Clinicaltrials.gov:NCT02063802).All patients were included in s standardized lifestyle intervention programe **Results:** Intervention had a positive effect on weight, height, BMI, waist circumference and fitness condition in all groups. For the primary outcome, Insulin Sensitivity M-value (mg/kg/min), there was a statistically significant difference between CLA group compared to PLB (6.53 ± 2.54 Vs 5.05 ± 1.46, $P = 0.035$). Fasting insulinemia and HOMA-IR significantly improved in CLA group ($P = 0.045$). Covariance analyses were executed to control the influence of BMI, Δ-BMI, age, Tanner stage, prescribed diet and fitness achievement over the Insulin Sensitivity M-value. Tanner stage showed statistical significant influence. **Conclusion:** A clinically relevant effect size on insulin sensitivity was evident in CLA treated patients (37%) that exceed lifestyle intervention program benefits.

FC15.6

Type 1 Diabetes Associated Serum Insulin-Like Growth Factor I (IGF-I) Reference Values in Children and Adolescents

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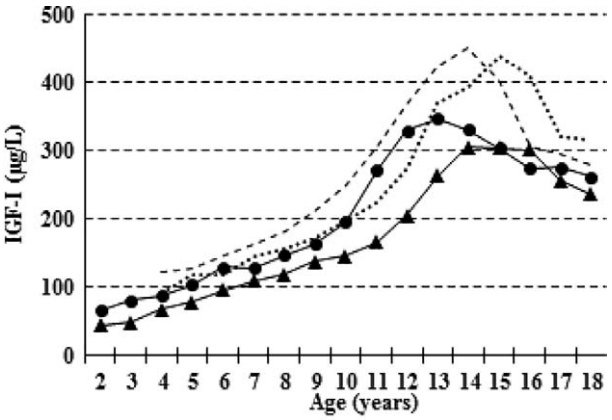
Background: The disturbance of the GH-IGF-axis in type 1 diabetes (T1DM) with low circulating IGF-I, GH hypersecretion, and hyperinsulinemia, which may be associated with high tissue IGF-I, have implications on long-term vascular complications.

Objective and hypotheses: To establish disease, sex and age related serum IGF-I reference values for children with T1DM and test the hypothesis that IGF-I SDS is lower in T1DM than in healthy controls and negatively correlated to HbA1c, age, diabetes duration, and BMI. **Method:** Annual IGF-I values were obtained from children and adolescents with T1DM. A total of 2,683 serum IGF-I values from 806 children were collected for up to 6 consecutive years. **Results:** Diabetes, sex and age related IGF-I SDS values were negatively correlated to HbA1c, age, and diabetes duration, but positively correlated to BMI. Children and adolescents with T1DM had lower mean IGF-I levels as well as lower cut-offs (± 2 SD) compared to healthy subjects. In boys with T1DM, mean IGF-I levels were -1.04 SD calculated from the healthy reference. IGF-I peaked at 15 years of age, similar to healthy controls, but with markedly lower levels in late puberty. Girls were more affected at later stages of puberty but with a slightly less depressed overall mean IGF-I of -0.69 SD. There was no correlation between IGF-I SDS and final height SDS or distance to TH SDS. **Conclusion:** We have established an IGF-I reference for children with T1DM and demonstrated that poor metabolic control and diabetes duration impact negatively on serum IGF-I levels. Low serum IGF-I may further elevate GH and increase insulin in extra-hepatic tissues leading to high tissue IGF-I and progression of vascular complications. IGF-I SDS may become a complement to HbA1c in predicting long term outcomes in T1DM.



Mean values of IGF-I in healthy girls = dashed line; healthy boys = dotted line; girls with T1DM = circles; boys with T1DM = triangles

Rapid Free Communications

RFC1.1

Tracing the Glucocorticoid Receptor Evolutionary Pedigree: Insights from a Comprehensive Phylogenetic Analysis of the Full NR Super-Family

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Background: The nuclear receptor (NR) family comprises three main subfamilies: the steroid hormones receptors, the thyroid/retinoid hormone receptors and the orphan receptors. Proteins within the NR family share common domain architecture. These closely related receptors and their cognate ligand compounds play a key role in homeostasis, reproduction, growth and development. Despite their biological significance, their evolution and diversification remains to be elucidated. **Objective and hypotheses:** To establish an in-depth phylogenetic tree of the NR family across all species in the tree of life in order to identify molecular and evolutionary traits specific to the glucocorticoid receptor (GR). **Methods and Results:** Combinations of key terms were employed in order to identify relative NR and GR protein sequences on both primary and tertiary/ quaternary structural levels. Sequence data were collected from the NCBI Database. Two distinct datasets were prepared for the purposes of this study. The first dataset comprised of all NRs, which involved 84566 entries across all known receptor sub-classes. In the second dataset, 217 GR entries were collected and clustered in groups using both evolutionary and physicochemical criteria. The clustered groups were then blasted against the PDB in a query for X-ray solved structures as templates for a holistic 3D homology modeling experiment of the GR family. Both datasets were aligned using progressive methods. The phylogenetic analysis was conducted using the UPGMA distance method and the 3D modeling was performed using MOE. **Conclusion:** Based on our comprehensive phylogenetic analysis of nuclear receptors, a reliable phylogeny "map" was constructed for GRs. It allowed to pinpoint evolutionary and structurally invariant patches on both the 1D and 3D level of the GR family, which led to the identification of structural 'hotspots' directly related to function that are of great interest as novel pharmacological targets.

RFC1.2

Glucocorticoid Deficiency Due to Disruption of Mitochondrial Steroidogenesis Leads to Dysregulation of Antioxidant Pathways and Nucleotide Biosynthesis

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Glucocorticoids are important regulators of systemic homeostasis. However, the role of these steroid hormones has been mainly studied by using synthetic glucocorticoids or in states of glucocorticoid excess. Thus, the pathophysiologic consequences of cortisol deficiency on metabolic and biosynthesis pathways remain largely elusive. Zebrafish is a well-established vertebrate model for studying whole organism biology. Similar to humans, zebrafish are day active and the key glucocorticoid in zebrafish is cortisol. Thus zebrafish are an ideal model to study the pathophysiologic impact of cortisol deficiency *in vivo*. Our recently published ferredoxin (fdx1b) null-allele zebrafish line, disrupted in mitochondrial glucocorticoid synthesis, has massively decreased cortisol concentrations and a severely impaired stress response. This study aimed to define the global pathophysiologic response *in vivo* to glucocorticoid deficiency. To address this question, systemic profiling of the fdx1b null-allele zebrafish line was performed by a combination of RNA-sequencing and metabolomics analysis. Our results revealed an enrichment of genes in the fdx1b null-allele zebrafish line linked with pathways linked to metabolic disease. This includes significant alteration in expression of genes acting in pathways of energy and biomolecule synthesis (e.g., amino acids), and also antioxidant pathways. Metabolic profiling using Nuclear Magnetic Resonance spectroscopy/ Mass spectrometry approaches supported the observed transcriptome changes of the affected pathways. In addition, we discovered post-transcriptional regulation of genes of nucleotide metabolism by glucocorticoids. For the first time, we provide *in vivo* evidence on the global pathophysiologic effects of glucocorticoid deficiency. Such data are vital improving the understanding of the pathophysiology of adrenal insufficiency in humans and develop more physiologic replacement strategies.

RFC1.3

Impaired Cardiac Function in a Mouse Model of Generalized Glucocorticoid Resistance

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Background: Glucocorticoids regulate a broad spectrum of physiologic functions essential for life and exert their actions through their ubiquitously expressed glucocorticoid receptor (GR). The GR interacts with several molecules, including the non-coding RNA growth arrest-specific 5 (Gas5), which decreases the transcriptional activity of the GR by preventing its binding to DNA, and reduces tissue sensitivity to glucocorticoids. **Objective and Hypotheses:** To create a mouse model of Generalized Glucocorticoid Resistance by inducible overexpression of Gas5 and to investigate its myocardial function. **Methods:** Two transgenic lines expressing the reverse transactivator (rtTA) under hnRNP promoter and the Gas5 under Tet responsive P tight promoter were generated and then crossed to create double transgenic mice (Gas5/rtTA), which were then tested for Gas5 inducibility of overexpression by qRT-PCR. The cardiac function was evaluated by echocardiography and 24-hour electrocardiography (ECG). **Results:** Genetic constructs of double transgenic mice inducibly overexpressing Gas5 after doxycycline administration (DOX+) were generated. The induction of overexpression of Gas5 in: Gas5/rtTA mice (2 weeks DOX+; 0.78±0.37) compared with i) Gas5/rtTA mice without doxycycline administration (DOX−; 0.14±0.04), ii) single transgenic DOX+ mice where the TetOn system is not functional (0.3*10−4±0.5*10−5), and iii) wild-type (WT) DOX+ mice (0.7*10−5±0.8*10−5) was verified in the myocardium. The cardiac function (% fractional shortening) was significantly decreased in Gas5/rtTA/DOX+ compared with Gas5/rtTA/DOX− mice (44.6±0.8 vs 48.5±0.4; $P=0.003$) but not compared with WT/DOX+ mice (46.9±0.4, $P=0.2$). This was mainly due to decreased systolic function in Gas5/rtTA/DOX+ vs Gas5/rtTA/DOX− mice (end-systolic dimension: 1.6±0.1 vs 1.8±0.1 mm; $P=0.05$). ECG studies did not show differences among the three groups of mice in terms of heart rate, ECG interval measurements and arrhythmias. **Conclusion:** We created a mouse model of Generalized Glucocorticoid Resistance and demonstrated impaired cardiac function. Ongoing studies aim to investigate the molecular mechanisms through which glucocorticoid resistance affects myocardial function.

RFC1.4

Mutations of *ABCD1* in 16 Vietnamese Patients with X-linked Adrenoleukodystrophy

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Background: X-linked adrenoleukodystrophy (X-ALD) is caused by a defect in the gene *ABCD1*, which maps to Xq28 and codes for a peroxisomal membrane protein that is a member of the ATP-binding cassette transporter superfamily. This disease characterized by progressive neurologic dysfunction, occasionally associated with adrenal insufficiency. **Objective and hypotheses:** To identify mutations of gene *ABCD1* in Vietnamese patients with X-ALD. **Method:** Genomic DNA from 16 Vietnamese patients from 14 unrelated families was extracted using standard procedures from the peripheral blood leukocytes. Mutation analysis of *ABCD1* was performed using Polymerase chain reaction (PCR) and DNA direct sequencing. **Results:** We identified 13 different mutations of *ABCD1* in 16 patients including missense mutations (8/13), deletion (4/13) and splice site mutation (1/13). Of which, six novel mutations including c.1202G>T (p.Arg401Trp); c.1208T>A (p.Met403Lys); IVS8+28-551bp del; c.1668G>C (p.Q556H); c.292_296delTCGGC (p.S98RfsX95); and the extent of deletion included between IVS1+505 and IVS2+1501, containing whole the exon 2 (4243bp), plus insertion of 79bp from BAP31 and 8bp from unknown origin in this deleted region were identified in six unrelated patients. Seven reported mutations including c.1628C>T (p.Pro543Leu); c.1553G>A (p.Arg518Gln); c.1552C>T (p.Arg518Trp); c.854G>C (p.R285P); c.1825G>A (p.E609K); c.1415_1416delAG (p.Q472RfsX83) and c.46-53del insG were identified in 9 patients from 7 families. **Conclusion:** Mutation analysis of *ABCD1* helped confirmation of diagnosis of X-ALD, genetic counselling and prenatal diagnosis.

RFC1.5

A Novel Animal Model to Study 21-Hydroxylase Deficiency *in vivo*

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Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (21OHD) is caused by mutations in the *CYP21A2* gene. Steroid 21-hydroxylase deficiency results in impaired synthesis of mineralcorticoids and glucocorticoids (GC), plus androgen excess. Hormonal imbalances in 21OHD are postulated to result in systemic transcriptomic and metabolomic alterations. Such perturbations are likely to be underlying co-morbidities, which are increasingly observed in individuals with CAH. Due to the lack of suitable animal models, *Cyp21a2* ko mice are not viable, systemic consequences of 21OHD are poorly understood. Therefore, we generated several zebrafish *cyp21a2* null-alleles by genome editing using a TALEN (transcription activator-like effector nuclease) approach. These lines serve as an *in vivo* model to study whole-organism consequences due to 21OHD. Zebrafish Cyp21a2 is highly conserved and converts 17-hydroxyprogesterone into 11-deoxycolesterol *in vitro*. Furthermore, we found that *cyp21a2* expression is largely restricted to the interrenal gland (adrenal counterpart), the brain and ovary. Two different null-allele strains were used to characterise the *cyp21a2* mutant phenotype. Homozygous *cyp21a2* mutants display a phenotype with altered visual background adaption (similar to hyperpigmentation) that has been described for zebrafish with defective GC

synthesis or action. Deficient cortisol synthesis in *cyp21a2* mutants was confirmed by steroid measurements using ultra-performance convergence chromatography tandem mass spectrometry. The expression of the GC regulated target genes *fkbp5* and *pck1* is reduced in mutants, validating systemic cortisol deficiency. The consequential up-regulation of the hypothalamus-pituitary interrenal axis in *cyp21a2* mutants was shown by increased *pomca* expression. Whole mount *in situ* hybridisation demonstrated interrenal hyperplasia in *cyp21a2* mutants. In conclusion, we have shown that *cyp21a2* mutant zebrafish represent a valid model to study the consequences of 21OHD. The whole-organism analysis of this model will provide urgently warranted insights into dysregulated pathways important for the pathophysiology of 21-hydroxylase deficiency and associated co-morbidities in patients with CAH.

RFC1.6

Pediatric Patients with Congenital Adrenal Hyperplasia have Unfavorable Changes in their Cardiovascular Risk Profile

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Background: Patients with congenital adrenal hyperplasia (CAH) are at risk of developing an unfavorable cardiovascular risk (CVR) profile. Data on the CVR profile in pediatric CAH patients are scarce. **Objective and hypotheses:** To evaluate the CVR profile of pediatric CAH patients. **Method:** A cross-sectional study in CAH patients (8–16 years) was performed ($n=27$). Blood was taken to evaluate several circulating CVR markers. Insulin resistance (IR) was evaluated by HOMA-IR. Blood pressure (BP) was evaluated by office BP measurements and 24 hour ambulatory BP measurements (24 h ABPM). Carotid intima media thickness (cIMT) was evaluated. In patients >12 years a DXA scan was performed. SD scores (SDS) were calculated if possible. **Results:** BMI SDS was significantly elevated (0.67; $P=0.012$) with 7 patients being overweight (25.9%) and 4 obese (14.8%). BMI SDS was associated with 17OHP ($r=0.394$; $P=0.042$) and androstenedione ($r=0.406$; $P=0.036$) concentrations, but not with hydrocortisone (HC) dose. DXA scan evaluation of body composition showed fat tissue mass SDS of 0.94 ($P=0.043$) and percentage body fat SDS of 1.59 ($P<0.001$). Body composition and HC dose were not associated. Office systolic and diastolic BP SDS were both higher than reference values (0.83, $P<0.001$; 0.56, $P<0.01$). The 24 h ABPM showed systolic hypertension in 5 patients (18.5%), while 11 patients (40.7%) had a non-dipping BP profile. The percentage of the dip in sleeping BP was negatively associated with BMI SDS ($r=-0.489$; $P=0.01$), but not with daily HC dose. HOMA-IR was above the 75th percentile in 12 patients (44.4%) and was positively associated with daily HC dose ($r=0.436$, $P=0.023$) and BMI-SDS ($r=0.500$, $P=0.008$). The lipid profile and cIMT were normal. **Conclusion:** CAH patients may develop an unfavorable CVR profile already in childhood with significantly increased BMI, increased fat mass, elevated BP levels, a non-dipping BP profile, and IR. BP levels, the percentage dip in sleeping BP, HOMA-IR values were associated with BMI SDS.

RFC1.7

The Recovery of Adrenal Function in Children with Chronic Asthma Assessed by Low Dose Short Synacthen Test (LDSST)

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Background: Hypothalamic-Pituitary–Adrenal (HPA) axis suppression is common during inhaled corticosteroid (ICS) treatment of asthma, and deaths due to adrenal crisis are described. Little is known about the optimal treatment or recovery of ICS induced HPA axis suppression. **Aims:** To describe the treatment and outcomes of children with ICS induced HPA suppression diagnosed on the low dose short Synacthen test (LDSST). **Method:** The data from ICS treated children between 2008–2014 were studied. Age, ICS dose at the time of LDSST (Beclomethasone equivalent) and the outcome of LDSST ('Normal': Peak cortisol ≥500 nmol/l, 'Suboptimal': Peak cortisol 350–499 nmol/l and 'Abnormal': Peak cortisol <350 nmol/l)) were noted. Abnormal basal cortisol levels at 9 am(0-min) <100 nmol/l were also analysed in detail. Children with 'suboptimal' responses were treated with hydrocortisone (20 mg/m^2 per day) during illness only; those with 'abnormal' responses were treated with hydrocortisone 5–7.5 mg/m^2 per day, and 20 mg/m^2 per day during illness. **Results:** Total of 218 tests were carried out in 113 children (M=74), mean age 10.2±3.3 years, 1.9 LDSSTs/child (range 1–6). Duration of follow up was 1.0±1.5 years. Peak cortisol responses were normal in 42(37%), suboptimal in 58(51%) and abnormal in 13(12%). The 9 am cortisol was <100 nmol/l in 9(8%) children. Two patients in this group recovered, but 4 remained abnormal after 1.8 (0–5.5) years, with failed follow up in 3/9. Adrenal function recovered in 23/38(61%) and 5/7(71%) of patients in suboptimal and abnormal group respectively over 1.38±1.6 years. In suboptimal group, 1/38(3%) worsened and

14/38(37%) still remained suboptimal. Persistent abnormality was also noted in 2/7(29%) patients of abnormal group [Table-1]. Statistical analysis comparing ICS doses in those not recovered (start 693 ± 321 mcgs Vs final 631 ± 424 mcgs) was significant ($P = 0.027^{*}$) after a follow up of 2.2 ± 1.6 years. Two patients with abnormal responses experienced adrenal crises, but none in the normal or suboptimal groups. **Conclusion:** Treatment with daily hydrocortisone in modest doses is compatible with HPA recovery.

Table 1.

Characteristics	Sub optimal	Abnormal
Total numbers (113)[M]	58 [39]	13 [10]
Age in years at first test -mean (SD)	10.5 (3.3)	9.8 (3.7)
F/U in Years -mean (SD)	1.5 (1.6)	1.0 (1.5)
Steroid dose in MCGS Mean (SD)	689 (289)	754 (260)
Average tests/person	2.2	2.1
Normalisation or improvement (%)	23/38 (61%)	5/7 (71%)
Worsening or no improvement (%)	15/38 (39%)	2/7 (29%)
No Follow up test (% of this group)	20 (34%)	6 (46%)

RFC1.8

Adrenal Dysfunction in HIV-Exposed Uninfected Infants Receiving Ritonavir-Boosted Lopinavir, an HIV Protease Inhibitor, for the Prevention of Breastfeeding HIV Transmission. An ANRS 12174 Substudy

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Background: We recently demonstrated that both ritonavir-boosted lopinavir (LPV/r) and lamivudine (3TC, a nucleoside analogue) given to breastfed infants can reduce the risk of post natal HIV transmission (ANRS 12174 trial; Nagot, Lancet 2016). In another setting we previously showed the occurrence of adrenal dysfunction in newborn perinatally exposed to LPV/r leading to acute adrenal insufficiency in premature babies (Simon, JAMA 2011). **Objective and hypotheses:** Within the ANRS 12174 trial, the administration, randomly assigned, of LPV/r as a monotherapy prophylaxis up to one year in exposed uninfected infants, as compared to 3TC, offered a unique opportunity to study the potential adrenal impact of LPV/r in infants. **Method:** According to protocol and ethical authorizations, frozen serum samples collected at Week 6 (W6) and Week 26 (W26) from infants enrolled in Burkina Faso were blindly analyzed using steroid profiling by GC-MS. **Results:** 96 infants (LPV/r: 49, 3TC: 47) samples were analyzed. A marked increase of dehydroepiandrosterone (DHEA) was observed in LPV/r exposed infants as compared to 3TC (median (IQR)): 3.0 (1.6–4.8) vs 1.4 (0.5–3.5) at W6 and 0.4 (0.0–0.8) vs 0.1 (0.0–0.3) ng/ml at W26 respectively, both $P < 0.001$). In infants with high DHEA level at W6 (> 5 ng/ml ($n = 11$)), other adrenal hormones were also significantly increased as compared with 38 with DHEA < 5). **Conclusion:** In comparison with lamivudine, LPV/r exposure during the first year of life is associated with a significant, early adrenal dysfunction sustained during exposure. This effect may result from the interactions between LPV/r and the immature infant's adrenal and/or an increased ACTH like effect. Further analyses on samples collected after LPV/r discontinuation are pending. There was no difference in severe adverse events incidence between the two treatment groups in the entire cohort ($n = 1236$), but subtle impact on growth and genital development are actively monitored.

RFC2.1

25-OH-Vitamin D Status in a Pediatric Population of Subjects Affected By Prader-Willi Syndrome Compared to Matched Obese Controls

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Background: Obesity is usually correlated with a higher prevalence of 25OH vitamin D (25OHD) deficiency. This might be due to either volumetric dilution of vitamin D in the large fat mass or its increased uptake by adipose tissue. To our knowledge, a systematic study on 25OHD levels in Prader-Willi syndrome (PWS), a genetic disorder associated with severe obesity, is not available. **Objective and hypotheses:** To analyze the 25OHD values in a population of pediatric PWS in comparison with a group of obese controls (CNT), highlighting the possible correlation with fat mass and GH therapy (GHT). **Methods:** 52 PWS (25 males) and 111 CNT (57 males), gender-, age- and BMI-SD matched were included. None of them was on calcium or vitamin D, while 20 PWS were undergoing GHT. **Results:** 16 PWS (30.7%) and 27 CNT (24.3%) had low 25OHD level (P = NS). Mean 25OHD was 28.9 ± 12.5 in PWS GHT vs 26.9 ± 12.6 ng/ml in no GHT (P = NS). The more relevant findings are reported in the table. Univariate analysis (Pearson's) showed in both groups a

negative correlation between 25OHD and fat mass% (FM%) (PWS $r=-0.0308$; $P=0.031$; CNT $r=-0.200$; $P=0.04$). In the group of PWS, GHT was correlated with lumbar Z score ($r=0.382$; $P=0.005$). **Conclusion:** Our data showed that PWS had similar values of 25OHD compared to CNT. As already described, FM seems to be the only parameter influencing 25OHD levels. Finally, GHT does not seem to influence 25OHD metabolism in PWS.

Table 1.

	PWS	CNT	*P*
Age (yrs)	13.1±3.4	12.9±1.9	NS
BMI SD	2.2±1.9	2.1±0.5	NS
Pubertal stage (Tanner)	2.1±0.8	2.8±1.1	0.05
Calcium (mg/dl)	9.7±0.4	9.8±0.4	NS
Phosphorus (mg/dl)	4.5±0.6	4.5±0.5	NS
PTH (pg/ml)	42.3±26.6	44.7±16.2	NS
25OH vitD (ng/ml)	27.6±12.6	28.3±12.9	NS
Lumbar Z score	−0.03±1.3	0.59±1.1	0.002
FM%	42.9±8.2	40.9±4.3	0.05

RFC2.2

Duration of Exclusive Breastfeeding: 'Game Changer' in a Sex-Specific Association Between Cord Vitamin D Status and Infant Linear Growth

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Background: Vitamin D deficiency in children clinically manifests as rickets causing growth impairment and bowing of the long bones, potentially increasing the ratio between crown-rump length and length (CRL:L) or sitting height and height (SH:H). **Objective and hypotheses:** We investigated whether CRL:L in 19-months-olds and SH:H in 36-months-olds were lower with higher cord 25hydroxyvitamin D (25OHD). **Method:** Participants were included from the population-based prospective mother-child cohort, Odense Child Cohort, with inclusion of healthy singletons with available 25OHD and CRL:L or SH:H measures. Multiple linear regression was stratified by sex *a priori* and adjusted for pre-pregnancy body mass index, smoking during pregnancy, maternal ethnicity, season of blood sampling and child age. Postnatal adjustment included vitamin D supplementation and duration of exclusive breastfeeding. **Results:** We included 520 participants (239 girls, 281 boys) at 19 months; and 989 children at 36 months (468 girls, 521 boys). Median (IQR) cord 25OHD was 48 (34.0–62.4) nmol/l. With every 10 nmol/l increase in cord 25OHD in boys, CRL:L increased 0.0008 ($P=0.03$) and SH:H increased 0.0004 (trend, $P=0.07$). Boys with cord 25OHD in Q4 had a 0.005 higher CRL:L ($P=0.02$) and a 0.003 higher SH:H ($P=0.002$) than boys in Q1. Post hoc regressions showed that subischial leg length decreased 0.1 cm with each 10 nmol/l increase in 25OHD ($P=0.002$, 19 months and $P=0.01$, 36 months). Adjustment for duration of exclusive breastfeeding eliminated the association between 25OHD and CRL:L while a trend remained in SH:H (0.0000, $P=0.07$). No such associations were found in girls. **Conclusion:** While cord 25OHD associated with longitudinal growth in boys, adjustment for breastfeeding eliminated this association at 19 months. Sex-specific patterns deserve further investigation.

RFC2.3

Cord Vitamin D is Inversely Associated with Systolic and Diastolic Blood Pressure in 3-Year-Old Girls, but not in Boys

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Background: Vitamin D may have cardio-protective properties due to its biological actions. In children, observational studies linking actual vitamin D level and blood pressure have yielded conflicting results. Whether early life vitamin D exposure may elicit a programming effect on later systolic blood pressure (SBP) and diastolic blood pressure (DBP) needs further investigation. **Objective and hypotheses:** We investigated whether higher levels of cord 25-hydroxyvitamin D (25OHD) correspond to lower SPB and DBP in 3 year-old children in the prospective, population-based birth cohort Odense Child Cohort (OCC). **Method:** Of children included from OCC, we included singletons with data on cord 25OHD and blood pressure. SBP and DBP were measured using a Welch Allyn device with appropriate size cuffs. Multiple linear and logistic regression models were applied adjusted for maternal educational level, season of birth and child height, weight and age. All models were *a priori* stratified by sex. 25OHD was applied as a continuous variable and grouped by study-specific median levels. **Results:** In 1110 children (530 girls, 580 boys) median (IQR) 25OHD was 46.3 (32.0;61.0) nmol/l; SPB 100.0 (95.0;105.0) mmHg; DBP 62.0 (59.0;66.0) mmHg. Adjusted analyses showed: In girls, SBP was 0.7 mmHg lower ($P=0.001$) and DBP was 0.4 mmHg lower ($P=0.016$) for every 10 nmol/l increase in cord 25OHD. Furthermore, girls with 25OHD levels >50 th percentile had 2.5 mmHg lower SBP ($P=0.002$) and 1.7 mmHg lower DBP ($P=0.009$) than the girls with levels <50p.

Moreover, the odds of having a blood pressure >90p were reduced with higher cord 25OHD (SBP; OR 0.97 (0.95–0.99), $P=0.004$; 25OHD>50p vs<50p OR 0.36 (0.15–0.85), $P=0.02$, DBP; OR 0.98 (0.96–1.00), $P=0.045$). No associations were observed in boys. **Conclusion:** SPB and DBP were significantly lower with higher levels of cord 25OHD in 3- year-old girls, but not in boys. This sex-specific pattern deserves further studies.

RFC2.4

Results of Orthopaedic Surgery in Children with X-Linked Hypophosphatemic Rickets (XLHR)

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Background: XLHR is due to mutations in the PHEX gene leading to unregulated production of FGF23, hence hypophosphatemia and decreased renal 1,25OH-vitamin D hydroxylation. Amongst other features, XLHR is characterized by leg bowing of variable severity. Phosphate supplements and oral 1,25OH-vitamin D, partially or, in some cases, fully restore the limb straightness. For severe or residual limb deformities, orthopaedic surgery may be recommended. **Objective:** To retrospectively assess the results of surgical limb correction in XLHR children. **Methods:** We analysed the relapse incidence and the post-surgical complications in 49 XLHR children (19M, 30F) bearing a PHEX mutation (mean age at diagnosis 5.6 years ($\pm$6.5)) who underwent at least one leg surgery. **Results:** At first surgery**,** the mean age was 13.4 years ($\pm$5.0), 70% of the patients had a genu varum. Except for 3 transient epiphysiodeses, most surgical corrections were done through osteotomies. 14/49 (29%) of the patients relapsed after the 1st surgery. The age at surgery was inversely correlated with the risk of relapse. The number of additional surgeries significantly decreased with age (2.0 ($\pm$0.9), 1.7 ($\pm$0.9) et 1.2 ($\pm$0.35) in children <11 years, between 11 and 15, and >15 years; $P<0.001$). Above the age of 11 years, patients having a good metabolic control of the rickets (normal alkaline phosphatases) seem to present with a lower incidence of relapse (28% vs 44% in children<11 years). 20% of the patients had complications (different from the recurrence of the bony deformity) including pseudarthrosis, infection or fractures. **Conclusion:** We report here the largest series of surgical procedures in XLHR. Our results confirm that phosphate supplements and vitamin D analogues therapy is the first line of treatment in XLHR to correct the leg bowing. Early surgeries are associated with a high risk of relapse of the limb deformity. Such procedures should be recommended, as a multidisciplinary decision, only in patients with severe distortion leading to mechanical joint and ligaments complications, or for residual deformities once growth plates are fused.

RFC2.5

Growth Patterns and Fractures in Boys with Duchenne Muscular Dystrophy: Insights from Over 800 Boys in the UK North Star Cohort

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Background: There is little information on growth and fractures in boys with Duchenne Muscular Dystrophy (DMD). **Objective & hypotheses:** To determine the extent of growth & skeletal morbidity in a contemporary cohort of DMD in the UK. **Method:** Clinical details of 832 boys with DMD in the North Star database (2006–2015) from 23 centres were analysed following categorisation into five age groups: A:<5 years (*n*, 113), B:5–7.9 years (384), C:8–10.9 years (421), D:11–13.9 years (299) and E:>14 years (160). **Results:** Proportion of boys on glucocorticoids (GC) ranged from 36% in GrpA to 88% in GrpC. Proportion of non-ambulant boys was 26% in GrpD to 56% in GrpE. Of the 46 GC-naïve boys in GrpA, 10/46 (22%) had height standard deviation score (HtSDS)<−2.0. Median HtSDS in GrpE was −1.8 (−4.9,1.0) with 48% <−2.0SD. The difference between the HtSDS of boys on GC and not on GC was only significant in Grp B, D and E ($P<0.05$). The number of boys with new reports of all fractures in the five groups were 7(6%), 23(7%), 51(12%), 52(17%), 31(19%), respectively. New symptomatic vertebral fractures (VF) were reported in Grps B-E: 2/384 (0.5%), 7/421 (1.7%), 6/299 (2.0%) and 8/160 (5%), respectively. Compared to VF, back pain was more commonly reported in GrpB-E: 16/384 (4%), 46/421 (11%), 42/299 (14%) and 29/160 (18%), respectively. Although there were no symptomatic VF in GrpA, asymptomatic VFs were reported in two boys, aged 4.0 and 4.9 years, who were treated with GC for only 0.5 and 1.0 year, respectively. **Conclusion:** In the largest cohort of boys with DMD to date with height and fracture data, short stature was already evident in 22%of young GC-naïve boys and its pathophysiology needs further investigation. VF are present across the age spectrum and the relationship between back pain and VF in this age group requires further exploration.

RFC2.6

Combining COLD and MAMA-PCR Real Time Taqman Tecniques to Detect and Quantify the R201 GNAS Mutation Causing McCune-Albright Syndrome

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Background: McCune-Albright syndrome (MAS; OMIM#174800) is a rare disorder hallmarked by the triad fibrous osseous dysplasia, cafè-au-lait skin spots and endocrine hyperfunctions, usually peripheral precocious puberty. It is caused by post-zygotic activating mutations at R201 codon of the GNAS gene, which lead to a somatic mosaic state; the clinical manifestations of MAS are highly heterogeneous due to variability of mutation abundance among affected tissues. **Objective and hypotheses:** To improve the mutational detection rate and to quantify the presence of R201 GNAS mutation in different DNA samples from MAS patients. **Method:** COLD and MAMA-PCR real time taqman techniques have been combined to search for the R201 mutation in the genome DNA from blood or affected tissues of previously molecular characterized MAS patients and controls. The ability of this new method in providing quantitative data was tested in a serial dilution of wildtype, R201H or R201C cloned plasmid DNA samples; the mutant abundance was then measured by spectrophotometry. **Results:** A linear correlation between true mutant abundance and relative mutation abundance (proportion of sequence reads containing the mutation) was observed until 2.5%, indicating reliable quantification of both R201H and R201C mutations (0.984 and 0.987, respectively). The assay sensitivity was determined by the lowest standard dilution consistently detectable in replicates at a frequency of 100% and it was found to be 0.05% for both mutations, similar to previously described molecular methods (PNA 1%, NGS 0.03% and for PNA-NGS 0.01%). **Conclusion:** Our results indicate that the COLD-MAMA-PCR real time approach is an efficient method for the enrichment of unknown mutant alleles poorly represented in DNA samples and that it can be applied to identify the degree of the R201 change distribution in different tissues from MAS patients for which the clinical course of the disease could correlate with the mutation abundance in each affected tissue.

RFC2.7

Effect of Paternal Loss-of-Function Mutations of *GNAS* on Growth During the Childhood: A Role for XL

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Background: Heterozygous GNAS inactivating mutations cause pseudohypoparathyroidism type Ia (PHP-Ia) when maternally inherited and pseudopseudohypoparathyroidism (PPHP) /progressive osseous heteroplasia when paternally inherited. Mutations on the paternal, but not the maternal, GNAS allele are associated with intrauterine growth retardation (IUGR). Moreover, birth weights were lower with paternal GNAS mutations affecting exons 2–13 (including XL and Gαs) than with exon 1/intron 1 (limited to Gαs) mutations suggesting a role for XL in fetal growth. (Richard et al, 2013). **Objective and hypotheses:** To assess the growth during childhood according to the mutation location. **Method:** We conducted a retrospective study in patients with paternal mutations on either exon 1 (group 1: $n=9$) or exons 2–13 (group 2: $n=19$). Weight (W) and height (H) were compared to sex-specific OMS reference charts. Data were gathered into three groups depending on the age. Results were expressed as the mean of *Z*-score. **Results:** Weight: The difference between groups 1 and 2 disappeared after birth. Despite being born with a severe IUGR, patients displayed weight-for-age values within the normal range (from −2 to +2 SD) after 10 years. Height: Patients from both groups are smaller compared to the OMS control references. Interestingly patients of group 2 remained significantly smaller than patients of group 1 (Table 1). **Conclusion:** Our results confirm a role for *XL* in the regulation of foetal growth. After birth, the patients recovered a normal weight during the first few years. Our data implicate a role for the paternal imprinting in the height in these patients.

Table 1.

Age range (months)	Group 1 (number of data) [quartile 1; quartile 3])	Group 2 (number of data) [quartile 1; quartile 3])	*P*-value
0–24	−2.0 (32, [−3.1;−1.2])	−3.1 (26, [−3.7;−2.1])	NS
24–120	−1.4 (10, [−1.5;−1.3])	−1.0 (41, [−2.1;−0.1])	NS
>120	−1.0 (12, [−1.2;−0.1])	−1.5 (29, [−2.3;−0.6])	**<0.05**

RFC2.8

Final Heights and BMI in Patients Affected with Different Types of Pseudohypoparathyroidism

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Background: Pseudohypoparathyroidism type 1A (PHP1A) and PseudoPHP are caused respectively by maternal and paternal mutations involving those *GNAS* exons that encode the alpha-subunit of the stimulatory G protein (Gsα). Common to different forms of PHP1B is a loss-of-methylation (LOM) at one or several maternal *GNAS* exons, which likely reduces Gsα expression in certain tissues. In most autosomal dominant PHP1B variants (AD-PHP1B), LOM is restricted to exon A/B and usually patients carry deletions affecting imprinting control elements; in contrast, sporadic PHP1B patients (sporPHP1B) display broad LOM at *GNAS*, yet lack deletions in the vicinity of this complex locus. PseudoPHP and, albeit to a less extent, PHP1A patients present with foetal and postnatal growth retardation, while PHP1B patients show with considerable overgrowth at birth. **Objective**

and methods: Compare the final heights (patients >18 years) and BMIs of 121 female (F) and 81 male (M) patients affected either by PHP1A ($n=72$), PseudoPHP ($n=26$), AD-PHP1B ($n=33$), or sporPHP1B ($n=71$). **Results:** Median of final heights and BMIs of each cohort (Table 1). BMIs of females affected by PHP1B were higher than those of males. sporPHP1B patients (F: $n=31$; M: $n=32$): 1.2 vs 0.3, $P=0.0001$; AD-PHP1B patients (F: $n=17$; M: $n=10$): 1.8 vs 0.7, $P=0.16$. 52 and 16% of the female PHP1B patients are overweighed (z-BMI > 1.0) or obese (z-BMI > 2.0), respectively. **Conclusion:** As previously described, patients with mutations in the coding sequence of *GNAS* have much reduced adult heights. Obesity was encountered only in PHP1A, not in PseudoPHP. Despite being born macrosomic, patients with LOM at the *GNAS* locus attained a normal final height and a normal BMI, suggesting a particular important role of *GNAS* in the regulation of foetal growth.

Table 1.

	PHP1A	PseudoPHP	sporPHP1B	AD-PHP1B
Height z-score (SD)	−2.8 (1.2)	−2.9 (1.5)	−0.3 (1.1)	−0.3 (1.4)
BMI z-score (SD)	1.3 (1.4)	0.6 (1.7)	0.7 (1.3)	0.8 (1.9)

RFC3.1

Endocrinopathy in Childhood Intracranial Germ Cell Tumours is Predicted by Disease Location not Treatment: 30 year Experience from a Single Tertiary Centre

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Background: Childhood pineal and/or suprasellar intracranial germ cell tumours (IGCT) are highly curable (>90%) with neuraxial radiation alone; international (SIOP) trials have aimed to decrease late radiation-induced neuroendocrine morbidity by substituting chemotherapy. However, without longitudinal study, disease and treatment contributions to long term outcomes remain unknown. **Objective:** To define tumour and treatment factors implicated in neuroendocrine morbidity across 2 patient cohorts: Group A ($n=20$) treated with neuraxial radiation alone; and Group B ($n=26$) with adjuvant chemotherapy/reduced field radiation between 1.1.83 and 31.12.14. **Method:** Retrospective longitudinal case note review of all confirmed IGCT cases. Nonparametric paired analyses and Kaplan Meier statistics were used to compare Endocrine Morbidity scores (EMS) and longitudinal evolution of pituitary endocrinopathies (EEFS), correlated with tumour location tumour 3D-volume ($n=28$) with TK-SNAPv3.2.0 software and treatment type. **Results:** 46(26 Male) patients aged median(range) 10.4(5.1–17.6) years presented with symptom duration of 0.4(0–2.5) year and were followed for 6.5(0.7–24.4) years. The 19 with pineal (P) tumours tended to present quicker (0.4 ± 0.7 vs 0.9 ± 1.3 months; pNS) and had fewer pituitary deficits ($P<0.0001$) than the 16 suprasellar (S) tumours, despite smaller volume disease (PvsS:1.2 cm^3 (0.2–11) vs 4.6 cm^3 (1.0–13.9), pNS). 37 had surgery (10 only biopsy). 18/24 suprasellar cases (of whom 5 were bifocal (B)) presented with DI, and 2 others were pineal with hypothalamic involvement ($P<0.0001$). A further 6 (4 suprasellar) developed DI after surgery. Neither surgery nor treatment type (GpAvsGpB) reduced pituitary deficits, visual or educational outcomes, or BMIsds increase, though renal ($n=2$), hearing ($n=2$) and cardiac ($n=1$) toxicity was only observed in chemotherapy (GpB), despite shorter follow up (3.70.2–24.4) vs 7.4(2.8–12.7) years, $P=0.013$). **Conclusion:** In patients with IGCT, tumour location dictates symptom duration and ultimate endocrinopathies. The latter are frequent (89%), multiple (69%), especially in suprasellar disease ($P<0.0001$) but are not influenced by treatment. Hence substituting chemotherapy for neuraxial radiation is unlikely to improve these outcomes, newer treatments may well add peripheral toxicity.

RFC3.2

Subfertility After Chemotherapy in PNET Tumours: 34 year Experience from a Single Centre (1980–2013)

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Background: PanEuropean(SIOP) trials of treatment for childhood brain cancers (medulloblastomas/PNET) showed a 5% survival advantage with 'sandwich' gonadotoxic chemotherapy (CT) over surgical excision, neuraxial radiation and tumour boost (RT) alone. But this was tempered by a reduced quality of survival at 7 years. **Objective:** To assess the long term prevalence of subfertility after CT with/without neuraxial radiation. **Methods:** Retrospective longitudinal case note review of all patients diagnosed with intracranial PNETs between 1.1.1980 and 31.12.2013 and follow-up >1year. Data on treatment, relapse, gonadotrophin levels, puberty and (in girls) estrogen/HRT replacement were collected from diagnosis. Time to, and cross-sectional rates of, subfertility (FSH > 15 IU/l and/or HRT use) at last follow-up were compared between patients groups with (A) and without (B) CT. **Results:** 158/284 with available fertility data were 6.5 ± 2.7 (2.6–9.9) years at diagnosis and 16.3 (2.3–29.7) years after 9.5 ± 4.6 (1.3–22.1) years follow-up; 64(40%) were

female and 22(20%) were infants (12 female). At last assessment, 95(60%) had CT (88(56%) of whom additional RT) and 62(40%) had RT alone (2 with CT only are not further discussed). 36/158(23%), being girls 25(69%)($P<0.0001$), had evidence of subfertility at 12.1 ± 4.7(1.72–16.54) years, whilst a further 26/158 (16.5%) were still under 10 y at last visit. Patients given CT had greater subfertility rates than those with radiation alone (30/95–31.6% vs 6/62–9.7%, $P=0.001$) and those on infant protocols (5.21 ± 4.41 y vs 13.41 ± 3.70 y, $P<0.0001$ demonstrated this earlier. None had gonadotropin deficiency. **Conclusion:** CT in the intracranial PNET treatment protocol significantly increased the prevalence of subfertility in children, which is especially evident in females and in infant protocols. This is likely to increase with time. By contrast, gonadotropin deficiency is not a radiation consequence despite even at a long 9.5 y follow-up. Pretreatment fertility preservation should be considered in adolescent boys, families should be warned of likely subfertility and need for routine endocrine referral for pubertal assessment.

RFC3.3

Unraveling the Link between Optic Nerve Hypoplasia and Pituitary Hormone Dysfunction

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Background: Optic nerve hypoplasia (ONH) is a congenital condition with high morbidity. Many children with ONH will develop pituitary hormone dysfunction (PHD), but it is unknown if, or when, this will occur. **Objective and hypotheses:** Our primary objective was to identify the type, timing and predictors of PHD in children with ONH to help guide the necessity and frequency for pituitary hormone testing. **Method:** A retrospective chart review was conducted; demographic, prenatal, neurobehavioural, radiologic, hormonal and ophthalmologic data were collected. Descriptive statistics were utilized (i.e. means, medians, proportions, Chi-Squared) and multiple regression modeling identified clinical predictors for PHD. **Results:** 254 pediatric patients with ONH were seen at the BC Children's Hospital endocrinology clinic between 1975–2014. Of these, 146 met eligibility criteria, of which 71 (49%) had PHD. Thyroid stimulating hormone (76%) and growth hormone (72%) deficiency were most common. The median age at diagnosis of the first PHD and median time from diagnosis of ONH to first PHD was 0.8 years (IQR 2.9) and 0.3 years (IQR 1.7), respectively. Among ONH patients with PHD, 80% developed their first PHD by 5 years of age and 90% by 5 years after diagnosis of ONH. On multivariate regression analysis, bilateral ONH (odds ratio (OR) 2.8 (95% CI:1.0–7.8) $P=0.04$)), posterior pituitary abnormalities (OR: 18.4 (95% CI: 3.4–98.6); $P=0.001$), and blindness (OR: 3.5 (95% CI: 1.2–10); $P=0.02$) were risk factors for developing PHD. Prematurity was protective (OR: 0.1 (95% CI: 0.0–0.7); $P=0.02$). **Conclusion:** We described the largest cohort of patients with ONH in Canada and report the first regression model that identifies predictors for developing PHD in patients with ONH. Prematurity was protective, a novel finding that requires more research. Next steps are to further develop our prediction model by validating these findings against a larger cohort of patients with ONH.

RFC3.4

Children and Adolescents with Severe TBI can Develop Late Pituitary Dysfunction Independently of the Results of the First Pituitary Evaluation

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Background: Traumatic brain injury (TBI) is common in childhood and can induce pituitary defects. Long-term endocrine consequences are missing. **Objective and hypotheses:** To determine in a prospective way if pediatric patients with a personal history of TBI developed long term pituitary deficiency independently of the results of the early hormonal investigation. **Method:** Prospective follow-up of an initial cohort of subjects (0–15 years old) with a personal history of severe TBI[1]. Clinical and hormonal evaluation at inclusion (first year after TBI) and at last visit. **Results:** In total of 37 patients are actually included in the follow-up (29 boys, median age: 13.4 years (yrs), 5.3 to 20.9). Median duration of follow-up was 5.9 yrs (3.9 to 7.1). 20/37 had normal pituitary function at first evaluation (group 1) and 17/37 had GH deficiency (GHD) (group 2). In group 1, one patient developed GHD requiring substitution (10 yrs of age - 5.1 yrs post TBI) and one girl developed precocious puberty (PP) (7.8–5.8 yrs post TBI). In group 2, 2 patients with biological GHD but regular growth velocity developed growth failure and had to be treated (11.9 yrs and 12.3 yrs – 4.3 and 5.1 yrs post TBI) and one boy developed PP (10 yrs – 6.3 yrs post TBI). No new patients developed gonadotropic, thyreotropic or corticotrophic deficiency or insipidous diabetes during the follow-up in both groups. **Conclusion:** Children with a personal history of TBI can developed a clinical expression of pituitary dysfunction even they had normal evaluation one year post-TBI. These results argue for a prolonged endocrine follow-up of those patients contrary to reports in adults. Supported in part by Pfizer SAS. [1]Personnier and al, JCEM 2014.

RFC3.5

Prospective Dynamic Evaluation of Hypothalamo-Pituitary Function in 30 Cases of Paediatric Craniopharyngioma, by Hypothalamic Injury and Treatment; A Single Centre Series

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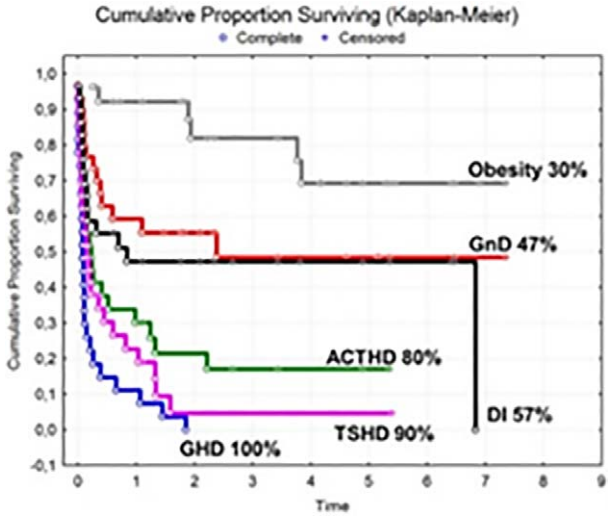
Background: Craniopharyngiomas are the commonest pituitary tumours of childhood. Though benign histologically, their localisation and invasive tendency can cause significant neuroendocrine morbidity and late mortality. **Objective and hypotheses:** To prospectively determine risk factors for neuroendocrine morbidity by longitudinal survival analysis. **Method:** All children with craniopharyngioma newly presenting to our quaternary centre between 1.8.08-9.5.15 underwent auxology, basal/dynamic pituitary function and hypothalamic invasion's assessment by Paris grade (PG[1]) at diagnosis with subsequently 3–6 monthly review. We studied patient, tumour and treatment factors on progression free survival (PFS[2]), endocrine event-free survival (EEFS[2]), total endocrine morbidity score (EMS[2]) using Kaplan-Meier and Cox-regression statistics. **Results:** In total of 30(22 M) children of median (range) age 7.6(1.1–17.2) years were followed for 4(0.3–7.4) years. Tumor volume was 16.1(1.8–193.3)cm^3. 13 with presenting hydrocephalus and 11 with cysts required decompression, after which 6/22 with PG2 downgraded (n7-PG1, n3-PG0 unchanged). Surgical strategy was decompression alone (n12) or with interval resection (n7, complete(CR) n3), primary resection (n10, CRn5) or watch/wait (n1). 20 received upfront (n18) or delayed (n2) IMRT (n7) or proton (n13) radiation; just 5/30(16%) relapsed 5(1.4–5.5) years later. Outcomes: Despite 100% survival and 83.4% 5year PFS, EEFS was 0%. At diagnosis, 17/23(74%) dynamically assessed had GHD and 4/30(13%) - all intrasellar tumours - had panhypopituitarism (3 with DI). Post-treatment deficits evolved hierarchically (Figure). Presenting hydrocephalus was protective for ACTHD ($P=0.04$) and TSHD ($P=0.006$) but not for DI ($P=0.04$); complete resection aggravated TSHD ($P=0.007$) and DI ($P=0.005$) and transphenoidal resection aggravated GnD ($P=0.0007$ and ACTHD ($P=0.0004$). Final EMS correlated directly with total number ($P=0.02$), transphenoidal ($P=0.02$) and resection surgeries ($P=0.0001$), but not with PG or radiation use. **Conclusion:** The evolving endocrinopathy, typical of suprasellar tumours is present from diagnosis, worse in small intrasellar tumours without mass effect and aggravated by surgical resection, but unaffected by PG or radiation.

[1]Puget Neurosurg 106:3–12,2007. [2]Gan JCEM 100(10):3787-99,2015.



RFC3.6

Priority Target Conditions of Growth-Monitoring in Children: Toward Consensus

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Background: Growth monitoring of apparently healthy children aims at early detection of severe underlying conditions.

Strong empirical evidence shows that current practices of growth monitoring are suboptimal. Practice standardisation with validated tools requires answering two questions: Which conditions should be targeted? How should abnormal growth be defined? **Objective and hypotheses:** To obtain consensus on a short list of priority target conditions of growth monitoring. **Method:** The RAND consensus method involved a panel of appointed experts from all French academic societies involved in the diagnosis and management of growth disorders, from primary care providers to experts in paediatric endocrinology, nephrology and gastroenterology, and members of parent associations. Participants were asked to select conditions fulfilling 4 previously established criteria [Scherdel, Lancet Diabetes Endocrinol 2016]: an "important health problem" in terms of their incidence and related morbidity and mortality, a natural history including a long paucisymptomatic period during which the main clinical expression was auxological, a high level of evidence for a relationship between early diagnosis and a more favourable outcome, and diagnosis criteria that are both robust and independent of auxological parameters that can be used to define abnormal growth. **Results:** After the first two rounds of consensus, the panel selected 8 conditions: growth hormone deficiency with pituitary stalk interruption syndrome, Turner syndrome, craniopharyngioma, hypothalamic-optochiasmatic astrocytoma, celiac disease, Crohn disease, renal tubulopathy and chronic renal failure. **Conclusion:** This national consensus will now be used to (1) build trans-speciality European consensus and (2) refine and optimize the current clinical decision rules proposed to define abnormal growth.

RFC3.7

Pituitary Structural Abnormalities in Idiopathic Isolated Growth Hormone Deficiency

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Background: Isolated growth hormone deficiency is the most common pituitary hormone deficiency, although the majority of cases are idiopathic. The presence of pituitary structural abnormalities may influence growth hormone (GH) deficiency severeness. **Objective:** Assess the effect of pituitary abnormalities in idiopathic isolated growth hormone deficiency (IIGHD). **Methods:** We analysed 65 children with IIGHD and pituitary magnetic ressonance imaging [MRI] data. Height-for-age and IGF1-for-age *Z*-scores, and GH requirements were compared between patients with or without pituitary MRI abnormalities. **Results:** Age at diagnosis (11.3 ± 3.1 vs 11.8 ± 2.6years) and gender proportion (female 25% vs 24%) were similar between patients with or without pituitary abnormalities, respectively. Most patients (61.5%) had MRI abnormalities (75% anterior pituitary hypoplasia, 40% thin pituitary stalk, 20% ectopic posterior pituitary, 7.5% intrasellar arachnoidocele, and one case of thickened pituitary stalk). After one year of treatment, children with pituitary anomalies had higher height-for-age *Z*-score gain (0.50 ± 0.29 vs 0.34 ± 0.23, $P = 0.03$) and IGF1-for-age *Z*-score gain (2.16 ± 1.87 vs 1.95 ± 1.49, $P = 0.89$). Furthermore, a positive correlation was found between the number of anomalies and height-for-age *Z*-score gain ($r_s = 0.35$, $p < 0.01$). Patients with thin pituitary stalk (0.59 ± 0.20, $P < 0.001$) or ectopic posterior pituitary (0.61 ± 0.31, $P = 0.04$) had higher height-for-age *Z*-score gain than children without pituitary abnormalities (0.34 ± 0.23). During follow-up, final height was reached by 36 (55%) children; those with pituitary anomalies required less GH dosages than those with normal pituitary (0.030 ± 0.004 vs 0.032 ± 0.004 mg/kg per day, $P < 0.001$). However, no differences on height-for-age *Z*-score gain were found between both groups. Children with thin stalk had higher final height-for-age *Z*-score gain than those with normal pituitary (1.77 ± 0.94 vs 0.93 ± 0.60, $P = 0.02$). **Conclusion:** Structural pituitary abnormalities were associated with higher stature improvement during the first year of treatment and lower GH requirements during follow-up. Irrespective of the etiology, patients with structural abnormalities will need lifelong follow-up in adulthood owing to the risk of developing other pituitary hormone deficiencies.

RFC3.8

Anthropometric and Endocrine Features in Children and Adolescents with Type 1 Narcolepsy

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Background: Childhood NT1 has been associated with endocrine disorders like obesity and precocious puberty. These comorbidities may challenge the diagnosis, require tailored treatments and call for a multidisciplinary approach. **Objective and hypotheses:** To evaluate the impact of type 1 narcolepsy (NT1) on anthropometric and endocrine features in childhood/adolescence, focusing on weight, pubertal development and growth, and their follow up in treated and untreated patients. **Method:** At diagnosis we collected anthropometric (height, weight, body mass index (BMI) z-scores), pubertal, metabolic and endocrine data from 72 NT1

patients and available premorbid anthropometric pediatric clinical records. Re-evaluation at one-year follow-up was contrasted with baseline data. **Results:** We detected a high prevalence of overweight (29.2%), obesity (25%), metabolic syndrome (18.8%), and precocious puberty (16.1%), but no signs of growth alterations at the diagnosis. Weight gain started closely after NT1 onset. At follow-up sodium oxybate was associated with a significant BMI z-score reduction (-1.29 ± 0.30, $P < 0.0005$) also after correcting for baseline age, sex, sleepiness, and BMI. Treatment did not influence growth. **Conclusion:** NT1 in children/adolescents induced a rapid weight gain up to overweight/obesity and precocious puberty without affecting growth. In our study we found that Sodium oxybate reduces weight excess in NT1 overweight/obese patients without compromising their growth.

RFC4.2

Adipocytokines Delay Pubertal Maturation of Human Sertoli Cells

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Background: Obesity and metabolic syndrome related co-morbidities are increasingly recognized in children. Reproduction is an important target of obesity complications, including adverse effects on spermatogenesis and steroidogenesis in males. Adipocytokines are key players in various complications of obesity. **Objective and hypotheses:** The aim was to study the potential effects of adipocytokines on Sertoli cell function and possibly link the findings to the observed attenuation of spermatogenesis in obese males. **Method:** Testicular biopsies were obtained from healthy human males (aged 25–45 years). Highly purified adult human Sertoli cells (HSCs) were isolated by fluorescence-activated cell sorting (FACS) using CD90 as a sorting marker. Cells were cultured and exposed to various concentrations of adipocytokines (10–1000 ng/ml) for 2–7 days. Gene expression in Sertoli cells was quantified by qPCR. **Results:** Exposure to lower concentrations (10–100 ng/ml) of adipocytokines for 48 h did not affect the expression of Sertoli cell-specific genes. In contrast, exposure to higher doses of several adipocytokines for 48 h, in similar levels as found in obesity, increased FSH receptor (FSHR) expression. CYP26A1 expression in HSCs was downregulated after exposure to irisin, Nampt and TNFα. Long term treatment for 7 days of HSCs with higher doses of chemerin, irisin, nampt, resistin and progranulin significantly suppressed FSHR expression (by 79, 83, 64, 71 and 26%, respectively) and upregulated CYP26A1 expression (by 48, 90, 126, 126 and 153%, respectively) as found in the prepubertal state. Further, those same adipocytokines significantly attenuated the expression of BMP-4, GDNF, LIF and FGF-2 by HSCs. **Conclusion:** We propose that adipocytokines at high concentrations, frequently observed in obese children, might delay maturation of Sertoli cells during puberty and keep the Sertoli cells in a quiescent state. This may negatively affect male reproductive function including spermatogenesis and steroidogenesis in adult life.

RFC4.3

Early Growth Patterns are Associated with Alterations in Adipocytokine Levels and Fat Distribution Measured by DXA in 982 Children/Adolescents

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Background: Early growth trajectories are associated with childhood BMI and fat distribution as well as adulthood type 2 diabetes. Mechanisms by which early growth determines later adiposity remain unclear, but the effect may be mediated through adipocytokines. **Objective and hypotheses:** We describe the association between infant growth, adolescent fat distribution and serum adipocytokines. We hypothesize that poor or rapid early growth is associated with circulating Leptin and Adiponectin levels and fat distribution by DXA. **Method:** A prospective population-based birth cohort study was performed with anthropometric measurements at 0, 3, 18 and 36 months of age and follow-up at 8–15 years. Delta (Δ) growth SDS from 0–3, 0–18 and 0–36 months was calculated. Catch-down and catch-up was defined as ΔSDS by more than -0.67 and more than 0.67, respectively. Total and regional fat percentage was measured by DXA (mean age 11.0 years) in 982 children (426 girls) and serum Leptin and Adiponectin levels were analyzed. Leptin-to-Adiponectin ratio was calculated as a measure of insulin resistance. Tanner Stage and age were included as covariates. **Results:** Early weight changes at each age interval (Δweight SDS, catch-up in weight, but not catch-down) were associated with android and gynoid fat% SDS (Δweight SDS: $\beta = 0.1$, catch-up: $\beta = 0.3$) and android-to-gynoid ratio (Δweight SDS: $\beta = 0.01$, catch-up: $\beta = 0.02$) in both sexes (all $P < 0.05$). Furthermore, Δweight SDS 0–18 and 0–36 months was associated with Leptin levels and Leptin-to-Adiponectin ratio (both $\beta = 0.04$, $P < 0.05$), but not with Adiponectin levels. Android fat% SDS was positively associated with Leptin-to-Adiponectin ratio (girls: $\beta = 27\%$, boys: $\beta = 20\%$, both $P < 0.05$) whereas gynoid

fat% SDS was inversely associated with Leptin-to-Adiponectin ratio in girls (β = −23%, $P<0.05$), but not boys (β = −3%, $P=0.85$), independently of total fat% SDS. **Conclusion:** Early weight gain predisposes to more abdominal than gluteofemoral fat deposition around puberty along and increased Leptin-to-Adiponectin ratio, reflecting altered fat metabolism.

RFC4.4

Metabolic Syndrome Markers Correlate with Gut Microbiome Activity in Children Born Very Preterm

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Background: Fifteen years ago children born very preterm (<32 weeks of gestation) were reported to be insulin resistant. Neonatal intensive care has since improved considerably, but it is unclear whether this has affected long-term outcomes in those born preterm. Abnormalities in gut microbiome, which influence host metabolism, have been found in preterm newborns. **Objective and hypotheses:** We aimed to assess whether children born very preterm still had lower insulin sensitivity than term controls, and whether there were differences in gut microbiome. We hypothesized that early life events in infants born very preterm lead to long-term alterations in gut microbiome, which contribute to later insulin resistance. **Method:** Participants were pre-pubertal children aged 5–11 years born very preterm ($n=51$; 61% boys) or at term (37–41 weeks; $n=50$; 62% boys). Insulin sensitivity was assessed using frequently-sampled intravenous glucose tolerance tests and the Bergman's minimal model. A fresh stool sample was collected from all children, and RNA extracted for assessment of gut microbiome composition and activity. **Results:** Children born very preterm were lighter (weight SDS −0.16 vs 0.47; $P=0.0005$), shorter (height SDS 0.31 vs 0.92; $P=0.0006$), and leaner (BMI SDS −0.20 vs 0.29; $P<0.0001$) than term children. Notably, children born very preterm had lower insulin sensitivity than term controls (9.2 vs 12.5×10–4· min^{-1}(mU/l); $P=0.0007$), even after adjustment for confounders. Stool metatranscriptomics identified Coriobacteriaceae, particularly *Collinsella* spp., as being associated with preterm birth. There were also different microbiome activities in children born preterm, such as increased catabolism of glutamate and arginine, which are involved in glucose homeostasis. **Conclusion:** Adverse metabolic programming (i.e. lower insulin sensitivity) remains a feature of pre-pubertal children born very preterm. Differences in gut microbiome composition and activity are also present in mid-childhood, suggesting a possible role of gut microbiome in defining the metabolic phenotype of those born preterm.

RFC4.5

Steroid Metabolomic Signature of Liver Disease in Childhood Obesity

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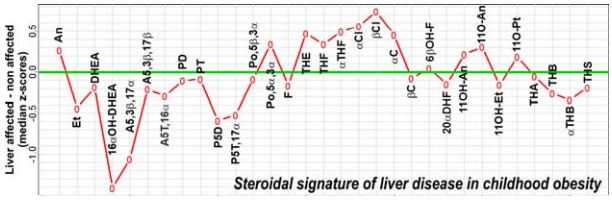
Background: Analysis of steroids by gas chromatography-mass spectrometry (GC-MS) defines a subject's steroidal fingerprint. Here, we compare the steroidal fingerprints of obese children with or without liver disease to identify the 'steroid metabolomic signature' of childhood non-alcoholic fatty liver disease. **Methods:** Urinary samples of 85 children (43 girls) age 8.5–18.0 with obesity (BMI > 97%) were quantified for 31 steroid metabolites by GC-MS. The fingerprints of 22 children with liver disease (L1) as assessed by sonographic steatosis (S+) and/or elevated liver enzymes (ALT+), were compared to 63 obese children without markers of liver disease (L0: S− and ALT−). The steroidal signature of the liver disease was generated as a difference of median profiles of L1 and L0 groups. **Results:** L1 and L0 children had similar age (mean 14.4 and 14.1 resp.) and z-scored BMI (2.82 and 2.67, resp.). Boys' livers were affected more than girls' (35.7% and 16.3%, resp.) The steroidal signature of the L1 group was characterized by high glucocorticoids and low androgens, higher 21OHase activity (THE+THF+αTHF) /PT and lower 11β-HSD-I activity (THF+αTHF)/THE ($P=0.029$, $P=0.01$, resp, ANOVA) (Fig). Patients with isolated ALT+ presented highest α-Cl concentrations compared to L0 group or patients with only S+ ($P=0.03$; ANOVA). An/Et ratio as a marker of 5 α-reductase was higher in children with ALT+ compared to ALT- patients ($P=0.001$, Student's two sided t-test). **Conclusions:** The steroidal metabolomic signature of liver disease in obese children is characterized by low androgens and highglucocorticoids, impaired 11β-HSD-type I activity, and high 21-hydroxylase and 5α-reductase



activity. These findings suggest decreased hepatic degradation of cortisone in liver steatosis, which is compensated for by increased adrenal cortisol generation. It may provide ways for personalized medicine in obese children with liver disease.

RFC4.6

Adipose Tissue – A Source of Hyperandrogenism in Obese Females?

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Background: Obesity in females is often associated with metabolic complications and hyperandrogenism. However, the source of androgens is not entirely clear. **Objectives and hypotheses:** Our objective was to find out if adipose tissue (AT) is a site of steroid production during childhood and adolescence, and if this source could add to hyperandrogenism in obese females. **Methods:** Parametrial and inguinal adipose tissue was collected and preadipocytes were isolated and cultured from young (day 20) and adult (day 60), lean female rats for gene expression analysis of steroidogenic enzymes and to measure testosterone in AT and in the supernatant of cultured cells. Thin layer chromatography (TLC) was performed on pre- and adipocytes to evaluate the conversion of pregnenolone to other steroids. Steroidogenic gene expression was measured at the transcriptional level by qPCR from AT of lean and obese rats. **Results:** We found significant amounts of testosterone in AT from both depots in young animals and adult rats (25 ng to 153 ng/g AT) and in the supernatants of pre- and adipocytes (0.33–0.69 ng/10000 cells) with the highest values in mature adipocytes of adult rats. Steroidogenic enzymes, including *Star, Cyp11A1, Cyp17A1, CYP19, Hsd3b2, Hsd17b3* and *5-alpha-reductase* were expressed in AT and isolated cells in culture, from both depots and ages, with higher expression levels in mature adipocytes. TLC data revealed that pre- and adipocytes were able to convert pregnenolone to testosterone and 3-alpha-diol. Finally we analysed expression of steroidogenic enzymes in lean and obese animals and found higher levels for all steroidogenic enzymes in both depots, being significant in inguinal AT (*StAR* +77.5% $P=0.048$, *Hsd3b2*+221% $P=0.015$, *Hsd17b3*+280% $P=0.009$; *CYP19*+246% $P=0.023$). **Conclusion:** Our study demonstrates that the whole steroidogenic machinery is expressed in AT and that it may serve as an additional site of steroid production. Thus, high levels of androgens in obesity might be produced by AT and thereby add to the vicious circle of metabolic complications in obese females.

RFC4.7

Prevalence and Characterization of Retinal Alterations in a Cohort of Overweight and Obese Children

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Background: Increasing incidence of pediatric obesity has been observed worldwide. Metabolic syndrome, characterized by visceral obesity, dyslipidemia, hypertension and impaired glucose metabolism, is associated with obesity. **Objective and hypotheses:** To evaluate early ocular signs of hypertension by retinography in a cohort of overweight (BMI > 85th)/obese (BMI > 95th) children, in order to define the prevalence of retinal alterations and characterize the patients. **Method:** All subjects underwent retinography, anthropometric examination, blood pressure measurement, oral glucose tolerance test (OGTT), lipid profile assessment, ECG and DEXA scan to evaluate body composition. The same paediatric endocrinologist examined all patients and all retinographies were evaluated by the same ophthalmologist. **Results:** A total of 115 children (59 males) aged 12.83 ± 1.96 years were included in the study: 105 patients (91.3%) showed normal retinographic pattern or aspecific retinal vessel alterations (Group A), 7 (6.1%) showed signs of hypertensive retinopathy (in 1 case papilledema) representing Group B, and the remaining 3 (2.6%) had different alterations, as coloboma or choroidal nevus. In the comparison between Group A and B, the latter showed significant higher values in BMI (29.9 ± 3.5 vs 33.4 ± 6.3 kg/m^2; $P=0.018$), BMI SDS (2.5 ± 0.7 vs 3.3 ± 1.4; $P=0.006$), abdominal circumference (CA) (100.9 ± 10.4 vs 109.6 ± 15.3 cm; $P=0.042$), wrist circumference (17.3 ± 1.1 vs 18.4 ± 2.1 cm; $P=0.024$), CA/height ratio (0.6 ± 0.0 vs 0.7 ± 0.1; $P=0.007$) and glycemia at 120' during OGTT (110.1 ± 19.9 vs 128.9 ± 25.0; $P=0.019$). No significant differences in blood pressure or between sexes were found. Interestingly, 3/7 patients of Group B were overweight but not obese. All but one retinographies with alterations were detected in pubertal patients. The only prepubertal child with altered retinography had a complex form of obesity and is currently being studied. No ECG alterations were found in Group B. **Conclusion:** Retinal alterations could represent early signs of hypertension in children with overweight and obesity, even when blood pressure appears normal at routine measurements.

RFC5.1

Adiponectin and Leptin in Children with Type 1 Diabetes for 3-5 years with or without Residual β cell Function

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Background: Studies in adults with type 1 diabetes (T1D) have indicated that adiponectin is negatively associated and leptin positively associated with measures of a residual beta cell function (RBF). **Objective and hypotheses:** To compare serum adiponectin and leptin levels and their ratio in children with T1D for 3–5 years with and without RBF and in healthy children. **Method:** We included 342 children (173 females) with T1D, hereof 136 pre-pubertal children (15 with stimulated C-peptide above 100 pM (RBF+)) and 206 pubertal children (hereof 42 RBF+). Seventy (40 females) healthy children, hereof 40 pre-pubertal served as controls. RBF was evaluated by meal-stimulated C-peptide. We performed multiple linear regression analyses to test for differences in adiponectin, leptin and leptin/adiponectin ratio between patients (+RBF/−RBF) and healthy controls, adjusting for age, gender, BMI-SDS and HbA1c, stratified by pubertal status. **Results:** In prepubertal children leptin and the leptin/adiponectin ratio were higher in RBF+ patients compared with RBF- patients and controls (all *P*-values <0.04). There was a trend towards elevated adiponectin levels in the RBF- group compared with the RBF+ group ($P=0.07$). In pubertal children adiponectin was higher in RBF- patients compared with controls ($P<0.04$), whereas the leptin/adiponectin ratio was lower in RBF- patients compared with controls ($P<0.05$). There was a trend towards the highest leptin levels in the RBF+ group ($P=0.2$). **Conclusion:** The highest leptin levels were observed in children with T1D and a positive RBF, whereas the highest adiponectin levels were found in children with T1D without a RBF. The mechanism remain undetermined, but the characteristics of our patient population excludes higher BMI-SDS in RBF+ patients or differences in diabetes duration or kidney function between RBF+ and RBF- patients, as proposed in adults. The question remains whether children with T1D and a positive RBF share phenotypic similarities with T2D patients?

RFC5.2

Limits of Agreement between HbA1c Levels Measured in Different Laboratories Following the Introduction of the International Federation of Clinical Chemistry and Laboratory Medicine Standardised Values

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Background: Between 2011 and 2015, 294 children from 15 UK centres were randomised to the SCIPI study (SubCutaneous Insulin: Pumps or Injections?), which compares insulin delivery by pump to multiple daily injections, during the first year following diagnosis of type I diabetes. HbA1c is measured every 3 months, locally by (1) a 'point of care' device or a local laboratory and (2) a central laboratory. Since 2009 HbA1c assays have been calibrated against the International Federation of Clinical Chemistry and Laboratory Medicine standardised values. This should remove the need for centralised measurement of HbA1c for clinical or research purposes. **Objectives:** To determine the limits of agreement between local and central measurements of HbA1c. **Methods:** Bias and 95% limits of agreement were determined using the Bland and Altman method. **Results:** About 590 pairs of measurement, representing 255 children and 15 trial-centres across 4 time-points, were compared. There was no significant bias: local measurements were an average of 0.16 mmol/mol (SD=4.5, 95% CI: −0.2 to 0.5) higher than central. The 95% limits of agreement were −8.6 to 9.0 mmol/mol (local minus central). 93% of local measurements were within 10% of corresponding central measurements. Some trial centres were more varied in the differences observed between local and central measurements; none indicated systematic bias. **Conclusion:** Variation in agreement between HbA1c measurements was greater than had been expected although no overall bias was detected. 5% of measures differed by > 9 mmol/mol, and 7% of pairs showed >10% difference between central and local measurements. Discrepancies were present across all participating centres. These findings have implications for the comparison of standards of clinical care between centres, the design of future multi centre RCTs and existing quality assurance processes for HbA1c measurements. We recommend that centralised HbA1c measurement is preferable in the multi-centre clinical trial setting.

RFC5.3

Sexual Lifestyle among Young Adults with Type 1 Diabetes

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Background: Sexual lifestyles including sexual activity, problems, satisfaction, and the formation of relationships, are greatly affected by physical health disorders. Fear from hypoglycemic episodes during sexual intercourse and intimacy issues can impact young adults with type 1 diabetes (T1DM). **Objective and hypotheses:** To assess sexual lifestyles of people with T1DM. **Method:** A total of 53 T1DM patients (51% males), mean ± SD age 27.9 ± 8.3 years completed the Hypoglycemia Fear Survey II (HFS II) and the Sex Practices and Concerns questionnaire. **Results:** Thirty-seven (70%) reported they never or almost never had concerns in their sexual lifestyles that were related to their diabetes. None experienced severe hypoglycemia during sex, but 21(40%) reported occasional mild hypoglycemic events. More than two-thirds do not take any measures to prevent hypoglycemia before sex (decreasing insulin dose, snacks, and measuring blood glucose levels). Fear of hypoglycemia during sex was reported by 18(35%); those who reported increased fear reported experiencing mild hypoglycemic events during sex (61.1% vs 26.5% $P=0.01$), were singles (94.4% vs 64.7% $P=0.02$) and had higher scores on the Worries subscale of the HFS II than did those who did not (42.8 ± and 12.8 vs 34.9 ± 10.5 $P=0.04$). **Conclusion:** Most young people with T1DM do not have concerns regarding sex that are related to their diabetes, and most do not take specific measures before or after sex. One-third, however, fear from hypoglycemia during sex, mostly singles and those who experienced hypoglycemia in the past.

RFC5.4

"Transient" Neonatal Diabetes In Adulthood: Metabolic Outcomes

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Background: "Transient" Neonatal Diabetes Mellitus (TNDM) is a rare genetic beta cells dysfunction leading to hyperglycaemia that resolves in early childhood. About 80% of patients relapse during adolescence or adulthood. Glucose homeostasis had not been investigated in adulthood. **Objective and hypotheses:** To investigate insulin secretion and insulin sensitivity in adults affected with TNDM or in their 1st degree mutated relatives. **Method:** The patients originated from the French Neonatal Diabetes Study Group cohort. We selected those with TNDM and aged 18 years or more in September 2013, and their 1st degree adult mutated relatives. We measured insulin sensitivity using a two-step hyperinsulinemic euglycemic clamp and maximal insulin secretion in response to a graded intravenous glucose infusion followed by a bolus of arginine. Body composition was assessed using dual energy X-ray absorptiometry. **Results:** We included 15 individuals (6 males, 9 females). Median age was 36 (18–55) years. Median BMI was 21 (17.5–30.9)kg/m^2. We identified abnormalities in 6q24 ($n=2$, 13.3%), and mutations in *ABCC8* ($n=9$, 60.1%) and *KCNJ11* ($n=2$, 13.3%) genes. 2 (13.3%) patients had no identified molecular defect. 8 (53%) patients had a TNDM. Among them 6 (40%) had a recurrence of

diabetes. 7 (47%) patients were 1st degree relatives. Among them, 4 (27%) had a diabetes. Mean insulin secretion rate in the last 40 minutes of the glucose ramp was as follow: 4.9 pmol/kg per min in 10 (67%) diabetic patients, and 12.5 pmol/kg per min in 5 (33%) non-diabetic patients, There was no significant disturbance in insulin sensitivity and the mean M-value was 12.8 mg/kg per min. **Conclusion:** Our study suggests that monogenic diabetes in adulthood is due to a partial insulin secretion defect, not associated with insulin resistance. These results underscore the importance of genetic evaluation in order to personalize the treatment in adulthood.

RFC5.5

The Efficacy of Insulin Degludec in Children and Adolescents with Type 1 Diabetes

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Background: Insulin degludec (IDeg; Tresiba®) is a novel basal insulin with an ultra-long, flat and stable action profile. In adults, it provides a more consistent glucose-lowering effect and lower rates of hypoglycaemia than glargine (IGlar). Data on children and adolescents are scarce. **Objective and hypotheses:** To assess efficacy of IDeg among children and adolescents affected by type 1 diabetes (T1DM) previously on IGlar. **Method:** The study included 20 (9 males) children and adolescents (15.1±4.0 years old, 7 prepubertal) with T1DM (mean duration 7.2±3.7 years), started on IDeg once daily as basal insulin after at least 1 year on IGlar. Anthropometric (BMI-SDS), metabolic (HbA1c (%), FPG (mg/dl) and severe hypoglycaemia rates (n)) and therapeutic parameters (IGlar or IDeg and short-acting or regular mealtime insulin dose (UI/kg per day)) were collected at baseline (T0) and after 3 and 6 months (T1 and T2) on IDeg. Data were analysed according to pubertal status. **Results:** BMI-SDS did not change on IDeg both in prepubertal and in pubertal patients. Even if HbA1c diminished on IDeg without achieving any statistical significance (ΔHbA1c T0-T1 −0.3%, *P* 0.1; T0-T2 −0.1%, *P* 0.6), FPG significantly decreased from T0 to T1 (−18.6±34.1 mg/dl, *P* 0.05). No severe hypoglycaemia was registered on IDeg. The doses of both basal insulin (IGlar vs IDeg: 21.8±8.9 vs 19.4±7.8 UI/day, *P* 0.003) and short-acting or regular mealtime insulin (T2 vs T0 0.50±0.15 vs 0.56±0.13 UI/kg per day, *P* 0.02) were significantly reduced. **Conclusion:** In our cohort, IDeg seemed to improve the glycemic control reducing FPG at a lower basal insulin dose if compared with IGlar. Moreover, it allowed the reduction of the dose of mealtime insulin.

RFC5.6

Clinical Management of the Mitchell-Riley Syndrome Due to RFX6 Gene Mutations: Aggressive Support Results in Improved Outcome

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Background: Homozygous mutations in the transcription factor *RFX6* are the cause of the Mitchell-Riley syndrome associating neonatal diabetes, pancreatic hypoplasia, gallbladder agenesis, duodenal atresia, and severe chronic diarrhea. Nine cases have been reported so far and the condition has a poor prognosis with five of nine patients died before the age of 6 months. **Objective and hypotheses:** To report on the clinical management and outcome of two new cases from two independent families. **Results:** The two patients were from first degree consanguineous families, had severe SGA and an antenatal diagnosis of duodenal atresia. Diabetes was diagnosed at day one and treated with intra-veinous insulin for several months, before switching to subcutaneous with doses between 0.6 and 0.8 UI/kg per d. In patient 1, abdominal imaging showed pancreatic tail and body agenesis, gallblader agenesis, and a normal biliary tract. He had moderate hepatic cytolysis without cholestasis. The chronic and severe diarrhea could only be controlled with total parenteral nutrition, with watery diarrhea recurring at every attempt to introduce enteral nutrition at the age of 30 months, needing a prolonged hospitalization. Patient 2 had hypoplastic pancreas, duodenal and jejunal atresia with gallblader agenesis and necrotizing enterocolitis after surgery. He had no cholestatic disease and was on parenteral nutrition until the age of 12 months due to the severe diarrhea. He has a normal enteral diet at 8 years. The diagnosis was confirmed in the two cases with homozygous mutations in the RFX6 gene: p.Arg181Trp in patient 1 (recently described in another family) and p.Val506Gly, never described previously in patient 2. **Conclusion:** These patients demonstrate

that an aggressive supportive management of patients with RFX6 mutations can result in improved outcome than previously described. The understanding of RFX6 role will open new therapeutic avenues, particularly the use of drugs that interfere with the gut endocrine system.

RFC5.7

Early Successful Hematopoietic Cell Transplantation (HSCT) in a Boy with IPEX Syndrome Caused by Novel C.721T > C *FOXP3* Mutation

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Background: IPEX (OMIM #304790) is a rare and fatal, X-linked immune dysregulatory disorder caused by mutation in transcription factor FOXP3 that result in either quantitative or functional deficiencies of Tregs causing autoimmune disease and allergic inflammation. HSCT is the only curative therapy available for IPEX patients. **Objective:** Presented boy was born at 38th GW with birth weight 3380 g and birth length 50 cm. Three maternal brothers died in early infancy due to malabsorption. At the age of 6 weeks the patient developed Type 1 diabetes (T1D) with typical clinical and laboratory presentation (glycaemia 38 mmol/l, severe ketoacidosis and extremely high GAD antibodies > 120 kIU/l). Subsequently he developed atopic dermatitis and progressive failure to thrive due to diarrhea. Immunosuppressive treatment with glucocorticoids was ineffective. At the age of 3 months he underwent HSCT from an unrelated HLA-matched donor. The HSCT course was uncomplicated, the outcome was favorable: gastrointestinal and skin symptoms fully resolved, the boy is fed orally and thriving well. C-peptide remained however undetectable (< 3.33 pmol/l), insulin treatment could not be stopped. Nowadays, at the age of 7 months is the patient's T1D well-controlled by CSII (HbA1c 45 mmol/mol) with daily insulin requirements of 0.63 IU/kg. **Method and results:** Direct sequencing of *FOXP3* gene revealed a novel c.721T > C (S241P) mutation in proband, his mother and sisters. The quantity of the patient's Tregs was in normal range (9.0%), but in immunosuppressive assay his Tregs failed to suppresses proliferation of effector T cells if compared to healthy controls. **Conclusion:** We describe a previously unreported c.721T > C (S241P) mutation in *FOXP3* gene. To our knowledge we reported the youngest patient with IPEX who underwent successful HSCT. We suggest that an early genetic diagnosis followed by an early HSCT offers the greatest potential to correct the disease process and thereby minimize end-organ damage.

RFC5.8

Stress Management and Health Promotion through Family Intervention Improves Metabolic Control in Children and Adolescents with Type 1 Diabetes

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Background: Optimal glycemic control in children and adolescents with type 1 diabetes mellitus (T1DM) is often hampered owing to psychologic maladjustment of both patients and their parents. Accumulating evidence suggests that hyperglycemia may be associated with prolonged activation of the stress system. **Objective and hypotheses:** To pilot test a 12-week intervention program including psychoeducation about stress, healthy lifestyle, diaphragmatic breathing, progressive muscle relaxation, guided imagery, cognitive restructuring, gratitude and health locus of control in children and adolescents with T1DM and their parents. We hypothesized that patients of the intervention group would have lower HbA1c levels and lower anxiety and depressive symptomatology than controls after the intervention. We also hypothesized that parents of the intervention group would have lower perceived stress, anxiety and depressive symptoms and a significant change in health beliefs than the control group. **Method:** Thirty-two patient-parent dyads were randomly assigned to the intervention ($n = 17$) and control ($n = 15$) group. HbA1c of the patients of both groups was recorded before and after the intervention. Moreover, patients completed the Screen for Child Anxiety Related Disorders and the Child Depression Inventory; the participating parent completed the Perceived Stress Scale, the Depression Anxiety Stress Scale and the Health Locus of Control Scale. **Results:** A significant reduction in HbA1c was observed in children and adolescents of the intervention group compared to controls (ΔHbA1c $= -0.34 \pm 0.23$ vs $+0.61 \pm 0.45$ ($P < 0.014$)). Moreover, a trend toward

decreased perceived stress in sparents of the intervention group was detected. Paradoxically, the external health locus of control significantly decreased only in the parents of the control group. **Conclusion:** A family-based intervention of stress management and health promotion could facilitate metabolic control in Greek children and adolescents with T1DM. Further studies in a larger sample are required to confirm the effectiveness of such an intervention within this population.

RFC6.2

RAB3IP and DGCR8 as a Potentially Pathogenic Novel Candidate Gene Involving in Growth Disorders

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Background: The majority of children with short stature are classified as idiopathic short stature. Whole exome sequencing can help identify genetic causes of short stature. **Methods:** We recruited 10 children with short stature of unknown etiology. We conducted whole exome sequencing of the patients and their family members. We used an analysis pipeline to identify rare nonsynonymous genetic variants that might cause the short stature. All rare allelic variants were confirmed by Sanger and were absent in 609 exomas of Brazilian healthy subjects and in a public database (EXAC). **Results:** We identified two novel candidate genes with loss of function (LoF) mutations. One patient has a homozygous nonsense allelic variant in *RAB3IP* (c.13A> T: p.K5*). The *RAB3IP* is an important factor for activation of specific proteins in the RAS family, known as RAB8A/B. These proteins participate in the ciliary and exocytosis process. This latter feature may be involved in hormone secretion. This patient has short stature with microcephaly, mild dysmorphic facial, mild disorder of sex development and a suggestive resistance hormonal profile with an important elevation of LH and FSH. The second patient has a *de novo* heterozygous variant in *DGCR8* gene (c.1321C>T/p.R441*). No phenotype was associated with DGCR8 alteration in humans. This gene participates in microRNA biogenesis and it is extremely intolerant for LoF alterations. It was mapped in the chromosome 22q11.2 in a critical region of DiGeorge syndrome, which is associated with growth impairment. This patient was small for gestational age without catch-up growth and had a neonatal hypomagnesemia, mild delay in initial development and mild dysmorphic facial features. **Conclusion:** It is possible that *RAB3IP* and *DGCR8* genes have a relationship with a dysmorphic features and short stature in these patients. The identification of other patient with similar phenotype and genetic findings is important to prove this relationship.

RFC6.3

Effect of Very Early Growth Hormone (GH) Treatment on Long-term Growth in Girls with Turner Syndrome (TS): A Multicenter, Open-Label, Extension Study

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Background: Late initiation of GH results in suboptimal adult height for many women with TS. In a landmark, randomized, controlled, clinical trial ("Toddler Turner" study) we showed that 2 y of early GH (ET group) started at 1.98±1.01 y, resulted in height SDS difference of 1.6±0.6 SDS vs. early untreated group (EUT). **Objective and hypotheses:** It was unclear if early height gains would result in taller adult heights, so patients were followed to near adult height (NAH) in a long-term extension. **Method:** Auxology, bone age x-ray, laboratory and safety assessments were obtained annually. Tympanometry and audiology assessments were performed at baseline, 10 y, 16 y or study endpoint. GH treatment was at the discretion of the investigator and subject's local physician. The primary efficacy measure was last height available when height velocity was ≤2.0 cm/y or bone age was ≥14.5 y (near-adult height (NAH)). **Results:** Of 88 eligible subjects, 69 entered the extension (ET=36; EUT=33); 68 received GH (average 41±14 μg/kg per d) and NAH was available for 51 after 12.98±2.62 y (ET=25) and 11.08±2.63 y (EUT=26) GH treatment. At entry to extension (ET vs EUT), chronological age was 8.46±1.19 y vs 8.54±1.28 y, bone age 9.12±1.45 y vs 8.51±1.56 y, and height SDS −0.68±1.21 vs −1.29±1.24. NAH SDS was: ET, −1.37±1.09 (153±7 cm) at age 14.64±0.25 y; EUT, −1.60±1.21 (152±8 cm) at age 15.26±0.23 y (P=0.590). Height SDS at ages 10, 13, and 16 y were −0.66±1.16 vs −1.28±1.17 (n=62); −1.29±1.24 vs −1.87±1.16 (n=58); and −1.66±1.11 vs −1.69±1.30 (n=36). ET subjects attained

thelarche slightly earlier than EUT (11.60±0.33 vs 11.96±0.34 y ($P=0.038$)) and had earlier start of estrogen replacement (12.11±0.96 vs 12.66±1.34 y ($P=0.143$)). Of 69 subjects, 1 died of leukemia, ≥1 serious adverse events (AE) were reported for 11 and non-serious AE for 66. Three cases of de novo neoplasia (colon adenoma, ganglioneuroma and medulloblastoma) were reported. There was no difference between groups for abnormal tympanometry/audiometry results. **Conclusion:** Girls with TS who received 2 y of GH starting at age 2 were somewhat taller (non-significant) at ages 10 y, 13 y and NAH than controls. Both groups attained NAH ~10 cm greater than if untreated, based on historical data. To our knowledge, this study represents the longest longitudinal follow-up of a TS cohort.

RFC6.4

Growth Hormone (GH) Treatment in Skeletal Dysplasias – Short-term Results in Prepubertal Children Reported in KIGS

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Background: A total of 83,803 patients who received rhGH therapy were enrolled in KIGS (Pfizer International Growth Database) including 748 patients diagnosed with a specified or unspecified skeletal dysplasia. The most prevalent diagnoses were hypochondroplasia ($n=238$: Female=111, Male=127), achondroplasia ($n=113$: F=51, M=62) and Leri-Weill dyschondrosteosis, LWD ($n=88$: F=59, M=29). **Objective:** To analyse the first year response in height and body proportions to rhGH treatment (GH Tx) in prepubertal patients with hypochondroplasia (Hch), achondroplasia (Ach) and LWD. **Methods:** For descriptive statistics median, 10 th and 90 th percentiles are presented. **Results:** Only data from children who remained prepubertal during the 1st year of treatment were analysed. The Table summarizes the findings. The percentage of children with a 1st yr Ht gain >0.5 SDS were for Hch, Ach and LWD 54%, 29% and 77%, respectively. Serious Adverse Events reported for the 3 groups were: Hch=2: oral discomfort and appendectomy; Ach=5: gastrointestinal pain, femur fracture, shunt occlusion, headache and hydrocephalus; LWD=2: scoliosis and limb asymmetry. **Conclusion:** Response to GH Tx was modest in Hch and LWD but poor in Ach prepubertal children. Body disproportion in Hch and LWD was unchanged by GH Tx but possibly increased in Ach.

RFC6.5

Abnormal Videofluoroscopic Swallow Studies (VFSS) in Infants with Prader-Willi Syndrome Indicate a High Rate of Silent Aspiration

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Background: Prader-Willi Syndrome (PWS), due to loss of expression from genes within the PWS imprinted region at chromosome 15q11.2-13, is characterized by hypotonia and

Table 1. (for abstract RFC6.4)

	Hch		Ach		LWD	
	n	median (*p*10 to p90)	*n*	median (p10 to p90)	*n*	median (p10 to p90)
Age at start	110	7.8 (3.5 to 10.9)	56	5.3 (1.9 to 10.4)	30	9.1 (4.8 to 11.9)
Height SDS						
At start	110	−3.8 (−4.7 to −2.9)	56	−5.5 (−7.2 to −4.1)	30	−2.8 (−3.9 to −2.0)
First year gain	110	0.5 (0.2 to 1.1)	56	0.4 (0.3 to 1.2)	30	0.6 (0.4 to 1.1)
Sitting height & relative sitting height SDS*						
First year change in sitting height	37	0.6 (−0.1 to 1.1)	26	0.4 (−0.3 to 1.6)	13	0.7 (0.0 to 1.0)
Relative sitting height at start	44	5.2 (2.6 to 7.9)	26	13.8 (9.5 to 18.6)	15	3.3 (2.4 to 4.1)
First year change in relative sitting height	37	0.1 (−1.6 to 1.0)	26	1.0 (−1.7 to 3.5)	13	0.1 (−1.1 to 0.6)
GH dose (μg/kg per day)	110	36 (24 to 53)	56	33 (17 to 46)	30	39 (23 to 51)

*Relative sitting height=sitting height/height; SDS calculations based on Rader (height) and Gerver (sitting height) references.

feeding intolerance in infancy with later development of hyperphagia and obesity. Growth hormone improves tone, body composition, and height and can be started in infancy. Morbidity and mortality in PWS include those secondary to hyperphagia and respiratory illness as well as a 17% reported incidence of sudden death in childhood. Choking is a known hazard with a 34% reported incidence. Despite well-described feeding intolerance in infants with PWS, there are no published reports of formal swallow studies. **Objective and hypotheses:** To evaluate the swallowing function of infants with PWS seen at Seattle Children's Hospital (SCH) with VFSS obtained for clinical indications of poor feeding. We hypothesize that VFSS will diagnose pathology missed by clinical observation and may help determine feeding safety in PWS infants. **Method:** VFSS results of infants followed in the interdisciplinary SCH PWS clinic between October 2014 - April 2016 were reviewed. The study was approved by the SCH IRB. **Results:** Six infants with genetically confirmed PWS underwent 10 VFSS (age: 3 weeks-15 months; gender: male 4, female 2; subtypes: deletion 3, uniparental disomy 2, imprinting defect 1). One patient received 5 studies over 14 months. Of all the studies, 100% indicated oropharyngeal phase dysphagia with abnormal pharyngeal clearance in 80% (5 infants). 100% showed silent aspiration with thin liquids, 60% with thickened liquids, 20% with purees. 60% were done while the infant was on growth hormone. Average age of growth hormone initiation was 2.5 months. The infant with multiple studies showed improvement over time, but still had an abnormal VFSS at 15 months old. **Conclusion:** VFSS showed oropharyngeal phase dysphagia and silent aspiration in all infants which may have been undiagnosed with only clinical observation. Abnormalities were present despite early initiation of growth hormone. Careful consideration should be made before starting oral feeds in infants with PWS, and VFSS can be a useful clinical tool in this decision. Swallow dysfunction may be a contributor to morbidity in PWS. Further longitudinal studies are needed to characterize swallowing function in PWS over time.

RFC6.6

Growth Hormone (GH) Deficiency Type II: Clinical and Molecular Evidence of Impaired Regulated GH Secretion Due to an Gln181Arg *GH-1* Gene Mutation

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Background: Main features of the autosomal dominant form of GH deficiency (IGHD II) include markedly reduced secretion of GH combined with low concentrations of IGF-I leading to short stature. **Objective and hypotheses:** We report on a girl referred for assessment of short stature (−4.6 SDS) at a chronological age of 7 yr 10 mo. The GH deficiency was confirmed by standard GH provocation tests, which revealed severely reduced GH and IGF-I concentrations. Genetic analysis of the *GH-1* gene identified heterozygosity for p.Q181R mutation and therefore IGHD II was diagnosed. **Method:** We aimed to characterize the new p.Q181R mutation by *in vitro* GH secretion study as well as *in silico* mutagenesis and molecular dynamics simulations. Moreover, we performed a detailed structural analysis concerning folding, stability and dimerization of the mutant by generating recombinant wt-GH and mutant GH protein in Escherichia coli. **Results:** In line with the clinical data of the patient, AtT-20 cells coexpressing both the *wt*-GH and the p.Q181R showed a reduced GH secretion after forskolin stimulation compared with cells expressing only *wt*-GH. Moreover; *In silico* mutagenesis and molecular dynamics simulations revealed a drastic change in interatomic contacts between the N and C terminus helices in hGH while the structural analyses of the mutant demonstrated a difference in folding and stability compared to the wt-GH. **Conclusion:** p.Q181R seems to severely impair the regulated GH secretion and may, therefore, cause this specific form of IGHD II. Our results suggest that the specific and detailed analysis of this mutant may shed light on a new mechanism of secretory pathophysiology causing IGHD II.

RFC6.7

Characteristics of Responders and Poor-responders to Increlex® Therapy – Data from Children Enrolled in the European Increlex® Growth Forum Database (EU-IGFD)

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Background: The post-authorization registry, EU-IGFD, was initiated in Dec-2008 to collect data in children with growth failure receiving Increlex® (Mecasermin [rDNA Origin] Injection). **Objective and hypotheses:** To report patient characteristics, safety and effectiveness data in poor-responders (i.e. with change

in year 1 Height SDS <0.3). **Method:** European, multicentre, open-label, observational study; eCRF data collection. **Results:** As of 06-Oct-2015, 221 patients were enrolled in 10 countries, among them 93 naïve prepubertal patients (NPP) with available data including 38 poor-responders and 55 responders. In NPP, at treatment initiation poor-responders were statistically older compared to responders (multivariate analysis: OR [95% CI] = 0.78 [0.69;0.90]; $P<0.001$). Neither gender, mid-parental adult height, height SDS, weight SDS, IGF-I nor Laron-syndrome were statistically different between groups. Median [95% CI] treatment duration in poor-responders was 1221 [891;1422], versus 1381 [1167;1829] days in responders; median dose (μg/kg BID) was 40 at treatment initiation in both subgroups, 107 versus 120 at Year 1, 120 at Year 2 in both subgroups. Baseline characteristics and effectiveness data (mean (SD)) were as follows. In the 93 NPP, the treatment-emergent adverse events (TEAEs) were 47% and 55% in poor-responders and responders, respectively, and the targeted adverse events (TAEs) were 37% and 45%. The most common TAEs in poor-responders were: hypoglycaemia (16% vs 20%), headache (13% vs 11%), tonsillar hypertrophy (11% vs 9%), and injection-site erythema (5% vs none). **Conclusion:** Naïve prepubertal patients defined as poor-responders (year 1 height SDS change $<$ 0.3) were older at the time of first Increlex intake. Other common predictors of poor response to growth promoting therapy were not identified. Poor-responders had lower second year gain in height SDS. TEAEs and TAEs were less frequent overall in poor responders. The first year Increlex response should be evaluated to determine whether to adjust treatment.

RFC6.8

The Actual Incidence of Small for Gestational Age (SGA) Newborns and their Catch-up Growth is Dramatically Lower than Previously Considered

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Background: SGA is defined as birth weight under 2 standard deviations (SD) from the mean. Previous studies indicate that 10% of SGA babies do not have "catch-up growth" (CUG). They are eligible for growth hormone (GH) therapy to increase final height. The unexpected low demand for GH therapy in SGA babies, triggered us to survey the actual incidence of SGA and failure in CUG. **Objective and hypotheses:** To find the actual incidence of SGA and failure in CUG in SGA children. **Method:** Our cohort included all-43,307 babies born at Hadassah hospitals in Jerusalem between 2008–2011. SGA was defined according to WHO parameters and the corresponding Israeli criteria (weight $<$2SD, Dolberg's table 2005). Our calculated birth weight percentiles were

Table 1. (for abstract RFC6.7)

		Baseline Characteristics in NPP				
	Boys (%; *n*)	Laron- Syndrome subjects (%: *n*)	Age at first dose (years)	Height SDS at first dose	Weight SDS at first dose	Mid-parental adult height (cm)
Poor-responders ($n=38$)	66; 25	8; 3	10.1 (3.9)	−3.53 (1.07)	−3.28 (0.94)	168.2 (9.3)
Responders ($n=55$)	58; 32	13; 7	7.2 (3.0)	−3.68 (1.38)	−3.22 (1.13)	165.7 (8.7)

		Effectiveness Data in NPP					
	*n**	Height SDS	ΔHeight SDS	*n**	Annualized Height Velocity (cm/year)	*n**	ΔAnnualized Height Velocity (cm/year)
Poor-responders							
Baseline	38	−3.53 (1.07)	–	17	4.3 (2.0)	–	–
Year 1	38	−3.53 (1.12)	0.00 (0.21)	36	5.7 (1.4)	15	1.1 (2.8)
Year 2	30	−3.46 (1.24)	0.19 (0.38)	30	6.0 (1.8)	13	2.0 (3.2)
Responders							
Baseline	55	−3.68 (1.38)	–	36	5.2 (1.6)	–	–
Year 1	55	−2.99 (1.27)	0.69 (0.30)	55	83 (1.7)	36	3.0 (2.1)
Year 2	43	−2.72 (1.29)	1.02 (0.55)	38	6.4 (1.4)	25	1.7 (1.7)

*number of available data.

compared to the nationally used percentile data (NUPD). Follow-up measurements of height and weight were obtained from the pediatrician or from the municipal pediatric growth follow-up centers. **Results:** Only 524 babies in the cohort (1.2%) were SGA (52% of expected). This finding was consistent annually. Birth weight percentile comparisons showed that 1st and 5th percentile weights in our cohort were significantly (20%) higher while the 95th and 99th percentiles were 5% lower than the NUPD. CUG parameters (currently available for 377/524 SGA) indicated that 356 (95.4%) had CUG in the first 2 years (height >2.5SD below the mean).CUG rate among term SGA infants was even higher-96.7%. **Conclusion:** This large cohort representing a heterogeneous (socioeconomic status and multiethnic) western Caucasian population indicates that the actual number of SGA newborns is nearly half of the expected according to WHO/NUPD definitions. The incidence of infantile CUG is also significantly higher than previously reported. As these findings may have an impact on morbidity, health cost planning and GH requirements in SGA babies, expanding this study to both Europe and the US is warranted.

RFC7.1

Tissue Engineered Collagen Based Tubular Scaffolds for Urethral Regeneration. A Novel Technology for the Surgical Treatment of VSD (Variation of Sex Development) Patients with Severe Hypospadias

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Background: Actual surgical procedures for the treatment of patients with VSD (Variation of Sex Development), in particular severe hypospadias, are associated with frequent post-operative complications. **Objective and hypotheses:** Tissue engineered collagen tubes are a promising alternative. **Method:** We elaborated a new, two layered, collagen based tube that can be sutured. Mechanical testing proved a better resistance of those tubes compared to our previous single layered collagen tube. They were used as urethral grafts in a rabbit model and sutured after a subtotal excision of the urethra. The graft was anastomosed between the prostatic urethra and the very distal native urethra. This subtotal urethral replacement (more than 80% of the total length) was done in 20 male New Zealand white rabbits, in Lausanne (Switzerland) and Kuala Lumpur (Malaysia). The constructs were all acellular, potentially off-the-shelf and no catheter was placed postoperatively. **Results:** The animals were evaluated at 1, 3, 6, and 9 months by contrast voiding cysto-urethrography, histological examination and immunohistochemistry staining. All rabbits survived the surgical implantation. This multicentric study revealed spontaneous regrowth of urothelial cells (UC) and smooth muscle cells (SMC) in all grafts at 9 months and reduced severe postoperative complications. The stenosis (20%) and fistulae (20%) could be potentially overcome by leaving the urinary catheter after surgery. **Conclusion:** Those novel compressed collagen gel tubes are easy to handle, can be sutured and therefore they are suitable for clinical applications. This may be an alternative to the existing surgical treatment of severe hypospadias.

RFC7.2

Reference Values for External Genitalia Size and Steroid Hormone Levels in Female Neonates

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Background: Prenatal androgen exposure can lead to variable virilization of external female genitalia. The lack of a consensus definition of clitoromegaly and the limited data available on normal steroid levels in female neonates makes its diagnosis difficult. **Objective and hypotheses:** The aims of this study were (i) to define reference sizes for external female genitalia in term and preterm neonates as a function of gestational age and birth weight; and (ii) to determine reference values for steroid hormones in female neonate serum. **Method:** We measured the clitoris (length, width) and the anogenital ratio for three-day-old female neonates born at a gestational age of 24 to 42 weeks. For neonates born after 35 gestational weeks the concentrations of nine steroids were analyzed by LC/MSMS, the main ones being testosterone (Testo), delta4 androstenedione (Delta4), 17-hydroxyprogesterone (17OHP), dihydroepiandrostenedione (DHEA), and dihydrotestosterone (DHT). **Results:** For the 452 full-term female neonates included, the mean clitoris length is 3.6 mm (P95 = 6 mm), the mean clitoral width is 4 mm (P95 = 7 mm), and the mean anogenital ratio is 0.45 (P95 = 0.58). Preterm neonates are still being included. The normal values in nmol/l for the main steroids are as follows: **Conclusion:** These results suggest (i) a definition of clitoridomegaly in full term neonates as a clitoris longer than 6 mm; (ii) an anogenital ratio greater than 0.6 is an indicator of possible in

Table 1.

N=452	Testo	DHT	Delta4	17OHP	DHEA
Mean	<0.125	0.083	0.742	0.956	7.157
P25-P95	<0.125	0.056–0.154	0.251–1.522	0.226–2.299	1.059–22.2

utero virilization. A set of reliable LC/MSMS-based reference values for steroid concentrations in female neonates are proposed.

RFC7.3

Harmonisation of Serum Dihydrotestosterone Analysis: Establishment of an External Quality Assurance Program

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Background: Serum dihydrotestosterone (DHT) is an important analyte for the clinical assessment of disorders of sex development. It is also reportedly a difficult analyte to measure. Currently there are significant gaps in the standardisation of this analyte, including no external quality assurance (EQA) program available worldwide to allow for peer performance review of DHT. **Objective and hypotheses:** We therefore proposed to establish an EQA program for serum DHT. **Method:** DHT was assessed in the 2015 Royal College of Pathologists of Australasia (RCPA) Quality Assurance Programs (QAP) Endocrine program material. The target (i.e. "true") values for the material were established using a measurement procedure based on isotope dilution GC-MS/MS. DHT calibrator values were based on weighed values of pure DHT material (>97.5% purity) from Sigma. The allowable limits of performance (ALP) were established as $\pm$0.1 up to 0.5 nmol/L and $\pm$15% for targets >0.5 nmol/L. **Results:** Target values for the six levels of RCPAQAP material for DHT ranged from 0.02 to 0.43 nmol/L (0.01 to 0.12 ng/mL). The material demonstrated linearity across the six levels with a best fit polynomial regression of $y = 1.024\ x + 0.002846$. There were five participating laboratories for this pilot study. Results of the LC-MS/MS methods were within the ALP when compared to the target values; whereas the results from the immunoassay methods were consistently higher than the target values and outside the ALP. **Conclusion:** The DHT pilot ran successfully throughout 2015, and has now been formally included in the RCPAQAP Endocrine Program. Through the establishment of this EQA program, we now have the first peer comparison of serum DHT measurement by mass spectrometry and immunoassay laboratories. This EQA program provides one of the pillars to achieve method harmonisation and eventual standardisation. This supports accurate clinical decisions where DHT measurement is required.

RFC7.4

A Mutation in *WT1* (*Wilms' Tumor Suppressor 1*) Associated with 46,XX TDSD

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Background: 46,XX DSD (Disorder of Sex Development) includes individuals with ovotestes (ovotesticular DSD (OTDSD)) or testes (testicular DSD (TDSD)). Most individuals with 46,XX TDSD carry the SRY gene. Other known causes of TDSD/OTDSD include chromosomal rearrangements involving *SOX9* or *SOX3* and mutations of *WNT4* and a WNT regulator, *R-SPONDIN 1*. However, our understanding of the molecular causes of TDSD and OTDSD remain incomplete. **Objective and hypotheses:** To identify novel genes/mutations associated with 46,XX TDSD/OTDSD. **Method:** Paired-end sequencing was performed on the Illumina HiSeq2000 platform using TruSeq v3 chemistry at an average coverage of x50. Reads were mapped using the Burrows-Wheeler Aligner and their local realignment were carried out with the GATK version 1.6. SNP novelty was determined against public databases. Potentially pathogenic mutations were verified by Sanger sequencing. The effect of mutation on the biological activity of the protein was assessed using an array of in-silico and in-vitro methods. **Results:** We identified a de novo missense mutation of a highly conserved arginine residue in the fourth zinc-finger of WT1 (p.Arg495Gly) in a patient with 46,XX TDSD. Normal ploidy was established by high resolution aCGH and qPCR indicated two copies of the *RevSex SOX9* enhancer. The p.Arg495Gly mutation is not present in public databases. The patient of Egyptian origin presented with dysgenic testis, microcephaly, a small uterus and no kidney tumour. Transient gene expression assays and protein-protein interaction studies showed that the mutant protein abnormally regulated/interacted with genes/proteins involved in both male and female gonadal development. **Conclusion:** Mutations in *WT1* have been previously reported in anomalies of testis formation in 46,XY individuals. This is the first time that a mutation has been identified in *WT1*, in a patient presenting with 46,XX TDSD. This raises the intriguing possibility that specific mutations in *WT1* may be associated with testis formation in 46,XX chromosomal context.

RFC7.5

Fertility Preservation in an Adolescent Boy: Inducing Puberty and Spermatogenesis Prior to Bone Marrow Transplantation

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Background: Bone marrow transplantation (BMTx) involves pre-conditioning regimens that compromise fertility Delayed puberty and hypogonadism are common in children with beta thalassemia major, due to chronic disease and transfusion requirements, due to iron overload in endocrine glands. **Objective and hypotheses:** Pubertal induction using hCG and FSH prior to gonadotoxic conditioning before BMTx should result in spermatogenesis sufficient to store sperm. We aimed to induce puberty and spermatogenesis, over a short time of 6–9 months before planned BMTx. **Methods:** After explanation and parental consent, a prepubertal 13 year old boy with beta thalassemia major, height 151.9 cm (25 th centile), mid-parental expectation (90 th centile) was administered human chorionic gonadotropin (hCG) 500IU x2/week by subcutaneous injection, increased to 1000IU x2/week after 3 months. When serum testosterone rose to 11.9 nmol/l, follicle stimulating hormone (FSH) 150IU x3/week was added, to induce spermatogenesis, increased after 3 months to 300IU x3/week. **Results:** Pubertal progress was mildly accelerated, height 169 cm, gain of 17.1 cm over 10 months. Adult virilisation with 20ml testes bilaterally occurred, with serum testosterone 17.6 nmol/L inhibin B 135 ng/L(50–350). Semen collection, 9 months after commencing FSH, demonstrated 0.5–1.8 $\times 10^6$/ml in three samples. Cryopreservation of 11 straws was undertaken. Four months after semen collection he underwent BMTx, preceded by Busulphan conditioning. **Discussion:** This report provides the first evidence of feasibility of inducing puberty and spermatogenesis adequate for future fertility, in a prepubertal adolescent male, prior to BMTx. Unlike transplant performed in the setting of malignancy where time is extremely limited, elective transplant for non-malignant conditions may in some cases be postponed for a reasonable period to permit the possibility of pubertal induction and sperm retrieval. Fertility preservation in this case is assured. In the setting of chronic disease mild loss of final height may occur. **Conclusion:** This option should be considered in future, for other adolescent males, prior to gonadotoxic treatments.

RFC7.6

The Hopeful Beginnings of Fertility Preservation in Children

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Background: Fertility Preservation (FP) in children and adolescents poses unique challenges as efficacy is unproven. **Objective and hypotheses:** To describe characteristics and evidence for potential fertility in ovarian and testicular tissue cryopreservation specimens (OTCP and TTCP respectively) taken from paediatric and adolescent patients, stratified by age, and prior chemotherapy. **Method:** Retrospective review of gonadal biopsies and clinical records of patients consented into the Royal Children's Hospital FP program between 1987–2015. Tissue was sectioned, with one section sent for histopathology prior to cryopreservation. In boys $\geq$ 12 years where spermatogenesis could be expected, a portion of tissue was dissected to look for mature sperm and if found, additional tissue was dissected and the suspension frozen. In girls, follicle density was assessed on histology. Cumulus oocyte complexes recovered, were cultured for 48 hours and mature oocytes frozen. **Results:** TTCP specimens in 44 males (0.3–16.2 years) provided an average of 8, 2–5 mm slices each. Eleven subjects had tissue dissected, mature sperm were found in 8 (all were pubertal; with testicular size 10–12 ml; all with histology had evidence of spermatogenesis; one had prior low-risk gonadotoxic therapy). OTCP in 50 females (1.0–19.6 years) provided 12–222 slices ($1\times1\times3$ mm). Follicle density was 0.3–134/mm^3. Mature oocytes were collected in 4 patients (12.6–17.7 years, all postmenarcheal and had no prior chemotherapy). Histology was free of malignancy. **Conclusion:** Both TTCP and OTCP can be offered to young patients without delay in cancer treatment. Retrieval of mature sperm and oocytes from some pubertal patients may offer realistic hope for future fertility.

RFC7.7

Clinical Decision-Making in Disorders of Sex Development (DSD): Physician Recommendations Pre- and Post-Consensus Statement

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Background: Despite advances in genetic diagnosis and surgical technique, and guidance from the Consensus Statement on Intersex Disorders, aspects of clinical management in disorders/differences of sex development (DSD) remain unsettled. Actively debated decision points include gender of rearing in specific syndromes, genital surgery prior to the patient developing the capacity to provide assent, and uncertainty over how and when to best educate young patients about diagnostic and medical management history details. **Objective and hypotheses:** To ascertain expert opinion and treatment recommendations regarding clinical management of children born with varying DSD.

Method: Pediatric endocrinologists (T1$n=300$; T2$n=337$) and urologists (T1$n=132$; T2$n=118$) were presented five case vignettes and asked for recommendations about gender of rearing, surgical decision-making, and disclosure regarding diagnostic and medical management history to paediatric patients. The web-based survey was administered three years before and four years following Consensus Statement publication. Clinical recommendations in each area are summarized on a case-by-case basis. Effects of physician characteristics (i.e., gender, age, experience, practice setting, subspecialty) and time (ie, pre- vs post-consensus) on clinical recommendations were assessed. **Results:** Within specialty, substantial variability existed in gender of rearing recommendations and, similarly, for surgical and disclosure decisions. Speciality was inconsistently associated with recommendations. Differences by physician demographic characteristics emerged, but did not form a systematic pattern across vignettes. **Conclusion:** Variability in clinical management recommendations, independent of case characteristics, is a cause for concern – particularly for parents faced with contrasting recommendations. There is an acute need to account for variability in provider recommendations which may be untethered to evidence.

RFC7.8

Premature Adrenarche in Girls at Pubertal Onset is Associated with High Androgens, but Lower AMH Concentrations

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Background: Premature adrenarche (PA) has been considered a benign condition. Recently, associations with increase androgen levels and PCOS have arisen. **Objective:** To determine whether PA in children at pubertal onset (TII) determines a different timing of pubertal events and a different pattern of ovarian and adrenal hormones. **Methods:** A total of 583 girls from the longitudinal cohort (Growth and Obesity Cohort Study, born 2002) were followed twice a year with a clinical evaluation, and at TII a complete hormonal profile (androstenedione, 17OHprogesterone, testosterone and AMH). PA was defined by DHEAS >42.0 μg/dl at 6.8 ± 0.6 yr (RIA). Statistics: Generalized linear models were used to assess the relation between PA and hormonal profile, adjusting by chronologic age at DHEAS sampling, HOMA and BMI. **Results:** At TII, girls who developed PA (PA+) were slightly younger (by interval censoring, Turnbull), taller and had higher BMI_SDS. In addition they displayed higher androstenedione, higher testosterone and lower AMH levels. No differences were observed in gonadotrophins, estradiol, 17OHprogesterone and SHBG levels. **Conclusions:** Girls with history of PA initiated their puberty at an earlier age. At this stage of puberty (TII) they also showed a mild hyperandrogenism in concert with lower concentrations of AMH. Continuous follow-up of this cohort is a unique opportunity to address prospectively the interrelationships of PA and PCOS development which does not appear possible at this stage (Fondecyt 1140447 & 1120326, WCRF:2010/245).

Table 1.

	Girls PA+	Girls PA−
Age (years)	8.8 (95%CI; 7.9–9.3)	9.3 (95%CI; 9.1–9.6)
Height_SDS	0.3 ± 0.9**	0.05 ± 1.0
BMI_SDS	1.1 ± 1.1**	0.8 ± 1.1
Androstenedione (ng/ml)	0.3 ± 0.2**	0.26 ± 0.1
Testosterone (ng/ml)	0.08 ± 0.05*	0.06 ± 0.04
AMH (ng/ml)	3.5 ± 2.1**	4.4 ± 2.5

*$P<0.05$; **$P<0.01$.

RFC8.1

Somavaratan (VRS-317) Treatment of Children with Growth Hormone Deficiency (GHD): Results at 2 Years (NCT02068521)

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Background: Somavaratan, a novel long-acting rhGH fusion protein with $t_{1/2}>100$ h, previously demonstrated clinically meaningful improvements in height velocity (HV) and IGF-I in prepubertal GHD children (Moore JCEM 2016). **Objective and hypotheses:** To evaluate maintenance of somavaratan treatment effects in the 2nd treatment year. **Method:** After subcutaneous pediatric doses were evaluated in a single dose PK/PD study ($n=48$), 64 subjects were randomized to weekly, twice-monthly (TM) and monthly dosing groups for total dose of 5.0 mg/kg per month for 6 months. Sixty subjects entered an extension study. Somavaratan dosing was adjusted to 3.5 mg/kg TM by start of Year 2, based on growth and IGF-I responses from the first 6–12 months of treatment. **Results:** A total of 24 females and 33 males were evaluable in Year 2 (mean age, 7.8 years). Baseline HT-SDS was -2.6 ± 0.6, IGF-I SDS -1.5 ± 0.8, and GH_{max} 5.3 ± 2.6 ng/mL. During Year 2, IGF-I SDS was 0.65 ± 1.2 at peak (3–5 days postinjection) and -0.45 ± 1.1 at trough (end of dosing cycle); 8 subjects had peak IGF-I SDS >2.0, of which two were >3.0 (range, 2.01–3.67). From Years 1 to 2, mean HV was maintained (8.1 ± 2.2 vs 7.8 ± 2.3 cm/year), and HT-SDS showed

continued improvement (-2.1 ± 0.6 vs -1.6 ± 0.7). Over two years, mean bone age (BA) advanced by 2.4 years, mean height age by 2.7 years. Differences between chronological age and BA (years) were 1.5 ± 0.8 at screening, 1.4 ± 0.9 at Year 1, and 1.0 ± 1.0 at Year 2. Related AE rates declined in Year 2 ($n=7$). Related AEs were generally mild and transient, with no new types reported. **Conclusion:** Somavaratan in prepubertal children with GHD improved IGF-I and HV through 2 years, with AE rates declining over time. The 3.5 mg/kg TM dose maintained HV at levels similar to second-year US NCGS data for daily rhGH, and is being evaluated in a Phase 3 study in treatment-naïve GHD children (NCT02339090).

RFC8.2

Pharmacokinetic Modelling Predicts Native hGH Levels Following Administration of a Sustained-Release Prodrug, TransCon hGH, to Children with GHD

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Background: TransCon Growth Hormone is a once-weekly sustained-release prodrug of recombinant human growth hormone (hGH, somatropin). Based on the inert TransCon prodrug technology unmodified hGH is released with a Cmax and AUC comparable to daily therapy. TransCon hGH leverages the known pharmacology of daily hGH and is being developed for the treatment of growth hormone deficiency (GHD). **Objective and hypotheses:** Both hGH levels and resulting IGF-I levels should be maintained at safe and efficacious levels as observed for daily hGH. A PK model was used to predict serum levels of unmodified hGH released from the TransCon hGH prodrug. **Method:** The PK model was constructed using first-order kinetics for hGH release from the TransCon prodrug, absorption from the injection site and elimination of hGH and prodrug, respectively. Values for absorption and elimination of unmodified hGH were obtained from the literature and the model used to predict unmodified hGH released from the TransCon prodrug in a Phase 2 study in children with GHD (NCT01947907, $n=53$). **Results:** In children with GHD serum concentration of unmodified hGH was predicted to be 13 ng/mL following administration of 0.21 mg/kg per week, correlating well with the observed 13 ng/mL in GHD children. Daily hGH at 0.03 mg/kg per day (0.21 mg/kg per week) resulted in a Cmax of 17 ng/mL, demonstrating that weekly TransCon hGH and daily hGH has comparable maximal serum levels of free hGH. **Conclusion:** The PK model provided excellent prediction of unmodified hGH levels following TransCon hGH administration to children with GHD. Clinical studies in children and adults with GHD have demonstrated that TransCon hGH has comparable safety and efficacy to daily hGH when administered at the same cumulative weekly dose. TransCon hGH has the potential to offer patients requiring growth hormone therapy a sustained-release alternative to daily injections, designed to maintain the same safe and efficacious growth hormone levels in the body as daily hGH.

RFC8.3

Batch-to-Batch Consistency of a Highly O-Glycosylated Long-Acting Human Growth Hormone (MOD-4023)

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Background: OPKO Biologics is a clinical-stage public company developing long-acting therapeutic proteins utilizing CTP technology. The technology involves fusion of the C-terminal peptide of human chorionic gonadotropin (hCG), which is highly O-glycosylated, to the target protein. CTP enabled the production of a long-acting human growth hormone (hGH) (MOD-4023), which supports a single weekly injection in growth hormone-deficient patients. MOD-4023 is manufactured as a non-viscous liquid formulation. **Objective:** The objective of the study was to develop a highly O-glycosylated drug product with respect to protein quality attributes, process reproducibility, and batch-to-batch consistency. **Methods:** The consistency of MOD-4023 glycosylation was tested by applying various analytical methods, including O-glycan and sialic acid analysis by HPLC, capillary zone electrophoresis (CZE), and isoelectric focusing (IEF). MOD-4023 potency was assessed *in vitro* by a cell-based assay (CBA), utilizing cells that stably express the human growth hormone receptor (GHR). **Results:** Similar O-glycan and sialic acid contents were obtained in different of MOD-4023 batches, supporting the consistency of the drug substance glycosylation profile for each batch. Comparable results for different batches were also obtained using both CZE and IEF analysis. Several batches of MOD-4023 had shown similar levels of binding and activation of the human GHR. **Conclusion:** A robust manufacturing process was developed for the production of MOD-4023 DS, producing a highly reproducible O-glycosylated product.

RFC8.4

A Hybrid Fc-fused Human Growth Hormone, GX-H9, Shows a Potential for Weekly and Semi-monthly Administration in Clinical Studies

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Background, Objective and hypotheses: GX-H9 is a hybrid Fc-based long-acting recombinant human growth hormone (hGH). The safety, tolerability, and PK/PD of single ascending dose in healthy volunteers were assessed to determine GX-H9 doses capable of normalizing IGF-1 level. The PK/PD, safety, efficacy and tolerability of multiple sequential doses of GX-H9 in adult growth hormone deficiency (AGHD) were compared to that of a daily recombinant hGH in AGHD. A Phase 2 study in pediatric GHD (PGHD) is also ongoing to investigate safety, efficacy and PK/PD of GX-H9. **Method:** A double-blind, randomized, placebo-controlled, single ascending dose Phase 1 study of GX-H9 was conducted in 4 groups of healthy subjects ($n=32$) with four sequential dose levels (0.2, 0.4, 0.8 or 1.6 mg/kg). Currently, a Phase 2, randomized, active-controlled, open-label, sequential dose study of GX-H9 (0.1 mg/kg per weekly, 0.2 and 0.3 mg/kg per semi-monthly) is being conducted in patients with AGHD ($n=45$). In addition, a Phase 2, randomized, active-controlled, open-label, multiple dose study of GX-H9 with weekly and semi-monthly administrations is being conducted in patients with PGHD ($n=48$). **Results:** Single doses of GX-H9 in the range of 0.2 to 1.6 mg/kg were well tolerated at all dose levels. Only mild adverse events were observed and no lipoatrophy or anti-drug antibodies were detected. Geometric mean of $t_{1/2}$ ranged between 69.2 and 138.0 hours. IGF-1 serum concentrations increased in a dose-dependent manner between 0.2 and 1.6 mg/kg. The interim Phase 2 results have indicated that AGHD patients ($n=11$) receiving the lowest dose of GX-H9 (0.1 mg/kg) weekly for 12 weeks were safe and comparable with those receiving 6 µg/kg of Genotropin® daily for 12 weeks ($n=2$) in the mean increases in IGF-1 (101.3 ± 31.2 ng/mL vs 109.1 ± 45.0 ng/mL, respectively). The administration of higher doses showed potential for semi-monthly treatment of GX-H9 in AGHD and PGHD. **Conclusion:** Phase 1 and interim Phase 2 results have demonstrated that GX-H9 is safe and well tolerated in healthy subjects and in patients with AGHD and PGHD. The data from ongoing Phase 2 studies will be presented in addition to the Phase 1 result.

RFC8.5

Optimal Sampling of IGF-1 During Weekly Administration of a Long Acting Human Growth Hormone (MOD 4023)

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Background: OPKO Biologics is developing MOD-4023, a long-acting growth hormone (GH), intended for weekly dosing for the treatment of idiopathic GH deficiency in children. At ESPE2015, we presented pharmacokinetic (PK) and pharmacodynamic (PD, based on IGF-1) models for weekly MOD-4023 administration in children aged 3–11 years. These models confirm that IGF-1 (and IGF-1 SDS) varies during the dosing interval. One critical clinical and research issue is when to optimally sample IGF-1 during a dosing interval and how to interpret that value. **Objective and hypotheses:** To evaluate the time course of IGF-1 SDS values during a dosing interval and to determine the relationship between samples obtained at various time points during the interval to peak and mean values. **Method:** The previously-described PK and PD models yielded individual (*post hoc*) parameters for each of 46 adults and 42 children. These models were then used to simulate the IGF-1 plasma concentration profile at steady state based on each subjects. IGF-1 SDS was calculated based on IGF-1, age, and gender. Each subject's peak IGF-1 SDS and values at each of Day 0 (pre-dose) through Day 7 were identified from the simulated data; mean IGF-1 SDS was calculated using linear trapezoids. The relationship between each of peak and mean SDS vs. the value at each day was assessed graphically and by linear regression. **Results:** Peak SDS was well predicted by the value obtained at Day 2 (48 hours post-dose) and mean SDS was well predicted by the value at Day 4. Peak SDS correlated strongly with values at Days 3–5 ($r > 0.98$) and mean SDS correlated strongly with values at Days 2, 4, 5 ($r > 0.98$); however, the linear regression deviated from the line of unity. **Conclusion:** In children, IGF-1 values at Day 2 can be used as a direct predictor of peak IGF-1 SDS; values at Day 4 are a direct predictor of mean IGF-1 SDS. Using the linear regressions, values at other days (2-5) can be used to model peak and mean IGF-1 SDS.

RFC8.6

A Six-Month Safety and Efficacy Study of TransCon hGH Compared to Daily hGH in Pre-Pubertal Children with Growth Hormone Deficiency (GHD)

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Background: TransCon hGH is a long-acting prodrug of recombinant human growth hormone (hGH) that releases fully active unmodified hGH into the blood compartment. This presentation will detail the final safety and efficacy results of TransCon hGH in a Phase 2 study in children with GHD over a treatment period of six months. **Objective and hypotheses:** The objective of this Phase 2 study in GHD was to investigate 1) safety and tolerability, 2) pharmacokinetics (PK) and pharmacodynamics and 3) efficacy of TransCon hGH in children with Growth Hormone 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 (0.03 mg hGH/kg per day = 0.21 mg/kg per

week) over a 6-month treatment period, in a randomized, comparator-controlled Phase 2 study. The patients' GHD diagnosis was established in accordance with international consensus guidelines, based on auxology (height & height velocity), GH stimulation tests & IGF-I. **Results:** Safety and efficacy (annualized height velocity), as well as PK and PD data of 53 GHD patients treated over a 6-month period with TransCon hGH or daily hGH will be presented. All TransCon hGH doses demonstrated an excellent safety/local tolerability profile (comparable to daily hGH) and an excellent growth - mean annualized height velocities ranging between 11.9 cm to 13.9 cm for the different dose levels of TransCon hGH compared to 11.6 cm mean annualized height velocity for daily hGH treatment. **Conclusion:** TransCon hGH has demonstrated efficacy (auxology) and safety comparable to that observed with daily hGH. Observed injection site reactions are similar to what is expected with daily hGH injections, with no nodule formation or lipoatrophy noted. The low immunogenicity, comparable to daily hGH treatments was confirmed. Hence, this TransCon hGH Phase 2 study conducted in a pediatric population with GHD confirmed the very good safety and efficacy profile of TransCon hGH, an hGH prodrug, and forms the basis for Phase 3 development.

RFC8.7

Safety and Tolerability of Once-Weekly Administration of CTP-Modified Human Growth Hormone (MOD-4023): 24-month Complete Dataset Results of a Phase 2 Study in Children with Growth Hormone Deficiency

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Background: Daily injections are currently required for growth hormone (GH) replacement therapy, which may cause poor compliance, inconvenience and distress for patients. MOD-4023 is a CTP-modified human GH (hGH) developed for once-weekly administration in growth hormone deficient (GHD) adults and children. **Objective and hypotheses:** In the present Phase 2 study, the safety and tolerability of once-weekly subcutaneous (SC) administration of MOD-4023 were assessed in children with GHD over a period of 24 months. **Method:** A randomized, controlled Phase 2 study was conducted in prepubertal GHD children receiving SC injections of one of three MOD-4023 doses in a once-weekly regimen (0.25, 0.48, and 0.66 mg/kg per week), or daily hGH (34 µg/kg per day) as control for 24 months. Safety assessments included monitoring of adverse events (AEs), injection site reactions, vital signs and physical condition. Laboratory assessments were also performed and included glucose and lipid metabolism, blood biochemistry, and immunogenicity. **Results:** No severe AEs were reported during MOD-4023 treatment. A similar rate of adverse events was reported by patients treated with MOD-4023 and by patient in the daily arm. No injection site-related reactions such as local discomfort, swelling, erythema or lipoatrophy were observed. Laboratory findings supported the tolerability of MOD-4023 treatment, and no significant overall changes were observed in glucose levels, insulin, HbA1c, or vital signs. **Conclusion:** MOD-4023 demonstrated excellent safety and tolerability during treatment for up to 24 months in a dose range of 0.25–0.66 mg/kg per week. No unexpected AEs were considered as MOD-4023-related. This supports the ongoing clinical development of MOD-4023 for once-weekly treatment of GHD children. Based on the above, a pivotal Phase 3 study will be initiated shortly at a dose of 0.66 mg/kg per week, and patients receiving the lower MOD-4023 doses will be switched to 0.66 mg/kg per week for long-term assessment.

RFC8.8

Efficacy of Once-Weekly Administration of CTP-Modified Human Growth Hormone (MOD-4023): 24-month Complete Database Results of a Phase 2 Study in Children with Growth Hormone Deficiency

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Background: Growth hormone (GH) replacement therapy currently requires daily injections, which may cause poor compliance, inconvenience and distress for patients. CTP-modified hGH (MOD-4023) has been developed by OPKO Biologics for once-weekly administration in growth hormone-deficient (GHD) adults and children. **Objective and hypotheses:** The 24-month efficacy of once-weekly subcutaneous (SC) administration of MOD-4023 was evaluated in a Phase 2 study in GHD children. **Method:** A randomized, controlled Phase 2 study was conducted in prepubertal children with GHD receiving once-weekly SC injections of one of three MOD-4023 doses (0.25, 0.48, and 0.66 mg/kg per week) vs daily hGH (34 µg/kg per day). Subjects were rolled over to continue with the same MOD-4023 dose in an open-label extension (OLE), which will routinely assess growth until marketing approval. Height velocity (HV) results during the 2nd year of MOD-4023 treatment were compared to historical controls (Ranke et al., 2010), and IGF-1 and IGFBP-3 levels were monitored as well. **Results:** The height velocity analysis included the full dataset for patients who completed 24 months of treatment. All 3 doses of MOD-4023 demonstrated promising 2nd year growth, while the two higher doses of MOD-4023 resulted in better growth in comparison to the

lower dose of MOD-4023 (0.25 mg/kg per week), and in line with reported age- and GHD severity-matched historical control (Ranke et al., 2010). **Conclusion:** The efficacy of single weekly MOD-4023 administration for the treatment of pediatric GHD was further confirmed during the 2nd year of treatment as part of the OLE of a Phase 2 study. This further affirms that a single weekly MOD-4023 injection has the potential to replace daily hGH in GHD children. Based on the above, a pivotal Phase 3 study will be initiated shortly at a dose of 0.66 mg/kg per week, and patients receiving the lower MOD-4023 doses will be switched to the 0.66 mg/kg per week dose for long-term assessment.

RFC9.1

Neonatal Diabetes due to NKX2.2 Mutation – Genotype, Clinical Phenotype and Therapeutic Challenges in a Very Low Birth Weight Diabetic Neonate

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Background: Insulin treatment in a very low birth weight neonate having persistent hyperglycemia is challenging. The very recently reported novel human genetic cause of neonatal diabetes due to NKX2.2 pancreatic transcription factor mutations is associated with very low birth weight deliveries. **Objective and hypotheses:** To study the diagnostic process, the molecular genetics, the clinical phenotype, and the significant therapeutic challenges in the management of an extremely low birth weight (1.080 Kg) infant of consanguineous Palestinian parents with early severe Neonatal Diabetes (NDM). **Methods:** Genetic investigations included homozygosity mapping and sequencing of ABCC8, KCNJ11, INS and EIF2AK3 genes followed by an exome sequencing. Therapeutic trials involved continuous intravenous insulin, sulphonyl urea, subcutaneous Long Acting Insulin Analogues (LAIA) and continuous insulin via insulin pump. **Results:** Homozygosity mapping identified three candidate genes, located in small homozygous areas: INS gene, RFX6 gene, and SLC19A2. Sequencing of those genes revealed no pathogenic mutation. Exome sequencing revealed delG, P119fs mutation in the NKX2.2 gene, expressed in the CNS and pancreas and required for the final differentiation of pancreatic beta cells in mice. Therapeutically, the thin subdermal fat tissue in this case limited the use of insulin pump or continuous glucose monitoring. Sulphonylurea treatment showed no benefit. The most optimal glycemic control without extreme fluctuations in glucose monitoring was achieved by 3 daily doses of 0.3 μ/Kg of Long Acting Insulin Analogues (LAIA). **Conclusion:** The delG, P119fs mutation in the NKX2.2 gene causes severe NDM associated with very low birth weight infants. Sulphonylureas are not effective and long-acting insulin analogues twice daily were associated with extreme glucose variability. If insulin is required LAIA in three or more daily doses are the optimal choice.

RFC9.2

Missense Mutation of *GLIS3* Gene Resulting in Neonatal Diabetes and Congenital Hypothyroidism

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Background: Neonatal diabetes, diabetes diagnosed before 6 months of age, is rare, with incidence of approximately 1:90,000–160,000 live births. In approximately half of cases, neonatal diabetes is transient and usually resolves between 6 and 18 months of life. In the remainder of cases, the diabetes is permanent. Mutations in the GLI-similar 3 (*GLIS3*) gene encoding the transcription factor *GLIS3* are a rare cause of permanent neonatal diabetes and congenital hypothyroidism with eight affected cases reported to date. We are reporting first *missense mutation* in *GLIS3* resulting in neonatal diabetes and congenital hypothyroidism. **Case:** A Libyan female, was born at full term with a weight of 2.4 kg and head circumference of 34 cm, to non-consanguineous parents. Intrauterine growth retardation was noted during pregnancy. Six weeks after birth, she was admitted to the hospital with hypovolemic shock found to have blood sugar of 1020 mg/dl without significant acidosis or ketosis. Target blood glucoses have been easy to achieve with just intermittent insulin therapy. At 5 months of age TSH found to be persistently elevated (10.7 μIU/ml) with freeT4 15.9 Pmol/l and started on levothyroxine replacement. Abdominal ultrasound scan performed at age of 6 months showed normal morphology of the liver, pancreas and both kidneys. The homozygous mutation c.1924A > T (p.Ser642Cys), was identified when the patient was tested for a monogenic etiology by sequencing a panel of 13 genes associated with neonatal diabetes. Patient now is at eight months of age with normal developmental milestones, as well as physical development and requires 0.1–0.2 units/kg per day of basal insulin with HbA1c 6.3%. **Conclusion:** This case extends the clinical spectrum associated with mutations in *GLIS3*. We are describing the first case of *GLIS3* gene missense mutation c.1924A > T (p.Ser642Cys) resulted in neonatal diabetes and congenital hypothyroidism. Mutations in *GLIS3* should be considered in all children with neonatal diabetes without an established cause, irrespective of reported parental relatedness or insulin requirements.

RFC9.3

Molecular Analysis of a Large Cohort of MODY Patients by Next Generation Sequencing

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Background: Maturity-onset diabetes of the young (MODY) is a monogenic form of diabetes that accounts for 2–5% of all cases but it is underestimated because it's often misdiagnosed as T1D or T2D whose symptoms are often overlapping. It is a phenotypically and genetically heterogeneous disorder characterised by autosomal dominant inheritance, a young age of onset and pancreatic β-cell dysfunction. **Objective and hypotheses:** Actually in about 50% of MODY patients is not identified causative mutations in known genes (MODYx). Recent advances in next-generation sequencing technologies make it affordable to search for rare and functional variants for common complex diseases systematically. On the bases of this observation, we decide to analyse 100 MODY patients through next generation sequencing (NGS) tecnology. **Method:** A set of 182 genes were chosen for targeted resequencing (454 Roche platform). We selected genes known implicated in the pathway of pancreatic β cells, candidate genes for T2D, and genes causative of diabetes in mice experiments. **Results:** In the 66% of cases we found, in association with known heterozygous/homozygous SNPs associated with diabetes, rare and pathogenetic variants, demonstrating that this approach leads to a genetic diagnosis in most of patients. Moreover, two mutations were identified in different genes in 40% of cases suggesting a complex etiology. **Conclusion:** The increased number of genes tested led to a higher mutation detection rate. This approach may help in understanding the molecular aetiology of diabetes and in providing a more personalised treatment for each genetic subtype.

RFC9.4

Prevalence of Monogenic Diabetes in the Lithuanian Pediatric and Young Adult Population

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Background: Monogenic diabetes is a heterogeneous group of metabolic disorders resulting from defects in single genes. Over 90% of the subjects remain undiagnosed, mainly because of lack of access to genetic testing. **Objective and hypotheses:** The aim of our study was to do a comprehensive genetic analysis of the whole pediatric and young adult autoimmune antibody negative diabetes population of Lithuania. **Method:** 860 children (age 0–18 years) and 349 young adults (age >18–25 years) with diabetes were screened for the presence of islet autoimmune antibodies. Genetic analyses were performed in 147 subjects, 80 of them had no detectable autoimmune antibodies and 67 had positive IAA antibodies only. We included the IAA positive probands under insulin treatment, because the antibodies were tested after introduction of insulin. Genetic analysis was performed by high throughput sequencing of DNA of 323 genes involved in diabetes and pancreas development. **Results:** We have analyzed 147 diabetic subjects with suspected monogenic diabetes. Four had neonatal diabetes (onset < 6 months of age), 134 pediatric onset (>6 months to 18 years) and 10 had diabetes onset between 18–25 years. Genetic analysis revealed mutations/variants in known MODY genes in 25.9% of the probands: 13.6% had mutations in the *GCK*, 4.8% in the *HNF1A*, 2% in the *HNF4A*, 1.4% in the *ABCC8*, 1% in the *INS* and 1% in the *KLF11* genes, overall we detected 12 novel variants. In addition, in 36.7% of the probands, we found variants in potential diabetes genes with a high-predicted pathogenicity. **Conclusion:** This testing approach yields a high rate of positive results. In the whole Lithuanian pediatric diabetic and young adult population (1209 probands), *GCK* mutations are found in 1.65%, *HNF1A* mutations in 0.6% and *HNF4A* mutations in 0.25% of the patients.

RFC9.5

Non-Mody Monogenic Diabetes: A Very Heterogenous and Problematic Group of Diabetes

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Background: Monogenic diabetes represents a group of disorders resulting from a single gene defect leading to disruption of insulin secretion or a reduction in the number of beta cells. Despite the classification of monogenic diabetes according to age of onset, with neonatal DM (<6 months of age) and maturity onset diabetes of young (MODY) (>6 months and <25 years of age); not every case can be classified into those groups. **Objective and hypotheses:** We aim to evaluate non-MODY monogenic diabetes diagnosed in our clinic, and emphasize the characteristics of patients. **Method:** We evaluated the patients with monogenic diabetes, during the last 10 years period. Type 1 DM, MODY, and patients with negative autoantibodies and no mutation were excluded from the study. **Results:** Twelve patients, aged 1 days to 11 years, were diagnosed with non-MODY monogenic diabetes. Half the patients were diagnosed after 6 months of age. Most patients had a KATP channel defect. Disruption of beta cells was detected in 6 patients, with 3 cases having a *WFS1* mutation, 3 had positive autoantibodies (2 an *LRBA* mutation, and one CD25 deficiency). Additional systemic findings including severe immune system dysfunction were seen in 6/12 patients (Table). Treatment with sulphonylurea was succesful in two patients with an *ABCC8* gene mutation. The other patients were given insulin in very heterogenous doses (0.4–1.6 U/Kg body weight). Four patients

died during follow-up, three of which had immune dysfunction. **Conclusion:** Monogenic diabetes due to a mutation in a non-MODY gene can be diagnosed after 6 months of age. Even with positive autoantibodies. Immune dysfunction was present in 50% of patients in our cohort and should be investigated in all patients with early-onset monogenic diabetes. Mortality of patients with monogenic diabetes and additional autoimmunity was high in our cohort and is likely to reflect the multisystem nature of these diseases.

RFC9.6

Emerging Pitfalls of Etiological Diagnosis of Diabetes in Children and Adolescents? Analysis of a French Cohort of 310 Recent-Onset Cases

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Background: A diagnosis of diabetes in children used to mean type 1 diabetes (T1D) and lifelong insulin therapy. However, over the last decades the spectrum of diabetes has widened and even if auto immunity remains the most prevalent etiology, confounding factors and overlap with other causes of diabetes types sometimes make a revision of the initial diagnosis necessary. **Objective and hypotheses:** To classify diabetes etiologies in youth with diabetes using a prospective and retrospective systematic approach to diabetes diagnosis. **Method:** Data on all new cases of diabetes 0–19 years old admitted in our unit (Paris, France) from January 1st 2010 to December 31st 2012 were prospectively collected. Diabetes etiologies were classified according family history, clinical (symptoms, age, gender, BMI), biological (ketones, pH, HCO3-, HbA1c), immunological (GAD, IAA, IA2, ZNT8), and HLA haplotypes findings at diagnosis, and retrospectively reviewed according to follow up data (insulin requirement, associated symptoms, genetic testing). **Results:** Among the 310 youth diagnosed with diabetes over the 3-year study period, 216 (70%) had autoimmune T1D. The most prevalent final diagnoses in the non autoimmune group were type 2 diabetes ($n=23$, 29.7%), hematologic disease- or post transplantation drug- induced diabetes (16.2%), MODY (13.5%), and transient hyperglycemia (10.8%). Less frequently diagnoses were type 1B diabetes, cystic fibrosis related diabetes, and specific rare cases of diabetes. Patients without autoimmunity were significantly older (10.1 vs 7.5 yrs old), had higher SDS BMI, and lower HbA1c (8.9 vs 11.8%) at diagnosis $P<0.01$. **Conclusion:** A systematic approach to diabetes etiology in a large hospital-based cohort of youth with newly diagnosed diabetes shows a large diversity of diagnoses with T1D accounting for "only" 70%. Further evaluation of auto-antibody-negative patients and use of the latest genetic testing methods are needed to avoid underestimating the other forms of diabetes and provide adequate care and treatment.

RFC9.7

Chronotype and Type 2 Diabetes Risk in Preadolescents

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Background: An individual's chronotype, or preference in the timing of sleep or food intake, may have metabolic implications. Late chronotype has been associated with higher body mass index (BMI) and hemoglobin A1c (HbA1c) in adults and greater BMI, portion sizes, and lower HDL cholesterol levels in adolescents. **Objective and hypothesis:** To examine associations between chronotype and risk factors for type 2 diabetes in children ages 10–13 years. We hypothesize that late chronotype associates with greater insulin resistance and higher glucose levels. **Method:** Ten (5 normal-weight (NW), 5 obese (OB)) preadolescents (age 11.4 ± 0.5 years, Tanner stages 1–3) underwent anthropometric measurements and fasting blood draw; glucose, insulin, HbA1c, and lipid levels were measured. Obese participants underwent a 3-hour oral glucose tolerance test (OGTT). Mid-sleep time on free days (MSF), a measure of chronotype, was assessed via actigraphy over 1 week and secondarily through administration of the Children's ChronoType Questionnaire (CCTQ) and Morningness-Eveningness Scale for Children (MESC). **Results:** Sleep parameters did not differ significantly between NW and OB children. As expected, OB versus NW participants had significantly higher fasting plasma insulin levels (20.9 ± 6.4 vs 4.2 ± 2.6 μI/ml, $P=0.002$) and HOMA-IR levels (4.7 ± 1.7 vs 0.9 ± 0.6, $P=0.004$). MSF did not associate significantly with metabolic outcomes. HbA1c was positively associated with CCTQ chronotype score ($r=0.64$, $P=0.047$) and lower MESC score ($r=-0.75$, $P=0.01$), indicating later chronotype is associated with poorer glycemic control. HbA1c was also associated with overall time in bed ($r=-0.84$, $P=0.005$), later bedtimes overall ($r=0.62$, $P=0.011$) and on weekdays ($r=0.81$, $P=0.002$). On regression analysis, later weekday bedtime predicted a higher HbA1c independently of time in bed. **Conclusion:** These preliminary findings suggest that a late chronotype in preadolescents may have a deleterious glycemic impact independent of bedtime duration and that advancing bedtimes may reduce glucose levels and lower risk of type 2 diabetes in preadolescents. Our preliminary findings call for expansion of our pilot study to a larger cohort.

RFC9.8

Micro RNA and Diabetic Nephropathy

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Background: MicroRNAs (miRNAs) are short non-coding RNAs that repress target gene expression via post-transcriptional

mechanisms. **Objective and hypotheses:** To study the expression of miRNA-25, miRNA-216, miRNA-21, miRNA-93, miRNA-377 in a sample of 100 type 1 diabetic patients with and without microalbuminuria to probe their role in development of diabetic nephropathy. **Methods:** Hundred type 1 diabetic patients, 50 with microalbuminuria and 50 without were recruited from the Diabetic Unit, Cairo University. Blood pressure measurement as well as HbA1C and lipid profile were assessed. Detection of mature miRNAs in serum was done by quantitative real-time reverse-transcription PCR (qRT-PCR). **Results:** Micro-RNA-21, miRNA93, miRNA25, miRNA were upregulated in 36.6, 76.7 and 30% respectively and downregulated in 60, 20 and 50% respectively of patients with microalbuminuria. miRNA-216 was upregulated in 20% and downregulated in 60% of patients with microalbuminuria. **Conclusion:** Some microRNA- might have a protective role against development of microalbuminuria, while others may increase its risk. More studies are still needed to unmask the potential role of different micro-RNAs in development of diabetic nephropathy.

RFC10.1

Paternal Loss-of-Function Mutations of *GNAS* and Growth Retardation in a Mice Model: A Specific Placental Transcriptomic Signature?

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Background: *GNAS* gene is a complex imprinted locus, resulting in the expression of at least four transcripts (*XL*, *NESP55, A/B* and $G_s\alpha$) characterized by their specific exon 1 and common exons 2-13. While *Gαs* is biallelically expressed in most tissues, *XL* is only expressed from the paternal allele. Maternally inherited, loss-of-function mutations affecting those *GNAS* exons that encode $G_s\alpha$ cause pseudohypoparathyroidism (PHP) type Ia, a disorder characterized by multiple hormonal resistance. A severe intrauterine growth retardation (IUGR) associated with placental hypotrophy is observed in patients presenting pseudopseudo-hypoparathyroidism (PPHP) due to paternal *GNAS* mutations. **Objective and hypotheses:** Given the role of placenta in the fetal growth, we suspected an alteration at transcriptional level, due to *Gnas* loss-of-function mutations. We used different mice models to compare placental transcriptome between wild-type (WT) and heterozygote (KO). **Method:** WT female mice were crossed with male mice harboring heterozygote mutation in exon 1 of XL, of E1 or E2 (exon shared between $G_s\alpha$ and $XL_{\alpha s}$). Placentas were obtained at E18 for each litters and the fetus genotyped. After extraction, placental RNA were hybridized on a microarray (GeneChip Mouse Transcriptome Assay 1.0.), and data were analysed by bioinformatics (GSEA, Webgestalt, String db, Venny Venn). **Results:** XL expression is dramatically decreased in $XL^{m+/p-}$ mice (relative quantification *vs* WT: 0.20, $P = < 0.0001$). We evidenced significant alterations in several genes involved in phenotypes and pathways, such as "Prenatal growth retardation" ($P = 3.0 \times 10^{-22}$) and "Decreased placenta weight" ($P = 2.4 \times 10^{-10}$). Transcripts such as *Meg3*, *Mest*, *Igf2*, already described in a IUGR human model (Kappil *et al.*, 2015), were also affected. **Conclusion:** Subtle variations of gene networks involving *XL* would be implicated in the pathogenesis of placental hypotrophy and IUGR associated to GNAS paternal mutation. *XL* shows a preferential placental expression from the paternal allele.

RFC10.2

Dysregulation of Placental Mirna in Maternal Obesity is Associated with Pre-and Post-Natal Growth

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Background: Human placenta exhibits a specific miRNA expression pattern. Some of these miRNAs are dysregulated in pregnancy disorders like preeclampsia and intrauterine growth restriction (IUGR), and are potential biomarkers for these pathologies. No studies have been performed in maternal obesity. **Objective and hypotheses:** (1) Define the placental miRNA profile in pregnant women with: a) pre-pregnancy (preOB) or gestational obesity (gestOB), b) gestational diabetes (GDM) and c) small for gestational age children (SGA). (2) Explore the associations of circulating miRNAs dysregulated in maternal obesity with pre- and post-natal growth. **Method:** TaqMan Low-Density Arrays (TLDAs) were used to profile the placental miRNAs in 30 pregnant women (6 preOB, 6 gestOB 6 GDM, 6 SGA and 6 controls). The miRNAs differentially expressed in maternal obesity were validated in 80 pregnant women (25 preOB, 25 gestOB and 30 control). Placentas and new-borns were weighed at delivery and at 1 month of life. **Results:** 9 miRNAs were specific of placentas from women with preOB; 8 miRNAs of placentas from women with gestOB, 8 miRNAs of placentas from GDM women; 13 miRNAs of placentas from women with SGA children, and 386 miRNAs were common in all groups. Among the common miRNAs, 6 miRNAs were decreased in preOB or gestOB (miR-1285, miR-1269, miR-487, miR-214, miR-185 and miR-181) (all $P < 0.05$). In silico analysis showed that these miRNAs were related with cell proliferation and insulin signalling pathway. The miR-1285, miR-1269 and miR-487 were predictors of decreased birth weight independently of maternal obesity (all $P < 0.010$ and $R^2 > 15\%$). Moreover, the miR-1285 was predictor of decreased birth height and increased weight gain in the first month of life (all $P < 0.008$ and $R^2 > 10\%$). **Conclusion:** We identified a specific placental miRNA profile in several pregnancy disorders including maternal obesity, GDM and SGA. The dysregulation of placental miRNAs may mediate the growth promoting effects of maternal obesity on the offspring.

RFC10.3

Vitamin D Depletion in Pregnancy Decreases Survival Time, Oxygen Saturation, Lung Weight and Body Weight in Preterm Rat Offspring

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Background: Animal studies suggest a role of vitamin D in fetal lung development although not studied in preterm animals. **Objective and hypotheses:** We tested the hypothesis that vitamin D depletion does not aggravate respiratory insufficiency in preterm rat offspring. Furthermore, the effects of vitamin D depletion on growth and lung surfactant were investigated. **Method:** Female Sprague-Dawley rats were randomly assigned low vitamin D (VD_L) or control diet before mating and followed with serum 25-hydroxyvitamin D (s-25(OH)D) determinations. After cesarean section at gestational day 19 (E19) or 22 (E22), placental weight, birth weight, crown-rump-length (CRL), oxygenation (SaO_2) at 30 min and foster-mother reared survival time were recorded. Lungs from the euthanized pups were analyzed for phospholipid concentration, surfactant mRNA and expression of the vitamin D receptor (VDR). **Results:** S-25(OH)D was lower in the VD_L group before mating (43 vs 64 nmol/L, $P=0.009$) and at cesarean section (12 vs 30 nmol/L, $P<0.0001$). Compared to the controls, E19 VD_L pups had lower birth weight (2.13 vs. 2.29 g, $P<0.001$), lung weight (0.09 vs 0.10 g, $P=0.002$), lung/birth weight ratio (0.042 vs 0.044, $P=0.011$), SaO_2 (54% vs 69%, $P=0.002$) as well as reduced survival time (0.50 vs 1.25h, $P<0.0001$). At E22, no such differences were observed, but VD_L pups had lower CRL (4.0 vs 4.5 cm, $P<0.0001$). A trend towards lower VDR expression was seen in VD_L at E19 ($P=0.068$), but not at E22, where the expression was significantly lower in both dietary groups compared to E19. The phospholipid concentration and the surfactant mRNA expression did not differ between the groups. **Conclusion:** Vitamin D depletion led to lower oxygenation and reduced survival time in the preterm offspring, associated with reduced lung weight and birth weight, but not with changes in phospholipids or surfactant. The role of vitamin D in respiratory insufficiency in human preterm neonates should be studied further.

RFC10.4

Pharmacokinetics of Intravenous Glucagon in Children with Hyperinsulinaemic Hypoglycaemia

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Background: Hyperinsulinaemic hypoglycaemia (HH) is one of the common causes of hypoglycaemia in infants and children. It can cause severe brain injury in children if not treated promptly. Diazoxide is first-line treatment for HH. Glucagon infusion is used in the management of children with HH. However it is unclear what dose of glucagon should be used in children. **Objective and hypotheses:** To evaluate the efficacy, safety and pharmacokinetics of intravenous (IV) glucagon therapy in children with HH. **Method:** Children admitted for management of HH in a tertiary hospital were included in the study. Plasma glucagon concentrations measured by radioimmunoassay (in pmol/l) were collected at times 0 min, +30 min, +60 min and +90 min after initiation of glucagon infusion (at 1 mcg/kg per hour; 2.5 mcg/kg per hour and 5 mcg/kg per hour respectively). Also, blood glucose was measured at the same times. Glucagon concentrations were checked for normality assumptions. Data was analysed using log transformation. **Results:** A total of 12 were included in the study. Mean log glucagon (LnGlucagon) concentration at glucagon dose of 1 mcg/kg per hour (four patients), 2.5 mcg/kg per hour (four patients) and 5 mcg/kg per hour (four patients) were 3.296 ± 0.448, 4.446 ± 1.426 and 3.928 ± 1.018 respectively, with an overall mean of 3.88 ± 1.12. There was a significant difference in concentrations between the dose of 1 mcg/kg/hour with 2.5 and 5 mcg/kg per hour whereas no significant difference was observed between 2.5 and 5 mcg/kg per hour doses. LnGlucagon concentrations significantly increased with all three doses (P-value <0.001). There was a strong positive correlation ($r=0.619$, P-value$=0.011$) between glucagon dose 5 mcg/kg per hour and blood glucose concentrations. **Conclusion:** This is the first study to measure plasma glucagon concentrations in response to an intravenous infusion of glucagon. This study shows that 2.5–5 mcg/kg per hour of IV glucagon can increase blood glucose levels significantly. These data will aid clinicians in the management of HH.

RFC10.5

Phenotype, Genotype and Short term Outcome in Congenital Hyperinsulinism (CHI)

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Background: Congenital Hyperinsulinism (CHI) is the commonest cause of refractory hypoglycaemia in infants. **Objective and hypotheses:** CHI is a rare disorder with varied

clinical manifestations, genotype often with poor outcome. This study describes the clinical profile, molecular characterisation, response to therapy and short term outcome in children with CHI presenting to Paediatric Endocrinology Division, B.J. Wadia Hospital for Children, Mumbai. **Method:** Records of 27 (15F) children with CHI diagnosed in last 10 years were studied. Historical, clinical, biochemical, hormonal and mutation details were analysed in two groups- Diazoxide Responsive (DR) and Diazoxide Unresponsive (DU). Syndromic and transient hyperinsulinism were excluded. **Results:** The age at onset and age at presentation ranged from 1 to 240 days and 0.3 to 68 months respectively with 74% (20/27) diagnosed in neonatal period. The mean gestational age and birth weight was 37.3 ± 0.99 weeks and 3240 ± 695 gms respectively. 33.3% (9/27) were LGA. 29.6% (8/27) were born of consanguineous marriage. All presented with hypoglycaemic seizure. At diagnosis mean plasma glucose was 30 ± 11.5 mg/dl with simultaneous serum insulin of 26.57 ± 56.23 uIU/ml. 51.8% (14/27) had mutation analysis and 37% (10/27) were abnormal. 9/10 mutations were found in ABCC8 and 1 in KCNJ11 gene. Two novel mutations were found in this cohort. Interestingly 2/10 were infants of diabetic mother. 59.2% (16/27) were DR. Of 11 babies who were DU, 7 responded to octreotide with 6 of them receiving long acting octreotide (LAR). 4 underwent near total pancreatectomy. Duration of follow up ranged from 1 to 72 months. At the last follow up mean weight, height and head circumference SDS was -0.3 ± 1.78, -0.31 ± 2.17 and -2.46 ± 2.12 respectively. 33.3% (9/27) were normal, 25.9% (7/27) had delayed development and 11% (3/27) had epilepsy. 2 children had died of infection. **Conclusion:** Early diagnosis and treatment helps improve outcome. ABCC8 was commonest mutation seen. Newer drugs can prevent pancreatectomy and its morbidity.

RFC10.6

Increased Islet Cell Neogenesis and Endocrine Cell Differentiation in Congenital Hyperinsulinism in Infancy

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Background: Congenital Hyperinsulinism in Infancy (CHI) is characterised by inappropriate insulin release. We currently attribute hypoglycaemia to β-cell dysfunction because of defects in the ion channel genes ABCC8 or KCNJ11. However, the CHI pancreas is also associated with inappropriate expression of foetal-like transcription factors and enhanced cell proliferation. **Hypothesis:** As the CHI pancreas bears similarities to the foetal pancreas, we hypothesised that stem cell differentiation and neogenesis are enhanced in CHI. **Method:** Tissue was obtained from 25 CHI patients positive for ABCC8 or KCNJ11 gene defects following surgery. Twelve patients had diffuse-CHI (age at surgery 2–13 months) and 13 patients had focal disease (1–10 months). Tissue samples were fixed and processed for immunohistochemical analysis. Quantification of both single insulin-expressing cells within ductal epithelia (differentiation) and islet cell clusters associated with ducts (neogenesis) was performed and normalised to the area of the tissue section. Control data was obtained from age-match pancreata ($n=8$, 1–12 months). **Results:** Both islet cell differentiation (13.6 ± 3.4 cells/μm^2 $n=12$ vs 4.5 ± 2.9 cells/μm^2 $n=8$) and islet neogenesis (10.2 ± 2.3 events/μm^2 $n=12$ vs 1.4 ± 0.6 events/μm^2 $n=8$) were enhanced in diffuse-CHI tissue in comparison to controls. To investigate whether these findings were related to ACCB8/KNCJ11 defects or as a direct consequence of hyperinsulinism, we also analysed focal-CHI tissue. No differences were found in the incidence of either cell differentiation (3.9 ± 2 vs 5.4 ± 1.6 cells/μm^2) or neogenesis (1.9 ± 1.5 vs 1.0 ± 0.4 events/μm^2) in lesion ($n=6$) and non-lesion domains ($n=12$). **Conclusion:** Diffuse CHI is associated with a 7-fold increase in islet cell neogenesis and a 4-fold increase in the incidence of islet cell differentiation from duct progenitors. As neither is enhanced in focal-CHI, this suggests that ABBC8/KCNJ11 defects in progenitor cells and not paracrine effects of insulin hypersecretion are likely to be responsible for inappropriately increased new islet cell formation in diffuse CHI.

RFC10.7

Expression of Insulin Receptor Isoforms and Type 1 Insulin-Like Growth Factor Receptor in the Placenta as a Function of Fetal Weight

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Background: Fetal growth is the fastest of all periods of growth in human life, mainly due to cellular hypertrophy and proliferation. It was recently discovered that the metabolic and mitogenic effects of Insulin are mediated by two Insulin Receptors (IR) isoforms, IR-A and IR-B. High expression of IR-A indicates proliferation and differentiation whereas IR-B indicates metabolic dominance. **Objective and hypotheses:** The aim of the study was to examin the expression of IR isoforms and IGF-1R in placentas according to the size of the newborn. **Method:** The study population included healthy women aged 21–41 years. The embryos were divided into four weight groups: appropriate (AGA), small (SGA), large (LGA) for gestational age and intrauterine growth restriction (IUGR). Immediately after birth, biopsies were taken from the following areas in the placenta: central, peripheral, maternal and fetal. **Results:** IGF-1R was significantly different

between the four groups, $P < 0.0072$. The main difference in IGF1-R expression was between the center and the peripheral fetal placenta. IGF1-R expression in the peripheral SGA placentas was 48% lower than in the AGA placentas, 14% than in the IUGRs and 32% of the LGA placentas. In the central SGA placenta IGF-1R expression was 57% lower than in the AGA placentas. IR-A expression in the central placentas of the IUGR group was 50% lower than in the peripheral placentas in both the maternal and fetal tissues. **Conclusions:** These findings support the claim that quantitative expression of IGF-1R is important for the development of both the placenta and the fetus. Expression of IRs in the IUGRs placenta is unique and unlike that of the other embryonic weight groups. The absence of differences in IR-B expression may indicate that IR-A is the dominant isoform in fetal tissues, while IR-B appears primarily in insulin target tissues during postnatal life and has mainly a metabolic function.

RFC10.8

Gestational Diabetes is Associated with Changes in Placental Microbiota and Microbiome

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Background: The human microbiota has emerged as an unexpected modulator of the immune system. The placenta, long thought to be sterile, harbors a unique microbiome and variations in their composition could be related to prevent pregnancy disorders. **Objective and hypotheses:** To profile the placental microbiota (microorganisms) and microbiome (collection of microbial genomes in an environment) in women with gestational diabetes (GDM) and study their relation to maternal metabolism and placental expression of anti-inflammatory cytokines. **Method:** Placental microbiota and microbiome and expression of anti-inflammatory cytokines (IL10, TIMP3, ITGAX and MRC1MR) were analysed in placentas from women with GDM ($n = 11$) and from control women ($n = 11$; all samples were obtained under sterile conditions). Fasting insulin, pre- and post-load glucose, lipids and white blood cell counts were assessed at 2nd and 3rd trimester of pregnancy. **Results:** Bacteria belonging to the *Acinetobacter* genus and *Pseudomonadales* order showed lower relative abundance in women with GDM compared to control ($P < 0.05$). In GDM women, lower abundance of placental *Acinetobacter* was associated with a more adverse metabolic (higher post-load glucose) and inflammatory phenotype (lower blood eosinophil count and lower placental expression of *IL10* and *TIMP3*) ($P < 0.05$ to $P = 0.001$). In GDM women, placental microbiome showed increased expression of genes involved in calcium signalling (PC1, PC2 and PC3). **Conclusion:** Placental microbiota and placental gene expression profiles were different in pregnant women with GDM compared to controls. Pregnant women with GDM showed lower abundance of *Acinetobacter* and decreased expression of IL-10. GDM could constitute a state of placental microbiota-driven altered immunologic tolerance, making placental microbiota a new target for therapy in GDM.

RFC11.1

Central Hypothyroidism and Biallelic Defect Near the D/ERY Motif of the *TRHR* Gene

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Background: The TRH receptor (TRHR) is a G-protein coupled receptor activated by hypothalamic TRH. In thyrotropes, TRH-TRHR signalling controls synthesis, secretion and bioactivity of TSH. Human *TRHR* defects are extremely rare, and only three cases are known with central hypothyroidism and short stature as variable presenting feature. **Objective and hypotheses:** Phenotypical characterization of a family with suspected central hypothyroidism and investigation of the molecular mechanism underlying the disorder. **Method:** Mutation screening of the *TRH*, *TRHR* and *TSHB* genes in seven individuals of a consanguineous pedigree. Determination of membrane expression, ligand affinity and transactivation properties of a TRHR mutant using ELISA, ligand ([^{3}H]MeTRH) binding and luciferase reporter assays, respectively. **Results:** A homozygous missense mutation in *TRHR* was identified (c.392T > C; p.I131T) in an 8 year old boy with mild central hypothryoidism (FT4: 0.74 ng/dl, TSH: 2.61 mIU/mL) and overweight, but normal stature. TRH test showed borderline-low TSH response, indicating pituitary hypothyroidism. The parents, three siblings and grandmother of the index patient were heterozygotes for the mutation, and showed isolated TSH elevation (4.6–8 mIU/L). The mutation localises in the 2nd intracellular loop of the TRHR, adjacent to the D/ERY motif involved in G protein activation. The I131T mutant does not interfere with the receptor trafficking to the membrane, but decreases its affinity to the TRH ligand (wild type = 9.1 ± 0.4 nM vs mutant = 3.1 ± 0.3 nM) and impairs transactivation of an AP1-

containing promoter by TRH (wild type $EC_{50} = 2.8 \pm 0.9$ nM vs mutant $EC_{50} = 20.4 \pm 0.8$ nM). **Conclusion:** A novel defect in *TRHR* causes central hypothyroidism in the homozygous state but leads to hyperthyrotropinemia in heterozygotes, suggesting compensatory elevation of TSH with reduced biopotency. The mutation impairs TRH-TRHR signalling by decreasing the affinity of receptor for TRH and suggests incomplete activation of G-proteins by dysfunction of the D/ERY motif.

RFC11.2

The Incidence and Genetic Analysis of Congenital Hypothyroidism in Guangxi, China and the Predictors for Differentiating Permanent and Transient Congenital Hypothyroidism

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Background: The incidence of congnenital hypothyroidism (CH) differs significantly among different ethnicity and regions, and early differentiation of transient CH is important to avoid unnecessary prolonged treatment with L-T4, it is also helpful for predicting prognosis and alleviating families' psychological burden. **Objective and hypotheses:** To investigate the incidence of CH based on the newborn screening program in Guangxi Zhuang Autonomous Region, China, to analyze the genetic factors of CH and to analyze the predictors that might allow for an early differentiation between permanent (P) and transient (T) congenital hypothyroidism (CH). **Method:** Data from newborn screening program over a six-year period (January 2009 to January 2015) at Guangxi Maternal and Child Health Hospital are analyzed. Blood samples were collected on filter paper between 72 h and 7 days after birth, TSH level was measured by time-resolved fluorescence assay. Individuals with increased TSH ($TSH \geq 8$ mIU/l) levels detected by newborn screening were recalled for further evaluation. Serum TSH, FT3 and FT4 were determined by electrochemiluminescence assay. Diagnosis of CH is based on elevated TSH levels ($TSH \geq 10$ mIU/l) and decreased FT4 levels ($FT4 < 12$ pmol/l). Patients with elevated TSH levels and normal FT4 levels (normal range 12–22 pmol/L) were diagnosed as subclinical congenital hypothyroidism (SCH). Permanent or transient CH was determined using results of thyroid function tests after temporary withdrawal of L-T4 therapy at approximately 2–3 years of age. All exons and their exon-intron boundary sequences of the 12 known CH associated genes in 66 CH patients were screened by next-generation sequencing (NGS). TPO genes, respectively. Patients with PCH during the first few years required an increasing dose of L-T4, whereas patients with TCH required a decreased doses of L-T4. The TSH levels at diagnosis and the dose of L-T4 used were significantly higher in permanent CH cases than in transient cases. The FT4 levels at diagnosis were significantly lower in permanent CH cases than in transient cases. The TSH levels at diagnosis, FT4 levels at diagnosis and L-T4 doses at 90 days were evaluated as predictors and their accuracy at their respective optimal cutoffs were determined to be 60.6%, 66.7% and 93.9%, respectively. **Conclusion:** The CH incidence in Guangxi Zhuang Autonomous Region is slightly higher (1:1854) compared to the worldwide levels (1/2000–1/4000). The permanent CH and transient CH ratio is close to 1, thus the estimated PCH incidence is 1/3708, which is similar to reported worldwide average incidence (1/3000). 50% CH patients had at least one potential pathogenic variant. We found relatively high frequency of DUOX2 (31.8%) and TG (13.6%) mutations in our cohort. The L-T4 dose required at 90 days (> 30 μg/day) has the highest predictive value for PCH. Earlier differentiation of PCH and TCH helps to determine appropriate treatment course.

RFC11.3

Germline and Somatic *DICER1* Mutations in Familial Papillary Thyroid Carcinoma and Multinodular Goiter

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Background: The inheritable component of familial Papillary Thyroid Cancer (fPTC) was recently attributed to monogenic defects in a reduced number of genes including *DICER1*. *DICER1* codes for a ribonuclease of the RNaseIII family essential for the biogenesis of microRNAs. **Objective and hypotheses:** We aimed to identify germline and/or somatic mutations in *DICER1* in a familial pedigree with PTC, multinodular goiter (MNG) and other tumours consistent with the *DICER1* Syndrome. **Patients and methods:** The index patient, an 11-year-old girl, was diagnosed with cystic nephroblastoma (CN) as an infant, MNG at age 8 and follicular variant PTC at age 10 (fvPTC1). Her mother presented MNG at age 9 and fvPTC at age 11 (fvPTC2), and her maternal aunt was thyroidectomized for compressive MNG

(MNG1) at age 30. The patient's father and maternal grandparents were healthy. Germline *DICER1* mutations were screened in peripheral blood lymphocyte DNA from 6 members (affected and non-affected) of the kindred. Somatic *DICER1* mutations were studied in DNA from all paraffin-embedded tissues available by PCR amplification of mutational "hotspots", T-A cloning and Sanger sequencing. "Hotspots" for *BRAF* in fvPTC1/2 and *H/K/N-RAS* in fvPTC1 were also analyzed. **Results:** The proband, her mother, and maternal aunt and grandfather carry a novel germline heterozygous pathogenic *DICER1* 2-bp deletion (c.1440_1441delTG), which prematurely truncates the functional RNase IIIa and IIIb domains of the protein (p.Gly481ThrfsTer25). Tissue samples showed three different heterozygous *DICER1* missense mutations affecting the RNase IIIb domain: c.5438A>G (p.Glu1813Gly) in fvPTC1, c.5113G>A (p.Glu1705Lys) in fvPTC2 and CN, and c.5432T>A (p.Ile1811Asn) in MNG1. *BRAF* and *RAS* mutations were absent in the studied tissues. **Conclusion:** A novel monoallelic germline mutation in *DICER1* increases the susceptibility to develop MNG and subsequently PTC. Phenotype segregation analyses suggests that additional tissue-specific mutations in the RNase IIIb domain, unreported to date in PTC, are necessary for the efficient neoplastic or hyperplastic transformation of the thyroid tissue.

RFC11.4

Thyroid Function in Monozygotic Twins with Intra-Twin Birth-Weight-Differences

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Background: Low birth weight (bw) and unfavourable intrauterine conditions are associated with a subsequent impact on the endocrine system. However, very little is known about the impact on thyroid function. **Objective and hypotheses:** In a longitudinal study we observed genetically identical twins with intra-twin bw-differences from birth until adolescence to objectify the impact of a lower bw on development and health in later life. **Method:** Bw-difference of <1SDS was defined concordant, bw-difference >1SDS discordant. Blood sampling was performed at a mean age of 9.8 yrs (12 concordant, 13 discordant) and 14.6 yrs (14 concordant, 11 discordant). **Results:** At 9.8 yrs, no significant differences in TSH, T3, T4 and TBG levels were represented in the concordant twins. However, in the discordant group, a significant difference in TSH levels was found ($P=0.016$). The former smaller twins had higher TSH mean concentrations than their former larger co-twins (3.76 vs 2.46 μU/ml). No significant differences were observed in T_3, T_4 and TBG levels. At 14.6 yrs, again, we did not observe any significant differences in TSH, T_3, fT_4, T_4 and TBG levels in the concordant group, whereas the discordant group showed a significant difference in TSH concentration ($P=0.016$). Once more, the former smaller twins revealed higher TSH mean levels than their former larger co-twins (2.86 vs 2.22 μU/ml) and no significant differences were observed in T_3, fT_4, T_4 and TBG levels. In all twin-pairs, at 14.6 yrs, the former smaller twins still had a significant lower BMI-SDS than their larger co-twins ($P < 0.001$). **Conclusion:** In this special group of monozygotic twins with intra-twin bw-differences, we could show that bw has a long-lasting impact on thyroid function. The significantly higher TSH concentrations at 9.8 and 14.6 yrs in the former smaller twins who were born with a greater bw-difference indicate the possibility of a TSH-set-point-alteration in low-bw-children.

RFC11.5

Novel Homozygous Mutation in the Sodium/Iodide Symporter (NIS) Gene Highlight by Next Generation Sequencing (NGS) in a Patient with Congenital Hypothyroidism

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Background: The ability to concentrate iodide actively is a characteristic feature of the thyroid gland. This function is mediated through the sodium iodine symporter (NIS), a glycoprotein located in thyrocytes'membrane. Iodide transport defect (ITD) by NIS defects can result in hypothyroidism with variable degree of goiter and low to absent radio iodide uptake. Mutations in SLC5A5 gene encoding NIS are reported to be a rare form of dyshormonogenetic congenital hypothyroidism (CH), with autosomal recessive inheritance pattern. **Objective and hypotheses:** To explore a patient with CH and phenotype compatible with NIS defect. **Method:** Genomic DNA was explored by next generation sequencing (NGS) targeting 18 genes (SLC5A5 included) involved in congenital hypothyroidism. **Result:** A boy was referred for high TSH level on neonatal screening. At D10, congenital hypothyroidism with eutopic thyroid gland was confirmed with: TSH > 150 μui/ml; T4L 1.7 pg/ml [7.5–16]; T3L 1.5 pg/ml [2–4.2]; Thyroglobulin high at 600 ng/ml; Ultrasound showed normal-size thyroid gland 1.4 ml [0.4 – 1.42]; Absence of radio-technetium uptake on scintigraphy. Baby's parents were relatives second degree. Thyroid hormone supplementation was immediately started with rapid normal-isation of hormones' levels. The DNA analysis revealed a homozygous C>G nonsense mutation in exon 13 SLC5A5 gene resulting in a premature stop at position 531 (p.Tyr531Stop). This mutation has been previously described as compound

heterozygous mutation but its impact on iodide transport or cell membrane targeting has not been clearly determined relative to the presence of other heterozygous mutation. This homozygous mutation of NIS leading to complete deletion of the 13th transmembrane and the carboxy-terminus part of the symporter underlines the role of this segment in the iodide trapping. **Conclusion:** We report the first patient with CH and severe ITD by homozygous nonsense mutation (p.Tyr531stop) in NIS encoding gene. NGS targeting CH appears as a high performance tool.

RFC11.6

Falsely TSH and Free Thyroid Hormone Measurements in Pediatric Patients Treated with High Dose of Biotin

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Background: Immunoassays are subjected to a number of interferences giving abnormal results which may lead to unnecessary investigations and treatment. We present clinical cases in which biotin treatment could be involved in abnormal results of thyroid function tests (TFTs) obtained by immunoassays based on biotinylated antibodies/analogs. **Objective and hypotheses:** Three infants were admitted to intensive care unit (ICU) during 2015, in Edmond and Lilly Safra Children's Hospital, because of respiratory distress and neurologic deterioration. Laboratory tests at admission revealed severe lactic acidosis. Thorough investigation led to the diagnosis of mitochondrial disease. During their hospitalization, near normal TSH and extremely highly elevated fT4 and fT3 were measured (Beckman-DxI analyzer). Those results were discrepant from their clinical presentations; as neither had goiter, signs of thyrotoxicosis or family history of thyroid disorders. **Method:** To assess the possibility of assay interference, and avoid unnecessary treatment and potentially further invasive investigations, TFTs in the same samples were evaluated by alternative methodologies (ADVIA-Centaur and Autodelfia analyzers), demonstrating normal fT3 and only moderately elevated fT4, as well as normal levels of tT3 and tT4. **Results:** Medications given to the patients and DxI TFTs assay principles were reviewed, pointing to potential interference, due to biotinylated antibodies/analoges used in fT3 and fT4 assays; thus, excess biotin in patients' serum competes with the biotinylated antibodies for binding sites on streptavidin, resulting in falsely high levels of the hormones. Indeed, fT3 and fT4 levels measured in samples obtained twelve hours after biotin intake, were significantly lower, compared with levels obtained in close proximity to biotin intake. **Conclusion:** High dose biotin ($\geq$ 10 mg/day) is used therapeutically in some metabolic disorders. Furthermore, many patients are taking biotin as dietary supplement. Therefore, physicians need to be aware that biotin could cause assay interference, especially when test results are discrepant from the clinical picture; Awareness will avoid misdiagnoses and unnecessary treatments.

RFC11.7

Secondary Thyroid Cancer among Childhood Cancer Survivors: A Single Institution Experience

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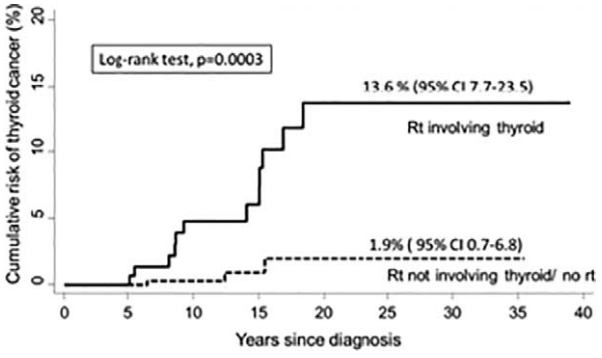
Background: Childhood cancer survivors (CCS) are at increased risk of developing secondary malignant neoplasms (SMN). Radiotherapy is one of the main risk factors, and secondary thyroid cancers (STC) are likely to occur among irradiated CCS. **Objective and hypotheses:** To evaluate frequency, characteristics, and of STC in the cohort of CCS treated and in follow-up at the Istituto Giannina Gaslini. **Method:** Survivors treated between 1975 and 2013 for a childhood cancer, and >2 years since elective end of therapies, were eligible. At follow-up all subjects had a clinical visit of the thyroid gland, and neck ultrasound evaluation was performed to subjects with a medical history of previous irradiation to fields potentially involving the thyroid. Fine needle biopsy was performed to subjects with >10 mm nodules. The cumulative risk of secondary thyroid cancer was calculated by Kaplan-Meir method. **Results:** A total of 632 (312 males; 49.4%) CCS with a median follow-up since



diagnosis of 10.1 years (range 22.2–38.9) were evaluated. Of these 155 (24.5%) received radiotherapy involving thyroid. 15 (2.4%) patients were diagnosed with STC between 5.1 and 18.4 years since diagnosis. All were of the papillary sub-type. Of these 11 (3.5%) occurred among males. STC were more likely to occur among the 155 CCS treated with RT involving the thyroid ($n=12$; 7.7%) than among those either not irradiated or irradiated in other fields ($n=3$; 0.6%) $P<0.0001$. Of the 3 not irradiated subjects with STC one was a female with Proteus syndrome; the second case lead to the diagnosis of MEN2b syndrome; while in the third case (Ewing sarcoma irradiated to the femur) no genetic predisposition was documented. The overall cumulative risk of developing SCT was 6.6% (95% CI 3.8–11.4). After stratification by radiotherapy exposure, the risk was 13.6% (95% CI 7.7-23.5) among CCS treated with thyroid radiotherapy and 1.9% (95% CI 0.7–6.8) among those not irradiated to the thyroid $P=0.0003$ (Figure). **Conclusion:** Active surveillance for STC is recommended for survivors previously exposed to radiotherapy potentially involving the thyroid.

RFC12.1

Molecular Genetic Diagnosis of Idiopathic Hypogonadotropic Hypogonadism by Using Targeted Next-Generation Sequencing

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Background: Idiopathic hypogonadotropic hypogonadism (IHH) is a congenital heterogeneous disorder characterized by a deficiency of gonadotropin-releasing hormone. IHH can be categorised as IHH with anosmia/hyposmia (Kallmann syndrome: KS) or as normosmic (n)IHH. More than 25 genes have been identified in IHH. Nevertheless, patients with IHH are genetically diagnosed in only less than 50%. **Objective:** The objective of this study is to confirm the application of genetic diagnosis of IHH by targeted next-generation sequencing and to gain a greater understanding of the frequency of causative genes in Japanese IHH and their phenotype-genotype correlation. **Method:** We developed a custom AmpliSeq panel of the coding sequences of 48 genes, of which 26 were causative genes of IHH and the remaining 22 genes were selected based on the protein-protein interaction network for IHH causative genes. These genes were sequenced in 23 patients with IHH from 21 unrelated Japanese families using the Ion PGM system. If a mutation was not detected and we had their parents' DNA, trio sequencing was performed with the Illumina MiSeq instrument using TruSight One panel of 4813 genes that are involved in known Mendelian genetic disorders. **Results:** Of the 23 patients, 17 had KS and 6 had nIHH. Molecular defects in ANOS1, CHD7, FGFR1, PROKR2 and TACR3 were identified in 11 patients from 9 families (43%, 9/21 pedigrees). Additionally, rare SNVs in CHD7, WDR11, and HS6ST1 were detected in 3 unrelated patients; however, we were unable to determine if they were pathogenic. Some patients with the CHD7 mutation had a cleft lip and/or plate and deafness. **Conclusion:** Certain phenotype-genotype correlations were identified here, but they were not enough. It was thought that targeted next-generation sequencing was useful because it was difficult to determine the causative gene in a patient with IHH from only clinical features.

RFC12.2

A Novel Mutation of *KISS1R* Causing a Normosmic Isolated Hypogonadotropic Hypogonadism

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Background: Loss of function mutations in *KISS1R*, which encodes kisspeptin receptor have been reported in very few patients with normosmic isolated hypogonadotropic hypogonadism (nIHH). **Objective and hypotheses:** To describe the phenotype of the nIHH female patient with a novel homozygous *KISS1R* mutation and to characterize functionally this mutation. The patient was a 28 year-old Senegalese woman with primary amenorrhea. She was the second child born to consanguineous parents. Hormone assays revealed low levels of estradiol and inappropriate normal levels of gonadotropins. Brain MRI showed normal pituitary and olfactory bulbs. Pelvic ultrasonography showed a small uterus and right small ovary with follicles. Her karyotype was 46,XX. **Method:** Exon and exon-intron boundaries of nIHH candidate genes were sequenced. Functional analysis of the mutated receptor was performed by intracellular inositol phosphate measurement, western blot and immunofluorescence staining in heterologous cells. **Results:** A novel homozygous mutation c.953T>C was identified in the proband, leading to the amino acid substitution of leucine 318 by proline (p.L318P). Functional analysis showed impaired inositol phosphate generation under kisspeptin stimulation. The mutated receptor was not detected at the cell surface in transfected HEK 293 cells. Western blot analysis showed the absence of mature glycosylated receptor but the presence of an immature form. **Conclusion:** The nIHH observed in this patient is due to a novel loss-of-function mutation in *KISS1R*. The L318P substitution impedes the intracellular trafficking of KiSSR. This patient is a novel candidate to a treatment by a chemical chaperone to rescue expression of the mutated receptor at the cell surface.

RFC12.3

Next Generation Sequencing and Precocious Puberty: A New Diagnostic Challenge to Identify the Molecular Basis of Complex Diseases

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Background: Precocious puberty is defined as the development of secondary sexual characteristics before the age of 8 years in girls and 9 years in boys. This condition results from a constant and complex interplay between predisposing genes and environmental factors. To date, the molecular analysis are all focused on reproductive-endocrine disorders such as Kallmann syndrome and hypogonadotropic hypogonadism, while the genetic bases of pubertal timing are still unclear. **Objective and hypotheses:** The identification of genes involving in this process is difficult because pubertal timing is a complex genetic trait, where a direct relationship between genotype and phenotype does not exist due to multigenic influences and interactions between genetic variants and environmental exposures. On the bases of this observation, we decided to analyse 27 patients through Next Generation Sequencing (NGS) technology. **Method:** By searching the available literature on puberty we selected 34 genes all implicated in several hormonal, nervous and metabolic pathways involved in the onset of puberty, followed by NGS. **Results:** In 16 cases we identified rare variants of unknown significance (VUSs) in hormones and hormone receptors. In one case we found a SNP recently reported in literature in association with puberty onset; in two cases we found VUSs in a gene which is required in rats for the organization of somatic cells and oocytes into discrete follicular structures. **Conclusion:** Additional studies will be required to confirm the pathogenetic role of these variants. However different genetic variants may display a differential response to therapeutic agents. The knowledge of the genetic background is essential not only for an accurate diagnosis, but also for the development of the most appropriate therapeutic strategies.

RFC12.4

Molecular Screening of MKRN3, DLK1 and KCNK9 Genes in Central Precocious Puberty

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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 has been found mutated for the first time in 5 families with familial precocious puberty. The inheritance pattern is particular being the MKRN3 a maternal imprinted gene. Moreover in a recent genome wide association study common intronic or intragenic variants harbouring this gene and other two imprinted genes, DLK1 and KCNK9, have been associated to age at menarche, demonstrating parent-of-origin-specific associations concordant with known parental expression patterns. **Objective and hypotheses:** Here, we investigated mutations in MKRN3, DLK1 and KCNK9 in a cohort of 60 girls with CPP. **Method:** We studied 60 Italian children with CPP (all girls, mean age 6.8 ± 1.8 years, 37% familial cases, normal brain MRI). The coding regions of MKRN3, DLK1 and KCNK9 were sequenced. **Results:** Genetic analysis revealed two already described mutations (Pro160Cysfs*14 and Arg328Cys) in MKRN3 in two unrelated girls, one with familiar CPP and one apparently sporadic respectively. No rare variants were found in DLK1 and KCNK9 genes. One already described synonymous variants in KCNK9 and 8 in DLK1 were found. **Conclusion:** We confirm that MKRN3 gene mutations represent a rather frequent cause of CPP in girls, even if different prevalence of mutation can depend on characteristics and selection criteria of patients studied (such as age at onset of CPP or definition of familiarity for CPP). We investigated for the first DLK1 and KCNK9 in CPP and our results do not support a role for mutations in the coding region of these two genes in the etiology of CPP. Involvement of these genes in regulation of pubertal timing in humans warrants further investigation.

RFC12.5

A Novel *MKRN3* Nonsense Mutation Causing Familial Central Precocious Puberty

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Background: The onset of puberty is influenced by the interplay of stimulating and restraining factors, many of which have a genetic origin. Premature activation of the GnRH secretion in central precocious puberty (CPP) may arise either from gain-of-function mutations of the *KISS1* and *KISS1R* genes or loss-of-function manner mutations of the *MKRN3* gene leading to MKRN3 deficiency. **Objective and hypotheses:** Explore the genetic causes responsible for CPP and the potential role of the

RING-finger protein 3 (*MKRN3*) gene. **Method:** We investigated potential sequence variations in the intronless *MKRN3* gene by Sanger sequencing of the entire 507 amino acid coding region of exon 1 in a Greek family with four girls three of them affected and which presented with CPP at the age of 3 and 5 and 6 years respectively. **Results:** A novel heterozygous p.Glu298Ter (p.E298*) nonsense mutation in the *MKRN3* gene was identified in all four siblings with the younger ones being identical twins. This nonsense variant is predicted to lead to premature termination of translation thus is a damaging and pathogenic alteration causing CPP. The imprinted *MKRN3* missense mutation was also identified as expected in the unaffected father and followed an imprinted mode of inheritance. The pathogenicity of the alteration at the protein level via an *in silico* structural model and a functional assay is also explored. **Conclusion:** A novel mutation in the *MKRN3* gene in four sisters with CPP was identified, supporting the fundamental role of this gene in the suppression of the hypothalamic GnRH neurons and also the ethnic diversity with this condition.

RFC12.6

Serum Antimüllerian Hormone and Inhibin B as Potential Markers for Progressive Central Precocious Puberty in Girls

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Background: Anti-Müllerian hormone (AMH) and inhibin B (INHB) are two hormones investigated as markers of ovarian reserve in female. serum AMH and INHB levels change through the progression of puberty, and might be markers for identifying pubertal progression rate in girls. **Objective and hypotheses:** To invetigate serum AMH and INHB levels as markers of pubertal progression rate in girls with central precocious puberty (CPP). **Method:** A total of 128 girls were enrolled, 65 with premature thelarche (PT) and 63 with CPP according to GnRH stimulation tests. serum AMH and INHB levels were also accessed in all the girls on the diagnosis. Girls with CPP underwent a six-month follow up for pubertal advancement, height acceleration, and bone-age maturation. Based on these criteria, the participants were assigned to two subgroups: progressive CPP (P-CPP) group (n = 50) and slowly progressive CPP (SP-CPP) group ($n = 13$). An additional 20 age-matched healthy girls were evaluated for AMH and INHB. **Results:** AMH and INHB were potential markers for distinguishing P-CPP from SP-CPP. By comparison with SP-CPP group, girls with P-CPP had lower AMH (4.82 (1.94–11.15) ng/ml vs 2.79 (1.04–6.16) ng/ml, $P = 0.0047$) and higher INHB (56.94 (16.54–123.60) pg/ml vs 27.61 (19.46–67.48) pg/ml, $P = 0.1628$). Based on receiver operating characteristics (ROC) analysis, the area under the curve (AUC) was 0.80 for AMH, 0.83 for INHB, and 0.88 for the combination of AMH and INHB. The combination of AMH and INHB (with cut-offs of 4.25 ng/ml and 31.35 pg/ml, respectively) results in 93% sensitivity and 71.5% specificity. **Conclusion:** Our results suggest that serum AMH and INHB levels provide a reliable method that assist in the distinction between P-CPP and SP-CPP.

RFC12.7

Prevalence of Organic Lesions in Males with Central Precocious Puberty

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Background: Organic lesions in males with central precocious puberty (CPP) have been reported in 40% of cases. This high prevalence decreases (20–29%) when patients with previously diagnosed alterations of central nervous system (CNS) are excluded. Reported predictors of organic lesions are age at puberty onset, bone age, BMI, LH peak response and testosterone levels. **Objective and hypotheses:** To determine the prevalence and type of intracranial lesions in males with CPP and to identify clinical and biochemical predictors of brain abnormalities. **Method:** All males diagnosed with CPP at a tertiary pediatric center were included. Patients with known CNS alterations, genetic syndromes or known endocrine disorders were classified as having secondary CPP (sCPP); the remaining as isolated CPP (iCPP). All patients underwent hypothalamus-pituitary MRI and the findings were classified as: normal, incidentalomas or organic lesions. **Results:** A total of 64 boys were included in the study; iCPP was diagnosed in 78.1% of cases (50/64). The comparison between iCPP and sCPP showed that iCPP patients had higher height SDS at diagnosis ($P = 0.014$), higher BMI SDS ($P = 0.037$) and lower prolactin levels ($P = 0.001$), probably related to the underlying diseases in sCPP patients. iCPP males showed normal MRI in 78% of cases (39/50), incidentalomas in 10% (5/50) and organic lesions in 12% (6/50). These lesions were represented by 3 microadenomas (2 of them not confirmed at a second evaluation), 2 hamartomas and 1 ganglioglioma. As microadenomas are often considered incidentalomas in pediatric population with CPP, after their exclusion the prevalence of organic lesions decreased to 6%. No predictive parameter of organic lesions was found. Radiological follow-up of the organic lesions showed no evolution after 2-years follow-up. **Conclusion:** In males with CPP the prevalence of organic lesions is lower than previously reported after excluding patients with known predisposing conditions.

RFC12.8

Circulating MKRN3 Levels Decline During Puberty in Healthy Boys

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Background: Initiation and progression of puberty requires concerted action of activating and inhibiting factors. Recently, cases of central precocious puberty have been linked to loss-of-function mutations of makorin RING-finger protein 3 (MKRN3) indicating a pivotal inhibitory role of MKRN3 on GnRH secretion. **Objective and hypotheses:** To investigate peripubertal circulating MKRN3 levels in healthy boys. **Method:** Healthy boys ($n=60$) aged [median (range)] 9.3 (5.8–11.8) years at baseline were followed for 6.0 (0.5–7.6) years (2006–2014) with blood sampling and clinical examinations every 6 months. Age at pubertal onset was approximated using the date between two visits when a boy's uni- or bilateral testicular volume increased from <4 to ≥ 4 ml. Serum levels of MKRN3 were measured: 623 samples, median (range) 12 (2–14) per boy. **Results:** Circulating MKRN3 levels exhibited a broad variation during puberty (all samples, median: 122 pg/ml, range <25–1285 pg/ml). MKRN3 levels declined prior to onset of puberty; the geometric mean (95% CI) 5 years prior to onset of puberty vs. last visit before onset of puberty was 216 (169–272) pg/ml vs 128 (118–139) pg/ml ($P<0.001$), respectively. MKRN3 levels continued to decrease as puberty progressed. Each boy seemed to maintain his individual MKRN3 set point during puberty. Prepubertal MKRN3 levels were not associated with age at onset of puberty ($r=-0.163$, $P=0.213$). Further, no significant correlations were observed between MKRN3 and gonadotropin levels nor total testosterone levels within each pubertal stage. **Conclusion:** Continuously declining MKRN3 levels in boys prior to pubertal onset support MKRN3 as an inhibitor of GnRH secretion during childhood. Marked inter-individual variation of MKRN3 at time of pubertal onset suggests an individual set-point for reactivation of GnRH secretion.

RFC13.1

Inhibition of Teneurin-2 (TENM2) Leads to Upregulation of UCP1 in Human White Adipocytes

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Background: Heat generation in UCP-1 active cells as present in brown adipose tissue contributes to the regulation of energy homeostasis. Brown adipose tissue is known to be present in neonates and infants and has recently also been demonstrated in children and adults. Interestingly, a transition of white adipocytes into a brown phenotype has been documented *in vitro* in mouse and human cells, yet the underlying mechanisms are still not resolved. Using transcriptome analysis comparing human white and brown adipocyte progenitor cells, we identified TENM2 as highly expressed in white progenitor cells. **Objective and hypotheses:** To test whether TENM2 deficient preadipocytes convert into the brown/beige adipocyte lineage. **Method:** Human SGBS preadipocytes were transfected with siRNA against human TENM2 or control siRNA two days before inducing adipogenic differentiation. Markers of adipogenesis and brown adipocyte marker genes were analysed using qRT-PCR and Western Blot. Mitochondrial mass was quantified by measuring citrate synthase activity. **Results:** During the course of adipogenesis, the mRNA expression on TENM2 was high in preadipocytes and decreased to nearly undetectable levels in adipocytes. Using siRNA we achieved a TENM2 knockdown by 70% in preadipocytes. Both TENM2 knockdown and control cells differentiated equally well into adipocytes as shown by quantification of adipogenic differentiation rates and adipocyte marker gene expression (PPARg, GLUT4, FASN). Their mitochondrial mass was comparable. The expression of the brown adipocyte marker gene UCP1 was significantly higher in TENM2 knockdown cells (mRNA 3-fold, protein 4-fold vs control). **Conclusion:** Our data show that the downregulation of TENM2 leads to the induction of a brown adipocyte phenotype. We therefore conclude that TENM2 is a candidate gene for pharmacological interventions aiming at an induction of brown adipogenesis.

RFC13.2

The Use of Proteomics in the Assessment of Health Status of Offspring Born after Intracytoplasmic Sperm Injection (ICSI)

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Background: Several studies have correlated Assisted Reproduction Technologies (ART) including classic IVF and Intacytoplasmic Sperm Injection (ICSI) with epigenetic alterations in the offspring that could have long lasting unfavorable metabolic effects. Proteomics, a state-of-the-art technology used for the identification of early biomarkers of disease, has already been implemented in the search of success in ART but not yet for such markers evaluation in offspring of ART. **Objective and hypothesis:** To investigate the metabolic status of children born after ICSI with the use of proteomics. **Methods:** Demographic, auxological, biochemical and hormonal parameters of 42 ICSI-conceived children and 42 age-matched controls were assessed (mean age: 6.8 ± 2.1 years). Amongst them, 10 couples of children (five females and five males) further matched for birthweight (SGA/AGA/LGA) and parity (twins/singles) were selected for comparative plasma proteomic analysis. **Results:** The ICSI group was characterized by a younger gestational age, increased percentage of caesarean sections, smaller birthweight and birth length and advanced maternal age. No differences were observed

regarding auxological and initial laboratory data, apart from decreased systolic blood pressure and increased T3 in the ICSI group. The proteomic analysis identified 22 differentially expressed proteins (19 overexpressed and 3 downregulated) in the ICSI group. The majority of the overexpressed proteins are implicated in the acute phase reaction, blood coagulation, complement activation and iron and lipid metabolism, suggesting an unfavorable cardiometabolic profile of these children, at a subclinical level. **Conclusions:** This is the first study to use proteomic analysis to assess the metabolic status of children born after ICSI. The results of this study support the importance of close, long-term follow-up of these children especially regarding cardiometabolic risk factors, and highlight the role of proteomics in the early identification of markers of metabolic disturbance.

RFC13.3

Effects of Eating Rate on Satiety Hormones, Meal Enjoyment and Memory for Recent Eating: An fMRI Study

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Background: Controlling eating rate may be a mechanism for reducing calorie consumption. We need to understand the physiological basis of this to design effective paediatric interventions. **Objective and hypotheses:** This study investigated the effect of eating rate during lunch on post-meal neural response (fMRI), satiety hormone levels, appetite ratings (VAS), meal enjoyment, memory for recent eating and snack consumption. **Method:** Twenty young people (mean age 23.0 years, normal BMI) were randomly assigned to consume 600 kcal at a 'normal' or 'slow' rate (6 vs 24 mins). fMRI was performed at baseline and 2 hours post-meal, including a memory task about the lunch. Appetite ratings and satiety hormone levels (PYY and ghrelin) were collected at baseline and change recorded half-hourly for 3 hours. Participants were given an ad-libitum snack 3 hours post-meal. **Results:** Relative to the slow group, immediately post-meal, the normal group reported greater fullness (effect size = −0.2), enjoyed the meal more (effect size = −0.5) and found it more satisfying (effect size = −0.6). However, 2 hours post-meal the slow group reported greater fullness (effect size = 0.7), scored higher on portion size memory task (M = 79%, vs M = 68%, effect size = 0.4), showed greater activation in the medial temporal lobe, and ate fewer snacks (M = 341.8 kcal, vs M = 445.4 kcal; effect size = 0.5). Ghrelin secretion was lower in the slow group than the normal group at 30 and 120 minutes post-meal (effect size = −0.8). Ghrelin levels at 180 minutes were correlated with ad-libitum intake (r = 0.590, P = 0.013). At 30 minutes, PYY levels were correlated with enjoyment of the meal (r = 0.451, P = 0.046) and positively associated with memory task activation in the precuneus, striatum and insula. **Conclusion:** Eating slowly improved memory for the meal, increased satiety and led to 25% less snacks eaten, but reduced ghrelin levels and enjoyment of the meal. Research is planned to confirm that these findings persist in the paediatric population.

RFC13.4

Which Amount of BMI-SDS Reduction is Necessary to Improve Cardiovascular Risk Factors in Overweight and Obese Children?

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Background: Knowing the changes of cardiovascular risk factors (CRF) in relation to weight loss would be helpful to advise overweight children and their parents and to decide whether drugs should be prescribed in addition to lifestyle intervention. **Objective and hypotheses:** The aim of the study was to determine the degree of overweight reduction to improve CRFs in overweight children. **Method:** We studied changes of blood pressure (BP), fasting HDL-, LDL- cholesterol, triglycerides, glucose, and insulin resistance index HOMA in 1388 overweight children (mean BMI 27.9 ± 0.1, mean age 11.4 ± 0.1 year, 43.8% male, 45.5% prepubertal) participating in the uniform 1-year lifestyle intervention "Obeldicks". Change of weight status was determined by delta BMI-SDS based on the recommended percentiles of the International Task Force of Obesity. **Results:** BMI-SDS reduction was associated with a significant improvement of all analyzed CRFs except fasting glucose and LDL-cholesterol after adjusting for multiple confounders such as baseline CRF, age, gender, BMI, pubertal stage and its changes in BMI-SDS reduction > 0.25–0.5 (systolic BP −3.2 ± 1.4 mmHg, diastolic BP −2.2 ± 1.1 mmHg, triglycerides −6.9 ± 5.8 mg/dl, HDL-cholesterol +1.3 ± 1.2 mg/dl, HOMA −0.5 ± 0.3). A reduction of > 0.5 BMI-SDS led to more pronounced improvement (systolic BP −6.0 ± 1.3 mmHg, diastolic BP −5.1 ± 1.3 mmHg, triglycerides −16.4 ± 7.1 mg/dl, HDL-cholesterol +1.6 ± 1.5 mg/dl, HOMA −0.9 ± 0.3). Per 0.1 BMI-SDS reduction systolic BP (−1.0 mmHg), diastolic BP (−0.7 mmHg), triglycerides (−2.3 mg/dl), and HOMA (−0.2) decreased significantly, while HDL-cholesterol (0.2 mg/dl) increased significantly in linear regression analyses accounted for multiple confounders. **Conclusion:** A BMI-SDS reduction > 0.25 improved significantly key factors of the Metabolic Syndrome such as hypertension, hypertriglyceridemia and low HDL-cholesterol, while a BMI-SDS > 0.5 doubled the effect.

RFC13.5

Protective Potential of Metformin on Membrane Linked Functions in Diabetic Aging Female Rats

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Objective: The objective of this study was to investigate protective potential of metformin on membrane linked functions and glucose transporter in diabetic aging female rats. **Background:** The emerging view is that diabetic brain features many symptoms that are best described as accelerated brain aging. **Methods:** Young (3 months) adult (12 months) and aged (24 months) rats will be diabetic by using alloxan monohydrate. After metformin was given i.p dose 200 mg/Kg for one months to both control and diabetic aging rats. Learning was tested in a Morris water maze. **Results:** Present study shows that there was a similar pattern of increased lipid peroxidation, neurolipofuscin, DNA degradation and monoamine oxidase activity and a decrease in membrane fluidity, Na + K + ATPse, Ca2 + ATPase, sueroxidase dismutase and glutathione S-transferases activities, glucose transporter-4 (GLUT4) in both aging and diabetes. Metformin was found to be an effective treatment in stabilizing and normalizing the membrane functions; therefore this therapy can be considered an alternative to be explored further as a means of diabetic and aged related disorders control. Metformin treatment also helped to reverse the age related changes studied, to normal levels, elucidating an anti-aging, antidiabetic and neuroprotective action. **Conclusions:** The cumulative deficits in learning and membrane functions in aged diabetic rats indicate that the effects of diabetes and ageing on the brain could interact. The results of this study will be useful for pharmacological modification of the aging process and applying new strategies for control of age related disorders including metabolic syndrome.

RFC13.6

Laparoscopic Sleeve Gastrectomy in Obese Adolescent Population

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Background: Obesity during childhood and adolescence can be accompanied by serious long-term adverse health and longevity outcomes. With increased use of bariatric surgery to treat obesity in these patients, diverse guidelines have been published, most of which exclude children aged younger than 14 years. Few reports describe laparoscopic sleeve gastrectomy in children and adolescents, delay in determining its safety and effectiveness and develop guidance regarding its use. **Method:** This study is a retrospective observational study that used data collected from January 2011 till September 2014. All adolescent patients who were less than (or equal) 21 years of age at the time of the study and have undergone laparoscopic sleeve gastrectomy at the American University of Beirut Medical Center and in Makassed General Hospital were included. **Results:** A total of 112 patients were enrolled in this study, most of were females (71.4%). The median age of the study group was 19 years ±9.6 (range, 11–21 years). The mean percentage of excess weight loss was 42.0%, 66.3%, 84.0%, 84.7%, and 83.4% at 3, 6, 12, 24 and 36 months respectively. No serious postoperative complications developed during the current follow-up. Available comorbidity data indicate resolution of dyslipidemia, 10 of 12 (83.3%); hypertension, 5 of 8 (62.5%); diabetes, 15 of 15 (100%); pre-diabetes, 17 of 19 (94.1%); asthma 13 of 15 (86.6%); obstructive sleep apnea 4 of 5 (80%); and osteoarticular disease 13 of 16 (81.2%). **Conclusion:** Our study showed that laparoscopic sleeve gastrectomy is an effective and safe weight loss procedure for morbidly obese adolescents offering good weight loss outcomes and significant resolution of many obesity related comorbidities. Moving forward, prospective studies that assess the quality of life of these patients on long-term follow up are recommended especially that data on the psychological impact of bariatric surgery in adolescent is scarce.

RFC13.7

Early Onset Obesity and Hyperphagia Associated with Defects in the *GNAS* Gene

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Background: Imprinted genes are known to regulate fetal growth and a 'parental conflict' model predicts that paternally and maternally expressed imprinted genes promote and inhibit fetal growth, respectively. GNAS is a complex imprinted locus with multiple oppositely imprinted gene products. Maternal, but not paternal, G(s)alpha mutations lead to obesity in pseudohypoparathyroidism type IA (PHPIA). However, the disorder rarely causes severe obesity in infancy as predominant clinical feature. **Objective and hypotheses:** To investigate the genetic basis of severe early hyperphagic obesity in childhood with clinical suspicion of obesogenic or macrosomic syndromes. **Method:** Clinical, hormonal and metabolic characterization of 3 pediatric patients with infantile obesity with clinical suspicion of MOMO and Prader-Willi syndromes. Chronological characterization of the phenotype, including nutritional behavior and energy expenditure. Investigation of the *GNAS* gene by Sanger sequencing. **Results:** Three children (2 males), 11 months to 5 years of age, were diagnosed with severe obesity (weight > 99th centile) at 9–18 months of age. At birth, none was obese or large for gestational age (weight < 83th centile and height < 54th centile). They developed hyperphagia with excessive caloric intake for age, which was restricted as part of clinical handling. One patient presented decreased resting energy expenditure (REE) at indirect calorimetry. At diagnosis, all patients presented asymptomatic hyperthyrotropinemia, hyperparathyroidism with hypocalcemia and hyperphosphatemia. Other features were psychomotor

retardation (3/3), overgrowth (1/3), macrocephaly (1/3) and cryptorchidism (2/2). Three missense heterozygous mutations in GNAS (p.M222T, p.D224H, p.R232H) were identified. **Conclusion:** Early-onset obesity with hyperphagia can be a prominent presenting feature of PHPIA, which should be considered in the differential diagnosis for monogenic childhood obesity. This type of obesity is postnatal and develops progressively, and its pathophysiology may include both low energy expenditure and excessive food intake through hyperphagia.

RFC13.8

Measuring Subcutaneous Adipose Tissue Using Ultrasound in Children

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Background: The method for assessing adipose tissue thickness using ultrasound has been used extensively in sport medicine. However, the reliability of this method in children was not evaluated. We aim to determine the inter-observer reliability in measuring uncompressed subcutaneous adipose tissue thickness (USAT) using ultrasound, in children. **Methods:** About 40 healthy children (20 male, 20 female), median age 11.8 years (5.3 to 18.1) were evaluated. Median body mass index standard deviation score (BMI SDS) was −0.13 (−3.9 to 4). Three observers used a Hosand BX2000 Ultrasonic Adipometer to measure USAT at three sites: triceps, subscapular, supraspinale. A single experienced observer used the three sites to measure the compressed adipose thickness using a skinfold caliper. **Results:** Individual observer deviations from the mean value of the three observers in adipometer measurement had SD = 1.74 mm, 92.8% were less than 3 mm. Analysis separated by anatomical sites showed high reliability values for triceps: linear regression $R^2 = 0.84$, $P = 0.000$; intraclass correlation coefficient ICC = 0.92 and standard error of measurement SEM = 0.63. For supraspinale site: $R^2 = 0.82$, $P = 0.000$; ICC = 0.89 and SEM = 1.17; while for subscapular the values were lower: $R^2 = 0.79$, $P = 0.000$; ICC = 0.78 and SEM = 1.02. The body fat percentage (BF%) calculated using skinfold measurements was highly correlated with the BF% calculated by the adipometer ($R = 0.92$, $R^2 = 0.83$, $P = 0.000$). Pearson correlation between BMI SDS and BF% calculated from skinfold was $R = 0.52$; $R^2 = 0.28$; $P = 0.001$, while for the adipometer it was $R = 0.53$, $R^2 = 0.27$, $P = 0.000$. **Conclusion:** This novel ultrasound measurement technique is a reliable fast and cheap method for measuring uncompressed subcutaneous adipose tissue thickness in children, sustaining its application for research and clinical purposes.

RFC14.1

Important Contribution of GH, *GHRHR* and *GHSR* Mutations in Isolated Growth Hormone Deficiency with a Normal Location of the Posterior Pituitary – Functional Characterization of New Variants

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Background: Although growth hormone (GH) and the GH releasing hormone receptor (GHRHR) are known as etiologic factors in non-syndromic isolated growth hormone deficiency (IGHD), very few mutations have been identified in this rare condition (accounting for only 6–12.5% and 0–6.7% of IGHD cases depending on studies). The functional consequences of the identified variants have rarely been assessed. **Objective and hypotheses:** To assess the contribution of mutations in *GH*, *GHRHR* and *GHSR* in IGHD pathogenesis in a large cohort of patients with a non-syndromic IGHD and normal posterior pituitary. **Method:** The *GH* gene was analyzed in 360 independent patients; the *GHRHR* gene was subsequently analyzed in the remaining 320 patients (those with no identified *GH* defect and available DNA); the *GHSR* gene was analyzed in a subset of 226 patients with partial IGHD. The GHRHR variants were assessed through a GHRH-induced CRE-dependent luciferase assay. **Results:** *GH* mutations were identified in 40 independent patients (40/360, 12%), 17 of them (42.5%) representing familial forms of IGHD. These include 6 novel mutations (1 nonsense, 1 splice, 4 missense). We identified *GHRHR* mutations in 22 patients (22/320, 7%), 8 of them (36%) representing familial cases. The *GHRHR* mutation spectrum (6 truncating, 2 splice, 9 missense) comprises 11 novel mutations. Functional studies showed that 6 of the *GHRHR* missense variations are loss-of-function mutations. *GHSR* mutations were identified in 7 independent probands (7/233, 3%). **Conclusion:** This study, which was performed in a large cohort of independent patients, identified unambiguous molecular defects in *GH*, *GHRHR* or *GHSR* in almost 20% of the patients (69/360). Such high rate of mutation detection underlines the need to screen these genes in non-syndromic forms of IGHD with a normal location of the posterior pituitary. Noteworthy, 58% (41/69) of the patients with a *GH*, *GHRHR* or *GHSR* defect represent sporadic cases.

RFC14.2

Contribution of GHR and IGFALS Mutations to Growth Hormone Resistance – Identification of New Variants and Impact on the Inheritance Pattern

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Background: Bi-allelic GHR mutations are classically responsible for Laron syndrome, a severe growth hormone (GH) resistance syndrome. A few GHR missense mutations have also been implicated in mild GH resistance or idiopathic short stature. IGFALS mutations are responsible for recessive or semi-dominant short stature with normal GH provocative test contrasting with extremely low IGF-I levels. **Objective and hypotheses:** To assess the contribution of GHR and IGFALS mutations to severe and mild non-syndromic GH resistance, and study the correlation between the genotype and resistance severity. **Method:** All GHR and IGFALS coding regions were analyzed by Sanger sequencing in 92 independent patients with normal or high GH secretion test (>20 mUI/l) associated with low IGF-I levels (<-2SD) and/or short stature. **Results:** GHR mutations were identified in 16% of the patients (15/92) and IGFALS mutations in 5% of them (5/92). Among the patients with GHR mutations, a recessive transmission was found for 11 probands with a severe growth delay (<-4SD). A less severe dominant phenotype was observed in 4 families. Among the recessive cases, 4 carried a bi-allelic truncating mutation, 1 was a compound heterozygote (splice, missense mutation), 4 had bi-allelic missense mutations in the GHR extracellular domain. A dominant GH resistance was associated with a GHR mutation in 4 families (1 splice, 3 missense mutations). Interestingly, 2 neighboring mutations c.876-2_876-1delAG and c.876G>T were respectively responsible for a recessive and a dominant form of GH resistance, underlining the impact of a complex alternative splicing pattern on nonsense-mediated mRNA decay. IGFALS mutations were identified in 5 independent patients: 2 homozygotes for truncating mutations, 1 compound heterozygote (whole gene deletion, missense mutation), and 2 heterozygotes (1 deletion, 1 missense). **Conclusion:** Overall, this study, performed in a large cohort of patients with GH resistance ($n=92$), identifies molecular defects in GHR and IGFALS in 20% of the patients.

RFC14.3

Whole Exome Sequencing Identifies a GH1 Gene Mutation Causing Familial Isolated Growth Hormone Deficiency with Normal Peak Growth Hormone Concentrations

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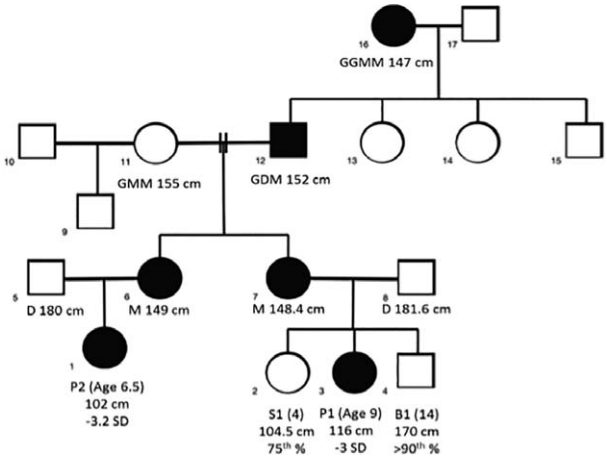
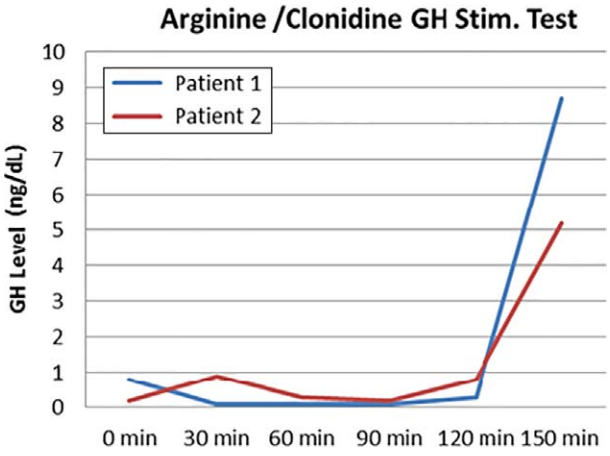
Background: Familial isolated growth hormone deficiency (IGHD) type II is autosomal dominantly inherited and caused by splice-site mutations and nucleotide substitutions in the GH1 gene. The missense mutation R183H is a well-described genetic variant that causes familial IGHD type II. Individuals with this mutation have releasable GH stores, but GH secretion is severely reduced resulting in short stature. **Objective and hypotheses:** This study aimed to report two female patients from a four-generation family with 6 individuals with short stature who carry the R183H mutation in GH1. **Method:** Two first degree female cousins with significant short stature were evaluated in the Cincinnati Center for Growth Disorders. Patient 1 (P1) was 9 years old and her height was 116 cm (-3.0 S.D.). She had been previously diagnosed with ISS based on a normal GH stimulation test. Patient 2 (P2) was 6.5 years of age and her height was 102 cm (-3.2 S.D.) After extensive evaluation whole exome sequencing (WES) was performed. **Results:** Via WES, we identified the pathogenic variant R183H in GH1 which segregated in the affected individuals. P1 and P2 underwent GH stimulation tests and were found to have delayed peak GH responses. P1 had a peak GH level of 8.7 ng/dl which is considered normal, and P2 had a peak GH level of 5.2 ng/dl. **Conclusion:** Patients with IGHD type II secondary to the R183H GH1 mutation can exhibit variable peak GH responses. Genetic testing should be strongly considered in cases of familial short stature even when peak stimulated growth hormone concentrations are normal. It remains unclear whether or not adult patients with this mutation suffer the consequences of adult GH deficiency. We are implementing a protocol to investigate body composition, skeletal integrity, cardiovascular risk profile and the overall quality of life in the affected adults of this kindred.





RFC14.4

Genetic Diagnosis of Congenital Growth Hormone Deficiency by Massive Parallel Sequencing Using a Target Gene Panel

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Background: Congenital GH deficiency (GHD) can be isolated (IGHD) or combined with other pituitary hormone deficiencies (CPHD). The identification of mutations has clinical implications for the management of patients and genetic counseling[1]. **Objective:** To prospectively conduct a molecular-genetic analysis in genes associated with IGHD or CPHD. **Method:** Forty patients with IGHD ($n=8$) or CPHD ($n=32$) were studied using target gene approach. Targeted regions (involving 26 genes associated with GHD and 57 genes associated with growth disorders without GHD) were captured using Agilent Sure Select technology. Sequencing was performed with Illumina NextSeq. Variants were analyzed considering allele frequency in the normal population and *in silico* prediction. **Results:** We identified 31 rare allelic variants located in exons (excluding synonymous) or splice sites in 17 of 26 genes associated with GHD in 19 patients. Of these, 3 variants were considered pathogenic: one patient was compound heterozygous for a *PROP1* mutation c.[109+1G>A];[301_302del] and another was heterozygous for a *TGIF1* variant (c.707A>T:p.Q236L)[2]. Six other variants in 6 different genes (*LHX3*; *KAL1*, *GLI2*, *GHSR*, *SHH* and *PROKR2*) were considered possibly pathogenic, mainly because several *in silico* models predicted them to be deleterious. In the majority of cases, only one pathogenic or possibly pathogenic mutation was identified in each patient. One patient, however, is heterozygous at two loci: one variant in *GLI2* and another in *SHH*; possibly a digenic condition. Interestingly, we identified an individual with IGHD who was compound heterozygous [c.2212C>T:p.Q738]; [c.494G>T:p.R165L] for *LZTR1*, a gene recently associated with Noonan syndrome (NS)[3]. This patient's phenotype is compatible with NS diagnosis and defects in another NS related gene (*SHOC2*) had also been previously associated with IGHD. **Conclusion:** The panel established the diagnosis of 3 patients and possibly 6 additional patients with GHD. The patients with negative results are candidates for whole exome sequencing. **References:**

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RFC14.5

Gene Expression Profiling of Children with GH Deficiency (GHD) Prior to Treatment with Recombinant Human Growth Hormone (r-hGH) is Associated with Growth Response Over Five Years of Therapy

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Background: The relationship of pre-treatment gene expression (GE) to long-term growth response in GHD is unknown. Prediction of long-term response to r-hGH therapy would allow better decision making about start and maintenance doses and hence cost:benefit. **Objective and hypotheses:** To assess the relationship of baseline GE to response to r-hGH over 5 years of therapy in GHD children. **Method:** Pre-pubertal children with GHD ($n=50$) were enrolled from the PREDICT studies (NCT00256126 and NCT00699855). Baseline whole blood GE was determined using Affymetrix U133 plus 2.0 microarrays and Gene Expression Barcode 3.0[1]. Height velocity (HV) on r-hGH over the 5 years of therapy was used as the marker of growth response. Two groups of patients were defined on growth response over 5 years of treatment (G1) always above and (G2) always below the median. The effect of age, gender and distance to target height (DTH) were assessed. Network models and random forest analysis were used to relate GE to growth response using area under the curve (AUC) of the receiver operating characteristic. The robustness of GE markers was assessed using permutation testing ($n=1000$). **Results:** There was no difference in age, gender and DTH ($P>0.05$) between the HV groups (G1 and G2) at the start of treatment. Uniquely expressed genes were

identified ($P<1\times10^{-5}$) in G1 ($n=69$) and G2 ($n=72$). Network models prioritised 94 of these 141 genes. PIK3R1 expression ($P=1.2\times10^{-9}$), associated with cell proliferation, was related to G1. DDX58 expression ($P=2.2\times10^{-10}$), associated with RNA secondary structure, was related to G2. Baseline GE could predict growth response consistently above and below the median over 5 years with an AUC of 0.86 and 0.89 respectively. **Conclusion:** We have identified genes expressed in pre-treatment GHD associated with growth response over 5 years of therapy. Further assessment to determine predictive value and functional significance of gene subsets is required.

RFC14.6

Effect of Small Size at Birth, Adult Body Size and Growth Hormone Treatment on Telomere Length

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Background: Small birth size followed by accelerated weight gain in early life is associated with an increased risk for age-associated diseases, such as cardiovascular disease (CVD) in later life. The underlying causes for this are largely unknown. Leukocyte telomere length (LTL) is a marker of biological age and short LTL is associated with increased CVD-risk. Subjects born small for gestational age (SGA) who remain short are treated with growth hormone (GH) to improve adult height. **Objective and hypotheses:** To investigate whether birth size and adult body size, including spontaneous and GH-induced catch-up growth, influence LTL, hypothesizing that catch-up growth to a normal body size, either spontaneous or GH-induced, is associated with shorter LTL. **Method:** We measured LTL in 558 young adults aged 18–24 years. LTL was measured using a quantitative PCR assay and expressed as T/S ratio. Using MR-analyses and by comparing clinically relevant subgroups, we analysed the influence of size at birth, adult body size, and GH-induced catch-up on LTL. **Results:** We found no association between birth size and LTL. SGA born subjects with spontaneous catch-up to a normal body size had shorter LTL (3.07 (0.4)) than those born SGA who remained short (3.30 (0.4), $p=0.003$)) and appropriate for gestational age born subjects with a normal stature (AGA-NS) (3.22 (0.5), $p=0.024$)). The SGA-GH subgroup had a mean LTL of 3.27 (0.5), which was similar to LTL in the AGA-NS subgroup ($p=0.74$) and the short-SGA subgroup ($p=0.73$). **Conclusion:** Birth size did not influence LTL. GH-treated young adults had similar LTL as subjects born AGA with a normal body size. Those born SGA with spontaneous catch-up in early life had the shortest LTL, suggesting that timing and tempo of early life growth influences telomere length, which could be one of the linkages between growth patterns and CVD-risk in later life.

RFC14.7

GH Influences Plasma Fasting Adropin Concentration in Patients with Turner Syndrome

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Background: Increased adiposity and insulin resistance are conditions frequently observed nowadays. Many hormones are involved in the pathogenesis of the condition but therapeutic options we can offer to the patients are still scant. Each newly discovered peptide give us hope. Adropin (Ad) is a newly discovered metabolic hormone involved in energy homeostasis. This homeostasis is frequently disturbed in patient with Turner Syndrome (TS). Patient with Turner syndrome are unique model for studies of an effect of the treatment with supraphysiological doses of growth hormone (GH) **Objective and hypotheses:** We studied adropin dependance and response in a group of TS patients treated with supraphysiological doses of growth hormone (rGH) **Method:** The study group consisted of 36 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: adropin, OGTT, insulin, lipids, IGF-1, and IGFBP-3. **Results:** The increase of IGF-1 concentration at the end of observation was significant (from 119.4 ± 62.46 to 413.37 ± 204.38 ng/ml, mean$\pm$S.D., $P=0.000$). The GH treatment influenced insulin resistance revealed by increased HOMA values (median 0.64 ± 0.45 before and 0.92 ± 0.97 after, $P=0.02$). rGH treatment cause a significant rise in Ad level. The correlation between adropin and IGF-1 and IGF-1 SDS levels was not significant neither before nor on the treatment ($r=0.17$ and $r=0.04$ respectively). Adropin concentration correlated with IGFBP3 level before rGH treatment but not on rGH therapy. Ad also correlated with insulin level before GH applying. Correlation with glucose levels at 30' of OGTT was stable and even rise on GH treatment ($P=0.33$ vs $P=0.48$). Similar observation was noticed for lipids, but close correlations between Ad adropin and total cholesterol, LDL cholesterol, triglycerides (TG) before GH applying changed on rGH therapy. The only correlation noticed in GH treated patients was between Ad adropin and TG ($P=0.34$). **Conclusion:** Result of the study showed an increase in adropin level following rGH application is not mediated by IGF-1. rGH treatment changes adropin influence on lipid metabolism, but ameliorates insulin action.

RFC14.8

ACAN Mutations in Short Children Born SGA; Growth Response During GH Treatment with Additional GnRHa, and a Proposed Clinical Scoring System

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Background: In children born SGA with persistent short stature, growth hormone (GH) treatment is an approved therapy for increasing adult height (AH). Some SGA children have an advanced bone age (BA) during GH. Heterozygous mutations in the ACAN-gene have been described in children with idiopathic short stature and advanced BA. **Objective and hypotheses:** To assess growth during GH treatment with additional GnRHa treatment, in children with ACAN-gene mutations. To determine a clinical scoring system for ACAN-sequencing. **Method:** Targeted ACAN-sequencing was performed in 22 short SGA children with advanced BA or midfacial hypoplasia. **Results:** Four children, 3 boys and 1 girl, had an ACAN-gene mutation. All 4 children were treated with GH and received additional GnRHa treatment for 2 years from onset of puberty. Height SDS improved with 0.7 SDS. At AH, one girl was 5.2 cm taller than her mother and one boy was 8.0 cm taller than his father, parents had the same ACAN-gene mutation. In boys, treatment with GnRHa followed by Letrozole successfully delayed BA. ACAN-gene mutations were found in 21% of the children with an advanced BA of $\geq$0.5 years. Based on parental height SDS, height SDS and clinical characteristics of the child, a scoring system was composed which identified children with an ACAN-gene mutation with a sensitivity of 100%. **Conclusion:** GH with additional GnRHa, in boys followed by Letrozole, might improve AH in children with ACAN-gene mutations. We propose a clinical scoring system to select patients for ACAN sequencing which should be based on advanced BA, parental height SDS and height SDS of the child.

RFC15.1

A Novel Homozygous Mutation in the Domain AF-2 of Alpha Estrogen Receptor Gene (*ESR1*), Generating a Bio-Inactive ERα Mutant, Resulting in Estrogen Resistance with Complex Metabolic Phenotype

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Context: The mouse $ER\alpha^{-/-}$ knock-out model and rare human *ESR1* gene mutations identified to date have demonstrated crucial role of ERα in control of energy homeostasis and glucose metabolism. Subjects with ERα deficiency show features of estrogen resistance (ESTRR) with continuous linear growth in adulthood. **Patient:** We describe a 20-year-old female, with unknown family history, who presented with primary amenorrhea and lack of breast development (Tanner stage: B1-P4-A4). Pelvic MRI revealed a rudimentary uterus and polycystic ovaries. The patient presented with tall stature (180 cm), continuous linear growth and bone age of 12 years. Her BMI was 28 kg/m^2 and she had increased abdominal adiposity assessed by DXA (trunk/limb fat ratio 1.3). Endocrine evaluations indicated ESTRR, with elevated LH (40 UI/l), FSH (44 UI/l), E2 (1670 pmol/l, reference values: 220–400), and hyperandrogenism (testosterone 7.7 nmol/l, delta-4-androstenedion 12.5 nmoL/l). Metabolic explorations revealed insulin resistance (HOMA-IR 11,8), elevated leptin (75 ng/ml), contrasting with normal adiponectin (3.1 ug/ml) and normal lipid profile. Hepatic triglyceride content measured by MR spectroscopy was of 7%. **Results:** The patient's phenotype was consistent with ERα deficiency. Sequencing of the *ESR1* gene revealed a novel homozygous T to C transition in exon 10, which resulted in a p.Met543Thr missense mutation. Met543, a highly conserved residue, is within the ligand binding domain (AF-2, helix H12). Preliminary reconstitution studies indicate a significant decrease in transcriptional activity of the mutant protein after treatment with estradiol. **Conclusion:** A novel missense *ESR1* mutation, p.Met543Thr has been identified in a patient who presented with a complex phenotype consistent with ERα deficiency. Only two *ESR1* mutations were reported in the literature to date. This new mutation resulted in a bio-inactive ERα variant. The phenotype of our patient, together with previously described cases, confirms the crucial role of ERα in pubertal growth as well as metabolic phenotype.

RFC15.2

NR0B1 Frameshift Mutation in a Boy with Precocious Puberty and Normal Adrenal Function

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Background: While hemizygous NR0B1 (DAX1) mutations usually lead to adrenal crisis during infancy or early childhood, p.Gln37*, p.Trp39*, and some other mutations result in late-onset or latent adrenal insufficiency. A small percentage of boys with NR0B1 mutations develops precocious puberty in addition to adrenal insufficiency. **Objective and hypotheses:** To report a boy with an *NR0B1* mutation who exhibited central precocious puberty without adrenal insufficiency. **Method:** A 4-year-old boy

presented with pubic hair, testicular enlargement, and advanced bone age. Blood examinations revealed increased testosterone levels and hyperresponses of gonadotropins to GnRH stimulation. The patient was clinically diagnosed with idiopathic central precocious puberty. GnRH analog treatment partially ameliorated the hormonal abnormalities, but did not improve the physical findings. On his latest visit at 7 years and 6 months of age, the patient showed no clinical or laboratory signs of adrenal insufficiency. The patient was subjected to mutation screening of 32 genes known to control the hypothalamic-pituitary-gonadal axis. **Results:** Molecular analysis identified a maternally-inherited hemizygous 1-bp deletion in exon 1 (p.Glu3fsAla*16) of *NR0B1*. The mutation was predicted to encode an N-terminally truncated hypomorphic protein, similar to that produced by p.Gln37*and p.Trp39*. No pathogenic mutations were found in other tested genes. **Conclusion:** These findings expand the clinical manifestations of *NR0B1* mutations to include male central precocious puberty without adrenal insufficiency. *NR0B1* mutations likely underlie testosterone overproduction through both GnRH-dependent and -independent mechanisms.

RFC15.3

Abstract withdrawn.

RFC15.4

The Effect of Sfrp5, Wnt5a, Adiponectin, and Chemerin on Blood Pressure Regulation in Obese Children

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Background: The dysregulation of adipocytokines with increasing fat mass may directly contribute to hypertension. It has been confirmed that chemerin and adiponectin can affect BP. However, the effect of other adipocytokines on the development of hypertension is still poorly understood. **Objective and hypotheses:** The aim was to evaluate the associations of Sfrp5 and Wnt5a with blood pressure (BP), and to examine whether BP can be influenced by changes in adipocytokines, such as Sfrp5, adiponectin, chemerin, and hsCRP, in obese children after lifestyle intervention. **Method:** A cross-sectional study was conducted in 263 obese children. In addition, a 6-month lifestyle intervention was performed in a subgroup of 89 obese children with hypertension. Anthropometric parameters, clinical data, adiponectin, chemerin, Sfrp5, and Wnt5a were measured at baseline and after lifestyle intervention. **Results:** Sfrp5 and adiponectin levels were significantly lower in obese children with hypertension, but Wnt5a, hsCRP, and chemerin levels were elevated in obese children with hypertension. In multivariable linear regression analysis, Sfrp5, Wnt5a, adiponectin, chemerin, and hsCRP were associated with both standard deviation score-systolic blood pressure (SDS-SBP) and -diastolic blood pressure (SDS-DBP). Lifestyle intervention resulted in a significant improvement in BP and weight loss. These were accompanied by significant decreases in hsCRP and chemerin, and significant increases in Sfrp5 and adiponectin, whereas Wnt5a was not changed. Furthermore, the changes in Sfrp5, adiponectin, chemerin, and hsCRP act as partial mediators of the relationship between weight loss and BP reduction. **Conclusion:** Although Sfrp5 and Wnt5a levels correlated with BP at baseline, after lifestyle intervention, Sfrp5 is more sensitive to reduction in BMI and BP compared to Wnt5a, and the relationship between weight loss and BP reduction were partially mediated by changes in Sfrp5. So we speculate if Sfrp5 and Wnt5a each play a role in regulating BP, it must be different roles.

RFC15.5

Effect of Melatonin on Proliferation and Differentiation of Human Dental Pulp Cells

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Background: Melatonin is known to regulate a variety of biological processes. The investigation and application of melatonin in oral development have got a lot of attention. The study was performed to investigate the effects of melatonin on development of human dentin formation. **Objective and hypotheses:** To investigate the role of melatonin in proliferation and differentiation of human dental pulp cells(hDPCs). **Method:** HDPCs were obtained from the human third molars or premolars, cultured *in vitro* and identified by immunocytochemistry. CCK8 assay were used to evaluate the effect of melatonin (10^{-12}mol/L,10^{-10}mol/L, 10^{-8}mol/L)on cells' proliferation for 1, 2, 3, 4, 5 days. Then the cells were treated with odontogenic medium (OM) and MT (10^{-8}mol/L). After 7 days'incubation the alkaline phosphatase (ALP) activity was analyzed with the kits and the expression of dentin sialophosphoprotein (DSPP) measured by immunocytochemical staining. Alizarin red staining were used to exam the formation of mineralized nodules in hDPCs treated with OM and MT for 14 days. **Results:** HDPCs were isolated cultured successfully and identified as the ecto-mesenchyme-derived cells. CCK8 assay demonstrated that absorbances in various levels of MT groups were lower than in control group in a time- and dose-dependent manner ($P<0.05$). The ALP activity and DSPP levels of OM+MT group were much higher than that of OM group after 7 days' incubation ($P<0.05$). Mineralization nodules were more observed in OM+MT group after 14 days' treatment. **Conclusion:** MT can inhibit the proliferation and stimulate the odontoblast differentiation of hDPCs.

RFC15.6

Safety of GH in Paediatrics: The GeNeSIS Prospective Observational Study Experience between 1999 and 2015 (NCT01088412)

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Background: Although GH's safety profile since 1987 is good, concerns remain regarding cancer (CA) risk, and French SAGhE data indicated increased mortality and cerebrovascular disease (CVD) in certain GH-treated patients (pts). **Objective and hypotheses:** To evaluate key safety outcome incidence in GH-treated pts of all short stature diagnoses (dx) who participated in GeNeSIS (1999–2015, 30 countries). **Methods:** Pt history/case ascertainment required review of study and corporate pharmacovigilance databases. Person-years (PY) of follow-up were calculated between first and last contacts (later of event onset, last study visit or summary date). Standardised mortality (SMR) and incidence (SIR) ratios were calculated using expected cases from contemporary general population registries (CDC, GLOBOCAN, SEER, SEARCH for Diabetes in Youth, WHO) adjusted for country, age, sex and ethnicity (where applicable). **Results:** Amongst 21178 pts eligible for analysis the predominant short stature dx were GH deficiency (63%), idiopathic short stature (13%), Turner syndrome (8%) and small for gestational age (6%). Mean ± SD study entry age was 10.5 ± 3.8Y and duration of follow-up was 4.4 ± 3.2Y (~92,000PY). The table shows cases, crude incidence and SMR/SIR for key outcomes. SMRs were not elevated for any specific dx except for pts with organic GH deficiency due to previous (prev) CA (SIR, 95%CI 5.87, 3.21–9.85). Most pts with incident type 2 diabetes (T2DM) had risk factors (incl. syndromic dx, prev irradiation, obesity). Haemorrhagic CVD occurred in 2 intracranial tumour (ICT) survivors and after renal transplant in 1 pt with renal insufficiency. **Conclusion:** Acknowledging the limited GeNeSIS follow-up duration, no increased risk for death or 1st CA was observed, and no strokes were recorded in dx studied in published SAGhE analyses. SIRs for T2DM were elevated so glucose monitoring of GH-treated pts with risk factors is recommended. All pts with prev ICT/CA should be monitored for recurrence/2nd neoplasm whether treated or not with GH.

RFC15.7

Long-Term Safety and Effectiveness of Daily and Weekly Growth Hormone Treatment in Pediatric GHD Patients (4-Years' Results)

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Table 1. (for abstract RFC15.6)

Outcome	Pts at risk	N affected/N at risk (%)	Affected/1000 PY, 95% CI	SMR/SIR, 95% CI
Any event	All	6365/21178 (30.1)	–	–
Death	All	42/21178 (0.20)	0.46, 0.34–0.62	0.61, 0.44–0.82
CVD	All	16/21178 (0.08)	0.17, 0.11–0.28	–
Haemorrhagic	All	3/21178 (0.01)	0.03, 0.01–0.10	–
T2DM	All	18/21178 (0.08)	0.20, 0.12–0.31	3.79, 2.25–6.00
1st CA	No prev CA	14/20556 (0.07)	0.16, 0.09–0.27	0.71, 0.39–1.20
ICT recurrence	Prev ICT	67/823 (8.14)	16.9, 13.3–21.5	–
2nd neoplasm	Prev CA	31/622 (4.98)	10.7, 7.5–15.2	–

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Background: The weekly sustained-release growth hormone (GH) has been approved for treatment in growth hormone deficiency (GHD). It provides a practical strategy for improving adherence. **Objective and hypotheses:** To evaluate the long-term safety and effectiveness of two formulations of daily (Eutropin®) and weekly (EutropinPlus®) GH in Korean pediatric GHD patients. **Method:** A multicenter, 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 Mar 2016. **Results:** Total 901 patients with GHD were analysed to compare the safety during the 4 years of GH treatment (daily ($n=647$), weekly ($n=254$)). And for effectiveness, 619 patients were analysed (daily ($n=444$), weekly ($n=175$)). Baseline demographics were similar between groups except age (Chronological age: 8.01 vs 9.05, Bone age: 6.36 vs 7.41 years, respectively). For daily vs. weekly GH group, Height SDS was -2.4 vs -2.5 at baseline. ΔHeight SDS during the first year of GH treatment was 0.67 vs 0.56 which was statistically different between groups but there was no statistical difference between groups when sub-analysed by <8 and ≥ 8 years. Height Velocity (HV) at the first year was 8.98 and 8.71 cm/year in the daily and weekly with no statistical difference, and same trend was showed during 4 years treatment. Adverse events (AEs) were reported in 18.4 vs 16.9% of patients in the daily vs weekly, and mostly reported as mild. The incidence of adverse drug reactions was 3.7 and 4.7%, respectively. **Conclusion:** Growth response of weekly GH is comparable that of daily GH in GHD. Also, weekly GH showed a similar profile to daily GH formulation without special safety concerns when used in GHD patients for 4 years.

RFC15.8

Replacement of Male Mini-Puberty

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Background: Hormonal replacement in boys with congenital HH remains a challenge. Micropenis has been traditionally successfully treated with 3 monthly injections of testosterone enanthate before the age of 2, but when bilateral cryptorchidism coincides, surgery is required. But even after a successful surgery, the hypoplastic testes with the deficient proliferation of immature Sertoli cells, due mainly to the lack of the male mini-puberty in the neonatal period as well as the subsequent midinfancy surge in pulsatile gonadotropin secretion, are condemned in azoospermia and the boys in infertility. **Objective and hypotheses:** We investigated whether early postnatal daily injections of the commercially available recombinant LH/FSH preparation (Pergoveris®) could mimic the physiological male mini-puberty and successfully resolve bilateral cryptorchidism, repair micropenis, reinstate normal growth velocity and restore the responses of the Leydig and Sertoli cells. **Method:** Five neonates and infants, all with bilateral cryptorchidism in intra-abdominal position and micropenis [$\leq$ 2 cm, (-2 SDS)] with absence of neonatal male mini-puberty, were treated for 3 months with daily s.c. injections of the recombinant LH 75 + FSH 150 IU preparation (Pergoveris®). Case 1 had CHARGE syndrome diagnosed before choanal atresia. Cases 2 and 4 had non syndromic Kallmann syndrome. Case 3 (septo-optic dysplasia) and 5 (aplastic pituitary) had panhypopituitarism diagnosed in the neonatal ICU before symptomatic hypoglycemia and/or cholestatic jaundice. **Results:** Median LH from undetectable reached high normal 6.5 IU/L and FSH supranormal levels 88 IU/L. Inhibine b and AMH from subnormal, reached high normal levels: median 248 pg/ml and 1025 pmol/L respectively. Testosterone increased from undetectable to a median of 2.42 ng/ml. In all cases testes descended in scrotal position by the end of the 1st in one, 2nd in two and 3rd month in two patients with a volume between 1.5 and 2.5 ml. In 4 cases with a follow-up of 1–5 yrs testes have slightly regressed to 0.5–1.5 ml but are still in scrotal position. Penile length increased to a median of 4.5 cm. During therapy all infants initiated catch-up growth. None presented any adverse events or reactions. **Conclusion:** The proposed regimen mimics neonatal male mini puberty repairing micropenis and cryptorchidism and inducing high-normal activation of Leydig and Sertoli cells.

P1-P1

Leptin is Associated with Serum Aldosterone in Paediatric Subjects, Independently of Body Mass Index, Blood Pressure and Plasma Renin Activity

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Background: Leptin is considered to play an important role in the development of hypertension in obesity. The excessive synthesis of aldosterone contributes to the development and progression of metabolic and cardiovascular dysfunctions. Leptin is a newly described regulator of aldosterone synthesis that acts directly on adrenal glomerulosa cells to increase CYP11B2 expression and enhance aldosterone production in human adrenal cells lines and in animal models. **Objective:** To analyze if there is association between leptin with serum aldosterone (SA), as well as with blood pressure (BP), plasma renin activity (PRA), transtubular potassium gradient (TTKG), fractional excretion of sodium (FENa) and 24 h-Na/K urine ratio. **Design:** Cross sectional study. **Subject and methods:** We studied 79 subjects between 6.1 and 18 years old (mean, 13.2 years; 42 females); 37 were normal weight, 18 were overweight, and 24 were obese. After overnight fasting: anthropometric parameters, SA, PRA, plasma and 24-h-urine electrolytes were measured and TTKG, FENa and 24 h-Na:K urine ratio were calculated. For variables without normal distribution Spearman correlation was used, and log transformation was calculated previously to partial correlation analyses. **Results:** Leptin was directly associated with SA ($\rho = 0.275$; $P = 0.016$). None association was found between leptin with systolic and diastolic BP ($P = 0.657$ and $P = 0.869$, respectively) and PRA ($P = 0.197$). Moreover, after controlling by age, body mass index z-score (BMI-z), $\log_{10}$ PRA and $\log_{10}$ 24 h-Na:K urine ratio, the association between $\log_{10}$ leptin and $\log_{10}$ SA increase (partial correlation $= 0.367$; $P = 0.002$). In other hand, SA was associated with PRA ($\rho = 0.400$; $P < 0.001$) and TTKG ($\rho = 0.330$; $P = 0.037$); and negative associated with FENa ($\rho = -0.246$; $P = 0.035$) and 24 h-Na:K urine ratio ($\rho = -0.276$; $P = 0.014$). **Conclusion:** In paediatric subjects, leptin was associated with SA. This association was independently of the effect of age, BMI-z, PRA and BP. Our clinical results agree with the recently described effect between of leptin upon aldosterone secretion in human adrenal cells lines and in animal models.

P1-P2

Mast Cells and Steroidogenesis in the Human Fetal Adrenal

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Background: We recently demonstrated the presence of mast cells in human fetal adrenal gland from 18–20 weeks of gestation (WG) within the subcapsular layer. In the adult adrenal, mast cells have been implicated in mineralocorticoid synthesis and secretion especially in aldosterone-producing adenomas. Because similarities exist between tumors and normal fetal development and as cell-to-cell interactions involving immune cells are implicated in organogenesis, we hypothesized a role of mast cells in steroidogenesis synthesis and/or secretion in fetal adrenal development. **Objective:** We thus investigated steroidogenic enzymes expression in relationship to the occurrence of mast cells in the human developing adrenal gland. **Method:** Immunochemical studies were performed on 28 paraffin-embedded adrenal glands at 16–40 WG using tryptase, Scavenger Receptor class B type I (SRB1), 17α-hydroxylase (17α-OH), 3β-hydroxysteroid dehydrogenase (3βHSD), 11β-hydroxylase (11β-OH) and aldosterone synthase antibodies. Moreover, steroidogenic enzymes mRNA levels were quantified at 22, 24, 29 and 30 WG and compared to adult tissue. **Results:** 3βHSD and CYP11B2 immunopositive cells were firstly detected at 18 and 24 WG respectively, within the adrenal subcapsular region close to the tryptase immunopositive cells. Conversely, no spatio-temporal correlation was observed with either 17α-OH or 11β-OH expression (detected at all fetal studied stages). In addition, SRB1 expression was early detected in the fetal zone extending to the subcapsular zone from 24 WG. QPCR confirmed the timing of

steroidogenic enzyme expression reported above. **Conclusion:** We show for the first time the expression profile of aldosterone and cortisol producing cells in the human fetal adrenal. Timing of the CYP11B2 expression could help better understand the pathophysiology of salt wasting syndrome in extreme premature infants. Moreover, the spatio-temporal correlation of tryptase and CYP11B2 expression suggests a contribution of mast cells in establishment of the mineralocorticoid axis. However, further studies are required to better understand this potential regulatory pathway.

P1-P3

Gender-Specific Differences in Hypothalamus–Pituitary–Adrenal Axis Activity in Children: A Meta-Analysis

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Background: Differences in hypothalamus–pituitary–adrenal (HPA-)axis functioning have been proposed to underlie gender-specific cardiovascular and neurocognitive disease susceptibility. **Objective and hypotheses:** We conducted a systematic review and meta-analysis to test the hypothesis that gender-specific differences in HPA-axis activity are already present in childhood. **Method:** We searched two electronic databases (PubMed and EMBASE) to identify potentially relevant studies. We included studies that assessed random, non-stimulated cortisol in serum or saliva, or cortisol in 24 h-urine in healthy males and females aged $\leq$18 years who did not use glucocorticoid-containing medications. Two researchers independently reviewed the data. Results were analyzed by age groups $<$8 years (prepubertal) and 8–18 years (peri-/postpubertal). **Results:** A total of 5834 articles were identified with our search strategy. 351 (6%) publications were selected for full-text screening, of which 70 (20%) met our inclusion criteria. Our meta-analysis included the data of $>$13.000 subjects. In both serum and saliva, differences between males and females seemed to be age-dependent, with cortisol concentrations (in nmol/l) in boys being higher before age 8 years (mean difference (95% CI): 0.37 (0.25–0.48) for serum, and 0.20 (0.04–0.36) for saliva and lower after age 8 years ($-$0.52 ($-$0.59 to $-$0.42) for serum, and $-$0.46 ($-$0.50 to $-$0.41) for saliva, as compared to girls. In 24 h-urine, gender-differences were found to be stable throughout childhood, with urinary cortisol excretion being higher in boys. **Conclusion:** Differences between males and females in cortisol production and/or metabolism are already present early in life, with cortisol being higher in boys. A gender-specific evolution of cortisol metabolism seems to be induced by puberty, resulting in higher random, non-stimulated cortisol levels in girls. Urinary cortisol excretion seems to be stable between genders with age. Although the differences found were small, these patterns might contribute to gender-specific differences in the origins of health and disease.

P1-P4

Prepubertal Children Born Large for Gestational Age have Lower Serum DHEAS Concentrations than those with Lower Birth Weight

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Background: In some studies, prepubertal children born small for gestational age (SGA) have had a higher prevalence of premature pubarche and higher serum DHEAS concentrations than children born appropriate for gestational age (AGA). The overall metabolic risk associated with birth weight is U-shaped, but it is not known if children born large for gestational age (LGA) have elevated serum DHEAS levels. **Objective and hypotheses:** The aim of this study was to examine the association between birth size, especially large, and serum DHEAS concentrations. **Methods:** A cohort of 49 LGA, 56 AGA, and 23 SGA children were studied at 5–8 years of age. Anthropometric data at birth, at the age of 2 years, and at examination were recorded. Fasting blood samples were collected for serum analyses of DHEAS, IGF1, and insulin concentrations. Children's physical activity was assessed with a survey. Differences in serum DHEAS concentrations between the three groups were analysed by ANCOVA and predictors of serum DHEAS levels were explored by linear regression analysis. **Results:** The LGA children had lower BMI-SDS-adjusted serum DHEAS levels than the AGA or SGA children. Lower birth weight SDS, higher weight gain during the first two years, and higher BMI-SDS at examination predicted higher serum DHEAS concentrations. Higher serum IGF1 but not insulin, and overall physical activity were also associated with higher DHEAS. **Conclusions:** The association of birth weight with childhood serum DHEAS concentration is more linear than U-shaped. However, early catch-up growth and childhood weight are even stronger determinants of serum DHEAS levels than birth weight. IGF-1 may be a mediator in this process.

P1-P5

Whole Exome Sequencing in Patients with Primary Generalized Glucocorticoid Resistance, who did not have Mutations in the *NR3C1* Gene

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Background: Primary generalized glucocorticoid resistance (PGGR) is a rare, familial or sporadic condition, characterized by

generalized, partial tissue insensitivity to glucocorticoids. The molecular basis of this condition has been ascribed to mutations in the *NR3C1* (human glucocorticoid receptor, hGR) gene, which impair the molecular mechanisms of hGR action and decrease tissue sensitivity to glucocorticoids. However, a considerable number of patients with PGGR do not have mutations in the *NR3C1* gene. **Objective and hypotheses:** Using whole exome sequencing, we investigated whether other genes are implicated in the pathogenesis of PGGR. **Method:** Ten adult patients (age range: 18–48 years; 6 males, 4 females) with PGGR, who did not have mutations in the *NR3C1* following Sanger sequencing and two patients with PGGR harbouring known mutations of the *NR3C1* gene (positive controls) underwent whole exome sequencing on an Ion Proton platform (ThermoFisher Scientific USA). **Results:** Each exome sequence revealed the presence of approximately 55 000 variants. Using a cut off value of 100 reads/variant, a total number of 507 non-synonymous and frameshift mutations were detected in all patients. These mutations corresponded to 390 genes involved in five different pathways, one of which was that of steroid hormone biosynthesis (*CYP1B1*, *CYP3A7*, *AKR1C4*, *UGT2A3*). Nineteen of the 390 genes were found to be regulated directly by *TP53* possibly indicating the presence of a cascade. One mutation of the *GP6* gene present in all patients was not annotated. The presence of mutations in the genes *HSP90AA1*, *NCOA1*, *SMARCA4*, *NCOA2*, *JUN*, *UBC*, *CREBBP*, *NFKB1*, *RELA* and *NCOA3* (functional partners of the *NR3C1* after searching the STRING database) was examined and no pathogenic variants were detected. **Conclusion:** Whole exome sequencing may allow us to expand the spectrum of genes associated with PGGR. Further bioinformatic analysis is required to establish pathogenic variants in genes related to this condition.

P1-P6

Novel *CYP11A1* Mutations in 15 Patients (13 Families) with Variable Clinical Presentations

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Background: The side chain cleavage enzyme (CYP11A1) catalyzes the conversion of cholesterol to pregnenolone, the first rate-limiting step of steroidogenesis. *CYP11A1* mutations are associate with primary adrenal insufficiency (PAI) and, in 46,XY patients, Disorders of Sex Development (DSD). A total of 35 patients (27 families) are reported including 15 intermediate forms with delayed onset of PAI, variable degrees of DSD or normal male phenotype. **Objective and hypotheses:** To report 15 patients (13 families) with 15 *CYP11A1* mutations (10 new) and variable clinical presentations **Method:** *CYP11A1* gene was analyzed by Sanger sequencing or massive parallel sequencing (MPS). **Results:** Nine patients with a severe classic form (neonatal PAI and female phenotype in seven 46,XY patients) were homozygous or heterozygous composite for 10 mutations: p.Gly94Asp, p.Pro104Leu, p.Gly138Arg, p.Ala277Ser, p.Asp329Gly, p.Arg 396Gly, p.Arg465Gln, p.Arg465Trp, p.Leu170Val*fs**30 (all unpublished) and p.Arg120*. Five patients with an intermediate form (delayed onset of PAI and variable degree of DSD in 46,XY patients) had the mutations: p.Arg120Gln, p.Ala269Val (11% residual activity), p.Glu314Lys and a new one: p.Gly454Asp. One 46,XY patient with complete normal male genital development had a mutation reported in similar cases: p.Arg451Trp (32% residual activity). Functional studies are underway but *in silico* studies predict good phenotype genotype correlation. **Conclusion:** The incidence of *CYP11A1* mutations (33%) is higher in our cohort of patient with first step of steroidogenesis deficiency (*STAR* and *CYP11A1* gene) than in global population. We report novel mutations with genotype phenotype correlation in these patients with varying clinical presentations, including one 46,XY patient without DSD. Is it due to a residual activity of the enzyme or to a tissue specific defect? Intermediate forms are rare but at risk to be misdiagnosed because the phenotype overlaps with other causes of PAI. This emphasizes the utility of MPS allowing the study of many causative genes all at once.

P1-P7

Transient Generalized Glucocorticoid Hypersensitivity Syndrome

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Background: Transient Generalized Glucocorticoid Hypersensitivity (TGGH) is a rare disorder characterized by increased tissue sensitivity to glucocorticoids and compensatory hypoactivation of the hypothalamic–pituitary–adrenal (HPA) axis. The condition itself and the underlying molecular mechanisms have not been fully elucidated. **Objective and hypotheses:** To present the clinical manifestations, endocrinologic evaluation and molecular studies in a patient with TGGH. **Method and results:**

A 14-year old boy presented with a 9-month history of clinical manifestations suggestive of Cushing syndrome. Endocrinologic evaluation revealed low 0800 h plasma ACTH (1 pg/ml), serum cortisol (0.08 μg/dl) and 24 h-urinary free cortisol (UFC) concentrations (2.75 μg/24 h). The oral glucose tolerance test (OGTT) indicated severe insulin resistance and hyperinsulinemia. Moreover, HbA1c levels were elevated (6.1%). Screening for synthetic glucocorticoids in both serum and urine samples was negative. Following stimulation with oCRH (1 μg/kg), ACTH concentrations increased significantly, while the response of cortisol was suboptimal for the degree of post-CRH ACTH elevation. Sequencing of the human glucocorticoid receptor (hGR) gene revealed no mutations or polymorphisms. Serological tests revealed elevated HSV-6 IgG titers (1/320). The dexamethasone-binding assays demonstrated increased affinity of the patient's hGR receptor for the ligand compared with a control subject matched for sex, age and body mass index (Kd = 5.7 ± 2.65 nM vs 14.7 ± 5.3 nM). The clinical manifestations of the disease gradually resolved over the ensuing 5 months. Plasma ACTH, serum cortisol and 24 h-UFC concentrations normalized (ACTH: 35.27 pg/ml, cortisol: 11.02 μg/dl, 24 h-UFC: 55.57 μg/24 h). Following OGTT, serum insulin concentrations remained persistently elevated, however, the HbA1c levels were normal (5.5%). The repeat dexamethasone-binding assays showed that the patient's hGR receptor had similar affinity for the ligand, compared with the control subject (Kd = 17.6 ± 0.0 nM vs Kd = 14.7 ± 5.3 nM). **Conclusion:** Our results suggest that a transient postreceptor defect may have enhanced glucocorticoid signal transduction, leading to TGGH.

P1-P8

The Effect of Obesity on the Stress Response: The Paradigm of Surgical Stress

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Background: The ability to respond to stress constitutes a defensive protective mechanism; both inadequate and excessive responses may be detrimental. **Objective and hypotheses:** To investigate the effect of increased body weight on the hormonal response to stress in children. Scheduled surgical procedures include two stressful parts, a psychological one (anticipation of operation) and a biological one (surgical stress per se) and were chosen as a study model. **Method:** A total of 30 children, scheduled for minor surgical procedures (hernia, orcheopexy) and well otherwise, were included in the study. Two groups were studied: obese (O) group (15 children, aged 5 ± 2 years, BMI-*z* score: 9.5 ± 1.9) and normal weight (N) group (15 children, aged 4 ± 2, BMI-*z* score: 1.7 ± 1.5). Blood samples were obtained prior to any manipulation (P1), after anaesthesia induction (P2), during surgery (P3) and one hour after the end of surgery (P4). **Results:** Prolactin was similarly increased at P1 in both groups and gradually fell in the N group, whereas stayed unchanged throughout in the O group ($P = 0.005$ at P4 between groups). GH was significantly lower in the O than the N group at start (P1 and P2, $P < 0{,}001$). T4 was significantly higher in the N than the O group at P2 and P3 ($P < 0.001$) combined with an inadequate TSH and T4 rise in the O group. Cortisol was significantly higher in the N compared to the O group at P1 and P2 ($P < 001$). Interestingly, cortisol in the N group peaked at P2, whereas in the O group peaked at P4. ACTH did not differ between the two groups, however, the cortisol/ACTH ratio was significantly lower in the O than in the N group ($P = 0.01$) throughout sampling. **Conclusion:** Timing and intensity of the endocrine stress response differs between obese and normal weight children. The biological mechanisms involved are not apparent but may reflect an insufficient response to environmental stressors in obese children.

P1-P9

Long-term Anthropometric Outcome of Girls with Non-classical Congenital Adrenal Hyperplasia Diagnosed in Childhood

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Background: Data on anthropometric outcomes in patients with non-classical 21-hydroxylase deficiency (NCCAH) are sparse. **Objective:** To investigate long-term effects of NCCAH on height and weight. **Method:** A retrospective, cross-sectional study of 105 girls with NCCAH aged 8.4 ± 4.1 years (0.4–18), mean follow-up 11.4 ± 7.5 years. Outcome measures were height, weight and BMI, expressed as standard deviation score (SDS), at diagnosis compared to last visit and also to those of their mothers, fathers and siblings. Patients were stratified by pubertal stage at diagnosis: prepubertal, pubertal (Tanner 2–4) and fully pubertal. **Results:** Median daily hydrocortisone dose was 10.0 mg/m^2 (3.5–27). At diagnosis, height-, weight- and BMI-SDS were similar to those of parents and siblings; bone age to chronological age ratio was 1.2 ± 0.2. Height-SDS at last visit was significantly lower than that at diagnosis (−1.7 ± 1.4 vs −0.2 ± 1.3, $P < 0.001$) and lower than that of mothers ($P < 0.001$), fathers ($P < 0.001$) and siblings ($P < 0.002$). Patients fully pubertal at diagnosis were significantly shorter than prepubertal ($P < 0.001$) and pubertal patients ($P < 0.001$), and at last visit shorter than prepubertal patients ($P < 0.005$). A significant association was found between lower height-SDS at last visit and longer treatment duration ($r = -0.46$, $P < 0.001$) but not with hydrocortisone dose ($r = -0.22$, $P = 0.07$). Current weight-SDS slightly decreased compared to baseline (0.1 ± 1.4 vs −0.5 ± 1.4, $P < .001$), while BMI-SDS was similar to baseline (0.3 ± 1.3 vs 0.5 ± 1.1, $P = 0.09$). Most recent weight- and

BMI-SDS were significantly lower than parental weight- and BMI-SDS. Age at menarche was earlier in affected girls than in their mothers (12.3 ± 1.3 vs 12.7 ± 1.2 years, $P < 0.05$). **Conclusion:** NCCAH diagnosed in childhood is associated with compromised height. Older age at diagnosis, earlier menarche, and longer steroid treatment duration may be risk factors. It is encouraging to see that BMI-SDS did not increase over time, despite hydrocortisone treatment.

P1-P10

Current Dilution Methods Cause Large Variations and Inaccuracies when Making up 1 μg Synacthen Dose

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Background: The low-dose short Synacthen test is a popular diagnostic test of adrenal insufficiency in children. It is employed by 82% of UK paediatric endocrinologists. Although various dosing strategies exist, 1 μg is most commonly employed, however none of the low-dose forms are commercially available. A BSPED survey revealed 14 different methods for diluting 250 μg/ml ampoules. **Objective and hypotheses:** Do various dilution strategies result in differences in the resultant Synacthen dose administered? **Method:** The ten most popular dilution methods were tested, encompassing different diluents (0.9% saline $n = 9$, 5% dextrose $n = 1$), single ($n = 6$) and double ($n = 4$) dilution strategies and varying initial quantities of Synacthen (0.1–1 ml). Each method was made up five times under simulated ward conditions and three samples taken from different parts of the bag of resultant solution. Samples were frozen then batch-analysed on an hACTH RIA validated for Synacthen. All samples were diluted to 250 pg/ml (most sensitive part of the assay measuring range) and the coefficient variation (CV) calculated. **Results:** There was marked variation in Synacthen detected from the three samples taken from the same solution (CV 13.4–194.6%) suggesting inadequate mixing, the five preparations of the same method, suggesting batch to batch variation, and between the 10 different preparation methods (CV range 24.2–163.7%) suggesting inequity between methods. Estimates of the likely Synacthen dose, if administered to patients, ranged from less than 0.04 μg to more than 2 μg. **Conclusion:** Considerable variation was observed both within and between dilution methods. Variables, which may affect the actual dose of Synacthen administered, include: poor dilution technique, inappropriate dilution strategies, pharmaceutical manufacturer variation, use of inaccurate ward equipment, volume inconsistencies, lack of adequate mixing and lack of a controlled environment. We recommend low-dose Synacthen be made up under laboratory conditions and call for a commercial preparation of 1 μg Synacthen.

P1-P11

Evaluation of the Glucocorticoid, Mineralocorticoid, and Adrenal Androgen Secretion Dynamics in A Large Cohort of Patients Aged 6–18 Years with Transfusion-dependent β-Thalassemia Major, with an Emphasis on the Impact of Cardiac Iron Load

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Background: The variable presence of adrenal insufficiency (AI) due to hypocortisolemia (HC) in patients with thalassemia is well established; however, the prevalence of adrenocortical hypofunction (ACH) in the zona glomerulosa and zona reticularis of the adrenal cortex is unknown. **Objective and hypotheses:** To establish the prevalence of ACH, we examined the cortisol response to 1 μg- and 250 μg- ACTH tests, plasma aldosterone (A)/plasma renin activity (PRA) ratio, and serum DHEAS levels in a large cohort of patients with thalassemia, and to investigate the impact of total body iron load (TBIL) on adrenocortical function. **Method:** One hundred twenty-one (52 females) patients with β-thalassemia major (β-TM) and 72 healthy peers (38 females) were enrolled. The patients underwent a 250-μg cosyntropin test if their peak cortisol was < 500 nmol/l in a 1-μg cosyntropin test. Magnetic resonance imaging (MRI) was performed to assess the MRI based liver iron content and cardiac MRI T2* iron. The associations between ACH and TBIL were investigated. **Results:** The patients with thalassemia had lower ACTH, cortisol, DHEAS, and A/PRA values compared with the controls ($P < 0.001$). Thirty-nine patients (32.2%) had HC [primary ($n = 1$), central ($n = 36$), combined ($n = 2$)], and 47 (38.8%) patients had reduced DHEAS levels; 29 (24.0%) patients had reduced A/PRA ratios. Forty-six (38.0%) patients had hypofunction in one of the adrenal zones, 26 (21.5%) had hypofunction in two adrenal zones, and 9 (7.4%) had hypofunction in all three zones. Patient age and TBIL surrogates were significant independent parameters associated with ACH. Cardiac MRI T2* iron was the only significant parameter that predicted the severity of ACH at a cut-off of 20.6 ms, with 81% sensitivity and 78% specificity. **Conclusions:** Patients with thalassemia have a high prevalence of AI due to HC and zona glomerulosa and zona

reticularis hypofunction. TBIL surrogates can predict ACH, but cardiac iron was the only surrogate that was adequately sensitive to predict the severity of ACH.

P1-P12

Testicular Adrenal Rest Tumours in 50 Boys, Adolescents and Adult Male with Congenital Adrenal Hyperplasia

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Background: Testicular adrenal rest tumours (TART) are common cause of infertility in males with congenital adrenal hyperplasia (CAH). **Objective and hypotheses:** Aim was to assess TART frequency and their impact on gonadal function in 46 children, adolescents and adult male patients with 21-hydroxylase deficiency (21-OHD) (24 salt wasting (SW), 14 simple vilirilizing, eight nonclassical) and four with 11-hydroxylase deficiency (11-OHD). **Method:** Scrotal ultrasound (SU), FSH, LH, testosterone, androstenedione, 17-hydroxyprogesteone, inhibin-B and bone age were performed in 50, and spermiogram in two patients. **Results:** TARTs were detected in 13 SW 21-OHD and one 11-OHD patients: 1/8 patients aged <7 years (2.3 year-old-boy is the youngest patient with TART reported until now), 1/8 patients aged <12 years, 5/17 patients aged <18 years and 7/17 adult patients. All patients with TART were compound heterozygous or homozygous for severe mutations. Poor hormonal control at the time of examination was detected in 5/14 patients with TART and 4/36 without TART. Poor long-term regulation (marked difference between bone age and chronological age or lower final height compared with target height) was detected in 6/14 patients with TART and 13/36 without TART. None of 14 patients with TART fathered the child. Two married, poorly regulated patients with low inhibin-B and high FSH level had azoospermia. Five other adults reported no cohabitation with females. Additionally, four patients had low inhibin-B level, three with high FSH (two adults and one adolescent) and one adult with suppressed FSH level. Six/36 patients without TART had lower level of inhibin-B but normal FSH level. Seven/36 patients without TART who are living with female partners fathered altogether 12 children. **Conclusion:** Besides optimizing glucocorticoid treatment, we recommend SU TART screening by from early childhood especially in CAH patients with severe forms of disease. If TART is found in adolescent or adult, sperm cryopreservation should be considered.

P1-P13

Establishment of Clinical and Lab Algorithms for the Identification Carriers of Mutations in CYP21A2 – A Study of 768 Children and Adolescents

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Background: Bi-allelic mutations of CYP21A2 encoding 21-hydroxylase are the most frequent cause of congenital adrenal hyperplasia (CAH). Non-classical CAH (NCCAH) or even just hyperandrogenism may be caused by mild or mono-allelic (single) heterozygous mutations of CYP21A2. These mutations are associated either with elevated basal or ACTH-stimulated levels of 17-hydroxyprogesterone (17OHP) in blood. **Objective and hypotheses:** The objective of this study was to identify the most suitable design of 17OHP measurements and determination of 17OHP cut-off levels in order to identify patients with NCCAH. **Method:** Between July 2006 and July 2015 ACTH-tests were conducted in 768 children and adolescents suspected to have NCCAH. Inclusion criteria were premature pubarche with accelerated bone age, hyperandrogenemia, hirsutism, or menstrual irregularities. 17OHP in blood was measured before, 30', and 60' after injection of 250 μg ACTH. The sum (sum17OHP), difference (diff.17OHP) and quotient (ratio17OHP) of 17OHP60, and basal 17OHP levels were monitored. Receiver operating characteristics (ROC) were plotted for the six test algorithms and the area under the curve (AUC) calculated for each. From genomic blood DNA of 371 of the subjects CYP21A2 was analyzed by DNA-sequencing and MLPA. **Results:** Molecular analysis revealed mutations in 88 (23.7%) of the 371 patients. 10 of them carried bi-allelic, i.e. compound heterozygous (6) or homozygous (4) mutations. The most common mutations were p.Val281Leu (30) and p.Gln318Stop (14). Among the six tested algorithms, diff.17OHP was the best, i.e. revealing the highest AUC with respect to identifying patients with single (0.762) or bi-allelic (0.920) mutations. A diff.17OHP cut-off of >3.4 μg/l showed best combined sensitivity and specificity for identification of mutation carriers. **Conclusion:** Not only bi-allelic but also heterozygous mutations of CYP21A2 can be associated with clinical signs. Our results suggest genotyping of CYP21A2 in patients with values exceeding 3.4 μg/l diff.17OHP. Bi-allelic mutations, i.e. CAH or NCCAH are associated with diff.17OHP >10 μg/l.

P1-P14

A Unique Case of Dual Opposing Pathologies

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Background: We present a patient with co-existence of two rare conditions 3β-Hydroxysteroid dehydrogenase type 2 deficiency (HSD3B2) the rarest form of Congenital Adrenal Hyperplasia (CAH) and Bartter's Syndrome (hypokalaemic alkalosis secondary to hyperaldosteronism). **Case Report:** A female infant (46XX) born at 34/40 weeks weighing 2.67 kg to non-consanguineous parents presented on day four of life with significant weight loss. Subsequent investigations revealed hyponatraema (Na:126 mmol/l), hypochloraemia (Cl:87 mmol/l), metabolic alkalosis, elevated levels of 17-hydroxyprogesterone >110 nmol/l (normal <1), ACTH: 553 ng/l (10–50) and renin: 2,206 mU/l (5.4–30). Urine steroid profile suggested HSD3B2 deficiency, confirmed by the identification of a homozygous *HSD3B2* mutation c.745C$>$T, p. Arg249*. Genitalia were normal with no virilisation. She was started on hydrocortisone, fludrocortisone and sodium chloride. Renin levels decreased to <500 mU/l, however, hypochloraemic alkalosis persisted. Hypokalaemia (as low as 2.1 mmol/l) persisted even after withholding fludrocortisone and an underlying renal tubulopathy was suspected. Bartter's type 3 was established by identification of a homozygous *CLCKNB* deletion. The co-existence of two rare recessive conditions due to homozygous mutations raised the possibility of uniparental isodisomy. A SNP microarray analysis confirmed 2 segments of homozygosity on chromosome 1 of maternal ancestry, encompassing both *HSD3B2* and *CLCKNB*. **Conclusions:** Uniparental isodisomy, the presence of two identical copies of a given genomic region inherited from one parent results from an error in meiosis. It predisposes to recessive diseases, as each heterozygous variant of that parent in the genomic region will be present in homozygous state in the child. Thus, identification of a homozygous rare mutation in an offspring of non-consanguineous parents should raise suspicion of this condition, especially if the phenotype is unusual, potentially encompassing more than one disorder. Despite identifying the genetic cause, hypokalaemic alkalosis, the biochemical fingerprint of hyperaldosteronism in a child with CAH (hypoaldosteronism) remains unexplained and challenges our current understanding of mineralocorticoid-mediated effects in the collecting duct.

P1-P15

Individualized Optimization with 17OHP-Saliva Profiles Leads to Changes in Hydrocortisone Dosing Pattern in Children with Congenital Adrenal Hyperplasia

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Background: Treatment of CAH in children is compromised by the pharmacokinetic of available hydrocortisone (HC) preparations resulting in un-physiological early morning rise of ACTH followed by elevated androgens. HC substitution usually follows a fixed dosing scheme (50%–25%–25%) monitored by blood sampling. **Objective and hypotheses:** We describe the individualized optimization of HC treatment by 17-OHP saliva profiles and the effects of the resulting late night dose of HC. **Method:** Retrospective analysis in 20 prepubertal children from birth to 5 years (females $n=11$, males $n=9$). HC was applied 8-hourly with 1st dose at 6–8 h, 2nd dose at 14–16 h and 3rd dose at (22–24 h). Treatment in newborns started using equal dose distribution. Adaptation by timed (prior to medication) saliva profiles started around 6 month of age. Saliva-17OHP outside the target range leads to adaptation of the HC dose before the sampling point. In 16 children (aged 0–4 years, females $n=6$, males $n=10$) blood (ACTH and androgens) was sampled exactly prior to the morning dose. **Results:** Newborns ($n=15$) started with a mean dose of 22.3 mg/m^2 per day and equal dose distribution. Individualized dose adaptation by saliva-17OHP levels between the age of 6 month and 2 years resulted in significantly lowered afternoon and increased late-night doses ($n=20$, HC distribution 44.4%–20%–38.2%). Similar dose-distribution was found at an age of 3–4 years ($n=7$, 38.5%–23.1%–33.3%) and 4–5 years ($n=3$, 38.1%–23.1%–38.5%). In the cohort with timed blood-sampling children with the highest late-night dose of HC had significant lower ACTH and higher cortisol levels in the morning prior to the next HC dose. **Conclusion:** Individualized treatment adaptation by saliva-17OHP-profiles resulted in higher late-night and lower afternoon dose. Adaptation by frequent saliva sampling is able to reduce morning ACTH and androgen levels and thereby able to prevent un-physiologic early morning rise of ACTH and androgens.

P1-P16

Cortisol Response to ACTH Stimulation Test in Non-Classical Congenital Adrenal Hyperplasia

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Background: The adequacy of cortisol response in NCCAH has not been fully elucidated. **Objective and hypotheses:** To evaluate cortisol response to ACTH stimulation test in children and adolescents with NCCAH and possible heterozygosity for CYP21 gene molecular defects. **Method:** Data of ACTH stimulation test from 146 children and adolescents with clinical hyperandogenism were evaluated retrospectively. Cortisol responses to ACTH stimulation among 43 children with NCCAH (mean age 7.6 ± 2.6) (group 1), 18 children with possible heterozygosity for CYP21 gene molecular defects (mean age: 6.8 ± 2.8)

(group 2) and 85 children with normal 60min 17OHP response to ACTH test (mean age 8.2±2,6) (group 3), were compared. NCCAH was detected from a 60 min stimulated 17OHP value >16.6 and <100 ng/ml and was confirmed by genotyping in most of the cases. The possibility of heterozygosity was evaluated from the 17 OHP nomogram in combination with the criterion of the sum of basal and 60 min 17OHP levels >4.9 ng/ml and confirmed by genotyping in a few cases. **Results:** There was no difference in baseline cortisol levels among the three groups: (group 1 vs group 2 vs group 3: 15.8 μg/dl ±9.8 vs 13.88 μg/dl ± 7.5 vs 14.08 μg/dl ±7.6, $P=0.5$). However the NCCAH patients (group 1) had lower cortisol peak response compared to the possible carriers (group 2) and the control group (group 3) (29.48 μg/dl ±12.1 vs 37.48 μg/dl ±7.8 vs 34.98 μg/dl ±6.7 μg/dl respectively, $P=0.001$). Peak cortisol was <18 μg/dl in 6/43 (13.9%) NCCAH patients and in one patient with heterozygosity confirmed by genotyping. All seven patients were on hydrocortisone treatment. **Conclusion:** 14% of patients with NCCAH showed inadequate cortisol response to ACTH stimulation. For children with NCCAH and inadequate cortisol response the discontinuation of treatment on completion of growth deserves consideration.

P1-P17

Altered Stress System Activity in Children with ADHD

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Background: Attention-deficit/hyperactivity disorder (ADHD) is the most prevalent neurodevelopmental disorder worldwide. Evidence suggests dysfunction of the fronto-subcortical pathways and the dopaminergic and noradrenergic systems, as well as dysregulation of the stress system, i.e., the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system (SNS). **Objective and hypotheses:** The aim of the study was to examine i) the diurnal secretion patterns of salivary cortisol and salivary alpha (α)-amylase, as peripheral biomarkers of the HPA axis and the SNS, respectively and ii) the stress response to a physical stressor, the venipuncture, in both ADHD and typically developing children. Our hypothesis is that children with ADHD demonstrate hypo-activity of the stress system. **Method:** Sixty-two prepubertal children (30.2% girls; mean age 8.63±2.27) with a clinical diagnosis of ADHD were compared with 40 typically developing children (35.9% girls; mean age 8.1±1.7). Saliva was collected at six time points over one weekend day as well as before and 10 min after a scheduled morning venipuncture. Chemilluminescence immunoassay and kinetic-reaction assay were used for the determination of cortisol and α-amylase in saliva, respectively. **Results:** Both groups demonstrated the typical circadian cortisol rhythm with highest levels in the morning and lowest in the evening. Significantly lower cortisol concentrations were observed in children with ADHD across the day compared to controls ($P<0.05$). Moreover, children with ADHD had significantly lower CAR and cortisol AUC ($P<0.001$). In both groups, the secretion pattern of α-amylase showed lowest levels in the morning and highest in the afternoon. Venipuncture-induced salivary cortisol concentrations tended to increase in controls, and decrease in ADHD children. The venipuncture-induced increase in salivary α-amylase tended to be more pronounced in controls.

P1-P18

Adult Individuals with Classic Congenital Adrenal Hyperplasia Exhibit Deficits in Executive Functions

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Background: Individuals with classic congenital adrenal hyperplasia (CAH) are treated postnatally with glucocorticoids. Earlier research with animals and other disorders with excess GC exposure implicate that GCs can influence memory. Deficits in working memory can be seen already during childhood in children with classic CAH. **Objective:** We tested the hypothesis that adult individuals with classic CAH show impaired cognitive functions. **Methods:** We evaluated cognitive functions in 100 adult subjects (42 with CAH, mean age 24 years; 58 population controls, mean age 20.5 years). They were assessed with standardized neuropsychological tests: WAIS-IV Matrices (estimation of fluid intelligence), Vocabulary (estimation of verbal intelligence), Digit Span (short term memory/verbal working memory), and Coding. Learning and long-term memory were assessed with the list learning test from WMS-III, and visual-spatial working memory was assessed with the Span Board test. The Stroop test was used to assess Processing speed and Inhibition. **Results:** Individuals with CAH showed impaired verbal working memory ($P=0.01$) and visual-spatial working memory ($P=0.01$) as well as slower speed of processing (all $P<0.05$) compared to population controls. The differences had large effect sizes with Cohen's $d=0.8$–2.5. There were no differences in verbal intelligence, logical reasoning, coding, or learning and long-term memory between CAH and control subjects. **Conclusion:** Having classic CAH seem to be associated with a poorer performance in executive functions. This may be a result of postnatal GC treatment, salt-losing crisis or hypoglycemic episodes. Early detection of deficits is warranted given the importance of working memory for academic performance. Appropriate support should be offered if needed.

P1-P19

Heterozygous Mutations in CYP11A1 Gene can Cause Life-Threatening Salt Wasting and Failure to Thrive

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Background: Cytochrome P450 side-chain cleavage enzyme (CYP11A1 gene) catalyses the conversion of cholesterol to pregnenolone in steroidogenic cells, the first step in the biosynthesis of all steroid hormones. SCC deficiency has been established as an autosomal recessive disorder caused by inactivating homozygous or compound heterozygous mutations in the CYP11A1 gene, with a wide phenotypic spectrum ranging from prematurity, complete underandrogenization and severe early-onset adrenal failure, to term birth with clitoromegaly and later-onset adrenal failure. No patient with P450scc deficiency has been described with the massive adrenal enlargement typical of congenital lipoid adrenal hyperplasia. **Objective and hypotheses:** A 3-month-old boy (46, XY) was admitted with extreme failure to thrive (3.2 kg – born 40 weeks 2.98 kg), hyponatremia, hyperkalemia, hypocortisolemia <3 mcg/dl with inappropriately elevated ACTH >50 pg/ml and undetectable adrenal androgens (DHEA-S), whereas male mini-puberty was normally expressed. Ultrasound showed normal adrenals. Five years later one of his twin sisters presented adrenal crisis with hyponatremia–hyperkalemia inside the neonatal ICU shortly after birth. **Method:** Direct sequencing of the entire coding region and all the intron–exon boundaries of the CYP11A1 gene was performed. **Results:** A novel heterozygous CYP11A1 c.235G$>$A missense variant was identified in exon 1 leading to the substitution of a valine by an isoleucine on amino acid position 79 to the patient, to one of his sisters and his father who suffered from failure to thrive during the first year of life and survived, according to his mother, grace to intensive feeding. Ffludrocortisone 100 μg twice daily immediately restored electrolytes and resolved failure to thrive. The boy needed proper hydrocortisone replacement for 4 years, but his sister on a need-only basis. Fludrocortisone was gradually diminished and discontinued at 5.5 years. The next year however despite low normal sodium (136 mmol/l) and high normal potassium levels (5.1 mmol/l), height velocity dropped from 6.5 to 3.5 cm/yr with an elevated renin which reached a plateau at a compensating drop from 837 to 224 ng/ml, similar to what is observed in primary hypoaldosteronism. **Conclusion:** A novel heterozygous mutation in CYP11A1 gene can cause early onset adrenal insufficiency with life-threatening failure to thrive.

P1-P20

HIV Drugs as a Possible Cause for Transient 21-Hydroxylase Deficiency in a Preterm Infant

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Background: Transient neonatal adrenal dysfunction is reported in association with antiretroviral therapy with Lopinavir and Ritonavir. Other drugs have not been tested. **Objective and hypotheses:** We report on a preterm girl, born 26 weeks gestation, with elevated 17-hydroxyprogesterone (17OHP) at newborn screening. During pregnancy the mother was treated for HIV with Atripla (Efavirenz, Tenofovir, Emtricitabin) and viral load was suppressed. Furthermore the baby was started on prophylactic antiretroviral therapy with Zidovudin on the first day of life to prevent vertical transmission of HIV. We hypothesised that the elevated 17OHP might be due to HIV treatment. **Method:** Case report and steroid profiling. **Results:** At birth the girl did not show signs of congenital adrenal hyperplasia such as genital virilisation or electrolyte disturbances, but did receive hydrocortisone for arterial hypotension. 17OHP was in the normal range for gestational age on d1, increased to 292 nmol (<141 nmol/l) on d15 and was at 132 nmol/l (<104 nmol/l) on d20, with normal ACTH (8.3 ng/l; 7.2–63.3) and cortisol (396 nmol/l; 171–536 nmol/l). The urinary steroid profile showed elevated progesterone and androgen metabolites with low-normal cortisol metabolites suggesting diminished 21-hydroxylase activity. In our patient 17OHP normalized within 4 weeks and after termination of antiretroviral therapy indicating that the abnormal 17OHP and thus the underlying relative 21-hydroxylase deficiency may have been caused by the antiretroviral drugs. The urine steroid profile of the mother under Atripla® treatment was normal. **Conclusion:** HIV drugs may affect steroid hormone biosynthesis in newborns and, therefore, lead to abnormal neonatal screening tests. Further evaluation of the effect of HIV drugs on adrenal steroid hormones are needed to investigate which compounds may cause a relevant (transient) adrenal dysfunction that may even require supplementation of glucocorticoids, especially in sick days. We are currently testing the drug in cell culture experiments to test their impact on steroidogenesis.

P1-P21

Increased Salivary and Hair Cortisol and Decreased Salivary Alpha-Amylase Concentrations in Obese Prepubertal Girls

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Background: Obesity has been associated with perturbations of the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system (SNS). Scalp hair cortisol has been recognized as a reliable index of long-term cortisol concentrations. **Objective and hypotheses:** Aim of this study was to compare indices of HPA axis and SNS activities, such as, respectively, the salivary cortisol and alpha-amylase diurnal patterns, and their relations in obese and normal weight prepubertal girls. Furthermore, we compared cortisol concentrations in scalp hair between groups and investigated whether they are correlated with salivary cortisol concentrations. **Method:** Five saliva samples were collected serially over a weekend day (at 9:00, 12:00, 15:00, 18:00, 21:00 hours) from 26 obese (mean age 7.4 ± 1.3 years, BMI 24.6 ± 3.3 kg/m^2) and 24 normal weight prepubertal girls (mean age 7.8 ± 1.1 years, BMI 16.9 ± 1.6 kg/m^2). Cortisol and alpha-amylase concentrations were measured and areas under the curve (AUCs) were calculated. We investigated cortisol and alpha-amylase linear correlations in each group. Hair samples from the posterior vertex of the scalp were collected and analysed for cortisol. **Results:** Positive linear correlations between hair cortisol and both BMI *z*-score and salivary cortisol AUC were found ($P < 0.05$). In obese girls, significantly higher salivary and hair cortisol concentrations were observed compared to normal weight girls ($P < 0.05$). Inversely, salivary alpha-amylase AUC was significantly lower in the same group ($P < 0.05$) and a negative linear correlation between cortisol and alpha-amylase was observed ($P < 0.05$). **Conclusion:** Obese prepubertal girls demonstrated changes in both salivary cortisol and alpha-amylase diurnal secretions compared to normal weight controls, suggesting altered stress system function in the obese group. Increased hair cortisol concentrations and positive correlations with salivary measurements suggest chronic stress-related activation of the HPA axis in obese girls. Hair cortisol appears to be a sensitive measure of hypercortisolism in obesity.

P1-P22

An Assessment of the Hypothalamic–Pituitary–Adrenal Axis in Children with Prader–Willi Syndrome

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Background: In children with Prader–Willi Syndrome (PWS), hypothalamic dysfunction plays a key role in the development of aberrant energy regulation, sleep-related breathing disorders, hypogonadism and impaired linear growth. Dysfunction of the hypothalamic–pituitary–adrenal (HPA) axis may contribute to the high incidence of sudden death. The prevalence and the extent of the dysfunction of HPA axis remain unclear. **Method:** Thirty-one (10M/21F) children with PWS, with a median age of 3.03 years (0.6,15.6), underwent insulin tolerance test (11/31, median age 6.96 years (4.08,15.6)) or glucagon stimulation test (20/31, median age 2.26 years (0.6,3.8)) as part of their assessment before commencing growth hormone (GH) treatment. Cortisol and GH were measured at 0, 15, 30, 45, 60, 90 and 120 min in relation to insulin/glucagon administration. Either cortisol peak of ≥ 550 nmol/l or cortisol increase of ≥ 250 nmol/l from baseline were considered as adequate cortisol responses. GH peak of ≥ 6.7 μg/l was considered an adequate GH response. **Results:** Median baseline cortisol was 308 nmol/l (22, 646). Median peak cortisol was 733 nmol/l (389,1297) and was negatively correlated with age(r, −0.52, *P*, 0.003). Median cortisol increase from baseline was 401 nmol/l (142, 1028) and was negatively correlated with age(r, −0.51, *P*, 0.003). Of the 31 children, 29 (94%) had adequate cortisol response. The 2 (6%) children with inadequate cortisol response had baseline cortisol of 208and 368 nmol/l and peak cortisol of 389 and 463 nmol/l, respectively. Six (19%) children had peak cortisol ≤ 550 nmol/l. These children were older (median age 5.5 years (2.1,15.6) vs 2.8 years (0.6,9.9), (*P*, 0.044)) and had lower baseline cortisol (median 229 nmol/l (22,308) vs 337 nmol/l(133,646), (*P*, 0.013)) than those (25/31, 81%) with peak cortisol ≥ 550 nmol/l. Median peak cortisol in the 9/31 (29%) children with adequate and in the 22/31 (71%) children with inadequate GH response was 922 nmol/l (659,1297), and 650 nmol/l (389,1173) respectively (*P*, 0.008). **Conclusion:** The majority of children with PWS showed a normal function of HPA axis. However, the lower peak cortisol levels in those with GH deficiency may reflect a more generalised hypothalamic dysfunction. Although cortisol secretion decreases continuously with age, age-specific peak cortisol thresholds are required.

P1-P23

The Urinary Steroidome of Children with Classic 21-Hydroxylase Deficiency Treated with Hydrocortisone

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Background: Monitoring treatment of children with classic congenital adrenal hyperplasia (CAH) is difficult and biochemical targets are not well defined. **Objective and hypotheses:** To analyse the urinary steroid metabolome of children with classic 21-hydroxylase deficiency (21-OHD) during treatment with hydrocortisone and fludrocortisone. **Method:** We retrospectively analysed 553 daily urinary steroid hormone metabolite profiles determined by gas chromatography-mass spectrometry of 153 children aged 3.0–18.8 years with classic CAH on hydrocortisone and fludrocortisone treatment. Data of 24-h urinary steroid hormone metabolite analysis were included only once a year for every patient to avoid overrepresentation of single patients. **Results:** Percentiles of the daily urinary excretion of glucocorticoid-, 17α-hydroxyprogesterone (17-OHP)-, and androgen

metabolites were calculated for age groups in 2 year intervals for children with classic CAH aged 3–18 years. The urinary excretion of the sum of the seven major cortisol metabolites ranged in median from 6000 μg/m^2 per day in toddlers to 9000 μg/m^2 per day in adolescence and reflected 60.5±23.7% of the prescribed daily oral hydrocortisone dosage without influence of age or gender. Boys aged 13 and 14 years and girls aged 15 and 16 years showed a relatively unsuppressed adrenal when compared to their surrounding age groups, as they show a relatively high 17-OHP and androgen metabolite excretion. However, neither the prescribed daily hydrocortisone dosage nor the absolute excretions of cortisol metabolites were lower in these age groups. 11β-hydroxyandrosterone was the dominant urinary adrenal-derived androgen metabolite in CAH children, whereas urinary metabolites of DHEA were disproportionally suppressed by hydrocortisone treatment. **Conclusion:** Values of urinary metabolite excretion rates of children with CAH are now available, allowing the clinician to adequately classify the individual patient regarding the androgen-, 17-OHP-, and glucocorticoid status in the context of the underlying disorder. Additionally, urinary 21-OHD-specific reference ranges could be important for research studies in children with CAH.

P1-P24

Adrenal Insufficiency in ROHHADNET Syndrome (Rapid-Onset Obesity with Hypothalamic Dysfunction, Hypoventilation, Autonomic Dysregulation and Neural Tumor)

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Background: Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, autonomic dysregulation and Neural tumor (ROHHADNET) is a rare condition. The first symptom is the appearance of rapid onset obesity (2–4 years) followed by central hypoventilation, hypothalamic dysfunction, dysautonomic symptoms and neural tumors. **Objective and hypotheses:** Aim of this study was to evaluate adrenal function in ROHHADNET patients from a single-center. **Patients and methods:** Six patients with ROHHADNET underwent clinical (BMI SDS) and biochemical evaluation for baseline cortisol and for Insulin Tolerance Test (ITT) at the mean age of 10.1±5.9 (range 4.7–19.9 years); four were also tested with low-dose ACTH test (Synachten 1 mcg/m^2) after an interval of 0–4 years. All subjects had a morning baseline cortisol evaluation at the time of ROHHADNET diagnosis. Pituitary defects were present ($n=4$) in one patient, ($n=3$) in one, ($n=2$) in two and ($n=1$) in two patients While hyperprolactinemia was documented in all of them; five had neural crest tumor. **Results:** BMI SDS was of 3.4±1.2 at the time of ITT and 3.7±1.4 at the time of ACTH test. None of the patients displayed hypercortisolism. Baseline cortisol pre-ITT was 8.5±5.3 mcg/dl with a peak cortisol of 14.2±8.1 mcg/dl. Baseline cortisol pre-ACTH test in those whot underwent ACTH test was 4.4±4.4 mcg/dl with a peak cortisol of 11.1±8.8 mcg/dl. Five patients received the diagnosis of Central adrenal Insufficiency (CAI). Baseline cortisol was not related to BMI SDS at any time point and it was variably associated with age (r's 0.02–0.94); correlations between baseline cortisol levels at three different time points were variable (*r*'s from 0.1 to 0.87). The association between baseline cortisol and peak response was strong after ACTH ($r=0.95$, P 0.07), and moderate after ITT ($r=0.7$, P 0.13). The relation between peak cortisol responses after the two tests was significant ($r=0.97$, P 0.04). Both baseline cortisol and peak cortisol after ITT negatively correlated with the number of pituitary hormone defects (r's $=-0.68$ to -0.93). **Conclusion:** Central Adrenal Insufficiency was documented in 83% of ROHHADNET patients after dynamic testing with ITT or ACTH-low testing. Baseline cortisol value is not reliable for the diagnosis of CAI. While the severity of hypothalamic dysfunction appears to be correlated with CAI, age and BMI SDS are not associated.

P1-P25

The Psychosocial Impact of Adrenal Insufficiency and Congenital Adrenal Hyperplasia on Children and their Parents

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Background: Those affected by adrenal insufficiency (AI) (including congenital adrenal hyperplasia (CAH)) are at risk of serious illness and growth problems, and as a result they require life-long daily hormone replacement therapy. Little is known about the psychosocial impact that living with and treating AI on a daily basis can have on both children and their parents. **Objective and hypotheses:** The aim of the study was to explore the psychosocial impact of AI from the perspective of parents, across three European countries. The study was conducted by Genetic Alliance UK as part of the European Commission funded Treatment of Adrenal Insufficiency in Neonates (TAIN) Project. **Method:** The study used mixed methods. In 2014, 17 semi-structured interviews with parents in the UK were conducted and analysed thematically using Computer Assisted Qualitative Data Analysis Software, NVivo 8. In 2015, an online survey was developed, piloted and disseminated (predominantly through support groups) to parents of children under the age of 6 in the UK, the Netherlands and Germany. Fifty-four responses were received and the data has been analysed with the support of SPSS. **Results:** The interviews and survey gathered parents' views in relation to a number of key themes including the diagnosis period; the impact of the condition on children and parents; support and awareness; treatment and use of healthcare resources. The findings flagged up a number of challenges associated with both the rarity of the condition and the treatment regime. The perceived

psychosocial impact on young patients was low, although parents reported several concerns regarding their children's future. **Conclusion:** The study has provided a rare insight into the wider impact of living with and managing AI and CAH, particularly from the perspective of parents. It has important implications for future research, and how families are cared for and supported in the future.

P1-P26

Sex-Specific Differences in Hypothalamus-Pituitary-Adrenal Axis Activity in Newborns with Very Low Birth Weight

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Background: Male preterm infants are at increased risk of neonatal mortality when compared to their female counterparts. The mechanisms explaining this male disadvantage are not fully elucidated yet. **Objective and hypotheses:** To compare glucocorticoid metabolite excretion in urine obtained at day 10 between male and female infants born with a very low birth weight (VLBW; i.e. <1500 g). We hypothesized that male preterm infants have impaired adrenocortical function. **Method:** Over a 4-h period, urine was collected of 40 infants (20 boys), who were born at a gestational age of 27.5 ± 1.6 weeks with a birth weight of 1022 ± 257 g. Glucocorticoid metabolites were measured using gas chromatography-mass spectrometry. Main outcome measures were: i) sum of all glucocorticoid metabolites, as an index of cortisol production rate (CPR), (ii) cortisol excretion, and iii) ratio of 11-OH/11-OXO metabolites, as an estimate of 11β-hydroxysteroid dehydrogenase (11β-HSD) activity. Differences between males and females, including interaction with Score of Neonatal Acute Physiology Perinatal Extension-II (SNAPPE II) and sepsis, were assessed by linear regression analysis. Analyses were corrected for gestational age (GA). **Results:** Boys and girls did not differ in perinatal characteristics, including GA, birth weight, illnesses and nutrition. No differences between sexes were found for CPR, cortisol or 11β-HSD activity. However, interaction between sex and SNAPPE II on 11β-HSD activity was observed ($P=0.02$), with the interconversion favouring cortisone in males with lower SNAPPE II. Furthermore, there was a tendency towards a lower CPR and cortisol excretion in males with sepsis (interaction $P=0.09$ and 0.07, respectively). **Conclusion:** This study provides some evidence for sex-specific differences in adrenocortical function in infants with VLBW. These patterns might contribute to sex-specific differences in neonatal mortality. Future research is necessary to explore sex-specific characteristics in steroid metabolism and its influencing factors in infants with VLBW.

P1-P27

Beckwith-Wiedemann Syndrome and Bilateral Phaeochromocytoma: A Diagnostic Challenge

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Background: Beckwith-Wiedemann Syndrome (BWS) is a rare overgrowth disorder secondary to various mutations in growth-regulatory genes on chromosome 11p15.5. A well-established association exists between BWS and both benign and malignant tumours, most commonly Wilms' tumour and hepatoblastoma. We present a less frequently described diagnosis of bilateral phaeochromocytoma in association with BWS. **Case report:** We report the case of a 14-year-old girl with genetically confirmed BWS. Previous routine screening detected a bladder rhabdomyoma and pancreatoblastoma (aged 2- and 7-years respectively), both surgically resected. Aged 14 years she developed headaches, sweating, palpitations and hypertension (systolic BP >180). Both urine and plasma normetadrenaline were elevated (22.3 μmol/24 h (NR 0.6–3.5) and 9514 pmol/l (NR 120–1180), respectively). MRI demonstrated bilateral complex adrenal cysts $\leq$ 2 cm, however iodine-123-meta-iodobenzylguanidine (MIBG)-scan showed no abnormal sites of activity. Due to strong clinical suspicion of phaeochromocytoma a fat-suppressed fludeoxyglucose (FDG)-PET scan was undertaken, with abnormal uptake seen within both adrenal glands, suggesting bilateral phaeochromocytoma and a lesion in the left shoulder, felt most likely an incidental avascular necrosis, but no other suspicious areas were noted. Further pre-operative investigations (ECG and echo) detected a cardiac mass, felt unlikely to be contributing to her hypertension, and biopsy undertaken following adrenalectomy was consistent with hamartoma. After stabilisation with alpha-blockers and intravenous fluids, the patient underwent bilateral adrenalectomies, following extensive MDT involvement. Histological analysis confirmed phaeochromocytomas and no other genetic mutations more commonly associated with phaeochromocytoma (MEN, SDH-A/B/C/D, NF-1) were discovered. Despite successful surgery, post-operatively she remains hypertensive and repeat plasma normetanephrines are persistently elevated (4152 pmol/l). Results of a Gallium-68 DOTANOC PET-CT scan are awaited. Further investigations of the cardiac and shoulder lesions are also planned (although felt unlikely a source of continued catecholamine over-secretion). **Conclusion/learning point:** BWS is well-recognised genetic condition commonly associated with certain embryological tumours. Phaeochromocytomas are rare adrenal tumours, less commonly described in BWS. This case demonstrates the importance of on-going vigilance for the development of any tumours in BWS and the importance of undertaking further imaging following negative MIBG scans if the clinical picture is highly suggestive of phaeochromocytoma.

P1-P28

Combined Glucocorticoid and Mineralocorticoid Deficiency Related to a New NNT Mutation: A Case Report

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Background: Familial glucocorticoid deficiency (FGD) is an autosomal recessive disorder characterized by specific failure of adrenocortical glucocorticoid production in response to adrenocorticotropic hormone (ACTH). Mutations of the nicotinamide nucleotide transhydrogenase (NNT) gene have recently been implicated in FGD. **Objective and hypotheses:** To describe a new case of FGD with combined mineralocorticoid insufficiency and extra adrenal manifestations. **Method:** Case report. **Results:** Suffering from a febrile viral respiratory disease, an eight-month-old boy presented with status epilepticus caused by hypoglycemia. Multiple medical complications occurred, and invasive ventilation was required for 18 days. The results of blood tests performed during hypoglycemia revealed adrenal insufficiency (cortisol $<$ 20 nmol/l, ACTH 1382 ng/l). Renin and aldosterone levels were high but considered consistent with the mild hyponatremia (135 mmol/l) and severe hypotension. Subsequent measurements revealed persistent high renin levels (278 ng/l) with low aldosterone concentration (179 pmol/l). Hyponatremia persisted despite high-dose sodium supplementation, confirming the diagnosis of partial mineralocorticoid deficiency. The patient required hydrocortisone, fludrocortisone and sodium supplementation. ACTH levels remained high after 6 months of suitable treatment ($>$2000 ng/l). His parents are consanguineous and his father has a glucocorticoid deficiency since he was 18 months old, without mineralocorticoid deficiency during childhood. Genetic analysis revealed a new homozygous NNT mutation (p.Arg129*) for the child and his father. Investigations to work up any associated disorders revealed thyroid stimulating hormone deficiency, a bradycardic sinus rhythm without cardiopathy. After 6 months, he presented neurological sequelae including severe hypotonia. **Conclusion:** This case illustrates combined glucocorticoid and mineralocorticoid deficiency related to a new NNT mutation and underlines intra-familial phenotype heterogeneity. NNT gene should be considered when the most common etiologies of adrenal deficiency have been eliminated even if there is mineralocorticoid deficiency, in order to limit the serious consequences by a delayed diagnosis especially in offspring and to investigate any associated disorders.

P1-P29

Testicular Adrenal Rest Tumours in Patient with X-Linked Adrenoleukodystrophy

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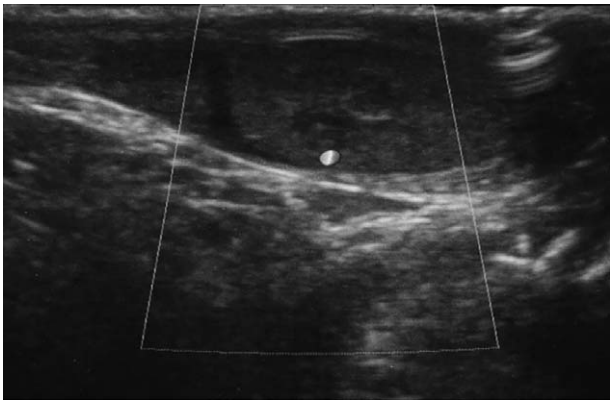
Background: Testicular adrenal rest tumours (TARTs) are benign tumors consisting of cells with adrenal-like features in mediastinum of testes. TARTs occur in up to 94% of adult male patients with classic 21-hydroxylase deficiency and also have been described in patients with Cushing syndrome and acquired adrenal insufficiency. Poor disease control is thought to be one of the main predictive factors for TARTs development. **Clinical case:** A boy presented at the age of 3 years with hyperpigmentation, weakness. Primary adrenal insufficiency was proved by low cortisol (9 nmol/l), high ACTH (1250 pg/ml), high renin (500 mU/l). Elevated plasma concentrations of very long chain fatty acids (VLCFA) (C24 96.2 μmol/l, range 22.6–80.0; C26 2.8 μmol/l, range 0.22–2.2; C24/C22 1.5, range 0.64–0.88) were revealed. Novel mutation c.1550N$>$C in ABCD1 gene was found. He was diagnosed with X-ALD. Neurological symptoms were absent, MRI of the brain was normal. The boy was on a replacement therapy with gluco- and mineralocorticoids since the age of 3 with good effect but ACTH level remained very high (1500–3000 pg/ml) during 3-year follow-up. Bilateral hypoechoic lesions, located close to the mediastinum of the testes with normal bloodstream on the colour Doppler evaluation, were found on scrotum ultrasound at the age of 6. Six months after the increasing the dose of hydrocortisone, TARTs volume decreased. **Conclusion:** To the best of our knowledge, this is the first report of TARTs development in patient with X-linked adrenoleukodystrophy. Ectopic adrenal cells in prepubertal testes may avoid damage by VLCFA and when stimulated by high ACTH form TARTs.



P1-P30

Reference Intervals for the Steroid Hormones of 6 to 14 year Old Normal Male Children with LC-MS Method

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Objective and hypotheses: The purpose of this research is to establish reference intervals for the steroid hormones of 6 to14 year-old normal male children using LC-MS method; study the variation pattern of steroid hormones in terms of different ages and Tanner stages of puberty. **Method:** A total of 1175 male

children from 6 to 14 years old from Shunyi District, Beijing, have participated in this research, with 820 children determined as normal-weight. Pregnenolone, 17α hydroxyprogesterone, corticosterone, dehydroepiandrosterone (DHEA), and androstenedione were measured by Liquid Chromatography-Mass Spectrometry method (noted as LC-MS method). Free testosterone was measured by chemiluminescence immunoassay method (CLIA). **Results:** The levels of pregnenolone and 17α-hydroxyprogesterone of normal male children did not exhibit significant variance at the adrenarche ages, from approximately 6–8 years old (before puberty initiation) to 9 years old. After 10–11 years old, the levels of pregnenolone and17á-hydroxyprogesterone increase with the age. The level ofcorticosterone did not change significantly with age. The levels of DHEA, androstendione, and free testosterone increased with age from the age of 6. Pregnenolone displayed a significant increase from Tanner stage I to stage II and steadied from Tanner stage III to stage V. 17α-hydroxyprogesterone rose evidently with the progression of puberty from Tanner stage I to stage III, and slowed down from Tanner stage IV to stage V. The corticosterone did not change with the progression of puberty. DHEA and androstendione exhibited significant increase from Tanner stage I to stage II, with no evident intersection and increased at a lower rate after Tanner stage III. Free testosterone level rose sharply during puberty from Tanner stage I to stage III without evident intersection and rose slowly at phase IV and V. **Conclusion:** The production of mineralocorticoid and its precursors in zona glomerulosa of the male children show no correlation with ages or the progression of puberty between 6 and 14 years old; the production of glucocorticoids and its precursors in zona fasciculate are correlated with the sexual maturation; the level of androgen are correlated with age and the sexual maturation.

P1-P31

Growth of Children with Congenital Adrenal Hyperplasia (CAH) During the First 2 years of Life – Data from the Duth Longitudinal Registry

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Background: A national database has been developed to register longitudinal data from all CAH children detected through neonatal screening from 2002 onwards. So far, data from 105 children have been registered (65% of Dutch CAH patients) to evaluate treatment and long-term effects in CAH. **Aims:** To evaluate height and weight in relation to medication used in the first 2 years of life. **Methods:** Biometric data and medication dosage were available for 68 children at 0, 6, 12 and 24 months. Mixed model analyses with manual backward selection were performed for height, expressed as height standard deviation score (SDS) corrected for target height SDS (HSDS-THSDS), and for SDS weight-for-height. **Results:** For HSDS-THSDS, a decrease of −0.019 SDS/month (95%CI −0.031 – −0.006; *P* 0.004) was identified, which amounts to −0.456 SDS at 2 years of age. HSDS-THSDS growth velocity was positively associated with hydrocortisone (HC) and fludrocortisone (FC) dosage at $t=2$ years only. SDS weight-for-height showed a decline of −0.027/month (95%CI −0.046 – −0.009; *P* 0.04) with HC and FC dosages in the first 6 months being negatively associated with the outcome (HC −0.176 SDS/month (95%CI −0.361 – 0.009; *P* 0.062) and FC −0.011 SDS/month (95%CI −0.017 – −0.004; *P* 0.002)). At $t=2$ years, FC was positively associated with SDS weight-for-height. Birth weight and parental height seemed to have positive and negative effects on growth, respectively. **Conclusions:** These preliminary results showed decreasing HSDS-THSDS and SDS weight-for-height values in the first 2 years of life among CAH children. The positive associations with HC and FC dosages at $t=2$ years probably reflect higher dosages due to growth, rather than a realistic positive effect on growth, whereas medication seemed to have a negative effect on SDS weight-for-height in the first 6 months. More detailed exploration of the data may reveal how dosage regimen effects growth.

P1-P32

Molecular Confirmatory Test Improves the Accuracy of Congenital Adrenal Hyperplasia Diagnosis in Newborn Screening Program

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Background: Newborn screening for CAH is effective in identifying the severe cases; however, the high rate of false-positive (FPR) results remains an important issue. Therefore, positive neonatal results must be confirmed by serum 17OHP levels, which present a great overlap among all forms. **Objective and hypotheses:** To evaluate the utility of molecular analysis to improve CAH diagnosis in NBS program. **Method:** Between 1999 and 2014, 86 newborns (NB) were submitted to DNA analysis due to positive tests for CAH in NBS program of Goias State – Brazil. Neonatal 17OHP levels were measured by IFMA assay and adjusted for birth-weight. Confirmatory tests included serum 17OHP, androstenedione, testosterone measurements. *CYP21A2*

genotypes were determined by allele-specific PCR and large gene rearrangements by MLPA technique; entire *CYP21A2* sequencing was performed when at least one allele remained with no mutation identified. **Results:** 46 NBs presented symptoms of CAH, 42 of them had genotypes predicting severe classical forms. The other four were a girl with NC genotype and three NBs with normal genotype, one premature girl with pseudo-virilized genitalia and two males with loss of weight and vomiting due to other neonatal disease. Forty patients were asymptomatic, among them seven males were identified with the classical form genotype. Thirty-three non-affected patients were prevented to receive unnecessary treatment and among them, the 16 with normal genotype, were discharged from follow-up. A great overlap of 17OHP levels among all genotypes was observed. Among affected newborns, mutations derived from pseudogene events were found in 88% of the alleles: 13% carried large gene rearrangements and 87% point mutations. Novel mutations, not derived from pseudogene, were found in 12% of the alleles, all presented with gene founder effect. **Conclusion:** We demonstrated that molecular testing was a useful supplemental tool identifying false-positive results in CAH-NBS, preventing unnecessary follow-up of newborns with inconclusive hormonal tests.

P1-P33

Usefulness of Corticotropin Test in Children and Adolescents with Clinical Hyperandrogenism

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Background: The usefulness of corticotrophin (ACTH) test in diagnosis of 21-hydroxylase deficiency and/or other enzymic defects in children and adolescents with serum levels of 17-OHP (before 2000 h) >2 ng/ml is known. **Objective and hypotheses:** To evaluate the usefulness of ACTH test in diagnosis of non-classical congenital adrenal hyperplasia (NCCAH) and heterozygosity of CYP21 gene molecular defects in children and adolescents with clinical hyperandrogenism and basal 17-OHP <2 ng/ml. **Method:** Data of ACTH test from 70 boys and 294 girls aged 0.2–19.5 years with basal levels of 17-OHP higher than the upper normal range for their age, but <2 ng/ml, were retrospectively analyzed. They were 332 children (mean age: 7.6 ± 2.1 years) with clinical signs of androgen excess (clitoromegalia, hyperpigmentation of external genitalia, advanced bone age, early growth of pubic or axillary hair, increased axillary body odor, acne, before the age of 8 years) and 32 adolescents (mean age: 14.7 ± 1.8 years) with hirsutism, intense acne and/or abnormal menses. The possibility of heterozygosity was evaluated from the 17 OHP nomogram in combination with the criterion of the sum of basal and 60 min 17OHP values >4.9 ng/ml. **Results:** Seven cases (1.92%) with NCCAH (60 min 17 OHP levels >16.8 ng/ml, confirmed by genotyping), one of them in adolescence, and 110 (30.2%) of possible heterozygozity, nine of them in adolescence, were detected. The rest of them had normal response. Basal 17OP values differed significantly among NCAH, heterozygotes and normal children (1.93 ng/ml (0.4) vs 1.28 ng/ml (0.4) vs 0.93 ng/ml (0.3), $P=0.000$). Stimulated 17OHP levels were higher in possible heterozygotes than in normal subjects (5.7 ng/ml (2.5) vs 2.5 ng/ml (0.7) $P=0.000$). **Conclusion:** It is confirmed that in a small number of subjects with NCCAH, basal 17OHP levels can be <2 ng/ml. The clinical significance of heterozygosity detection is not clear, however its value in genetic counseling is obvious.

P1-P34

Primary Adrenal Insufficiency in Children: Results from a Large Nationwide Cohort

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Background: Primary adrenal insufficiency (PAI) is a rare life-threatening disorder. Data on PAI in children are scanty, with the exception of Congenital Adrenal Hyperplasia (CAH) due to 21-hydroxylase deficiency (21OHD). **Objective and hypotheses:** Evaluate etiology of PAI in a large cohort of children and characterize clinical presentation in subjects with PAI not due to 21-OHD. **Method:** Children followed in eight tertiary centers were retrospectively included. **Results:** Eight-hundred thirteen children were included; 83.9% patients ($n=682$) had 21-OHD CAH and were not reviewed further. Different etiologies were found in 16.1% subjects ($n=131$): 37.4% had autoimmune PAI (42.8% isolated; 57.2% polyendocrine syndromes); 25.9% had steroid biosynthetic defects (DAX1 $n=12$; 17α-hydroxylase $n=1$; familial glucocorticoid deficiency $n=6$; 11β-hydroxylase $n=5$; 3-3β-hydroxysteroid dehydrogenase $n=8$; glycerol kinase deficiency $n=2$); 19% had adrenoleukodystrophy; 6.1% had rare

syndromes (Triple A, Pearson); two patients had infections and hemorrhage and in 13 no defined etiology was found. Mean age at diagnosis was 6.8 ± 5.5 years; common signs/symptoms were fatigue (70%), hyperpigmentation (44%), dehydration (31.3%), neurologic signs (29%) and hypotension (28.2%); most common biochemical finding was increased ACTH (86.2%), followed by hypocortisolism (64.1%) and hyponatremia (47.3%) whereas hyperkalemia and hypoglycemia were found in 27.4 and 25.9% of subjects, respectively. Time between onset and diagnosis ranged from 0 to 56 months. Overall mortality was $<1\%$ and severe adrenal crisis during a mean follow-up of 10 years were rare. **Conclusion:** This large nationwide study document that the most common cause of PAI in childhood is 21-OHD CAH followed by autoimmunity, steroid biosynthetic defects and adrenoleukodystrophy. In non 21-OHD CAH subjects, symptoms at diagnosis are not specific, with the exception of hyperpigmentation; increased ACTH associated to hypocortisolism and hyponatremia are common, while hyperkalemia and hypoglycemia are less frequent. Health outcome in our cohort is favorable with low mortality and incidence of adrenal crisis during follow-up.

P1-P35

Follow-up of Growth and Puberty in Girls and Boys with Premature Adrenarche

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Background: Premature adrenarche (PA) has been linked with early pubertal development, but only few longitudinal studies on PA girls and boys born appropriate for gestational age (AGA) have been reported. **Objective:** Our objective was to study growth and pubertal development in PA children, and to explore which factors in prepuberty predict early menarche in girls. **Methods:** PA ($n=43$, 36 girls) and control children ($n=63$, 52 girls) had been examined at the mean age of 7.6 years. Their parental pubertal timing, growth, pubertal signs, serum DHEAS, androstenedione, IGF-1, and insulin concentrations had been recorded. The current visit at the mean age of 12.1 years (95% CI 12.0–12.2) included pubertal and anthropometric assessment. Factors predicting early menarche were analysed with a logistic regression analysis. **Results:** The PA girls but not the boys were taller and heavier than the controls (160.1 vs. 153.3 cm, $P<0.001$; 154.9 vs. 153.8 cm, NS; BMI 21.6 vs. 19.2 kg/m^2, $P<0.01$; 23.5 vs. 21.7 kg/m^2, NS; respectively). The same percentage of the PA and control boys were at Tanner genital stage ≥ 2 (43 vs. 46%, NS). A higher proportion of the PA than control girls had reached menarche (64 vs. 26%, $P<0.001$). In a univariate logistic regression model, having a history of PA, earlier maternal menarche, higher childhood BMI, serum DHEAS, androstenedione, IGF-1, and insulin concentrations, were all associated with the appearance of early menarche. However, in a multivariate stepwise forward model, only the history of PA, earlier maternal menarche, and higher IGF-1 were significantly associated with early menarche. **Conclusions:** AGA-born PA girls have advanced pubertal development and linear growth, and they are slightly heavier than control girls still at 12 years of age. In boys, larger cohorts need to be evaluated. Prepubertal IGF-1 and the history of PA are strong predictors of earlier timing of menarche.

P1-P36

Early Onset Hypertension with Primary Hyperaldosteronism through Mutation in the Calcium Channel CACNA1H – Case Report

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Background: The genetic causes of primary hyperaldosteronism are still being discovered. **Results:** We present the case of a 17-years-old girl who was found by accident with severe hypertension (TA 180/100 mmHg, bilateral). Her personal history was unremarkable. Her father had hypertension and a paternal aunt had died at 55 due to a stroke. Both her sisters and mother had normal blood pressure. The cardiological examinationshowed concentric left ventricle hypertrophy (posterior wall 11 mm; interventricular septum 13 mm) with diastolic dysfunction of delayed relaxation. The renal and vascular ultrasound was normal. The biochemical panel, including ionogram and renal function was normal. The clinical exam showed a slightly overweight girl with normal pubertal development and no signs of virilising or glucocorticoid excess. An abdominal CT was normal. The hormonal panel showed normal thyroid function; low normal ACTH (11.17, normal range 3–66 pg/ml); high normal cortisol (17.35, normal range 6.2–19 μg/dl); normal urinary and plasmatic metanefrines and normetanefrines and normal cromogranin A. The plasmatic renin was very low (<0.3; normal range 4.4–46.1 μUI/ml), with high normal aldosterone (341 pg/ml, normal range standing 25.2–392 pg/ml) and an increased aldosterone/renin ratio (1136, normal range <19). After 2 days of dexamethasone (0.5 mg every 6 h) her aldosterone remained high (428) with low renin and high aldosteon/renin ratio (856). She was diagnosed with secondary hypertension due to primary hyperaldosteronism. Genetic testing showed she was heterozygous for a mutation in CACNA1H witch causes hyperaldosteronism and hypertension. **Conclusion:** Primary familial hyperaldosteronism determines primary hypertension with early age onset and severe evolution. Rare causes are being discovered like the activatory mutation in the calcium channel ($Ca_V3.2$), which in abundant in the human adrenal glomerulosa. The mutation – $CACNA1H^{M1549V}$ causes much slower inactivation of the calcium channel and thus higher aldosterone secretion.

P1-P37

DNA Methylation Signatures Associated with Prenatal Dexamethasone Treatment

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Background: Prenatal treatment with dexamethasone (DEX) has been used since the mid 80's to minimize virilisation of girls with congenital adrenal hyperplasia. Long-term data on treatment safety and health outcome are still limited. It has been shown in animal models that prenatal dexamethasone treatment affects DNA methylation signatures as well as metabolism and behavior. We have previously shown that DEX affects working memory in children who were treated with DEX during fetal life. There is therefore an absolute necessity for further evaluation of patients with respect to treatment related risk. **Objective:** To test the hypothesis that prenatal treatment with DEX is associated with a distinct DNA methylation profile that persists into adolescence and adulthood. We also hypothesize that the effects on the epigenetic state may be different in healthy, short-term treated individuals versus long-term treated girls with CAH. **Method:** We isolated DNA from CD4+T-cells from 108 DEX treated individuals and controls (31 healthy, DEX-treated; 38 non-treated population controls; 11 CAH, DEX-treated; 28 CAH, non-treated). The Illumina Infinium Human Methylation 450 BeadChip Array was used to determine locus specific DNA methylation levels in T cells at 480.000 CGs across the genome in search for changes associated with prenatal DEX treatment. The GREAT annotation tool was used to investigate the functional relevance of the differentially methylated CpG sites. **Results:** Global methylation changes could not be identified in DEX treated cases. However, locus-specific changes in methylation were observed in DEX treated cases. Functional investigation in GREAT showed that the changes occurred in several important biological systems with a clear difference between long- and short-term treated subjects. Investigation of short term treated healthy subjects also showed that effects on DNA methylation associated with DEX were moderated by gender. **Conclusion:** These data provide the first evidence in humans that prenatal dexamethasone treatment causes long-lasting and functionally organized DNA methylation signatures in T cells and that the epigenetic changes are modified by duration of DEX treatment and sex. The findings may have important implications for the future health of DEX treated individuals.

P1-P38

Twenty Years Experience in Congenital Adrenal Hyperplasia: Clinical, Hormonal and Molecular Characteristics in a Large Cohort

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Background: Most congenital adrenal hyperplasia (CAH) patients carry mutations derived from conversion events involving the pseudogene, and the remaining carry new mutations varying according to ethnicity. A good genotype-phenotype correlation is observed, allowing the use of molecular analysis in clinical practice. **Objective and hypotheses:** To review the molecular diagnosis in a large cohort of CAH patients in order to create a diagnostic panel in our population. **Method:** DNA was extracted from 480 patients (158 SW, 116 SV, 206 NC); Point mutations were screened by allele- specific PCR and large gene rearrangements by Southern blotting/MLPA; *CYP21A2* sequencing was performed in those with incomplete genotype. Gene founder effect was analyzed through microsatellite studies. Patients were divided into 4 genotypes, according to *in vitro* enzymatic activity (Null, A:<2%, B:37%, C: >20%). **Results:** Targeted methodologies identified mutations in both alleles in 89% of SW, 86% of SV and 80% of NC patients. *CYP21A2* sequencing allowed genotype definition in 100% of classical and 87% of NC patients. Seven rare mutations (p.G424S, p.R408C, IVS2-2A>G, p.Ser170fs, p.R426H, p.H365Y, p.W19X) and a novel variant (p.E351V) were identified in 11% of alleles. Gene founder effect was observed in all but the p.W19X. Genotypes Null, A (I2 splice), B and C comprised mainly patients with SW (88%), SW (70%), SV (98%) and NC form (100%), respectively. The median basal 17OHP level was significantly higher in genotype A/C (median 17.5 ng/ml) than in C/C (median 7.6 ng/ml) as was ACTH–stimulated 17OHP level ($P=0.005$). The lowest stimulated-17OHP level in group C was 11 ng/ml. **Conclusion:** We identified a good genotype–phenotype correlation providing useful results regarding prediction of disease severity and genetic counseling. Sequencing is essential to optimize molecular diagnosis in our population, considering the high frequency of gene founder effect mutations.

P1-P39

Chronic Adrenal Insufficiency Due to a Mutation of Nicotinamide Nucleotide Transhydrogenase 1 (NNT1): Case Report

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Background: Congenital adrenal insufficiency represents a life-threatening condition. Among its multiples causes, mutation of NNT1 is the most recently discovered. We had the opportunity

to observe one case. NNT1 is a gene coding for a membrane protein which protects cells from oxidative stress. **Objective and hypotheses:** As few cases have been published until now, we describe a new case. **Results:** In a consanguineous (second grade) Algerian family, a first-born female child deceased at the age of 4 years, in the context of urinary infection. A second female child presented in Algeria melanodermia detected at the age of 8 months. At this time, plasma ACTH at 500 pg/ml and undetectable aldosterone levels indicated global adrenal insufficiency. She was then treated with 20 mg/m^2 per day hydrocortisone only. Melanodermia disappeared under treatment. However, ACTH levels remained incompletely corrected at 1 year of age. When she was 8 years old, during holidays in France, she suffered from asthenia, muscular weakness, bone pains and anorexia, without melanodermia. External genitalia were normal. Biologically, cortisol was undetectable, all intermediate plasma adrenal steroid compounds undetectable too, 17 hydroxyprogesterone included. ACTH was 356 pg/ml. Renin plasma activity was moderately increased (56 ng/ml per h) witnessing a residual moderate mineralocorticoid deficiency. SRY sequencing was negative. All known causes of adrenal global deficiency were eliminated. Exon sequencing of NNT 1 gene revealed a p.Met337Val or c.1009A>G homozygous mutation in exon 9. This mutation corresponded to the NADH binding domain of the protein (Pr Y Morel, Lyon). Extension investigations (growth, liver functions, cardiac ultrasound, skeletal X rays) were normal. Then hydrocortisone and fludrocortisone doses were adjusted. **Method:** Case report. **Conclusion:** Intrafamilial severity of NNT1 mutation may be variable. Mutations determining other functions of the gene have also been described. Following up extension investigations, especially cardiac, is mandatory.

P1-P40

Cognitive Functions in Congenital Adrenal Hyperplasia

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Background: There is controversy regarding cognitive affection in patients with congenital adrenal hyperplasia (CAH). **Objective and hypotheses:** Assess cognitive functions in children with CAH, and their relation to hydrocortisone (HC) therapy and testosterone level. **Method:** Thirty children with CAH due to 21 hydroxylase deficiency were compared with 20 age and sex matched healthy controls. Hydrocortisone daily dose and cumulative doses were calculated, socioeconomic standard was assessed, and free testosterone was measured. Cognitive function assessment was performed using Wechsler intelligence scale – revised for children and adults (WISC) which reflects the intellectual performance through verbal, performance, and full scale IQ, Benton visual retention test to assess visual perception, memory and visual-constructive abilities, and Wisconsin card sorting test (WCST); a tool for recognizing frontal cortical dysfunction. **Results:** The mean age (S.D.) of patients was 10.22 (3.17) years (11 males (36.7%), 19 females (63.3%)). Mean (S.D.) HC dose was 15.78 (4.36) mg/m^2 per day. Mean (S.D.) cumulative HC dose 44 689. 9 (26 892.0) mg. No significant difference in age, gender, socioeconomic standard, and anthropometric data existed between patients and controls. Patients had significantly lower scores in all domains of WISC test, performed significantly worse in Benton Visual Retention test, as well as in the Wisconsin Card Sorting Test. There was no significant difference in cognitive performance when patients were subdivided according to daily HC dose (<10, 10–15, >15 mg/m^2 per day), or according to salt wasting state. A positive correlation existed between cumulative HC dose and worse results of Benton test. No correlation existed between free testosterone and any of the three tests. **Conclusion:** Patients with CAH are at risk of cognitive impairment. Hydrocortisone therapy may be implicated. This study highlights the need to assess cognitive functions in CAH.

P1-P41

RET and TP53 Concomitant Mutations: A Challenging Approach to a Unique Association of High Tumor Predisposing Conditions

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Background: A 33-year-old woman with a history of adrenocortical carcinoma (ACC), surgically treated aged 4, presented for prenatal screening at 20 weeks gestation. Ultrasound examination identified that the female foetus had a 3-cm adrenal lesion. She had a positive family history for multiple-endocrine-neoplasia-type 2/MEN2 (paternal grandmother) and her father's cousin was diagnosed with ACC and Li-Fraumeni syndrome (LFS) at 30 year old. Calcitonin, PTH and cathecholamine were in the normal limits. The rest of pregnancy and delivery were uneventful and two months later her daughter's CT confirmed an unchanged adrenal mass with predominantly low attenuation. No evidence of cathecholamine excess, neither increased urinary steroid metabolites, precursors of androgens or glucocorticoids were identified. **Objective and hypotheses Method:** Aged 2 months, she underwent an adrenalectomy and no histopathological feature of malignancy were reported. **Results:** Genetic testing confirmed that the mother was *RET* (Val804Met) and p53 (Arg158His) mutation positive. The daughter, accordingly with mother's informed decision, was tested only for RET and the same *RET* mutation was found. The mother had a prophylactic

thyroidectomy. Daughter's suggested management was thyroidectomy before age 5 years; clinical examination, abdomen ultrasound and hormone evaluation every 6 months. **Conclusion:** LFS is an autosomal dominant disorder associated with abnormalities in the p53 oncosuppressor gene. It is characterized by a wide range of malignancies, often at a young age. ACC is one of the LFS core tumors. 68% of individuals with p53 germline mutation develop an ACC before age 4 and before age 20 in about 90%. Any individuals with ACC or family history should be considered for testing for p53 mutations. RET Val804Met mutation is correlated with the MEN2 familiar-medullary-thyroid-cancer phenotype and with low tumor aggressiveness. This is the first case of a concomitant carriage of RET and p53 mutations, both high tumor predisposing conditions. Due to this unique association, a safe, appropriate and effective screening program is mandatory.

P1-P42

Acute Lysis of a Giant Pediatric Adrenal Cortical Carcinoma Following One Dose of op'DDD

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Background: op'DDD can be used in adrenal cortical carcinoma (ACC) i) when surgery is impossible ii) or as an adjunct to surgery when local extension or metastases are present. **Objectives and hypotheses:** To report the unexpected spectacular effects of op'DDD in an unoperable ACC. **Patient and results:** A 3-year-old black African girl presented in poor shape with a 2-year history of pubic hair, clitoromegaly, abdominal distension. The CT scan revealed a giant ACC (28 cm×25 cm) that compressed the right kidney, inferior vena cava, diaphragm, right lung, right hepatic lobe, with no metastases. Serum testosterone was 27 ng/ml, SDHA 4270 ng/ml. Given the risk of a primary surgery, surgeons refused to attempt tumorectomy, thus op'DDD treatment was attempted. Twelve hours after a first 500 mg dose of op'DDD, the child experienced acute intense abdominal pain and oliguria due to a typical lysis tumor syndrome with hyperkaliemia (9.4 mmol/l), hyperphosphatemia (2.8 mmol/l), hyperuricemia (572 µmol/l) and high LDL (843 UI/l). The patient went into intensive care for hemofiltration and recovered. op'DDD treatment was maintained under cover of hyperhydration and uricolytic drugs. One week after the acute lysis, the CT scan showed that the tumor had shrinked while large zones of necrobiosis had appeared. Serum testosterone was 0.65 ng/ml and SDHEA 268 ng/ml. Six weeks later, a 14-h surgical intervention (Pr H. Martelli and S. Branchereau) allowed the complete exercise of a 1.5 kg tumor. One month later, the CT scan showed no tumoral remnants. **Conclusion:** The induction of an acute lysis of ACC by op'DDD has not been reported before.

P1-P43

Severe Hypertension in a Girl: Cushing Syndrome or Apparent Mineralocorticoid Excess Syndrome? Utility of Molecular Study

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Background: Apparent mineralocorticoids excess syndrome (AME) is an unusual cause of hypertension, caused by genetic mutation of type 2 11β-hidroxysteroid desydrogenase (11BHSD2) enzime, which metabolizes cortisol(F) to cortisone(E). Patients with AME born from consanguineous parents, are small for gestagional age (SGA) and could have nephrocalcinosis, hypokalemia and high plasma cortisol/cortisone relation (F/E). **Objective:** To tell the clinical and laboratory presentation of a girl with hypertension because of AME. **Clinical case:** 2-year-old girl with severe hypertension (197/133), requiring four drugs to control partially her blood pressure. Fullterm SGA newborn. Second daughter of normotensive parents who are first degree cousins; she has a normotensive sister. She had recurrent pneumonia and hypertrophic myocardiopathy. **Physical exam**: normal; no Cushing signs. **Hypertension study**: Renal US: bilateral nephrocalcinosis, no arterial stenosis; normal renal function. High urine calcium/creatinine index. Aldosterone: <1 (reference value (RV): 5-80) and plasmatic renin activity: <0.2 ng/ml/hr (RV1.1-3.8). Urinary free cortisol in 24-hour (two samples) resulted elevated: 1413 years 262 ug/g creatinine (RV:7-26); midnight plasmatic cortisol: 3.8 ug/dl (RV <0.1); morning cortisol was not supressed post 23-h dexhametasone administration; nocturnal salival cortisol was 0.132 and 0.146 ug/dl (RV: <0.1 ug/dl) in two different samples. ACTH: 33 pg/ml (RV:10-60); F/E relation: 175.5 (RV: 1.7-5.6). Urinary catecholamines, urinary metanephrines; androstenedione; 17OH progesterone, prolactine and thyroid hormones were normal. Head and abdominal MRI: normal. **11BHSD2 genetic study** was performed and showed the mutation R213C on exon 3, confirming AME. **Conclusion:** Although AME is a really unusual disease it must be considered in the differencial diagnosis of severe hypertension in childhood when the clinical record is compatible. AME has normal levels of cortisol, therefore the biochemical hypercortisolism difficulted the diagnosis in this patient, but molecular study helped to do the correct diagnosis.

P1-P44

An Infant with X-linked Adrenal Hypoplasia Congenita and Xp21 Contiguous Gene Deletion Syndrome

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Background: Contiguous gene syndromes are disorders caused by deletions of genes that are adjacent to one another. It is caused by partial deletion of Xp21, which includes the genes responsible for glycerol kinase deficiency, congenital adrenal hypoplasia, Duchenne muscular dystrophy (DMD) and intellectual disability. We report the case of a 14-day-old patient with this rare disease. **Case report:** A 14-day-old newborn was referred to our clinic for scrotal hyperpigmentation. He was born at 40 weeks of an uneventful pregnancy. His parents were first-degree cousins. Family history was unremarkable. On examination; blood pressure was 70/39 mmHg and his testes were 2 ml in volume bilaterally and he had scrotal hyperpigmentation. Laboratory findings showed hyponatremia, hyperpotasemia, elevated adrenocorticotropic hormone (485 pg/ml) with cortisol 8.48 μg/dl suggesting adrenal insufficiency. Karyotype was 46,XY. Hydrocortisone and florinef treatments were started. When he became 2 months of age, he was hypotonic and he had high creatine phosphokinase (2111 IU/l) and high trigliseride (732 mg/dl) levels suggesting DMD and dystrophin gene deletion was detected. We suspected contiguous gene deletion syndrome in Xp21 and array CGH study confirmed the existence of a deletion in Xp21 of the genes responsible for DMD, glycerol kinase deficiency, mental retardation (IL1RAPL1), and the congenital adrenal hypoplasia (gene DAX1 or NROB1 gene: Xp21.2-21.1). **Conclusion:** The Xp21 contiguous gene deletion syndrome should be considered in any infant with adrenal insufficiency. Symptoms depend on the size of deletion and appear almost exclusively in the male gender. Usually the first and most severe are the signs of adrenal hypoplasia. Measurement of serum triglycerides and creatine kinase activity are simple screening tests that may facilitate early diagnosis and appropriate genetic counseling about risks of recurrence in subsequent offspring.

P1-P45

Polymorphisms Analyze in Gene *CYP21A2* Gene Associated with Congenital Adrenal Hyperplasia

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Congenital adrenal hyperplasia is an autosomal recessive inborn error of metabolism due to impaired activity of one enzyme required for cortisol biosynthesis. Steroid 21-hydroxylase (21OH) deficiency is the cause in more than 90% of the patients. The 21OH is encoded by the *CYP21A2* gene located on the chromosome 6 in the region known as the RCCX module. Due to the high homology and tandem-repeat organization of the RCCX module, this region of the genome is subjected to unequal crossover events leading to large rearrangements. Different clinical presentations are classified in classical form that can be salt-wasting (0–1% of enzyme activity) or simple-virilizing (1–5% of enzyme activity) and late-onset non-classical form (15–60% of enzyme activity). This work aims to standardization of fast and cheap molecular techniques to detect *CYP21A2* gene polymorphisms in Brazilian newborns from public health network of *Rio Grande do Sul state*. First of all DNA extraction was carried by salting out methodology from peripheral blood of patients with high dosage of 17-hydroxyprogesterone (21OH enzyme substrate) on newborn screening, followed by quantified of total DNA. *CYP21A2* gene was amplified as Krone et al, 2002. Primers were designed on Primer 3 software to nested PCR multiplex reaction for amplified six regions, followed by SNaPshot reaction to analyze the 13 SNPs most frequently in Brazilian population. The standardization of these techniques was validated by sequencing techniques. For detection large rearrangements was used the commercial MLPA kit. Blood sample from 235 patients was collected and standardized the *CYP21A2* gene amplification and Nested PCR multiplex. Commercial MLPA kit was already validated. Standardization process of SNaPshot is still in development. Therefore, with this work we will be able to do a population study relating the polymorphisms more present in this population with their phenotype.

P1-P46

The Effect of Intrauterine Stress on Leukocyte Telomere Length in Newborns

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Background: Telomeres are specialized nucleoprotein structures located at the ends of chromosomes playing a crucial role in genomic stability. They consist of tandem repeats of the noncoding hexameric TTAGGG sequence. Telomere shortening has been associated with cardiovascular disease, hypertension, type 2 diabetes, atherosclerosis, coronary heart disease and stroke, and has been proposed as a biomarker for ageing and a prognostic factor for age-associated diseases. **Objective and hypotheses:**

To determine whether decreased or increased intrauterine growth, representing stressful conditions, affects leukocyte telomere length (LTL) at birth. **Methods:** One hundred and fifty nine ($n=159$) full-term newborns participated in the study. Neonates were categorized as IUGR (intrauterine growth restriction) ($n=18$), LGA (large for gestational age) ($n=12$) or AGA (appropriate for gestational age) ($n=129$) based on their customized centiles at birth. Cord blood was collected for DNA extraction, and LTL was determined by multiple monochrome quantitative real-time PCR (MMQRTPCR) and the telomere restriction fragment assay. The mean LTL for each group of newborns was compared and correlated with selected anthropometric parameters of the newborn and the mother. **Results:** IUGR and LGA neonates did not have significantly shorter LTL compared with the AGA newborns (IUGR: 12.3 ± 0.46 vs AGA 11.57 ± 0.48, $P=0.28$ and LGA: 11.55 ± 0.42 vs AGA 11.57 ± 0.48, $P=0.98$). There was no correlation between the LTL of the newborn and the mother's BMI and age. Furthermore, no statistically significant difference in LTL between boys and girls was noted (boys: 11.52 ± 0.39 vs girls: 12.01 ± 0.42, $P=0.4$). **Conclusions:** IUGR and LGA neonates have similar LTL to that of AGA neonates. Further studies using a larger sample size of IUGR, LGA and AGA newborns are required to confirm whether size at birth and intrauterine stress influences LTL.

P1-P47

Predictive Factors for Premature Pubarche in a Large Cohort of Italian Children

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Background: Premature pubarche refers to the appearance of pubic hair without other signs of puberty or virilization before 8 years in girls and 9 years in boys. The etiology of premature pubarche is not known. It has been suggested that an early maturation of the zona reticularis of the adrenal cortex is at the basis of premature pubarche, leading to an increase of adrenal androgens to levels that are normally seen in early puberty. In alternative, in children with normal androgen levels, premature pubarche might be due to hypersensitivity of hair follicle to steroid hormones. At present, predictor factors able to identify the evolution of premature pubarche are not known. **Objective and hypotheses:** To evaluate the etiology of premature pubarche in a cohort of Italian children, and to detect some predictor factors able to identify the evolution of pubarche. **Method:** We evaluated all children born between 2001 and 2014 and referred to Pediatric Endocrinology Service of our hospital for a premature pubarche. All of them were submitted to clinical exams to identify the etiology of premature pubarche. In particular, bone age and hormonal levels were determined. **Results:** We identified 334 children (F 271, M 63) with premature pubarche. In the 92.5% of them premature pubarche was idiopathic and in 6.6% it resulted in a central precocious puberty, while in 0.9% a nonclassic forms of congenital adrenal hyperplasia was detectable. The only predictive factor for an idiopathic premature pubarche was the BMI. We identified an early maturation of the zona reticularis of the adrenal cortex by finding higher DHEAS levels than 40 μg/dl and higher Δ4-androstenedione levels than 0.81 ng/ml. **Conclusion:** In most cases the premature pubarche was idiopathic, leading to an increased BMI. Higher values of DHEAS than 40 μg/dl and higher Δ4-androstenedione than 0.81 ng/ml suggest that premature pubarche was progressing.

P1-P48

Cardiac Function in Pediatric Patients with Congenital Adrenal Hyperplasia

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Background: Congenital adrenal hyperplasia (CAH) is characterized by cortisol deficiency and hyperandrogenism. Both hyperandrogenism and treatment with supraphysiological doses of glucocorticoids may cause unfavorable changes in the cardiovascular risk profile of CAH patients. Data on the cardiac function in CAH patients is scarce. **Objective and hypotheses:** To evaluate the cardiac function in pediatric CAH patients. **Method:** The cardiac function of 27 pediatric CAH patients, aged 8–16 years, was evaluated by conventional echocardiography and 2D myocardial strain (rate) imaging. Results were compared to a selected cohort of 27 age and gender matched healthy controls. Data on hydrocortisone dosage in CAH patients were collected. Blood was withdrawn in CAH patients to evaluate 17-OH-progesterone and androstenedione concentrations. **Results:** Left ventricular parameters (IVSd, LVIDd, LVIDs, EF and FS) are normal in all CAH patients, and do not differ from controls. In contrast, LVPWd is significantly lower in CAH patients compared to controls (5.55 vs 6.53 mm; $P=0.009$). The LVPWd Z-score is significantly lower in CAH patients yet within the normal range (-1.12 vs -0.35; $P=0.002$). LV mass and LV mass index are normal and comparable in both patients and controls. Isovolumetric relaxation time is significantly lower in CAH patients (49 vs 62 ms;

$P=0.003$). No associations were found between left ventricular parameters and BMIS SDS, hydrocortisone dose, androstenedione and 17-OH-progesterone, respectively. Global longitudinal, radial and circumferential strain were normal compared to controls. Global radial strain rate was significantly higher compared to healthy controls (2.58 vs 2.06 1/s). Time to peak global longitudinal, radial and cicumferential strain did not differ between CAH patients and controls. **Conclusion:** Cardiac evaluation of pediatric CAH patients showed no signs of left ventricular hypertrophy or ventricular dilatation. We found a thinner LVPWd in CAH patients, this finding was not associated with treatment or hyperandrogenism. A shorter isovolumetric relaxation time in CAH patients suggested increased left atrial pressure.

P2-P49

Evaluation of the Combination of Anti-androgen and Anti-estrogen Treatment in Classical Congenital Adrenal Hyperplasia in Boys: Retrospective Study of 11 Cases

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Background: Final height (FH) is reduced in congenital adrenal hyperplasia (CAH), due both to overtreatment by hydrocortisone therapy and to advanced epiphyseal closure linked to hyperandrogenism by Hydrocortisone therapeutic insufficiency. **Objective and hypotheses:** To evaluate the efficacy and safety of the addition of an androgen receptor competitor and an aromatase inhibitor to reduced hydrocortisone doses. **Method:** Retrospective study. Eleven boys (chronological age 9.4 ± 1.6 years, bone age -BA- 12.3 ± 1.6 years, initially predicted final height –IPFH- -1.5 ± 1.3 SDS) were administered a treatment combining hydrocortisone (6 mg/m^2/d instead of 15.6 ± 9.9 mg/m^2/d previously), Testolactone (40 mg/kg/d) and later letrozole (2.5 mg/kg/d) and flutamide (10 mg/kg/d). The additive treatment was stopped when statural age = bone age or when bone age was 14 years. The average chronological age at the end of the treatment was 13.2 ± 2 years. FH or near FH (NFH) were observed. **Results:** FH or NFH were 171.3 ± 6.6 cm (-0.7 ± 1.1 SDS). FH or NFH minus IPFH was 0.9 ± 0.6 SDS. No hepatic nor renal side effect were observed. Hydrocortisone dose reduction did not result into any sign of adrenal insufficiency and bone mineral density remained normal in 4/11 studied patients. 6/10 patients developed testicular adrenal rest tumours. Among four patients investigated at the end of treatment, three suffered from severe semen abnormalities. **Conclusion:** The addition of anti-androgen and aromatase inhibitor to Hydrocortisone treatment has improved the prognosis of FH in male CAH patients. The combined treatment can be considered as generally safe, excepted for a presumption of impaired fertility. However, it must be taken into consideration that included patients are the most affected ones. Notwithstanding ethical issues, subsequent randomized studies are theoretically needed to evaluate precisely the accountability of the additive anti-androgen and anti-estrogenic treatment in most severe CAH.

P2-P50

Ovarian Cysts in a 46,XX Patient with Congenital Lipoid Adrenal Hyperplasia and with Spontaneous Puberty

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Background: Congenital lipoid adrenal hyperplasia (CLAH) is the most severe form of congenital adrenal hyperplasia, characterized by lack of synthesis of all kinds of steroids in adrenals and gonads due to defects in gene of Steroidogenic Acute Regulatory protein (StAR). 46,XX patients can have a spontaneous puberty due to residual estrogen synthesis by a StAR-independent pathway in ovary. Development of ovarian cysts may be derived from persistent anovulation and impairment of ovarian StAR-independent steroidogenesis by lipoid deposition. **Case report:** We report a 13-years-old 46,XX patient with CLAH, which presented a spontaneous puberty and enlarged policystic ovaries. A congenital adrenal insufficiency was diagnosed due to hyponatremia, hyperkalemia and hyperpigmentation at 3 weeks after birth. She was successfully treated with hydrocortisone and fludrocortisone. The decreased level of all steroid hormones was determined by multisteroid analysis. Two heterozygous mutations (466delG and W245X) were detected in the StAR gene. Brest development was observed at the age of 11. It progressed to the Tanner stage 4 by 13.5 years old, but no pubic and axillary hair was observed. At the age of 13 giant cyst in the right ovary (200 cm^3) was revealed by ultrasound, which was successfully treated with cyclic progesterone therapy. Estrogen therapy was not prescribed because of normal gonadotropins and estradiol levels (Table 1). After 5-month of treatment with progesterone the increase of LH level (20.9 U/l) was detected and enlarged polycystic ovaries was revealed by MRI (right ovary $38\times35\times38$ mm; left ovary $35\times28\times36$ mm). The combined therapy with estrogen and progesterone was started. **Conclusion:** Ovarian cysts can be seen in 46,XX CLAH patients at puberty. Replacement therapy with estrogen and progesterone can prevent the ovarian cysts formation. The long-term follow-up is necessary in female patients with CLAH.

P2-P51

Bone Health Index in Children and Adolescents with Congenital Adrenal Hyperplasia

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Introduction: Patients with congenital adrenal hyperplasia (CAH) require life long glucocorticoid (GC) therapy. In CAH, the adverse effect of GC on bone health (BH) may be counteracted by the effect of modest elevations in adrenal androgens. **Aim:** To examine relationships between BH index (BHI) SDS, calculated by

Table 1. Clinical and Laboratory data of female patients with CLAH (for abstract P2-P50)

Age	Tanner slage	LH, U/l	FSH, U/l	Estradiol, pmol/l	Ovaries, cm^3	Progesterone (P) or estrogen (E) treatment
11 years	Brest 2 Pubis 1	0.2 (1.5–4.1)	5.3 (1.0–10.8)	45 (35–90)	Ovarian cyst 1.8 cm	–
12 years	Bresl 3 Pubis 1	0.6 (2.0–6.3)	3.2 (1.5–12.8)	40 (50–220)	Ovaries volume 4.5 cm^3	–
13 years	Bresl 3 Pubis 1	5.89 (2.0–6.3)	4.16 (1.5–12.8)	221.9 (50–220)	Ovarian cyst 200 cm^3	P
13.5 years	Brest 4 Pubis 1	20.9 (3.2–9.8)	10.1 (1.5–11.7)	101.7 (80–330)	Polycistic ovaries 21.6–26.2 cm^3	E + P

BoneXpert on bone age (BA) x-rays, BA, hydrocortisone (HC) dose (mg/m^2 per day), and mean 17-hydroxyprogesterone (17-OHP) concentration on 24 h blood spot profile. **Methods:** Retrospective study of data collected during annual review. Data were analysed in two age groups: <10 years and ≥ 10 years. BA was reported according to Tanner Whitehouse II reference data. **Results:** Data were available for 22 (11M) patients, age 10.7 ± 3.4 years. Results are reported in Table 1. BA was advanced in both age groups. BHI-SDS was < -1.5 in four subjects (18%). BHI-SDS was not related to either HC dose or 17OHP concentrations. BHI-SDS correlated positively with chronological age and BA advance (BA – chronological age) in age <10 years, $r = 0.48$ and $r = 0.35$ respectively, and with BA for all patients ($r = 0.55$, $P < 0.0001$). **Conclusion:** As anticipated, we observed modest BA advance, consistent with modestly elevated 17OHP concentrations. BHI SDS was < -1.5 SDS in 18% of patients, suggesting a negative effect of HC persists despite the protective effect of elevated androgens. These relationships may be more evident in a larger cohort of patients. The clinical significance of this observation, if any, is unknown. However, osteoporosis in adult patients with CAH is reported (1) and this observation deserves further evaluation in a larger cohort, studied prospectively. **Reference:**
1. Paula et al. 2008 *Eur J Endocrinol* **158** 879–887.

P2-P52

Occasional Detection of an Adrenal Incidentaloma in a Female Adolescent Evaluated for Cardiac Arrhythmias

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Background: Adrenal incidentalomas(AIs) are adrenal masses discovered occasionally by radiological evaluation in the absence of clinical features of adrenal disease. Clinical evaluation is important in patients with AIs. AIs are bilateral (10–15%); manifest as nonfunctioning cortical adenomas (70–80%), pheochromocytomas (1.1–11%), subclinical Cushing syndrome (5–20%), primary aldosteronism (1–2%), primary adrenocortical carcinomas ($<5\%$) and metastases (2.5%). AIs are relatively rare in children. **Case presentation:** MRI of the heart of a 14-year-old girl with cardiac arrhythmias revealed a mass in the right adrenal gland (RAG). Personal and familial medical histories were unremarkable. She had normal growth, completed puberty and had regular menstruations. She had no symptoms apart from arrhythmias which presented in 24-h Holter monitoring as ventricular bigeminy and trigeminy. Blood pressure, biochemical, hematological evaluations were normal. Pituitary gland (PG) hormonal investigation was normal. Normal serum cortisol concentrations were found following a circadian rhythm. Free cortisol and vanillylmandelic acid levels in a 24-h urine collection were normal. Retroperitoneal space MRI revealed a mass (10.5 cm, with solid and cystic parts) in the RAG, which presented an inhomogeneous enhancement after the intravenous administration of the paramagnetic contrast agent; it was in contact without invasion to the inferior vena cava; there were no signs of lymphadenopathy in the upper abdomen. MRI of brain, hypothalamus and PG was normal. Whole-body I-123-metaiodobenzylguanidine scintigraphy scan revealed a normal distribution of the radioiodinated drug in heart, liver and salivary glands, without uptake from the lesion under investigation. Removal of the RAG and the lesion was performed. Pathology revealed an encapsulated nonfunctioning adrenal cortical adenoma without signs of malignancy. **Conclusion:** The incidence of AIs increases even in children because of improved imaging and the use for nonspecific symptoms. Incidentalomas should be differentially diagnosed from malignancies. Surgery is indicated for secretory

Table 1. (for abstract P2-P51)

Age range	**Patients** (gender) (episodes)	**Age** (years)	**BA** (TWII score)	**BA-chronological age** (years)	**BHI SDS**	**Mean 17OHP** (nmol/l)	**Hydrocortisone** (mg/m^2 per day)
<10 years	12 (7M:5F)(20)	6.9 (3.15–9.93)	11.1 (6.39–14.3)	3.47 (-1.9 to $+6.82$)	-0.65 (-4 to $+2.3$)	30.2 (4–147.2)	10.4 (7.5–16.6)
≥ 10 years	15 (8M,7F)(31)	12.75 (10.2–17.5)	14.9 (9.22–18.1)	2.06 (-1.6 to $+5.14$)	-0.3 (-2.9 to 2.5)	23.9 (0 − 230.3)	10.0 (5.8–17.3)

Data are reported as median (range).

tumors and those with increased dimensions or radiological features for malignancy.

P2-P53

Final Height in Congenital Adrenal Hyperplasia: A Retrospective Study

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Background: A compromised final height (FH) is a concern in patients diagnosed with congenital adrenal hyperplasia (CAH). The lack of achievement of the genetic target height (TH) can be attributed to treatment with high doses of corticosteroids and high levels of adrenal androgens. Despite the emergence of new therapeutic modalities such as the use of anti-androgens and growth hormone it has been shown that a favorable FH can be achieved with careful use of corticosteroids. **Objective and hypotheses:** Evaluate the FH in patients with CAH comparing it with the TH, using z-scores (zFH and zTH) from the World Health Organization height-for-age Child Growth Standards. **Method:** Retrospective study with review of clinical processes. **Results:** The study included 23 patients who had already reached the FH: 10 classical forms (seven salt losers and three simple virilizing) and 13 non-classical forms. Eight of our patients were male. All had been treated with corticosteroids, 8 of them started the treatment in the neonatal period and in the remaining patients the average age of onset of treatment was 10.6 years. In 20 patients it was possible to obtain the TH, the median being (Perc 25; Perc 75) −0.92 (−1.29, −0.14). The median (Perc 25; Perc 75) FH was −0.76 (−1.52, 0.44) and corrected final height (zFH - zTH) was 0.09 (−0.17; 0.56). There was no significant difference in corrected final height between classical and non-classical forms. **Conclusion:** The authors were able to conclude that, in their sample, although the FH was inferior to the average height in general population, the majority of patients achieved their genetic potential for height. Differences in bone age, time of diagnosis and early initiation of treatment can be key factors in the final height outcome, however the use of corticosteroid therapy alone allowed, in this sample, the achievement of the TH.

P2-P54

Hyperandrogenism in a 12-year Old Girl with a Congenital Porto-Systemic Shunt and Congenital Hepatic Fibrosis

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Background: Hyperandrogenism in children is associated with excessive adrenal or gonadal androgens secretion. The most common causes of androgens hypersecretion are PCOS, adrenal tumors, Cushing's syndrome, CAH, and gonadal virilizing tumors. Within the last 15 years single case-reports of hyperandrogenism in female patients with congenital porto-systemic shunts were described in literature. The mechanism of such coincidence is unknown but the role of hyperinsulinism, impaired androgens liver metabolism due to escape of some part of hormones via shunt from portal to systemic circulation are mentioned. **Objective and hypotheses:** A 12-year old girl with increasing hyperandrogenism was admitted to Endocrinology Clinic. On examination: hirsutism (13–14 pts in *Ferriman*-Gallwey scale), severe acne, clitoromegaly and low-pitched voice were noted. On anamnesis, in this patient congenital liver fibrosis with mild portal hypertension was observed. At the age of 11 she underwent surgery because of pancreas tumor – histopathological examination revealed solid pseudopapillary tumor (Gruber-Franz Tumor). **Method:** Laboratory tests and imaging. **Results:** On laboratory tests we found elevated concentration of testosterone – maximum 2402 pg/ml ($n < 950$ pg/ml) and androstenedione – maximum 622 ng/dl ($n < 470$ ng/dl), whereas dehydroepiandrosterone sulfate was within normal range. In steroid urinary profile augmented excretion of androgen's metabolites was present. In dexamethasone suppression test adrenal androgens and cortisol were fully suppressed but partial testosterone and androstenedione suppression were found. This suggested an ovarian contribution in androgen overproduction. Oral glucose tolerance test revealed hyperinsulinemia (0′-40 uIU/ml, 120′-239 uIU/ml) with impaired glucose tolerance. Serum ammonia concentration was also elevated −120–180 μg/dl (normal range 20–80 μg/dl). Diagnostic imaging – brain and abdominal MRI didn't show any changes. In abdominal angio-CT examination we found porto-systemic shunt – persistent umbilical vein connecting portal with femoral vein. **Conclusion:** Taking under consideration clinical and diagnostic findings, absence of hormonally active lesion in our opinion hyperandrogenism in this case may be related with congenital porto-systemic shunt, similarly to cases previously described in literature.

P2-P55

The Treatment of a Functional Adrenocortical Cancer with Mitotane

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Introduction: In the pediatric age group, the incidence of the adrenocortical cancer (ACC) is 0.2%. The effective treatment is surgical resection. The only medical option is mitotane but it has negative effects on steroidogenesis. The difficulty in the management of mitotane therapy is discussed in this case. **Case report:** An $11^{10/12}$ years-old boy was referred with A 5 cm diameter solid-hypoecoic mass observed by sonography in the left surrenal region. The physical examination was all normal at presentation. His pubertal stage was Tanner grade 3. His clinical findings were

normal. In the adrenal hormone profile, DHEA, androstenedion, total testesterone (TT) elevated while the others (11-deoxycortisole, 17-OH progesterone, cortizole) were normal. His plasma renin activity and aldesterone were normal. Analysis of 24-h urine specimen revealed high cortisole levels. The case was diagnosed as grade 3 ACC and treated via surgical resection. Postoperatively chemotherapy, mitotane and hydrocortisone treatments were started. In the first month of the treatment hormonal profile was all normal but TT levels started to increase (>1500 ng/dl) at second month. In the follow-up, height growth stopped and bilateral gynecomasty developed. Magnetic resonance imaging and pozitron emission tomography scans and scrotal US were negative for recurrance or metastases at 6 months. The clinic was diagnosed as hypergonadotropic hypogonadism (HH) due to mitotane treatment. The follow-up of the case is continuing. **Discussion:** Mitotane treatment leads to HH via reducing the gonadal steroidogenesis. Additionally, treatment increases the levels of sex-hormone binding globuline and decreases the activity of 5-alfa reductase that results with high levels of testesteron. In our case the testosterone levels were high but free androgen index was normal. The high levels of testesterone can be the result of metastase, recurrance or mitotane treatment adverse effect. This is a struggling problem in the management of mitotane therapy.

P2-P56

The Effect of Anti-TNF on the Metabolism of Adrenal Hormones; A Steroid Metabolomic Approach

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Background: Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease seen in children. The systemic features of JIA are mediated by cytokine products of an activated immune system. Recent studies showed that the median level of urine cortisol in active JIA patients is significantly lower than remission period and control groups. **Objective and hypotheses:** One of the najor drugs in JIA is TNFα blocker (Enbrel). The aim of the study was to evaluate adrenal metabolaites production and adrenal enzymatic activity by using urine GC-MS analysis before and after Enbrel. **Method:** Eleven JIA patients were enrolled into the study, eight female and three male, age 12 ± 6.2 years (range 3–21 years). The average disease duration was 6.3 ± 5.2 years (range 1.6–18 years) and the duration of Enbrel reatment was 3 ± 2.8 years (range 6 months to 10 years). The patients were treated once weekly with Enbrel injection (0.8 mg/kg). Age and sex-matched healthy controls were matched to each patient. Patients were not treated with corticosteroids in the preceding 3 months. **Results:** Of the 35 metabolites measured, 23 were significantly lower in JIA patients before Enbrel treatment compared to healthy control group. One day after the injection 30 metabolites normalized and were similar to the control group. only five metabolites were lower in the JIA patients. We did not fined significant differences in the metabolites ratios that reflects changes in the enzymatic activity. The most significant reduction in JIA patients were 17OH pregnenolone metamolites. **Conclusion:** Perior to Enbral treatment almost all adrenal metabolites in the urine are significatly low mainly due to the active inflamatory proces. Immidiatly after the treatment many matabolaites raised to normal valalues as found in the contol group. We could not fined differences in metabolites ratios that reflects changes in adrenal enzymes activity. Blocking TNFα imidiatly restors adrenal function in JIA.

P2-P57

False-Positive Increases of Steroid Hormone Precursors Mimicking 11β-Hydroxylase-Deficiency in a Preterm Infant

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Background: In premature and small-for-date infants, immature adrenal enzyme activity, adrenal stress responses and impaired hepatic clearance may lead to mild to moderate false-positive increases of steroid hormone precursors. This complicates screening programs for congenital adrenal hyperplasia (CAH) in these patients. **Objective and hypotheses:** We present a preterm female infant (born at 33 weeks of gestation) who's newborn screening 55 h after birth revealed abnormally high concentrations of 17α-hydroxyprogesterone (176 nmol/l, ref. <88 nmol/l). Subsequent 'second tier' steroid hormone profile analysis was suggestive for 11β-hydroxylase deficiency, the second most common form of CAH (11-desoxycortisol 962 nmol/l, ref. <17 nmol/l; androstendion 129 nmol/l, ref. <17.8 nmol/l). **Methods and results:** Further detailed workup did not reveal any clinical features of androgen or mineralocorticoid excess, such as virilization or hypertension, at that time. Additional confirmatory blood samples were collected, and hydrocortisone treatment was initiated. Unexpectedly, all subsequent blood samples revealed a normal steroid hormone profile, and sequencing of the coding region of 11β-hydroxylase (*CYP11B1*) was normal. Re-analyses of the initial screening blood sample confirmed previous abnormal results. A confusion of patient's and sample identity as well as drug-induced 11β-hydroxylase-inhibition (i.e. etomidate exposition) was excluded. Hydrocortisone replacement therapy was ceased, and an ACTH stimulation test that was performed 8 weeks later was normal. **Conclusion:** Mild and unspecific increases of different steroid hormone precursors are well known in preterm and small-for-date infants. However, some patients may present with excessive false-positive increases of steroid hormone precursors, transiently completely mimicking a specific adrenal enzyme deficiency. This has to be taken into consideration when interpreting steroid hormone profiles of such patients.

P2-P58

Isthmic Spondylolisthesis in a Pre-pubertal Boy with Congenital Adrenal Hyperplasia During Aromatase Inhibitor Treatment

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Background: The aim of therapy in patients with congenital adrenal hyperplasia (CAH) is to use glucocorticoid doses as low as possible to achieve adrenal suppression. Both chronically increased androgen secretion and increased glucocorticoid exposure may adversely affect adult height and in some patients this therapeutic balance is difficult to achieve. In these particular cases aromatase inhibitors (AI) could be indicated with de aim to reduce glucocorticoid doses avoiding the subsequent increase of bone age. However, potential safety concerns of the inhibition of oestrogen biosynthesis should be taken into account since some publications report negative effects on bone physiology. **Case report:** A 6 year-old boy with CAH was diagnosed at 2 years of age: with pubic hair and bone age of 8 years according to Greulich and Pyle. He required high hydrocortisone dosages (20 mg/m^2 BSA per day) to suppress excessive androgen secretion with consequent slowing of growth velocity (-6.2 S.D.). At four years of age, treatment with AI (anastrazole) was considered. Two years after the start of AI therapy the diagnosis of isthmic spondylolisthesis was made by X-ray. The patient did not report lumbar pain or movement limitation. **Discussion:** Spondylolisthesis has not been previously described with anastrazole treatment and is not pathologically related to changes in vertebral morphology that have been reported with AI. However, the spondylolisthesis was weird of the age of our patient since his height and weight were insufficient to cause mechanical stress. These findings led us to consider the pathological role of anastrazole. **Conclusion:** Use of anastrazole therapy, particularly in prepuberty may predispose to vertebral changes. We recommend the use of anastrazole with serial evaluation of vertebral morphology by X-ray and orthopaedic evaluation, before and during treatment.

P2-P59

Hospitalisation in Children with Adrenal Insufficiency and Hypopituitarism: Is there a Differential Burden Between Boys and Girls and Between Age Groups?

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Background: There is a paucity of information on the utilisation of hospital services by children and adolescents with adrenal insufficiency (AI) and hypopituitarism. **Objective and hypotheses:** To determine the number of episodes of hospitalisation in children with adrenal insufficiency (AI) and hypopituitarism in Australia, and to analyse trends in these admissions. **Method:** An analysis of all admissions to Australian hospitals in patients aged 0 to 19 years with AI and hypopituitarism over a 14 year period using an administrative database. Crude rates were calculated overall and for the age and sex specific groups. Poisson regression models were used to assess the significance of the observed differences. **Results:** There were 3786 admissions for treatment of AI and hypopituitarism in patients aged 0–19 years, corresponding to an average admission rate of 48.8/million/year. Hypopituitarism comprised 40.1% of the admissions and 22.2% were for congenital adrenal hyperplasia (CAH). There were 470 (12.4%) admissions for an adrenal crisis (AC) and the incidence of adrenal crises increased significantly over the study ($P<0.01$). Overall, admission for AI was comparable between the sexes and 40.1% of the admissions were for children aged 0–4 years. Admission rates for AI, hypopituitarism, CAH and 'Other and unspecified causes' of AI were highest among infants and decreased with age. Admissions for Primary AI increased significantly with age. Males had higher rates of admission for hypopituitarism ($P<0.01$) but females had significantly rates of admission for CAH and 'other and unspecified causes' of AI. **Conclusion:** In the age group 0–19 years, admissions for the combined causes of AI decreased with age, males had higher rates of admission for hypopituitarism and females had higher rates of admission for CAH and 'other and unspecified causes' of AI. Adrenal crises increased over the study.

P2-P60

A Case of Cushing's Syndrome Due to Adrenocortical Adenoma with Pubarche and Obesity

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Background: Adrenocortical tumors in childhood represent very rare about 0.2% of all pediatric malignancies. Cushing's syndrome (CS) is characterized by clinical features caused by autonomous excessive glucocorticoid production from adrenal cortex. In ACTH-independent CS, the most common cause is unilateral cortisol-producing adrenocortical adenoma. **Objective and hypotheses:** Fifteen months old girl was admitted with gradually gain weight, pubarche, and acne of the face since five months. There was no history of using drugs which contain

steroid. Length was 74.4 cm (−1.31 SDS), weigh was 13.2 (2.16 SDS), moon facies, buffalo hump, facial plethora with acne on her forehead and cheeks. Her pubic stage was 3. In laboratory, glucose (fasting) 93 mg/dl, insulin (fasting) 24.99 μIU/ml, total testosterone 76 ng/dl, cortisol (morning) 37.69 mg/dl, ACTH (morning) 5.04 pg/ml, cortisol (evening) 30.4 μg/dl, ACTH (evening) 5.32 pg/ml, DHEA-SO4 238 pg/ml, sodium 138 mmol/l, potassium 4.53 mmol/l, WBC 20.8×10^3/ml, RBC 5.05×10^6/ml, hemoglobin 15.3 g/dl, and platelet 391×10^3/ml. After evening dexamethasone implementation, cortisol (morning) was 29.36 μg/dl. In magnetic resonance imaging identified pronounced thickening and nodularity in lateral crus of left adrenal gland. **Results:** Patient was diagnosed with Cushing's syndrome due to adrenocortical tumor and administered laparoscopic left adrenalectomy. The removed mass was consistent with adrenal adenoma histologically. Postoperative fourth day control Cortisol (morning) 4.73 mg/dl, ACTH 18.7 pg/ml, and DHE-SO4 <15.0 pg/ml. **Conclusion:** In adrenocortical tumors, distinguishing to adrenocortical cancer and adenoma is difficult. Herein we represent a rare case of CS because of adrenocortical adenoma with clinical features of excessive glucocorticoid production.

P2-P61

Severe Neonatal Cushing Syndrome with Multi-Organ McCune Albright Manifestations

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Background: Reports of Cushing syndrome during the first month of life are rare. Mortality is high, despite medical (metyrapone) or surgical (adrenalectomy) treatment. **Objectives:** To report a new neonatal case of Cushing due to McCuneAlbright syndrome (MAS). **Patient and results:** Although a healthy baby at age 10 days, a newborn girl presented with sudden manifestations within the following 2 weeks: facial and truncal plethora, severe hypertension, cardiomyopathy with ventricular hypertrophy, hyperglycemia (15 mmol/l), elevated transaminases (around 200 UI/l), major hypercalcemia (3.7 mmol/l), bone dysostosis (left femur, forearms), and large bilateral adrenal hyperplasia. Laboratory data confirmed adrenocorticotropic hormone-independent Cushing's syndrome with plasma cortisol 975 ng/ml. The baby girl underwent bilateral adrenalectomy at 40 days. Medical treatment included glargine insulin (3–4 units/d) and propranolol (40 mg/d), which allowed the control of hyperglycemia, hypercalcemia, hypertension and cardiomyopathy. The baby received 10 mg/d hydrocortisone, 50 μg/d fludrocortisone and 1 g/d ClNa. Transaminases normalized, while gamma-GT remained >1000. Mild hyperthyroidism (treated with 5 mg/d carbimazole), failure to thrive, large-café-au-lait spots appeared during the 3rd month of life. A mosaic activating GNAS gene mutation was found on DNA extracted from blood cells and the adrenals. **Conclusion:** Although the interpretation of mosaic multi-organ involvement is difficult in a sick baby, current disease evolution supports the efficacy of propanolol to control some of.

P2-P62

Final Height Data in a Cohort of Patients with Congenital Adrenal Hyperplasia Treated with Tailored Doses of Hydrocortisone

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Background: Patients with congenital adrenal hyperplasia (CAH) are glucocorticoid deficient and require cortisol replacement to maintain homeostasis and prevent adrenal crises. Hydrocortisone dosing needs to be individualized because of variable cortisol clearance rates. Patients are thus prone to be either over or undertreated, both of which compromises final height. **Objective and hypotheses:** Performing 24-h cortisol profiling serially may allow for more accurate titration of hydrocortisone dosage, resulting in a possible improvement in final height. **Method:** Paediatric patients with CAH due to 21 hydroxylase deficiency were retrospectively recruited from a single tertiary centre between 1990 and 2015. We included those patients who had reached their final height and had had at least two serial 24-h cortisol profiles performed. **Results:** We identified 50 children, 34 children (7 M) had neonatal onset CAH whilst 16 (8 M) had late onset simple virilising disease. Their final heights

Table 1. (for abstract P2-P62)

	Final Height (SD) (cm)	**Mean adult height SDS** (SE)	**Mid-parental height SDS** (SE)	**Mean BMI** (kg/m^2)	**Mean HC dosages** (mg/m^2 per day) (SD)
Neonatal onset CAH Boys	170±5.0	−0.98±0.37	−0.92±0.35	26.0±2.6	13.95±2.86
Neonatal onset CAH Girls	160±5.2	−0.57±0.11	0.96±0.12	24.7±8.2	14.55±2.88
Late onset Simple virilising boys	168±6.7	−1.17±0.42	−1.4±0.50	30.0±12.6	13.79±3.20
Late onset Simple virilising girls	165±8.2	0.24±0.28	0.03±0.08	25.6±3.3	10.50±2.80

were compared to mean adult height of the population (British 1990 growth reference centiles published by Cole et al) and mid parental height. The mean of hydrocortisone dose prescribed from 3 to 18 years of age was lower than that previously reported in an ESPE survey. **Conclusion:** Apart from late onset virilising boys, final height lies within one SDS from mean adult height of the population and the mean mid-parental height, and BMI is close to normal range. These results are encouraging compared to previous similar cross sectional studies and affirm that cortisol profiling may optimise dosing with better control of CAH and improved final height.

P2-P63

The Evolution of Bone Age in Girls with Premature Adrenarche

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Background: In premature adrenarche (PA) children bone age (BA) may be greater than chronological age (CA), however final height is usually within target height (TH). **Objective and hypotheses:** Aim of the study was to evaluate the evolution of BA in girls with PA. **Method:** We studied retrospectively the files of 60 girls with PA followed in our unit. Anthropometric data and Tanner pubertal status were determined in each visit and BA was evaluated in 12-month intervals. Predicted adult height (PAH), estimated at presentation and at last visit, was compared to TH. **Results:** Mean follow-up time was 3.6 years. At presentation, mean age (S.D.) was 6.55 (1.0) years, Height SDS 0.868 (1.0), BMISDS was 1.23 (1.1) and BA was +1.13 (0.86) years greater than CA. 19/60 girls (31.7%) were obese (BMISDS > 2). PAH at presentation was 0.454 SDS less, whereas at the last visit (3 years later) was 0.244 less than mean parental height (TH). We subdivided the PA girls, according to baseline ΔBA-CA, into three subgroups. Group 1 (ΔBA-CA < 1 year) consisted of 21 girls (35%) with age at presentation 6.36 (1.17). BA increased from +0.36 (0.46) at baseline to +1.12 (0.75) years, at year 3, $P < 0{,}001$. In Group 2 (ΔBA-CA > 1 but < 2 years) consisted of 30 (50%), mean age 6.49 (1.0), no statistical difference in BA evolution was noted. Group 3 (ΔBA-CA ≥ 2 years), consisted of nine girls (15%), mean age 7.18 (0.6), BA decreased from +2.49 (0.35) to +1.38 (0.59), at year 3, $P < 0.001$. **Conclusion:** The majority of PA girls present advanced BA. It seems that the norm for BA in PA girls is to be advanced by about one year. Girls with ΔBA-CA < 1 year or ≥ 2 years are expected to present in the next 3 years after diagnosis, an increase or decrease in BA advancement, respectively. The evolution of BA resembles to the statistical phenomenon of regression to the mean, only that the mean is one year BA advancement. The latter could be attributed to the above average height of PA girls.

P2-P64

Cushing Syndrome Due to Adrenal Adenoma in an Adolescent Patient and Successful Treatment with Laparoscopic Surgery

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Cushing syndrome (CS) is a rare disease in children associated with weight gain and stunting of their linear growth. In older children, pituitary adenomas are a more common cause of CS. The clinical presentation of CS varies in children such as truncal obesity, striae, facial plethora, hypertension, and PKOS-like (polycystic ovary syndrome) feature. Here in we report an adolescent presented with obesity, short stature and late puberty but without metabolic syndrome or hirsutism and diagnosed as unilateral adrenal adenoma. A 15 years-old female patient evaluated for stature. There was a history of weight gain and stunting of her linear growth especially last three years. When examined she had a facial plethora, abdominal obesity, non-specifically maculopapuler rash on the extremities. Her height standard deviation score (SDS) was −4.3 (136.6 cm) and relative body weight was 145% (47.3 kg). Her breasts were at Tanner stage I with lipomastia. Her bone age was 11 years-old. On laboratory examinations were revealed that FSH 0.17 mIU/ml, LH 0.05 mIU/ml with low estradiol levels. Plasma testosterone (101 ng/dl; *N*: 6–55) and 24-h urinary free cortisol level were increased (829 mcg/m^2 per day; $N < 70$) with suppressed adrenocorticotrophic hormone (< 5 pg/ml) level. Plasma levels of androstenodione (0.76 ng/dl; *N*: < 2.0), dehydroepiandrosterone sulfate (57.5 μg/dl; *N*: 17–350), and 17-hydroxyprogesterone (0.5 ng/ml; *N*: < 2) were normal. Abdominal imaging showed a right surrenal mass, which was 3.0 cm axis. Laparoscopic surgery was performed to resect the mass. Histologically, the neoplasm was diagnosed as an adrenocortical oxyphilic adenoma. There was a clinically and laboratory full recovery after surgery. After 6 months of surgery, her weight loss was 9 kg, and height gain was 4.4 cm. CS and adrenal adenoma should be kept in mind in patient with short stature with obese children and late puberty adolescent. All hormones secreted from the adrenal cortex should be measured in every patient with an adrenal tumor. Laparoscopic adrenalectomy is a safe and feasible, method for curative therapy for patient with surrenal adenoma.

P2-P65

A Novel Mutation of DAX-1 (NR0B1) in a Boy with X-linked Adrenal Hypoplasia Congenita

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Background: DAX-1 (NR0B1) plays a key role in adrenal and reproductive development. It interacts with other nuclear receptors; however, its exact biological role remains unclear. In men most patients with X-linked adrenal hypoplasia congenita (AHC) present with acute adrenal failure. To date DAX-1 mutations have been found in more than 100 families or patients with X-linked AHC. **Results:** We report the case of a 2.5-year-old boy who presented with a history of recurrent vomiting and progressive hyperpigmentation of the skin over 6 months. Finally, acute adrenal failure with salt loosing crisis was diagnosed and treated accordingly. Family history revealed sudden death of three brothers of the mother during infancy. Direct sequencing of PCR fragments amplified from genomic DNA of the patient revealed the presence of a novel hemizygous nonsense mutation, c.870C > A in Exon 1, leading to the formation a premature stop codon. **Conclusion:** In any child presenting with isolated vomiting acute adrenal failure has to be assessed. Furthermore, this report shows a novel DAX-1 mutation and underlines the importance of genetic confirmation of the diagnosis to counsel the family and prevent other fatal outcomes.

P2-P66

Clinical-Laboratory Findings of the Cases with Premature Pubarche and the Value of Acth Stimulation Test in the Differential Siagnosis

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Background: Premature pubarche is a diagnosis of exclusion, and it is a benign period. Non-classic congenital adrenal hyperplasia (NC-CAH) is one of the most important causes in the differential diagnosis of premature pubarche. **Objective and hypotheses:** In this study it was aimed to evaluate the clinical and laboratory data, of 75 cases (five male, 70 female) diagnosed as premature pubarche. Additionally basal 17-hydroxyprogesterone levels determined as NC-CAH criteria according to ACTH stimulation test results were revaluated. **Method:** Premature pubarche patients who were admitted to Trakya University Medical Faculty Pediatric Department, Pediatric Endocrinology Outpatient Clinic were evaluated. **Results:** The mean diagnosis age was 7.2 ± 0.7 years and the female/male ratio was 14/1. Seven percent of the cases were born small for gestational age and 57% of the cases were overweight. The cases were divided into three groups on the basis of 17-hydroxyprogesterone response to ACTH stimulation test and the groups were compared for the clinical and laboratory findings (stimulated 17-hydroxyprogesterone < 4.9 ng/ml, 5–9.9 ng/ml and < 10 ng/ml, respectively). Three of the cases (4%) were diagnosed with NC-CAH. No differences were found in anthropometric findings, basal DHEAS, 17-hydroxyprogesterone, androstenedione and cortisol levels among the groups. Body mass index SDS was directly correlated with height SDS and bone age SDS. Two NC-CAH cases had a basal 17-hydroxyprogesterone level less than 1.5 ng/ml. Cortisol responses to ACTH stimulation test were significantly lower in NC-CAH cases compared with the other cases. **Conclusion:** According to the results of study, premature pubarche is the problem of girls and being overweight is a risk factor. Basal 17-hydroxyprogesterone level > 2 ng/ml should be reconsidered in the use of differential diagnosis of NC-CAH. Due to the suboptimal cortisol response to ACTH stimulation test, also there is a need for trials to define approach to NC-CAH cases with clinical signs in severe trauma and stress.

P2-P67

Successful Medical Management of Severe Neonatal Cushing Syndrome with Metyrapone, Guided by Mass Spectrometry Monitoring

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Background: Neonatal Cushing syndrome is a rare and severe condition, mostly associated with the McCune-Albright (MCA) syndrome. Management options include medical treatment (with ketoconazole or metyrapone resulting in 11-beta-hydroxylase blockade) and radical treatment with bilateral adrenalectomy. Spontaneous regression in late infancy has been reported. **Objective and hypotheses:** To report on the outcome of a 14 month-old girl with severe neonatal Cushing syndrome on long-term treatment with metyrapone. **Results:** The patient was born with severe growth restriction (-4DS for height and weight) and initially presented with neonatal hyperglycaemia requiring insulin treatment during 1 month. At the age of 2 months she was referred for severe Cushing syndrome with growth arrest, clinical Cushingoid features, elevated circadian cortisol > 1000 nmol/l not suppressible by dexamethasone and undetectable ACTH levels. She showed severe complications including hypertension requiring three medications, hypotonia and immune depression resulting in Pneumocystis infection. Medical treatment with metyrapone, administered by nasogastric tubing was initiated at the dose of 80 mg every 6 h. The evolution of hormonal markers by UPLC-MSMS are reported on the table. At the patient's most recent visit, at the age of 14 months, hypercorticism was controlled with catch-up growth, disappearance of Cushingoid features, normal blood pressure and no clinical hyperandrogenism. Adrenal

Table 1. (for abstract P2-P67)

	D0	D14	M1	M3	M8	M12
Cortisol (nmol/l)	835	73	105	77	169	128
Deoxycorticosterone (pmol/l)	108	1304	1163	987	2730	3270
S compound (nmol/l)	0.13	206	201	107	81	56
Testosterone (nmol/l)	0.3	1.9	2.6	1.6	2.1	0.7

imaging showed bilaterally enlarged adrenals. She had no other features of the MCA syndrome. A search for activating mutation of the *GNAS* gene in PBMC DNA was negative and sequencing of several genes involved in adrenal function (MC2R, ARMC5, PRKAR1A) was normal. **Conclusion:** Long-term treatment of severe neonatal Cushing syndrome with metyrapone is efficient, well tolerated and can avoid bilateral adrenalectomy in transient cases. Mass spectrometry (UPLC-MSMS) for monitoring steroid changes is needed. This ultra specific method avoids over-estimation of actual levels related to crossreactions between close molecules of steroids.

P2-P68

Family Character Isolated Pheochromocytoma by Mutation in Vhl gen

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Background: Pheochromocytoma is an uncommon tumor, producer of Catecholamines and causing hypertension in childhood. It is associated to genetic alterations, generally related with RET gene disorders. **Method:** We present the case of a unilateral familial isolated pheochromocytoma, present in father and son, carriers of a heterozygous mutation in the VHL gene (c.235C > G; p.R79G). **Case:** Male, 9 years-old with history of fever, profuse sweating, intense headache and 190/120 blood pressure. Family history: father intervened at 40 years of unilateral pheochromocytoma, without other adjacent pathology. Initial biochemical data: glucose 82 mg/dl, cortisol 26.7 µg/dl (3.1–22.4), ACTH 15 pg7 ml (10–50), noradrenaline 1188 ug/T (15–80), Vanillylmandelic acid 57.6 mg/T (2–8). Renal ultrasound: identified a 5.5× 4.4 cm mass with cystic areas, inside right adrenal gland, with mainly peripheral vascularization. Scintigraphy with I-123 MIBG: pathological uptake in the right adrenal gland, without affecting other levels. MRI of abdomen: right adrenal mass with defined margins and cystic areas inside, this mass mark at the bottom contour of the liver and upper pole of kidney without signs of infiltration. Normal left adrenal gland. Surgically intervened: surgically laparoscopy after performing block, first alpha, and then beta adrenergic. Complete tumor resection. Postoperative care: the child needed important volume contributions, vasoactive drugs and corticosteroids, which were withdrawing after 24 h. Currently asymptomatic with normal hormonal controls. **Conclusion:** The genetic study in the child observing the mutation in the VHL, is identical to that of the father, which supports that this mutation is associated with unilateral familial pheochromocytoma.

P2-P69

Exaggerated Adrenarche and Exogenous Obesity: A Diagnostic Challenge

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Background: The exaggerated adrenarche is an extreme variant of the maturation of the adrenal cortex, often associated with hyperinsulinemia and obesity. Hyperandrogenism by congenital adrenal hyperplasia (CAH) and adrenal neoplasms are differential diagnoses. **Case report:** Male, 8 years and 3 months, who came from another service with diagnosis of Precocious Puberty and Obesity, already being treated with Leuprolide acetate for 1 year and half. His complaint was weight gain and growth of body hair since 5 years old. Physical exam: *cushingoid* face, weight 52.5 kg (BMI 35.9 – Z = +4.87), height 121.5 cm ($z = -1.24$), abdominal perimeter 99 cm, acne, gynecomastia, *Acanthosis nigricans*, Tanner stage P5G2, testicles = 3 cm^3. Initial exams. Bone age 10 years, ACTH = 43 pg/ml, cortisol = 7.6 mcg/dl, urinary cortisol = 576 mcg/24 h, renina = 1.2 ng/ml per hour, DHEAS = 4080 ng/ml, adrenal ultrasound, abdomen computed tomography and pituitary gland magnetic resonance image were normal. Lab work-up: 17OHPregnenolone = 1719 ng/dl e ACTH test results DHEAS T0 = 4080 ng/ml, T60 = 4260 ng/ml, Androstenediona T0 = 3.2 ng/ml, T60 = 4.6 ng/ml, 17OHProgesterone T0 = 0.6 ng/ml, T60 = 7.2 ng/ml. It was suggested the hypothesis of CAH due to 3-Hydroxysteroid Dehydrogenase, and therapy with corticosteroids was started, but turned out unsuccessful. Then exaggerated adrenarche associated with exogenous obesity was the hypothesis, and he started treatment with Metformin for insulin resistance (HOMA-IR = 7.1), aromatase inhibitor due to the advanced bone age (BA = 13 years 6 months CI = 10 years 7 months) and GH replacement. The patient reached the final height of 161 cm ($z = -1.43$), and remains an outpatient. **Conclusion:** Although it is a diagnosis of

exclusion, the exaggerated adrenarche associated with obesity is becoming more common. However, the diagnosis is still a challenge.

P2-P70

Vitamin D Insufficiency is Related to Premature Adrenarche

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Background: Vitamin D, mainly important in calcium phosphate homeostasis and bone health, has been recently suggested as an important factor in pathogenesis of numerous chronic conditions such as type 2 diabetes, metabolic syndrome and polycystic ovarian syndrome (PCOS). **Objective and hypotheses:** The aim of this study is to investigate the relation between PCOS and premature adrenarche (PA), suggested as predictor of PCOS. **Method:** A total of 71 girls with PA and 52 healthy girls, as the control group, were consecutively recruited. Axillar and/or pubic hair development before the age of 8 years were defined as PA. Bone age and anthropometric measures including height, weight, BMI were obtained. Levels of androgens, 25 hydroxyvitamin D (25(OH)D), 1,25 dihydroxy vitamin D ($1,25(OH)_2D$), follicule stimulating hormone (FSH), luteinizing hormone (LH), fasting plasma glucose and insülin were measured. Vitamin D insufficiency was defined as <20 μg/ml. **Results:** There were no significant differences between the patients with PA and control group with in terms of age, birthweight, $1,25(OH)_2D$, 11-DOCA, LH, FSH, fasting plasma glucose and insulin levels. On the other hand, bone age, BMI-SDS, HOMA-IR, and androgen levels were significantly higher in patients with PA. Vitamin D insufficiency was determined in 38 patients with PA (38/71) and in 19 healthy children (19/52). HOMA-IR was signicantly higher in patients with vitamin D insufficiency ($P=0.044$). There was a statistically significant correlation between 25(OH)D and HOMA-IR. **Conclusion:** Vitamin D level is associated with PA and insulin resistence (IR) can be suggested as an important factor in relation between vitamin D insufficiency and PA.

P2-P71

A Case of 17-Years-Old Boy with Relapsing Cushing Disease Presenting Vertebral Compression Fracture

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Background: Cushing disease defined as hypercortisolism due to pituitary adrenocorticotrophic hormone (ACTH) secreting adenoma is a very rare disease, especially in childhood and adolescence. The purpose of this report is to follow up Cushing disease patient who presented with osteoporosis, rapid weight gain, decreased growth rate, and relapsing pituitary adenoma after transsphenoidal adenomectomy (TSA). **Case:** A 17-years-old boy visited our hospital for evaluation of vertebral compression fracture and obesity. His height was 149.5 cm (-4.1 SDS), body weight was 63.6 kg (-0.01 SDS), and his BMI was 38.5 kg/m^2 (3.0 SDS). He looked a moon shaped face, a buffalo hump, multiple abdominal striae, truncal obesity, relatively thin limb, and hypertrichosis. The volume of testis was 8 ml, and Tanner stage of pubic hair was 3. The *Z*-score of bone densiometry was -4.3. The hormone findings showed high 24-h urinary free cortisol (UFC) and loss of cortisol's diurnal rhythm. Also, cortisol was not suppressed by low dose of dexamethasone, but was suppressed by high dose of dexamethasone. For the evaluation of the laterality of the ACTH secretion, the bilateral inferior petrosal sinus sampling (BIPSS) after injection of corticotropin-releasing hormone (CRH) was done, resulting in no difference of the peak ACTH levels between left and right inferior petrosal sinus sampling. However, the MRI finding showed only left pituitary microadenoma sized 8 mm. Left hemihypophysectomy was performed by the TSA and the histological finding was compatible with pituitary adenoma, and the immunohistochemistry was positive in ACTH. Transiently clinical improvement was observed, but the follow-up pituitary MRI finding showed newly developed right pituitary microadenoma six months after the left hemihypophysectomy. We are planning to perform the right hemihypophysectomy. **Conclusion:** This case report describes the relapsing Cushing disease patient presenting osteoporosis, rapid weight gain, and growth failure. Thus, the need for careful clinical and radiographic follow-up in surgically 'cured' patient should be emphasized in search for potential progression of relapsing Cushing disease.

P2-P72

The ımpact of 21 Hydroxylase Deficiency on Cardiac Repolarization Changes in Children with 21-hydroxylase-deficient Congenital Adrenal Hyperplasia

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Background: To the best of our knowledge, no study has been conducted to assess the impact of 21 hydroxylase deficiency and hidrocortisone treatment on electrocardiographic measures in children with 21-hydroxylase-deficient congenital adrenal hyperplasia. **Objective and hypotheses:** The purpose of this study is to compare the12-lead electrocardiographic measures such as

PWd, QT interval, QTd, Tp-e interval, Tp-e/QT and Tp-e/QTc ratio in patients of 21-hydroxylase-deficient congenital adrenal hyperplasia with that in healthy control subjects matched for age, sex, height, weight and BMI. **Method:** Twenty-five patients of 21-hydroxylase-deficient congenital adrenal hyperplasia and 25 control subjects were enrolled into this observational, cross-sectional, controlled study. The evaluation consisted of anthropometric measurements, biochemical parameters, and electrocardiographic (ECG) measures. The standard 12-lead electrocardiography was performed in all patients and P-wave dispersion (PWd), QT interval, QTd, QTcd, Tp-e dispersion, Tp-e/QT and Tp-e/QTc ratios were calculated. **Results:** There were no significant differences in the groups for age, sex, height, weight and BMI (median age 112.8 (90.4) vs. 80.7 (109.5) months, mean weight 37.6 ± 21.5 vs. 27.9 ± 18.3 kg, mean height 125.4 ± 28.9 vs. 114.7 ± 31 cm, mean BMI 21.4 ± 5.7 vs. 18.9 ± 3.4 kg/m^2, respectively). P dispersion and Tp-e dispersion were significantly higher in patients of 21-hydroxylase-deficient congenital adrenal hyperplasia compared to the controls (median P dispersion 50 (25) vs. 40 (40) ms, mean Tp-e dispersion 48 ± 15.5 vs. 35.2 ± 17.5 ms). **Conclusion:** Our study revealed that P and Tp-e dispersion were increased in 21-hydroxylase deficient children. 21 hydroxylase deficiency and treatment might be risk factor for atrial and ventricular arrhythmias in children with congenital adrenal hyperplasia 21-hydroxylase-deficient.

P2-P73

Patients with Congenital Adrenal Hyperplasia have Significantly Higher Healthcare Utilisation than the General Paediatric Population

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Background: Congenital adrenal hyperplasia (CAH) is a rare disorder of steroid synthesis. Patients have multiple health problems. Healthcare utilisation has not previously been assessed in the paediatric population with CAH. **Objective and hypotheses:** To assess healthcare resource use in patients in England with CAH. **Method:** The English Clinical Practice Research Datalink (CPRD) database is an observational and interventional research service overseen by the UK Department of Health. Approximately 50% of CPRD patients link to more detailed records than the standard dataset and we selected patients eligible for linkage to Hospital Episode Statistics (HES) data. We analysed data from 351 CAH patients of all ages as defined by Read and ICD-10 coding, alongside 3510 age- and sex-matched controls. Patients' resource use and costs were analysed by age group: 51 patients/510 controls 0–6 years, 33 patients/330 controls 7–17 years, and compared by Mann-Whitney test. Neonatal utilisations were only captured after a patient was registered with primary care. **Results:** Primary care usage was approximately double for paediatric patients compared with controls, with a median 9.0 vs 4.0 consultations/year ($P < 0.001$) in 0–6 years and 4.0 vs 2.0 consultations/year ($P < 0.001$) in 7–17 years. Secondary care usage was higher in CAH with higher median outpatient appointments: 8.0 vs 0.0 ($P < 0.001$) (0–6 years) and 5.0 vs 0.0 ($P < 0.001$) (7–17 years). Median inpatient admissions were also more common in CAH 2.0 vs 0.0 ($P < 0.001$) (0–6 years) and 1.0 vs 0.0 ($P < 0.001$) in 7–17 years. **Conclusion:** This study shows a significantly increased healthcare utilisation from CAH throughout childhood. Refining and improving treatment for patients with CAH should help to reduce this burden on the healthcare system.

P2-P74

Cholestasis and Hypercalcemia Secondary to Panhypopituitarism in a Newborn

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Cholestatic hepatitis and hypercalcemia are rare features of hypopituitarism in the newborn. So diagnosis of hypopituitarism is frequently delayed. Herein, we report a newborn that was investigated for cortisol deficiency and other pituitary hormone deficiencies and diagnosed with panhypopituitarism upon detection of cholestasis after referral to the endocrinology department for hypercalcemia, a very rare sign of cortisol deficiency. It is unclear which hormone causes cholestasis in patients with congenital panhypopituitarism. Some authors suggested that growth hormone deficiency is the major cause of cholestasis. But there is now good evidence that central adrenal insufficiency is the main cause of cholestatic hepatitis in hypopituitarism. Glucocorticoids were shown to augment bile flow *in vitro* as well as in rats and dogs. Hypercalcemia was reported in 5.5% of primary adrenocortical insufficiency in adults. The proportion of hypercalcemia is unknown in secondary adrenocortical insufficiency. Although the mechanism of hypercalcemia in adrenocortical insufficiency is unknown, lack of serum cortisol is considered to be related increased calcium reabsorbtion from renal tubules and release from bone. Herein, we report a newborn that was investigated for cortisol deficiency and other pituitary hormone deficiencies and diagnosed with panhypopituitarism upon detection of cholestasis after referral to the endocrinology department for hypercalcemia, a very rare sign of cortisol deficiency. Diagnosed with panhypopituitarism clinically and biochemically, the patient's cholestasis recovered at 45th day. A hypophysis MRI revealed a hypophyseal height of 1.5 mm and an ectopic neurohypophysis. This case repot was reported to stress that newborns with cholestasis and hypercalcemia should definitely be investigated for cortisol deficiency and panhypopituitarism.

P2-P75

Clinical Management in Secondary Pseudohypoaldosteronism: A Case Series

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Background: Secondary PHA is a transient aldosterone resistance condition mostly occurring in relation with urinary system infection and/or malformations. Secondary PHA cases and very few case series have been reported in the literature. In this article, we reported a case series of eight patients including different clinic presentations which have not as yet been reported in the literatüre and their long-term follow-ups. **Method:** Patients who have secondary PHA reasons in addition to hyponatremia (<130 mEq/l), hyperpotassemia (>6 mEq/l) and high serum aldosteron levels for the age in Erciyes University Faculty of Medicine Pediatrics Department were included in the study. **Results:** All the patients in our case series were younger than 3 months old. Among eight patients in our case series, seven patients were diagnosed with PHA secondary to obstructive uropathy (OUP), one patient was diagnosed with PHA secondary to ileostomy. Six patients were diagnosed with OUP together with urinary tract infection (UTI) and in all except one patient, secondary PHA recovered with only UTI treatment before applying surgical correction. All the patients in our case series were younger than 3 months old. Three patients with PUV diagnosis, salt wasting recurred in an UTI attack recurring under 3 months of age. Although they had an UTI attack in later follow-ups, salt wasting did not develop. Salt supplementation was made with IV/oral NaCl of 3 mEq/kg per day at least and 32 mEq/kg per day at most. The salt supplementation lasted between 3 days and 6 months. **Conclusion:** Infants known to have UOP should be closely observed for salt wasting in the presence of urinary tract infection, especially in the early infancy period.

P2-P76

High Sensitivity C-Reactive Protein (hsCRP) Levels as Predictor of Salivary Cortisol Acute Response to Mental Stress and/or Mobile Phone Call in Healthy Adolescents

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Background: The hypothalamic–pituitary–adrenal (HPA) axis responds to several acute or chronic environmental stessors, including those of social stress. **Objective and hypotheses:** To assess the HPA axis acute response during mental stress and mobile phone call exposure in healthy adolescents through salivary cortisol measurements and to investigate the modulatory effect of baseline biochemical or low-inflammation markers during this response. **Method:** Twenty healthy children aged 11–14 (12.5 ± 1.5) years, recruited in their schools, entered this cross sectional study, after parental informed consent was obtained. Trier Social Stress Test for Children (TSST-C: 5 minutes oral task followed by 5 min arithmetic task) was performed and salivary cortisol samples were taken at baseline (time #1), immediately after the oral (time #2) and the arithmetic (time #3) task and after a three minute long mobile phone call (time #4). Serum cortisol, ACTH, TSH, T_3, T_4, insulin, glucose and high sensitivity C Reactive Protein (hsCRP) levels were also measured at baseline. **Results:** Salivary cortisol levels suppressed significantly only between baseline and after the mobile phone call (time #4). Baseline blood hsCRP levels correlated to baseline (time #1) and post mental stress (time #2, 3) salivary cortisol levels, but not after the mobile phone call. Baseline blood cortisol levels significantly correlated to the salivary cortisol level assessed after the mobile phone use. No correlation was observed between baseline ACTH, TSH, T_3, T_4, insulin, glucose and salivary cortisol levels of any time sample. **Conclusion:** In adolescents, acute salivary cortisol response to mental stress and/or during a mobile phone call was predicted by baseline hsCRP and serum cortisol levels, with different effect over time: hsCRP effect weakened with time, whereas, serum cortisol effect increased.

P2-P77

Management Dilemmas in a Genetically Female Child with Congenital Adrenal Hyperplasia Raised as a Male

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Background: Conventionally, 46 XX infants with congenital adrenal hyperplasia (CAH) were reared as females, even if considerably virilised at birth. However, lately there has been some debate on this stance, and male gender of rearing is also being considered. **Objective and hypotheses:** We report on a 9 year old genetically female child (N) with salt wasting CAH reared as a male, with precocious female puberty, currently suppressed with GnRH analogs, and discuss his future management. **Method:** Baby N had ambiguous genitalia at birth, and elevated serum 17-OHP, and was diagnosed with CAH due to 21 hydroxylase deficiency. Karyotype was 46 XX and ultrasound scan showed both ovaries and an infantile uterus. The external genitalia however, showed considerable virilisation (Prader stage 4). Despite extensive counselling, parents were adamant to rear the baby as a boy. He was started on long term hydrocortisone and

fludrocortisone, and hypospadias repair performed. Treatment compliance and follow up were suboptimal. **Results:** At 8 ½ years of age, the child presented with bleeding per urethra, and ultrasound scan revealed a haematocolpus. The bone age was significantly advanced (14 years). He was also hyper pigmented, but had not experienced adrenal crisis. He was commenced on GnRH analogues to suppress puberty, and hydrocortisone and fludrocortisone doses were optimised. Child appeared well adjusted to a male gender identity. Psychological assessment was compatible with a male gender identity and role. **Conclusion:** His future management is currently being discussed at ongoing multidisciplinary meetings including endocrinology, psychology and surgical teams. We are planning to continue GnRH analogs, until patient able to give consent for oophorectomy (>18 years). The timing of male hormone replacement therapy, counselling and psychological support for the child and family and transitioning of care are ongoing issues for discussion.

P2-P78

Primary Pigmented Nodular Adrenocortical Disease (PPNAD) Justifying a Pediatric Case of ACTH-independent Cushing Syndrome (CS)

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Background: CS is characterized by excess glucocorticoid excess, either endogenous or exogenous. In children younger than 7 years, the adrenal origin is the most common cause. From this age until adulthood predominates Cushing's disease (central cause). We can divide CS in ACTH-dependent and independent according to laboratory findings. When ACTH-independent, etiologies are related to benign or malignant diseases of the adrenal or McCune Albright syndrome. **Case report:** Two-year-old boy with progressive weight gain, acne, axillary odor, hirsutism, and early aggressiveness for about 9 months. At physical exam: full moon facies, facial acne, hirsutism, mild virilization, behavioral changes, tachycardia and hypertension. Initial investigation showed ACTH-independent CS. Despite an adrenal 5 mm lesion finding at CT, PPNAD was suspected. Initial investigation for Carney complex was normal (skin, testis, heart, thyroid, pituitary). Initially left adrenalectomy was performed followed by the removal of the right adrenal after histopathological examination by intraoperative frozen that suggested architectural changes of the adrenal. He received hydrocortisone protocol intraoperatively and was maintained with stress dose, with subsequent gradual reduction. The clinical outcome was favorable, with improvement of acne and tissue infiltration. He was monitored as an outpatient with hydrocortisone dose of 14 mg/m^2 per day and fludrocortisone 0.1 mg/day. **Conclusion:** PPNAD is a benign disease of the adrenal, with bilateral involvement, which is responsible for <2% of all cases of endogenous CS. In more than 90% of the time, PPNAD is related to the Carney Complex, an autosomal dominant disease that coexists with multiple tumors. The diagnosis of CS is challenging, in the case of a child is even more. Although a rare and benign disease, PPNAD should be remembered as an important diagnosis of ACTH-independent CS.

P2-P79

Three Chinese Patients from Two Kindreds with Aldosterone Synthase Deficiency: Clinical Characteristic with Mutation Analysis Report

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Aldosterone synthase deficiency (ASD) is a rare autosomal recessive disease caused by inactivating mutation in the CYP11B2 gene, usually presenting with severe salt-wasting in infancy or stress-induced hyperkalaemia and postural hypotension in adulthood. ASD is unable to be detected by Neonatal screening of 17-hydroxyprogesterone, hence patients would not be diagnosed until they suffer from salt-wasting crisis. Due to this potentially life-threatening risk, early detection and adequate replacement therapy will significantly improve the prognosis. **Objective:** We summarized the clinical features of three cases from two unrelated families with ASD; to improve physicians in the understanding and diagnosing of ASD. **Method:** By describing clinical symptoms, biochemical characteristics and outcomes; conducting CYP11B2 molecular genetic analysis using direct DNA sequence. **Result:** Three patients from two unrelated, non-consanguineous families. Two brothers (M1 and M2) visited our unit for the first time at 2 m and 2.5y respectively; the other patient is a girl (F) at 5 m. All of three patients had repeated vomiting with poor feeding at newborn period (1–2w) and failure to thrive. They all visited local hospitals and were found to have hyperkalaemia, hyponatremia and metabolic acidosis. Treatment of underlying condition was started at that time, followed by giving additional sodium supplementary 2.0–4.5 g/day. Patient F also received 'Sodium bicarbonate, Sodium polystyrene sulfonate, etc' to reduce blood potassium concentration. Patient F has a healthy elder sister; and a baby brother who died 10 days after birth, he presented similar symptom during his first week after birth, was also suspected to be affected. No hyperpigmentation were observed on all three patients, all of them have normal external genitalia. Patients M1 and F's laboratory test revealed: hyperkalaemia (K^+ 7.64–7.69 mmol/l), hyponatremia (Na^+ 123–132 mmol/l), patient F had metabolic acidosis (TCO2 13.4 mmol/l). Plasma ACTH, Cortisol, Testosterone, Progesterone, 17-hydroxyprogesterone, Androstenedione were in normal range. Plasma renin was highly elevated (864.3–1287 pg/ml; the normal range in adult is 4–24 pg/ml), while plasma aldosterone was in normal range for patients age (117–672.11 pg/ml; NR 10–160 pg/ml). Sequencing of CYP11B2 gene showed that patients M1 and M2 both carried same heterogenous pathogenic mutation: c.1121G>A (p.Arg374Gln) was inherited from their father and c.1486delC

p.(Leu496fs) was inherited from their mother. Patient F homozygous for c.1303G > A p.(Gly435Ser) which is a known pathogenic mutation. We later learnt that her mother has the same mutation site and she also has generalized weakness with unknown newborn condition; her father does not have any mutation on CYP11B2 gene. Patient M2 had been given only sodium supplementation treatment till 6 month old then gradually discontinued. He presented normal growth development and normal blood electrolyte till his last follow up at 4.33 years old. Patients M1 and F received fludrocortisone therapy at dosages of 0.1 mg Qd, and 0.1 mg Bid respectively, with sodium supplementation 2–3 and 3–6 g/d respectively. Patient M1's mother only gave him fludrocortisone at 0.1 g Qd and discontinued sodium supplement therapy by herself when M1 started to receive his food supplements at 6 months old. He regularly followed up till his last visit at 1 years old. He did not present any undesirable clinical effect; his blood electrolyte and growth was in normal range. Patient F last visit was at 1 years old, still needed NaCl 3–6 g/d supplementation and fludrocortisone therapy 0.1 g Bid. Her blood electrolyte was normal but her growth is slower than others her age. **Conclusion:** We reported three Chinese patients from two kindreds that have newborn salt-wasting clinical features; molecular genetic testing will very helpful for accurate diagnostic. Adequate fludrocortisone replacement therapy and sodium treatment brings good prognosis for patients.

P2-P80

Addisonian Crisis Due to Autoimmune Adrenalitis in a 14 Year Old Boy with a History of Stem cell Transplantation (HSCT)

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Background: Various endocrine complications are common after HSCT but primary adrenal insufficiency (Addison's disease, AD) is absolutely rare. To the best of our knowledge, there is only one case of AD reported in a 9-year-old girl after HSCT and busulfan and cyclophosaphamide-based conditioning for myelodysplastic syndrome. **Objective:** We report on a 14-year-old boy from Albania who developed an Addisonian crisis 12.7 years after HSCT. **Case report:** At the age of 17 months juvenile myelomonocytic leukaemia (JMML) was diagnosed and treated with HSCT after myeloablative conditioning chemotherapy. Three months after HSCT, he developed a severe graft versus host disease (skin and intestines), which was treated with 6-mercaptopurin until the age of 26 months. Thereafter, yearly after-care visits were performed at our oncological outpatient clinic. At the age of 9 years. Hashimoto thyroid autoimmune disease (subclinical hypothyroidism with goiter) was diagnosed and treated with L-thyroxine. Auxological data at the age of 14 years: Height 165.5 cm (−0.37 SDS), weight 46.8 kg, BMI 17.1 kg/m^2 (−0.9 SDS); Tanner stage: pH 3, testes volume 8 ml. Two weeks after his last follow-up visit, he went to a ski camp, where he and the majority of his classmates became ill with fever and bronchitis. He was admitted to our hospital in a reduced general condition with nausea and a weight loss of 1.3 kg. Laboratory data: serum sodium 114 mmol/l, potassium 6.0 mmol/l, cortisol (4 pm) 264 nmol/l. Elevated levels of plasma ACTH (625 pg/ml), and serum renin (2550 pg/ml) led to the diagnosis of primary adrenal insufficiency, which was confirmed by positive autoantibodies to the adrenal cortex (1: 32). **Conclusion:** We speculate that our patient has autoimmune polyglandular syndrome (APS) type 2 with no coherence to the diagnosis of JMML and to HSCT.

P2-P81

Assessment of Cardiac Function in Children Followed up for Congenital Adrenal Hyperplasia: A Case Control Study in Cameroon

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Background: Diagnosis of congenital adrenal hyperplasia (CAH) is delayed in developing countries and children are long exposed to high levels of androgens. These androgens have deleterious effect on heart. **Objective and hypotheses:** Evaluate cardiac function of children followed for CAH and compared it to a group of healthy children. **Method:** We carried out a case-control study, 1 case for 2 controls matched for age and genotypic sex, among children followed up for CAH in the single endocrinology unit of the Mother and Child Center of Chantal Biya's Foundation. Standard echocardiography measurements were done in time mode motion, two-dimensional and doppler. We analyzed the ejection fraction (LVEF), fractional shortening and left ventricular mass; output and cardiac index; E and A waves, E/A ratio; deceleration time and diameter of the left atrium; tricuspid annular plane systolic excursion. **Results:** We included 19 patients with a median age of 6 years and 38 controls stackable distribution. One subject had dilated cardiomyopathy. LVEF ranged between 60 and 83%. Systolic function of two ventricles and diastolic of the left one were comparable in the two groups. **Conclusion:** Excess androgens does not seem detrimental to the cardiac function in our study population.

P2-P82

A Novel Mutation of HSD3beta2 Presenting as Hypospadias with Salt-wasting in a Male Infant

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Background: HSD3B2 is a rare cause of autosomal recessive primary adrenal insufficiency, potentially associated with under virilisation of XY males and virilisation of XX females. We present a case of a male infant presenting at term with ambiguous genitalia (DSD) with underlying diagnosis confirmed biochemically and genetically with a novel mutation of HSD3beta2. **Objective:** Case report. **Patients and methods:** Baby was born as FTND with no risk factors. Newborn examination revealed perineal hypospadias with chordae; stretched penile length 1.6 cm. Gonads impalpable but identified by ultrasound in inguinal canals as normal testis volumes. **Results:** Day 2 bloods; Testo 15 nmol/l (androstenedione >35 nmol/l; 17-OHP 40 nmol/l – both raised – results not available for $>$ 2 weeks); LH <0.1, LH <0.1 IU/l). Short Synacthen Test Day 5 (Baby clinically well but plasma Na 134 mmol/l): cortisol basal 110, 30 min 147, 60 min, 109 nmol/l confirmed adrenal insufficiency. Baby discharged home on hydrocortisone 1.25 mg 6-hourly oral. **Progress:** Patient readmitted age 5 days in salt-losing crisis: vomiting, dehydrated, Na 108, K 7.1, urea 12 mmol/l. Treated successfully with IV/oral saline, hydrocortisone and fludrocotisone added in standard doses. Patient stable in follow-up. Urine steroid profile from Day 2 identified 3Beta HSD with cortisol metabolites almost undetectable (in context of normal electrolytes at that time) and high 3B-hydroxy-5-ene steroids. DNA analysis has confirmed a novel, nonsense mutation in HSD3B2 gene: g.5554dupT, c.65dupT, p.Leu22Phefs*27 (nomenclature based on HGVS recommendations (www.hgvs.org//)). **Conclusion:** We report a case of DSD male undervirilisation with primary adrenal insufficiency resulting from a novel, nonsense mutation in HSD3 beta 2 gene. Micropenis is an important sign to merit extended investigation in patients with hypospadias.

P2-P83

Testicular Adrenal Rest Tumors in two Young Patients with Congenital Adrenal Hyperplasia

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Background: Testicular adrenal rest tumours (TART) may develop in males with congenital adrenal hyperplasia (CAH), with a widely variable prevalence. Having no malignant features, there seems to be no need to remove them. However, these lesions may increase in size and number when exogenous hormone therapy is inadequate. Untreated, may lead to infertility and irreversible damage of the surrounding testicular tissue. **Case report:** We present two cases, diagnosed with CAH at the age of 3 weeks due to total 21-hidroxylase deficiency. **First case:** 15 years boy, treated with glucocorticoids and salt supplementation until the age of 6, then interrupted by GP. In the last six months presented progressive enlargement of the scrotal bursae and was directed to surgery. The endocrinological evaluation diagnosed TART. Glucocorticoid therapy was again initiated, with significant hormonal and imagistic improvement. **Second case**: 10 years boy, received intermittent steroid supplementation (poor compliance). At the age of 8, the scrotal ultrasound revealed increased size of testes, with bilateral TART. Long-term evolution of adrenal hyperplasia with inconsistent and incomplete therapy resulted in early onset of central puberty. Given the elevated gonadotropins, advanced bone age and stature, the therapy with GnRH analogues was introduced with improvement. **Discussions and conclusions:** The early diagnosis of TART and the implementation of appropriate treatment approaches are important for the protection of gonadal functions. TART may regress with administration of exogenous glucocorticoids, intensifying therapy being the first step in their management. The presence of TART in these two patients is significant, suggestive of suboptimal hormone replacement therapy. Untreated TART may expand and destroy the testicular parenchyma, resulting in infertility. A future system of regular follow-up and standards in therapeutic concepts is needed to guarantee an improved fertility and quality of life in patients with CAH.

P2-P84

Hyperreninemic Hypoaldosteronism: Clinical and Genetic Features in Pediatric Patients

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Background: Isolated hyperreninemic hypoaldosteronism due to aldosterone synthase deficiency is a rare autosomal recessive disorder linked to aldosterone biosynthesis defect (involving CYP11B2 gene). Its clinical presentation varies with age: during the first weeks of life it usually presents with salt-wasting syndrome (with severe hyponatremia, hyperkalemia, metabolic acidosis, vomiting, signs of dehydration) while in children it is usually characterized by failure to thrive, anorexia, mild dehydration and electrolyte abnormalities. Growth retardation may persist throughout childhood without appropriate therapy. **Objective and hypotheses:** We describe the clinical onset and course and the genetic evaluation of five patients with primary hyperreninemic hypoaldosteronism in Tuscany. **Method:** Five patients (two males, three females) came to our attention for electrolytes disorder (hyponatriemia and hyperkaliemia, increased plasmatic renin activity, low or normal aldosteron level) with normal cortisol and sex hormones values. Two of them presented with neonatal salt-wasting syndrome. They all have been suspected for primary hyperreninemic hypoaldosteronism on the basis of clinical and laboratory features. Appropriate therapy with fludrocortisone was started in four of them with general improvement. All of the patients underwent genetic analysis: amplification by PCR and Sanger sequencing of nine exons of CYP11B2. **Results:** Three patients showed mutations in homozygous state: c.1231G$>$C (p.Gly411Arg) in exon 8, c.554C$>$T (p.Thr185Ile in exon 3, c.780G$>$A (p.Trp260*) in exon 4. One patient showed two mutations in heterozygous state:

c.554C>T (p.Thr185Ile) in exon 3 and c.763G>T (p.Glu255*) in exon 4. They all supported the diagnosis of hypoaldosteronism. One patient present not detectable gene mutations. **Conclusion:** Clinical and laboratoristic suspect of hyperreninemic hypoaldosteronism should be supported by genetic confirmation. Therapy with fludrocortisone should be life-long administered in these patients in order to ensure a good quality of life and reduce long-term damage.

P2-P85

Peculiarities of Manifestation and Short-term Effects of Hormonotherapy in Children With Congenital Adrenal Cortical Hyperplasia

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Objective and hypotheses: To establish clinical, laboratory peculiarities of manifestation, short-term effects of performance of hormonotherapy children with CACH. **Method:** We examined 32 children with CACH (29 children – with salt-losing form (SLF) (boys/girls = 18/11), 3 – virile form (VF) (boy/girls = 1/2)) in onset and after 1 year of therapy. Weight and growth dynamics, parameters of potassium (K), sodium (Na), glucose, adrenocorticotropic hormone (ACTH), 17-Hydroxypregnenolone (17OHP), pH, buffer bases (BE)) were analyzed in blood. We used StatSoft Statistica v6.0. **Results:** Age of onset: boys with SLF – 59.41 ± 4.66 days, girls – 65.3 ± 13.15 days ($P < 0.05$); boy with VF – 110 days, girls – 1285 ± 233.35 days ($P < 0.05$). Hyperpotassemia (5.66 ± 0.25 mmol/l, $P < 0.01$), hyponatremia (130.19 ± 1.81 mmol/l, $P < 0.005$), euglycemia (4.57 ± 0.1 mmol/l, $P < 0.05$), 17OHP levels increasing (358.8 ± 3912 nmol/l, $P < 0.05$), ACTH increasing (69.6 ± 7.95 pg/ml, $P < 0.05$), metabolic acidosis - pH (731 ± 0.02; $P < 0.05$), BE (−7.96 ± 0.77 mmol/l, $P < 0.05$) were in children with SLF. The elevation of 17OHP values (158.83 ± 15.11 nmol/l, $P < 0.05$), ACTH (63 ± 0.79 pg/ml, $P < 0.05$) in onset of VF were revealed. Initial doses of glucocorticoid (hydrocortisone, mg/m^2/d) and mineralocorticoid (fludrocortisone, mg/m^2/d) in children with SLF: 26.09 ± 2.82 and 0.46 ± 0.03 respectively (maintenance doses one year after: 13.28 ± 1.14 and 0.2 ± 0.02 respectively). The initial doses of hydrocortisone (mg/m^2/d) in children with VF: 15.35 ± 3.85 (maintenance doses one year after: 12.68 ± 3.85). The normalization of K (4.32 ± 0.1 mmol/l), Na (138.2 ± 0.84 mmol/l) levels were in patients with SLF after one year of treatment. Negative correlations between the age of onset of the disease and initial mineralocorticoid dose ($r = -0.37$, $P < 0.001$) in patients with SLF, initial glucocorticoid dose and 17OHP levels in children with SLF ($r = -0.3$, $P < 0.05$), initial glucocorticoid dose and rate of growth in patients with SLF and VF ($r = -0.3$, $P < 0.01$) were noticed. **Conclusions:** i) Suitably glucocorticoid and mineralocorticoid doses ensure normal growth rates in children with CACH; ii) age of onset is one of the factor defining initial mineralocorticoid dose.

P2-P86

Congenital Adrenal Hyperplasia Revealed by Adrenal Nodules

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Background: Congenital adrenal hyperplasia (CAH) is a pathology with a genetic deficiency of one of the enzymes of steroidogenesis. It is due to 21 –Ohase deficiency in 90–95% of cases. The complete deficiency of this enzyme is responsible for the classic form (sexual ambiguity at birth with or without salt loss). While the partial deficiency results in a polymorphic clinical presentation occurring in childhood or adolescence. In rare neglected cases, the diagnosis is made during the exploration of adrenal masses. **Objective and hypotheses:** Reporting phenotypic characteristics of adolescents with CAH revealed later during the exploration of adrenal masses. **Method:** This is a retrospective study involved six teens carry a CAH unknown. A clinical and oriented paraclinical (biological and radiological) assessment was conducted. **Results:** All patients were female. Their average age was 14 ± 0.8 (15–18). The CAH was due to deficit in 21 -OHase. Diagnostic circumstances are: exploration of amenorrhea: 4; Radiological discovery: 2. The clinical picture found in all cases, an array of significant virilization with primary amenorrhea and small stature (average size - 2.5 SD/M Sempe, - 2 DS/TC). Laboratory tests were in favor: DHA S average:1245 ug/dl, 17 OH P average: 49.6 ng/ml, ACTH average: 90 pg/ml. Abdominal CT found bilateral nodular adrenal hypertrophy n: 6. Pelvic ultrasound found a small uterus with polycystic ovaries. **Conclusion:** CAH late-onset is a diagnosis to be systematically sought in front adolescent patients with signs of hyperandrogenism associated with virilization and cycle disorders. The diagnosis must be as early as possible to allow normal growth, female puberty and satisfactory fertility.

P2-P87

Urosepsis or Pseudohypoaldosteronism in a Neonate?

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Background: Pseudohypoaldosteronism (PHPA1) is a disorder of impaired renal electrolytes re-absorption and excretion. Primary PHPA1 has two clinically and genetically distinct forms: (i) Renal autosomal dominant form, which involves a mutation in the

mineralocorticoid receptor; (ii) Systemic autosomal recessive form, which involves a mutation in the epithelial sodium channel. PHPA1 can be also transient secondary to urinary tract infections (UTI)/ malformations. **Objective and hypotheses:** To emphasize the nature of secondary PHPA1 and the need for long-term follow-up. **Method:** Case presentation of a neonate with a salt-wasting crisis. **Results:** A 17-day-old male presented with a two-day history of poor feeding, irritability and dyspnea. Physical examination revealed a baby in septic shock. Initial blood work showed severe hyponatremia (Na-121 Meq/l), hyperkalemia (K-9.2 Meq/l), metabolic acidosis (pH – 6.6, HCO3- 2.2, pCO2 – 23.6), and elevated BUN, creatinine and urine Na/K ratio. The baby was treated intensively in the PICU with intravenous fluids, antibiotics, electrolyte and acid-base corrections and hydrocortisone. The differential diagnosis included congenital adrenal disorders, Barter's syndrome and forms of PHPA1. Further labs revealed normal cortisol, normal androgens, high aldosterone (109,000 pmol/l, normal range up to 4000 pmol/l) and high renin acitivity (>50 ng/ml/h). Microbiology cultures were positive for *E. coli* bacteremia and UTI. Renal ultra-sound was normal and cystogram showed vesico-urethral reflux. Despite normal electrolytes, due to failure to thrive and persistently high aldosterone and renin levels we added salt supplements and weight gain improved. Infant's sweat test and paternal aldosterone and renin were normal. Finally, at the age of 2 years aldosterone and renin levels returned to normal. **Conclusion:** We present a case of secondary PHPA1 due to *E. coli* urosepsis in a baby with vesico-urethral reflux. It emphasizes how secondary PHPA1 is part of the differential diagnosis of a salt-wasting crisis and the need for a long-term management.

P2-P88

A Case Report of Adrenocortical Adenoma in a Young Girl

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Adrenocortical tumors are rare childhood neoplasms. More than 95% are functional and present with virilization, Cushing's syndrome, hypertension, or hyperestrogenism. We present a exceptionally rare case of a patient with androgen- and cortisol-co-secreting adrenal adenoma. A 4-year-old girl was referred to us for appearance of symptoms of virilization: moustache, pubic hair, and gradual enlargement of clitoris for 1 year. Her voice gardually deepened and changed to male pattern. On systemic examination, her weight was 26 kg, height was 112 cm, BMI 17.46. Pulse was 100 beats/min, blood pressure was 100/60 mmHg. She had no Cushingoid features. The laboratory showed that she had elavated 24 h urine free cortisol level: 362.7 μg/dl (21–143 μg/dl) and serum testosteron: 286.5 ng/dl (14–76 ng/dl). The serum ACTH was low: 1.58 pg/ml (7.2–63.3 pg/ml). Levels of DHEAS were normal: 0.914 μg/ml (0.5–3.5 μg/ml). Levels of 17OH(P), LH, FSH, estrogen were normal range. The bone-age was 11 years. Abdominal CT scan showed a left adrenal mass. It was decided to manage her with surgery to remove the tumor. Subsequently adrenalectomy was performed and histopathology study revealed a 5.5×5×3.5 adrenal adenoma. Follow-up of the patient showed that signs of virilization were suppressed. Serum testosterone levels dropped to normal after surgery, and remained normal. Two to 6 months after adrenalectomy, she was noticed to have significant symptoms of adrenal insufficiency and gradual enlargement of breast (Tanner B2). Laboratory tests showed: AM cortisol levels and ACTH levels were low on several occasions. The tests of diagnosis for precocious puberty (PP) were performed. After confirming the diagnosis adrenal insufficiency and PP the patient was given 5 mg of hydrocortisone a day and 3.75 mg of Diphereline a month. In summary, a diagnosis of adrenal cortical adenoma requires surgical removal as early as possible to prevent the untoward effects of virilization or corticosteroid excess. Although the girl in the present study seems to have been cured, long-term follow-up is warranted.

P2-P89

Abstract unavailable.

P2-P90

A Genetic Diagnosis of Familial Glucocorticoid Deficiency Resulting in Cessation of Long-term Mineralocorticoid Treatment in Three Siblings

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Background: Familial glucocorticoid deficiency (FGD) is a rare autosomal recessive disorder characterised by ACTH resistance and leads to isolated glucocorticoid deficiency. Mutations in the gene encoding the ACTH receptor (MC2R) are responsible for around 25% of cases. **Case report:** The female index case was hyperpigmented at birth. At one week of age her ACTH level was >1200 ng/ml, plasma renin activity (PRA) 11.4 pmol/ml/h with an aldosterone of 520 pmol/l. Adrenal ultrasound scan did not identify the left adrenal but the right adrenal appeared to be of a normal size. She was diagnosed with adrenal hypoplasia congenita (AHC) and commenced on hydrocortisone and fludrocortisone supplements. Investigations revealed persistently elevated ACTH levels often >1250 ng/l/h yet persistently low PRA below 2 nmol/l/h. Subsequently a male and female sibling were also diagnosed with AHC and received hydrocortisone and fludrocortisone supplementation. They similarly had persistently low plasma renin levels. Genetic testing revealed a homozygous mutation of the MC2R gene in all 3 siblings resulting in a diagnosis of FGD. Therefore fludrocortisone supplementation was gradually weaned then stopped. Subsequent blood pressure readings and sodium levels remained within normal limits. The index case, who had been taking fludrocortisone for 14 years, had ambulatory blood pressure monitoring pre

and post withdrawal of mineralocorticoid. This was normal. Extended testing showed that both parents and a number of other family members to be heterozygous for the MC2R gene mutation. **Conclusion:** In our family, despite many years of treatment it was possible to withdraw the fludrocortisone and thus potentially prevent unnecessary iatrogenic effects such as hypertension. A genetic cause should be pursued in all individuals with AHC. In the presence of persistently low or normal PRA levels a diagnosis of FGD should be considered.

P2-P91

Corticosteroid-Induced Adrenal Insufficiency in a Child with T Cell Lymphoblastic Lymphoma

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Background: Glucocorticoids play a major role in the treatment of lymphoblastic lymphoma. However, supraphysiological glucocorticoid therapy may cause the secondary adrenal insufficiency. **Presentation of case:** A 11-year-old boy with T cell lymphoblastic lymphoma, treated according to COG A5971 protocol, experienced sudden onset of tremor and general weakness in the first day after tapering 28 days of glucocorticoid therapy. He had a moon face and pigmentations around his neck. Early-morning plasma cortisol, ACTH level and the combined pituitary hormone test using insulin suggested adrenal insufficiency. Plasma cortisol, ACTH level were normalized and other symptoms were improved after glucocorticoid replacement therapy. **Discussion:** Secondary adrenal insufficiency commonly occurs after cessation of glucocorticoid therapy. Adrenal insufficiency is considered when children complain of sumptoms related with hyponatremia after glucocorticoid therapy.

P2-P92

A Rare Endocrine Association of Dilated Cardiomyopathy with Congenital Adrenal Hyperplasia due to 11 Beta Hydroxylase Deficiency

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Background: Cardiomyopathy is a heterogeneous group of disorder of myocardium associated with mechanical and/or electrical dysfunction that usually exhibit inappropriate ventricular hypertrophy or dilatationleading to heart failure. Congenital adrenal hyperplasia (CAH) due to 11β-hydroxylase deficiency is rare inherited disorder of cortisol biosynthesis, due to genetic defects of CYP11B1 gene presenting as hypertension, features of androgen excess, and peripheral precocious puberty in children. **Objective and hypotheses:** To demonstrate the association between dilated cardiomyopathy and CAH secondary to 11β-hydroxylase deficiency. **Method:** Two year old boy born to non-consanguineous parents was diagnosed with CAH at 18 months of age when he presented with features of virilisation and hypertension. **Results:** He also suffered from respiratory distress, tachycardia with gallop rhythm, and cardiogenic shock. Chest X-ray and 2D echocardiography suggested massive cardiomegaly and Doppler studies revealed dilated cardiomyopathy with significantly reduced left ventricular dysfunction (Ejection Fraction of 15–20%). He was treated with furosemide, spironolactone, hydrocortisone and enalapril following which the blood pressure normalized and the repeat echocardiography suggested improvement in cardiac function (Ejection Fraction 36%). **Conclusion:** We report a rare association of dilated cardiomyopathy with CAH due to 11β-hydroxylase deficiency. The cardiac function improved following hydrocortisone therapy suggesting the possible direct effect of corticosteroids on cardiac function. Animal studies have shown reduced cardiac muscle contractility following adrenalectomy which is reversible with the use of dexamethasone. Significant decrease in calcium uptake from sarcoplasmic reticulum could be potentially responsible for myocardial dysfunction.

P2-P93

Use of an F-DEX Monocyte Binding Assay to Measure Steroid Responsiveness of Patients and their Related Donors Undergoing Stem Cell Transplant

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Background: Graft versus host disease (GVHD) is a complex disease resulting from donor T-cell recognition of a genetic disparate recipient, which is unable to reject donor cells after allogeneic transplant. Glucocorticoids (steroids) are the mainstay of acute GVHD therapy. Glucocorticoid resistance has been characterized in several inflammatory conditions including asthma, rheumatoid arthritis, systemic lupus, erythematosus, ulcerative colitis, and Crohn's disease. Glucocorticoid resistance has also been seen in a subset of patients with GVHD. However, to date, the biology of this steroid refractoriness in the treatment of GVHD has not been examined. **Objective and hypotheses:** We propose to study the steroid sensitivity of bone marrow transplanted patients and their related donors using a Fluorescein labelled dexamethasone (F-DEX) monocyte binding assay to help in the treatment of these patients. **Method:** Collection of pre- and post-BMT blood samples from 20 patient/donor pairs who plan to undergo allogeneic bone marrow transplant. The samples will be analysed using a F-DEX monocyte binding assay of collected monocytes. **Results:** Currently preliminary results are being ascertained. **Conclusion:** We hope that the data collected from these patients will help to examine steroid sensitivity in these patients and help to design better treatment strategies for these patients.

P2-P94

11β- Hydroxylase Deficiency due to a Novel Compound Heterozygous Mutation and Literature Review

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Background: The incidence of 11β-hydroxylase deficiency is quite low in China, less is reported about the gene mutation in Chinese population. **Objective and hypotheses:** To analyze the clinical features and CYP11B1 gene mutations of a family with 11β-hydroxylase deficiency (11β-OHD) and literature review were also included. **Method:** Physical examination and laboratory tests were done on a 4 years old girl and gene mutation screening was conducted in her and her parents. **Results:** The adrenocorticotropic hormone (ACTH), 17-hydroxyprogesterone(17-OHP) were normal and testosterone, DHEA, estradiol, serum sodium levels increased while potassium and renin levels decreased. Bilateral adrenal enlarged according to CT scan. A novel compound heterozygous mutation R453Q/R374W was found in the patient and the mother was found to carry R374W allele and the father was found to carry R453Q allele. R453Q was a missense mutation previously reported to cause the disease. R374W was a novel missense mutation that was predicted to lead to decreased 11β-hydroxylase activity. The indicators of the patient recovered and keep normal under hydrocortisone. According to the literature review, the prevalence of the disease is likely to be lower in China than previously reported in other countries. **Conclusion:** A novel compound heterozygous mutation was found to be a disease-causing mutation. Hydrocortisone is suggested other than dexamethasone in treating 11β-OHD in Child.

P2-P95

Early Adrenarche: A Common Query but not Easily Resolved

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Introduction: Early/advanced adrenarche is a frequent reason for consultation in Children Endocrinology. **Objectives:** To evaluate the number and characteristics of cases of early/advanced adrenarche referred for assessment to the Children's Consultation Endocrinology in the period between January 2015 and December 2015. **Results:** In this period are rated 522 first consultations of which 39 (7%) have been prematurely adrenarche. In the 39 cases; 28 cases were girls (71%) and 11 children. 30 cases were born in Spain (76%) and 8 in Africa. In three cases there was a history of hyperandrogenism found in first-degree family. As for perinatal history three were born preterm with weight and suitable length and a case (born at term) was small for gestational age. The average age of consultation was 7 years 9 months (minimum 4 years 9 months) in girls and 8 years 4 months (minimum 5 years 9 months) in children. 64% (25/39) had a weight according to age. 11 were diagnosed of overweight and obesity three, the latter three had advancement of bone age of 2 or more years for chronological age. Bone age was according to their chronological age in 15 of the 39 cases. Study has been made of 17-OH progesterone, testosterone and DHEA-S in all cases with bone age advancement, resulting in normal range * values in all but one case with testosterone levels of 2.7 ng/dl and advancement of bone age 2.5 years (child finally diagnosed a Leydig cell tumor). **Conclusions:** The results conform to the published literature; the highest incidence of early/advanced in girls in immigrant population and its relationship to overweight adrenarche. A closer contact with the Primary Care Pediatrics could provide those children with advanced bone age adrenarche and according to their chronological age were controlled by their Pediatrician thus avoiding unnecessary travel and consultations.

P2-P96

Assessment of Clinical Effectiveness and Safety of Using Flutamide in Children with Pre-menarche Hierperandrogenismo

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Today we have an increase in patients with early-ahead forecast pubarche with impaired bone carving for advancement but organicidad criteria (HSC) but if dysfunction or adrenal hyperandrogenism and/or ovarian There are several anti-androgen drugs, all without usual pediatric use (use 'of label'). Low-dose flutamide 62.5 mgr/day has been postulated as a treatment in these cases, but its use is restricted due to the risk of side effects (gynecomastia and liver involvement). **Objective:** To study the clinical safety and efficacy of flutamide in adrenal hyperandrogenism girls affected with bone age advancement and premenarchal. **Methods:** Girls significant over 6 years, early pubarche not thelarche, of course affected adrenal hyperandrogenism (ACTH test compatible with functional hyperandrogenism, no HSC), bone advancement. Use 'off label' drug, informed consent. Control at baseline, 3.6, 9 and 12 months after implantation. voluntary use. Cost for families. Variables blood count, transaminases, basal androgens, EO (G-P), height, weight, Tanner. Comparative study. IBM SPSS 19.0 Stastistics, Nonparametric paired samples $n<30$. **Results:** Twenty girls, mean age 6.8 to (6–8). previous size +0.8 SDS (0.2–1.7) for target height SDS 0.2 (−0.5,0.6); EO (G-P) average 19.5 months advance (15–30) and prognosis of size (B-Pinau) SDS −0.6 0.8 Difference parental height SDS. Average drug use 13.4 months (12–15) at doses of 62.5 mgr/day. After follow-up period event No clinical side effects. No alterations in the blood count, BQ, lipid profile and blood count. Size +0.7 SDS (0.3–1.5) (*P*: 0.23), EO (GP) advancement average 12.1 months (11–24) (only observer) difference of 7.3 months ($P=0.001$) and forecast size (B -Pinau) −0.3 0.3 Difference SDS SDS (*P*: 0.04) **Conclusion:** The use of low-dose flutamide and in a limited time does not appear in our series associated with biochemical alteracions, limitarparciaelmente allows the advancement of bone maturation and improve the prognosis of final height. Further studies are required in this regard.

P2-P97

Congenital Adrenal Hyperplasia – Subtle Presentations with Critical Electrolyte Imbalances and Cardiac Arrhythmias. Experiences from one Hospital

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Background: Congenital adrenal hyperplasia (CAH) can present with salt loss, hyperkalemia and arrhythmias in the neonatal period. If CAH is not diagnosed and treated early, neonates are susceptible to sudden death in the first few weeks of life. This problem is particularly critical in boys who have no genital ambiguity to alert physicians before the onset of dehydration and shock. **Objective and hypotheses:** We recommend that a diagnosis of CAH be considered in neonates presenting with hyponatremia, hyperkalemia and shock. **Method:** A 10 day old presented to the emergency department with a history of poor feeding. He was afebrile and had lost 5% of his body weight. His heart rate was 65/min with normal saturations and a systolic murmur. ECG showed broad complex bradycardia. Blood gas analysis showed a ph of 7.3, sodium of 112 mEq/l and potassium of 9.7 mEq/l. On obtaining the electrolyte results, a presumptive diagnosis of CAH was made. Examination showed that he had normal male genitalia with scrotal hyperpigmention. Saline bolus, nebulised salbutamol, calcium gluconate and IV hydrocortisone were commenced. A brief focussed history from parents revealed first degree consanguinity. Following administration of calcium gluconate his heart rate increased to 150/min with regular sinus rhythm He was later confirmed to have 21-hydroxylase deficiency with a 17-OHP of 280 nmol/l. His heart murmur was confirmed to be innocent. **Results and conclusion:** In the index case, CAH presented with a life-threatening arrhythmia the presence of a cardiac murmur was a confounding factor. Timing and appropriate medical management in the emergency unit can prevent fatality. Finally a combination of hyperkalemia and hyponatremia with metabolic acidosis is suggestive of adrenal insufficiency and treatment with hydrocortisone gives excellent response.

P1-P98

Knock in of the Recurrent R368X Mutation of PRKAR1A that Represses cAMP-dependent Protein Kinase A Activation: A Model of Acrodysostosis Type 1?

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Background: In humans, activating mutations in the PRKAR1A gene cause acrodysostosis1 (ACRDYS1). Two striking features of this rare developmental and skeletal disorder are renal resistance to PTH and chondrodysplasia resulting from the constitutive inhibition of PTHR1/Gsa/AC/cAMP/PKA signaling caused by the PRKAR1A mutations. **Objective and hypotheses:** Document the consequences of the germline expression of a PRKAR1A mutation causing a dominant repression of cAMP-dependent PKA. **Method:** Develop a mouse knock-in of the recurrent acrodysostosis R368X PRKAR1A mutation. **Results:** No litters, thus no homozygous [R368X]/[R368X] mice, were obtained from [R368X]/[+] females. In [R368X]/[+] mice born from [R368X]/[+] males crossed to WT females, western blots analysis confirmed mutant allele heterozygous expression. Growth retardation, peripheral acrodysostosis (including brachydactyly affecting all digits) and facial dysostosis were demonstrated in [R368X]/[+] mice by weight curves and skeletal measurements (micro CT scan) as a function of time. [R368X]/[+] male and female mice were similarly affected. Unexpected, postnatal cartilage (alcian blue) and bone (alizarin red) analysis revealed a striking delay in mineralization of the cartilage and epiphyseal secondary ossification centers in mutant mice. Plasma PTH and basal urinary cAMP were significantly higher in [R368X]/[+] compared to WT mice. PTH injection increased urinary cAMP similarly in [R368X]/[+] and WT mice. PKA catalytic PRKACA subunit expression was regulated in a tissue (kidney not bone and liver) and subunit (not the regulatory PRKAR2A and PRKAR2B) manner. **Conclusion:** This model, the first describing germline expression of a PRKAR1A mutation causing dominant repression of cAMP-dependent PKA, reproduces the main features of ACRDYS1 in humans. It should be helpful to decipher the specificity of the cAMP/PKA signaling pathway, a pathway playing a crucial transduction role for numerous stimuli. In addition, our results raise the possibility that PRKAR1A is a molecular hub at the crossroads of signaling pathways orchestrating chondrocyte proliferation and differentiation.

P1-P99

Automated Greulich-Pyle Bone Age Determinations in Children with Chronic Endocrine Diseases

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Background: Prediction of adult height is a standard procedure in pediatric endocrinology, but it is associated with considerable interrater variability. **Objective and hypotheses:** To compare the new adult height prediction (PAH) method by automated bone age determination (BoneXpert™) with the conventional PAH method by Bayley Pinneau (BP) based on bone age determination according to Greulich & Pyle. Furthermore, to assess measures of bone health by bone health index (BHI) and pQCT. **Method:** Height and near final height was determined in 82 patients (48 females) with chronic endocrinopathies at time of transition to adult care and with 10.45 ± 2.12

years. In addition, pQCT and X-rays of the left hand were performed to obtain BHI and to assess bone ages according to Greulich and Pyle (manually by three experts) and by BoneXpert™. PAH was calculated using BP and BoneXpert™. **Results:** The conventional and the automatic bone age determination revealed a mean difference of 0.23 ± 0.74 years ($P = 0.0027$), negligible if bone age was retarded or accelerated. The automated prediction of adult height by BoneXpert™ in females was 156.96 ± 5.50 cm, in males PAH was 171.75 ± 6.70 cm, the latter overestimated by 2.81 ± 4 cm. When bone age was accelerated PAH by BoneXpert™ was slightly overestimated in females (2.7 ± 2.9 cm) and in males (1 ± 1.9 cm) compared to final height. If bone age was retarded there was a good accordance of PAH in females and males compared to final height. The mean BHI-SDS was reduced in comparison to the reference population (SDS −0.72 ± 1.24). BHI correlated with bone mineral content ($r^2 = 0.5$; $P < 0.0001$), total bone mineral density ($r^2 = 0.35$; $P < 0.0001$), and muscle cross sectional area ($r^2 = 0.47$; $P < 0.0001$) determined by pQCT and grip force ($r^2 = 0.29$; $P < 0.0001$) determined by a dynamometer. **Conclusion:** BoneXpert™ allows an objective and time-saving bone age assessment in children with chronic endocrinopathies and is suitable to predict valid PAH. BHI correlated with parameters of the 'gold standard' pQCT, but further studies are needed to validate BHI.

P1-P100

Cord 25-Hydroxyvitamin D and Infant Cranial Growth: An Odense Child Cohort Study

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Background: Vitamin D deficiency can cause rickets and impaired bone growth in infants. In India, randomization to higher vitamin D supplementation doses in pregnancy led to decreased anterior fontanelle and increased head circumference at 0 and 9 months. **Objective and hypotheses:** To investigate the impact of cord 25-hydroxyvitamin D (25(OH)D) concentrations on cranial measures. **Method:** In a Danish prospective birth cohort of 2549 mother/child pairs, we investigated the association between cord 25(OH)D and infants' anterior fontanel size ($n = 766$), head shape ($n = 1528$) and head circumference (n = 1777). Included were infants between 2.5 and 6 months of age with available cord 25(OH)D and cranial anthropometrics. Excluded were multiples and conditions affecting growth. Fontanel area was calculated from the transverse and longitudinal diameters, head circumference *z*-scores were generated from national growth charts. 25(OH)D was analyzed using liquid chromatography mass spectrometry. Linear and logistic regression analyses were stratified by prematurity and adjusted for age, sex, smoking, body mass index, educational level, parity, maternal age, skin tone and season of birth. **Results:** Mean (S.D.) cord 25(OH)D was 47.1 (21.7) nmol/l, head circumference 41.5 (1.5) cm. At median (IQR) age 3.7 (2.5-6) months, fontanel transverse diameter was 23 (0–58) mm; longitudinal diameter 20 (0–64) mm; area 225 (0–1690) mm^2. Asymmetric/flat head shape was present in 846 (55.3%). No differences were seen between boys and girls in fontanel size or risk of asymmetric head shape, however boys had significantly larger head circumference than girls. No crude or adjusted associations were found between cord 25(OH)D and any cranial measure. **Conclusion:** Cord 25(OH)D is not associated with infant cranial measures in a well-off western population.

P1-P101

Effect of Bisphosphonates on Bone Fragility Due to Chronic Liver Disease in Ten Children

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Background: Children suffering from chronic liver disease (CLD) may develop rickets, impaired bone mineralization and are exposed to an increased risk of osteoporotic fractures. Bisphosphonate (BP) is used in children to increase the bone density and reduce the fracture incidence. Up to date, no study showing the effect of this treatment in children suffering from CLD has been reported. **Objective and hypotheses:** Evaluate the effect of BPs in children with CLD and osteoporotic fractures. **Method:** In this monocentric retrospective study, children with a CLD and osteoporotic fracture/s treated with BP were included. Clinical, biological, osteodensitometric data and type and doses of BP were collected. **Results:** Ten patients (7M/3F) were included in the study. The mean bone mineral density (BMD) before BP was −2.2 S.D. ($n = 6$). They experienced 6.6 fractures/patient in the 6 months preceding the BPs. The treatment with BP was started at an average age of 6.8 years (±1.6). Three patients were liver transplanted 5 months (in average) after the first BP treatment. After 1 year of BP therapy, the rate of fractures significantly decreased from 6.6 to 0.3 fractures/year and 8/10 patients did not present any new fracture. The average cumulative doses of BP was 2.8 mg/kg. patient (±1.9). No serious adverse event was observed on BP therapy. **Conclusion:** Our results suggest that BP therapy could be effective and safe in children with osteoporosis and chronic liver disease.

P1-P102

Radiologically Confirmed Fractures in a Scottish Nationwide Cohort of Boys with Duchenne Muscular Dystrophy

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Background: Published studies of radiologically confirmed fractures in sufficiently large cohorts of boys with Duchenne Muscular Dystrophy (DMD) are limited. **Objective:** To determine the incidence of fractures in a contemporary cohort of 91 boys with DMD managed in all Scottish centres. **Method:** Radiologically confirmed fractures were classified into vertebral fracture (VF) and non-VF in a retrospective audit of all boys currently managed in Scotland. Probability of fractures was determined by Kaplan–Meier plot. **Results:** At last assessment at a median age of 11.2 years (range, 2.3–18.9), 45/91 (50%) were non-ambulant. Of 91, 51 (56%) were on Glucocorticoid (GC) at last assessment, 11/91 (21%) were GC naïve, 23/91 (25%) were previously treated with GC and in 6 (7%), this information was unavailable. By last assessment, 43 boys (47%) had sustained fractures. On Kaplan–Meier analysis, 50% of the cohort had sustained a fracture by the age of 10.2 years and 75% had sustained a fracture by 12.8 years. Non-VF occurred in 36/91 (40%). Seven (8%) of those boys who sustained non-VF were GC-naïve, median age of 3.5 years (2.0,10.1). Symptomatic VFs were reported in 8/91 (9%). In those who were started on GC, there was a period of 2.3 years before the first symptomatic VF was diagnosed and 50% had sustained VF by 8 years after start of GC (95% CI: 6.3–9.6). Multivariate analysis including boys currently and previously treated with GC showed that no single clinical factor (age at starting GC, duration GC, age lost ambulation) was associated with fractures. **Conclusion:** In this study of a contemporary nationwide cohort of boys with DMD, it is clear that radiologically-confirmed non-VFs can occur irrespective of GC therapy, whereas there is a latency period of 2 years before detection of the first symptomatic VF. The data gleaned from this large cohort will inform the design of future interventional studies of bone protective therapy powered on fracture reduction.

P1-P103

Monostotic Fibrous Dysplasia is a Single Disorder Caused by Somatic Mosaic Activating Mutations in GNAS

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Background: Monostotic Fibrous Dysplasia (MFD) is thought to be caused by somatic mosaic activating mutations in *GNAS*. However, previous *GNAS* mutation analyses of MFD patients using direct sequencing of bone samples detected activating *GNAS* mutations only in 21 of 40 cases (52.5%) (*Hum Pathol* 2012; 43: 1234). We reported that next generation sequencing (NGS) detected somatic activating *GNAS* mutations sensitively from peripheral blood samples in McCune-Albright syndrome (*PLoS One* 2013; 8: e60525). **Objective and hypotheses:** To determine if we could detect somatic activating *GNAS* mutations in MFD patients using direct sequencing of bone samples and NGS of peripheral blood samples. **Method:** The study included eight patients with MFD who underwent operation at our institution. We performed direct sequencing of bone samples and NGS of blood samples from all patients. **Results:** We detected somatic activating *GNAS* mutations in all patients by direct sequencing of bone samples and/or by NGS of blood samples (Table 1). **Conclusion:** This result indicates that MFD is a single disorder caused by somatic mosaic activating mutations in *GNAS*. Formic acid used for decalcification might cause DNA degradation in case 1, 2 and 5.

P1-P104

Clinically Significant Fracture Incidence in Czech Children: A Population-based Study

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Background: Before reaching adulthood, every second boy and every third girl will sustain a fracture. This growth spurt-related bone fragility is partially caused by a quick longitudinal growth and a relatively slower increase in bone width. However, no study has focused particularly on clinically significant fractures, a criterion for osteoporosis diagnostics. **Objective and hypotheses:** The aim of this study was to describe the incidence of clinically significant fractures (i.e., extremity long bone and vertebral fractures) in healthy Czech population aged 0–20 years and thus establish a control data for comparison of fracture incidence in chronically ill children. **Method:** The extremity long bone and vertebral fractures were recorded from the National Registry of Hospitalised Patients and the demographic data were obtained from the Institute of Health Information and Statistics of the Czech Republic. Number of fractures per age- and gender-specific population count was calculated. Data for years 2008–2014 were averaged. **Results:** The median fracture incidence was 6.2‰ in boys and 2.4‰ in girls. Whereas there were two peaks of fracture incidence occurring at the ages of 6 (7.1‰) and 13 (9.7‰) years in boys, there was no clear peak but a plateau between the

Table 1. (for abstract P1-P103)

Patients	Age (years)	Sex	PCR amplification using bone sample			Detection of *GNAS* mutations		
			Material	*GNAS*	*GAPDH*	DS-bone	NGS-blood	Type of mutation
1	10	M	FFPE	−	−	ND	+	R201H
2	14	F	FFPE	−	−	NO	+	R201C
3	19	M	Frozen sample	+	ND	+	−	R201C
4	23	F	Frozen sample	+	ND	+	+	R201H
5	34	M	FFPE	−	−	ND	+	R201H
6	41	M	Frozen sample	+	ND	+	−	R201H
7	42	F	Frozen sample	+	ND	+	−	R201H
8	67	F	Frozen sample[1]	−	−	ND	+	R201C

DS: direct sequencing, FFPE: formalin fixed paraffin embedded sample. ND: not done.
[1]Previous repeated operations caused severe bone calcification.

ages 6 and 11 years in girls, with a fracture incidence around 5.5‰. The fracture incidence was similar in the first 3 years of age between the sexes (0.4–2.0‰), but from the fourth year the incidence was consistently higher in boys and remained more than two times higher at the age of 20 years (3.2‰ vs 1.4‰, $P<0.001$). **Conclusion:** The incidence of fractures important for osteoporosis diagnostics is higher in boys than in girls and increases until the mid-puberty in boys and early puberty in girls. The role of bone quality and physical behaviour on fracture incidence remains to be elucidated.

P1-P105
Effects of Selective GPER-1 Agonist G1 on Bone Growth

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Background: Abnormal growth is a common problem in children. Some children do not respond to growth hormone therapy and alternative treatments selectively targeting the growth plate are needed. High doses of estrogens induce growth plate closure and stop further growth. However, high-dose estrogen treatment may also have severe side effects, including increased risk of cancer and reduced fertility. The expression of estrogen receptors (ER), including GPER-1, has been demonstrated in growth plate cartilage in humans as well as mice. **Objective and hypotheses:** We hypothesized that GPER-1 mediates estrogenic effects on growth plate cartilage. **Method:** Murine postnatal metatarsal bones were cultured with 1, 10, 100 and 300 nM of the selective GPER-1 agonist G1 for 2 weeks. Moreover, 12-week old ovariectomized female C57BL/6 mice were treated with daily subcutaneous injections of G1 at 0.2 mg/kg body weight for 4 weeks. Lengths of metatarsal bones, tibiae, and femur were measured and growth plate morphology was analyzed. The effects of G1 on chondrocyte proliferation in cultured metatarsal bones were analyzed by PCNA staining. **Results:** In G1 treated cultured metatarsal bones, resting and proliferative zone heights were increased when compared to control bones. Furthermore, chondrocyte proliferation was also increased in the metatarsal bones cultured with G1. However, when measuring bone length this was not significantly affected when exposed to G1 *in vitro* as well as *in vivo*. **Conclusion:** Our data suggest that estrogen may affect the growth plate via GPER-1 mainly by increasing chondrocyte proliferation and proliferative zone height. To clarify if this effect will translate into increased bone length, a longer treatment study would be needed.

P1-P106
Bone Mineral Density, Pubertal Status and Ability to Walk are Associated to Fracture Incidence in Patients with Rett Syndrome

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Background: Rett (RTT) syndrome is a neurodevelopmental disorder related to mutations in the MECP2 gene that affects girls almost exclusively. In Rett syndrome patients have a high incidence of fractures that can occur at a young age. **Objective and hypotheses:** One of the objectives of this study was to identify clinical, radiographic and biological parameters associated to fracture incidence. **Method:** 89 RTT patients bearing a *MECP2* mutation who had no past history of bisphosphonate treatment or orthopedic surgery to the spine were recruited prospectively. The following clinical, radiographic and biological parameters were evaluated: history of fractures and anti-epileptic drugs, ability to walk, BMI, pubertal status, Kerr severity score, daily calorie,

calcium and vitamin D intake, bone mineral density (BMD) at the spine and hip using DEXA, X-rays of the spine and urinary calcium excretion. **Results:** Mean age of patients was 11.8±7.1 years. 19/89 (21%) of patients had a history of fracture(s). Ambulatory patients had a higher incidence of fractures (41%) compared to those unable to walk (14%) even though they had a higher BMD of −1.72±0.18 *Z* score SDS at the spine and −2.48±0.23 *Z* score SDS at hip compared to −3±0.23 and −2.48±0.23, respectively, in non-walking RTT patients. Even though pubertal patients had a higher BMD compared to non-pubertal patients, −1.6±0.33 vs −2.27±0.15 *Z* score SDS at the spine, the incidence of fractures was the highest (30%) in the pubertal ambulatory patients. BMD at the spine and the hip was significantly lower in patients who had fractures, respectively at −2.78±0.3 and −3.21±0.36 SDS *Z*-score compared to patients with no history of fractures, respectively at −1.76±0.16 and −2.24±0.18 SDS *Z*-score. No difference was found for the other studied parameters between the fractured and non-fractured patients. BMD was significantly correlated to the disease severity Kerr score and BMI *Z*-score. **Conclusion:** Pubertal ambulatory RTT patients have the highest incidence of fractures. BMD, ambulatory status and pubertal development are related to fracture incidence in RTT patients.

P1-P107

Bone Mineral Status in Children and Adolescents with Klinefelter Syndrome

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Background: Klinefelter syndrome (KS) has long-term consequences on bone health. However, studies regarding bone status and metabolism in childhood and adolescence are very rare. **Objective and hypotheses:** The purpose of our study was to evaluate bone status and metabolism in a cohort of KS children and adolescents. **Method:** This cross-sectional study involves 40 (mean age 13.7±3.8 years) KS children and adolescents and 80 age-matched healthy subjects. In patients and controls, we evaluated serum levels of ionised and total calcium, phosphate, total testosterone, luteinising hormone, follicle stimulating hormone, parathyroid hormone (PTH), 25-hydroxyvitamin D (25[OH]D), 1,25-dihydroxyvitamin D, osteocalcin, bone alkaline phosphatase, and urinary deoxypyridinoline concentrations. We also calculated the phalangeal amplitude-dependent speed of sound (AD-SoS) and the bone transmission time (BTT) *z*-scores. **Results:** KS children and adolescents showed a significantly reduced AD-SoS ($P<0.005$) and BTT ($P<0.0005$) *z*-scores than the controls. However, KS patients presented a significantly higher PTH ($P<0.0001$) and a significantly lower 25(OH)D ($P<0.0001$), osteocalcin ($P<0.05$), and bone alkaline phosphatase levels ($P<0.005$). Interestingly, these metabolic bone disorders were present already in prepubertal subjects. AD-SoS and BTT *z*-scores correlated negatively with PTH ($P<0.005$) and with age ($P<0.0001$) and positively with 25(OH)D levels ($P<0.005$). PTH correlated significantly with calcium ($P<0.005$), age ($P<0.0001$), LH ($P<0.0001$), FSH ($P<0.0001$), total testosterone ($P<0.0001$), vitamin D ($P=0.04$), and osteocalcin ($P=0.002$). **Conclusion:** KS children and adolescents exhibit an impaired bone mineral status and metabolism with a frequent increase of PTH levels and a significant reduction of 25-OH-D and bone formation markers. Interestingly, this impairment is already evident in prepuberal KS patients, even if we showed a deterioration with LH and FSH increase and the reduction of testosterone.

P1-P108

Tolerability and Feasibility of Whole Body Vibration and its Effects on Muscle Function and Bone Health in Patients with Dystrophinopathy

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Background: Dystrophinopathies, including Duchenne (DMD) and Becker (BMD) muscular dystrophy, are X-linked muscle wasting disorders caused by mutations in the dystrophin gene. Dystrophin deficiency compromises functional integrity of the muscle fibers leading to progressive weakness, accompanied by a gradual bone loss. **Objective and hypotheses:** This study's goal was to evaluate the effect of whole body low magnitude vibration (WBLMV) on timed motor performance and bone health. The hypothesis was that WBLMV would stabilize muscle function and prevent bone loss in patients with dystrophinopathies. **Method:** This pilot study included 3 DMD (5.9; 7.5; 12.5 years old) and 2 BMD (16.4 and 21.7 years old) boys, all ambulatory (able to walk ≥75 m unassisted). Each patient was given a Marodyne Low Intensity Vibration plate with an oscillating frequency of 30–90 Hz for daily use at home for 10 consecutive min/day for 6 months. Baseline measurements were taken twice within two weeks before treatment began, then at 6 months and 12 months, and included 6 min walk distance, 10 m walk, 'stair climb' test, 'supine to stand' test and peripheral quantitative computed tomography (pQCT) of the tibia (3% and 38% sites) to evaluate trabecular and cortical

bone. Statistical analyses used mixed linear models to account for correlation of measurement times within subject. **Results:** Motor function remained stable during the 6 months of intervention with WBLMV, followed by deterioration during the subsequent 6 months without WBLMV in a 'stair climb' test (73% slower at 12 mo vs 6 months, $P<0.0001$) and 'supine to stand' test (74% slower at 12 mo vs 6 months, $P=0.027$). There was a trend toward an increase in trabecular cross-sectional area during the intervention phase (680 vs 544 mm^2 at 6 mo vs baseline, respectively, $P=0.069$). Other indices of bone geometry did not change significantly. **Conclusion:** WBLMV was well tolerated and appeared to have a positive effect on stabilizing muscle function and possibly bone health in patients with dystrophinopathies.

P1-P109

Nonsense Mutation in *SPARC* Gene Causing Autosomal Recessive Ostegenesis Imperfecta

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Background: Osteogenesis imperfecta type XVII (OI17) (MIM#182120) have been described recently due to mutation in secreted protein, acidic, cysteine-rich (*SPARC*) gene located on 5q33.1. **Objective and hypotheses:** Here we report a novel mutation in *SPARC* causing OI17. **Case:** Two siblings presented to our clinic at the age of 10.3 and 0.5 years old. Parents were consanguineous. The older one was born with birth weight −2.5 SDS and had contracture in distal part of the extremities. Severe scoliosis and hypotonicity was noted in early infancy. His first fracture in long bones has been detected at the age of 3 years. He was diagnosed as OI and pamidronate therapy had been initiated. Several long bone fractures, deformities, joint hyperlaxity, blue sclerae and inguinal hernia operation was noted in the patient. He had no dentinogenesis imperfecta. His sister was born term via C/S with a BW of −1.2 SDS. She had congenital fractures, axial hypotonicity and blue sclerae. They both had gross motor developmental delay, the brotherhad mild conductive hearing loss. His lumbar DEXA *Z*-score was −0.2 under pamidronate therapy for 6 years. They have no nephrocalcinosis. Whole-exome sequencing was performed and in the *SPARC* gene, homozygosity for nonsense variant, c.160G>T,p.Glu54X was identified in both siblings. No other variants for known OI genes were detected. The parents without OI were heterozygous for c.160G>T and this mutation was not found in IGBAM in house exome database including 1013 samples. This mutation was confirmed by Sanger sequencing. **Conclusion:** Here we described clinical characteristics of two siblings with recently describedOI17, new mutation in *SPARC* gene, which can be clinically classified as Sillence type 4.

P1-P110

Increase in Sclerostin After Rapid Weight Loss in Children

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Background: Sclerostin is secreted by the osteocyte and inhibits bone formation by osteoblasts and is thus a negative regulator of bone formation. In adults, sclerostin levels increase after weight loss, which may be prevented by exercise training. The effect of weight loss on sclerostin in children is unknown. **Objective and hypotheses:** To compare sclerostin levels in children before and after a 10 weeks stay at a weight loss camp (WLC). **Method:** A total of 116 (65 females) obese Caucasian children with a median age of 12.3 (7–15) years were included in the study. At the WLC all children attended regular school classes, were physically active at least 1 h every day and had a fixed diet plan with focus on reduced intake of calories. Just before attending -, and after 10 week stay at the WLC, the children were exposed to a physical examination and fasting blood samples followed by a standard glucose tolerance test. Sclerostin was measured by ELISA (Biomedica, Vienna, Austria). The insulin sensitivity index (ISI – HOMA) was calculated as: 22.5/(insulin (mU/l)×glucose (mmol/l)). **Results:** Sclerostin increased significantly from mean (95% CI) – 55.7 pmol/l (53.0–58.4) to 61.3 pmol/l (58.4–64.3) ($P<0.001$) during the 10 week WLC stay. Concomitantly, BMI decreased significantly with a median of 3.0 kg/m^2 (0–6.5) ($P<0.01$), and insulin sensitivity increased significantly ($P<0.01$). There was no correlation between change in sclerostin and change in BMI and no correlation between change in sclerostin and change in ISI-HOMA. **Conclusion:** Sclerostin increases after 10 weeks of weight loss in children even though the weight loss program is combined with moderate physical activity. Thus, a rapid weight loss in children may have a negative impact on bone formation.

P1-P111

Impact of Conventional Medical Treatment on Bone Mineral Density and Bone Turnover in Adult XLH Patients: A 6 Year Cohort Study

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Background: X-linked hypophosphatemia (XLH) are rare, inheritable disorders caused by excessive renal phosphate wasting

manifesting as rickets in children and osteomalacia in adults. While conventional medical treatment with oral phosphate and alfacalcidol is recommended in childhood, where it heals rickets and rescues some of the growth potential prior to fusion of the growth plates, it is controversial whether adults should continue therapy. There is little evidence for the long-term effect of medical treatment on the adult skeleton. **Objective and hypotheses:** The aim of the study was to determine the impact of conventional medical treatment on bone mineral density (BMD) and bone turnover in adult patients with XLH. **Method:** DXA scans of the lumbar spine (L2-L4) and total hip BMD were evaluated in 44 adults aged (18+ years) with XLH, 27 of whom were re-examined after six years. Bone formation (N-terminal propeptide of type 1 procollagen, P1NP) and resorption (carboxyterminal cross-linked telopeptide of type 1 collagen, CTX1) markers were analysed in serum samples at baseline (stored at −70° Celcius) and follow-up in one lot. Eleven of the 27 XLH patients had received conventional medical treatment throughout the study period. **Results:** The mean change in BMD during the study period was not different between treated and non-treated XLH patients at the lumbar spine (−1.9% vs −0.2%; $P=0.55$) or hip (−5.2% vs −3.2%; $P=0.55$). However, bone turnover was higher in the treated compared to non-treated XLH patients as indicated by higher P1NP (+73.7%, $P=0.05$) and CTX1 (+138%, $P=0.04$). **Conclusion:** Conventional medical treatment for 6 years did not affect the BMD of the hip or spine in XLH adult patients. Although treatment resulted in a state of high bone turnover, bone formation and resorption were balanced, resulting in no net loss of bone mass.

P1-P112

Bone Health and Body Composition in Childhood Onset Growth Hormone Deficiency at Time of Initial Evaluation and Retesting

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Background: Childhood onset growth hormone deficiency (CO-GHD) may contribute to low bone mass and alterations of body composition. However, the mechanisms by which CO-GHD effects bone health are not yet clearly defined. **Objective and hypotheses:** To evaluate musculoskeletal health in CO-GHD subjects at initial evaluation and retesting after final height. **Method:** A cross-sectional study of assessing bone health and body composition by imaging (DXA and pQCT), muscle strength by mechanography, and biochemical assessment in children undergoing GH stimulation tests for short stature (total – 25, GH deficiency – 15, median age (range) 10.9 years (5.6–16.0)) and biochemical revaluation at final height after GH therapy (total – 11, GH deficiency – 7, age 16.7 years (14.9-18.6)). **Results:** After adjusting for age, height, and bone area, GH deficient subjects did not differ in bone and body composition parameters (as measured by DXA and pQCT) from those who had normal GH levels at initial evaluation and retesting after final height. When assessing muscle strength by mechanograph, the median of maximum-force in naive GHD was significantly lower than normal subjects (0.5 kN (0.3, 2.8) vs 2.7 kN (2.2, 3.3) respectively, $P=0.03$). This was proportional to their tibia muscle cross sectional area. There were no differences in bone profiles and bone formation markers between all studied groups. However, the bone resorption marker, C-terminal telopeptide (CTX) was significantly higher in naive GHD vs the normal in the first time assessment group (2.0 ng/ml (1.4, 3.9) vs 1.6 ng/ml (0.9, 2.8), respectively, $P=0.02$). A positive correlation was found between CTX and parathyroid hormone (PTH) at time of initial evaluation ($r=0.46$, $P=0.02$) and retesting ($r=0.77$, $P=0.02$). **Conclusion:** Subjects with CO-GHD have normal bone mass and body composition at initial evaluation and retesting at final height. However, significant lower muscle force and higher CTX was found in naive GHD compared to the normal. Our results suggest that muscle force and PTH are important determinants of bone health in subjects with CO-GHD. However, a large-scale study is required to verify our findings.

P1-P113

Extension of The Bone Health Index to Adults, and Reference Curves of Four Indices of Cortical Bone for Healthy Europeans

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Background: The BoneXpert method for automated determination of bone age from hand X-rays has always included a determination of the Bone Health Index (BHI) from the cortical thicknesses in the metacarpals. **Objective and hypotheses:** The aim was to extend this so-called digital X-ray radiogrammetry method into adults, and present reference curves for BHI and three other indices: the metacarpal index, the Exton-Smith index and the volume-per-area (proportional to areal BMD). **Method:** The reference curves were based on a cross-sectional study of 1662 hand radiographs of healthy subjects of age 9–100 years collected in Jena in 2001–5. We also evaluated a longitudinal study of 116 healthy Danish children born 1952 with on average 11 images taken over the age range 7–40 years. **Results:** The Danish BHI data were found to be consistent with the Jena data, and also with the published BHI reference for healthy children. BHI was found to have smaller relative SD than the other three indices in the Jena cohort over the age range 20–80 years. **Conclusion:** With this extension, it is possible to follow pediatric patients at risk of poor bone health continuously from childhood into adulthood with exactly the same method. For instance, it can be useful for monitoring treatment effects of GH therapy for transition patients with GH deficiency until 'peak bone mass'. The relevance of cortical thickness has been shown in this context (1), and the new implementation inside BoneXpert makes this assessment readily available to clinicians. **Reference:** 1. Hyldstrup L, Conway GS, *et al.* Growth hormone effects on cortical bone dimensions in

young adults with childhood-onset growth hormone deficiency. *Osteoporos Int* 2012 **23** 2219–26.

P1-P114

Extension of Automated Bone Age Determination to the End of Puberty

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Background: The BoneXpert method for automated determination of bone age (BA) from hand X-rays was introduced in 2009, covering the Greulich-Pyle BA range up to 17 years for boys and 15 years for girls. **Objective and hypotheses:** To present an extension of the BA range of the automated method up to 19 years for boys and 18 years for girls and to validate it against manual rating. **Method:** The extension was developed based on images from the First Zurich Longitudinal Study of 231 healthy children born in 1954–56 and followed with annual X-rays of both hands until the age of 20 years. The method was validated on two cross-sectional studies of healthy children from Rotterdam and Los Angeles. **Results:** We found a root-mean-square deviation from manual rating of 0.68 and 0.49 years respectively in these two studies for boys in the BA range 17–19 years. For girls in the BA range 15–18 years, the deviations were 0.77 and 0.63 years respectively. Note: For girls in the BA range 17–18 years, the deviations were relatively high, indicating that the Greulich-Pyle BA scale should perhaps stop already at 17 years for girls. Further arguments for this are: 1) Beyond 17 years, ratings become unreliable, putting too much interpretation on the epiphyseal scar, which can persist for years; 2) the end-point of the BA scale is not a distinct event but a fading out; 3) BA beyond 17 years has no clinical importance in physical education or orthopaedics, only in forensics; 4) this would match the end-point at 19 years in boys well, since female bone development is about two years ahead of male development. **Conclusions:** With this extension, the automated method performs BA rating as well at the end of puberty, as in the rest of the BA range. The clinical use of BA at the end of puberty includes: 1) the assessment of growth potential, so that GH treatment can be stopped at the optimal time, 2) the assessment of growth potential in pediatric orthopaedics prior to surgical intervention.

P1-P115

A European Survey to Identify New Roads for Care, Training and Research Around Rare Metabolic Bone Diseases

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Background: Rare metabolic bone diseases (RMBD) are at the crossways of Endocrinology, Nephrology, Orthopaedic surgery and Rheumatology. Most of RMBD lead to short stature, bone pain, tooth anomalies, leg deformities, bone fragility and disability of variable importance. The organization of care varies immensely amongst European countries. Several European networks dedicated to RMBD already exist, supported by societies such as ESPE, ECTS or research grants, albeit their focus is primarily on research. **Objective:** The announcement of the future organization of European Reference Networks (ERNs) for rare diseases by the European Commission prompted us to conduct a survey in order to identify and map the field of expertise, the organization of care and the current activities around RMBD. A google questionnaire based on the future call for ERNs was sent to the existing networks; the information about the survey was conveyed through the ESPE, ECTS and ESE societies. **Results:** 33 centres from 12 countries responded. Altogether, the expert centres follow more than 4500 patients with RMBD including 1003 with an abnormal regulation of Ca^{++} and/or Pi, 2121 with a defect of the bone mineralization and 718 with a skeletal dysplasia. Paediatric patients are overrepresented (3141 vs 1025). The centres are fully equipped to image the bone, measure the circulating biomarkers and perform the molecular diagnosis of RMBD. However, multidisciplinary care is uneven amongst the centres. Training and research activities are fully implemented mostly through collaborations. Improvement is awaited for database interoperability and implementation, as well as for evaluation of clinical/training/research practices. **Conclusion:** Our survey pointed the needs to i) improve the visibility of expert centres towards patients and families, caregivers, and European health authorities; ii) guide the transition from child care to adult care; iii) harmonize care, and enable clinical trials; iv) share the expertise and disseminate the knowledge of RMBD through e-tools. Our survey shows that European networking is a major instrument to improve the care of patients affected with RMBD.

P1-P116

Clinical and Molecular Characterization of 25-Hydroxylase Deficiency in Saudi Patients

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Background: Vitamin-D deficiency becomes a worldwide issue, and major cause of rickets in younger age groups. Multiple causes lead to vitamin-D deficiency in which nutritional causes contribute the major factor. The synthesis of bioactive vitamin-D requires hydroxylation at 1α and 25 positions by cytochrome-P450 in the kidney and liver, respectively. Recently, human CYP2R1 has been reported as a major factor for 25-hydroxylation, in which it contributes for the inherited forms of vitamin-D deficiency. Till now, five cases with CYP2R1 mutation were reported worldwide. **Method:** A retrospective cohort study conducted in King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia. We included 36 patients who presented with classical symptoms of vitamin-D deficiency whom minimally responded to vitamin-D supplement. Their charts were reviewed for demographic, clinical, laboratory and radiological data. Genetic testing was sent for CYP2R1 mutation. **Results:** Of 36 patients, 14 were homozygous affected, 19 were heterozygous carrier and three without detected mutation. Two different mutations were identified: c.367+1,G>A (25.7%) and c.768,insT (68.6%). The commonest presentation was bone pain (50%), followed by limitation of physical activity (33.3%) and short stature (27.8%). Some patients showed improvement with high doses of vitamin-D supplement, where others required the active form (1,25OH vitamin-D) for their treatment. **Conclusion:** Our data identify that CYP2R1 plays a major role in 25-hydroxylation, which is a fundamental role in activation of vitamin-D. Higher percentage of CYP2R1 mutation related vitamin-D deficiency might find in our community. This result will help in diagnosing, treatment and prevention of similar cases in the future.

P1-P117

No Severe Hypercalcemia During a 12-Month High-Dose Vitamin D Intervention in Infants

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Background: Vitamin D supplementation is widely recommended to infants, but the optimal dose remains unclear. Vitamin D regulates calcium metabolism, and overdosing and high intake may result in hypercalcemia. **Objective and hypotheses:** We measured serum pH-adjusted ionized calcium (Ca-ion/pH 7.40) concentrations at 6 and 12 months and 25-hydroxyvitamin D (S-25-OHD) at 12 months in order to evaluate the risk of hypercalcemia during vitamin D_3 supplementation. **Method:** In an ongoing double-blinded vitamin D_3 intervention trial 987 healthy children were randomized to receive daily vitamin D_3 supplementation of 400 IU (10 μg) or 1200 IU (30 μg) from 2 weeks to 2 years of age. In addition to S-25-OHD concentration at 12 months, as a part of the safety protocol, Ca-ion concentration was analyzed at 6 and 12 months. Significant hypercalcemia was defined as a level exceeding the upper reference limit (ref.1.16–1.39) by 10%. **Results:** Ca-ion concentrations at 6 months ($n=890$) ranged between 1.28 and 1.52 mmol/l (median 1.37, mean 1.38, S.D. 0.04) and at 12 months ($n=850$) between 1.17 and 1.43 mmol/l (median 1.33, mean 1.33, SD 0.03). None of the participants had significant hypercalcemia. S-25-OHD levels at 12 months ($n=801$) ranged between 23.0 and 241.0 nmol/l (median 96.7, mean 99.1, SD 29.0). A correlation between S-25-OHD and Ca-ion concentration at 12 months was seen ($P=<0.001$). S-25-OHD in infants with Ca-ion exceeding the upper reference limit ($n=14$) did not differ from infants with Ca-ion within normal range ($n=777$) ($P=0.127$; mean 110.8 vs. 98.9 nmol/l). **Conclusion:** At 12 months S-25-OHD did not exceed 250 nmol/l. None of the participants had severe hypercalcemia. Mild hypercalcemia at 12 months was present in 2%; no symptoms of hypercalcemia were observed. It remains unknown how these values relate to actual vitamin D dosage. Further analyses are warranted at the end of intervention later in 2016, when the randomization code will be opened.

P1-P118

Management of Tracheobronchomalacia During Asfotase Alfa Treatment in Infants with Perinatal-onset Hypophosphatasia: A Case Series

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Background: Hypophosphatasia (HPP) is a rare, inherited metabolic disease caused by loss-of-function mutations in the gene encoding tissue nonspecific alkaline phosphatase (TNSALP), resulting in hypomineralisation of bone. HPP presenting <6 months of age is often lethal due to respiratory insufficiency, with survival of 42% at 1 year. Asfotase alfa, a human recombinant TNSALP replacement, promotes bone mineralisation, with survival of 95% at 1 year in infants with HPP. **Objective:** We characterised tracheobronchomalacia (TBM) occurring in infants with HPP treated with asfotase alfa. **Methods:** Patients with perinatal- or infantile-onset HPP who received asfotase alfa in a clinical study or a compassionate-use programme were identified as having severe TBM. Clinical data analysed included: presenting features; predetermined manifestations of interest including TBM; and management of TBM. **Results:** Four patients (two female, two male) with TBM were identified; three enrolled in Study

ENB-010-10 (NCT01176266); one received asfotase alfa in a compassionate-use programme. All patients received ongoing treatment with asfotase alfa starting at $\leq$2 months of age (dose 6–15 mg/kg per week). All four patients required ventilation at birth and experienced frequent respiratory distress, two experienced respiratory arrests. Management included tracheostomy and continuous positive pressure ventilation with positive end-expiratory pressure (upto 12 cm H_2O). At the time of this report, the TBM had resolved in two patients (15 and 24 months old; off ventilatory support), partially resolved in one (27 months old, ventilatory support) and remained significant in one patient (23 months old, tracheostomy *in situ*). **Conclusion:** This is the first report of TBM in infants with HPP. We recommend screening infants with HPP who require intermittent positive pressure ventilation for TBM with flexible bronchoscopy. Further data are needed to determine the role that asfotase alfa may have played in the improvements, beyond enabling prolonged survival and subsequent maturation of the airways.

P1-P119

Novel p.Asn628Ser Heterozygous Mutation in *FGFR1* is Associated with Hartsfield Syndrome and Tumoral Calcinosis

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Background: Our patient, a male infant has bilateral cleft lip and palate, bilateral split hand and foot, semilobar holoprosencephaly and specific pituitary defects (cranial diabetes insipidus, gonadotrophin deficiency). He developed tumoral calcinosis at 16 months. **Objective and hypotheses:** Our patient's phenotype is suggestive of Hartsfield syndrome. We hypothesise that he harbours a *FGFR1* mutation given recently published findings associating novel homozygous/heterozygous *FGFR1* mutations with the condition. Tumoral calcinosis can be inherited in an autosomal recessive manner (loss of function mutations in *FGF23, KLOTHO* and *GALNT3).* The circulating factor FGF23 promotes phosphate excretion. Klotho directly converts the splice variant FGFR1 (IIIc) into the FGF23-specific receptor raising the possibility that an inactivating *FGFR1* mutation may contribute to tumoral calcinosis development. **Method:** Direct Sanger sequencing of *FGFR1*, incisional biopsy (histology consistent with tumoral calcinosis) and serum for bone biochemistry and C-terminal/ intact FGF23 levels was taken. **Results:** Our patient has a novel, *de novo* heterozygous missense mutation, c.1883A$>$G; p.Asn628Ser, affecting an amino acid residue in the ATP binding pocket of the tyrosine kinase domain, with predicted impairment of FGFR1 kinase activity. Biochemical findings were consistent with familial tumoral calcinosis with normocalcemia, normal 1, 25(OH) Vitamin D, hyperphosphataemia, and low fractional excretion of phosphate. In comparison to other causes of familial tumoral calcinosis C-terminal FGF23 was only mildly raised (111 RU/ml, NR $<$100) and intact levels were within normal limits. Studies have implicated FGFR1 activation in regulating *FGF23* gene transcription which may account for the paucity of elevation of FGF23 seen despite increased renal phosphate reabsorption. **Conclusion:** This novel mutation in *FGFR1* provides further compelling evidence of the association of *FGFR1* mutations with Hartsfield syndrome. We also expand the phenotype with the first report of tumoral calcinosis with mildly raised C-terminal FGF23 levels, which may reflect loss of function of FGFR1.

P1-P120

Practicalities of Bisphosphonate use in UK Paediatric Tertiary Centres

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Background: On reviewing practical aspects of intravenous bisphosphonate use in our tertiary Children's Hospital, we noted disparity between departments who prescribed these drugs. This included issues pertinent to patient safety and hospital management, e.g. the need for overnight admission for the first infusion, blood tests and monitoring for adverse events (AEs). We therefore decided to survey the practices of other tertiary Paediatric Endocrinology Centres. **Objective and hypotheses:** To gather information on differences in practice when prescribing and administering intravenous bisphosphonates, in order to attempt to generate a consensus among paediatric endocrinologists in the UK. **Method:** An online survey was sent to all members of the British Paediatric and Adolescent Bone Group (BPABG) with ten questions exploring how intravenous bisphosphonates are prescribed and monitored in their unit. Questions included choice of bisphosphonate, checking of blood tests, use of calcium supplementation and need for overnight admission after the first infusion. We received eighteen responses from twelve tertiary centres across the UK. **Results:** All centres use Pamidronate, of whom 78% also use Zoledronic Acid. Over 89% check renal and bone profiles and vitamin D prior to infusions. 75% routinely prescribe calcium supplementation after Zoledronic Acid. Practices vary around infusion duration, overnight admission (61% admit children for the first infusion, 11% admit younger children, and 28% do not routinely admit) and post-infusion serum calcium monitoring (50% do not). Discussion indicated that anecdotal evidence of early AEs influenced practice. Further detail on occurrence, timing and severity of AEs would aim informed development of a consensus guideline. **Conclusion:** Clinical governance around prescribing intravenous bisphosphonates in most UK Paediatric Endocrine units is good. However hospital admission remains a difficult issue and more evidence on occurrence, timing and severity of AEs of bisphosphonates is required, in order to generate a consensus on practicalities of their use.

P1-P121

Computer-assisted Diagnosis of Dyschondrosteosis Based on Skeletal X-ray Geometry

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Background: Bone X-rays provide the main diagnostic parameters for chondrodysplasia, including common dyschondrosteosis (DC). Skeleton is usually studied piece by piece by visual analysis in search of characteristic signs. The phenotypic spectrum of DC is large. Indeed, children who have seemingly idiopathic short stature (ISS) may have subtle forms of DC that can be unrecognized. **Objectives:** Provide a user-friendly computer-assisted program that facilitates the identification of subtle forms of DC within a population of children with ISS. **Methods:** 84 points were placed on various key points of six radiographic images (ilia, ischia, lumbar spine, forearm, hand, leg), giving 39 measures. Angles and distances were drawn between points of the same skeletal piece and precisely quantified. Angles and distances from different regions were modelled. **Patients:** The program was trained on age-matched ten patients with typical DC (SHOX mutations), and ten patients with a diagnosis of ISS. Thereafter, it was tested on 54 patients with ISS in whom skeletal X-rays were considered normal by visual inspection. **Results:** The more specific and more sensitive parameters for the diagnosis of DC seemed to be the largest distance measured between radius and ulna, carpal angle, length of 4th metacarpal and its relationship with length of 4th proximal and distal phalanx, interpeduncular distance of lumbar spine. Our computerized program was able to detect 21 children with subtle forms of DC among the 54 children considered to have ISS. **Conclusion:** In field conditions, it may be useful to paediatricians to identify subtle forms of DC among children with ISS. Our computerized quantitative analysis of skeletal morphology may be helpful in this respect.

P1-P122

Bisphosphonates Therapy in Girls with Rett Syndrome and Bone Fragility

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Background: Rett Syndrome (RS) is a disabling condition due to mutations in MECP2. Girls affected with RS are at risk of developing osteoporosis and fractures at a young age because of their lack of mobility and though a direct effect of MECP2 on bone mineralization. In these girls, bone fragility inflicts pain and may seriously impair the quality of life. **Objective:** To retrospectively assess the effect of pamidronate on fractures, bone mineral density (BMD) and bone markers in RS girls with bone fragility. **Methods:** Once diagnosed with bone fragility, RS girls received 1.5 mg/kg of pamidronate IV every 3 months cycle for 2 years. Values are median (min; max). **Results:** 13 patients were studied (age: 9.5 years (6; 42)) . All were not ambulatory. 24 fractures for 13 patients were observed in the 6-months interval preceding the start of therapy, whereas 0 fracture occurred during or after pamidronate (length of follow-up: 32 months). The DXA BMD Z-score improved from -3.7 (-5; -2) to -1.3 (-0.7; -3.8), $P<0.01$. Most parents reported a decrease in chronic pain; two patients started to walk around the end of the 2-years therapy. The urinary calcium excretion, which reflects bone resorption, decreased significantly from 0.6 (0.2; 1.5) to 0.3 (0.0; 0.5) mmol/mmol of creatinine. Except for moderate hypocalcemia and fever, pamidronate was well tolerated in all girls. **Conclusion:** Our result are in accordance with the beneficial effect of bisphosphonates in children with cerebral palsy. Impaired bone mineralization in RS girls should be screened and prevented through measures including vitamin D supplements, nutritional support and careful mechanical loading. In girls experiencing fractures, IV bisphosphonates may be an adjuvant treatment to diminish the risk of fracture and restore the bone density.

P1-P123

Skeletal Manifestations in APECED

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Background: Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED or APS1) is an autosomal recessive disorder characterized by chronic candidiasis and autoimmune destruction of endocrine organs. Hypoparathyroidism (HP), adrenocortical failure (AF) and hypogonadism are the most common endocrinopathies, which together with their treatment may impact bone health. However, very little is known about the long-term skeletal health in patients with APECED. **Objective and hypotheses:** Aim of the study was to determine the prevalence of, and risk factors for, osteopenia and osteoporosis in children and adults with APECED. **Method:** The cross-sectional cohort consisted of 29 patients (21 females) who were examined clinically, their bone mineral densities (BMD) were measured with dual-energy X-ray absorptiometry and radiographic abnormalities were evaluated with spinal X-ray imaging. Fracture history was collected with questionnaire. **Results:** The patients' mean age was 35 years (range 12–71 years). 26 (90%) patients had HP, 26 (90%) patients had AF and 17 (59%) patients had hypogonadism. Ten (34%) patients had scoliosis. Altogether 16 (55%) patients had had 1–5 fractures and seven of them had low-impact fractures. Spinal compression abnormalities were evident in four (14%) patients. The mean BMD Z-scores (95% CI) were 0.5 (-0.0–1.1) for whole body, 1.2 (0.5–2.0) for lumbar spine, 0.7 (0.1–1.2) for femoral neck. Osteopenia was present in 20%. **Conclusion:** Patients with APECED are not at high risk for low BMD, but based on fracture prevalence their bone structure may be altered and warrants further studies.

P1-P124

Two French Families with Vitamin D Dependency Rickets Type 1B Harbor Homozygous Recessive Expression Of CYP2R1 Mutations L99P and G42_L46DEL INSR

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Vitamin D dependency rickets type 1B (VDDR-1B) is a rare condition classified as rickets due to inadequate 25-hydroxylation of vitamin D. In this study, we describe rickets and loss-of-function *CYP2R1* mutations in 6/10 individuals tested from two unrelated families. Five patients in family 1 (F1) have homozygous L99P mutations; while one member of family 2 (F2) has novel homozygous mutations at G42_L46del insR. The mutations, as well as another variant M248I found in the French population, were recreated and tested using an *in vitro* mammalian expression system described previously (JBiolChem 286:28729). L99P and G42_L46del insR showed $<5\%$ of wild type CYP2R1 enzyme activity and are presumed to be loss-of-function mutations, while the M284I variant had 75% activity and is thus likely a polymorphism. In F1, the eldest child presented with marked limb amyotrophy and genu valgum also found in his younger 7 year brother; his youngest 4 year sister was asymptomatic. At diagnosis, all children had hypocalcemia, hypo-/normo-phosphatemia; high PTH and alkaline phosphatase (ALP) levels. Serum 1,25-$(OH)_2$D levels were within the normal range (48–182 pmol/l), but 25-OH-D levels were undetectable (<4 ng/ml). The aunt and uncle had genu valgum during infancy and were treated with 25-OH-D_3 but were free of treatment for many years until the molecular investigation was made at 32 and 34 years respectively. Both had normocalcemia and slightly elevated PTH levels, normal 1,25-$(OH)_2$D, but undetectable 25-OH D levels. In F2, the child presented with typical vitamin D deficiency rickets: short stature, genu varum deformity and hypotonia. He was given high doses of alfacalcidol (1α-OH-D_3) and calcium supplementation. Serum calcium normalized, but PTH and ALP levels remained elevated. 1,25-$(OH)_2$D levels were supranormal (194 pmol/l up to 383 pmol/l), while 25-OH-D was 2.7 ng/mL by LC-MS/MS. Calcifediol (25-OH-D_3) therapy resulted in complete normalization of biochemical and bone defects. The major finding of the present study is identification of six new patients with VDDR-1B rickets harboring known (L99P) or novel (G42_L46del insR) mutations of the *CYP2R1* gene and very low serum 25-OH-D_3 which when corrected by 25-OH-D_3 therapy cures the bone defect.

P1-P125

Spectrum of the Genetic Defects in Hypophosphatemic Rickets in A Group of Turkish Children

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Background: There exists limited data regarding genetic etiology of hypophosphatemic rickets in Turkey. **Objective and hypotheses:** To investigate the type of genetic defect in 16 index children and their families (12 unrelated, 1 related). **Method:** Following clinical and laboratory assessment, *PHEX* analysis was made initially unless a mutation in another gene was suspected. If negative, *FGF23*, *SLC34A3*, *SLC34A1,* and *CYP27B1* genes were analyzed sequentially. **Results:** We identified 21 patients (16 children, five adults) with hypophosphatemic rickets. Sixteen of them (76.2%) had findings related with rickets and 12 (56%) had short stature. Calcium levels were normal, phosphorus low, ALP markedly elevated, and parathormone normal or mildly elevated in all patients. We found 10 different *PHEX* mutations in 17 patients (80.9%), two novel *SLC34A3* mutations in two siblings (9.5%), and no mutation in two patients (9.5%). Five *PHEX* mutations were de novo. Four novel *PHEX* mutations were: c.978_982dupCTACC (frameshift), c.1586+2T>G (splice site), c.436+1G>T (splice site), and c.1217G>T (p.C406F). Affected parents were all symptomatic but none were diagnosed previously. **Conclusion:** Present study revealed that PHEX mutation seems to be the most prevalent mutation in Turkey as well. More attention should be paid to hypophosphatemia by the clinicians since some cases remain undiagnosed both during childhood and adulthood.

P1-P126

Impact of Intercurrent Illness on Calcium Homeostasis and Hypoparathyroidism Management

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Background: Hypoparathyroidism is typically managed with calcitriol/alfacalcidol. Close monitoring of serum calcium is required as under-treatment causes symptomatic hypocalcaemia while over-treatment will cause nephrocalcinosis. We report three cases who demonstrated resistance to treatment during an intercurrent illness, necessitating increase in medication doses and monitoring. **Objective/hypotheses/method/results:** Case series *Case 1*: Two-month-old boy with newly diagnosed hypoparathyroidism due to *GCMB2* mutation normalised his Ca on standard treatment withalfacalcidol and calcium supplements. He however developed bronchiolitis during admission, resulting in precipitous drop in cCa (1.53 mmol/l) and seizures requiring IV Ca infusion and significant increase in medication to normalise serum Ca (alfacalcidol 400–1500 ng/day and calcium supplements 12–48 mmol/day). He eventually needed rPTH to achieve Ca homeostasis. *Case 2*: A male infant diagnosed with hypoparathyroidism at birth responded to standard treatment. At 2 months he presented with bronchiolitis and recurrent hypocalcaemic seizures

requiring increase in dose of alfacalcidol (400–1500 ng/day) and Ca supplementation. However, following resolution of illness, he required rapid reduction in dosage due to hypercalcaemia. *Case 3*: A 6-month-old boy with Sanjad-Sakati syndrome on standard treatment for hypoparathyroidism presented with symptomatic hypocalcaemia following viral gastritis. He required increase in dose of alfacalcidol upto 3000 ng/day to normalise serum Ca. He was however lost to follow-up and presented again at 2 years of age with symptomatic hypercalcaemia (Ca > 3 mmol/l) and severe nephrocalcinosis. To normalise his serum Ca and prevent further progression of nephrocalcinosis, he was commenced on rPTH. **Conclusion:** Intercurrent illness in infants with hypoparathyroidism can lead to marked resistance to standard treatment and symptomatic hypocalcaemia. The underlying pathophysiology remains unknown, but would seem to involve more than just intolerance to oral medication or feeds. During such periods, close monitoring of calcium levels is required, with quick escalation in medication doses, as well as reduction to baseline on recovery to prevent over-treatment.

P1-P127

Transient Pseudohypoaldosteronism and Failiure to Thrive in A 5-Month-Old Infant

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Hyponatremia with hyperkalemia in infancy may be seen in many endocrinologic and metabolic disorder such as congenital adrenal hyperplasia, congenital adrenal hypoplasia, and other forms of hypoadrenalism in infancy. Here, we report a infants who presented with hyponatremia with hyperkalemia finally diagnosed as pseudohypoaldosteronism (PHA) due to urinary tract infection (UTI) with reflux nephropahy. A 5-month-old female initially was transferred for poor weight gain for 2 months. The body weight was 5.0 kg (<3rd percentile). She looks pale and not well-being. Virilization of genitalia or pigmentation were not noted. Initial serum sodium was decreased (125 mEq/l) and serum potassium was elevated (6.1 mEq/l). The serum CRP level was elevated (4.08 mg/dl), and serum ESR level was also elevated (60 mm/h). Urine analysis revealed pyuria. Intravenous saline and antibiotics were started after urine culture. Catheter urine culture was positive for Serratia marcescens. The initial serum 17-Hydroxyprogesterone level was 0.73 ng/ml and aldosterone level was markedly elevated 17,800 pg/ml (normal: 30–900), urinary sodium centration was 30 mg/l, so pseudohypoaldosteronism (PHA) was diagnosed. Her serum sodium and potassium were normalized after 48 h of intravenous fluid and antibiotics therapy, and inflammatory markers were also normalized. The VCUG showed right-sided grade 5 and left-sided grade 4 vesicoureteral reflux, the renal sonography showed mild atrophy of right kidney and compensatory hypertrophy of left kidney. The electrolyte levels remained normal range and aldosterone level was decreased without sodium replacement and proper weight gain was achieved. It is important that transient PHA due to urinary tract infection should be considered in infant particularly after the first 1 month of life with hyponatremia and hyperkalemia without virilization.

P1-P128

Childhood Cancer Survivors (CCS) are at High Risk of Reduced Bone Mass During the Second Decade of Life

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Background: Childhood cancer survivors (CCS) are at risk for low bone mineral density (BMD). **Objective:** Aim of our study was to evaluate the prevalence of low BMD and it's determinants in a single-center cohort of CCS. **Method:** One-hundred-eighty-five CCS (103M, 84F) diagnosed with liquid-LT-($n=48$), solid-ST-($n=88$) and brain tumor-BT-($n=51$) at the age of 5.3 ± 3.2 years underwent height, BMI (SDS), Tanner staging and DXA scan for total body-TB and spine-L1-L4 BMD (gr/cm^2, *Z*-score), BMC (gr) and for TB fat mass(FM, kg) and free fat mass (FFM, kg). Endocrine defects were found in $n=9$LT, $n=16$ST and $n=50$BT; 48/51BT underwent CRT(mean total dose 5397.5 ± 1426.1 cGy). **Results:** Patients were evaluated 6.8 ± 3.3 years after off therapy at the age of 13.0 ± 2.0 years. LT were significantly younger than BT (12.9 ± 1.8 vs 13.7 ± 1.7 years) and BT shorter than ST (-0.60 ± 1.26 vs 0.24 ± 1.37 SDS, $P<0.001$); the 3 categories did not differ for Tanner stage nor for BMI SDS (range 1.34-LT to 1.57-BT). BT presented a lower TBBMD (-0.61 ± 0.89) and L1-L4BMD *Z*-scores (-0.74 ± 1.14) compared to ST and LT (*P*'s<0,01). A TBBMD *Z*-score <-2 and between -2 and -1 was found in 4.8% (7.8%-BT, 6.5%-LT and 2.2%-ST) and 14% (23.5%-BT, 6.2%-LT and 12.6%-ST) of CCS, respectively; a L1-L4BMD *Z*-score <-2 and between -2 and -1 in 7% (13.7%-BT, 6.5%-LT and 3.4%-ST) and 15.6% (19.6%-BT, 16.7%-LT and 12.6%-ST), respectively. TBBMD *Z*-score was directly associated to FFM (*r*'s=0.51) and inversely to RT dose in BT ($r=-0.30$, $P=0.037$); hormone defects were inversely related to L1-L4 and TBBMD *Z*-scores in LT and ST, but not in BT. Multiple regression analyses showed that L1-L4BMD *Z*-score was independently and inversely predicted by age and hormone defects and directly by FFM and FM after correction for Tanner stage and height SDS (R^2 0.33, $P<0.0001$), while TBBMD *Z*-score by all the previous parameters, except for Tanner stage (R^2 0.50, $P<0.0001$). **Conclusion:** Up to 14% of BTCCS and 6.5% of LTCCS present a low bone mass at the age of 13 years. Older age, hormone defects and CRT are negative predictors of low BMD.

P1-P129

Trabecular Bone Score in Children from Mexico City: Preliminary Report

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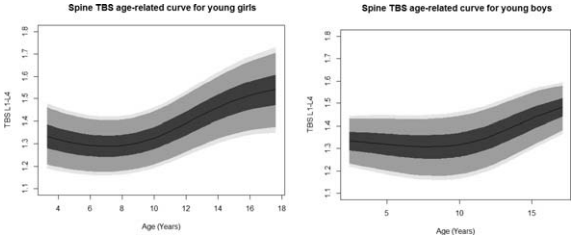
Background: Trabecular Bone Score (TBS) is a software-based tool for analysis of DXA images to assess bone microarchitecture in the lumbar region. Several studies have addressed its value in adult population, however, little research has been done in children in which may be useful for bone evaluation during growth. **Objective:** To evaluate bone density and TBS during childhood and its relationship to other variables such as bone age and height. **Method:** Pseudo volumetric BMD (3D BMD) was calculated based on cylindrical model proposed by Kroeger et al. (Bone Mineral, 1992). TBS assessment has been realized with a custom version of TBS (Med-Imaps SASU, France) that includes a dedicated soft tissue correction for pediatric subjects based on ex-vivo data and taking into account spine tissue thickness and acquisition mode. The LMS statistical method proposed by Cole and Green (Stat Med, 1992) was used to construct aBMD, vBMD and TBS age-related curves using R software (v2.15.3). Height, weight and BMI *Z*-scores were evaluated and compared to CDC (2000) standards. Bone age was evaluated according to Greulich and Pyle. **Results:** Eighty boys and 86 girls ages 2.4–17.6 year were included (9.4 ± 3.5). In both boys and girls we observed first a decreasing phase until the puberty follow by an increasing phase until 17, more pronounced in girls than boys. **Conclusion:** Results are consistent with those obtained by Del Rio *et al.* (ICCBH 2013). We also observed a TBS negative peak between 5 and 10 years old.



P1-P130

Triple X Syndrome: An Evaluation of Bone Mineral Status and Metabolism

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Background: However, no study has considered the effect of a supernumerary X chromosome on bone mineral status and bone metabolism. **Objective and hypotheses:** To evaluate bone mineral status and metabolism in a cohort of patients with nonmosaic triple X syndrome. **Method:** Nineteen girls (median age 10.9, range 7.7–15.9 years) with nonmosaic triple X syndrome were cross-sectionally studied and compared to an age- and body-size-matched control group. We evaluated ionised and total calcium, phosphate, parathyroid hormone (PTH), 25-hydroxy-vitamin D (25[OH]D), 1,25-dihydroxyvitamin D, osteocalcin, bone alkaline phosphatase levels, and urinary deoxypyridinoline concentrations. We also calculated the phalangeal amplitude-dependent speed of sound (AD-SoS) and the bone transmission time (BTT) *z*-scores. **Results:** Triple X patients showed significantly reduced AD-SoS ($P < 0.005$) and BTT *z*-scores ($P < 0.0001$) than the controls. These results persisted when we divided the sample into prepubertal and pubertal patients ($P < 0.05$). Triple X patients also had significantly lower calcium ionised ($P < 0.005$), and higher phosphate ($P < 0.0001$) and PTH ($P < 0.0001$) levels. However, triple X patients also showed significantly reduced 25(OH)D levels ($P < 0.005$). AD-SoS and BTT *z*-scores values were significantly inversely correlated with age ($P < 0.005$), PTH ($P < 0.005$), and 25(OH)D ($P < 0.005$). **Conclusion:** Subjects with nonmosaic triple X syndrome exhibit a significant reduction in bone mineral status and showed an impaired bone metabolism similarly to other X polisomy such as Klinefelter syndrome, hypothesizing the presence of a primary bone deficit. This suggests the need to closely monitor these subjects.

P1-P131

Frequency of Recessive Osteogenesis Imperfecta in a Turkish Cohort and Genetic Causes

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Background: Osteogenesis imperfecta (OI) is a heterogeneous group of brittle bone disease mostly caused by quantative or qualitative defects in type I collagen. In most populations, more than 90% of the patients with OI have dominant mutations in *COL1A1* or *COL1A2* genes (AD-OI). Less than 10% of the cases have recessive inheritance (AR-OI). Currently 12 genes have been identified as a cause of AR-OI. **Objective and hypotheses:** We assumed higher frequency of AR-OI in our population because of high consanguineous marriages and aimed to detect AR-OI rate and distribution of genetic causes in our cohort. **Method:** Eighty-nine patients from 73 families were evaluated for inclusion. The patients having parental OI history (27 families) and/or patients with mutations in COL1A genes (5 families) were excluded because of AD-OI. The patients born to consanguineous parents were

included as AR-OI (29 patients/25 families). In AR-OI group, two patients had osteoporosis-pseudoglioma and five patients (four families) had epidermolysis bullosa and found to have founder mutation of p.delGly107_Leu117del in *FKBP10* gene. Remaining 19 families were called for genetic analyses. Three patients were died. Whole exome sequencing (WES) was performed to seven index patients. **Results:** Novel mutations in *LEPRE1*, *CRTAP* and *FKBP10* genes were detected in WES We also detected a nonsense mutation in *SPARC* in two siblings which is a newly described AR-OI gene. Two cousins with severe platyspondily had mutation in *BMP1* gene. The other two index cases are still under investigation. Overall, the frequency of recessive OI was 34.2% of the families and 32.6% of the patients. **Conclusion:** In our cohort of OI, 1/3 of patients have AR-OI. In 11 families with genetic results, five *FKBP10*, two *LRP5*, and one each *LEPRE1*, *CRTAP*, *BMP1* and *SPARC* gene mutation have been detected. Distribution of mutations seem to differ from AR-OI cohorts of Spain (n:10) and India (n:7).

P1-P132

Spinal and Forearm Bone Mineralization in Adolescents with Klinefelter Syndrome

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Background: Patients with Klinefelter syndrome (KS) have an increased risk for osteoporosis and fractures in adulthood. Data on bone mineralization in adolescence are limited, although it is a known at-risk period for vitamin D deficiency, low calcium intake and evolving hypogonadism. **Objective and hypotheses:** To study the bone mineralization in KS adolescents and its relationship with vitamin D/calcium and gonadal status. KS adolescents with low calcium intake, lower 25-OH vitamin D levels and lower testosterone and/or higher LH levels were expected to have a lower BMD. **Method:** Lumbar spine bone mineral density (BMD) was measured by dual energy X-ray absorptiometry (DXA) and trabecular BMD at the distal radius by quantitative peripheral computed tomography (pQCT) in 29 (25 pubertal) KS adolescents without testosterone or vitamin D supplementation, who were between 10.1 and 18.1 years (median 14.8 years) old. 25 OH vitamin D, LH and testosterone concentrations were analysed by commercial immuno-assays. Pubertal status was assessed by Tanner score and calcium intake by a simplified food frequency questionnaire. **Results:** Mean (SD) *z*-scores of standing height, spinal areal BMD and forearm trabecular volumetric BMD were 0.82(0.85), −0.40(0.97) and −0.09(0.99). Respectively 5/29 and 4/21 KS patients had a lumbar spine BMD and a radius trabecular BMD score below – 1, but none had a score < -2. Respectively 15/29, 15/29 and 11/24 had a high (>10 mIU/l) LH status, a low (<20 µg/l) 25-OH vitamin D status and a low (<500 mg/day) calcium intake. Spinal BMD *z*-score correlated significantly with height SDS ($\rho = 0.66$, $P < 0.005$), but not with 25-OH vitamin D, testosterone, LH concentrations or calcium intake. **Conclusions:** Spinal and radial bone mineralization is normal during adolescence in KS patients, irrespective of their vitamin D and genital status. BMD results in KS adolescents have to be related to their height and pubertal status.

P1-P133

Treatment with Zoledronic Acid in Children with Duchenne Muscular Dystrophy

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Background: Paediatric Osteoporosis can be a devastating complication of Duchenne muscular dystrophy (DMD). Treatment with intravenous bisphosphonates such as pamidronate is currently the first treatment choice for paediatric osteoporosis of different etiologies. **Objective and hypotheses:** The aims of our study were i) to identify the proportion of boys with DMD with osteoporosis in our service and ii) to evaluate the side-effect profile of those treated with zoledronic acid. Zoledronic acid was selected in our DMD cohort in preference to pamidronate due to the shorter administration and thus reduced time spent in hospital. **Method:** All boys under 16 years with a diagnosis of DMD seen in a tertiary referral centre were included in this cohort. Patient characteristics were collected both from hospital records and via direct patient contacts. Patients treated with bisphosphonates were interviewed following their first infusion of zoledronic acid to establish the tolerability and side-effect profile of treatment. **Results:** Of 61 patients (mean age 10.0 years, range 1 to 16 years) with DMD, 62% had been treated with corticosteroids. 11% had a diagnosis of osteoporosis and were commenced on zoledronic acid. Patients treated with zoledronic acid were older compared to non-treated patients (Mean ± S.D., 13.6 ± 5.4 vs 10.1 ± 4.3 $P < 0.05$) and more likely to be treated with steroids (100 vs 42% $P < 0.01$). All DMD boys with osteoporosis were in wheelchairs and had on average been treated for 8 years on corticosteroids. 43% of them had pubertal delay. Side effects after first infusion included pyrexia (29%), vomiting (14%), aches and pain (42%). Increased energy levels were noted in 14% patients. All patients reported that the side effects were mild and tolerated well. **Conclusion:** 11% of paediatric DMD patients were diagnosed with osteoporosis and started on treatment with zoledronic acid. This was well tolerated with only minor short-term side effects being reported.

P1-P134

A RCT Comparing the Effect of Three Different Vitamin D Supplementation Regimens on Se 25 OH Vit D in Asymptomatic Vit D Deficient Children

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Background: Vitamin D plays a significant role in musculoskeletal health and various extraskeletal functions making the prevention and treatment of this vitamin (now considered as a hormone) of utmost importance. Literature on requirement/supplementation of vitamin D in asymptomatic children is scarce and this study was an attempt to see the effect of three different doses of cholecalciferol supplementation regimens in children with

asymptomatic vitamin D deficiency. **Objective and hypotheses:** To compare the efficacy in raising Se 25OH Vit D levels and the side effects of three different vitamin D supplementation protocols. Also, to analyse if BMI influenced Vit D levels after supplementation. **Method:** Asymtomatic Vit D deficient children were recruited and randomized into three groups to receive oral cholecalciferol for 6 weeks. The three different schedules were 6000 units daily, 10 000 units daily or 60 000 unit every week. Se calcium, Se phosphorous, S alkaline phosphatase, Se PTH, and Se 25OHD were obtained at the time of recruitment, 8 weeks and 14 weeks after recruitment. Urine spot calcium/creatinine ratio were done at the third week, eighth week and 14th week after the initiation of supplementation. **Results:** Baseline characters at enrolment such as sex ratio and mean age were similar among the three groups. The BMI centiles were comparable among two groups, but was higher in one group. Baseline Se calcium, phosphate and PTH were similar among the groups. At 8 weeks, all three treatment protocols showed approximately fourfold rise in mean Se 25OHD level from the baseline. The Se 25OHD level at 14 weeks were also comparable among the groups with a decline in values after cessation of supplementation. But the decline was lesser with the weekly higher dosing schedule. **Conclusion:** All three regimens had equal efficacy in raising 25OH Vit D, though the decline was lesser with the weekly higher dose schedule. There were no hypervitaminosis D documented.

P1-P135

Low Bone Mineral Density in Adolescents with Leukemia After Hematopoietic Stem Cell Transplantation

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Background: Hematopoietic stem cell transplantation (HSCT) has improved the prognosis of children with malignant hematologic disease. However, it has had significant adverse effects on the endocrine system, including bone health. Limited studies are available to assess osteoporosis in survivors of adolescents after HSCT. **Objective and hypotheses:** We investigate the bone mineral density (BMD) and endocrinopathy/treatment factors associated with low BMD in adolescents with leukemia treated with HSCT. **Method:** Demographic measurements and dual-energy X-ray aborptiometry assessment of 61 adolescents (F = 28, M = 33; lymphoid = 28, myeloid = 33) over 14 years of age (16.6 ± 1.3) who were referred to the pediatric endocrinology clinic between September 2009 and September 2014 after HSCT at the Catholic HSCT center were evaluated. Low BMD was classified when lumbar spine (LS)-BMD SDS adjusted for age and current height was below −2.0. **Results:** Twenty-three (37.7%) out of 61 patients revealed low BMD. In low BMD group, LS-SDS was -3.2 ± 1.1. In low BMD group, the incidence of chronic graft-versus-host disease (cGVHD) (73.9% vs 42.1%, $P < 0.019$), and hypogonadism (78.3% vs 44.7%, $P < 0.016$) were higher than normal BMD group. There were no significant differences of age, sex, weight-SDS, weight-SDS, diagnosis, preparative regimen, acute-GVHD, duration of steroid or cyclosporine treatment for GVHD, growth hormone deficiency. In a multivariate logistic regression analysis, the development of hypogonadism was associated with low BMD ($\beta = 1.371$, $P = 0.026$). **Conclusion:** One thirds of adolescents with leukemia treated with HSCT showed low BMD. Monitoring these patients at regular intervals may be necessary for improving bone health during adolescence and adulthood.

P1-P136

Growth Characteristics of a Girl with Multicentric Carpo-Tarsal Osteolysis Caused by Novel Mutation in the *MAFB* Gene

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Background: Recently, mutations in the highly conserved transactivation domain of *MAFB* gene have been identified as a cause of multicentric carpo-tarsal osteolysis (MCTO), rare skeletal disorder characterised by extensive bone resorption predominantly of the carpal and tarsal bones and frequently accompanied by progressive renal impairment. The MAFB is a basic leucine zipper transcription factor that is involved in the regulation of osteoclastogenesis and renal development. Clinical presentation of *MAFB* mutations carriers is very heterogeneous. **Objective and hypotheses:** To describe genetic background and growth characteristics in a child with clinical suspicion of MCTO. **Method:** Direct sequencing of the *MAFB* gene. **Results:** The 6-year-old girl presented with progressive restricted mobility, pain and edema of wrists. Radiographs revealed osteolysis of proximal phalangs of thumbs, cuneiform and scafoid bones on both ankles. The carpal bones had atypical configuration. Markers of inflammation and juvenile idiopathic arthritis associated antibodies were negative. These findings together with significant proteinuria led us to suspicion of MCTO that has been proven by detection of a heterozygous *de novo* p.Thr58Ile (c.173C > T) substitution in the *MAFB* gene. The observed mutation was novel, but located within the mutation hotspot region and predicted to be damaging. In spite of chronic disease and prepubertal status, the patient has accelerated bone age (TW3-RUS 8 years) and dentition. Growth has been accelerated since age of 2 years, in the last 2 years growth velocity has been 8 cm/year (+2.5 S.D.). Actual body height is 124.4 cm (+1 S.D.). She has disproportionally longer extremities, macrocephaly 54.2 cm (+2 S.D.) and orofacial stigmatisation (strabisms, retrognatism, short mandibula and gothic palate). **Conclusion:** We present a case of a girl with MCTO caused by novel mutation in the *MAFB* gene. For the first time, we report accelerated growth and bone age in MCTO patient.

P1-P137

Treatment Experience and Long-Term Follow-Up Data in Two Severe Neonatal Hyperparathyroidism Cases

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Background: Inactivating mutations in the calcium sensing receptor (*CASR)* may result in disorders of calcium homeostasis manifesting as familial benign hypocalciuric hypercalcemia (FBHH) and neonatal severe hyperparathyroidsm (NSHPT). **Objective and hypotheses:** We report two cases with NSHPT together with their treatment and long-term follow-up. **Method:** Two cases were referred with severe hypercalcemia in the neonatal period. Laboratory evaluation revealed severe hypercalcemia and elevated PTH. The parents also had mild hypercalcemia. **Results:** The serum calcium level did not normalize with conventional hypercalcemia treatment and there was also no response to cinacalcet in case 1. Total parathyroidectomy was performed when the patient 1 was 70 days old. Genetic analysis revealed a novel homozygous p.Arg544* mutation in the *CASR* gene. This patient 1 is now 1.5 years old. His height is 81 cm (25-50p) and weight is 10.7 kg (10-25p). The neuromotor development is consistent with age. Patient 2 underwent total parathyroidectomy and auto-implantation when 97 days old but the parathyroid gland implanted into the forearm was removed 27 days later because the hypercalcemia continued. Genetic evaluation revealed a novel homozygous p.Pro682Leu mutation. The case 2 is now 15 years old with a weight of 64.6 kg (1.21 SDS) and height of 165.9 cm (1.2 SDS). Neuromotor development is normal. IQ score of 60 is consistent with mild mental retardation. Normocalcemia was ensured with calcitriol. BMD evaluation revealed an L1-2 value of 1.514 g/cm^2 and a *Z*-score of +3. No bone deformity or fracture developed during follow-up. **Conclusion:** There are only a few cases diagnosed with NSHPT in the literature and very few of them have short and long-term follow-up data. There is good information on the responses to pamidronate and cinacalcet as well total parathyroidectomy with or without partial replantation that will help clinicians in future cases of NSHPT.

P1-P138

Biochemical Parameters Associated with Serum Intact FGF23 Levels in Patients with X-Linked Hypophosphatemic Rickets

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Background: Fibroblast growth factor 23 (FGF23) decreases renal phosphate reabsorption and serum 1,25-dihydroxyvitamin D [1,25(OH)2D] levels. X-linked hypophosphatemic rickets (XLH) is caused by mutations in the *PHEX* gene and accompanied by decreased serum inorganic phosphate (IP) and elevated serum FGF23 levels. Patients with XLH are generally treated with oral active vitamin D and phosphate, but some previous reports indicated that serum FGF23 levels increased with this treatment. However, biochemical parameters associated with serum FGF23 levels during the treatment in XLH patients remain unclear. **Objective and hypotheses:** We analyzed biochemical parameters associated with serum intact FGF23 levels in treated XLH patients to obtain better outcomes. **Method:** Sixteen patients (male 12, female 4) with XLH and normal kidney function were included. The mean age at the first visit was 8 months, and the mean observation period was 5.6 years. We used all the data measured or obtained during the observation period as follows. We examined the association of serum intact FGF23 levels with age, doses of active vitamin D (alphacalcidol) and phosphate, serum calcium (Ca), IP, alkaline phosphatase (ALP), intact parathyroid hormone (PTH), 1,25(OH)2D, and creatinine (Cr) levels in the XLH patients before and during the treatment using linear mixed-effects models in SPSS ver.23 software as statistic analysis. **Results:** Serum FGF23 levels in the XLH patients were positively associated with serum Ca ($P=0.000$), IP ($P=0.000$), 1,25(OH)2D ($P=0.001$) and Cr ($P=0.001$) and negatively with age ($P=0.000$) and ALP ($P=0.007$). **Conclusion:** These results indicate that Ca might induce FGF23 production as well as IP and 1,25(OH)2D. We might be careful not to overcorrect serum Ca, IP and 1,25(OH)2D levels during the treatment of XLH patients because increased FGF23 could exacerbate bone phenotypes and biochemical parameters. Considering the association of intact FGF23 with age and serum Cr levels in XLH patients, age and serum Cr levels could be involved in serum FGF23 levels, although their mechanisms are unclear.

P1-P139

Dental Effects of Intravenous Bisphosphonate When Administered in Early Infancy

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Background: Osteogenesis imperfecta (OI) is characterized by abnormal bone development with low bone mass and increased bone fragility. Dominant mutations affect synthesis & structure of type 1pro-collagen. Recessive mutations affect post-translational processing or tracking of type 1 pro-collagen. OI may be associated with dentinogenesis imperfecta type 1, for both primary and permanent dentition, particularly primary, manifested as tooth discoloration, reduced enamel thickness in some, with vertical enamel fracture, associated short roots and bulbous crowns. Bisphosphonates, acting primarily as osteoclast inhibitors, have been used for over 20 years to increase bone hardness and reduce

fracture risk in OI. The drug is taken up rapidly into bone and bound to the crystal structure. Bisphosphonates are reported to disrupt odontoblast(dentine formation) and ameloblast (enamel formation) activity in an animal model. There are no similar reports in humans. **Objective and hypotheses:** To report dental appearance and progress of 3 children with severe OI (Sillence type 3 (progressively deforming OI with normal sclerae) treated with IV bisphosphonate from the first postnatal week. **Method:** Each child received intravenous zoledronic acid infusions 4 monthly, from week 1, due to multiple pre and early postnatal long bone fractures. Infusions were administered for >8 years, with increasing intervals between treatment cycles based on improving bone mineral density. **Results:** Primary dentition demonstrated abnormal teeth in all, with brown discolouration of all teeth, increased wear, progressive loss of dental height and increased rate of tooth loss. Secondary dentition by contrast revealed almost white teeth with normal colour and appearance and no signs of reduced enamel or dentine. **Conclusion:** Very early treatment of dentinogenesis imperfecta associated with OI can result in improved dental health. For dosages used in children it does not have any adverse effect on clinical outcome and may enhance tooth quality, compared to primary dentition.

P1-P140

Bone Mass and Vitamin D Status in Children and Adolescents with Generalized Epidermolysis Bullosa

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Background: Inherited epidermolysis bullosa (EB) comprises a cluster of genetic disorders characterized by blistering of skin and mucosae following minimal mechanical traumas. Severely affected individuals have high risk of extracutaneous complications, including chronic undernourishment and low bone mass. **Objective and hypotheses:** The aims of this study were to assess the areal bone mineral density (aBMD) and vitamin D status of children and adolescents with generalized forms of EB; and to search for clinical and biochemical parameters correlated to the aBMD. **Method:** Fourteen patients with EB (mean age 10.6 ± 3.5 years; 8 females) and 42 healthy controls (mean age 9.9 ± 3.1 years; 23 females) were evaluated for anthropometry, serum 25-hydroxy-vitamin D (25OHD), and adjusted for height-age lumbar spine (L1L4) and total-body-less-head (TBLH) aBMD obtained through dual X-ray absorptiometry scans. EB patients had also complementary biochemical evaluation and were scored according to their mobility level. **Results:** Six patients presented EB simplex -EBS (three females) and eight presented the severe recessive dystrophic EB -RDEB (five females). 25OHD and TBLH aBMD *Z*-scores were not different between EB group (30.7 ± 6.1 ng/ml; 0.1 ± 0.8 SDS) and controls (25.2 ± 10.7 ng/ml, $P=0.36$; 0.3 ± 1.0 SDS, $P=0.424$, respectively); neither between EBS (30.2 ± 5.9 ng/ml; $-\ 0.2\pm0.5$ SDS) and RDEB (31.0 ± 6.9 ng/ml, $P=0.835$; 0.3 ± 0.9 SDS, $P=0.24$, respectively) groups. DREB group (the more severely affected) presented lower *Z*-scores of height (-2.3 ± 1.3 SDS), weight (-3.8 ± 1.8 SDS) and L1L4 aBMD (-1.9 ± 0.9 SDS) compared with EBS group (0.1 ± 1.0 SDS, $P=0.004$; -0.2 ± 0.9 SDS, $P=0.0008$; -0.4 ± 0.6 SDS, $P=0.0052$, respectively). Two patients with DREB presented lumbar spine fractures. Low mobility was significantly associated with lower height, weight and L1L4 aBMD Z-scores. **Conclusion:** Disease severity and low mobility are clinical parameters significantly associated with both compromised nutritional status and reduced L1L4 bone mass in children and adolescents with generalized EB. Clinical osteoporosis is an actual occurring event among paediatric patients with DREB.

P1-P141

Off-Label Use of the Aromatase Inhibitor Letrozole in Pubertal Boys to Improve Final Height: Laboratory, Auxological and Bone Age Data

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Background and aims: The aromatase inhibitor letrozole is used to improve final height in boys with predicted short stature by delaying bone age (BA) maturation due to suppression of estradiol levels. There are few data regarding its effects, especially when used as single medication. **Methods:** Ten pubertal boys with predicted low final height treated with letrozole 2.5 mg/d p.o. (no other medication) for up to 24 months were analysed for auxological, laboratory and BA data. **Results:** Height-SDS showed only small changes during the time of treatment (means between -0.06 and $+0.10$ SDS) with wide interindividual variability (-0.65 to $+0.89$ SDS). BMI raised between 0 and 6 months of treatment (mean: $+0.42$ SDS) remaining quite constant afterwards. While BA was average in most patients at start (mean difference between BA and chronological age (CA): -0.63 years) and even advanced during the first 6 months (mean difference BA - CA: $+0.34$ years compared to values at start), an increasing delay compared to the initial values was first seen at 12 month (-0.19 years). This trend continued until 24 months (mean: -0.29 years), but in the whole, the additional delay was relatively small. IGF-I SDS decreased in all with the largest difference between 0 and 6 months, but continued to descent until 24 months, falling below -2 SDS in four patients. Testosterone clearly increased between 0 and 6 months (mean: $+440$ ng/dl), then remaining unchanged. Suppression of estradiol, the main effect of letrozole, was achieved only in in 5 of the 10 patients after 6 months but in 5 of 6 after 12 months. Changes of predicted final height varied widely interindividually (-5.0 to $+6.95$ cm at 18 months compared to

start, mean: +1.92 cm, median: +2.91 cm) and also intraindividually during the course of treatment. There were no significant correlations of the changes in delay of BA or predicted final height with any of the initial data. **Conclusion:** Letrozole as a monotherapy increases final height in the majority, but not in all treated boys. Decrease of IGF-I SDS by letrozole could eventually reduce the value of the gain of growth potential. Delay of maturation of BA as well as estradiol suppression were achieved only after 12 months, so it is to discuss if a higher dose of letrozole, at least during the first 6–12 months could further improve the effect.

P1-P142

Effect of Bisphosphonates and Denosumab on Trabecular Bone: Results of a Pilot Study in Children with Osteogenesis Imperfecta

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Background: Osteogenesis imperfecta (OI) is a hereditary connective tissue disorder due to mutations related to collagen type 1. OI presents itself with low bone mass, resulting in high bone fragility. Bone mass is relevant for determination of the severity of OI. Although bisphosphonate treatment is able to increase areal bone mineral density (aBMD) measured by DXA, there is no correlation to fracture rates. **Objective and hypotheses:** The aim of this study was to retrospectively analyse the trabecular bone score (TBS) in children with OI, who were treated with bisphosphonates during the first year and with denosumab during the second year. TBS, already used in adults with osteoporosis, is supposed to represent the cancellous bone and by that the stability of the bone more accurately than aBMD. **Method:** Three DXA scans (GE lunar iDXA, lumbar spine) of six children with OI were performed at intervals of 12 months each. The first two scans were carried out during bisphosphonate treatment. The last was performed after 1 year of denosumab treatment. Paediatric TBS assessment was realized with a custom version of TBS iNsight (Med-Imaps SASU, France). TBS and BMD variations were expressed in % from baseline and normalized at 12 and 24 months. **Results:** DXA assessment showed an increase in aBMD of about 8.9%/17.6% after 12/24 months. TBS showed an increase of 1.7/3.4%. In single case analysis there is a difference between trends of aBMD and TBS. **Conclusion:** In our pilot trial no correlations between TBS and DXA parameters have been observed. The minimal increase of TBS demonstrates a stronger effect of antiresorptive drugs on cortical than trabecular bone. Even without available reference data at the moment TBS offers the possibility to analyse trabecular bone in more detail without a bone biopsy.

P1-P143

Impact of Anti-Tumour Necrosis Factor Therapy on the Insulin Like Growth Factor Axis and Bone Development in Childhood Crohn's Disease

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Background: There is currently no published study evaluating the role of the IGF axis on bone development following anti-tumour necrosis factor (TNF) therapy in Crohn's disease (CD). **Method:** Prospective, 12-month study in 19CD(12M) who were clinical responders to antiTNF therapy, median age 14.9 years (range 11.2–17.2). IGF1, insulin growth factor binding protein 3(IGFBP3), acid labile subunit (ALS), bone-specific alkaline phosphatase (BALP) and c-telopeptide of collagen cross links (CTX) were adjusted for bone age and gender. Assessment of bone mineral density (BMD) and geometry at tibia were performed using peripheral quantitative tomography (pQCT). **Results:** At baseline, IGF1 SDS was +0.1(−3.8,2.1)[$P=0.80$ vs zero), IGFBP3 SDS +1.4(−2.9,3.0)[$P=0.02$ vs zero] and ALS SDS −0.9 (−2.2,1.5)[$P<0.0001$ vs zero]. IGF1 SDS was <-2.0 in 5(26%) at baseline and none at 12 months. At 12 months, IGFBP3 SDS was +0.5(−1.1,2.9) and not different from zero [$P=0.09$]. ALS SDS was <-2.0 in 1(5%) at baseline and none at 12 months. BALP SDS of −1.7(−3.6,1.0)[$P<0.0001$ vs zero] and CTX SDS of −1.1(−2.6,0.4)[$P=0.01$ vs zero] at baseline reflect a low bone turnover state. BALP SDS increased significantly by 6 weeks [$P=0.01$], whereas CTX remained unchanged, leading to net increase in bone formation. pQCT bone and muscle remained unchanged over 12 months: trabecular BMD −1.6(−3.2,1.1) to −1.3(−2.6,1.2), cortical thickness −0.1(−2.1,1.0) to −0.3 (−2.0,0.7), muscle −2.4(−4.3,−0.3) to −2.0(−4.3,0.2). Mixed model regression analysis showed that ALS SDS ($P=0.007$) and muscle area ($P=0.003$) were positively associated with trabecular BMD; muscle area ($P<0.0001$) and IGFBP3 SDS ($P=0.004$) were associated with cortical thickness positively and negatively. **Conclusion:** Comprehensive assessment of the ternary complex in childhood CD demonstrated disproportionately low ALS for the first time. AntiTNF therapy was associated with improvement in IGF axis for those with low levels. Markers of the IGF-1 axis and muscle mass show independent associations with bone mass and structure. Interventions to improve muscle mass or manipulation of the GH/IGF axis in combination with antiTNF therapy needs further exploration.

P1-P144

Effects of Phylloquinone and Magnesium on ATDC5 Prechondrocytes

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Background: Cell-mediated initiation of enchondral ossification is essential for growth plate maturation. The matrix mineralization inhibitors matrix Gla protein (MGP) and osteocalcin (OC) represent key regulators of matrix mineralization and are highly expressed in growth plate chondrocytes. Pharmacological or nutritional phylloquinone (K1) depletion is known to affect skeletal mineralization by reduced gamma-carboxilisation of MGP and OC. Constituents of mineral matrix such as calcium and magnesium (Mg) additionally regulate expression of mineralization inhibitors on gene expression level. **Objective and hypotheses:** The effects of clinically relevant modifiers of mineralization inhibitor activity on growth plate chondrocytes is unclear. This study aims to investigate the effects of K and Mg on growth plate chondrocyte differentiation and proliferation. **Method:** Chondrogenic ATDC5 alginate bead cultured are treated with 1, 10 or 100 uM K1 with or without presence of 2.5 mM Mg for 14 d. Chondrocyte differentiation marker and matrix inhibitor expression is investigated by RT-PCR. BrdU and EZ4U assays are used for cell proliferation and metabolic activity determination. **Results:** K1 reduces expression of collagen type I, II and X in a dose dependent manner. Presence of 2.5 mM Mg partly rescued collagen expression resulting in significantly increased collagen type II and X expression during differentiation. **Conclusion:** We found K1 and Mg as modifiers of MGP and OC activity, to affect chondrocyte differentiation inversely. While K1 downregulates collagen expression in ATDC5 prechondrocytes, Mg reverses these effects. Our data point to a possible counter regulation of matrix mineralization and growth plate maturation by Mg and K1.

P1-P145

To Study the Efficacy and Safety of Growth Hormone (GH) Therapy in Children with Pycnodysostosis

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Background: Pycnodysostosis is a rare recessive condition with mutation in the cathepsin K gene, causing reduction in bone reabsorption resulting in abnormally dense and fragile bones. Characteristic features include deformity of the skull, maxilla causing craniofacial, dental abnormalities with skeletal changes and short stature. Growth hormone therapy has been attempted in a small group of patients with Pycnodysostosis to promote final adult height, however has not been shown to be efficacious. **Objective:** To evaluate the efficacy of GH therapy for short stature in Pycnodysostosis. **Methods:** A retrospective analysis of growth data from paediatric outpatient clinic on $n=3$ children, (two siblings female (A and B aged 16 and 14 year); and one male (C) 15 year). Both siblings received GH ($\sim$3 mg/m^2 per day) privately from an external center abroad (Europe), for approximately 4 year period along with puberty blocker injections for $\sim$1 to 2 years. Subject (C) received growth hormone (0.4 mg/m^2 per day) trial for 4 months at an endocrine center within UK. All patients tested negative for growth hormone deficiency prior to starting GH therapy. Serial anthropometric data pretreatment was compared with that during GH therapy. **Results:** The pre-treatment height centile for $n=3$, was $<$ 1st percentile. Height SDS mean ($\pm$S.D.), in (A) pretreatment and end of therapy (-2.23 ± 0.2) and (-2.24 ± 0.4); (B) (-2.9 ± 0.2) and (-3.28 ± 0.3) at 4 years; (C) (-3.8 ± 0.2) and (-3.28 ± 0) at 4 months. The height velocity changed from 5.4 ($\pm$0.4) to 5.2 ($\pm$1.5); 5.5 ($\pm$1.5) to 5.9 ($\pm$1.4) cm/year after 4 year treatment in (A) and (B); 5.4 ($\pm$2.2) to 5 cm/year after 4 months of treatment in C. IGF1 during GH treatment showed stark rise above normal range. Moreover, BMI *z*-score worsened on treatment in (A) $+1.67$ to $+1.93$ and (B)$+2.8$ to 3.19 respectively. Symptoms of sleep apnea and insulin resistance worsened on GH therapy, no signs of raised intracranial pressure were noted. **Conclusion:** GH therapy failed to show any improvement in growth velocity or height SDS. Increased insulin resistance, weight gain, exponential rise in serum IGF1 level was seen in 2/3 patients raising concerns about its safety. In contrast to previous report this case series shows no beneficial effect from growth hormone therapy. High IGF1 levels are associated with a greater risk for prostate and breast cancer therefore challenging the potential benefit of GH therapy for treatment of short children with skeletal dysmorphology.

P2-P146

Bone Mineral Status and Metabolism in Patients with Williams-Beuren Syndrome

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Background: Despite the multiple endocrine, cardiovascular, and gastroenterologic problems of patients with Williams-Beuren Syndrome (WBS), Studies considering metabolism and bone quality in WBS are almost entirely absent from the literature. **Objective and hypotheses:** We evaluate bone mineral status and metabolism in a cohort of patients with WBS. **Method:** Thirty-one children (15 females, 16 males; mean age 9.61$\pm$2.74 years) and ten young adults (six females, four males; mean age 21.4$\pm$5.1 years) with WBS were evaluated and compared with two

age-, sex-, and body-size-matched healthy control groups. IN WBS and controls we evaluated ionised and total calcium, phosphate, parathyroid hormone (PTH), 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, osteocalcin, bone alkaline phosphatase levels, and urinary deoxypyridinoline concentrations. We also calculated the phalangeal amplitude-dependent speed of sound (AD-SoS) and the bone transmission time (BTT) z-scores. Spearman's (rank) correlation test showed that AD-SoS z-score values were significantly inversely correlated with age ($P<0.005$). Both BSAP and osteocalcin levels also showed a significant correlation with total calcium values ($P<0.005$). PTH correlated significantly with ionised calcium ($P<0.05$) and osteocalcin ($P<0.005$). **Results:** WBS patients showed a significantly reduced AD-SoS z-score ($P<0.0001$) and BTT z-score ($P<0.0001$) than the controls. This finding persisted when we divided the sample into paediatric or adult patients. WBS also had significantly higher ionised ($P<0.001$) and total calcium ($P<0.0001$) levels as well as higher PTH levels ($P<0.0001$) compared with the controls. However, WBS children and adolescents had significantly lower serum osteocalcin levels ($P<0.001$) and urinary deoxypyridinoline concentrations ($P<0.0001$) than the controls. **Conclusion:** WBS subjects exhibit a significant reduction in bone mineral status and impaired bone metabolism; this suggests the need to closely monitor these subjects.

P2-P147

The Beneficial Effect of Cinacalcet on the Treatment of vitD Resistant Rickets

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Background: Patients with vitD resistant rickets (VDRR) due to vitD receptor (VDR) mutations have extreme rickets along with alopesia, severe hypocalcemia, hypophosfatemia secondary to hyperparathroidism and elevated 1,25(OH)2vitD. Although there is no standard therapy for this patients, long-term or intermittanat i.v. or high dose oral calcium suplementations are recommended to correct the hypocalcemia and secondary hyperparathyroidism. Preliminary studies revealed that calcimimetics may be safe and effective therapeutic choise in children with secondary hyperparathyroidism. **Objective and hypotheses:** To observe the efficacy of cinacalcet on the normalization of secondary. **Method:** Two siblings, one at the age of 2 years – 6 months and the other at 4 months old were admitted to the hospital with severe hypocalcemia. Radiological and biochemical findings showed advanced features of rickets. Analysis of VDR gene identified a homozygot stop-codon mutation in exon 4 at nucleotide position 148 (c.148C>T) from both siblings. They were treated with high dose calcitriol and intermittant i.v. calcium infusions. Secondary hyperparathroidism was normalized temporarly, but not improve completly. We started cinacalcet (0.25 mg/kg) once a day along with high dose oral calcium and calcitriol, after 3 months biochemical and radiologic findings were return to normal status. **Conclusion:** We observed that cinacalcet is succesfull to normalize of secondary hyperparathyroidism and hypophosphatemia and to restore bone findings.

P2-P148

A Preliminary Report on Body Composition Profile of Young Patients with Chronic Hemolytic Conditions

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Background: Chronic hemolytic anemias may compromise growth through multiple mechanisms. To date, no data exist on growth and body composition (BC; bone, muscle and fat mass) of children and adolescents with chronic hemolysis. **Purpose:** To evaluate growth and BC of patients with thalassemia intermedia (not on regular transfusions; thal-intermedia), alpha-thalassemia and congenital spherocytosis. **Methods:** Patients and controls underwent clinical examination, dual-energy X-ray absorptiometry (DXA) of the spine and total body (less head) and laboratory bone profile. All growth and BC parameters were converted to Z-scores. **Results:** 35 patients (17 female, 19 pubertal), aged 11.9 ± 3.4 years, of which 13 with thal-intermedia, 16 with α-thalassemia and six with spherocytosis were studied. The control group consisted of 57 subjects. As a whole, our patients had lower weight and body mass index (BMI) (Z-scores -0.2 and -0.3, respectively, $P<0.01$). They had lower lumbar spine bone mineral density (LS BMD), (Z-score$=-0.6$, $P<0.01$), whereas muscle and fat mass were unaffected. A positive correlation was found between LS BMD and total body BMD ($r=0.582$, $P<0.01$), as well as between total body BMD and height ($r=0.368$, $P=0.03$). Of note, patients with adequate calcium intake and regular exercise were taller than the other patients (Ht Z-score$=0.3$, $P=0.02$). Laboratory markers for bone formation and resorption were normal in the majority of cases (85%), as well as vitamin D and PTH levels. When each subgroup was analysed separately, patients with thal-intermedia appeared more affected in terms of BMD and BMI, whereas in the other subgroups only LS BMD was lower, all other parameters being comparable to controls. **Conclusion:** Chronic hemolysis may adversely affect BMI and LS BMD. Muscle and fat mass are not particularly affected. Counselling on a healthy lifestyle and regular surveillance of bone health is justifiable, especially in Thal-intermedia patients.

P2-P149

Bone Status in a Patient with IGF-I Receptor Deletion Syndrome: Bone Quality and Structure Evaluation Using DXA, pQCT, and QUS

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Background: Various aspects of *IGF1R* defects have been analysed to date, but the effects of IGF1R haploinsufficiency bone status and metabolism were rarely investigated. **Objective and hypotheses:** To study bone metabolism and structure in a case of *Insulin-like growth factor-I (IGF-I) receptor* (*IGF1R*) gene deletion. **Method:** Genetic analysis, GH stimulation, rhGH treatment, CGH-array, dual-X-ray absorptiometry (DXA), peripheral quantitative computed tomography (pQCT), phalangeal bone sonography, bone metabolism study were carried out in this patient. **Results:** We report a patient referred to our centre at the age of 18 months for failure to thrive. GH stimulation tests revealed a GH deficiency (GH peak after arginine 8.92 ng/ml, after clonidine 6.92 ng/ml), whereas IGF-I was 248 ng/ml. rhGH treatment (0.23 mg/kg per week) showed only a slight improvement (from −5.1 to −3.5 SDS). Target height was 166.5 cm (0.67 S.D.). So, at 10 years of age, the child was re-evaluated: CGH-array identified a heterozygous *de novo* 4.92 Mb deletion in 15q26.2, including the *IGF1R* gene. DXA showed a normal BMD *z*-score (the BMD *z*-score corrected for height was 0.6), while pQCT revealed very reduced cortical (−6.9 SDS) and increased trabecular density (3.8 SDS). The total density was normal (0.7 SDS), whereas we showed a significantly reduced bone area for muscle area (−4.0 SDS) and for height (−4.1 SDS). The SSI polar (−2.2 SDS) was significantly reduced. Fat area was also poorly represented (−1.8 SDS). Phalangeal bone sonography showed significantly reduced AD SoS and BTT values. Bone metabolism study revealed a reduced bone modelling and accrual with moderately high PTH and reduced osteocalcin, bone alkaline phosphatase and urinary deoxypyridinoline concentrations. **Conclusion:** Our study showed the presence of changes in bone architecture, quality, and metabolism in heterozygous *IGF1R* deletion patients, supporting IGF-I as key in bone modelling and accrual.

P2-P150

Prevalence of Vitamin D Deficiency in Haitian Infants and Children

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Background: Vitamin D deficiency in children is a common cause of rickets, and a potential risk factor for extraskeletal adverse health outcomes. Its prevalence in Haiti has not been assessed. **Objective and hypotheses:** To examine the prevalence of vitamin D deficiency in dark-skinned young children in Haiti. **Method:** Cross-sectional study of healthy Haitian children 9 months to 6 years across three geographical regions in Haiti (coastal (C), mountainous (M), urban (U)). We obtained anthropometrics, information on family income, 25-OH-vitamin-D levels (25OHD), and, in vitamin D deficient children, alkaline phosphatase levels. Vitamin D insufficiency, deficiency and severe deficiency were defined as 25OHD <30, <20 and <10 ng/ml, respectively. **Results:** 292 subjects (mean age 3.3 ± 1.6 years, 50.3% females, median family income USD 30/week) participated, 100 in C,94 in U, and 98 in M. Moderate-severe malnutrition was present in 16.4%, and more common in M (25.5%) vs. C (11%) and U (12.8%), $P=0.01$. Mean 25OHD was 30.7 ± 9.2 ng/ml. Prevalence of vitamin D insufficiency, deficiency and severe deficiency was 43.2, 8.6 and 0%, respectively. Deficiency was highest in C (21%) vs. U and M (both 2%, $P<0.0001$). No subject had elevated alkaline phosphatase levels. In univariate analyses, higher weight and height *z*-scores, shorter breast feeding duration and less sun exposure were predictive of lower 25OHD, whereas diet, skin darkness, and income were not. In a multivariate model, region C and weight *z*-score remained significant predictors of lower 25OHD. In univariate and multivariate logistic models, only region was a significant predictor of vitamin D deficiency. **Conclusion:** While the prevalence of vitamin D deficiency in young children in Haiti is $<10\%$, close to half have sub-optimal vitamin D levels. Public health recommendations such as increased sun exposure, fortified food products and/or routine vitamin D supplementation should be considered. Reasons for higher deficiency rates in coastal areas need further exploration.

P2-P151

Progressive Development of PTH Resistance in Patients with Maternal GNAS Inactivating Mutations

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Background: Pseudohypoparathyroidism (PHP) is a group of disorders characterized by end-organ resistance to the parathyroid hormone (PTH). PHP type 1A is caused by mutations in GNAS exon 1 through 13 with multihormone resistance (PTH, TSH and gonadotropins), Albright's hereditary osteodystrophy, and obesity. However, patients often do not present with elevated levels of PTH until after the first years of life. **Objective and hypotheses:** Assessment of the development of PTH and TSH resistance over time in 20 patients affected by PHP1a, diagnosed because of familial history, ectopic ossification or short stature and carrying a maternal *GNAS* mutation. **Method:** Data for serum calcium, phosphate, TSH and PTH levels were collected from the date of PHP1a diagnosis until calcidiol treatment. PTH infusion test was performed in one patient. **Results:** Patients were diagnosed around 5 years of age and had a mean duration of follow-up of

2 years. PTH levels significantly increased over time (184–338 pg/ml; $P<0.05$), while TSH resistance was already observed at diagnosis in all patients. Calcium levels decreased from 2.31 to 2.19 mmol/l ($P<0.05$), while phosphate levels did not change with age. One patient born with ectopic ossification and familial history showed an increase in cAMP and phosphaturia upon PTH infusion, similar to controls, at 7 months old, but an impaired response at 4 years old, therefore establishing PTH resistance. **Conclusion:** This work suggests that, an early diagnosis of PHP1A patients could be achieved by screening for maternal *GNAS* mutation in the presence of varying degrees of AHO, resistance to TSH even in the absence of PTH resistance at diagnosis. An early diagnosis of PHP1A will permit to start calcidiol treatment at early stages of the disease in order to improve the care of PHP1A patients.

P2-P152

Effect of Hydroxyurea Therapy on Growth Parameters in Older Children with Sickle Cell Disease

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Background: Growth impairment is a known complication of sickle cell disease (SCD). Effects of hydroxyurea (HU) on growth in older children with SCD have never been reported. **Objective and hypotheses:** This study was done to explore the potential effects of HU on growth parameters of older children with SCD and correlate these changes with clinical improvement. **Method:** A prospective study was conducted on 97 SCD patients started on HU at Sultan Qaboos University Hospital (Q16UH), Oman during the period between January 2013 and October 2015. Weight, height, and BMI were collected at baseline, 6 and 18 months after start of HU. Anthropometric data were converted to *Z* scores and compared with World Health Organization (WHO) standards. *Z* scores were also compared between SCD patients who showed significant clinical improvement in annual vaso-occlusive crisis (VOC) rate and those who did not. **Results:** The initial *Z* scores of included SCD patients were lower than WHO norms for their age and sex. The follow up *Z*-scores of the whole studied patients at 6 and 18 months from starting HU did not change significantly for both weight and height parameters, however, BMI *Z*-scores improved significantly at both 6 and 18 months follow up after HU (*P* value 0.044 and 0.028 respectively). Similarly no significant changes were observed in weight or height *Z* in those who showed clinical improvement and those who did not during the period of follow up. BMI *Z* score improved significantly at 18 months follow up for the clinical improvement group ($P=0.014$). Patients with minimal or no clinical improvement in annual VOCs showed non-significant changes in BMI *Z* scores after HU therapy. **Conclusion:** Hydroxyurea therapy did not adversely affect nor improve the weight and height in older children with SCD even in those with significant clinical improvement. BMI *Z* scores improved at 18 months of follow-up for the whole studied patients and in those with clinical improvement however, a longer follow up is recommended.

P2-P153

Evaluation of ALP Value in Early Prediction of the Effects of Growth Hormone Treatment in Children with Growth Hormone Deficiency (GHD)

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Background: Serum bone turnover markers may serve as parameters for predicting the growth response to growth hormone (rhGH) treatment. **Objective and hypotheses:** Assessment of the alkaline phosphatase (ALP) value in early prediction of the effects of rhGH treatment in children with growth hormone deficiency. **Method:** The study group consisted of 50 children with GHD. ALP, bone-ALP, vitamin D and IGF-1 concentrations were evaluated at baseline and after 6 and 12 months of rhGH treatment. The group was divided into two subgroups depending on puberty status. The subgroups did not differ significantly in terms of GH deficiency defined as the maximum secretion of growth hormone in tests. IGF-1 concentration was normalized for bone age. **Results:** ALP after 6 months of rhGH treatment was significantly higher in the pubertal group. In the prepubertal children there was a tendency for increased ALP, but it was not statistically significant. In the following 6 months of treatment, ALP levels were not significantly altered. There was a statistically significant weak correlation between ALP at baseline and IGF-1 S.D. ($r=0.29$) in the pubertal group. No such correlation was found in the prepubertal children. In the prepubertal children a correlation was found between ALP at baseline and a decrease in height deficiency S.D. ($r=0.26$). In the pubertal group, there was no correlation between ALP and the growth response in the first year of treatment. **Conclusion:** The results suggest that bone turnover is increased after 6 months of rhGH treatment and reaches comparable levels after 12 months of therapy. In prepubertal children ALP may be a valuable marker in predicting the growth response to rhGH treatment. In pubertal children ALP cannot be used as an isolated parameter in predicting the effects of rhGH treatment.

P2-P154

Comparison of Two Different Stoss Therapy Doses in Children with Vitamin D Deficiency or Insufficiency without Rickets

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Background: There is no agreement on the optimal treatment of children with vitamin D deficiency or insufficiency without obvious signs of rickets. **Objective and hypotheses:** To compare the efficacy and side effects of two different stoss therapy regimens (10 000 IU/kg and 300 000 IU vitamin D_3) in children with vitamin D deficiency or insufficiency without rickets. **Method:** A total of 64 children and adolescents who had vitamin D deficiency or insufficiency without rickets were retrospectively studied. Serum levels of calcium, phosphate, alkaline phosphatase (ALP), 25-OH-D, parathyroid hormone, spot urine calcium/creatinine ratio before and after treatment and renal ultrasonography (USG) outcomes were evaluated in two groups. A serum level of 25-hydroxyvitamin D (25-OH-D) between 15 and 20 ng/ml was considered as vitamin D insufficiency and <15 ng/ml levels was considered as vitamin D deficiency. **Results:** Thirty-two patients were treated with the dose of 10 000 IU/kg and the remaining 32 patients received 300 000 IU single dose oral vitamin D_3. No significant difference was found in the levels of 25-OH-D between the two groups at presentation (10.8 ± 4.9 and 8.8 ± 3.6 ng/ml, respectively). The mean level of 25-OH-D was significantly higher in 10 000 IU/kg group at the second week of therapy, but vitamin D levels were not different between the groups at the post-treatment 4 and 12 weeks. 25-OH-D level was found below optimal level ($\geqq 30$ ng/ml) in 66.5% and below 20 ng/ml in 21.8% of the patients at the third month of therapy in both groups. None of the patients in both groups developed hypercalcemia or hypercalciuria. Nephrolithiasis was detected only in one patient in the 10 000 IU/kg group. **Conclusion:** 10 000 IU/kg and 300 000 IU single dose vitamin D_3 are not superior to each other. However, the optimal serum level of 25-OH-D cannot be maintained for more than three months.

P2-P155

Bisphosphonate Treatment of Hypercalcemia in a Child with Jansen'S Metaphyseal Chondrodysplasia

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Background: Jansen's Metaphyseal Chondrodysplasia is a rare autosomal dominant condition caused by activating mutations in the parathyroid hormone/parathyroid hormone related peptide receptor (PTH1R). It is associated with persistent PTH-independent hypercalcemia and hypercalciuria from an early age. Our patient, a 2 year old boy with genetically proven Jansen's Metaphyseal Chondrodysplasia, developed bilateral medullary nephrocalcinosis secondary to persistent hypercalciuria. A single previous case report noted improvement in hypercalciuria in an adult patient with bisphosphonate therapy. **Objective and hypotheses:** Bisphosphonates are a well-recognised treatment for hypercalcemia due to malignant and non-malignant bone disorders. We posited that intravenous bisphosphonate administration would improve serum and urine calcium concentrations, and potentially halt progression of nephrocalcinosis. **Method:** Our patient received three intravenous infusions of Pamidronate disodium over a five month period – 0.25 mg/kg at 0 months, 0.5 mg/kg at 1 month, and 0.5 mg/kg at 5 months, in combination with a low calcium diet. The infusions were administered in hospital according to local protocol. Serum and urine calcium and phosphate were measured at baseline and following treatment **Results:** There was no appreciable improvement in serum or urine calcium concentrations following pamidronate infusion. Serum alkaline phosphatase also remained mildly elevated. The degree of nephrocalcinosis was also unchanged. Intravenous bisphosphonate in combination with low calcium diet was not successful in decreasing chronic hypercalcemia or hypercalciuria in our patient.

P2-P156

Physical Exercise Level is Associated to Peak Bone Mass in Undergraduate Students

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Background: Promotion of high pick bone mass is one of the strategies to prevent osteoporosis in adult life. Undergraduate students are still in the age group of mineral acquisition and, therefore, their lifestyle may influence this process. Physical exercise is an important lifestyle characteristic for optimize peak bone mass (PBM). **Objective:** To evaluate bone mass in undergraduate students with different lifestyle. **Methods:** Observational study in 142 (62 males) undergraduate students (74 medical and 68 physical education students) aged 17–28 years (22.3 ± 2.9). Socio-demographic, clinical, and lifestyle variables were obtained through densitometric anamnesis. Bone mineral density (BMD) at lumbar spine (LS), total body (TB), femoral neck (FN) and total femur (TF) were evaluated by DXA (Explorer, Hollogic). Low PBM was defined as Z-score <-1 DP. Anthropometry was performed before the DXA examination. Statistical tests used were Student's *t*-test, Mann-Whitney *U* and χ^2. Human Ethics Comity approved the study. **Results:** Physical education students dispended more time doing exercise than medical students (483.0 vs 128.1 min/week). Moreover, frequency of regular practicing of physical activity (>150 min/week) was also higher in this group (95.6% vs 63.5%; $P<0.01$). Medical students presented higher frequency of low PBM in al sites except femoral neck (CT: 51.4% vs 85.3%; LS: 72.9% vs 91.2%; TF: 77.0% vs 92.6%; $P<0.001$). BMD *Z*-score was lower in medical students in al sites. *Z*-score differences varied from 0.76 in TF to 0.92 in LS ($P<0.0001$). High impact exercises was more frequent in physical education students (54.4% vs 33.8%; $P<0.05$). Students with normal PBM presented more frequency of regular practicing of physical activity than those with low PMB (71.9% vs 50.0%). There were no differences in age, gender, BMI and calcium intake between groups. **Conclusion:** Higher physical exercise level was associated to high peak bone mass in undergraduate students.

P2-P157

A Case with Lethal Perinatal Hypophosphatasia

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Background: Hypophosphatasia (HPP) is a rare metabolic bone disease caused by loss-of-function mutations in the gene ALPL encoding the tissue nonspecific alkaline phosphatase. HPP is associated with significant morbidity and mortality in pediatric patients, with high rates as high as %100 in perinatal-onset HPP. Serum alkaline phosphatase (ALP) activity is markedly reduced, which leads to increased serum/urine phosphoethanolamine (PEA), pyridoxal-5'phosphate (PLP). Asfotase alfa is the first-in-class, bone-targeted, enzyme-replacement therapy designed to reverse the skeletal mineralization defects in HPP. **Objective and hypotheses:** We present here a male infant with perinatal lethal HPP. **Method:** He was a full-term infant of a G6P1 mother who delivered by Cesarean section. After birth, he was promptly intubated and ventilated because of respiratory distress. Prenatally, bone deformities had been noticed. On physical examination his weight was 3020 g. His skull bones were not formed. Radiographs demonstrated thin ribs, poor ossification of the skull, and epiphysis of the long bones. Laboratory examinations revealed serum ALP was 0 U/l, serum phosphate was 7.3 mg/dl (range 2.5–4.5), serum calcium was 9.8 mg/dl. Parathyroid hormone and serum 25-hydroxy vitamin D levels were normal. Perinatal lethal HPP diagnosis was based on physical findings, laboratory investigations, and radiographic skeletal features. Urine PEA and plasma PLP levels were markedly elevated (1081 μmol/l (range 15–341), 3942 μg/l (range 0–50) respectively).Asfotase alfa (Strensiq) therapy (2 mg/kg per day s.c three times per week) was started at 30 day of age. **Results:** Serum calcium and phosphate levels were normal but ALP levels increased as high as 12,700 U/l during treatment. He died at the age of 65 days because of ventilator associated pneumonia. **Conclusion:** Perinatal lethal hypophosphatasia is the most severe form of HPP. These severely affected babies often die at or soon after birth from respiratory insufficiency due to pulmonary hypoplasia, a consequence of poorly mineralized bones of the chest. Therefore early treatment is crucial for prognosis.

P2-P158

Anthropometric and Nutritional Parameters in Egyptian Children with Osteogenesis Imperfecta: Effect of Zoledronic Acid Therapy

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Background: Patients with osteogenesis imperfect (OI) present with various degrees of short stature and nutritional disorders. **Objective and hypotheses:** To evaluate anthropometric and nutritional parameters in OI children and their variability among various types. **Methods:** Eighty-four patients with OI (types I, II, and IV) were subjected to the following anthropometric measurements: standing height (Ht), sitting height (SH), arm span, weight (Wt), and head circumference (HC), with calculation of Ht, SH, Wt, BMI, and HC SDSs, and relative arm span. Triceps skinfold thickness (TSFT), subscapular skinfold thickness (SSFT), and mid upper arm circumference (MUAC) were measured, as well as dietary intake of macronutrients and calcium; also, energy requirements were calculated. Ht and Wt SDSs were re-evaluated after 1 year of zoledronic acid therapy. **Results:** Ht SDS was reduced in OI-III and OI-IV compared to OI-I; SH SDS was reduced in OI-III compared to OI-I. HC SDS was more increased in OI-III than in OI-I and OI-IV. BMI SDS correlated with TSFT, SSFT, and MUAC. OI-III patients had the highest percentage of energy intake. The frequency of low macronutrient and calcium intake was highest in OI-III, while the frequency of low fat intake was highest in OI-I. **Conclusion:** Anthropometric and nutritional parameters differ among OI types. Assessment of anthropometric measurements and nutritional status in OI patients is important. Zoledronic acid therapy improves height SDS in such patients.

P2-P159

Low Bone Mineral Density in Adolescents with Joint Hypermobility

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Background: Generalized joint hypermobility is quite common and seems to be a risk factor for low bone density. **Objective:** The goal of this study was to determine the bone mineral density in adolescents with hypermobility syndrome. **Materials and methods:** In a cross-sectional study, we measured the bone mineral density (BMD) and bone mineral apparent density (BMAD) of 32 children, 13 to 18 years old with benign hypermobility syndrome diagnosed by Beighton score and 29 age- and sex-matched controls. Age, stage of puberty, height, weight, and body mass index were evaluated and matched between the two groups. Bone age, gonadotropins, IGF1, thyroid function test, sex steroids, serum vitamin D, and calcium intake were also assessed. None of the children were taking any drugs affecting bone metabolism or had any systemic disease. **Results:** Bone mineral accretion in both groups occurred at a slowed and consistent pace, with a sharp increase during the pubertal growth spurt. Puberty had a significant delay in onset and peak height velocity in both boys and girls of the hypermobility group. Bone age and IGF-1 levels progressed more slowly in this group. Age at onset of puberty, independent of its length was a strong predictor of bone measurements at skeletal maturity. After correcting the onset of puberty and other interfering factors, the hypermobility group had

still significant lower BMAD compared to the control ($P=0.02$). BMD and BMAD z-scores were significantly lower in hypermobile children compared to the control group ($P<0.005$). Significant negative correlations were found between the Beighton scores and BMAD z-score ($r=-0.30$) in hypermobility children. Low bone mass was more frequently found among subjects with hypermobility ($P=0.004$). Hypermobility was found to increase the risk for low bone mass by 2.6 times (95% CI 1.01–3.38). **Conclusion:** These findings suggest that adolescents with joint hypermobility have lower bone mineral density when compared to the controls, and hypermobility increases the risk for low bone mass.
Keywords: hypermobility, BMD, BMAD

P2-P160

Fractures in Children with Type 1 Diabetes are Associated with Poorer Bone Mineral Status and Glycaemic Control

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Background: Type 1 Diabetes (T1D) is associated with increased fracture risk. **Aim:** Understand the association between glycaemic control and bone health in children with T1D. **Method:** Children (n, 32) with T1D and a median (range) age of 13.7 years (10.4,16.4), were recruited to study bone mineral content (TB & LS) and body composition by DXA. All data were corrected for size. Vitamin D, Bone alkaline phosphatase (BAP) and C-terminal cross-linked telopeptides (CTX) were measured and converted to SDS. Anthropometry, disease details, xray-confirmed fracture history, HbA1c over the previous 12 months and physical activity scores were recorded. **Results:** The median HbA1c was 65 mmol/mol (27,100). TB and LS BMC SDS was −0.1 (−1.1, 0.9) and LS −0.3(−1.0, 1.8), both lower than average for local normative data ($P=0.02$, and $P=0.01$, respectively). BMC SDS did not show any correlation to glycaemic control, age at diagnosis, or disease duration. However, vitamin D levels were associated with LS BMC SDS (r,−0.4, $P=0.03$). The cohort had a low median BAP SDS and CTX SDS of −0.57 (−2.5, 8.7) and −1.05 (−2.49, 0.51), respectively ($P<0.01$). CTX was inversely related to TB BMC SDS (r, −0.5, $P<0.01$). A lower BAP was more likely in those with a HbA1c of >65 mmol/mol. Of 32, 10 had suffered a fracture after the diagnosis and the fracture group had a HbA1c of 72 mmol/mol (49,100) vs 62 mmol/mol (27,87) in the non-fracture group ($P<0.01$). The TB BMC SDS in the fracture and non-fracture groups was −0.5 (−1, −1.8) and 0 (−0.5, 0.9), respectively ($P<0.01$). There was no difference in the body composition of these two groups and the physical activity score was higher in the fracture group ($P=0.04$). **Conclusion:** Children with T1D display a low bone turnover state and marginally low bone mineral status. Those who suffer a fracture are likely to have a worse bone mineral status and glycaemic control.

P2-P161

Identification of Predictor Factors of Growth Outcome in Children with Hypophosphatemic Rickets

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Background: The goal of treatment in children with hypophosphatemic rickets (HR) attempts to correct growth and leg deformities. However, growth is compromised despite treatment and patients are at risk of developing nephrocalcinosis in the future. Some factors (sex, age and height at diagnosis) have been related to height outcome, but little is known about the impact in growth of different dosage of treatment or alkaline phosphatase (ALP) levels. **Objective and hypotheses:** 1) To evaluate growth improvement in relation to: doses of phosphate, calcitriol and the decline of ALP. 2) To assess the relation between dose and duration of treatment with the incidence of nephrocalcinosis. **Method:** Retrospective review of patients with HR (2006–2016). Patients were divided as responders in G1: height improvement >0.5 S.D.; G2≤0.5 S.D. We evaluate improvement in relation to sex, age and height at diagnosis, treatment dose and ALP. **Results:** Nine children were identified. The children improved their height 0.5 S.D. (−0.04, 0.65) after 4.4 years (3.9–8.0) of treatment. Eight children had a Z score-height ≤−2 S.D. (−2.9 S.D.), and were below their midparental height (−1.8 in relation to MPH). Genu varus was present in all children and improved in 66% of them. There were no differences in phosphate dose (G1 68.5 vs G2 70 mg/kg per day) or calcitriol dose (25.7 vs 23.4 ng/kg per day) between groups. After treatment, ALP decreased more in G1, but it did not reach statistical significance ($P=0.41$). Five children developed nephrocalcinosis and tended to need higher phosphate doses, lower calcitriol doses, longer duration of treatment, and had a higher ALP at the last visit ($P=0.048$). **Conclusion:** The children improved their growth but remained below their MPH at the last visit. We can not identify a treatment protocol associated with better height outcome. Children with nephrocalcinosis had ALP higher at the last visit, which could reflect a more aggressive phenotype.

P2-P162

Effects of Socioeconomic Status on Bone Mineral Density and Vitamin D Concentrations in Healthy Female College Students

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Background: Skeletal mass approximately doubles at the end of adolescence. Socioeconomic Status (SES) and Vitamin D status may play a role in the development of bone mass. **Objective and hypotheses:** The aim of the present study is to examine the effects of different socioeconomic conditions on bone mineral density (BMD) and vitamin D status in healthy female college students and to determine the possible association between Vitamin D status and BMD. **Method:** Female college students ($n=138$) aged between 18 and 22 years old were recruited in this cross-sectional study. Socioeconomic status was determined by a questionnaire in all subjects. Blood samples were obtained for 25-hydroxy-vitamin D (25OHD) analysis in May. Lumbar spine and total body BMD was performed by dual-energy X-ray absorptiometry (DEXA). Osteopenia was defined by a Z-score below -2. Female students were grouped into three study groups as low, middle and high according to SES. **Results:** Although 25OHD level was found to be lower in females with lower socioeconomic status, there was no significant ($P=0.851$) difference between the three different socioeconomic levels. Similar results ($P>0.05$) for total body, lumbar spine BMD values and Z scores were obtained. Frequency of osteopenia was significantly higher ($P=0.02$) in females belonging low SES. Similar results were obtained for frequency of inadequate daily calcium intake ($P=0.02$). But, none of the participants have osteoporosis. No correlations were found between BMD, Vitamin D levels and daily calcium intake. Physical activity levels of females were irregular. **Conclusion:** Vitamin D status and BMD levels did not show any difference between the study groups of SES in females at the late adolescence. Daily calcium intake was inadequate in the majority of the females. This condition is prominent in females belonging low SES. Osteopenia is more common in same groups as well. Besides, vitamin D status and calcium intake are not related with BMD values in young females.

P2-P163

Bone Health Index is Low at Diagnosis of Growth Hormone Deficiency, and Improves During Growth Hormone Therapy

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Background: BoneXpert software calculates bone health index (BHI) from cortical thickness and mineralisation of three metacarpals, and bone age (BA) using 13 bones: Radius, ulna and bones in ray 1, 3, 5. Strong correlations between BoneXpert BHI and dual-energy x-ray absorptiometry (DXA) and peripheral quantitative computed CT (pQCT) measurements are reported 1. Low bone mineral density (BMD), measured by DXA, and improvement with GH is described in childhood GH deficiency (GHD) 2. The effect of GH on BHI has yet to be reported. **Objective and hypotheses:** To describe BHI SDS at diagnosis of GHD and after one year of treatment. **Method:** Children treated between 2005 and 2016 were identified. Children with midline defects, diagnosed before significant height loss, were included. Those with additional diagnoses or medications that may affect BHI were excluded. Change in baseline parameters was determined by paired t-test, and associations between parameters examined using Pearson correlation. **Results:** 120 patients (90M), age (mean $\pm$1 SD.) 11.5 $\pm$ 3.5 years were studied. At diagnosis height SDS was -2.5 ± 0.9, BA delay 1.9 ± 1.5 years and BHI SDS -1.0 ± 1.0. After 1 year of treatment height SDS increased by 0.7 (95th CI, 0.6, 0.8), BHI SDS by 0.8 (0.61, 1.05) and BA delay decreased by 1.1 years (-1.4, -0.8) ($P<0.001$ for each parameter). Change in BHI SDS related to height SDS ($P=0.04$) and BHI SDS at diagnosis ($P<0.001$). **Conclusion:** These data are consistent with previous reports of the effect of GH on BMD, measured using DXA, and lend support to the use of BHI, a simple measure obtained at the time of BA estimation, for the identification and monitoring of children at risk of impaired bone health.

P2-P164

Vitamin D Dependent Rickets Type II in Saudi Children

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Background: Vitamin D dependent rickets type II (VDDR II) is a rare autosomal recessive disorder, inherited due to mutation on vitamin D receptor (VDR) leading to end organ unresponsiveness to vitamin D. It is characterized by an early onset refractory rickets, hypocalcaemia, hypophosphatemia, growth retardation, hyperparathyroidism and elevated circulating levels of 1,25-dihydroxyvitamin D3 which is the hallmark of the disease. **Objective and hypotheses:** The aim of study is to describe clinical, genetic, biochemical and long term management of eight Saudi children diagnosed with VDDR II. **Method:** All patients underwent complete clinical evaluation including: age at diagnosis, initial rickets symptoms and signs, family history of VDDR II, presence or absence of alopecia and their growth parameters, biochemical workup including: serum calcium, phosphate, alkaline phosphatase (ALP) and parathyroid hormone (PTH) levels and genetic study of VDR mutation; done by Paediatric Endocrinologists in King Faisal Specialist Hospital and Research Centre in Riyadh/Saudi Arabia. We presented patients data at baseline, first, second, fifth and tenth year interval post calcium infusion treatment (management protocol will be attached). **Results:** All patients had full clinical and biochemical features of rickets including alopecia. The mean age of diagnosis was 3.6 year. Most of the patients had growth retardation at diagnosis (height below -2 SD. below mean). Clinical and biochemical parameters were improved in all cases (detailed data will be attached). The mutation in VDR (Y295X Homozygous) was positive in all patients. **Conclusion:** Early diagnosis of VDDR II with early treatment of IV calcium infusion will improve growth velocity; decrease rachitic manifestation and normalized calcium, phosphate, PTH and ALP levels (but not alopecia). More studies require to see the effect of early vs. late treatment on bone density.

P2-P165

Bone Health and Metabolic Syndrome in Childhood Cancer Survivors

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Background: Metabolic syndrome and impaired bone health are common complications in childhood cancer survivors, and both are possibly related with decreased physical activities. **Objective and hypotheses:** We aimed to evaluate the prevalence rates of metabolic syndrome and osteopenia in adolescent/young adult childhood cancer survivors. We also aimed to investigate the relationship between physical activity and these complications. **Method:** Subjects were 88 childhood cancer survivors aged 15–25.7 years. Controls were 159 healthy participants of 2011 Korean National Health and Nutrition Examination Survey (KNHANES). Demographic and medical characteristics were obtained from the patients' medical records. Metabolic syndrome was defined by NCEP criteria and was evaluated by physical examination and laboratory test. Physical activities were evaluated using questions from KNHANES. **Results:** Eighty-eight survivors participated in the study (45 males and 43 females). Of the 52 adult participants, 42 replied to the questionnaire about physical activity. Childhood cancer survivors had higher walking performance rate than control group, and there was no significant difference in performance rate of other kinds of activities. Thirty-four (38.6%) survivors had one or more components of metabolic syndrome, and there were no differences in the prevalence rates of components of metabolic syndrome between patients and control group. Survivors had significantly lower BMDLS than normal reference population, with BMDLS z score of -0.50 ($P=0.001$). Prevalence rates of metabolic syndrome and osteopenia were not different according to walking performance. **Conclusion:** The prevalence rates of osteopenia in young childhood cancer survivors was higher than healthy reference group, which requires earlier intervention.

P2-P166

Diversity in Phenotype of Two Siblings and their with X-Linked Hypophosphatemic Rickets due to PHEX Mutation

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Background: Hypophosphatemic rickets (HR) is a group of rare disorders caused by an excessive renal phosphate wasting. The dominant form of X-linked HR (XLHR) is caused by mutation in *PHEX* (phosphate-regulating endopeptidase) gene. XLHR phenotype is characterized mainly by rickets, bone deformities, short stature, dental anomalies, hypophosphatemia, low renal phosphate reabsorption, normal serum calcium level, hypocalciuria, normal/low serum level of vitamin D (1,25(OH)2D3), normal serum level of PTH, and increased activity of serum alkaline phosphatase. **Objective and hypotheses:** The aim of the study was to investigate the clinical phenotype and molecular background of HR in a family in which XLHR was suspected. **Method:** Two siblings, an older brother aged 14 years and 1 month and his younger sister aged 12 years and 10/12 months, were diagnosed with HR due to clinical and biochemical picture. All exons of *PHEX* gene were amplified using PCR and directly sequenced. **Results:** The dominant clinical sign in both patients was bowing of legs (genu varum in a boy and genu valgum in a girl). Short stature, predominantly affecting the brother, and lumbar hyperlordosis were also observed. Short stature and genu varum were also seen in affected mother. The difference in height was probably due to the time of treatment introduction, as it was initiated in the girl in the infantile period before the clinical signs appeared. In both patients a novel c.1483-1G>A mutation in intron 13 was identified. This mutation was also present in the affected mother leading to changes in the transcription of the RNA. **Conclusion:** The early diagnosis of XLHR is very important for proper treatment and to prevent severe bone deformities and improve final height. The molecular analysis of *PHEX* gene is very important for the confirmation of clinical diagnosis of HR and highlights the role of further genetic counselling in families with HR patients.

P2-P167

Expression of Brdu, VEGF, IGF-1R and Change of the Growth Plates from Sex Hormone-Inhibited Adolescents Rats – Pilot Study

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Background: GnRHa (gonadotropin releasing hormone analogue) inhibits growth spurt during treatment of precocious puberty. So they have limitation of final height gain. **Objective and hypotheses:** It is need to study about what factor associated with growth decrement and ideal suppression level of sex steroid during GnRHa treatment. **Method:** Female Sprague–Dawley rats of 3 weeks of age (Total 15) were divided into three groups; (1) normal control ($n=5$), (2) GnRHa (25), (3) GnRHa (100). Each group were injected normal saline, 25 and 100 mcg of GnRHa intramusculary at day 1 respectively. Study measure was as follows. Day 1: Measurement of head to tail length, leg length and body

weight. Day 13: Brdu injection. D 14: repeated measurment of body size as same of day 1. Then rats were decapitated and harvested growth plate of tibia. Growth plate was stained by H-E method. Brdu, VEGF, IGF-1 receptor and GnRH receptor were calculated by Immunocytochemistry. **Results:** Mean body weight were 175.9 ± 4.5 g, 176.6 ± 7.5 cm and 194.1 ± 5.9 cm. Mean total length were 36 ± 0.1, 35.6 ± 0.7, 34.9 ± 0.3 cm. Growth plate thickness were 8.86 ± 1.2, 8.18 ± 1.4 and 9.6 ± 1.5 mm in normal, GnRHa (25) and GnRHa (100) respectively. Expression of IGF-1 receptor, Brdu and VEGF were decreased at the treated group. Small scattered GnRHa receptors expressed at the growth plate. **Conclusion:** In this pilot study, sex hormone inhibited rats showed body weight gain and short leg length than control. To investigate the effect of GnRHa about growth plate, it is needed more sophisticated experiments.

P2-P168

A Case of Genetically Proven Carbonic Anhydrase II Deficiency

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Background: Carbonic anhydrase II (CAII) deficiency is extremely rare (< 1:1 000 000) autosomal recessive disease, which is characterized by the triad of osteopetrosis, basal ganglia calcifications and renal tubular acidosis. In addition short stature, facial dysmorfism and different degree of mental retardation are possible features. Different mutations of the gene for CAII on 8q21.2 lead to impaired enzyme activity and typical clinical, biochemical and imaging manifestations. **Objective and hypotheses:** A 5-year-old girl, from normal pregnancy of parents, who deny consanguinity was referred to endocrinology department because of short stature, developmental delay and basal ganglia calcifications on CT scan, found incidentally. **Method:** Clinical evaluation, laboratory tests of hormones, electrolytes, biochemical indices, acid-base status, infections, kidney ultrasound, radiological examination of bone age, neurologic, ophthalmologic examination and molecular genetic analysis. **Results:** Clinical evaluation confirmed mild dysmorphic features, short stature SDSh(−2, 97), low weight, SDSw(−3,0) and some developmental delay. Laboratory testing proved severe decompensated normal anion gap metabolic acidosis, low normal Ca, Ca^{2+}, high P, Cl^{-} and blood urea nitrogen, normal values of intact PTH, ACTH, serum Cortisol at 0800 h and 2000 h, TSH, fT_4. Imaging studies showed delayed by 2 years bone age and increased bone density, as well as mild nephrocalcinosis. A molecular genetic analysis revealed homozygous mutations c.275A > C, pGln92Pro on the gene for CAII on 8q21.2, which confirmed the clinical diagnosis. This mutation is found only in two other patients of gypsy origin from Czech Republic and Germany. The child receives oral 8,4% Sodium bicarbonate for correction of metabolic acidosis and showed improvement in clinical manifestations and laboratory data. **Conclusion:** Children with this rare syndrome may come into medical attention for failure to thrive, short stature, developmental delay or brain calcifications. It is crucial for the patient's quality of life and long-term prognosis to receive an early diagnosis and efficient treatment, because metabolic compensation provides normal adult height and hematologic and neurologic complications of osteopetrosis are not severe.

P2-P169

Rickets as Precocious Sign of Celiac Disease

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Background: Vitamin D insufficiency is more frequent than expected also in Western Europe, however the relieve of a 'health' child with rickets is uncommon in Caucasians. **Objective and hypotheses:** Explain clinical severity by a genetic background. **Method:** We describe the clinical case of a 2.5-year-old girl with skeletal deformities. She was 86.5 cm (10° Cent), 12.5 kg (3–10° Cent); PH1B1. She showed typical rickets-linked signs (costo-chondral swelling; Harrison's groove; genu varum; widening of wrist; skull bossing). She underwent a total-body X-ray study that showed: poor bone mineralization, femurs bowing; rachitic rosary; curved back; wrist and malleolus cupping. She had anamnestic record of insufficient sunlight exposure. She has four brothers with no signs of rickets. Blood examinations revealed: Ca: 8.7 mg/dl; P: 4.7 mg/dl; Mg: 2.45 mEq/l; alkaline phosphatase: 685 IU/l; 25-OHVitamin D: < 7 ng/ml; PTH: 442 pg/ml (n.v.: 11–67); bone alkaline phosphatase: 21 (n.v.: 5–27); P1NP: 1044 (n.v.: 27–127); osteocalcin: 62.32 (n.v.: 1–11). **Results:** Deamidated gliadin antibodies were negative. However for the severe clinical presentation and the significant difference with the clinical condition of her brothers, she was studied for the genetic forms of vitamin D deficiency. The VDR gene did not show any mutation; however the gene carried a homozygous transition c.2T > C, considered a polymorphism. Furthermore a heterozygous polymorphism c.1056T > C was documented in exon 9. The sequence of CYP27B1 and PHEX genes was normal. She received vitamin D and calcium with a significant improvement of clinical, hematological, radiographic data. However she showed a significant increase of anti-transglutaminase antibodies (IgA): 89 U/ml; (IgG): 34 U/ml (n.v.: < 4); Deamidated gliadin antibodies (IgA): 1.8; (IgG): 26 (n.v.: < 7). **Conclusion:** The two polymorphisms (one heterozygous, associated with one homozygous) could explain the severity of rickets manifestations before celiac markers were detectable in our patient, highlighting the role of VDR polymorphisms in bone health and growth.

P2-P170

Clinical and Genetic Analysis of Five Patients with Vitamin D-Dependent Rickets Type 1A

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The CYP27B1 gene encodes 25-hydroxyvitamin D-1α-hydroxylase. Mutations of this gene cause vitamin D-dependent rickets type 1A (VDDR-IA, OMIM 264700), which is a rare autosomal recessive disorder. Herein we report five patients with 1α-hydroxylase deficiencies. We studied six patients from three families who diagnosed as 1α-hydroxylase deficiency clinically. All patients had hypocalcemia, hypophosphatemia, hyperphosphatasemia, elevated serum PTH, normal or high vitamin D levels, and low or inappropriately normal calcitriol levels at presentation. Patients were diagnosed less than 18 months years old. All patients had a family history of consanguinity. Homozygous mutations in the CYP27B1 gene were found in all the patients. Four of them have splice donor site mutation in intron 1 (c.195+2 T>G), causing partial retention of the intron and a shift in the reading frame. Clinically, all the patients required calcium and calcitriol initially and then continuously calcitriol treatment. Autosomal recessive diseases are common in countries where the consanguineous marriages are common. VDDR-IA should be kept in mind patients with vitamin D resistant rickets.

P2-P171

About a Case of a Family of Pycnodysostose

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Background: The pycnodysostose is a genetic lysosomal disease wich is characterized by a ostéosclérose of the skeleton, a small and an osseous brittleness. The pycnodysostose is very rare, its exact prevalence is unknown but it is lower than 1/100,000. The disease is discovered at a variable age, has going from 9 months to 50 years. Transmitted according to a recessive autosomic mode of to a deficit in cathepsine K enzyme which plays a central role in the osseous resorption by osteoclasts. **Objective and hypotheses:** To evoke the diagnostic of pycnodysostose when we have a short stature associated with a facial dysmorphia and fractures. **Method:** The reported cases result from the same family: three children, two sisters and a brother who present same dysmorphia: bulky skull, of the frontal bumps, persistence of fontanelle former which was closed tardily, anomalies dental, atrophic ends (hands and feet) and a delay of growth which was the reason for consultation. The interrogation finds a consanguinity of second degree and what is striking it is that two children among the three made between 2 and 3 fractures of the lower extremities. **Results:** The delay of growth with facial dysmorphia, hands and feet which are short and massive, the bulky skull with an excessive projection of the frontal and occipital bumps, notion of the late welding of fontanelle former, a little projecting eyes with the sclerotic light one slightly bluish, the teeth decayed with repeating fractures, one made make radiographies of the members and skull or one was struck by the generalized thickening of the skeleton, acro-ostéolyse, widening of the joinings making evoke the diagnosis of pycnodysostose. The assumption of responsibility is symptomatic and multidisciplinary. It includes an orthopedic monitoring, an assumption of responsibility of the fractures whose consolidation is sometimes slowed down, and a monitoring of vertebral statics in order to detect frequent the spondylolisthésis. The forecast east will be favorable. **Conclusion:** The three children who present a pycnodysostose not only will have a short stature but require a follow-up in order to detect the orthopedic complications and jawbones.

P2-P172

Potential Role of Vitamin D in Pathogenesis of Acute Rheumatic Fever

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Background: Acute rheumatic fever (ARF) is a non-suppurative complication of Group A beta-hemolytic streptococcus pharyngitis. The underlying mechanisms have not been fully elucidated. A series of autoimmune processes are thought to be involved in pathogenesis. Low vitamin D levels have been reported in various autoimmune diseases. **Objective and hypotheses:** The aim of the present study is to evaluate the association of vitamin D levels and its impact on the disease phenotype in children with ARF. **Method:** Thirty patients diagnosed with ARF according to the modified Jones criteria and 16 age- and sex-matched healthy controls recruited. An echocardiographic evaluation was performed and serum calcium, phosphorus, alkaline phosphatase, magnesium, parathormone, and 25(OH) vitamin D (25(OH)D) levels were measured in all participants. Patients with ARF had been evaluated according to the presence and severity of carditis. **Results:** Serum 25(OH)D levels was significantly lower in patients with ARF compared to the control group (14.56±8.31 μg/l vs 25.41±1.38 μg/l, $P=0.002$) (Figure 1). A 25(OH)D level<50 nmol/l (20 ng/ml) suggesting vitamin D deficiency was detected in 23 of 30 patients with ARF (77%) and 8 out of 16 controls (50%) ($P=0.066$). Serum magnesium levels were found higher in ARF group compared to controls (2.17±0.28 mg/dl vs 1.95±0.09 mg/dl, $P=0.001$). **Conclusion:** In this, to our knowledge the first study evaluating the 25(OH)D levels in

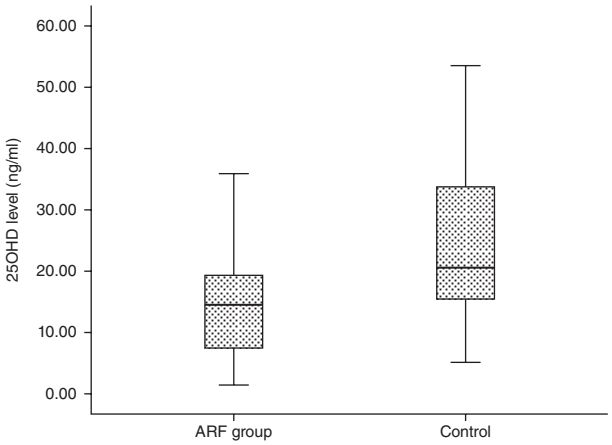

Figure 1 Serum 25(OH) D levels in study group were significantly lower than those of controls.

children with ARF, 25(OH)D levels was found lower in patients with ARF suggesting potential role of vitamin D deficiency in development of ARF.

P2-P173

Bartter Syndrome with Bone-Destroying Hyperparathyroidism: About Two Cases, Genetically Proved, with Long-Lasting Follow-Up

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Background: Bartter syndrome represents a rare severe condition, autosomal recessive, corresponding to several genes, characterized by an illness of the renal ascending branch of the handle of Henle. Only 15 cases of BSHPT have been communicated, either in publications or orally, but none presented such severe bone manifestation as ours. **Objective and hypotheses:** To present bone features of two patients suffering from severe BHSPT, so as the therapeutic attempts. **Results:** Two female patients are described, the first one bearing an homozygous mutation of gene SLC1.2A1 coding for NKCC2 ion channel and the second one a composite heterozygous mutation of gene BSND, coding for Barttin protein. Both presented hydramnios and severe intrauterine growth retardation without catch up. At the age of 6 years and a half, patient number one suffered from non-inflammatory, painful and disabling arthritis of elbows, knees and feet. Patient number 2 was affected by two pyelonephritis episodes. Both shared different complications: limb deformations, articular stiffness and worsening dwarfism, resulting into most severe handicap; nephrocalcinosis; extended bone demineralization, subperiostal resorption and bone deformations, so as signs of chronic arthropathy and the absence of synovitis at-X-ray exams; biologically, hypercalcemia (up to ~120 mg/l), hypercalciuria, high parathyroid hormone levels (up to ~1500 pg/ml in number one, ~270 pg/ml in number 2). Different treatments were tried: cinacalcet, a calcium-sensing receptor agonist (30 mg/d), which partially corrected hyperparathyroidism in number one and had to be stopped, because of major hypocalcemia in number 2, intravenous biphosphonates (pamidronate and zoledronate), growth hormone, which failed on growth and even surgical ablation of two parathyroid glands in number one, without any success. Several mechanisms of BSHPT have been mentioned, most appropriately an autonomous development of hyperparathyroidism reactive to hypercalciuria. **Conclusion:** In antenatal Bartter syndrome, parathyroid hormone should be monitored early, to assume early bone-protective measures.

P2-P174

Management of Hypoparathyroidism: Follow-Up of 20 Patients

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Background: Hypoparathyroidism is a rare disease characterized by inadequate parathyroid hormone (PTH), resulting in hypocalcemia and hyperphosphatemia. Hypoparathyroidism can be transient, inherited, or acquired, and is caused by inability to synthesize or secrete PTH, abnormal parathyroid gland development, destruction of parathyroid tissue, or peripheral resistance to PTH. **Methods:** Medical records from 20 children and adolescents diagnosed with hypoparathyroidism during 1992–2015 were reviewed. **Results:** Twenty patients (5 males, 15 females) diagnosed at the age of 8.5 ± 6 years (0.12–16.9 years) were evaluated. HP developed after surgery in 4 (primary hiperparathyroidism; 2, thyroid cancer; 1, graves disease; 1) of the patients. Six of the patients were diagnosed as isolated HP, 3 as pseudohypoparathroidism, 4 as polyglandular autoimmune syndrome, 1 as Di-George syndrome, 1 as HDR syndrome and 1 as HP secondary to hemosiderosis due diamond blackfan anemia. Sixteen of the patients admitted because of convulsions and tetany. One patient was diagnosed incidentally. The patient with hemosiderosis and the patient with polyglandular autoimmune syndrome were diagnosed during follow-up. Patient with HDR syndrome was diagnosed as HP during an evaluation of psoriasis. 8 patients had calcifications in cranial CT and 2 patients had cataract at the initial diagnosis. All of the patients received calcium and 1,25 OH vitamin D initially. During follow-up two patients developed nephrolithiasis and three patients nephrocalcinosis. Due to hypercalciuria hydrochlorthiazide was initiated in two patients. Recombinant human PTH was initiated to the three patients with nephrocalcinosis but was seized because the dosing problems. Chronic treatment of hypoparathyroidism may be difficult to manage due to the need for a sensitive balance between calcium and phosphate levels in order to prevent nephrolithiasis, nephrocalcinosis, and soft tissue calcification in the kidney.

P2-P175

Assessing the Serum Levels of Ferritin and Selenium in Three Important Infections of Childhood, Compared to a Control Group

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Background: Micronutrients play a fundamental role not only in general health, but also in treatment and protection of various diseases. Selenium and iron are two of the five major elements, aside from vitamins, detected as anti-oxidant agents, widely used with the aim of preventing diseases. **Objective and hypotheses:** The purpose of this study is to evaluate serum levels of selenium and ferritin in acute infections of childhood. **Method:** Patients aged 2–15, hospitalized from autumn 2010–2011 in infectious ward of Rasoul-e-Akram hospital were recruited to the study. Patients with documented diagnosis of GI, RTI, UTI were case groups, who were compared to one control group, including patients hospitalized in the same hospital in surgery ward without any active infection. Blood samples were gathered from all patients and ferritin and selenium serum levels were measured in serum specimens. Diagnosis of the three infections was made by a unique infectious specialist. **Results:** The mean and standard deviation of serum selenium concentration of GI, RTI, UTI and control groups were 64.70 ± 21.43 μg/l, 61.60 ± 19.25 μg/l, 66.37 ± 22.11 μg/l and 62.20 ± 22.08 μg/l, respectively without significant differences in serum selenium levels between these groups (P-value $= 0.608$). The median of serum ferritin levels in GI, RTI, UTI and control groups were 60.05 (48.82–78.01), 62.00 (49.07–79.35), 60.60 (51.78–79.52) and 58.75 (45.32–76.72), respectively. The difference in ferritin levels between these groups was statistically significant (P-value < 0.001). Compared with the control, the RTI and GI groups had significantly higher levels ($P < 0.001$); however, the UTI group was not statistically different from the control ($P = 0.098$). **Conclusion:** None of the children had ferritin constrictions below 12. As far as selenium and ferritin deficiency is an important issue in developing countries, it would be valuable to assess the role of micronutrients in infectious diseases, as we may be able to prevent such fatal infections by micronutrient supplementations.

P2-P176

A Case: Hydrocephalus Secondary to Suprasellar Arachnoid Cyst with Reset Osmostat and Isolated GH Deficiency

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Background: Hyponatremia is defined as a serum sodium level below 135 mEq/l. It is associated with increased morbidity and mortality. Hyponatremia has many causes and can be classified as acute/chronic or hypo/hypo/euvolemic. The main rule in fluid and electrolyte disorders (and especially in hyponatremia) is excluding hypothyroidism and hypocortisolism and then making the correct diagnosis. Hypothyroidism and hypocorticolism can also cause euvolemic chronic hyponatremia but the most common cause is the Syndrome of Inappropriate Anti Diuretic Hormone Secretion (SIADH). We present a case who developed the SIADH subtype reset osmostat secondary to hydrocephaly where the hyponatremia continued postoperatively and GH deficiency was also diagnosed during follow-up as we did not come across any similar cases in the literature. **Case presentation:** A male patient aged 6 years and 3 months was brought for short stature and was found to have isolated hyponatremia (131.6 mEq/l) without findings of dehydration or edema in addition to the pathological short stature. Hypothyroidism and hypocortisolism were excluded. The plasma osmolarity was low (271.3 mosm/kg) and urinary sodium was high (251.6 mmol/l). The sodium level continued within the 128.1–133.2 mEq/l range despite oral sodium and fludrocortisone treatment. Hypophysis and brain MR revealed hydrocephaly due to pressure from a suprasellar arachnoid cyst. Ventriculocystocisternostomy was performed through the endoscopic route. Postoperative serum sodium levels were in the 128–132 mEq/l range and there was no percentile increase in growth. The response to GH stimulation tests was inadequate and the patient was put on GH treatment with a diagnosis of GH deficiency. **Conclusion:** The discovery of the cation canal protein Transient Receptor Potential Vanilloid (TRPV) that regulates the neuronal response to systemic tonicity changes has enabled a new approach to SIADH and reset osmostat cases. Further research on the TRPV gene will perhaps clarify the relationship between chronic hyponatremia and growth retardation. We present a rare case with reset osmostat and GH deficiency due to hydrocephaly where the reset osmostat continued even after the etiology was treated and discuss the current knowledge on water metabolism in the light of new developments.

P2-P177

Cinacalcet Treatment in a Child with Concurrent Juvenile Idiopathic Arthritis and Hypocalciuric Hypercalcemia

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Familial hypocalciuric hypercalcemia (FHH) is a genetically heterogeneous condition resembling primary hyperparathyroidism but not curable by surgery. Cinalcelcet may improve symptoms some patients but limited experienced especially in children. A 10 years old child evaluated by uveitis, sacroileitis, spondyloarthritis and diagnosed as HLA-B27 positive juvenile idiopathic arthritis (JIA). Also at the same time he evaluated by high calcium, low phosphate and inappropriately high PTH level and hypocalciuria. Therefore he diagnosed as hypocalciuric hypercalcemia. He screened for calcium sensing receptor (CASR) mutations with negative results. Further genetic analyses will plan for other reason of FHH. His JIA and associated symptoms resolved after anti-inflammatory therapy, but his hypercalcemia and associated symptoms persisted; also osteoporosis was detected on dual-energy X-ray absorptiometry. As a result of symptomatic hypercalcemia, the patient was treated with a calcimimetic (cinacalcet). During the treatment, plasma calcium and PTH level normalized and symptoms were decreased. Cinacalcet treatment was well tolerated without significant side effects. Cinacelcet therapy may be useful option for control hypercalcemia and related symptoms at least short term in children.

P2-P178

Pseudohypoparathyroidism 1a with Turner's Syndrome: A Diagnostic Dilemma

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Background: Pseudohypoparathyroidism (PHP) is a rare condition with heterogeneous presentation. It is divided in various subgroups depending upon the manifestations. Type 1a Pseudohypoparathyroidism usually presents with brachydactyly, short stature along with other manifestations of Albright's hereditary osteodystrophy (AHO) like obesity, mental retardation. The basic pathology is resistance to hormonal actions associated with G protein coupled receptors due defective GNAS activity. This leads to resistance to other hormones like TSH, gonadotropins and GHRH. Turner's syndrome usually manifests with short stature with lack of secondary sexual characters along with other stigmata like increased propensity to autoimmune disorders, short 4th metacarpals, cubitus valgus, shield chest etc. **Objective and hypotheses:** To diagnose a case of association of Turner's Syndrome and Pseudohypoparathyroidism Type1a. **Method:** We describe a case of a 15 year old Asian Indian female who presented with short stature and delayed puberty. On examination she was found to have round facies, significant short stature, brachydactyly and no pubertal changes. On the biochemical evaluation patient had hypocalcemia, hyperphosphatemia, increased parathormone and hypergonadotropic hypogonadism and subclinical hypothyroidism. X-ray hand revealed the characteristic manifestations of PHP. The tentative diagnosis of PHP was made. Patient's ultrasound abdomen revealed streak ovaries along with hypoplastic uterus and finally patient's karyotype showed 45, XO confirming the diagnosis of Turner's syndrome. **Results:** The patient was diagnosed to be a case of Turner's Syndrome associated with Pseudohypoparathyroidism Type 1a and was treated with adequate dose of thyroxoine along with calcium and calcitriol supplementation. **Conclusion:** At times it becomes difficult to differentiate between PHP and Turner's syndrome due similar presentation of both disorders and also because of heterogeneity of presenting features. A timely diagnosis and treatment can prevent devastating complications.

P2-P179

Bisphosphonate Use for Control of Chronic Severe Bone Pain in Children with Malignancy Associated Bone Involvement

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Background: Bone involvement occurs commonly in pediatric malignancies, due to infiltration, metastasis or avascular necrosis. Pain is frequently chronic, debilitating, requires narcotic analgesia and can result in immobilization in bed or wheelchair. Intravenous bisphosphonates whilst primarily acting as osteoclast inhibitors also result in rapid and often complete pain relief in primary bone fragility disorders. When administered to children with malignant conditions affecting bone, significant improvement in pain, associated morbidity mobilization has been seen. **Objective and hypotheses:** To describe results of use of zoledronic acid for management of bone pain in children with various malignant conditions. **Methods:** Eleven children with chronic bone pain are described. Four had acute lymphoblastic leukaemia (ALL), 3 had acute myeloblastic leukaemia and 4 had metastatic neuroblastoma, rhabdomyosarcoma or hepatoblastoma. Six had glucocorticoid induced avascular necrosis (AVN) related to chemotherapy for haematological malignancies, four had widespread bony metastases from solid tumours and one had multiple vertebral fractures related to ALL but continuing long after remission. All received intravenous zoledronic acid 0.04 mg/kg 4 monthly for 12–24 months. **Results:** Complete resolution of pain occurred in all after 1–2 infusions of zoledronic acid. No further analgesia was required. Mobility was restored in all and schooling resumed where appropriate. As previously reported, once bony collapse occurred in AVN, restoration of normal joints was impossible. Hip replacement was needed later in one. Death from malignancy occurred later in another. **Conclusion:** Intravenous zoledronic acid administered in the setting of severe chronic bone pain associated with bony metastases, AVN or vertebral collapse in children and adolescents with malignancy results in sustained remission of bone pain, improved mobility and cessation of need for narcotic and other analgesia. This class of drug should be considered for management of malignancy related bone pain in children and adolescents.

P2-P180

Renal Tubular Acidosis Causing Severe Growth Delay and Rickets in Two Siblings in Haiti

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Background: Renal tubular acidosis (RTA) is an uncommon cause of growth failure and rickets. In Haiti, diagnostic evaluation and management is challenged by limited access to comprehensive diagnostic tools. **Case presentation:** An 8-year-old Haitian girl was evaluated at an academic referral center for bony deformations and bone pain, progressive over the previous six years. Her 2.5 year-old sister presented similar symptoms, associated with dental caries and inability to walk for the past 6 months. There was no history of bone deformation in the family, and no parental consanguinity. Both siblings were exclusively breastfed for six months and were since consuming a balanced diet. Neither was taking any medications and they were adequately exposed to sunlight. On exam, weight and height were 17.2 kg (−3 standard deviation scores (SDS)) and 99 cm (−5.6 SDS) in the older, and 9.8 kg (−3 SDS) and 77 cm (−3 SDS) in the younger sibling. Mild Kussmaul breathing was evident. Both had a sawtooth enamel and multiple dental caries, asymmetrical chests, costal rosary, distended abdomen, wide wrist, epiphyseal beads, multiple bone deformity, the older had a waddling gait and bilateral genu valgus. Remainder examination, including cognitive development, was normal. Laboratory testing in the older sibling revealed non-anion gap metabolic acidosis (bicarbonate 9 mmol/l) with alkaline urine (pH 9.3), 1+ proteinuria but no glycosuria, hypophosphatemia (phosphorus 2.8 mg/dl), hyperphosphatasia (alkaline phosphatase 880 U/l), normal values for total calcium, 25-OH-vitamin D, parathyroid hormone, serum albumin, BUN, and creatinine. Radiographic findings were consistent with severe rickets. Results were similar in the younger sibling. **Conclusion:** We present the first cases of severe growth delay and rickets due to RTA in a sibling pair in Haiti. While detailed evaluation and genetic testing was unavailable, a clinical diagnosis was possible and allowed for initiation of therapy with oral bicarbonate.

P2-P181

Pseudohypoparathyroidism Type IB Associated to Assisted Reproductive Technologies: Case Report

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Background: Pseudohypoparathyroidism type Ib (PHP-Ib) is due to a maternal loss of GNAS exon A/B methylation and leads to decreased expression of the stimulatory G protein (Gsα) in specific tissues. Evidence suggests an increased incidence of imprinting disorders in children conceived by Assisted Reproductive Technologies (ART). Nevertheless, no associations between ART and PHP – Ib have been found to date. **Clinical case:** 7.4-years-old male with history of impaired neurological development. Conceived by ART, born adequate for gestational age. Presented at 4 years of age with a creatine kinase (CK) persistently increased (200–278 IU/l, NV < 140). At 6 years an elevated PTH was detected (199 pg/ml NV < 60) with normal calcium and alkaline phosphate, normal high phosphorus and a low 25(OH) Vitamin D (18.3 ng/ml). He was asymptomatic and diagnostic work-up excluded systemic diseases, thyroid, adrenal compromise, inborn errors of metabolism, skeletal and chromosomal abnormalities. Physical exam was unremarkable except for a narrow forehead, nasal bridge hypoplasia and micropenis (penile length 3.2 cm, < −2 SDS). His height was at 0.63 SDS, and BMI 1.48 SDS. Vitamin D supplementation increased 25(OH)D to 25.9 ng/ml, but PTH remained high. PHP-Ib was considered but analysis of the microsatellites for the GNAS region on Chr. 20q did not reveal paternal uniparental disomy (patUPD20q). Instead, an almost complete loss of methylation at GNAS exons A/B and AS, and a gain of methylation at exon NESP were found. There were no changes at exon XL and no evidence of a micro deletion within the GNAS/STX16 region. After 1 year of 0.5 ug QD of calcitriol treatment he remains asymptomatic and presents biochemical improvement: 25(OH)D 25.9 ng/ml, calcium 9.5 mg/dl, phosphorus 4.8 mg/dl, PTH 105 pg/ml, and CK 133 UI/l. **Conclusion:** We present a patient with PHP – Ib due to impaired methylation at GNAS exons A/B, AS and NESP most likely associated to ART.

P2-P182

Primary Hyperparathyroidism- A Cause of Metabolic Syndrome in Children?

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Introduction: We report a case of a 15 year old male with metabolic syndrome due to primary hyperparathyroidism. **Case report:** A 15 year old male was admitted in our department for the evaluation and management of obesity. His medical history revealed a progressive weight gain in the last 3 years in an emotional familial context. *Clinical features*: Obesity: *Z*-score of +2.32 DS, a height of 1.80 m and a weight of 108 kg, with a BMI of 33.33 kg/m^2 at the 99th centile, with a round facies with erythema, abdominal obesity with red striae, a BP of 180/100 mmHg and a HR of 78/min, Tanner stage P5G5. *Laboratory*: Extensive investigations for secondary hypertension were initiated, which excluded hypercortisolism, hyperaldosteronism, pheochromocytoma, hyperthyroidism and reno-vascular

hypertension. The routine blood tests (the blood glucose, the low HDL cholesterol, the insulinemia and HbA1c) together with the high blood pressure and waist circumference over the 90th centile confirmed the IDF based criteria for metabolic syndrome. In an adult patient the diagnosis of metabolic syndrome is a sufficient reason for high blood pressure but taking into account the patient's age we continued the etiological investigation. A secondary cause of hypertension was confirmed as a primary hyperparathyroidism was diagnosed by a high calcium level of 12.2 mg/dl, a high PTH of 166 pg/ml and a low 25OHvitamine D of 20.1 ng/dl. Moreover a parathyroid adenoma was diagnosed at the neck ultrasound. We normalized the calcaemia and the patient was referred to surgery due to the high calcium values and the apparition of complications- hypertension, with the normalization of the calcium, PTH and BP levels in postop. **Conclusion:** The favorable outcome after surgery confirmed not only the diagnosis of primary hyperparathyroidism but also the link between the metabolic syndrome, high blood pressure and this condition, with high cardiovascular morbidity and mortality.

P2-P183

Hyperphosphatemic Familial Tumoral Calcinosis: Novel Indication to Sevelamer Carbonate

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Background: Hyperphosphatemic familial tumoral calcinosis (HFTC) is a condition characterized by hyperphosphatemia and abnormal deposit of phosphate and calcium most often around the hips, shoulders and elbows and rarely in the brain. **Case presentation:** A four-year-old-girl from Arabian origin was referred to the regional paediatric endocrine clinic from the Orthopedics Team due to: recurrent calcinosis of the right calcaneus and incipient left wrist pain. Examination: weight 17.5 kg (SDS 0.19) and height 105 cm (SDS 0.24). General examination unremarkable, in particular no signs of inflammation of joints. No evidence of neurological impairment. Inicial investigations: serum sodium, chloride, potassium and creatinine levels were normal. Serum calcium 9.9 mg/dl (8.1–10.4), phosphorus 8.6 mg/dl (2.7–4.5), magnesium 2.1 mg/dl (1.7–2.5), intact parathyroid hormone 24.2 pg/ml (15–88), and 25-vitamin-D 19 pg/ml (12–54). Random urinary calcium/creatinine ratio 0.015. TmP/GFR 3.9 mg/100 ml. Homozygosity for the mutation c.814_815 insA in the GALNT3 gene was found, which helps to regulate fibroblast growth factor 23 by glycosylation of protein called ppGalNacT3. Diagnosis: hyperphosphatemic familal tumoral calcinosis. Further investigations: no eye abnormalities, no cardiac/coronary calcifications, no pathological features on kidneys ultrasound scan. Head CT scan: bilateral superficial linear cortex brain calcifications. Management: low phosphorus diet and calcium acetate. After treatment optimization, biochemical results: phosphorus 7.8 mg/dl and TRP 98.6%. Clinical evolution: new joints pain. At this point the patient received treatment with sevelamer carbonate, which binds phosphate from food in the digestive tract. No side-effects were reported. Progress: serum phosphorus level decreased and the patient experienced an improvement of her symtoms. **Conclusion:** i) In cases of calcinosis in paediatric patients, phosphorus and calcium metabolism assesment is recommended as part of initial approach in order to avoid future complications. ii) Management of hyperphosphatemia is complex in hyperphosphatemic familial tumoral calcinosis. This case suggests sevelamer carbonate as an option to decrease serum phosphate levels in the setting fail in previous known therapeutic options.

P2-P184

DiGeorge Syndrome and 10p Deletion

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Background: Hypoparathyroidism, deafness and renal dysplasia (HDR) syndrome is a rare condition inherited as an autosomal dominant trait. The responsible genetic defect is in the region 10p. Phenotype is very similar to DiGeorge Syndrome (DGS) which occurs due to 22q11 microdeletion. **Method:** An 8-year-old girl was referred to Pediatric Endocrinology outpatient department because of hypoparathyroidism. She was born at 36 weeks after a normal pregnancy and her birth weight was 2500 g. The patient has presented with facial dysmorphic features and psychomotor retardation soon after birth. She was investigated by department of pediatric nephrology due to consecutive urinary tract infections. Vesicoureteral reflux and renal dsyplasia were detected. The other findings were broad forehead, hypertelorism, flattened nose, anteverted nostrils, micrognathia, underdeveloped and low-set ears. Low serum PTH and calcium level (PTH 5.8 pg/ml, calcium 7.8 mg/dl) were detected. Auditory brain stem response testing revealed that the patient had sensorineural deafness. **Results:** Due to atypic facial features, hypocalcemia, hypoparathyoidism, renal displasia and deafness HDR Syndrome was considered as diagnosis. Karyotype analysis demonstrated 10p deletion. **Conclusion:** 10p deletion should be considered in patients with hypoparathyroidism who has not DGS phenotype or in cases in which 22q11 deletion was not detected inspite of DGS phenotype presence.

P2-P185

Multifocal Osteonecrosis after Short Term Methylprednysolon Therapy: A Case Report

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Background: Osteonecrosis is a common sequela of long-term steroid therapy. This paper presents the only case of multifocal osteonecrosis to occur after a short-term course of methylprednisolone for treatment Steven Johns syndrome. **Objective and hypotheses:** To report a case with multifocal osteonecrosis after short-term methylprednysolon therapy. **Method:** The child A.N. 15 years old with multifocal osteonecrosis after 3 weeks methylprednisolone therapy. At the age of 4 years old, the child has his first neurosurgical intervention for Craniopharyngeoma. After the second surgery the child presents with epileptic seizures – left hemiconvulsions. The post operatory therapy consisted in Carbamazepine (Tegretol) and hormone replacement therapy for the pituitary: Levothyroxine, Hydrocortisone and Desmopressin (Minirin). The antiepileptic therapy with Carbamazepine is terminated 4 years after the 3rd surgery (6 years old). Six months after the termination of the AED the child presents with refractory seizures. The antiepileptic therapy is started again, with Depakine Chrono and then Lamotrigine was added to the therapy. One month later the child manifests a hypersensitivity skin reaction from lamotrigine that presents with Steven-Johnsons syndrome. The patient is admitted in the adult dermatology clinic. The hydrocortisone is stopped and he is treated with i.v. methylprednisolone, 150 mg/day, for 3–4 weeks. During the time of hospitalization in the dermatology clinic the child feels severe pain in the vertebral column while walking, falls into the ground on both his knees and after that he is unable to walk and is admitted back to the Pediatric Hospital. **Right Knee Joint MRI** and Scintigram of total body demonstrates multifocal osteonecrosis. **Results:** Despite the therapy with Pamidronate (Aredia) and supportive therapy with Calcium and Vitamin D, the state of the child continues to be moderately severe. He continues to live with complain of pain joints. Methylprednisolon induced aseptic necrosis, a very serious multifactorial disease. **Conclusion:** In conclusion, glucocorticoid use is one of the commonest and most important causes of non-traumatic AVN. To minimise the treatement with corticosteroids.

P2-P186
Unclear Origin of Avascular Necrosis – Clinical Case

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Background: Glucocorticoid (GC) treatment is associated with many unwanted effects but osteoporosis and fractures are the most serious adverse events. Several large case–control studies have shown strong associations between exposure to glucocorticoids and the risk of fractures. By other hand, multiple factors have been associated with avascular necrosis (AVN) in systemic lupus erythematosus (SLE), but it is steroid use that has been routinely thought of as a risk factor for developing AVN. **Case report:** A 14-year-old girl with severe SLE requiring glucocorticoid therapy for the past 6 months presents for care. The onset of the disease was extremely severe with a hemorrhagic cerebrovascular event, MODS syndrome, positive antiphospholipid antibodies. In the past, she received prednisone at a dose of 15 mg or more per day. At 6 months after the onset of the disease, she presented a severe pain syndrome (VAS = 90 mm) located at the right hip and bilateral knees, no amelioration on antalgic drugs and with impaired mobility. On physical examination, range of motion of the right hip and both knees were severely limited and painful in all ranges, with most pain being felt in abduction and internal rotation. Palpation of those regions revealed extreme tenderness. *X*-ray revealed erosions and signs for lacunar osteoporosis in the knees and hips. The CT-scan of the hip showed a marginal fracture of the right capitis femoris with dislocation of 2 mm. Knee CT-scan presented bilateral aseptic necrosis of femoral condyles, with signs of pathologic fracture at these levels. **Conclusion:** Whenever a patient presents with joint pain secondary to corticosteroid use, the clinician must include avascular necrosis as a differential. In addition to the clinical picture, diagnostic imaging should be performed to confirm the presence and extent of multiple AVN. Requirement of a multidisciplinary team is the key of a good choice for treatment. Corticosteroids, Avascular necrosis

P2-P187
Is NOTCH-Sonic Hedgehog Signalling Pathway the Missing Link Between Hajdu-Cheney Syndrome and Syringomyelia?

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Background: Hajdu-Cheney syndrome (HCS) is a rare autosomal dominant condition characterized by osteoporosis, acro-osteolysis, short stature and specific craniofacial features and is caused by mutations in the NOTCH2 gene which codes for a single-pass transmembrane protein that plays a critical role in skeletal development and bone remodelling. Syringomyelia has been reported in 5 of 75 reported cases of HCS worldwide. The mechanism for this association is unknown and has not been explored. We report a 17 year old white Caucasian male who had the typical dysmorphic features of the condition, osteoporosis and multiple wedge fractures of the thoracolumbar vertebrae as well as metatarsals and metacarpals and had a pathogenic NOTCH2 mutation. He also developed a thoracic and cervical syrinx necessitating foramen magnum widening though there was no Arnold Chiari malformation or platybasia. **Objective:** Postulate a mechanism for the association between HCS and syringomyelia. **Method:** A literature search was undertaken to examine the relationship between NOTCH mutations and its effects on bone

and the nervous system. **Results:** NOTCH mutations are associated with over-activity of RANKL system and resultant osteoclast mediated osteoporosis. NOTCH signalling also plays a crucial role in enabling neural progenitors to attain sufficiently high levels of sonic hedgehog (SHH) pathway activity which in turn is needed to direct the fates of the ventral-most cells in the developing nervous system which ultimately forms the spinal cord. **Conclusion:** Abnormalities in NOTCH and SHH signalling is a potential mechanism to explain the abnormalities present in bones and the nervous system in HCS. We propose that impaired NOTCH signalling is responsible for osteoporosis and the effect of impaired NOTCH on SHH pathway is a potential explanation of syringomyelia in HCS.

P2-P188

The Unexpected Cause of Vitamin D Deficiency in a Resource Limited Setting: A Rare Case Report of Primary Intestinal Lymphangiectasia

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Background: Vitamin D deficiency is a common problem in paediatrics caused by a number of factors ranging from malnutrition, limited exposure to sunlight, chronic illness and chronic medications. **Objective and hypotheses:** We report on a rare case of Primary Intestinal Lymphangiectasia (PIL) presenting in a tertiary centre in Botswana with Vitamin D deficiency and failure to thrive. **Method:** A 2 months old boy initially presented with fever, diarrhoea and seizures. The full septic work up for infections was negative. However, he was noted to have very low calcium 0.38 mmol/l, inorganic phosphate 1.19 mmol/l, elevated alkaline phosphate 883 IU/l, elevated Para-Thyroid Hormone 370.70 pg/ml and very low 25 hydroxy-vitamin D < 4 ng/ml. A diagnosis of hypo-calcaemic seizures secondary to vitamin D deficiency was made and he was treated with intramuscular vitamin D and calcium supplements. Subsequent clinic visits revealed failure to thrive and persisting vitamin D deficiency, 20 ng/ml, despite therapy with calcium supplements and intramuscular vitamin D. Additional further investigations included abdominal ultrasound, barium meal, stool sample for microscopy, culture and parasites, MRI of brain, enzyme profile, HIV test, chest X ray and investigations for tuberculosis. They were all unremarkable and he was subsequently referred for explorative laparotomy. **Results:** There was moderate chylous ascites and the entire small bowel had prominent network of lymphatics (white cobwebs). That network was larger in size and reduced in number further down the terminal ileum. There was focal partial villous atrophy with dense infiltrate of lymphocytes, reactive hyperplasia of the mucosa, lymphoid tissue containing secondary lymphoid follicles and lymphangiomatosis. **Conclusion:** The diagnosis of vitamin D deficiency, failure to thrive due to protein losing enteropathy secondary to PIL was made. Clinicians must consider PIL in cases of vitamin D deficiency and failure to thrive where there is poor or no response to conventional therapy.

P2-P189

About a Case of Dwarfism Idiopathic

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Background: The syndrome of Taybi-Linder (TALS) or paramount dwarfism microcephalic of type 1 (MOPD1) is an uncommon illness characterized by an intra-uterine delay of growth, multiple malformations (short members, facial dysmorphie) and especially of the cerebral abnormalities. The infants carrying this disease can live until the age from 2 to 3 years and, often at the time of an infection, their state worsens quickly in a few hours (conscience disorder, convulsions) until the death. No identified metabolic anomaly explains this death. **Method:** We report the case of a young boy of 2 ans and 3 months old SGA which consults for a delay of growth and malformatif syndrome. The clinical examination objectifies a dwarfism 68 cm (-6.1 SDS) with a microcephaly, a short neck, small ears, dry skin, bilateral polydactyly post axial, bilateral cryptorchidism and a genu varum. Neurologically exist a delay of psychomotor acquisitions. Microcephaly and the psychomotor delay, a Brain MRI concludes with a partial agenesis of the corpus callosum, lissencephaly with diffuse parenchymatous atrophy. The radiography of the members shows us a skeletal dysplasia. **Results:** All this evoke the diagnosis of the paramount dwarfism of type 1 of TAYBI LINDER for which unfortunately no treatment exists for the moment with a forecast alas fatal. Our patient presented himself for a delay of growth and this in spite of the preexistent syndrome malformatif what enabled us to pose the diagnosis of dwarfism primorial microcephalic of type 1 which remains very rare besides it exists about it in the world approximately 30 CA whose treatment is only symptomatic. **Conclusion:** The forecast is severe, with a death during the first year of the life noted at most reported cases. Our patient unfortunately died at the age of 2 ans and 6 months.

P1-P190

The Association of HLA Class II, CTLA-4 and PTPN22 Genetic Polymorphisms and β-Cell Autoantibodies in Development of Type I Diabetes in Patients with Autoimmune Thyroid Disease

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Background: Co-occurrence of type 1 diabetes (T1D) and autoimmune thyroid disease (AITD) denote variant of autoimmune polyglandular syndrome type 3 (APS3v). Thyroid autoimmunity in T1D was widely studied, but a few studies examined β-cell autoimmunity among AITD patients. Several susceptibility genes for APS3v have been identified: HLA class II, CTLA-4 and PTPN22 gene. **Objective and hypotheses:** To investigate β-cell autoimmunity and genetic polymorphism of HLA class II, CTLA-4 and PTPN22 genes in AITD patients. **Method:** The study comprised of 158 unrelated AITD patients (127 with autoimmune thyroiditis, AT and 31 with Graves disease, GD) aged 4.3–25.9 years and 94 healthy control subjects aged 4.7–21.5 years. Islet cell cytoplasmic (ICA), glutamic acid decarboxylase (GADA) and thyrosin phosphatase islet (IA-2) autoantibodies as well as HLA-DRB1, -DQB1 alleles, A49G CTLA-4, C60T CTLA-4 and R620W PTPN22 gene polymorphisms were analyzed. **Results:** β-cell autoimmunity was found in 10.76% (17/158) AITD patients, significantly more than in controls (0%, 0/94; $P=0.001$), with higher prevalence found in AT (11.81%, 15/127) than GD (6.45%, 2/31) patients. All three β-cell autoantibodies were positive in three patients, and three patients were positive for two autoantibodies. All six of them developed T1D during the investigation period of 2.5 years. No difference in high risk HLA haplotypes for development of T1D was found between the groups. However, low risk HLA haplotypes for development of T1D were found more frequently in controls than in AITD patients (69.9% vs 31.3%, $P=0.003$). Disease associated G/G genotype of CTLA-4 A49G gene was significantly more common in AITD patient with β-cell autoimmunity than in controls ($P=0.024$), while there were no differences in PTPN22 and C60T CTLA-4 gene polymorphisms between groups. **Conclusion:** Patients with AITD are prone to develop β-cell autoimmunity and T1D, especially those with multiple islet autoantibodies and G/G genotype of CTLA-4 A49G gene.

P1-P191

Insulin Pump Does Not Allow a Better Control than Injections in Childhood Type 1 Diabetes (T1d) in the ISIS-Diab Cohort

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Background: The use of insulin pumps is rapidly spreading within the paediatric T1D community. A few small studies have promoted pump usage, while large registries have shown almost no advantage of this treatment. **Objectives:** Compare the results of treatment with insulin pump ('Pump') with insulin injections ('Inj') in a large cohort of children with T1D in field conditions. **Patients:** We studied 3137 children of the ISIS-Diab cohort with ≥ 1 year of T1D duration recruited by 99 diabetes centers of various size covering all French regions. HbA1c, severe hypoglycemia (SH), ketoacidosis (DKA), and weight were compared between 'Pump' ($n=694$) and 'Inj' ($n=2443$) groups of children over their last 6 months of treatment. **Results:** The ratio of 'Pump'/'Inj' varied from 0 to 65% across centers. 'Pump' children were slightly younger (9.2 ± 3.9 years vs 10.6 ± 3.4 years for 'Inj', $P=2.10^{-6}$), and had comparable socio-educational level than 'Inj'. Mean HbA1c was 7.8 ± 1.0% in 'Pump' and 7.9 ± 1.2% in 'Inj' (NS). SH occurred in 3.5% of 'Pump' and 5.4% of 'Inj' ($P=0.053$). DKA occurred in 2.7% of 'Pump' and 2.7% of 'Inj'. Overweight was present in 10.7% of 'Pump' and 10.4% of 'Inj'. Insulin dosage was 0.82 ± 0.28 U/k.d in 'Pump' and 0.95 ± 0.29 U/k.d in 'Inj' ($P<2.10^{-16}$). Large expert centers had the same pump results than small centers (HbA1c 7.8 ± 1% vs 7.8 ± 1.0%). **Conclusion:** In field conditions, insulin pump shows no clear superiority. The choice of this costly and more demanding mode of treatment should thus be balanced at the individual and public health level.

P1-P192

Diagnostic Features of Lipodystrophy in Children with Type 1 Diabetes

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Background: Insulin therapy by creating a subcutaneous depot remains an integral part of the treatment of diabetes in children. Places of insulin administration are restricted to certain parts of the body and the condition of subcutaneous fat affects the variability of glycaemia no less than quality of insulin. Formation of lipodystrophies (LD) causes glycaemia variability, difficulties in selection of insulin doses and achieving disease compensation. **Objective and hypotheses:** The use of ultrasonic method for studying injection sites for early detection of presence and form of LD. A working hypothesis about the possibility of identifying the nature of LD by an ultrasound (US) investigation of subcutaneous fat has been considered in the study. **Method:** We have investigated the hypothesis about the possibility of identifying the nature of the LD by ultrasound investigation (US) of subcutaneous fat. In order to confirm it 108 children 6 -16 years old have been surveyed, patients with type 1 diabetes treated with insulin from 6 months to 12 years. **Results:** In 74 children (68.5%) pathological changes of injection sites were verified by ultrasound investigation of subcutaneous fat. Muscular form of LD, which is manifested by clinically atrophic areas on the thighs, has been revealed in 2 (3%) subjects. 45 (60.5%) patients have a diffuse form of LD, 17 subjects (23%) – its focal form, and 10 children (12.5%) have a mixed form of LD. In the structure of focal and mixed forms of LD has been singled out LD with a heterogeneous echostructure with predominance of hyperechogenic inclusions. Such patients do not change needles often enough (every 4.5 days on an average). The muscular form is difficult to treat and does not disappear after the change of injection site. **Conclusion:** Hyperechoic areas in the subcutaneous fat may serve as an early marker of LD and develop due to multiple injuries in violation of insulin therapy technique.

P1-P193

Recombinant Human Insulin-Like Growth Factor 1 (rh IGF1) Treatment of a Case of Leprechaunism: A Two and a Half Year Follow-Up

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Background: Leprechaunism, due to a mutation of both alleles of insulin receptor gene, is a most severe and precociously life-threatening condition, difficult to treat. **Objective and hypotheses:** In leprechaunism rhIGF1 may replace insulin through I the insulin-like metabolic properties of its own receptor. **Method:** rh IGF1 was continuously subcutaneously administered through a.pump from the age of four months and adjusted according to 2–3 S.D. plasma IGF1 levels from a 300 to 400 μg/kg per day. **Results:** Case report: a first pregnancy of unrelated French Caucasian healthy parents was marked by a severe intrauterine growth retardation. All birth measurements at normal term were – 4 SDS. Immediately were noticed typical dysmorphic signs of leprechaunism. The alternance of fasting intolerance, and of ketotic hyperglycaemia, became soon evident. Insulin and C-peptide levels were extraordinarily high, respectively 14 000 U/l and 30 ng/ml. IGF1 was undetectable in the plasma and leptin was present, 2.5 mg/l. She is heterozygous composite for mutations of the insulin receptor gene coding for V555D in the insulin-binding domain, coming from her father and A1055V in the tyrosine kinase domain, coming from her mother. Under continuous enteral nutrition, metformin corrected hyperglycaemia but not hyperinsulinaemia. Extension investigations evidenced the persistence of growth retardation, hypotonia, hypertrophic cardiomyopathy, bulky multifollicular ovaries at US, hyperandrogenism, hypercalciuria with low parathyroid hormone levels and nephrocalcinosis, treated by bisphosphonates. rhIGF1 administration medication allowed insulin levels to fall to 1000 U/l levels, without worsening of hyperglycaemia. Cardiomyopathy was contained with the help of a beta adrenergic blocking agent, lipoatrophy disappeared, leptin levels doubled, growth improved, ovary volume halved, hyperandrogenism vanished, but adenoids grew dramatically, needing several nasal curettages. **Conclusion:** In leprechaunism, early rh IGF1 administration improves growth, adipogenesis, hyperinsulinaemia and ovarian hyperstimulation but adverse effects may occur, linked either to this medication or to the natural evolution of the condition.

P1-P194

Longitudinal Monitoring of Pediatric Insulin Treatment in Germany and Austria: Age-Dependent Analysis of 63 967 Children and Adolescents with Type 1 Diabetes from the DPV Registry

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Background: Depending on age, needs and preferences in insulin therapy strongly differ between children and adolescents with type 1 diabetes (T1D). **Objective and hypotheses:** To analyse trends in insulin regimen and type of insulin used over the last two decades in three age-groups of pediatric patients with T1D from Germany/Austria. **Method:** 63 967 subjects (<18 year of age) with T1D documented between 1995 and 2014 from the 'Diabetes-Patienten-Verlaufsdokumentation' (DPV) database were included. Patients were assigned to age-groups (0.5–<6, 6–<12, and 12–<18 year). Regression models were built for insulin regimens (<3 and 4 or more injection time points/day, or continuous subcutaneous insulin infusion (CSII)), use of rapid- and long-acting insulin analogues, use of NPH insulin, and frequency of self-monitoring of blood glucose (SMBG)/day. Confounders: sex, diabetes duration, and migration background. *P* value for trend (SAS:9.4). **Results:** The number of patients with <3 injection time points/day decreased from 1995 to 2014 to <5% in all age-groups ($P<0.0001$; respectively). Proportion of patients with four or more injections/day increased until the early 2000s, and decreased again until 2014. CSII increased in age-groups ($P<0.0001$, respectively), especially in patients <6 year to 79.2% (2014). The use of rapid-acting insulin analogues increased in all age-groups ($P<0.0001$, respectively) accounting for 78.4% (2014) for all subjects. The use of NPH insulin declined whereas the use of long-acting insulin analogues increased (all $P<0.0001$) and were most frequently used in the oldest age-group by 46%. Number of SMBG/day increased from 2.2 (1995) to 6.4 (2014) with a similar rise in all age-groups (all $P<0.0001$). Frequency of SMBG/day was highest in subjects <6 year. **Conclusion:** In all age-groups, treatment in T1D was intensified over the last 20 years. Differences in age-groups were present in the number of patients on CSII, in the proportion with 4 or more injections/day, in the use of long-acting insulin analogues, and in the frequency of SMBG/day.

P1-P195

Two Patients with HADH (SCHAD) Hyperinsulinism without Detectable 3-Hydroxybutyrylcarnitine/ 3-Hydroxyglutarate

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Background: Congenital hyperinsulinism of infancy (CHI) is the most common cause for persisting hypoglycaemia in infancy. Genetic causes are mutations in *ABCC8* or *KCNJ11* (coding for K^+_{ATP}-channel subunits), less frequently mutations in *GCK* or *GLUD1*. Further genetic examinations are usually performed only if phenotypic aspects point to other specific genes, such as the rare short chain 3-hydroxylacyl-CoA dehydrogenase (*SCHAD*, *HADH*) deficiency (worldwide <30 documented cases). It is characterized by an accumulation of 3-hydroxybutyrylcarnitine in blood and 3-hydroxyglutarate in urine which usually leads to initiation of specific genetic testing. **Objective and hypotheses:** We report on two patients of Turkish origin with HADH (SCHAD) hyperinsulinism without detectable levels of 3-hydroxybutyrylcarnitine in blood as well as 3-hydroxyglutarate in urine. **Patients and methods:** Patient 1: male, 17 years, postnatal macrosomy, recurrent hypoglycaemia, diazoxide responsive, older sister and grandmother also suffering from CHI. No mutations in ABCC8, KCNJ11. Patient 2: female, 9 years, recurrent hypoglycaemia since birth, diazoxide responsive. Grandfather and cousin as well suffering from CHI. No mutations in ABCC8, KCNJ11, GCK, GLUD1. In both of them: Analysis of acylcarnitine profiles by tandem-mass spectrometry in dry blood samples. GC-MS analysis of organic acids in urine. Next-generation sequencing (NGS) of further CHI genes. **Results:** Patient 1: Homozygous *HADH* c.428T$>$A (p.Ile143Asn), new mutation. Patient 2: Homozygous *HADH* c.706C$>$T (p.Arg236*). In both patients 3-hydroxybutyrylcarnitine in blood as well as 3-hydroxyglutarate in urine were below the detection limit. **Conclusion:** HADH deficiency should be considered in patients with CHI who are negative for ABCC8 and KCNJ11, even when its specific biochemical markers are not present. These data underline the broad clinical and genetic heterogeneity of CHI and other hypoglycaemia disorders, and the value of extensive sequencing, e.g. using NGS, to detect the molecular basis of the disease.

P1-P196

Development of Type 1 Diabetes in a Child with Inherited CD59 Deficiency Treated with Eculizumab

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Background: CD59 is a complement regulatory protein which inhibits membrane attack complex protecting self-cells from complement-mediated damage. Recent evidence suggests CD59 may suppress T cell activation via a complement-independent mechanism. Other than an immune regulator, CD59 is shown to regulate glucose stimulated insulin secretion. Herein we report a patient with inherited CD59 deficiency who developed type 1 diabetes. **Case:** 11 year-old girl was admitted for polyuria and polydipsia. Previous history revealed intracranial bleeding at 6 months of age, acute motor axonal neuropathy in the course of otitis media at 18 months, and chronic Coombs' negative intravascular hemolysis. Parents were first cousins, a sibling with similar symptoms died at 16 years. The patient had a homozygote missense mutation (c.A146T:p.Asp49Val) in the CD59 gene. She was on eculizumab for 2 years, and received aripiprazole for behavioral problems in the last year. In the family both parents, maternal grandmother, two paternal uncles and one aunt had diabetes. On PE she was prepubertal with normal height and weight, she had asymmetrical weakness and rigidity with distal atrophy in lower extremities, and a wide-based gait. Laboratory investigations revealed a blood glucose of 326 mg/dl with ketonuria, low insulin (2.4 uIU/ml) and c-peptide (1.38 ng/ml) levels. HbA1c was 9.1%, and antiGAD was positive (14.3 U/l N:<1). She was treated with insulin infusion at the ketotic state, and put on basal bolus insulin treatment. **Conclusion:** A number of factors may have led to overt diabetes in the current patient, i.e. FH of diabetes, use of aripiprazole. Among them inherited CD59 deficency is a good candidate considering its suppressive role in MAC formation (in the light of recent evidence of complement deposition in T1DM pancreatic tissue suggesting possible involvement in pathogenesis), in complement independent T cell activation, and its role in glucose mediated insulin secretion.

P1-P197

Diagnosis of Non-Autoimmune Paediatric Diabetes by Targeted Next Generation Sequencing (NGS): Findings in Two Families with Rare Mono- and Digenic forms of Diabetes

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Background: Nearly 10% of paediatric onset diabetes are auto-antibodies negative. Among them monogenic diabetes are frequently under-diagnosed. The major increase in the prevalence of childhood obesity is misleading with a risk of confusion between type 2 diabetes (T2D) and monogenic causes of diabetes. **Objective and hypotheses:** To report on two informative

families with negative auto-antibodies childhood-onset diabetes cases. **Method:** Next generation sequencing (NGS) analysis of a panel of genes with a role in insulin secretion was applied to two index cases. Segregation analysis was subsequently performed by Sanger sequencing and quantitative PCR (MLPA) in relatives. **Results:** In the first family, with three cases of diabetes diagnosed between the ages of 10 and 15 years, and a family history of T2D, diabetic subjects carried either a large deletion of the glucokinase gene (father inheritance), a variant of the ABCC8 gene (mother inheritance), or both (digenic inheritance). These genetic findings are likely associated with the variation in clinical presentation and evolution of diabetes in the family. In the second family, the onset of diabetes at the age of 15 years in an overweight but non-obese girl (HbA1c = 14%, non-ketotic) with a father diagnosed as T2D at the age of 44 years, lead to the diagnosis of a novel pathogenic missense mutation of the insulin gene. **Conclusion:** The identification of these rare causes of monogenic diabetes was made possible by the NGS approach**.** The paediatric community should be aware of these new technical possibilities for the etiological diagnosis of atypical forms of diabetes, to allow an accurate diagnosis and an appropriate management.

P1-P198

Neonatal Siabetes, Gallbladder Agenesis and Cholestatic Giant Cell Hepatitis: A Novel Homozygote Mutation in PDX-1 Gene

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Background: It is known that PDX-1 gene mutation is related to neonatal diabetes, pancreas agenesis and intrauterine growth retardation. Here the aim was to present a novel defined mutation in PDX-1 gene in case born with IUGR, diagnosed with neonatal diabetes and in which exocrine pancreas deficiency and gallbladder agenesis were detected. **Case presentation:** Blood glucose was measured as 185 mg/dl in the first hour after birth and insulin infusion was given at intervals to the case whose blood sugar was >250 mg/dl during observation and the case was referred to our clinic. In the physical examination of the male baby born with a weight of 1520 g in the 37th week as G1P1 from 19 year old mother with a story of 1° cousin marriage in his parents, the body weight was 1400 g (<3p), height was 42.5 cm (<3p) and the head circumference was 31 cm (<3p) and they were smaller when pregnancy week was considered. Referral blood sugar was found 216 mg/dl and it reached up to 500 mg/dl in the follow-ups. Cholestatic giant celled hepatitis was detected in the liver needle biopsy of patient whose faecal elastase level was >200 ng/ml and had direct hyperbilirubinemia. Blood sugar regulation was provided with insulin pump to the case whose satisfactory nutrition could not be provided due to exocrine pancreas function disorder and who was experiencing hypoglycemia and hyperglycemia even though 0.2 U/kg per day SC insulin dose was given. Gallbladder imaging was impossible in ultrasonography and magnetic resonance cholangiography. A novel homozygote mutation was detected in PDX-1 gene Exon 2 with Whole Exom sequencing method [c.593G>C;p.Arg198Pro(p.R198P)]. It was observed that the parents had heterozygote mutation. The patient was discharged with insulin pump in the postnatal fourth month. **Conclusion:** PDX-1 was detected to play a very significant role including pancreas and islet functions and we think that the new mutation we defined would contribute to the literature.

P1-P199

Anthropometry and Glucose Homeostasis in a Patient with Donohue Syndrome (Homozygous Insulin Receptor Mutation): Effect of Continuous s.c. rIGF-I Therapy

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Background: Donohue syndrome (DS) is caused by autosomal-recessive loss of function mutations of the insulin receptor gene. DS is associated with diabetes mellitus unresponsive to conventional insulin therapy due to severe insulin resistance. Patients exhibit IUGR and postnatal failure to thrive. They develop a characteristic facies, hypertrichosis and acanthosis nigricans. Most patients die within the first two years of life because of respiratory infections. To date, no causal therapy is available. **Case report:** The patient was born at term in Libya with a birth weight of 1300 g. Postpartally, he rapidly developed postprandial hyperglycemia. Despite high-caloric nutrition he exhibited severe and progressive dystrophy. Mutation analysis revealed a homozygote mutation in exon 2 of the INSR gene (c(591delC); p.(A198PFS*84)). First presentation in our institution was at 12 month of age with a weight of 3300 g. HbA1c was 10%, IGF-I and IGFBP-3 were below detection limits. We started a probatory therapy with rIGF-I (Mecasermin) s.c. twice daily (max. 515 mg/kg per day, bid). Since we were unable to achieve satisfactory glucose control we decided to switch towards continuous s.c. rIGF-I therapy via insulin pump. Mecasermin dosage was adapted throughout the day. A critical adverse effect of this regimen was the development of adenoid hyperplasia, requiring adenotonsillectomy. Within 9 months, we saw an improvement of HbA1c from 9.7 to 7.6% and a weight gain from 3.3 to 5.2 kg body weight. Unfortunately, the patient died at an age of 23 months in Libya during the course of a respiratory infection. **Conclusion:** Using s.c. rIGF-I therapy we observed a significant improvement of glucose homeostasis and moderate weight gain. Therefore we consider that a trial with continuous Mecasermin via insulin pump should be considered in patients with DS.

P1-P200

Driving Paediatric Diabetes Care Forward in the UK: Improvements in Outcomes in the North West Following National Initiatives

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Background: Type 1 diabetes mellitus (T1DM) continues to pose serious health risks with devastating long-term complications. UK management and control of T1DM in children and young people (CYP) remains amongst the poorest in Europe and significant variations in diabetes health outcomes are evident. In 2012–13 a Best Practice Tariff (BPT) for paediatric diabetes care was introduced and a National Peer Review Quality Assurance programme (DQuINS) developed. Both were developed to drive improvements in paediatric diabetes care. **Objective and hypotheses:** To explore trends in paediatric diabetes care within the CYP North West Diabetes Network, UK and to assess the impact of national initiatives on health outcomes. **Method:** Data was collected from each paediatric diabetes unit (PDU) in the region and extracted from the National Paediatric Diabetic Audit (NDPA) from 2010 to 2014. We compared staffing before and after the national initiatives, and values for mean HbA1C and percentage of patients with HbA1C <58 mmol/mol. Data was analysed using paired student T-tests. **Results:** Data was received from all 28 PDUs for staffing levels before and after BPT and DQuINs. There was a significant increase in admin staff ($P<0.001$), consultants ($P=0.03$), dieticians ($P<0.01$), specialist diabetes nurses ($P<0.01$) and psychologists ($P=0.01$) across the network. Data was extracted from the NPDA for the years 2010–11, 2011–12, 2012–13 and 2013–14. There was statistically significant improvement in percentage of HbA1C <58 mmol/mol when compared for each successive year to 2010–11. The mean HbA1C was significantly improved for each year compared to 2010–11 prior to the national initiatives **Conclusion:** There have been significant increases in staffing dedicated to the care of children with diabetes across the North West UK following DQuINS and BPT, as well as significant improvement seen in HbA1c. Set standards for paediatric diabetes care and appropriate staffing levels are critical to delivering good service and improving health outcomes.

P1-P201

Non-Surgical Treatment of Diazoxide-Resistant of Early Diffuse Hyperinsulinism Using Long-Acting Octreotide, A Somaatostatin Analog: Follow-Up of Six Cases

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Background: Early diffuse hyperinsulinism represents a life- and brain-threatening condition. Besides enteral or parenteral additional supply, diazoxide represents the first line treatment. For diazoxide-resistant (DREDHI) patients, ablative surgery exposes to severe local complications, exocrine pancreas insufficiency and diabetes or residual hypoglycaemia. **Objective and hypotheses:** To evaluate the pros and cons of non-surgical treatment of DREDHI. **Method:** Diazoxide-resistance was defined as persistent hypoglycemia despite 15 mg/kg per day doses. After subcutaneous injections or continuous pump infusion, octreotide was administered as a LA formula by monthly intramuscular injections, excepted in one patient who kept on subcutaneous infusions. **Results:** Six patients, three boys and three girls, were followed up. Three had ABCC8 homozygous mutation, one an ABCC8 heterozygous one and one an heterozygous KCNJ11 mutation. Maximal long-acting (LA) somatostatin injections, ranged from 20 to 50 µg/kg per day, according to glycaemia optimization. Carbohydrate supply had to be realized through gastrostomy in 5/6 patients, but maintained only in three younger ones. Clear hypoglycaemias were registered in three patients, fasting hyperglycaemia in two and characteristic diabetes in two respectively, the latter detected at $12_{1/2}$ and 4 years of age, with 2.7 and 2.1 glycaemia values. LA somatostatin could be stopped in one patient, at the age of 3.3 and 13.4. Follow-up age ranged from 2.9 to 13.8 years. At the last visit, height SDS was normal, but two patients developed obesity (BMI 2.7 and 4.1 S.D.). No clear developmental delay was detected. Severe difficulties of parental origin occurred in two patients. **Conclusions:** LA octreotide generally allows to avoid surgery. 2) Non-surgical treatment is very demanding at younger ages. 3) Natural evolution towards diabetes is a possibility. 4) Despite potential effects of somatostatin on GH, growth is preserved. 5) Obesity is to be prevented. 6) The choice of non-surgical treatment is to decide individually, according to parental skills.

P1-P202

Screening for Autonomic Neuropathy in Children and Adolescents with Type 1 Diabetes Mellitus

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Background: Diabetic neuropathy is among the least recognized complications of diabetes, despite its significant negative impact on survival and quality of life. Characteristic neuronal alterations may occur subclinically early in the course of the disease, even in childhood. The prevalence of subclinical neuropathy in paediatric population ranges from 7.9 – 19% in different studies. **Objective and hypotheses:** Our objective was to study the prevalence of subclinical autonomic and peripheral

neuropathy in T1DM children and adolescents and its correlations with associated factors. **Method:** We evaluated 97 T1DM children and adolescents (mean ± S.D. age 12.9 ± 2.8 years, T1DM duration: 5.14 ± 3.5 years) and 80 controls (mean ± S.D. age 11.9 ± 2.7 years). We examined pupillary dilatation (PD) in darkness, an index of autonomic neuropathy, using a Polaroid pupillometer and vibration sensation threshold (VST), an index of peripheral neuropathy, using a Biothesiometer. Abnormal cut-off values (>95% or <5%) were calculated from control values distribution. PD and VST were compared between patients and controls and were analyzed according to confounding factors. **Results:** PD impairment was more frequent in the T1DM group, compared to controls (31.6% vs 3.3%, $P<0.001$). Moreover, in the T1DM group impaired VST were more frequent than in the controls in the lower (left: 23.3% vs 6.7%, $P<0.001$, right: 28.3% vs 4%, $P<0.001$) and upper limbs (left: 17.1% vs 2.67%, $P<0.001$, right: 23.2% vs 2.6%, $P<0.001$), respectively. PD was associated with age ($r=0.16$, $P=0.038$), HbA1c: ($r=0.23$, $P=0.048$) and diabetes duration ($r=0.20$, $P=0.022$). Moreover in the whole group, older age ($P<0.001$) and puberty were associated with greater proportion of abnormal VSTs in the lower limbs in pubertal vs prepubertal children (left: 17.7% vs 2.8%, $P=0.001$, right: 19.4% vs 0.0%, $P<0.001$). **Conclusion:** Impaired indices of peripheral and autonomic neuropathy are present in a significant proportion of T1DM children and adolescents, although asymptomatic. Indices of diabetic neuropathy are associated with age, diabetes duration, puberty and the quality of glycaemic control.

P1-P203

Diabetes Mellitus Caused by Bone Marrow Transplantation and Total Body Irradiation – Experience from a Regional Single Centre

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Background: Diabetes is a recognised long term sequelae in childhood cancer survivors following bone marrow transplantation and total body irradiation (BMT/TBI), due to a combination of insulin deficiency and resistance. **Aim:** To characterise presentation, treatment and clinical course of diabetes in childhood leukaemia survivors post BMT/TBI. **Method:** A single centre retrospective case note review of diabetes post BMT/TBI identified from departmental database. **Results:** 11 cases were identified as having diabetes of 40 BMT/TBI survivors investigated. 6/35 screened by routine OGTT (oral glucose tolerance test) included 4 with raised 120 min postprandial glucose only and 2 with both raised fasting and post prandial glucose; five diabetes cases were identified from referring regional clinicians. One patient presenting with a random glucose of 31.5 mmol/l. Median (range) age of primary diagnosis was 2.6 (0.5–9.7) years, with TBI at 14.4 (10–14.4) Gy in 6 (1–8) fractions. Two had had additional cranial irradiation and two graft vs host disease. Age of diabetes diagnosis was 15.5 (11–26) years, 12.5 (9–18.2) years post BMT. At presentation 4/7 were asymptomatic, 1/7 unclear from notes, 1/7 complained of fatigue, 1/7 complained of polyuria, polydipsia and weight loss. Median (range) Hba1c was 7.6 (5.2–12.4) % at presentation. Initial treatment included: basal bolus regime ($n=2$), once daily detemir ($n=1$), dietary and lifestyle modifications ($n=3$) and metformin ($n=1$). One patient on insulin subsequently had gliclazide and sitagliptine added. One patient initially on basal bolus insulin switched to metformin and gliclazide and discontinued insulin. One patient had improvement of glycaemic control after dietary and lifestyle/exercise interventions with subsequent OGTT demonstrating impaired glucose tolerance. Complications included dyslipidaemia ($n=3$), microalbuminuria ($n=2$) and hypertension ($n=1$). **Conclusion:** Childhood leukaemia survivors presenting with diabetes following BMT/TBI can be asymptomatic. There is a variation in the initial choice of management and disease progression, highlighting the need for careful ongoing evaluation and individualised management plans.

P1-P204

A Syndrome of Permanent Neonatal Diabetes Mellitus and Neurological Abnormalities due to a Novel Homozygous Missense c.449T>A (p.I150N) Mutation in NEUROD1 Gene

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Neonatal diabetes mellitus (NDM) is a rare form of monogenic diabetes presenting in the first 6 months of life. NEUROD1 is a transcriptional factor involved in the development of endocrine pancreas. A few patients with maturity onset diabetes of the young (MODY) due to heterozygous NEUROD1 mutations and only two cases with permanent NDM (PNDM) associated to neurological disorders and cerebellar hypoplasia due to homozygous mutations in the NEUROD1 gene have been reported. **Case report:** A 13 years-old female was referred to our endocrine department due to hyperglycemia. She was on insulin therapy due to diagnosis of NDM whilst missed her regular follow-up visits. Parents were third cousins. Father and one aunt had a diagnosis of Type 2 DM. Auxological measurements were within normal ranges. In the laboratory examination HbA1c was 8.9% and fasting c-peptide was undetectable (<0.1 ng/ml). She had developed difficulty in walking at the age of 4 years which had worsen over time. In the further evaluation the diagnosis of visual impairment, mental retardation, ataxic gait, retinitis pigmentosa and sensori-neural deafness was considered. Cranial MRI revealed cerebellar hypoplasia. Molecular genetics analysis using targeted next generation sequencing detected a novel homozygous missense

p.I150N (c.449T > A) mutation in exon 2 of *NEUROD1*. This mutation affects a highly conserved residue within the DNA-binding domain of *NEUROD1* and current evidence suggests that the mutation is likely to be pathogenic. Both parents and two siblings were heterozygous for the mutation. **Conclusion:** Homozygous *NEUROD1* mutations cause a rare syndrome of PNDM associated to neurological abnormalities. Heterozygous mutations, however, may present with MODY phenotype with extremely variable penetrance among individuals who carry identical mutation, even within same family.

P1-P205

Are We Screening Appropriate Age Group for Early Diagnosis of Cystic Fibrosis Related Diabetes in UK?

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Background: Nutrition plays a pivotal role in long-term survival in cystic fibrosis (CF). Early insulin treatment for glucose intolerance promotes anabolism and stabilises lung function. However there is a variation in cystic fibrosis related diabetes (CFRD) screening across centres (recommended age for start of CFRD screening varies between 10 and 12 years as per CF trust, CFF & ISPAD guidelines). **Aims:** To assess if early screening of glycaemic status helps in early identification of glucose intolerance in CF and the correlation between OGTT and glycosylated haemoglobin (HbA1c). **Methodology:** Retrospective data on OGTT, HbA1c and patient demographics were collected on all CF patients in a tertiary paediatric hospital ($n = 84$, 35M). Patients were categorised as < 10, 10 to < 12 & ≥ 12 years. The data was analysed to assess the incidence of glucose intolerance and to compare OGTT and HbA1c. **Results:** Total of 127 OGTT were carried out in 35 CF patients with median age of 13 years (3–17.3) and median follow-up of 4 years(0.8–11.1). OGTT: Eleven patients (13%) were diagnosed with CFRD requiring various forms of insulin therapy including insulin pump. This includes three patients (27%) diagnosed with CFRD as a result of the early OGTT screening in 10 to < 12 years. OGTT was undertaken in symptomatic children < 10 years of age and identified one CFRD patient (aged 9.4 years). Five eligible patients (≥ 10 years of age) did not undergo OGTT (Table 1). HbA1c: Total of 89 HbA1c analyses was undertaken along with simultaneous OGTT (Table 2). The HbA1c was ≤ 42 mmol/mol in patients with IGT and > 42 mmols/mol in patients with postprandial hyperglycaemia. **Conclusions:** i) Application of CFF guideline (CFRD screening ≥ 10 years of age) promotes early diagnosis and management of CFRD. ii) OGTT may not be routinely needed in children < 10 years of age unless there are strong clinical indications. iii) A national consensus guideline on CFRD screening would be very useful.

P1-P206

When to Screen for Coeliac Disease in Children with Type 1 Diabetes Mellitus: The Controversy

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Background: Routine screening for Coeliac disease (CD) beyond the first year of diagnosis with Type 1 Diabetes Mellitus (T1DM) is controversial due to a paucity of high-quality evidence. The UK guidelines (NICE) only recommend screening at diagnosis with T1DM or if subsequently symptomatic; whereas the International Society for Paediatric and Adolescent Diabetes (ISPAD) recommends routine screening every 1 to 2 years. **Objective and hypotheses:** We hypothesised that annual screening for CD in asymptomatic children with T1DM is more sensitive than only screening when newly diagnosed with T1DM or symptomatic. **Method:** A retrospective observational study was undertaken in a large general hospital that screens annually for CD. An open cohort was studied using electronic and paper records for all patients with T1DM, who had been under the care of Paediatrics at anytime from 2005 to 2014. Patients with Type 2 Diabetes Mellitus were excluded. Data were extracted in relation to demographics, screening for CD, TTG results, small bowel biopsy, and defined symptoms suspicious for CD. **Results:** We identified 187 (90.78%) patients with T1DM who were tested for CD. The proportion of tested patients who were diagnosed with CD was 9.63% (95% CI = 5.4–13.86%). Analysis of 16 patients with CD revealed that only five (31.25%) were diagnosed through screening at the point of presentation with T1DM, and two (12.5%) were diagnosed following testing prompted by clinical suspicion. The majority (56.25%) were diagnosed by routine screening whilst

Table 1. Age groups and OGTT results (for abstract P1-P205).

		OGTT		
Groups	**Age in years median** (range)	Total	Normal	Abnormal (details)
< 10 years	6.7 (3–9.8)	24	23	1 (PP-1)
10- < 12 years	10.9 (10–11.7)	16	12	4 (F-2, PP-2**)
≥ 12 years	13.8 (12–17.3)	87	68	19 (F-2, PP-7, IGT-10)
Total	127	103	24	

Fasting hyperglycaemia (F) = blood glucose > 7.0 mmol/l, Post prandial hyperglycaemia (PP) = blood glucose ≥ 11.1 mmol/l, Impaired Glucose tolerance (IGT) = post prandial blood glucose between 7.8 and 11.0 mmol/l. ** Same patient had two abnormal OGTT.

Table 2. Comparison between OGTT and HbA1c (for abstract P1-P205).

OGTT	HbA1c ≤ 42 mmol/mol	HbA1c > 42 mmol/mol	Total
Normal	63	6	69
Abnormal	12 (F-2, IGT-10)	8 (F-1, PP-7)	20
Total	75	14	89

asymptomatic, ranging from 1 year and 9 months to 6 years and 9 months after their diagnosis with T1DM. **Conclusion:** This study supports growing evidence that the UK guidelines should mirror the ISPAD recommendation to routinely screen for CD beyond the first year of presentation with T1DM. Targeted RCTs and studies of cost-effectiveness may provide evidence to recommend putative screening intervals.

P1-P207

Interrelation between ACE Gene I/D Polymorphism and Chronic Kidney Disease Severity in Uzbek Children and Adolescents with Type 1 Diabetes Mellitus

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Background: Generally, diabetic nephropathy onsets and progresses within 5–10 years after DM onset resulting in chronic kidney disease (CKD) causing death in every 4–5th patient with type I DM. Molecular-genetic studies of endogenous/genetic CKD risk factors are of high relevance in understanding of pathogenetic mechanisms underlying formation of nephrosclerosis, and in improvement of interventions. **Objective and hypotheses:** To assess renal function and to study interrelation between ACE gene I/D polymorphism and CKD in Uzbek children and adolescents with type 1 diabetes mellitus as per K/DOQI (2012) recommendations. **Method:** We examined 120 children and adolescents with type 1 diabetes mellitus with mean age 13.8 ± 2.7 years. Schwartz equation was used to calculate the estimated GFR for all children. **Results:** Analysis of HbA1c by CKD severity demonstrated presence of II CKD stage in 23.8% and III CKD stage in 8.3% of children with HbA1c ≤7.5%. Among the examined patients with type 1 diabetes mellitus no cases of V CKD stage (<15 ml/min/1.73 m^2) were registered. GFR can be significantly declined even on the stage of normoalbuminuria, when no clinical signs of diabetic nephropathy were present. Thus, GFR value of 80.6 ± 7.5 ml/min/1.73 m^2 corresponding to II CKD stage was found in 61.9% of normoalbuminuric Uzbek children and adolescents with type I diabetes mellitus. Analysis of ACE gene distribution demonstrated that 49 (40.8%) patients were the carriers of II genotype; I/D and DD genotypes occurred in 28 (23.4%) and 43 (35.8%) of the patients, respectively. **Conclusion:** GFR decline could be seen even in the disease duration less than 5 years ($n = 38$, 31.7%). In 31.6% ($n = 12$) GFR decline corresponded to the one typical of II, III and IV CKD stages. Significant correlation of DD genotype with CKD severity was found in analysis of interrelation between ACE gene genotype distributions in Uzbek children and adolescents with type I diabetes mellitus to confirm effect of genetic factors in CKD progression. ACE gene I/D polymorphism is a molecular-genetic marker of CKD onset and progression in this population.

P1-P208

Improvement of Diabetic Screening System for School Children Achieved by Close Cooperation with a Local Government of Atsugi City

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Background: In Japan, diabetic screening for school children using urinalysis has been performed to detect diabetes mellitus during childhood throughout the country. However, inadequate follow-up system after urinary screening caused several problems. The rate of participation in workup examination still remains less than 30%. Also, accurate annual incidences of children with type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) detected by screening of urine glucose have not been determined. **Objective:** Under the cooperation with Atsugi city (population: around 224,000), the present study was performed to achieve full participation of children with positive urine glucose in workup examination, and to clarify accurate annual incidences of children with T1DM and T2DM in Atsugi city. **Subjects and method:** Workup examination of diabetes mellitus, including HbA1c and anti-GAD antibody, at our hospital was carried out for children with positive urine glucose for seven years from 2009 through 2015. In addition, we retrospectively analyzed clinical diagnosis and course of them. **Results:** Thirty six of 129,125 school children, who were tested by urinalysis, showed positivity of urine glucose. Continuously, all of them could receive secondary workup examination by active support of Atsugi city. Through this screening system, three children were diagnosed as having T2DM. The overall incidence of T2DM was 2.28 per 100,000 per year. On the other hand, two children were diagnosed as having T1DM. The overall incidence of T1DM was 1.58 per 100,000 per year. Furthermore, one child was diagnosed as having insulin receptor abnormality (Rabson–Mendenhall syndrome). **Conclusion:** The annual incidences of children with T2DM in Atsugi city was comparable with those in other municipalities (2.65–3.57 per 100,000 per year). However, the annual incidences of children with T1DM was almost three times higher than that in Tokyo (0.51 per 100,000 per year). The reason for this difference is unclear, and therefore further study is required.

P1-P209

Association between Hypothalamus–Pituitary Adrenal Axis Activity and Anxiety in Prepubertal Children with Type 1 Diabetes

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Background: Animal models of insulin-dependent diabetes show hyperactivity of hypothalamus–pituitary adrenal (HPA) axis, independently of hypoglycaemia. Few data exists regarding type 1 diabetes (T1D) in children. **Objective:** To describe HPA axis activity according to the anxiety levels in prepubertal T1D children. **Method:** Prepubertal T1D children and siblings of T1D children (controls) were included. State-Trait Anxiety Inventory (STAI) test was performed at inclusion. Glucocorticoids metabolites (LCMS)/creatinine ratio on nocturnal urines and morning salivary cortisol (SC) were measured at home during five consecutive days without identified nocturnal hypoglycaemia. Expressed results were mean of the five samples for each child. Tetrahydrocortisol (THF) + allo-THF/tetrahydrocortisone (THE) ratio (i.e. THFs/THE ratio) was considered as an estimate of type 1 11β-hydroxysteroid dehydrogenase (11β-HSD1) activity. **Results:** Forty-nine T1D children (mean age 9.0 ± 1.7 yrs) and 26 controls (9.3 ± 1.4 yrs) were recruited. STAI scores were not different between T1D children (29.7 ± 6.6) and controls (33.0 ± 7.8).Total glucocorticoid metabolites/creatinine were decreased in T1D children vs controls (552 ± 170 vs 673 ± 170 µg/mmol, $P < 0.01$). THFs/THE was increased in TD1 children vs controls (0.46 ± 0.10 vs 0.41 ± 0.09, $P = 0.02$). SC at awakening and 30 min after awakening (SC+30) were not different between groups. In both groups, STAI scores were associated with SC+30 when adjusted for BMI (controls $\beta = -1.1$, $P = 0.03$; T1D children $\beta = -1.0$, $P = 0.04$). STAI score was associated with THFs when adjusted for BMI in T1D children ($\beta = -0.05$, $P = 0.03$) but not in controls. **Conclusion:** Subtle changes of HPA axis activity, independently of recognized hypoglycemia, are present in prepubertal children with T1D, particularly for nocturnal glucocorticoid synthesis, 11β-HSD1 activity and its associations with anxiety.

P1-P210

Screening for Liver Disease in Children and Adolescents with Type 1 Diabetes Mellitus: A Cross-sectional Analysis

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Background: The liver is one of the most important organs in glucose metabolism and closely related to diabetes pathophysiology. Non-alcoholic fatty liver disease (NAFLD) is well known in type 2 diabetes mellitus (DM), but also adult patients with type 1 DM are at increased risk for NAFLD. **Objective and hypotheses:** Here, we studied the prevalence of liver disease in a representative number of children and adolescents with type 1 DM in Germany. **Method:** We used laboratory investigations, ultrasound, and liver stiffness measurements (Fibroscan and acoustic radiation force imaging) as noninvasive screening methods for liver disease in a cross-sectional analysis of $n = 93$ children and adolescents with type 1 DM. **Results:** Eighty-one patients (87%) had completely normal results. Only four patients (4.3%) had significant indicators of NAFLD (increased liver stiffness, elevated liver transaminases). Of these, three were overweight/obese and all four had suboptimal glycemic control with HbA1c >58 mmol/mol (>7.5%). Eight patients (8.6%) showed only one single mildly pathologic aspect of the examined items, in summary probably not indicating significant hepatic pathology. Variables indicating hepatic abnormalities did not show any correlation with HbA1c, body mass index, or diabetes duration. **Conclusions:** Our results do not indicate a significantly increased prevalence of liver pathology in this cohort compared to prevalence data from the general population. Therefore, our data advocate against systematic screening for liver disease in paediatric patients with type 1 DM.

P1-P211

Exploration of Social Network, Social Integration, and Socioeconomic Status in Families with Young Children with Type 1 Diabetes

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Background: Psychosocial factors are important for patients with chronic diseases such as type 1 diabetes. Lack of social network and poor social support are risk factors that affect morbidity. Little is known about social network and social integration of families with children with type 1 diabetes. **Objective and hypotheses:** Aim was to explore the social network of families with young children with type 1 diabetes and to examine associations between indices of social network and integration, socioeconomic status, and glycaemic control. **Method:** Families with children aged less than 12 years with type 1 diabetes were included in the cross-sectional study. Clinical data and HbA1c levels were collected. Self-report questionnaires were used to assess socioeconomic status. Interviews using the Multidimensional Social Contact Circle-Questionnaire were performed for exploration of social network. Social net size

and integration index were calculated. Statistical analysis including regression analysis was performed. **Results:** A total of 83 families with children with type 1 diabetes (mean age 8.9±2.4 years, mean diabetes duration 5.2±2.7 years, mean HbA1c 7.8±0.8%) participated in the study. High socioeconomic status was significantly associated with better glycaemic control compared to moderate and low socioeconomic status (HbA1c 7.5±0.7% vs 7.9±0.7% and 8.0±0.8%; $P=0.008$). The caregivers reported a total size of their social net of 12.4±7.4 persons in on average 4 out of 7 potential areas. No significant correlations were seen between social net size and HbA1c. Higher socioeconomic status was associated with higher integration index ($P=0.018$). Low integration index was associated with poor glycaemic control ($P=0.03$). Regression analysis identified longer diabetes duration and low socioeconomic status as risk factors for poor glycaemic control. **Conclusion:** This study describes the social network and social integration of families with young children with type 1 diabetes. Diabetes duration and socioeconomic status were significant risk factors for glycaemic control.

P1-P212

Permanent Neonatal Diabetes Mellitus due to a Novel Homozygous GCK Mutation in a Premature Baby with IUGR and Its Management

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Background: Glucokinase (GCK) acts as the glucose sensor of β-islet cells, regulating insulin secretion in response to changing glucose concentrations. Homozygous *GCK* mutations are a rare cause of permanent neonatal diabetes. Heterozygous mutations lead to GCK MODY, causing mild hyperglycaemia, not usually requiring treatment. **Case:** The index case was born to consanguineous parents at 36+2 weeks gestation, weighing 1610 g (0.4th centile). Hyperglycaemia (16–20 mmol/l) developed on day 1. Investigations showed insulin <1 mU/l, C-peptide 75 pmol/l and normal pancreas on USS. Both grandmothers and the father were diagnosed with Type 2 DM at 40–50 years (Metformin treated). Mother had gestational DM and continues on Metformin. Two sisters were diagnosed with anti-GAD negative Type 1 DM at 12–13 years (HbA1c 11%, insulin requirement 1–1.5 U/kg). **Genetic analysis:** Sanger sequencing excluded mutations in *ABCC8*, *KCNJ11*, *INS* and *EIF2AK3*. Methylation analysis showed normal 6q24 methylation. Targeted next-generation sequencing revealed a homozygous missense mutation (c.661G>A, p.Gly221Lys) in a highly conserved region of *GCK*, coding for the hexokinase domain. In the heterozygous state, p.Gly221Lys causes GCK MODY. Homozygous mutations have not been described. SIFT, PolyPhen2 and AGVG analysis predict a deleterious effect. **Treatment:** Intravenous insulin (0.6–0.8 U/kg) was started. A referral was made to our unit for CSII via Medtronic pump (G640). Pump adjustments were needed, including dilution of insulin x 10 in 0.9% saline, adapted cannula insertion and low glucose suspend, manual corrections for hyperglycaemia and manual bolusing for feeds. At 6 months, insulin requirement is 0.5 U/kg (35% basal) and HbA1c 6.3%. **Discussion:** This is the first description of a homozygous p.Gly221Lys mutation in neonatal diabetes. Grandmothers and parents likely have GCK MODY and may not require treatment. Sisters have unusually high HbA1c for a heterozygous *GCK* mutation. Family genetic test results will provide further insight. Specialist CSII therapy with neonatal adaptations achieves good control of neonatal diabetes.

P1-P213

The Impact of Diet on Insulin Dynamics over a 2-Year Period in Children with a Family History of Obesity

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Background: Despite extensive evidence in adults that lifestyle modification, including a healthy diet, may prevent the onset of type 2 diabetes, studies examining the impact of chronic dietary exposures on insulin dynamics in at-risk children are lacking. **Objective and hypotheses:** To assess how dietary intake predicts insulin sensitivity and secretion over a 2-year period in children with a family history of obesity. **Method:** Data stem from the QUebec Adipose and Lifestyle InvesTigation in Youth (QUALITY) cohort, consisting of 630 children recruited at age 8–10 years, based on a family history of obesity. Macronutrients (including %carbohydrates, %fat, %saturated fat, %protein, fiber, sugar-sweetened beverages) were assessed at baseline using three non-consecutive 24-h dietary recalls. Insulin sensitivity, assessed by Matsuda Index, and insulin secretion, assessed by the ratio of the AUC of insulin:glucose at 30 min (AUC30) and at 120 min (AUC120) after an oral glucose tolerance test, were carried out both at baseline and 2 years later. Physical activity (PA) was evaluated by 7d accelerometry and fitness by peak oxygen consumption (VO_{2peak}), percent fat mass by DXA. Regression analysis with smoothing splines for non-linearity were used and models were minimally adjusted for age, sex, PA, fitness, screen time, adiposity, season and pubertal stage. We accounted for missing data using multiple imputation. **Results:** Saturated fat intake was deleterious to insulin sensitivity over time: for every 1% increase in baseline saturated fat intake, Matsuda index decreased by 1.6% (95% CI = −3.2, −0.06) 2 years later, even after adjusting for other lifestyle habits and adiposity. No dietary component predicted any measure of insulin secretion after adjusting for PA, fitness, screen time and adiposity. **Conclusion:** Interventions that aim to lower saturated fat intake in children may be beneficial to prevent later development of type 2 diabetes in youth with a family history of obesity.

P1-P214

Analysis of Short-Term Efficacy of MiniMed 640G with SmartGuard in Pediatric Patients with Type 1 Diabetes

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Background: Fear of hypoglycemia is a major constraint on achieving a good metabolic control in T1D. Sensor augmented insulin pump therapy with threshold-suspended features (MiniMed 640G-SG) might alleviate burden of hypoglucemia and improve outcomes. **Objective and hypotheses:** Evaluate the effectiveness of this system to prevent day and night hypoglycemia and its impact on HbA1c in a pediatric population with T1D. **Method:** Descriptive and retrospective study including 21 children treated with MiniMed 640G-SG (age 10.0±3.4 years (2.4–16.3), 57% female, diagnosis age 4.3±3.2 years (0.9–11.9, previous therapy: 8 CSII+CGM, 10 CSII alone, 3 MDI). We compared before and after 640G-SG use: HbA1c, average glucose levels, variation coefficient (VC), hypoglycemia (<70 mg/dl) and hyperglycemia (>180 mg/dl) events, and number of capillary blood glucose (CBG). Last month period: fasting glucose, sensor use, and suspension pump events. Statistical analysis: SPSS 17.0, Data expressed by absolute value, mean±S.D., median, range and percentage. **Results:** Time of CSII use before 640G: 5.3±2.9 years (0.2–10.4). None of the patients presented previous episodes of severe hypoglycemia or DKA. Indications for 640G-SG: frequent hypoglycemic events (>10%) 48%, hypoglycemia unawareness 19% and improve quality of life 33%. All patients wore the system continuously: 5.0±2.1 months, sensor use 92% (53–97). Duration of pump suspension 3.1±1.2 h/day (0.6–5.4), with 40.4% of overnight stops. We found a significant decrease in the number of hypoglycemias ($P=0.044$) and CBG ($P<0.001$) without increasing hyperglycemia; moreover, a trend towards lower fasting glucose (Table 1). There were non-significant changes in HbA1c, average glycemia level nor VC. Three patients removed 640G-SG as family decision. **Conclusion:** Automatic insulin pump suspension as implemented in the MiniMed 640G system can help avoid hypoglycemia, without significantly increasing hyperglycemia, and reduce the burden of additional capillary glucose controls in our pediatric population.

P1-P215

The Influence of ß-Cell Autoimmunity on Cystic Fibrosis Related Diabetes Mellitus – A DPV Registry Analysis

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Background: Knowledge on the role of diabetes antibodies in CF related diabetes mellitus (CFRD) is scarce. **Objective and hypotheses:** We aim to inquire the relevance of ß-cell autoimmunity in CFRD. **Methods:** The German/Austrian/Luxembourgian diabetes registry DPV was searched for CFRD patients. 878 individuals were analyzed by multivariable regression models. **Results:** 8.7% of patients with CFRD in our cohort were positive for ß-cell autoantibodies ($n=76$). Analysis showed no association between antibody status and sex (females: 68.4 vs 57.2%), height (median SDS (IQR): −1.06 (−1.91–−0.164) vs −0.90 (−1.74–−0.20)) and BMI (SDS −0.81 (−1.61–−0.20) vs −1.0 (−1.80–−0.23)). Patients with ß-cell antibodies were younger at diagnosis (14.4 (11.4–16.0) vs 16.1 (13.5–20.9) years,

Table 1. (for abstract P1-P214)

	PRE- MiniMed 640G-SG	MiniMed 640G-SG	*P*
Average glycemia (mg/dl)	149.3±12.5	147.1±13.8	*NS*
S.D.	65.1±10.0	64.9±12.2	*NS*
Variation coefficient (%)	43±6	44±5	*NS*
Normoglycemia (%)	61.7±8.5	65.2±9.0	*NS*
Hipoglycemia (%)	10.4±5.2	7.6±3.3	***0.044***
Hiperglycemia (%)	28.2±8.2	27.4±9.2	*NS*
N° BCG (n)	11.3±2.2	8.1±2.2	***0.0001***
Fasting glycemia (mg/dl)	139.7±27.3	130.9±18.6	*NS*
Fasting glycemia (mg/dl) after overnight suspension	–	138.9±14.6	*NS*
HbA1c (%)	6.8±0.5	6.9±0.5	*NS*

$P<0.001$). After adjustment for age and sex, these patients were treated with insulin more often (92.1 vs 75.7%, $P=0.003$) and required higher insulin doses (0.94 ± 0.07 vs 0.75 ± 0.02 IU/kg/d, $P=0.008$). Moreover, insulin pump therapy was used more frequently (CSII 15.0 vs 6.7%, $P=0.015$). HbA1c differed slightly, but not significantly (7.5 ± 0.2 vs 7.2 ± 0.1%, $P=0.10$). Hypoglycemia with coma occurred in two out of 76 patients with ß-cell antibodies (eight out of 802 patients without ß-cell antibodies). Diabetic ketoacidosis was observed in three out of 76 patients with ß-cell antibodies (two out of 802 patients without ß-cell antibodies). **Conclusion:** ß-cell autoantibodies are present in a relevant proportion of CFRD patients in our cohort. Onset of diabetes was earlier, insulin doses were higher and patients with ß-cell autoimmunity were treated more intensively. Nonetheless, HbA1c did not differ clinically relevant. CFRD patients with ß-cell antibodies might need a more intense therapy and should be treated with special attention. **Funding:** Mukoviszidose e.V. and Federal Ministry of Education and Research within the German Competence Network for Diabetes mellitus which has been integrated in the German Center for Diabetes Research (DZD) as of January 2015.

P1-P216

Thyroid and Islet Autoantibodies Predict Autoimmune Thyroid Disease Already at Diagnosis of Type 1 Diabetes

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Background: Screening for autoimmune thyroid disease in children and adolescents with type 1 diabetes lacks consensus. Optimal screening methods should benefit the patients and reduce costs to healthcare. **Objective and hypotheses:** To, at diagnosis of type 1 diabetes, determine the predictive value of thyroid autoantibodies, thyroid function, islet autoantibodies, and HLA-DQ for autoimmune thyroid disease. **Method:** At diagnosis of type 1 diabetes, children ($n=2433$) were analysed for autoantibodies against thyroid peroxidase (TPOAb), thyroglobulin (TGAb), glutamic acid decarboxylase (GADA), insulin (IAA), insulinoma-associated protein-2 (IA-2A), and the three variants of the zinc transporter 8 (ZnT8A) as well as HLA-DQA1-B1 genotypes and thyroid function. After 5.1–9.5 years disease duration children treated with thyroxine were identified in the Swedish National Board of Health and Welfare Prescribed Drug Register. **Results:** Thyroxine had been prescribed to 6% (147/2433; 66% girls). In patients below 5 years, female gender (HR=4.60 CI: 1.50–14.45, $P=0.008$) and GADA (HR=5.80, CI: 1.32–25.4, $P=0.02$) were significant predictors. In patients 5–10 years, TPOAb (HR=20.56, CI: 8.40–50.35, $P<0.0001$), TGAb (HR=3.40, CI: 1.42–8.13, $P=0.006$) and thyrotropin outside the reference limit (HR=3.64, CI: 1.72–7.69, $P<0.001$) were predictors while in the 10–15 year olds, TPOAb (HR=17.00, CI: 8.40–34.44, $P<0.001$) and thyrotropin outside the reference limit (HR=4.11, CI: 2.41–7.03, $P<0.001$) predicted future thyroxine prescription. **Conclusion:** In this large nationwide study we found that TPOAb and thyrotropin in addition to GADA in the very young, analyzed at diagnosis of type 1 diabetes, were predictive of autoimmune thyroid disease. Since hypothyroidism in children and adolescents is important to recognize, we suggest that all children below 18 years of age would benefit to be tested for those parameters at clinical diagnosis of type 1 diabetes, and thereby optimize individualized screening during follow-up.

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Hemolysis in a Girl with Type 1 Diabetes Mellitus and Glucose-6-Phosphate Dehydrogenase Deficiency

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Background: Glucose-6-phosphate dehydrogenase (G6PD) deficiency is a X-linked enzymopathy. Hemolysis during type 1 diabetes mellitus (T1DM) treatment in patients with G6PD deficiency has been reported, but the underlying pathogenesis is not fully clarified. **Objective and hypotheses:** We try to explore the association between the two diseases. **Method:** We report a girl in whom hemolysis occurred after diabetic ketoacidosis (DKA) treatment, and review relevant literature. **Results:** A 10 year-old girl was admitted for T1DM and a moderate DKA. She was treated with insulin and rapidly recovered. Hemolysis was recognized on day 9 after admission when she appeared transient hypoglycemia, and results of G6PD activity and gene analysis confirmed the diagnosis of G6PD deficiency. Two mutations c.1376G>T and c.1388G>A were detected in her family. Her mother was heterozygous for mutation c.1376G>T, and father was hemizygous for mutation c.1388G>A, while the girl was double heterozygous. The parents had never show hemolysis, probably because the mosaic proportion of deficient red blood cells is too low and the enzymatic activity may relatively decrease not obviously. The mechanism of our patient's hemolysis may includes two points. One is that, severe hyperglycemia reduced G6PD activity so that antioxidant from erythrocyte decreased, meanwhile metabolism disorder of DKA promoted the erythrocyte depletion in antioxidant. The other is that, during DKA treatment the glucose levels progressively decreased and even hypoglycemia occurred, making the source of glucose that should have involved the pentose phosphate pathway decreased, and enhancing the inability of the old red blood cells to generate the antioxidant. **Conclusion:** The possibility of hemolysis in patients with G6PD deficiency would be increased in case of diabetes crisis. Reducing of G6PD activity by reason of hyperglycemia and decrease source of glucose in the pentose phosphate pathway because of decrease glucose levels may be the mechanism of hemolysis during DKA treatment.

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Clinical Characteristics and Molecular Analysis of Patients with Neonatal Diabetes

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Background: Neonatal diabetes mellitus (NDM) is a form monogenic diabetes diagnosed under 6 month of age. **Objective and hypotheses:** To describe the clinical and molecular features of NDM patients in a Turkish cohort. **Method:** Fifteen patients (13M, 2F) with diabetes onset before 6 months of age were included in the study. Clinical and molecular data were evaluated retrospectively. **Results:** Mean age at diagnosis was 2.4 ± 1.5 months (median 2, range 0.5–6 m). Gestational ages were between 35 and 40 weeks. Birth weight (BW) was between 1400 and 3680 g and BW-SDS -1.7 ± 1.7 (median -1.1; range -5.0 to 0.6). Small for gestational age (SGA, BW < -2 SD) ratio was 40%. Consanguinity ratio was 66.7%. Mean serum glucose level at diagnosis was 29.4 ± 8.9 mmol/l. Mutations are given in Table 1. In two siblings with *ABCC8* mutations (p.E382K mutation), insulin therapy was switched to glibenclamide at the age of 15 and 11 years. They have been on sulphonylurea (SU) monotherapy for 9 years, recent HbA1c values were 6.5%. The third patient with ABCC8 mutation (p.R826W) was planned to transfer SU. The two patients with *PTF1A* mutation had exocrine pancreatic deficiency due to pancreatic hypoplasia. One patient with unknown genetic etiology was SGA and had also exocrine pancreatic deficiency. Patient with *SLC19A2* mutation has sensorineural deafness, megaloblastic anemia, AV block, still on thiamine and subcutaneous insulin therapy (0.8 U/kg per day) at the age of 7 years. Patients with mutations in *INS, PTF1A* and two patients with unknown genetic etiology were SGA. One patient had no mutation in *ABCC8* and *KCNJ11* gene. Genetic cause was not studied in six patients. **Conclusion:** With high consanguinity ratio in this cohort, Wolcott Rallison syndrome was not the most common cause of NDM, contrary to previous reports. Male dominancy of our cohort was also noteworthy. In NDM patients with SGA and exocrine pancreatic deficiency *PTF1A* should be analysed first.

Table 1. Genotype analyses of the patients

	Patients (n)	**Mutations detected**
ABCC8	3	p.E382K and p.R826W
PTF1A	2	g.23508437A > G distal enhancer
Thiamine responsive megaloblastic anemia	1	p.S214fs in *SLC19A2*
Wolcott Rallison syndrome	1	p.S718TfsX723 in *EIF2AK3*
INS	1	c.-331C > G
Not known	7	-

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Impact of Continuous Glucose Monitoring System on Therapy of Cystic Fibrosis Related Diabetes in Children and Young Adults

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Background: Cystic fibrosis related diabetes (CFRD) is one of the most common complications of CF. CFRD has great impact on progressive deterioration of lung function, poor growth and increased mortality. The need for early detection of disturbance in glucose metabolism was recognized long ago. Current recommendations include screening that begins at age of 10 by performing oral glucose tolerance test (OGTT) but it cannot reveal the initial glucose disturbances. Many centres are using continuous glucose monitoring system (CGMS) to discover hyperglycaemia in real time, during normal activities. There is still no agreement on the application of this method for diagnostic purposes, but it certainly contributes to earlier detection of hyperglycaemia and enables early initiation of insulin therapy. **Objective and hypotheses:** The aim of this study was to evaluate profile of glycaemia in patients with CF followed up in a single centre. The indications for CGMS were abnormalities during OGTT or hyperglycaemia detected during regular visits. **Method:** Patients were recruited during 2015. Glucose meter and strips were provided to all patients; four blood glucose measurements (BGM) per day were required. CGMS was performed by iPro2 system during 7 days. Patients were instructed to record all BGM and dietary intake in the diary. None of them was on corticosteroid therapy. **Results:** Ten patients were included, four males, with a mean age of 22.4 years (11.1–36.7). In all patients CGMS revealed peaks of glucose higher than 11 mmol/l, after meals even above 19 mmol/l. Asymptomatic hypoglycaemia was noticed in nine patients. In four patients insulin treatment was introduced and all of them changed dietary habits. **Conclusion:** We observed abnormal glucose values in almost all patients. According to this experience, it seems that CGMS allows better insight of glucose impairment than OGTT in patients with CF as well as early initiation of insulin therapy.

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Effect of Allopurinol Versus Angiotensin Converting Enzyme Inhibitors in Decreasing Microalbuminuria in Type 1 Diabetic Patients

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Background: Diabetic nephropathy is a major microvascular complication of diabetes. It affects 25–35% of diabetic patients diagnosed under the age of 30 years. It is the leading cause of premature death in young diabetic patients. **Objective and hypotheses:** This study was primary designed to assess the short-term effect (6 months) of allopurinol treatment compared to angiotensin-converting enzyme inhibitor (ACEI) and placebo in type 1 diabetic patients (T1DM) with microalbuminuria. **Method:** The study included 90 (46 males and 44 females) type 1 diabetic adolescents who were recruited from the regular attendants of the Pediatric Diabetes Clinic. Adolescents with T1DM, less than 18 years with diabetes mellitus more than 5 years, microalbuminuria positive, repeated twice monthly were included. Patients were divided into the following groups: Group A: Patients who received allopurinol (zyloric 100 mg tablet), Dose: 100 mg/day. Group B: Patients who received Angiotensin Converting Enzyme Inhibitors (ACEI) Capoten 25 mg tablet with a dose of: 1 mg/kg dose every 12 h. Group C: Patients who did not receive any medications for microalbuminuria and served as a control group. Investigations: HbA1C, CBC, Blood urea nitrogen (BUN), Serum uric acid, Serum total proteins and serum albumin and micro-albumin in urine all were measured. Patients were followed up at 2-4-6 month respectively by comparing the studied parameters. **Results:** After 6 months of receiving treatment; the microalbuminuria level did not change significantly either in the allopurinol group or in control group ($P=0.124$, $P=0.89$). ACEI proved to be superior to both in improving microalbuminuria ($P=0.000$). Serum levels of uric acid were significantly lower in patients on allopurinol tablets ($P=0.02$) whereas other groups showed increase in its level ($P=0.38$, $P=0.24$ respectively). There were positive correlations between Hb1Ac ($r=0.440$, $P=0.001$), duration of diabetes ($r=0.968$, $P<0.001$), blood pressure ($r=0.232$, $P=0.028$) and microalbuminuria. A borderline correlation between uric acid and microalbuminuria was found ($r=0.207$, $P=0.050$) that emphasizing on the role of uric acid in pathogenesis of DN. No Side effects of the given medications were observed. **Conclusion:** Low-dose allopurinol was not effective in reducing microalbuminuria after 6 months of drug administration. Combination strategy should thus be a more effective tool for obtaining optimal control in patients with diabetic nephropathy.

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Continuous Glucose Monitoring and Hypoglycemia Unawareness in Children and Adolescents with Type 1 Diabetes

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Background: Seeking strict normoglycemia in type 1 diabetes mellitus increases the risk of hypoglycemia, exposing to hypoglycemia unawareness. Hypoglycemia unawareness (HU) is defined as the occurrence of hypoglycemic symptoms directly without autonomic symptoms. This study is designed to determine the incidence of HU in children and adolescents with continuous subcutaneous glucose monitoring system and to assess the effect of structured education to improve awareness. **Method:** In this prospective controlled quantitative study, randomly selected 39 Type 1 diabetic children and adolescents with a diabetes duration of at least 5 years were included. Continuous Subcutaneous Glucose Monitoring System, Medtronic Ipro2 was used to determine HU. A diary was kept for the symptoms of hypoglycemia. Hypoglycemia was defined as sensor glucose level <70 mg/dl. Patients who were diagnosed with HU initially undergone a structured education and after 3 months CGMS was used again in HU patients to detect the influence of education. **Results:** Thirty seven type 1 diabetic patients (mean age 13.8 ± 2.42 years, 43% male, mean diabetes duration 7.67 ± 1.66 years, mean hemoglobin A1c $8.0\pm1.2\%$) participated in the study. Twenty-four patients were on MDI therapy while the rest were on continuous insulin infusion therapy (CSII). 24.3% ($n=9$) of the patients were diagnosed as having HU with CGMS. Six of them were on MDI, three on CSII. 27.3% of the patients with a diabetes duration of 5–8 years and 72.7% of the patients with a duration of 8–11 years had HU. Mean HbA1c of the patients with and without HU within the preceding year was $7.9\%\pm0.97\%$ and $8.4\pm1.2\%$ respectively (P: 0.230). HU patients were hypoglycemic for 4.44 ± 3.78 h, AUC for hypoglycemia was 0.43 ± 0.47 and the number of low excursions were 5.22 ± 3.99. Though AUC and hypoglycemia duration statistically decreased compared to the initial findings, the number of hypoglycemic excursions did not change with structured education. **Conclusion:** HU is commonly seen in patients with type 1 diabetes mellitus. Continuous subcutaneous glucose monitoring system is effective in determining HU. Rate of HU can be reduced by structured education.

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Transient, Neonatal Hyperinsulinemic Hypoglycemia May be Monogenetic, Not Only Secondary to Fetal Life Events

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Background: Congenital hyperinsulinism (CHI) is a rare, heterogeneous disease with a transient, recurrent or persistent course. Transient CHI (tCHI) is considered to be caused by non-genetic risk factors e.g. birth asphyxia and intrauterine growth restriction (IUGR), while persistent hyperinsulinism is known to be caused by mutations in at least nine genes: *ABCC8, KCNJ11, GLUD1, GCK, HADH, SLC16A1, HNF4A, HNF1A* and *UCP2.* **Objective and hypotheses:** The aim of the study is to investigate genetic causes in children with tCHI, not secondary to maternal diabetes, who has been treated at Odense University Hospital,

Denmark, from 1994 to 2016. **Method:** Retrospective hospital file review to determine i) the phenotype of tCHI patients defined as patients with clinical remission of hypoglycemia before 1 year of age and ii) the genotype in tCHI patients and their parents. Risk factors of tCHI (ultrasound-verified IUGR; severe asphyxia defined as APGAR score 1 and 5 min <4 or <7, respectively, or cord pH $<7{,}0$) and adverse neurological outcome were recorded. **Results:** In 70 patients with tCHI, 10 (14%) of the patients had a mutation, *ABCC8*; $n=2$, *KCNJ11*; $n=4$, *HNF1A*; $n=3$, *HNF4A*; $n=1$. Seven of the mutations were known pathogenic; three had predicted pathogenicity. Affected family members were discovered in seven. Only 11 (16%) had a tCHI risk factor (severe asphyxia, $n=6$, IUGR, $n=5$), of whom one had a *KCNJ11* mutation and asphyxia. Relapse was documented in five (7%), of whom one had a *HNF1A* mutation. Seven patients (10%) with tCHI developed neurological sequelae (cerebral palsy; $n=3$, microcephaly; $n=1$, mental retardation; $n=1$, epilepsy; $n=2$), of whom none had a genetic mutation or hypoglycemia relapse. **Conclusion:** Transient CHI is not only caused by fetal life events, but also by CHI mutations in at least four different genes. Genetic testing may improve treatment and individual prognosis for tCHI patients and their families.

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The Relationship between the Serum Irisin Levels and the Metabolic Control in adolescents with Type 1 Diabetes

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Background: Irisin is an adipomyokine secreted by many tissues. Because it has known relationships with the energy metabolism and exercise, its relationships with obesity and type 2 diabetes (T2D) are being focused on. Its relationship with type 1 diabetes (T1D) is unknown. **Objective and hypotheses:** In this study, the relationships between the serum irisin level and the metabolic control were investigated in adolescents with T1D. **Method:** The study group consisted of 125 T1D patients with diabetes duration of at least 2 years, 57 obese and 44 non-obese children, all were aged between 10 and 18 years. The metabolic parameters, anthropometric characteristics and body fat distributions and *z*-scores (by DXA) were measured and relationships of these with the serum irisin levels were examined. **Results:** When all subjects were evaluated together, irisin levels were 3.08 (2.54–3.54) mcg/ml in girls and 3.12 (2.52–3.46) mcg/ml in boys, and no significant difference was found according to gender ($P>0.05$). When the serum irisin levels of the T1D, obese and normal patient groups (3.20 (2.78–3.66), 3.08 (2.46–3.42) and 2.60 (2.17–3.19) mcg/ml respectively) were analyzed, irisin levels in the diabetic group were found to be significantly higher ($P<0.001$). **Conclusion:** Serum irisin levels of T1D adolescents were higher than the group consisting of obese and non-obese individuals.

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Space-time Environmental Associations in Childhood Type 1 Diabetes (T1D). A Case-control Geographical Approach in the ISIS-Diab Cohort

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Background: T1D concordance in MZ twins being $\sim$40%, non-heritable factors play a major causal role in this autoimmune disease. T1D has recently increased in young European children. Collecting prospective environmental data in a cohort of millions children-years starting soon after birth seems unpracticable. Retrospective case-control studies are an alternative, provided biased controls and recall bias can both be avoided. **Objectives:** To develop a 'virtual control' (VC) geographical approach to unravel environmental factors significantly associated with T1D. **Methods:** Four dimensions of environmental exposures were tested by mapping socioeconomic, infectious, climatic and land cover databases at the geolocalized address of the child before T1D diagnosis. Levels of exposures were compared between T1D patients and age-matched geographic VCs. A test was considered significant (**) when the median p value computed over 100 comparisons of cases with 100 sets of VCs was below the Bonferroni limit, and indicative (*) of a possible difference when it was <0.05. **Patients:** 3548 children (age-at-onset 7.2 ± 3.7 years) with diagnosis after 1984. **Results:** The socioeconomic and land cover environment of T1D children was comparable to controls. The T1D children showed a greater past exposure to influenza (**) and acute diarrheas (*) and a lower past exposure to varicella (*). T1D children were more frequently exposed to heatwaves (**). **Conclusion:** Our exploratory approach with four databases provides a proof-of-concept to space-time environment associations studies. Environmental markers (not causes) of T1D can be found. By using more databases, a larger part of a child's environment can be covered.

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Association Between Vascular Endothelial Markers and Carotid Intima-media Thickness in Children and Adolescents with Type 1 Diabetes Mellitus

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Background: Type 1 diabetes mellitus (T1DM) is an important risk factor for cardiovascular events. Endothelial dysfunction and carotid intima-media thickness (CIMT) lead to increased cardiovascular complications. Adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1) and intercellular

adhesion molecule-1 (ICAM-1) are markers of early atherosclerosis and play a significant role in developing atherosclerosis. The general aim of the present study was to investigate the association between the levels of ICAM-1 and VCAM-1, and CIMT in the children and adolescents with T1DM. **Objective and hypotheses:** In this descriptive, cross-sectional study conducted between April 2013 and September 2014, 29 children aged 7–20 years with T1DM for at least 2 years and 29 age and sex-matched, healthy individuals were included. **Method:** CIMT was assessed by Doppler ultrasound, and the level of ICAM-1 and VCAM-1 was measured by ELISA. The data were analyzed by SPSS 16. **Results:** Independent *t*-test indicated a significant difference in ICAM-1 level between the patients and controls ($P<0.001$) Further, CIMT was derived significantly different between the patients and the controls ($P<0.001$). Pearson's correlation coefficient indicated that CIMT was not significantly associated with the level of VCAM-1 and ICAM-1 in the patients ($P>0.50$). **Conclusion:** The studied vascular endothelial markers were not associated with CIMT. But, CIMT and level of ICAM-1 were significantly different between the patients and controls, and therefore could be used as appropriate tools to examine the progression of early atherosclerosis in children and adolescents with T1D.

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Abstract unavailable.

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Rising of Type 1 Diabetes Mellitus Incidence in Chilean Children Between 2006 and 2014

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Background: T1DM incidence in children varies across regions and countries, showing a continue rise Worldwide. **Objective and hypotheses:** To determine the incidence of T1D in Chilean children under 20 years between 2006 and 2012. **Method:** We reviewed mandatory notifications of T1D (GES Program) in Chile's public health system in population younger than 20 years between 2006 and 2014. Data were obtained from the Department of Information Management of the Chilean Ministry of Health. Data were analysed according to sex, age, region and season. Time trends of T1D incidence were analysed by linear and exponential regressions. **Results:** 4.153 T1D cases in children under 20 years were notified from 2006 to 2014. Median age was 14 (IQR) and 51% were male. Highest caseload of T1D incidence occurred in winter (28%) and lowest in autumn (21%). The average annual T1D incidence was 12.5/100 000 new cases, with an increase from 10.3 in 2006 to 16.3 in 2014 (β 0.8 95%CI 0.6–0.9, $P=0.001$). A significant increasing linear trend of T1D incidence was observed in groups of age 0–4 years (β 0.3, 95% CI 0.06–0.6, $P=0.02$), 5–9 years (β 0.7 95% CI 0.2–1.27, $P=0.009$) and 10–14 (β 0.88, 95% CI 0.62–1.14, $P<0.001$), but not in age group 15—19 where a non-significant increasing or decreasing trend was observed (β 0.027, 95% CI −0.31 to 0.37, $P=0.85$). There was an association between latitude and T1D incidence during the study period. The incidence in the Metropolitan region is 12/100 000 new cases in the period. The lowest regional incidence of T1D was observed in the Araucanía (IX) and Los Rios (XIV) region with 6.9 and 7.1/100 000 new cases respectively. This difference is significate less than the incidence of the Metropolitan region, ($P<0.03$ and $P<0.05$ respectively, with 95% CI) Araucania region has the largest percentage of population of indigenous Mapuche ethnicity in the country. The highest incidence in the period was observed in Coquimbo region (IV) with 18/100 000 new cases, with a significant difference with the Metropolitan region ($P<0.06$ with 95% CI). **Conclusion:** Our study shows that incidence rates of T1D in Chile are rapidly increasing in population under 20 years, particularly in group between 5 to 9 and 10 to 15. If increasing trends persist we estimate Chile will reach T1D incidence rates of western developed countries in the next years.

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Frequency and Risk Factors of Depression in Type 1 Diabetes in a Developing Country

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Background: Living with type 1 diabetes especially in developing countries can feel overwhelming for parents and children because constant vigilance is required for proper care with inadequacy of resources. **Objectives and hypothesis:** Our aim was to investigate the frequency of depressive symptoms in children and adolescents with type 1 diabetes and their association with demographic, diabetes-specific, and family-functioning risk factors. **Method:** The study was conducted using Epidemiologic Studies Depression Scale. 86 (42 males and 44 females) patients with type 1 diabetes from Diabetes Clinic in Alexandria University Children's Hospital, Egypt, have completed the questionnaire during 1 November to 31 December 2015. Their mean age was 11.14 ± 3.02 (Range 5.8–16.2 year). Logistic regression models were used to detect the predictors of depression. **Result:** In the current study 44 children (51.16%) had score >15 indicating depressive state. Children who had depression were found to have significant longer duration of diabetes (5.7 ± 2.5 year), higher mean total daily insulin dose (1.3 ± 0.44 unit/kg), HbA1c level (9.9 ± 1.7) and were less frequently treated with basal bolus insulin regimen (29.6%); $P<0.001$. Univariate logistic regression model

showed that older age (OR, 1.2; 95% CI, 1.2–1.39), achieving puberty (OR, 0.3; 95% CI, 0.1–0.7), lower socio-economic status (OR, 0.19; 95% CI, 0.04–0.95), having less educated mother (OR, 0.28; 95% CI, 0.08–0.96), not on basal bolus insulin regimen (OR, 5.3; 95% CI, 2.1–13.4), receiving <3 daily injections (OR, 1.2; 95% CI, 0.27–0.55), DKA admission (one (OR, 3.6; 95% CI, 1.19–11.06), two (OR, 5.1; 95% CI, 1.2–21.4), three times (OR, 11.3; 95% CI, 1.8–122.5) were independent predictors for depression. For each one unit increase in total daily insulin dose or in HbA1c the log odds of having depression increased 5.3 and 3.3 respectively; $P<0.001$. Multivariate logistic regression model adjusted for significant predictors in the univariate model showed that HgbA1c is the only significant predictor for depression with C statistics of 0.83. **Conclusion:** Children and adolescents with type 1 diabetes have higher frequency of depressive symptoms in a developing country. Poor glycemic control is the most significant predictor for depression in these patients.

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Phenotypic Variability of Identical Mutations in the ABCC8 Gene in Two Families

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Background: Mutations in the SUR1 subunit of the K_{ATP} channel encoded by the *ABCC8* gene can result in diverse phenotypes ranging from Transient Neonatal Diabetes (TNDM) to type 2 diabetes in adulthood. These patients may benefit from sulphonylurea treatment. **Objective and hypotheses:** To describe the course of diabetes in two families with *ABCC8* gene mutations and to assess the effect of sulphonylurea treatment. **Method:** Direct sequencing of the *ABCC8* gene. Trial of sulphonylurea treatment. **Results:** Family 1: a boy presented with TNDM at the age of 12 days with glycaemia of 25mmol/l (BW 2240g at 35 weeks gestation). Genetic analysis revealed mutation F132V in *ABCC8* in this patient. Although this mutation had been previously described in a case of Permanent NDM unresponsive to sulphonylurea (Klupa *et al.*, Clinical Endocrinology, 2009), we performed test with glibenclamide with C-peptide increase (63 to 502 pmol/l). The boy was then successfully treated with gliclazide which could be stopped at the age of 5 weeks. The same mutation was indentified in his mother having diabetes since the age of 13 years. She was treated with insulin pump and after her son's diagnosis she was started on gliclazide which let to significant insulin dose reduction. Family 2: a girl presented with TNDM immediately after birth with glycaemia of 30 mmol/l (BW 1530 g at 37 weeks gestation). Novel mutation R933Q in *ABCC8* was identified and the response to glibenclamide was positive (C-peptid increase from 199 to 776 pmol/l). She was successfully treated with gliclazide until the age of 7 weeks when the treatment could be stopped. The same mutation was found in her father who had been on sulphonylurea treatment for diabetes since the age of 39 years. **Conclusion:** Identical mutations in the *ABCC8* gene show different phenotypic expressivity and responsiveness to sulphonylurea therapy. The predictors that influence the diabetic phenotype remain unclear. We have shown that the F132V mutation previously described as unresponsive could be responsive to sulphonylurea.

P1-P230

Growth and Glucose Metabolism after Allogenic Bone Marrow Transplantation for Thalassemia Major

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Background: Growth failure and abnormal plasma glucose level are common in patients with thalassemia major (TM), which are usually due to iron overload after repeated blood transfusion. Patients after successful bone marrow transplantation (BMT) will be free from further blood transfusion and thus spared from complications of iron overload. This study aimed at determining the incidence of abnormal glucose level in TM patients and studying the height difference between the TM patients who underwent BMT and who did not. **Objective and hypotheses:** The 'BMT group' consisted of 19 patients with TM who had undergone BMT and were followed up for at least two years. 54 TM patients of similar age who did not undergo BMT were recruited as the 'non-BMT group'. **Method:** The age at BMT, present age, weight, height, height standard deviation score (SDS) and weight SDS values, serum ferritin (SF), the fast blood glucose and insulin level were evaluated. **Results:** The mean age was 10.3 ± 3.6 years and transplantation age was 6.29 ± 3.4 years. The SF of the BTM was lower than the non-BTM group ($P=0.002$). The height SDS score in BTM was found better than the non-BTM ($P=0.039$). There were no statistical differences in fast blood glucose and insulin level between two groups. 15.79% (3/19) of BTM patients had insulin resistance, while it was 14.81% (8/54) in non-BTM group ($P=1$). None of the BTM had impaired fast glucose (IFG) or diabetes mellitus (DM). While in non-BTM group, the prevalence was 18.5% (10/54) and 3.7% (2/54) respectively ($P=0.029$). **Conclusion:** Allogeneic BTM may improve short stature of TM patients. Although BMT did not alter the abnormal glucose status of TM completely, it prevented this disease from exacerbating. The patients should be followed up regularly after transplantation.

P1-P231

A Rare Form of Insulin Resistance with Pseudoacromegaly

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Background: Insulin resistance occurs in a variety of common endocrine disorders including obesity, type 2 diabetes, polycystic ovarian syndrome, and metabolic syndrome. Additionally, rare syndromes exist that result in extreme insulin resistance. These conditions help contribute to our knowledge of the mechanisms of insulin signalling and resistance. **Objective and hypotheses:** We report a case of a 12 year old female presenting to endocrinology clinic for evaluation of new onset diabetes. She was found to have extremely tall stature, acanthosis nigricans, severe hirsuitism, obesity, and acromegaloid features. We hypothesized that she had a syndrome of growth hormone excess resulting in acromegaly, tall stature, insulin resistance, and diabetes. **Method:** The patient underwent non-fasting blood work as well as a 2 h oral glucose tolerance test (OGTT) measuring growth hormone and insulin. The patient and her first-degree relatives underwent whole exome sequencing. **Results:** The patient had normal levels of IGF-1. However she was noted to have extremely elevated insulin level (1279 μIU/ml) postprandially. She also had evidence of biochemical hyperandrogenism with an elevated free testosterone (16 pg/ml). The patient had a bone age of 14 years. Therefore her predicted adult height was 1.83 m (+3.23 SDS). She then underwent a 2-h OGTT. After ingesting 75 g oral glucose solution, her growth hormone level was undetectable at 90 min. However, her fasting insulin level was 27.7 μIU/ml. The subsequent levels were 752, 799, 488, and 390 mIU/ml at 30, 60, 90, and 120 min respectively. Whole exome sequencing identified potential genetic causes. **Conclusion:** We report a novel case of a 12 year old patient with tall stature, acromegaloid features, normal growth hormone secretion, and severe postprandial insulin resistance. This condition, insulin mediated pseudoacromegaly, is poorly represented in the medical literature. We hypothesize that this condition is caused by genetic factors. Whole exome sequencing has been performed to reveal the molecular pathogenesis underlying this condition.

P1-P232

Extrahepatic Biliary Atresia in Combination with Toxic Cholestasis Due to Glibenclamide in a Case of Neonatal Diabetes

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Background: More than 20 gene loci are known to cause monogenic neonatal diabetes today. A definite mutation can be found in 65–70% of all cases. Mutations in the ATP sensitive potassium channel can frequently be treated by sulfonylurea. Glibenclamide is on of the drugs known to inhibit the bile salt export pump (BSEP). However most drug induced cholestasis cases are reported in adults. **Objective and hypotheses:** Glibenclamide is used frequently to treat neonates with monogenic diabetes. To date there is no case of drug induced cholestasis reported in neonates. Extrahepatic biliary atresia seems to develop either intrauterine but in some cases even after birth. Causing factors are not known exactly. We hypothesize that the coincidence of extrahepatic biliary atresia in a patient treated with glibenclamide because of neonatal diabetes could be partially explained by drug induced cholestasis. **Method:** We report about a boy with neonatal diabetes due to a KCNJ11 missense mutation diagnosed in the age of 2 weeks. **Results:** Glibenclamide was started with very low doses (0.0125 mg/kgKG) immediately after diagnosis. Cholestatic icterus developed with age of 9 weeks. Glibenclamide was stopped immediately. Liver biopsy showed signs of extrahepatic cholestasis but also possible toxic signs. There was no improvement with conservative treatment. Intraoperative exploration and cholangiography showed an extrahepatic billary atresia. Biliodigestive anastomosis with Y-Roux (Kasai) was established by the pediatric surgeons. Diabetes is in remission at the moment. Cholestasis has completely recovered. **Conclusion:** Cholestasis due to glibenclamide has to be taken into account when treatment is initiated in neonates with monogenic diabetes. Therefore we would recommend to monitor cholestatic parameters in a certain algorithm.

P1-P233

Higher-Than-Conventional Subcutaneous Regular Insulin Doses Following Diabetic Ketoacidosis are Associated with Better Short-term Glycemic Control

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Background: While some guidelines recommend 0.5–1.0 units/kg per day of subcutaneous insulin following resolution of diabetic ketoacidosis (DKA), up to 2 units/kg/day are used in various centers. **Objective and hypotheses:** To test the hypothesis that higher initial insulin doses would be more efficient during first 48 h of subcutaneous insulin therapy after DKA in cases with new-onset type 1 diabetes. **Method:** Records of patients presented with DKA in the last 3 years ($n=76$, median (25th–75th percentile) age = 10.0 (6.0–12.0) years, M/F:44/32) were reviewed. Patients given high-dose subcutaneous regular insulin ($\geq$1.0 units/kg per day) constituted Group 1 ($n=46$, median dose = 1.39 (1.02–1.47)) while those treated with conventional-dose ($<$1.0 units/kg per day) constituted Group 2 ($n=30$, median dose = 0.90 (0.82–0.95)). Clinical and laboratory data were collected and analyzed. **Results:** Groups were similar regarding age, gender, pubertal status, HbA1c, insulin dose administered for DKA, and blood glucose levels at the start of subcutaneous insulin

treatment. Median and minimum blood glucose levels of Group 1 in the first 48 h were significantly lower than that of Group 2 (230 (198–270) vs 266 (221–315), $P=0.008$ and 102 (85–151) vs 129 (105–199), $P=0.043$, respectively). The number of patients who experienced hypoglycemia (<70 mg/dl) were similar (Group 1, 7 (15.2%) vs Group 2, 2 (6.7%), $P=0.469$) and none had severe hypoglycemia. In Group 1, ratio of blood glucose levels in the target range (100–200 mg/dl) were higher and the number of measurements >200 mg/dl were lower compared to Group 2 ($P=0.014$ and $P=0.004$, respectively). Subcutaneous insulin doses (units/kg per day) administered in second day in both Group 1 (1.48 (1.19–1.71) and Group 2 (1.05 (0.97–1.17)) were significantly higher compared to starting doses ($P<0.001$ for both). Glycemic variability indices were similar among the groups. **Conclusion:** After resolution of DKA, a dose of 1.0–1.5 u/kg per day regular insulin is associated with better glycemic control without increased risk of hypoglycemia.

P1-P234

Assessment of Selected Carbohydrate Parameters in Children Exposed to Gestational Diabetes in utero

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Background: Children exposed to gestational diabetes mellitus (GDM) in utero have higher risk of development of glucose intolerance and diabetes mellitus. **Objective and hypotheses:** The study was undertaken to assess the selected carbohydrate parameters in children exposed to gestational diabetes in utero. **Method:** 50 children exposed to gestational diabetes were compared with 46 control subjects. Anthropometric parameters of a newborn were obtained from the medical records. In all participants height, body mass, waist and hip circumferences were measured; BMI, WHR and WHtR were calculated. Values of fasting glucose, insulin, C-peptide and HbA1c were measured and HOMA2-IR, HOMA2-S, HOMA2-B were calculated. In obese children (BMI ≥95th percentile) OGTT was performed. Mothers' pre-pregnancy and current BMI was calculated. **Results:** The prevalence of overweight/obesity in the study group was 38%, in the control group 41% ($P=0.19$). Higher fasting glucose level ($P=0.02$) and HbA1c ($P=000004$) were found in the study group comparing to the control. In children exposed to GDM in utero a positive correlation of fasting insulin and WHR (Rs=0.31, $P=0.028$) as well as significantly lower HOMA2-B ($P=0.03$) were observed. In the study group higher HOMA2-IR ($P=0.0002$) and HOMA2-B ($P=0.0000039$) and also lower HOMA2-S ($P=0.0002$) were observed among participants with overweight/obesity comparing to children with normal body weight. In the study group a correlation of HOMA2-IR and SD of the birth weight was found (Rs=0.28, $P=0.049$). In children exposed to GDM the correlation of fasting insulin level, HOMA2-IR, HOMA2-B and mother's (pre-pregnancy and current) BMI was observed. **Conclusion:** Children exposed to gestational diabetes in utero, in spite of similar prevalence of overweight/obesity comparing to their non-exposed peers, could have higher risk of glucose intolerance and diabetes mellitus in future. Towards observed decreased insulin sensitivity and compensatory increase in insulin secretion, prevention of overweight and obesity in this group seems to be essential.

P1-P235

The Genetic Causes and Phenotypic Characteristics of Egyptian Patients with Neonatal Diabetes Mellitus

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Background: Neonatal Diabetes Mellitus (NDM) is a rare form of monogenic diabetes that typically presents during the first 6 months of life. Its prevalence is about 1:100 000 live births; however it may rise up to 1:29 000 in highly consanguineous populations. Mutations in 22 different genes are reported; with the most common cause being potassium channel subunit gene (*KCNJ11/ABCC8*) mutations. However, causative mutations among consanguineous populations seem to differ. Studies on NDM in these populations are still limited. **Objective and hypotheses:** Our aim was to identify the causative mutations among a group of Egyptian patients with NDM and to describe their clinical phenotypes. **Method:** The study was performed on 16 Egyptian patients with NDM onset at or before the age of 6 months who attended the Diabetic Endocrine and Metabolic Paediatric Unit (DEMPU) at the Children's Hospital of Cairo University in Egypt. Sanger sequencing was undertaken for the common causative genes (*KCNJ11, ABCC8, INS* and *EIF2AK3*) as a first test, followed by targeted next generation sequencing for the remaining known genes. **Results:** Mean age of onset of NDM was 2.6 months, 10/16 were born from consanguineous parents and 11/16 presented with diabetic ketoacidosis. Eight mutations have been detected so far; only 4/16 patients had potassium channel gene mutations: two in *KCNJ11* and two in *ABCC8*. One homozygous *GCK* gene mutation was detected. A chromosome 6q24 methylation defect was detected in one patient with transient NDM, a homozygous *EIF2AK3* mutation was detected in one patient with Wolcott Rallison syndrome and a homozygous *SLC19A2* mutation was detected in a patient with Thiamine

Responsive Megaloblasic Anaemia syndrome. **Conclusion:** Potassium channel subunit gene mutations are not common among the studied group. Further studies are required to determine common mutations among the Egyptian population.

P1-P236

Does Adherence to a High HbA1c Policy Improve Outcomes in a Paediatric Diabetic Clinic Population?

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Background: Poor glycaemic control, indicated by a high HbA1c level, increases the risk of developing complications of type 1 diabetes. It is, therefore important to reduce HbA1c levels aiming for the new target outlined by NICE (2015) of 48 mmol/mol. To try and improve HbA1c levels in patients attending a large urban diabetic clinic a policy was developed, targeting patients with an HbA1c level of 64 mmol/mol or higher. **Objective and hypotheses:** To assess whether the policy was implemented correctly and if it was effective in reducing HbA1c levels. **Method:** A computer database search was made of patients with a latest HbA1c of >57 mmol/mol. Patients without type 1 diabetes or diagnosed within 1 year, those with a first high HbA1c within 6 months and those who had not had a high HbA1c over the past year were excluded. The database was reviewed over 1 year, recording HbA1c levels, appointments, telephone calls and hospital admissions. **Results:** 138 patients were identified but 39 excluded, leaving 99 patients. Average initial HbA1c was 76 mmol/mol. 72.7% were offered 100% of appointments as recommended. Patients with initial HbA1c of >86 mmol/mol were most likely to have a lower Hba1c after 1 year (76% vs 50% of HbA1c of 64–75 mmol/mol) but were more likely to not attend appointments (2.76 missed appointments/patient/year vs 1.79). Of the patients with HbA1c of 64–75 mmol/mol those who had no telephone calls had a smaller increase in HbA1c than average (0.46 vs 1.23) and those with 100% attendance had an average decrease in HbA1c of 0.69. Elective hospital admission led to reduction in HbA1c at 3 months (97.5–82.25 mmol/mol) but an increase to 95.14 at 6 months. **Conclusion:** 100% clinic attendance is linked to lower HbA1c, hospital admission reduces HbA1c in the short term only, but telephone calls did not lead to lower HbA1c.

P1-P237

The Prevalence of Diabetic Ketoacidosis in Children with New-Onset Type 1 Diabetes Mellitus

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Background: Children at type 1 diabetes (T1DM) diagnosis can develop ketoacidosis (DKA), a life-threatening condition, which is most frequently associated with the onset of diabetes in children aged <5 years. **Aims and objectives:** We studied the prevalence of DKA at T1DM diagnosis and the frequency of partial remission (PR) in children from Wielkopolska province, Poland. **Method:** The cohort comprised 735 children aged 0–18 years with newly diagnosed T1DM. Clinical and biological features were collected at diagnosis and during follow-up. DKA was defined as blood pH <7.30. To confirm autoimmune diabetes origin typical autoantibodies were tested. Questionnaire on diabetes was completed by children's parents. PR was defined using the insulin-dose-adjusted A1C definition. P value <0.05 was considered significant. **Results:** DKA was diagnosed in 36.0% of patients: 12.9% had mild form, while 14.5% and 8.7% moderate and severe, respectively. In children aged 0–4, 5–9, 10–14 and 15–18 years DKA was present in 48.5, 34.7, 31.4 and 28.2%, respectively. In individuals aged <4 years DKA occurred significantly often ($P=0.001$). The highest severe DKA frequency was associated with symptoms' duration (>28 days) ($P=0.014$) and diabetes misdiagnosis ($P=0.001$). ZnT8 autoantibody was detected significantly often in children with DKA ($P=0.44$). Children with DKA had higher levels of blood ketones ($P=0.0001$), HbA1C ($P=0.0004$), blood glucose ($P=0.00001$) and lower levels of insulin ($P=0.0001$), c-peptide (0.0001). In the first year after diagnosis PR occurred in 62% patients. Individuals with DKA had lower PR incidence (24% vs 76% without DKA). **Conclusion:** The prevalence of DKA is high in children from Wielkopolska. Children aged <4 years have the greatest risk of developing ketoacidosis. The highest frequency of severe DKA is related to symptoms' duration and diabetes misdiagnosis. ZnT8 autoantibodies are associated with the worst general condition at the time of diagnosis.

P1-P238

Correction of Carnitine Deficiency in Children with Recent Onset Type 1 Diabetes

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Background: Carnitine deficiency (CD) has been reported in children at time of type 1 diabetes (T1D) diagnosis. By impairing free fatty acid ß-oxidation in liver, muscle mass and pancreatic ß cells, CD might impair glucose homeostasis and residual insulin secretion. We postulate that reversed of these FAO defects may help regenerate a healthier ß cell mass and increased the diabetes honeymoon duration. **Objective:** Evaluate the effects of carnitine supplementation during the first months following the diagnosis of childhood T1D. **Patients:** 24 children chosen at random at diagnosis of T1D (age 3–16 years, with positives antibodies) were

assigned to carnitine supplementation ("carn+") with 100 mg/k carnitine per day. They were compared to 25 non-treated children ("carn-"). Severe ketoacidocetosis at diagnosis excluded. Non-compliance was excluded by an elevation of plasma carnitine in "carn+" group compared to "carn−" group during the follow up. **Results:** Children of the "carn+" and "carn−" groups were comparable at diagnosis for duration of nycthuria, weight loss, HbA1c, C peptide, pH, sexe, age. At diagnosis, the mean plasma carnitine level for all patients was 32.7 µmol/l (min:18–max:47) (normal values: 43–65 µmol/l). At 3–4 months, HbA1c was 6.7% in "carn+" and 6.5% in "carn−", with insulin doses 0.7U.K.d and 0.6U.k.d respectively. C peptide was 0.1–1.8 in "carn+" and 0.3–3.5 µg/l in "carn−" (NS). Gained weight was 11% of initial body weight in the two groups. **Conclusion:** CD at T1D diagnosis is confirmed. No change was observed between the two groups during the first 3 months after the diagnosis of T1D. A longer follow up is necessary to see if carnitine suplementation could increase remission duration and magnitude in T1D.

P1-P239

Fetal Growth Restriction Due to Maternal Congenital Hyperinsulinism Associated with a Novel Variant in GLUD1 and Intrauterine Diazoxide Exposure

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Background: Congenital hyperinsulinism (CHI) is a rare disease mostly due to loss-of-function mutations of the *ABCC8* or *KCNJ11* genes, encoding the two subunits of the K_{ATP} channel. Gain-of-function mutations in glutamate dehydrogenase 1, encoded by the *GLUD1* gene, are the second most common cause of CHI. **Objective and hypotheses:** The majority of patients with a *GLUD1* CHI respond to diazoxide, but little is known about the consequences of fetal diazoxide exposure. **Method:** We report the neonatal outcome after fetal diazoxide exposure (50 mg t.i.d) and maternal CHI. **Results:** Whole exome sequencing with bioinformatical targeted analysis of 10 genes known to cause CHI (*ABCC8, KCNJ11, GLUD1, GCK, HADH, HNF1A, HNF4A, SLC16A1, UCP2, CDKN1C*) revealed a maternal novel heterozygous missense *GLUD1* variant c.1496G>T; p.(Gly499Val), predicted to be pathogenic. The baby was born by cesarean section at 40 weeks of gestation with intrauterine growth restriction (IUGR), birth weight 2300 g (< −2 S.D.), length 46 cm (< −2 S.D.), head circumference 32.5 cm (<-2 S.D.). The genetic analysis showed that he was not carrying the maternal *GLUD1* variant. No malformations were visible. No structural anomalies were identified on the brain MRI done on day of life 10. **Conclusion:** This newborn had a 50% risk to inherit CHI and was exposed to diazoxide *in utero*. Diazoxide passes the placenta and fetal concentration is supposed to be the same as in the mother. Intravenous diazoxide has been used in pregnant women for its hypotensive action with risks of placental hypoperfusion, fetal death and neonatal hyperglycemia. We did not find such adverse effects; however the newborn presented with IUGR, which could be secondary to maternal hypoglycemia or to a direct effect of diazoxide. No structural brain anomalies attributable neither to teratogenicity of diazoxide nor to IUGR were observed, however this child is at risk of neurodevelopmental impairment.

P1-P240

Effect of Vitamin D Supplementation on Lipid Profile in Vitamin D Deficient T1D Patients with Dyslipidemia

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Background: It was suggested that vitamin D has both direct and indirect effects on modifying the lipid profile in patients with diabetes through its regulatory action that increases the activity of lipoprotein lipase in adiposity. **Objective and hypotheses:** To detect the relationship between serum 25(OH) D and lipid profiles in patients with T1D and dyslipidemia and to study the effect of vitamin D supplementation on lipid profiles of vitamin D deficient T1D patients with dyslipidemia. **Method:** This cohort study included 50 patients with T1D and dyslipidemia with history of T1D more than 2 years. Vitamin D level was assessed and patients were divided accordingly into two groups: 20 patients with vitamin D sufficiency and 30 patients with vitamin D deficiency who were allocated to vitamin D3 supplementation in a dose of 4000 IU/day for 4 months, then lipid profile was re-evaluated for both groups. **Results:** The mean age of the studied patients was 12.56±3.53 years, 25(OH)D levels ranged from 0.1 to 62 ng/ml with a mean of 25.95 ng/ml. There was no significant correlation between vitamin D level and different studied parameters (age, diabetes duration, hypoglycemia frequency, DKA frequency, insulin dose, HbA1c, thyroid functions and lipid profile) within the study group ($P>0.05$). When patients with vitamin D deficiency were compared to those with normal levels, no significant difference was found except in family history of coronary heart disease ($P=0.036$) and free T_4 ($P=0.035$). After 4 months of vitamin D supplementation for those with vitamin D deficiency, the mean difference (at 0 & 4 months) in HbA1c and LDL between the two groups was statistically significant ($P=0.04$ & 0.02 respectively). **Conclusion:** Vitamin D deficiency was highly prevalent in patients with T1D. There was no significant correlation between 25OHD levels and lipid profile. Vitamin D supplementation for 4 months had a significant lowering effect on LDL.

P1-P241

Renal Functional Reserve in Children with Type 1 Diabetes

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Background: Early detection of diabetic nephropathy is of great importance. Renal functional reserve (*RFR*) is the difference between glomerular filtration rate (*GFR*) in basal conditions and *GFR* after a protein meal. **Objective:** To examine renal functional reserve in children with type 1 diabetes mellitus (T1D) in order to detect diabetic nephropathy at early stage. **Method:** Case control study included patients with duration of T1D more than 3 years, older than 10 years and normal microalbuminuria. We measured creatinine clearance, cystatin C and calculated RFR after a protein meal (PM) challenge. Study group consisted of 20 patients and control group included 16 children with T1D, who did not give a consent for oral (PM) load. *GFR* was calculated and 24 hour ambulatory blood pressure was performed in all patients. **Results:** Baseline clinical characteristics did not differ between those two groups. Mean age was 15.3 ± 2.2, duration of diabetes 6.8 ± 3.3 years, insulin dose 1.0 ± 0.3 U/kg per day, HbA1c was $8.4 \pm 1.8\%$ and GFR was 121.6 ± 26.2. None of patients were hypertensive, but 76.5% were non-dippers. Mean serum creatinine levels and creatinine clearance were within normal values before and after a (PM). Average serum cystatin C was elevated before and after a (PM) and was 1.03 ± 0.56 and 0.37 ± 0.94 mg/l, respectively. Mean RFR was $-0.13 \pm 9.6\%$ and was reduced in all patients. **Conclusion:** Although this was a pilot project and the sample size was small, all patients had reduced RFR. Poor metabolic control might be the reason but all patients were normotensive and had normal microalbuminuria. Those results imply that we need to look for new markers of early nephropathy.

P1-P242

The Prognostic Role of Non-alcoholic Fatty Liver Disease in Children with Type 1 Diabetes Mellitus with and without Dyslipidemias

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Background: Recently it is shown that the clinical manifestation of non-alcoholic fatty liver disease (NAFLD) is not related only to liver, but also to cardiovascular complications and mortality. Nowadays there is growing evidence that dyslipidemia and NAFLD association is multisystemic disease, affecting other systems and regulatory pathways. Furthermore, diabetes mellitus worsens the risk of later chronic cardiovascular and atherogenic complications. **Objective and hypotheses:** The aim of current work is to reveal the potential connection between dyslipidemias and NAFLD. **Method:** 120 type 1 diabetic children were included in the investigation with mean age-11.5 ± 1.4, male/female ratio-64/56. Total cholesterol, triglycerides, VLDL, LDL, HDL, HbA1c levels were measured, and USG examination was performed. **Results:** 60% of children found to have NAFLD, only 6.9% from which developed hypertriglyceridemia, 12.5%- increased LDL levels. No significant connection has been found between quantitative dyslipidemias and NAFLD ($P > 0.05$). But, interestingly, in 47.2% of diabetic patients with NAFLD increase in VLDL was found versus to 2.1% of patients without NAFLD ($P < 0.05$). Dyslipidemias and NAFLD exhibited not significant connection with HbA1c $> 8\%$–10.8% and 33.3% from total, respectively ($P > 0.05$). **Conclusion:** It is assumed that poor glycemic control probably has impact on dyslipidemia and NAFLD development, but is not the only pathway. Some qualitative abnormalities of potentially atherogenic lipoproteins are found in diabetic children. Thus, measurement of only HDL, LDL, cholesterol and triglycerides is not enough informative for early prognosis of later atherogenic and cardiovasvular risks. NAFLD seems to have higher predicting role in development of qualitative but not quantitative dyslipidemias. However, the precise consequences of these qualitative lipid changes and NAFLD on the duration and complications of type 1 diabetes should be evaluated profoundly.

P1-P243

Associated and Familial Autoimmunity in Children and Adolescents with Type 1 Diabetes Mellitus

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Background: Type 1 Diabetes Mellitus (T1DM) often coexists with other autoimmune diseases, either individually or as a part of polyendocrine syndrome (APS I-III). It is frequently associated with autoimmune thyroid, celiac, gastric and Addison's disease. In the families with T1DM patients frequently coexist different autoimmune diseases (familial autoimmunity). **Objective and hypotheses:** Evaluating the frequency of associated and familial autoimmunity in T1DM patients and predisposing factors. **Method:** We studied 93 T1DM children and adolescents (boys/girls: 44/49) with a mean $\pm$ S.D. age of 12.5 ± 4.7 years (range: 1.5–18 years), disease duration 4.7 ± 4.0 years and age at T1DM diagnosis 8.0 ± 3.5 years. The following autoantibodies were recorded: a) celiac disease: against tissue transglutaminase (anti-tTG-IgA) and endomysium (anti-EMA-IgA and IgG),

b) Hashimoto thyroiditis (HT): against thyroid peroxidase (anti-TPO) and thyroglobulin (anti-Tg), c) autoimmune gastritis: against gastric parietal cells (APCA), d) Addison's disease: against adrenal cortex (ACA). **Results:** Double autoimmunity was found in 25/93 patients (26.9%) and triple in 6/93 (6.5%). HT was diagnosed in 20 (21.5%) patients, celiac disease in 11 (11.8%), autoimmune gastritis in 5 (5.4%) and psoriasis in one patient (1.0%). Familial autoimmunity was present in the families of 46% patients: HT in 32 (34.4%), T1DM in 17 (18.3%), gastritis in 2 (2.1%), multiple sclerosis 2 (2.1%), while celiac disease, Myasthenia Gravis and psoriasis occurred in 1 relative (1.1%) each disease. The appearance of associated autoimmunity was not correlated with gender (boys 12/44 (27.3%) vs girls 21/49 (42.8%), $P=0.088$) and the age at T1DM diagnosis (<5 years: 10 (45.5%) vs $>/5$ years: 17 (30.3%), $P=0.290$). **Conclusion:** Associated autoimmunity is quite common (33.3%) among T1DM children and adolescents, with Hashimoto's thyroiditis being the most frequent, followed by celiac disease. Familial autoimmunity was observed in 46% of patients, with HT and T1DM being the most frequent. It is therefore necessary the regularly assess children with T1DM for associated autoimmunity and look for familial autoimmunity.

P1-P244

Factors Affecting Dyslipidaemia in Children and Young People with Type 1 Diabetes Mellitus: A Multicentre Study

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Background: Diabetic dyslipidaemia is characterized by high triglycerides (TG), low HDL cholesterol (HDL-C) and the presence of small, dense LDL. The UK National Paediatric Diabetes Audit (NPDA) 2013/14 reported that 16.1% of children and young people (CYP) with type 1 diabetes mellitus (T1DM) have a total cholesterol (TC) of $\geq$ 5 mmol/l. TG, LDL and TC-HDL-C were not reported in the NPDA. The significantly high prevalence of hypercholesterolemia in CYP with T1DM is concerning. **Objective and hypotheses:** To evaluate the factors associated with dyslipidaemia in CYP with T1DM. **Method:** We examined TC, LDL, TG, TC/HDL-C ratio, BMI SDS, mean HbA1c over 12 months (mmol/mol), duration of diagnosis, pubertal status and total daily insulin requirement (TDI) in units/kg/day of CYP with T1DM between 2014 and 2015 in four paediatric diabetes centres within the Northwest of England. **Results:** There were 371 CYP (201 males); 250 were on multiple daily insulin regimen, 102 on continuous subcutaneous insulin infusion (CSII) and 19 on twice-daily insulin regimen. Mean of variables $\pm$ S.D. was – Age at diagnosis: 7.55 $\pm$ 3.9 years; BMI SDS 0.62 $\pm$ 1.02; TDI 0.91 $\pm$ 0.36; HbA1c 68 $\pm$ 17; TC 4.4 $\pm$ 0.84 mmol/l; TC/HDL-C ratio 2.94 $\pm$ 0.86; LDL 2.18 $\pm$ 0.77 mmol/l; TG 1.11 $\pm$ 0.73 mmol/l. 93 CYP were prepubertal, 170 pubertal and 107 post-pubertal. There was significant positive correlation between TC and HbA1c ($r=0.3$, $P=0.002$) and between TC/HDL-C ratio and HbA1c ($P<0.001$). Total daily insulin ($P<0.001$) and duration of diagnosis ($P=0.02$) were significantly associated with higher TC/HDL-C ratio. Multivariable regression analyses of factors affecting TC, LDL, TG, TC/HDL-C ratio (BMI SDS, pubertal status, HbA1c, duration of diagnosis and TDI) showed that HbA1c was an independent factor affecting TC ($P<0.001$), TG ($P=0.01$), LDL ($P=0.04$) and TC/HDL-C ratio ($P<0.001$). TDI was also an independent factor affecting LDL ($P=0.02$) and TC/HDL-C ratio ($P=0.005$), and BMI SDS was an independent factor affecting TC/HDL-C ratio ($P=0.008$). **Conclusion:** There was a significant relationship between poor glycaemic control and higher TC levels and TC:HDL-C ratio. HbA1c was an independent factor affecting TC, TC:HDL-C, LDL and TG. Poor glycaemic control increases the risk of diabetes dyslipidaemia in CYP with T1DM.

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Abstract withdrawn.

P1-P246

Wolcott Rallison Syndrome due to a Novel Mutation in EIF2AK3 Gene

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Background: Wolcott Rallison syndrome is a rare autosomal recessive disorder, characterized by early onset diabetes, skeletal dysplasia and growth retardation. Fewer than 100 cases have been reported in literature. We report a case of Wolcott Rallison syndrome caused by a novel mutation. **Objective and hypotheses:** To report a novel mutation of EIF2AK3 gene, which has never been reported previously. **Method:** Blood sample of a suspected case of infantile diabetes, along with blood samples of both her parents were sent to Royal Devon & Exeter NHS foundation trust, England, for genetic studies. Sequence analysis of EIF2AK3 gene was done. Analysis of exons 1, 6, 7, 9, 11, 14, 16,

and 17 of the EIF2AK3 gene was done by Sanger sequencing. **Results:** Index case was found to be homozygous for a novel EIF2AK3 missense mutation, p.R1064Q. This mutation has never been reported previously, and in silico evidence suggests that it is likely to be pathogenic. Both of the parents were found to be heterozygotes for this same mutation. **Conclusion:** The results of genetic studies are consistent with the diagnosis of Wolcott Rallison syndrome.

P1-P247

Which is the Best Site for Catheter Placement in Young Children with Type 1 Diabetes (T1D) and CSII?

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Background: Few data exist for young children regarding the proper site for insulin catheter insertion for pump (CSII) users. **Objective and hypotheses:** To evaluate the proper site for catheter insertion in very young children (<8 year old) with T1D and CSII. **Method:** The study comprised 10 children [7 females, median age 4.43 years (range 2.3–7.18), median disease duration 1.65 years] with T1D who were on CSII. Ultrasound measurement of subcutaneous (SC) depth at different sites where insulin catheter was inserted was performed by a linear 9–15 Mz transducer. Distance from the end of insulin infusion after a bolus to muscular fascia was measured. Weight, height, BMI, waist and hip circumference, upper arm and thigh mid circumference diameter were measured. Skin folds at catheter insertion site were also taken. All children used the 6 mm catheter. **Results:** The buttock (mean $1.56 \pm$ S.D. 0.55 cm) and the side upper third of the thigh (SUTT) (mean $1.49 \pm$ S.D. 1.00 cm) were the sites with the deepest SC fat compared with the upper (mean $0.39 \pm$ S.D. 0.20 cm), the lower (mean $0.60 \pm$ S.D. 0.37 cm) abdomen, the front (mean $0.69 \pm$ S.D. 0.16 cm) and back side (mean $0.96 \pm$ S.D. 0.27 cm) of the arm [buttock vs upper ($P<0.0005$) vs lower abdomen ($P=0.002$) vs front of the arm ($P=0.006$) and SUTT vs upper ($P<0.0005$) vs lower ($P=0.010$) abdomen vs front of the arm ($P=0.024$)]. The distance from the end of insulin infusion to muscular fascia was significantly less in the abdomen compared with the buttock ($P=0.020$), reaching the muscular fascia in all children with the abdominal catheter. BMI, waist circumference and skin folds were not different between those with the distance of the bolus to fascia <0.5 cm vs >0.5 cm. **Conclusion:** In very young children with T1D and CSII the buttock and the SUTT are better sites for catheter placement compared with the abdomen and the arm.

P1-P248

GCK Mutations in Chinese MODY2 Patients: A Family Pedigree Report and Review of Chinese Literature

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Background: Maturity-onset diabetes of the young, type 2 (MODY2), caused by mutations in the glucokinase (GCK) gene is rare in a Chinese population. **Objective and hypotheses:** We report three Chinese families with MODY2 and sequenced the GCK gene to find novo mutation. **Method:** Three unrelated Chinese families with MODY2 and pedigrees were investigated. In Family 1, the proband was a 7-year-old girl with impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). Her mother and maternal grandfather had IFG. In Family 2, the proband was a boy who had diabetes mellitus at 11 years old. His sister had IFG. His father and grandmother had diabetes mellitus at 22 years old and 25 years old, respectively. In Family 3, the proband was a boy who had IFG and IGT at 12 years old. His sister had diabetes mellitus at eight years old. His father and grandfather had IFG and/or IGT. The GCK gene was directly sequenced. **Results:** Diabetes mellitus or IFG/IGT was found among three consecutive generations in three families. One novel nonsense heterozygous mutation in exon 5 (c.556 C>T, p.Arg 186 Stop) was detected in Family 1. Another novel frameshift mutation in exon 4 (c.367-374dupTTCGACTA, p.Ile 126 fs) was found in Family 2. A previously reported missense heterozygous mutation in exon 5 (c.571 C>T, p.Arg 191Trp) was detected in Family 3. **Conclusion:** A thorough investigation of the three Chinese families with MODY2 revealed two novel mutations and one known mutation. GCK gene sequencing helps in MODY2, especially when there is uncertain IFG or IGT.

P1-P249

Autoimmune Limbic Encephalitis Associated with Type 1 Diabetes Mellitus

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Background: Limbic encephalitis (LE) is a neurological disorder characterized with amnesia, seizures, personality changes.

LE is usually considered as paraneoplastic disorder. Infections, paraneoplastic disorders and autoimmunity should be considered in LE etiology. Association of type 1 diabetes mellitus and LE is very rare. Here in we report a patient who was diagnosed with type 1 diabetes mellitus (T1DM) six months after LE occurrence. **Case:** A 17-year-old boy was admitted to the emergency department with amnesia and personality changes. Laboratory tests of viral infections and autoantibodies were negative. Fluorine-18 fludeoxyglucose positron emission tomography and electroencephalography revealed findings of LE. Despite negative antibody results idiopathic LE was considered. Pulse steroid were administered during 5 days. After steroid treatment symptoms improved but hyperglycemia occurred on the third day of treatment. His glycemia level reached 502 mg/dl. Concurrent insulin level was 42 μIU/mL and C peptid level was 3.3 ng/ml. Insulin infusion was administered. Hyperglycemia improved after cessation of steroid treatment and he was considered as steroid induced hyperglycemia. After discharge he was lost to follow up. After 6 months he was diagnosed with LE he administered with dyspnea and abdominal pain in emergency department. Laboratory findings were as follows: serum glucose 386 mg/dL, arterial blood gas analysis (pH 7.1, HCO3 8.5 mmol/L), serum osmolality 285 mOsm/kg, glycated hemoglobin (HbA1c) 12.6%, insulin 1,8 (2.6-24.9) μIU/mL, C-peptide 0,3 (1.1-4.4) ng/mL, Islet cell antibody was positive, anti glutamic acid decarboxylase (anti-GAD) was $>$2000 IU/ml (0-10). He was diagnosed with type 1 diabetes. Patient's spinocerebral liquid analyses revealed high anti-GAD levels as etiology of LE. **Conclusion:** Type 1 diabetes mellitus and LE pathogenesis are similar because of anti GAD antibodies. LE are considered T1DM patient's neurologic and psychiatry symptoms occurrence.

P1-P250

Type 1 Diabetes (T1D) Management with Few Blood Glucose (BG) Measurements but Frequent Free Adjustment of Treatment with Cell Phones or E-mails

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Background: Many children with type 1 diabetes (T1D) are asked to measure blood glucose (BG) 4–6 times a day routinely to adjust insulin dosages. There is no evidence though that such high frequency is beneficial to HbA1C or glycemic profile, although this is often claimed. **Objectives:** We challenged 'the more BG measurements, the better control' dogma for alleviation of T1D burden in child life and evaluation of HbA1C. **Patients:** During 3 years, we studied 100 children (aged 5–15 years with T1D $>$6 months) with HbA1C $<$ 9% at entry and no selection based on socio-economic criteria. Users of insulin pumps were excluded. **Methods:** Patients were asked to measure 20 BG monthly, concentrated over a 10-day period chosen to be representative of usual child's life, including five measurements at four different times: 0730 h, 1200 h, 1630 h, 2130–2230 h, then get expert advice through phone calls or e-mail at the end of the 10-day period. Phone calls were handled by doctors (CB, ALC, PB) and specialized nurses (BA, PL). Patients were seen at outpatient visits every 3 months with HbA1c measurement and could give 'emergency calls' *ad libitum*. **Results:** Studied children measured 19$\pm$3 BG per month (instead of 120–180 with common recommendations). Advices were about insulin doses, place and timing of injections, diet, special events. Mean HbA1c was 7.7$\pm$0.3% (vs 7.8$\pm$0.3% at entry). 0.6$\pm$0.3 severe hypoglycaemia occurred per studied year (unchanged). Ketoacidosis was not observed. QoL of the parents and child was significantly improved. **Conclusion:** Multiplication of BG measurements is not synonymous of good control. Free, easy-to-reach, frequent expert guidance is more important.

P1-P251

Metabolic Impairments among Adult Survivors of Paediatric Abdominal and Pelvic Tumours in the St Jude Lifetime Cohort Study

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Background: Adverse changes in metabolic parameters and body composition are frequently reported among childhood cancer survivors treated with cranial or total body irradiation. Data regarding the occurrence of metabolic impairments among survivors following abdominal and pelvic radiation are lacking. **Objective and hypotheses:** To define the prevalence of metabolic impairments among survivors of paediatric abdominal and pelvic solid tumours and to assess the contribution of adverse body composition to metabolic impairments. **Method:** Participants included 347 10+ year survivors of abdominal or pelvic tumours who were $\geq$18 years of age at study. All participants underwent evaluation for insulin resistance (HOMO-IR $>$2.86), diabetes and dyslipidaemia (laboratory values and medication usage). Relative lean mass *Z*-score (LM) and percent whole body fat (%BF) were determined using dual X-ray absorptiometry. Poisson regression was used to evaluate associations between body composition and metabolic impairments. **Results:** The median age at evaluation was 29.9 (range: 18.7–55.1) years. The prevalence of insulin resistance, diabetes, and dyslipidaemia was 40.6, 7.0, and 50.6%, respectively. Overall, 44% of participants received abdominal/pelvic radiation. Radiation was associated with low LM among males (mean [S.D.]; irradiated, $-$1.16 [1.38], vs non-irradiated, $-$0.22 [1.03], $P<0.01$) and females (irradiated, $-$1.01 [1.40], vs non-irradiated $-$0.45 [1.23], $P<0.01$). After adjusting for chronological age and age at diagnosis, low LM was associated with an increased risk of insulin resistance among both males (relative risk [RR]=1.61, 95%CI=1.39–1.86) and females (RR =1.64, 95%CI=1.41–1.91). However, an association between dyslipidaemia and low LM was only observed in females (RR=1.23,

95%CI = 1.08–1.41). In multivariable models, %BF was associated with an increased risk of insulin resistance (males, RR = 1.08, 95%CI = 1.05–1.11; females, RR = 1.08, 95%CI = 1.04–1.11) and dyslipidaemia (males, RR = 1.04, 95%CI = 1.02–1.06; females, RR = 1.04, 95%CI = 1.02–1.07) among both males and females. **Conclusion:** Body composition influences metabolic health among solid tumour survivors. Interventions targeting LM and %BF may improve metabolic health in this population.

P1-P252

Clinical Case of a 10-year-old Girl with Papillomatosis Due to Severe Insulin Resistance Type A

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Background: Severe insulin resistant (IR) type A is a rare inherited disorder characterized by glucose metabolism disturbances without obesity, acanthosis nigricans and hyperandrogenia due to *INSR* defects. **Case report:** A 10-year-old girl was admitted because of skin papillomatosis and hyperpigmentations since her 7 years. She had early puberty with pubarche at 8 years and telarche at 9 years. Examination revealed normal height and weight (SDS BMI +0.49), acanthosis nigricans, clitoromegaly, no lipoatrophy, puberty stage Tanner P3B3. Laboratory tests revealed diabetes mellitus (2-hour glucose level was 11.4 mmol/l) with fasting low glucose levels (3.5 mmol/l), severe insulin resistance (hyperinsulinemic euglycemic clamp showed M-value 1.22 mg/kg/min) and hyperandrogenemism (testosterone 3.6 nmol/l, LH 3.3 U/l, FSH 4.1 U/l). Ovaries volume was 5 ml with multifollicular structure. Severe IR with signs of hyperandrogenism corresponded with *INSR* defects. Novel heterozygous p.E12228K mutation with uncertain pathogenicity in *INSR* was found. Patient's father with the same mutation had multiple papillomas but normal glucose and insulin levels. Treatment with Metformin 2000 mg/day was started. After 3 months 2-hours glucose level normalized (5.7 nmol/l), the level of IR decreased (M-value 2.11 mg/kg/min). The level of testosterone remained elevated (4.89 nmol/l) and volumes of ovaries increased (11.2 and 9.1 ml). **Conclusion:** Patients with acanthosis nigricans and papillomatosis should be investigated for IR. Severe IR is associated with signs of hyperandrogenia. Absence of IR in parent with the same mutation can be possibly explained by the penetrance. In our case of type A IR metformin normalized glucose metabolism but did not treat hyperandrogenism.

P1-P253

Sulphonylurea Treatment in a Patient with Intermediate DEND Syndrome

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Background: DEND syndrome is characterized by developmental delay, epilepsy, and neonatal diabetes mellitus (NDM) due to mutations in *KCNJ11* and *ABCC8* genes. Intermediate DEND (iDEND) syndrome is a rare mild form with mild motor, speech or cognitive delay and an absence of epilepsy. Improvement in glycemic control and neurologic symptoms has been reported in three cases with iDEND syndrome. **Objective and hypotheses:** To present the results of sulphonylurea therapy in a 17-year-old girl with iDEND syndrome. **Method:** The patient was diagnosed with NDM at the age of two months. Her motor and cognitive development was delayed (IQ score: 49) and she was diagnosed with attention deficit and hyperactivity disorder. There was no history of epilepsy. She was on insulin therapy at a dose of 1.2 U/kg/day. Random C peptid level was <0.1 ng/ml, diabetes auto-antibodies were negative and HbA1c was 10.9%. There was no history of severe hypoglycemic attacks to explain her mental retardation. **Results:** Genetic analysis revealed a heterozygous missense mutation in the *KCJN11* gene (p.V59M). Glibenclamide was started at a dose of 0.1 mg/kg/day and the dose was increased gradually up to 1.3 mg/kg/day. After glibenclamide, HbA1c level (10.9–8%) and daily insulin requirement (1.2–0.9 U/kg/day) were reduced and C-peptide level (<0.1–0.68 ng/ml) was increased. However, insulin could not be weaned-off and no clinically significant improvement in the patient's cognitive functions was observed. **Conclusion:** Previously, sulphonylurea treatment has been reported to improve neurologic symtomps in iDEND sndrome. In our case, although glycemic control was improved and daily insulin requirement was decreased, there was no clinically significant improvement in cognitive functions possibly due to late diagnosis. DEND syndrome should be considered in NDM patients with neurological findings and sulphonylurea should be started as soon as possible.

P1-P254

A Case-Control Search of Environmental (E) Factors for Childhood Type 1 Diabetes (T1D) Using Lifeline Questionnaires in the ISIS-Diab Cohort

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Background: The rapidly increasing T1D incidence in European children suggests the recent emergence or extension of predisposing E factors, or the decrease of protective E factors acting during pregnancy, infancy or early childhood. E research has preferentially focused on specific candidate factors, such as hygiene hypothesis, enteroviruses, alimentation, in cohort or case-control studies. The risk of bias is a major concern in E studies.

Objectives: To compare retrospectively T1D and controls for markers of E exposures recalled from the period preceding diagnosis. **Method:** ISIS-Diab is a large multicenter cohort of T1D children, who were asked to find controls among their healthy friends. An original 846-item questionnaire was first designed to characterize pregnancy, infancy and childhood E makers. Analyses were done using two complementary methods i) matching 428 patients and 567 controls with Cochran–Mantel–Haenszel (CMH) (binary responses) or conditional logistic regression (ordinal responses) and ii) propensity score method (out-of-bag estimate of the random forest, stratification, then CMH test between the question of interest and disease status) to control for bias in 1127 patients and 642 controls. **Results:** Strong associations for both categories of analyses were found. Their relationship with outdoor activities, dental hygiene, specific nutrients, infectious events will be discussed. **Conclusion:** This study opens a few original directions for E research in T1D.

P1-P255

Transient Neonatal Diabetes Mellitus in Hanoi, Vietnam: Clinical Feature and Outcome

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Background: Transient neonatal diabetes mellitus (TNDM) is a rare form of diabetes mellitus that presents within the first 6 months of life with remission in infancy or early childhood. TNDM is mainly caused by anomalies in the imprinted region on chromosome 6q24; however, recently, mutations in the *ABCC8* gene, which encodes sulfonylurea receptor 1, have also been implicated in TNDM. **Objective and hypotheses:** To describe clinical features and laboratory manifestations of patient with TNDM and evaluate outcome of management. **Method:** Clinical features, biochemical finding, mutation analysis and management outcome of five cases from five 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 would be done to detect the loss of methylated region on chromosome 6q24. **Results:** Five cases (two girls and three boys) onset at 19.5 ± 11.8 days of age with gestation age of 38.6 ± 2.6 weeks, birth weight of 2440 ± 512 g (three cases has BW $<$ 3 percentile). Two out of five cases admitted with the feature of diabetic ketoacidosis. The investigation showed pH of 7.14 ± 0.2, HCO_3^- of 12.17 ± 10.4 mmol/l, blood glucose of 36.6 ± 10.9 mmol/l, HbA1C of $7.02 \pm 0.96\%$. Methylation-specific PCR showed: one case with heterozygous for two difference mutation 7450delT and 7812C$>$CT, one case with three heterozygous mutations of the ZFP57 gene: a frameshift and premature termination in this coding region (398delT:L133HfsX49), and two further heterozygous mutations in this region (499C$>$CT:167R$>$RC and 760C$>$CT:254L$>$LF); one case with maternal hypomethylation at TND (6q24), IGF2R (6q27), SNRPN (5q11) and GRB10 (7q12) loci; one case with maternal hypomethylation at the GRB10 and PEG3 loci, characteristic of mutations in *ZFP57;* one case with heterozygous for *ABCC8* missense mutation, p.R1183W. During of treatment and follow up: four out of five patients stopped insulin after 5–6 months of treatment. Among them, one case had been treated with insulin for a long time and recovered by 18 months of age. Currently, the patients are 51.6 ± 28.9 months old and are euglycemic and normal HbA1C without any insulin or oral hypoglycemic agents. Now four cases have normal development, one case has mild development delay. **Conclusion:** It is important to perform screening gene mutation for patients with diabetes diagnosed before 6 months of age to control blood glucose and follow up the patients.

P1-P256

The Incidence of Type 1 Diabetes in the Pediatric Population in Pomeranian Region in Poland

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Background: It is observed from nearly 50 years that the incidence of diabetes worldwide is increasing. Also the incidence of type 1 diabetes, which is most common in paediatric population, rises across Europe. **Objective and hypotheses:** The aim of the study was to analyze the incidence of type 1 diabetes in Poland in Pomeranian province in the years 2005, 2010 and 2015. The hypothesis was an increased incidence of type 1 diabetes. **Method:** Data from the years 2005, 2010 and 2015 was analysed and the number of new cases of diabetes diagnosed in children in Pomerania was calculated. **Results:** In 2005, type 1 diabetes was diagnosed in 67, in 2010 in 85 and in 2015 in 115 children. In the age group 0–4 years – 13 cases of diabetes were diagnosed in 2005 and accordingly 25 in 2010 and 17 in 2015. In the group aged 5–9 years – 22 cases in 2005, 24 cases in 2010 and 49 cases in 2015 were diagnosed. In group aged 10–14 years the overall number of new diagnoses in the years 2005, 2010 and 2015 were 25, 29 and 33, respectively. In the group aged 15–18 years in 2005 – seven cases were reported, in 2010 also seven cases of diabetes, and in 2015 – 15. In the group aged 0–14 years, the incidence of diabetes has changed from 15.8/100 000 in 2005 and 21/100 000 in 2010 to 26.6/100 000 in 2015. The highest increase in incidence was reported in group aged 5–9 years from 11.4/100 000 in 2005 and 21/100 000 in 2010 to 36.8/100 000 in 2015. **Conclusion:** The incidence of type 1 diabetes increased in the last 10 years in Pomeranian Province in Poland. The increase was noted particularly in the group aged 5–9 years old.

P1-P257

Health-Related Quality of Life and its Associated Factors in Children With Type 1 Diabetes Mellitus

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Objective: To assess health-related quality of life (HRQOL) in a cohort of children and adolescents with type 1 Diabetes (T1DM) and its associated factors. **Methods:** This was a descriptive study of 136 patients with T1DM from five hospitals in Catalonia, Spain (72 girls, mean age 13.4 years (range 8–19). Inclusion criteria were more than 6 months from diagnosis, more than 8 years old and without cognitive problems. Sociodemographic (age, sex, family level of education, type of family and origin) and clinical variables (type of insulin therapy, duration of disease, adherence to treatment, BMI and HbA1c) were collected. HRQOL was assessed using the EuroQol-5D (EQ-5D-Y) and KIDSCREEN, collected via web. Mental health status was assessed using the Strengths and Difficulties Questionnaire. **Results:** Physical-well-being mean scores were lower (worse) than the European average (<50) and especially in girls, older children (>11 years old), those from single-parent families, and those with low adherence. Older children and patients with poor metabolic control (HbA1c $>7.5\%$ (58 mmol/mol)) showed worse scores in the KIDSCREEN-10 index. Similar results were observed with the EQ-5D-Y. HRQOL showed negative correlation with age, HbA1c, and mental health. Multivariate models showed that age, single-parent families, adherence and mental health were the most influential factors. **Conclusions:** Diabetic patients report similar HRQOL than the population of the same age with slightly worse physical well-being. The study shows some factors to be taken into account to improve HRQOL, and also the feasibility of using web to collect information in clinical practice.

P1-P258

Possible Monogenic Diabetes Mellitus Including Mody is Highly Prevalent in Korean Children with Diabetes Mellitus

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Background: As the human genome is further explored, multiple genetic anomalies at different loci are being found that confer varying degrees of predisposition to diabetes. MODY is the most common form of monogenic diabetes, accounting 2–5 percent of diabetes. Recently, we have found and reported three noble gene variants relating to MODY in Korean children (Shim et al, Horm Res Pediatr, 2015). **Objective and hypotheses:** This study was done to see the frequency of possible monogenic diabetes in Korean children with diabetes mellitus and their clinical and laboratory characteristics. **Method:** Study patients consisted of 126 children with diabete mellitus (DM) who visited our institute between 2008 and 2015. Their medical records were reviewed retrospectively. They classified into three groups; type I (T1DM), type II (T2DM) and monogenic diabetes mellitus (MDM) including MODY by the ADA classification of DM. Various clinical and laboratory data was analyzed. **Results:** The frequencies were 48 (38%) in T1DM, 42 (33%) in T2DM, and 36 (29%) in possible MDM. Majority of possible MDM was MODY (22 out of 36, 61%). Ages (years) at diagnosis were 9.2 ± 4.1 in T1DM, 13.4 ± 2.4 in T2DM, and 12.3 ± 3.1 in MDM. The age at diagnosis was significantly older in T2DM compared to T1DM ($P=0.000$). BMI (kg/m^2) was significantly higher in T2DM compared to T1DM or MDM, 25.9 ± 4.7 vs 16.9 ± 5.1 vs 19.7 ± 5.1, respectively ($P=0.001$). Initial fasting insulin levels (IU/ml) were significantly higher in T2DM than T1DM or MDM, 13.01 ± 9.45 vs 2.10 ± 2.68 vs 4.85 ± 5.25, respectively ($P=0.000$). C-peptide levels (ng/ml) were significantly higher in T2DM compared to T1DM or MDM, 3.19 ± 1.40 vs 0.29 ± 0.15 vs 1.17 ± 0.39, respectively ($P=0.000$). HbA1c levels (%) were significantly higher in T1DM compared to T2DM, 13.31 ± 3.09 vs 11.22 ± 2.40, respectively ($P=0.001$). **Conclusions:** It appears that possible monogenic diabetes including MODY in Korean children with DM is more prevalent than expected. Further large scaled studies including genes related to monogenic DM are necessary.

P1-P259

Phenotype and Clinical Course of Diabetes Mellitus in Individuals with Pancreatic Hypoplasia Due to a PTFA Enhancer Mutation

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Background: Recently PTF1A enhancer mutations have been described in subjects with early-onset exocrine and endocrine pancreas insufficiency. **Objective:** To describe the clinical course in three children with PTF1A enhancer mutations, in particular anthropometric development, insulin requirement and diabetes control. **Method:** Retrospective analysis of growth, weight and BMI development as well as insulin requirement and HbA1c level in three children with mutations in the PTF1A enhancer. **Result:** We report on three female siblings with a PTF1A enhancer mutation (g.23508437A>G), born to consanguineous parents. Age at onset of diabetes was at birth, at 10.6 and 7 years; all exhibited pancreas hypoplasia leading to pancreatic exocrine insufficiency, requiring pancreatic enzyme substitution. Islet cell,

insulin, GAD and IA2 antibodies were negative in all. However, transglutaminase antibodies were detected in one sibling; duodenal biopsy confirmed a diagnosis of celiac disease. Regarding anthropometry, birth parameters were as follows: BW-SDS: −3.09, −1.87 and −1.92, BL-SDS: −4.0, −0.17 and −1.77; current height at 10.5, 11.8 and 18.5 years: 146.8 cm (+0.37 SDS), 167.7 cm (+1.91 SDS), 165.7 cm (−0.38), corresponding BMI: 15.1 kg/m^2 (−1.03), 18 kg/m^2 (−0.06), 18.9 kg/m^2 (−1.00). Insulin therapy was started at diagnosis of IDDM. Average HbA1c levels for the last 24 months were at a current age of 10.5, 11.8 and 18.5 years 7.8%, 8.0% and 8.9% respectively, with a most recent requirement of insulin 0.5, 0.32 and 0.7 IU/kg body weight. Current pancreatic enzyme substitution therapy consists of pancreatin 2000–3000 IU/g fat per day. **Conclusion:** Subjects with PTF1A mutations seem to exhibit adequate anthropometric development and acceptable diabetes control under insulin and pancreatic enzyme substitution. Despite a non-immune etiology of IDDM, patients should be monitored for additional autoimmune disorders such as celiac disease, which can complicate the clinical course and affect diabetes control.

P1-P260

Microalbuminuria in Type 1 Diabetes – Audit of Management of Children and Adolescents in a Single Diabetes Centre

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Background: There are international guidelines on screening for Microalbuminuria (MA) in children with Type1 Diabetes Mellitus (T1DM). But the National Paediatric Diabetic Audit, UK suggests that screening is missed in over 50% of cases. Further, there is little data on the management and natural course of MA in children by frontline units. **Objective and hypotheses:** To describe the prevalence, management and natural course of MA in children and adolescents with T1DM. **Method:** All patients with T1DM noted to have MA between April 2013 and April 2015 were included in the study. Data on demographic factors and laboratory results at onset of MA and during the study period was collected retrospectively from electronic records and databases. MA was diagnosed by ACR >3 mg/mol on a random urine sample. **Results:** 18 out of 185(9.3%) children with T1DM were noted to have MA during the study period. Median age of presentation with MA was13.6 years (5.0–18.0). Mean duration from diagnosis of TIDM to MA was 5.9years (0.8–15.6) with nine patients (50%) presenting within 5 years.39% of the patients presented with MA under the age of 12 years. Mean duration of follow up of MA was 3.6 years. ACR normalised in 9 (50%) at a mean follow up of 4.3 years, was intermittent in 3 (16.7%) and persisted in 5 (27.8%). Frequency of retesting varied between 4 months to 3 years. The mean HbA1C was 81 mmol/mol (32.2–171), but one third achieved an HbA1C <58.5 mmol/mol. No one developed macroalbuminuria, or required treatment. The one child referred to the nephrologist was diagnosed to have orthostatic proteinuria. **Conclusion:** A significant proportion of patients presented with MA outside recommended screening criteria (>12 years and >5 years duration). A significant proportion also had good glycaemic control. MA either resolved or was non-progressive in the vast majority of patients.

P1-P261

Johansson-Blizzard Syndrome with Pan-hypopituitrism, Type 2 Diabetes and Pancreatic insufficiency: Effect of Treatment

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Background: Johanson-Blizzard syndrome (JBS) is a disease characterized by poor growth, variable dysmorphic features, including aplasia or hypoplasia of the nasal alae, sensori-neural deafness, abnormal hair patterns or scalp defects, and oligodontia. Other features of JBS include pan-hypopituitarism, imperforate anus, and PI. Pancreatic endocrine insufficiency (PI). **Case study:** AM is a 10 years-old boy, born at term with aplasia of the alae nasi and congenital sensori-neural deafness, severe prenatal growth retardation and mental retardation. He presented at the age of 1.5 year with severe post-natal growth retardation and PI. He was started on Pancrex. Endocrine tests showed low TSH and FT_4 and cortisol deficiency. He was started on L-thyroxine and hydrocortisone. In spite of his weight gain his linear growth was slow. At 2 years his peak GH responses to glucagon and clonidine stimulation tests were 3 and 5 ng/ml respectively with low IGF-I. MRI head showed hypoplastic pituitary gland. GH therapy was started and at that time he was dignosed genetiaclly with JBS. At 7 years he attained complete catch up growth (Height at 50th centile for age) At 10 years of age his random blood glucose (RBS) was noticed to be abnormal 8.5 mmol/l. OGTT showed fasting hyperglycemia and post prandial hyperglycemia (Table 1) he did not have acanthosis or goiter and the other systemic examination showed no new findings. He was prepubertal. Oral glucose tolerance test with insulin measurement showed hyperglycemia and high insulin secretion (insulin resistance). The diagnosis of Type 2 DM was given. Oral metformin 500 mg twice daily was prescribed with excellent response to the treatment (table). After a year on treatment his HbA1C=5.9%. **Discussion:** DM is a rare complication of JBS with only three cases reported in the literature, two of which had history of pancreatic exocrine insufficiency and found to have insulin deficiency. The third case had DM with insulin resistance without pancreatic exocrine insufficiency. This is the first case with pan-hypopituitarism, type 2 DM in a pancreatic insufficient JBS patient. **Summary:** In this patient with JBS and type 2 DM glycemic control was successfully achieved with oral Metformin.

Table 1.

	Fasting	2 h prandial
Glucose (mmol/L)	7.1	17.4
Insulin (μunit/ml)	19	48
Cpeptide (ng/ml)	3	5.88

P2-P262

Comparison of the Occurrence of Islet Autoantibodies in Siblings of Patients with Type 1 Diabetes Mellitus to Healthy Children

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Objective and hypotheses: The aim of the study is comparison of the occurrence of islet autoantibodies in healthy siblings of children with T1DM to healthy children from non-diabetic families. **Method:** Determination of anti-decarboxylase of the glutamic acid antibodies (anti GAD-Ab), anti-protein tyrosine phosphatase (anti IA2), and antibodies against zinc transporter eight (anti ZnT8) in 75 children with T1DM, their siblings – 105, and 77 healthy children. All antibodies were determined by ELISA. The results were analyzed with the May-Whitney Wilcoxon test. **Results:** The highest level of anti-GAD (median 28.2 IU/ml), anti IA2 (median 26.19 IU/ml), and anti ZnT8 (median 94.73 IU/ml) was noted in children with T1DM and significantly lower levels were noticed in their siblings (median: anti GAD 2.61 IU/ml, anti IA2 3.53 IU/ml, anti ZnT8 5.14 IU/ml). This level of anti-GAD was statistically significant higher in comparison to the control group of healthy children (anti-GAD 0.21 IU/ml). The levels of anti IA2 antibodies and anti ZnT8 Ab were similar to that in the control group. In two children from the siblings, elevated levels of all antibodies were observed, in two siblings, elevation of anti-GAD and anti-ZnT8 Ab was noticed, and in 18 siblings only ZnT8 Ab was increased. Only in three healthy children an increase in ZnT8 Ab was observed and no increased anti-GAD or anti IA2 were observed in any healthy child. **Conclusion:** The anti-GAD antibody is most characteristic in siblings of T1DM patients, especially in children with two or three autoantibodies predisposed to development of T1DM.

P2-P263

The Role of 24-h Ambulatory Blood Pressure Monitoring in Children and Adolescents with Type 1 Diabetes: Early Experience of a Single Centre

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Background: Ambulatory blood pressure monitoring (ABPM) permits the observation of blood pressure (BP) in a nonmedical environment. In adults, ABPM is better related to renal damage and cardiovascular morbidity than office BP readings. In early stages of type 1 diabetes (T1DM), the role of ABPM is still controversial. **Objective and hypotheses:** To detect blood pressure abnormalities using 24-h ABPM in children and adolescents with T1DM and to determine their relation with anthropometric features, renal function and metabolic control. **Methods:** We enrolled 34 children and adolescents (13.32 ± 2.56 years old, 19 males) with T1DM. We collected in all subjects: anthropometric (BMI-SDS) and metabolic data (HBA1c (%), serum lipids and vitamin D levels (ng/ml)), renal function parameters (albumin/creatinine ratio and glomerular filtration), BP during routine visit and 24-h ABPM. A patient was defined as hypertensive when BP was above 95°centile according to age, gender and height centile during a routine visit (definition A) or when, along ABPM, systolic BP was above 95°centile in more than 25% of 24 h (definition B). **Results:** According to definition A, 23.5% of our patients would be classified as hypertensive, while, using ABPM, this prevalence increased to 56%. In hypertensive group (definition B), the duration of T1DM was longer than in normotensive (7.57 ± 3.20 vs. 5.46 ± 1.76 years, P 0.02) but no other differences in anthropometric and metabolic features were documented apart from higher levels of vitamin D in normotensive patients (14.08 ± 7.45 vs. 20.82 ± 6.57 ng/ml, P 0.01). Only four patients did not present the phenomena of dipping (2/4 classified as hypertensive). Considering the whole population, mean systolic and diastolic BP (mmHg/24 h) correlated with BMI-SDS (r 0.38, P 0.02) and vitamin D levels (r −0.37, P 0.04), respectively. No correlations with renal function parameters were found. **Conclusions:** Observations show a high prevalence of hypertension in our cohort of children and adolescents with T1DM, but a clear link between metabolic control, renal function and BP regulation is not supported.

P2-P264

Clinical, Biochemical, Genetic and Immunological Features of Mexican Recent-Onset Type 1 Diabetes Patients

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Background: The pathogenesis of type 1 diabetes (T1D) is multifactorial, caused by interaction of genetic, epigenetic and environmental factors that lead to the production of antibodies early on life and a gradual loss of insulin secretory capacity of the pancreas. The genetics and immunological characteristics of our T1D population have not been precisely identified. **Objective and hypotheses:** To compare biochemical, genetic and immunological features of patients with recent-onset T1D against their first-degree relatives. **Method:** Design: cross-sectional analytical. Material: T1D patients with disease onset <3 months and first-degree relatives. Methods: Anthropometry was registered. HbA1c, glucose, lipid profile, C peptide, GAD and IA2 antibodies, and class II HLA haplotypes were determined. Statistical analysis with Student t, Mann-Whitney U, ANOVA or Kruskal-Wallis test.

Results: There were 23 patients, 56.5% ($n=13$) women; 23 mothers, 21 fathers; and 32 siblings. The mean age of the patients was 9.3 ± 3.6 years, 45.2 ± 20.6 days from the onset of diabetes. 27.3% ($n=12$) of parents and 3.1% ($n=1$) of the siblings had the metabolic syndrome. 56.6% ($n=13$) of patients, 4.5% ($n=2$) of parents and 6.3% ($n=2$) of the siblings had positive anti-GAD antibodies; 78.2% ($n=18$) of patients, 45.5% ($n=20$) of parents and 31.3% ($n=10$) of the siblings had anti-IA2. 82.6% ($n=16$) patients, 75% ($n=33$) of parents and 87.5% ($n=28$) of the siblings showed haplotype DR4/DQ8. DR5 haplotype/DQ6 appeared in 19.6% ($n=11$) of patients, 31.8% ($n=14$) of parents and 46.9% ($n=15$) of the siblings. **Conclusion:** Our findings suggest that in Mexican pediatric population, T1D has a predominant presence of IA2 rather than GAD antibodies; also first-degree relatives show a high proportion of antibody positivity especially for IA2 antibody.

P2-P265

Efficacy and Safety of Continuous Subcutaneous Insulin Infusion Treatment in Pre-schoolers. Long Term Experience of a Tertiary Care Centre in Spain

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Background: There is limited knowledge in children younger than 6 years of age about the safety and efficacy of CSII treatment during long periods of time. **Objective and hypotheses:** Evaluate the efficacy and safety of CSII treatment in pre-schoolers with T1D, assess if ISPAD/ADA criteria for good metabolic control are achieved and define general and specific characteristics of the treatment in this range of age. **Method:** Charts of patients younger than 6 who started CSII treatment between 2003 and 2014 were reviewed. The cohort consisted of 27 patients (age 4 (2.9–4.7) years, 56% males). Age at start, T1D duration, HBA1c (HPLC, Menarini, normal value $5.1 \pm 0.31\%$), insulin dose, number of capillary blood glucose measurements (CBG), number of basal rates (BR) per day, % basal/total insulin (B/TI), insulin ratios at different meals, severe hypoglycaemia (SH episodes/100 patients years), DKA events, percentages of normoglycaemia (70–180 mg/dl) and hypoglycaemia (<70 mg/dl) (N/H%), average glycemia and SD (GLSD) were analysed. Statistical analysis was performed by SPSS. **Results:** HbA1c decreased to 6.8% in the first year. Afterwards, it remained under 6.8% during the follow-up (median 5 (3–6), range 1–9 years). Prior to CSII, 74% of children met ISPAD criteria. At one year, 96% had HbA1c $<7.5\%$. CBG median per day was 10 (9–11). Total insulin dose did not change significantly. There was 1 episode of DKA and 1 episode of SH. Insulin needs at breakfast were higher (first year 0.92 vs 0.55, 0.6 and 0.5). **Conclusion:** CSII is effective and safe in pre-schoolers. It allows to achieve and maintain good metabolic control (based on ISPAD/ADA criteria) during long periods of time without increasing adverse effects.

P2-P266

Gene-Environment (GxE) Interactions in Childhood Type 1 Diabetes (T1D): A Case-only Geographical Approach in the ISIS-Diab Cohort

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Background: T1D concordance in MZ twins being $\sim 40\%$, non-heritable factors play a major causal role in this autoimmune disease. T1D has recently increased in young European children. Collecting prospective environmental data in a cohort of millions children-years starting soon after birth seems unpracticable. Retrospective case–control studies are an alternative, provided biased controls and recall bias can both be avoided. **Objectives:** To develop a 'virtual control' (VC) geographical approach to unravel environmental factors significantly associated with T1D. **Methods:** Four dimensions of environmental exposures were tested by mapping socioeconomic, infectious, climatic and land cover databases at the geolocalized address of the child before T1D diagnosis. Levels of exposures were compared between T1D patients and age-matched geographic VCs. A test was considered significant (**) when the median p value computed over 100 comparisons of cases with 100 sets of VCs was below the Bonferroni limit, and indicative (*) of a possible difference when it was <0.05. **Patients:** 3548 children (age-at-onset 7.2 ± 3.7 years) with diagnosis after 1984. **Results:** The socioeconomic and land cover environment of T1D children was comparable to controls. The T1D children showed a greater past exposure to influenza (**) and acute diarrheas (*) and a lower past exposure to varicella (*). T1D children were more frequently exposed to heatwaves (**). **Conclusion:** Our exploratory approach with four databases provides a proof-of-concept to space-time environment associations studies. Environmental markers (not causes) of T1D can be

Table 1. (for abstract P2-P265)

	Prior n=27	**1y** n=27	**2y** n=24	**3y** n=20	**4y** n=17	**5y** n=13
HbA1c	6.9 (6.7–7.5)	6.8 (6.4–7.1)*	6.6 (6.3–7)*	6.7 (6.2–6.9)*	6.6 (6.2–7.1)*	6.7 (6.2–7.1)*
(B/TI)	40 (36–50)	29 (24–42)*	34 (29–44)	39 (27–46)	37 (30–45)	34 (27–47)
N/H%	48/9	54/11	55/9	52/11	56/10	58/9
BR		7 (6–8)	7.5 (6–8)	8 (7–9)	7 (7–8)	6.5 (5–7)

*$P<0.05$.

found. By using more databases, a larger part of a child's environment can be covered.

P2-P267

NBAS Mutations, a New Monogenic Cause of DISOPHAL, a New Syndrome with Type 1 Diabetes (T1D)

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Background: While non-autoimmune T1D is rare in late childhood, few monogenic causes have yet been identified. **Objective:** i) to identify the genetic basis of the yet unreported disease phenotype associating late childhood antibody-negative T1D, short stature, optic atrophy (OA), Pelger-Huët anomaly (PHA) of leukocytes and recurrent liver cytolysis: the 'DISOPHAL' syndrome; ii) to attract comparable cases for further genetic investigation. **Method:** Whole-exome sequencing combined with genetic mapping of disease loci. **Results:** Compound heterozygous mutations of neuroblastoma amplified sequence (NBAS) were found in three siblings of the same African family who had late childhood antibody-negative insulin-requiring T1D associated with dwarfism, OA, PHA and recurrent episodes of liver cytolysis. **Conclusion:** NBAS is a new gene associated with non-autoimmune T1D. NBAS mutations have been reported before in non-diabetic patients with dwarfism, OA and PHA ('SOPH' syndrome) or a separate disorder of recurrent liver failure ('RALF' syndrome). NBAS mutations can induce a wide and heterogeneous clinical spectrum, which showed its complete form in our patients.

P2-P268

A Patient with a Rare Monogenic Diabetes Syndrome

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Aim: To delineate the diagnosis in a case of antibody negative infantile onset diabetes with deranged liver function. **Case Report:** A female child, first born of consanguineous couple presented with Diabeteic Keto Acidosis and acute liver failure at 9 months of age. She has been treated as a case of Type I diabetes and was discharged on insulin. Child was further evaluated at our center at 11 months of age. On examination, she had a normal anthropometry and few dysmorphic features namely depressed nasal bridge, tented upperlip, tapering fingers and clinodactyly. Her glycemic indices were high, liver enzymes remained elevated, had mild hepatomegaly and repeated anti GAD antibody were negative ruling out auto immune diabetes. Infective and metabolic causes of hepatitis were ruled out and she had a normal function with respect to Hypothalamo–Pituitary axis. In view of the Arab ethnicity, consanguinity, dysmorphic features and presentation of antibody negative infantile diabetes with hepatic involvement, a possibility of Wolcott-Rallison Syndrome (WRS) was considered. This was confirmed with EIF2AK3 gene analysis which revealed a homozygous mutation in exon 9 (c. 1635_1638delGAAA) **Discussion and conclusion:** WRS is a rare autosomal recessive disease, characterized by neonatal/early-onset non-autoimmune insulin-requiring diabetes associated with skeletal dysplasia and liver dysfunction. This is now recognised as the most frequent cause of PNDM in areas of high consanguinity. Because of the high clinical variability, syndrome often goes unrecognized leading to delayed diagnosis and early death. Given the high morbidity and mortality associated, early identification of the disease is crucial in clinical management and prenatal diagnosis.

P2-P269

Which Group of Children Achieved the Best Results During Insulin Pump Therapy – Long-term Outcome in Children with Type 1 Diabetes?

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Background: CSII has some potential advantages and disadvantages for young children. For many young patients, it is easier and more convenient to take multiple daily doses of insulin with CSII than with a syringe or insulin pen. **Objective and hypotheses:** The growing popularity of type 1 diabetes (DM1) treatment based on continuous subcutaneous insulin infusion (CSII) raises a question of the group of patients that benefit most from the treatment. **Method:** Clinical observation was carried out in 285 1-18-year-old patients diagnosed with DM1 treated with CSII. Every 3 months, HbA1c was determined by an agglutination inhibition immunoassay. The patients were followed for 6–10 years. **Results:** The greatest benefits from the treatment with CSII using an insulin pump were noted in type 1 diabetes children aged 1–5: the mean HbA1c decreased in these patients from 7.98% to 6.75% ($P < 0.01$) over 6 years. Slightly lesser outcomes were noted in the group of 6–10-year olds: the mean HbA1c value increased slightly from 7.6% before the CSII to 7.89% after 6 years of treatment ($P > 0.01$). Somewhat worse outcomes were reported in the group of 11–15-year-old children: HbA1c increased from 8.05% to 8.72% ($P > 0.01$). The lowest outcomes were found in the group of the 16–19-year-old patients, as HbA1c rose from 7.8% to 8.82% ($P < 0.01$) over 6 years. The children receiving the CSII treatment as early as in the first year of treatment exhibited better diabetes control (HbA1c 8.1% declined after 6 years to do 7.1%, $P < 0.01$) than patients who received CSII at an older age (HbA1c increased from 7.92% to 8.2%, $P < 0.01$). **Conclusion:** The CSII on offers the greatest benefits for patients aged 1–5 and those with the treatment commenced in the first year after diagnosis of type 1 diabetes. The best results this group of children achieved 6 or more years after start of the pump therapy.

P2-P270

Seasonality of Type 1 Diabetes in Children and Adolescents According to Date of Diagnosis and Date of Birth in a Large Diabetes Centre

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Background: There are studies supporting the seasonality of diabetes according to date of diagnosis and date of birth, with most T1D children being diagnosed in fall and winter and most of them been born in the same period. That is in concordance with previously published data from 1978 to 2008 in our country. **Objective and hypotheses:** To assess whether there is a seasonal variation of diabetes onset according to date of diagnosis and date of birth of incident cases, in a large cohort of newly diagnosed T1D children aged 0–16 y, between 2010 and 2015. **Method:** We retrospectively collected data of 256 children and adolescents (121 females) aged 0–16 years (mean age 8.4 ± 4.07 years) admitted in our clinic with newly diagnosed T1D between 2010 and 2015. We investigated whether there was a seasonality of diabetes onset according to date of diagnosis and date of birth of the patients. **Results:** In our cohort there was a significant prevalence of children aged > 5 years (92, 36.7% for the age group 5–10 years and 92, 36.7% for the age group 10–15 years) comparing to those < 5 years (61, 24.3%), (*P*: 0.036). According to date of diagnosis there was no statistically significant seasonal variation of diabetes onset (*P*: 0.625). However, according to date of birth, there was a statistically significant difference between children born in fall (81 children, 31.6%) than those born in spring (56, 21.9%) and winter (57, 22.3%), respectively (*P*: 0.037). **Conclusion:** In our cohort of newly diagnosed T1D children and adolescents there was no apparent seasonal variation according to date of diagnosis-probably due to the mild temperature variations through the year in Mediterranean countries. However, there was a significantly higher percentage of T1D children born in fall than in winter and spring respectively.

P2-P271

Abnormal Glucose Level in Patients with Thalassemia Major

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Background: Abnormalities in glucose homeostasis are fairly common complications in thalassemia major (TM) patients. This study aimed at determining the incidence of diabetes mellitus (DM) and studying the potential factors responsible for secondary DM of TM patients. **Objective and hypotheses:** A total of 54 (33 male) transfusion-dependent TM patients were in the 'TM group '; 25 age- and gender-matched healthy children were recruited as the 'control group'. **Method:** The height, weight, fast blood glucose (FBG) and insulin level, serum ferritin (SF), superoxide dismutase (SOD) and ultrasensitive C-reactive protein (hsCRP) were evaluated in all subjects. Insulin resistance index (IRI) and β cell function index (BFI) were also estimated. **Results:** The mean age was 10.35 ± 4.3 years. The SF level of the TM group was 3302.3 ± 2431.4 ng/ml. The TM group had significantly higher levels of FBG and IRI than the control group ($P = 0.018$, $P = 0.022$ respectively). There were no statistical differences in insulin level and BFI between two groups. None of the control group had impaired fast glucose or DM. In TM group, the prevalence was 18.5 and 3.7% respectively ($P = 0.014$). The incidence of abnormal glucose occurred since age five and increased obviously after age ten ($P = 0.029$). The incidence of abnormal glucose patients were higher with SF ≧2500 ng/ml than those whose SF were less than 2500 ng/ml ($P = 0.038$). The TM had significantly higher levels of SOD and hsCRP than the control. The level of SOD was well correlated with IRI and BFI. **Conclusion:** Insulin resistance happened earlier than abnormal glucose level in TM patients. Age and the degree of iron overload were closely associated with the morbidities. The glucose metabolism should be followed up regularly after age five in TM patients. The free radical content may induce the morbidities.

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A Case Report of Wolfram Syndrome due to a Novel Homozygous Mutation in *WFS1* Gene

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Introduction: Wolfram Syndrome (WFS: OMIM 222300), also known as DIDMOAD (diabetes mellitus, optic atrophy and deafness) is an autosomal recessive, progressive, neurologic, and endocrinologic, degenerative disorder caused by mutation in the WFS1 Gene. This report presents a case with a new defined mutation in WFS. **Case presentation:** Fourteen-year-old male patient was diagnosed with non-autoimmune type I diabetes at the age of 5 and insulin treatment was applied to him. He has been diagnosed optic nerve degeneration at 7 years old and diagnosed sensory neural hearing loss at the age of 9 and implanted cochlear implants to him. His parents were not relative. Physical

examination revealed that body weight 52.5 kg (−0,95 SDS), height 157.5 cm (0.95 SDS), testicular volume 5/5 cc, pubic and axillary hair were consistent with stage 2. There were no clinical and lab findings about diabetes insipidus. Neurological examination and cranial imaging were normal. Genetic testing for WFS1 gene mutation was performed and a new homozygous mutation in *WFS1* gene were identified in the genetic analysis (c.15361549dupCTATCTCTTCTTC). **Conclusion:** Non-autoimmune diabetes mellitus is the first and the most frequently seen symptom of WFS. Optic atrophy, and deafness generally appears in the first decade of patients. Diabetes insipidus, renal and neurologic signs may appear in the second 10 years. Patients should be monitored multidisciplinary. Genetic studies will provide early diagnosis and genetic counseling for families.

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Lower Basal Insulin Dose – Better Control in Type 1 Diabetes

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Introduction: There is no valid evidenced-based recommendation for the optimum basal insulin dose in type-1 diabetes mellitus when supplied either by continuous subcutaneous insulin infusion (CSII) or multiple daily injections (MDI). We studied this previously by evaluating the dose associated with successful fasting. Another way of looking at this is by evaluating the association between basal insulin dose and HbA1c. To this end we performed a retrospective study of 89 children and young adults with T1DM. **Patients and methods:** Eight-five (mean age 14.67 ± 4.8 years (range 3–29)) patients were enrolled. Forty-six were treated with CSII and 43 with MDI (glargine as basal insulin). Basal insulin used was either downloaded from the insulin pump or taken as the dose registered in the chart. Glucose data were downloaded from patients' glucometers. Mean time between data download and HbA1c determination was 0.9 ± 0.78 months. We divided patients by quartiles according to HbA1c and determined the average basal insulin for each quartile. The second and third quartiles were joined and are presented together in the graph. **Results:** With lower basal insulin levels lower HbA1C was achieved despite a similar total daily bolus dose (see graph). The optimal basal dose as determined by this study for 18 patients who had the lowest HbA1c (average 6.49% 0.34) (0.28 ± 0.08 u/kg/d) is similar to that shown for fasting individuals of similar age (0.2 ± 0.16 u/kg/d). **Conclusion:** This study provides evidenced for a recommendation to optimize treatment by relying mainly on alterations in the bolus while keeping a low rate of basal insulin since patients with lower basal insulin doses did better in their overall control.

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'Comparison of Neutrophil/Lymphocyte Ratio According to Degree of Glycemic Control in Children with Recent-onset Type 1 and Type 2 Diabetes

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Background: There is a direct relation between C-reactive protein and leukocyte count as indicators of inflammation. The neutrophil lymphocyte ratio (NLR) is the balance between both cells and is considered a marker of low-grade inflammation and an indicator of high risk of cardiovascular events. An elevated NLR is related with type 2 diabetes (T2D), however, even when in type 1 diabetes (T1D) there is an underlying inflammatory process, an elevation of circulating neutrophils isn't observed. NLR is associated with hyperglycemia in adult patients with long-duration T2D. However, reports in pediatric populations with recent-onset type 1 (T1D) and T2D are scarce. **Objective and hypotheses:** To evaluate the association between NLR and the degree of glycemic control in pediatric patients with recent-onset T1D and T2D vs healthy controls. **Method:** Design: Analytical cross-sectional. Subjects 8–16 years of age were included, with T1D or T2D with diagnosis ≤ 3 months, who, with their guardians, signed an informed consent. A physical examination included anthropometric measurements. A blood sample was used for glucose, lipid profile and creatinine concentrations, hematic biometry and HbA1c. Subjects were classified according to metabolic control (good control HbA1c <7.5%). **Results:** There were 131 subjects, 46 (35.1%) with T2D, 49 (37.5%) with T1D and 36 (27.4%) controls. Differences were observed among the three groups in leukocytes (7.6 ± 2.0, 6.4 ± 1.7 and 6.8 ± 2.0 K/μL for T2D, T1D and controls, respectively). NLR was similar among the groups: 1.58 ± 0.61 in T2D vs 1.55 ± 1.07 in T1D and 1.53 ± 1.04 in controls. According to metabolic control, NLR was significant in T2D ($P = 0.045$) and T1D ($P = 0.035$). **Conclusion:** Our findings show higher NLR with poor glycemic control in T2D, and lower with poor control in T1D, from the early stages of the disease in Mexican pediatric population.

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Pancreatic Reserve and Metabolic Control of Type 1 Diabetes in a Cohort of Spanish Children and Adolescent

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Objective: To evaluate the pancreatic reserve and metabolic control in our patient diagnosed of type 1 diabetes over the last 20 years. **Method:** Retrospective cohort study of all patients <15 years, diagnosed in our community between 01/01/1995 and 31/12/2014. Variables: gender, age at diabetes debut, age at study, c-peptide after stimulation with glucagon at debut and 1 month after, HbA1c at debut, 1 month, 1 year, 2 years, 5 and 10 years of debut. Comparison between groups. **Results:** Two hundred and seven patients: 51% female. Average age at debut of diabetes 8.8 ± 3.7 years: 0–4 years 16%, 5–9 years 38%, 10–14 years 4%. Average HbA1c at debut was 11.5%, it was higher in older children ($P<0.001$). Average c-peptide after stimulation with glucagon at debut moment 0.9 ng/ml (0–4 years 0.60, 5–9 years 0.91, 10–14 years 0.98). Average c-peptide after stimulation with glucagon 1 month after debut 0.8 ng/ml (0–4 years 0.53, 5–9 years 0.72, 10–14 years 0.85), statistically significant differences between groups: lower in younger children ($P<0.001$). Average age at study moment 18.4 ± 7.3 years, evolution of diabetes 9.4 ± 6.1 years. Average HbA1c, 1 year of diabetes $7.0 \pm 0.9\%$ ($n=195$), 2 years of diabetes $7.3 \pm 1.0\%$ (182), 5 years of diabetes $7.5 \pm 0.8\%$ ($n=120$), 10 years of diabetes $7.6 \pm 0.8\%$ ($n=34$). Group comparison: statistically significant differences after 5 years ($P=0.043$), higher in group: 10–14 years at debut. **Conclusion:** The older children have higher HbA1c and pancreatic reserve (c-peptide) at debut of diabetes type 1. At 5 years of diabetes the HbA1c is higher in children that had 10–14 years at debut moment. The children of our community have a quite good metabolic control, with average HbA1c around 7.5% along the last 20 years.

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The Best Practice Tariff for Paediatric Diabetes Care within England: A District General Experience

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Background: The Best Practice Tariff (BPT) was introduced in England in 2011–2012 to improve paediatric diabetes care. An enhanced amount is paid based on the attainment of 14 standards. **Objective and hypotheses:** We describe the experience of a District General Hospital working with the new Tariff, including the structural changes and the effect on diabetic control. **Method:** We observed the changes to the local service since the introduction of the BPT. We analysed unit-wide HbA1c data. We conducted a retrospective audit examining specific cohorts of patients. Group A were children diagnosed 2008–2009; we collected data from this group between April 2010–March 2011 (pre-BPT), and April 2014–March 2015 (post-BPT). Group B were children diagnosed 2012–2013; we collected data from this group between April 2014 and March 2015 (post-BPT). **Results:** The funding received per patient per year has increased to £2988. This has enabled the diabetes team to expand to include an extra dietician, family support worker and shortly a clinical psychologist. The average HbA1c within the unit has fallen. Within the audit cohorts, there were 19 children in group A and 32 in group B. Post-BPT all children were offered four multi-disciplinary team (MDT) appointments and 69% had another eight contacts through the year. Pre-BPT only 74% were offered four MDT appointments and none had a further eight contacts in the year. The average HbA1c increased in group A despite the introduction of the BPT (8.64% pre-BPT, 9.18% post-BPT). However, the average HbA1c in newly diagnosed patients fell following introduction of the BPT (8.36% in Group B post-BPT vs 8.64% in Group A pre-BPT). **Conclusion:** The introduction of the BPT has increased the funding and improved the care that we deliver to our children. This is demonstrated in the reduction in HbA1c across the unit, and in newly diagnosed children.

P2-P277

Prevalence of Cardiovascular Risk Factors and Obesity in Youth with Type 1 Diabetes in Lithuania

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Background: Cardiovascular risk and obesity are rising problems among individuals with type 1 diabetes (T1D). Interventions targeted at decreasing cardiovascular risk in patients with diabetes may be most effective during adolescence and young adulthood, before atherosclerotic lesions become advanced or cardiac changes become irreversible. **Objective and hypotheses:** The aim of this study was to evaluate the prevalence of cardiovascular risk factors and obesity in T1D children, adolescents and young adults in Lithuania. **Method:** A cohort of 883 patients diagnosed with T1D for at least 6 months was investigated. 66.8% of the study cohort were children and adolescents (<18 years, $n=590$) and 33.2% – young adults (18–25 years, $n=293$). Anthropometric parameters and blood pressure were measured, and lipid profile and HbA1c were determined. Dyslipidemia was diagnosed if at least one lipid profile parameter was outside the normal range. All patients were evaluated for microvascular diabetes complications. **Results:** Study subjects' mean HbA1c was $8.5 \pm 2\%$, 19.5% ($n=171$) were overweight and 3.6% ($n=32$) were obese. Hypertension and dyslipidemia were diagnosed in 29.8 and 84.7% of participants, respectively. HbA1c concentration was directly related to levels of total cholesterol ($r=0.274$, $P<0.001$), low-density lipoprotein ($r=0.271$, $P<0.001$)

and triglycerides ($r=0.407$, $P<0.001$), and inversely correlated with levels of high-density lipoprotein ($r=-0.117$, $P=0.001$). Prevalence of dyslipidemia increased with duration of diabetes ($P<0.05$). Hypertension was more prevalent in overweight and obese compared to normal weight patients (44.6 vs 25.6%, respectively, $P<0.001$). Adjusted for disease duration and HbA1c, frequency of microvascular complications was higher among patients with dyslipidemia (24.5 vs 21.5%, respectively, $P<0.001$) and among those with hypertension (25.9 vs 23.2%, $P<0.001$). **Conclusion:** The frequency of cardiovascular risk factors is high in young people with T1D and is associated with diabetes duration, obesity and poor metabolic control.

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Childhood Type 1 Diabetes (T1D) Management with e-learning through Self-educational Tools

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Background: Children with type 1 diabetes (T1D) and their parents need personalized i) information about the disease and glucose homeostasis and ii) knowledge and guidelines about diet and insulin therapy. **Objectives:** To set a complete educational program that allows children with T1D to improve disease management and daily life. **Methods:** Education modules were written and trained with children and parents at outpatient visits. Each module is a 10–20 slide Power Point presentation that can be read in 30 min maximum. Individual personalized work sessions were made of different modules depending on the appreciation of the diabetes team. **Patients:** During the year 2015, 100 children (age 2–15 years) and families served as a randomly composed training group for the 'Design' phase of the educational program. They were asked to go through selected modules adapted to patient's age, try to learn, answer questions, thereafter comment the strengths and weaknesses of the program. **Results:** The full program now includes 300 modules adapted to child and parents' educational level. Learning modules have been tested and modified by the training group. Interactive modules now allow the testing of knowledge and of appropriateness of practical decisions regarding diabetes self-management. **Conclusion:** Our program provides a solid basis for education of T1D children and their parents, which will be used on computers, tablets and smart phones.

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Mucormycosis and Type 1 Diabetes: A Case Report

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Background: Mucormycosis which is an invasive fungal disease and commonly seen in immunocompromised patients is very rare in the diabetic children. **Case report:** We present a case with type 1 diabetes with mucormycosis. A 14-year-old male patient was referred to our department due to polyuria, polydipsia, weight loss, headache, altered consciousness, fever, and rhinorrhea. After the diabetic ketoasidosis treatment, left facial paralysis, anisocoria, and ptosis were noted. MRI revealed fronthoethmoid fungal sinusitis, orbital cellulitis, frontobasal cerebritis and abscess formation. Mucormycosis was confirmed by biopsy. Amphoterisin B and posaconasol treatment were started. Hyperbaric oxygen treatment as adjuvant was commenced as well. Regression of fungal lesions were demonstrated by MRI. The patient is still on oral posaconasol treatment which is planned to continue for 1 year. He is followed up by neurologically for unilateral vision loss and facial paralysis. **Conclusion:** It should be kept in mind that untreated or uncontrolled diabetes causes immune deficiency which is a risk for mucormycosis. Early detection and treatment of mucormycosis is very important to reduce morbidity and mortality.

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Insulin Pump Therapy in Type 1 Diabetes: The Indian Experience

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Background: Insulin pumps have been used for the management of type 1 diabetes for over 15 years in the west. However similar experience is lacking in India where multi dose insulin injections still form the mainstay of management of type 1 diabetes. In a first study of its kind from India, we attempt to highlight the effectiveness, safety and superiority of insulin pump use in type 1 diabetes. **Objective and hypotheses:** To determine the impact of insulin pump therapy on short and long term

Table 1. (for abstract P2-P280)

Age group	**No. of Pts.** (52)	**Duration of diabetes before starting on insulin pump** (years)	**Average pre-pump HbA1C** (last HbA1C before pump)	**Average pre-pump BMI** (BMI at last visit before pump)	**Average post-pump HbA1C** (6 m) $N=52$	**Average post-pump HbA1C** (long term) (1 year) $N=27$	**Post pump BMI** (after 6 months of starting pump)
0–5 years	2	0.85 (0.25–1.5)	8.4	16.2	7.9 (0.5)	7.8 (0.6) $N=2$	16.3 (0.1)
6–10 years	16	2.75 (0.5–5)	8.0	16.3	7.8 (0.2)	7.7 (0.3) $N=11$	17.5 (1.2)
11–15 years	20	4.3 (0.5–11)	9.0	17.8	7.6 (1.4)	7.6 (1.4) $N=9$	19.1 (1.3)
16–20	10	5.6 (1–9)	9.2	21.2	7.6 (1.6)	8.0 (1.2) $N=4$	22.5 (1.3)
21–25	4	10.7 (7–16)	9.5	19.7	8.0 (1.5)	8.0 (1.5) N=3	21.2 (1.5)

glycaemic control, BMI, rate of severe hypoglycaemia and diabetic ketoacidosis (DKA) in children, adolescents and young adults. **Method:** Retrospective analysis of data from case records of patients at our clinic. Out of the 64 patients on insulin pump, 52 were included in the study. Age of the patients at initiation of insulin pump ranged from 3 to 26 years. Data regarding pre-pump HbA1C (average HbA1C in the 6 months before starting insulin pump), pre-pump BMI (BMI at last visit before pump), pre-pump episodes of hypoglycaemia and DKA and post pump HbA1C (at 6 months and 1 year after pump initiation), post pump BMI (BMI at 6 months after pump) and post-pump episodes of hypoglycaemia and DKA (in the 1 year after pump) in each patient was recorded and compared. **Results:** Of the 52 patients included, only 27 followed up for one year or more after initiation of pump and 25 had visits only up to 6 months. There was a drop in HbA1C and increase in BMI across all age groups with the maximum difference seen in the oldest age group after starting pump therapy. Only three episodes of DKA were recorded after pump therapy against ten episodes in the pre pump period. However there were three episodes of severe hypoglycaemia in the post pump period as compared to two episodes in the pre pump period (Table 1). **Conclusion:** This study suggests that insulin pump therapy is effective, safe and superior in children, adolescents and young adults with type 1 diabetes.

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Child with Mutation in GATA 6 Gene – Case Report

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Background: The GATA family of zinc finger transcription factors including GATA4 and GATA6 are known to play an important role in the development of the pancreas. **Aim:** The aim of this case-report study is to present a patient with GATA6 mutation treated in Clinic of Pediatric, Diabetology and Endocrinology, Medical University of Gdansk. **Case report:** Child was born prematurely in 36th week of pregnancy with birth weight of 1520 g, with breathing problems supported by mechanical ventilation. Echocardiography, detected tetralogy of Fallot in this patient. From third day of life, hyperglycemia was noticed and intravenous insulin infusion started. Because of meconium obstruction in the newborn, cystic fibrosis was suspected. In neonatal screening, congenital hypothyroidism was diagnosed and thyroxin was prescribed. Genetic test did not confirm CF (mutation on one allel CFTR gene – F508del) and Hirschsprung disease was suspected. In genetic test, reciprocal translocation between chromosome 1 and 7, and pericentric inversion of chromosome 9 was found. Child received thyroid hormons, insulin, pancreatic enzymes, antispasmodic agents, ursodeoxycholic acid, rectal ingots and vitamins. In first month of life, insulin was injected intravenously and when child reached a weight of approximately 2.5 kg, insulin pump therapy was started with insulin dose of 0.8 U/kg per day. The child was qualified to cardiosurgical correction of cardiac heart defect which was performed with good outcomes. On the basis of clinical picture, mutation in GATA 6 was suspected. In genetic laboratory of Medical University of Łódź, genetic tests were performed and GATA 6 mutation was detected. Metabolic control of diabetes is poor. **Conclusion:** Persistent neonatal diabetes with exocrine insufficiency of pancreas and heart defect in patient were caused by GATA6 gene mutation.

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A Case Report of a 14 Year Old Female with a Known History of Type 1 Diabetes Mellitus Who Developed Tracheal Stenosis as a Result of Prolonged Intubation from Diabetic Ketoacidosis and Subsequently Developed Acute Pancreatitis

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Background: Diabetic Ketoacidosis (DKA) is a serious and common complication of type 1 diabetes mellitus. Often it occurs due to non-compliance of the patient's insulin regimen, especially of the basal insulin. In this patient, about 6 months after being diagnosed, she presented to the emergency department in DKA, with a pH of 6.9 with altered mental status, which required intubation for 1 week. She was treated with an IV insulin drip and fluids. As a result of her management, she developed tracheal stenosis and cerebral edema. She also developed right hand monoplegia and has not regained full function, despite physical therapy. As a result of her stenosis, she developed stridor on exertion and had to be admitted to the hospital on four different occasions for tracheal dilation. After this failed, a tracheoplasty was done by cardiothoracic surgery. On follow up, a fasting lipid panel was done and the triglyceride value was >3000 mg/dl. She was then started on 600 mg twice daily of Gemfibrozil. After following up on the phone, she did admit that she was not compliant with her insulin regimen and Gemfibrozil. After 1 week, she presented to the hospital with abdominal pain and vomiting. A serum lipase was elevated at 500 U/l. She was admitted and kept NPO for 1 day and her abdominal pain improved. An abdominal ultrasound was consistent with acute pancreatitis. After in-patient management, her triglyceride level decreased to 200 mg/dl and her lipase levels normalized in 2 days. **Objective and hypotheses:** Diabetic ketoacidosis is a serious complication of type 1 diabetes mellitus, which can cause severe morbidity and uncommon complications like tracheal stenosis. Also uncontrolled diabetes mellitus can cause complications from hypertriglyceridemia, like acute pancreatitis. **Method:** We examined a 14 year old female with a known history of type 1 diabetes mellitus for 1 year through chart review. **Results:** This is a 14 year old female who developed serious acute complications from type 1 diabetes mellitus, including tracheal stenosis, which required tracheoplasty, cerebral edema, monoplegia of her hand, and subsequently acute pancreatitis. **Conclusion:** Proper management of type 1 diabetes mellitus is needed to avoid serious complications from DKA and from hypertriglyceridemia, like acute pancreatitis.

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Continuous Glucose Monitoring Can Alleviate Parental Fear of Hypoglycaemia in Children with Type 1 Diabetes Mellitus

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Background: Type 1 diabetes mellitus (T1DM) in children carries significant psychological stress for families, as well as considerable long-term complications if good metabolic control is not achieved. Tighter metabolic control carries increased risk of hypoglycaemic episodes, and previous research suggests that families with a high fear of hypoglycaemia will run blood sugars higher in order to avoid this. Continuous glucose monitoring (CGM) provides real time temporal measurements of blood glucose levels and a recent Cochrane meta-analysis showed that CGM technology can reduce HbA1c level without increase of hypoglycaemia. **Objective and hypotheses:** To investigate fear of hypoglycaemia before and after use of CGM. **Method:** Parents of children and patients aged over 12 years using CGM for a minimum of 6 months were asked to complete a modified version of the Hypoglycaemia Fear Survey for parents of young children (HFS-PYC), a measure designed to assess fear and avoidance behaviours associated with hypoglycaemia, for before and after CGM. **Results:** Questionnaires were returned for 13 patients (eight male), nine patients were 12 years or older (age range 2–19 years, median 13 years) of which six returned patient questionnaires. Two patients and one parent were excluded from analysis as incomplete. Significant improvement was seen for parental fear of hypoglycaemia following use of CGM ($P<0.001$). Three out of four patient questionnaires analysed showed decreased fear of hypoglycaemia following CGM use, however these figures were not statistically significant ($P=0.10$). Mean HbA1c in the preceding 6 months before CGM use was 66.7 mmol/mol compared to 61.4 mmol/mol 6 months post-CGM ($P=0.52$). **Conclusion:** Parental fear of hypoglycaemia was significantly reduced following the use of CGM in children with T1DM. Reducing the level of fear of hypoglycaemia is an important aspect in helping patients and families work towards improving metabolic control in T1DM.

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The Implementation of a System of Continuous Monitoring of Blood Glucose and Open (FREE STYLE FREE) Improves Metabolic Control of Affected Children DMtipo1

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It is known that more checks of blood glucose, metabolic control of patients with type 1 suffering Dm improvement. Improved technology has made it possible to develop devices interstitial glucose control both blinded (retrospective) and open (in real time). The FREE STYLE free device is the latest appearance on the Spanish/European market. Although initially not seem indicated in <18 th, these are the a priori more could benefit from an improvement of metabolic control. **Objective:** To evaluate the impact of the implementation of the use of free FREESTYLE in children with DM1 to 3.6 and 12 months after implantation. It is valued changes in HbA1c, hypoglycemia and hyperglycemia events. Satisfaction level of families. **Methods:** DM1 children over 2 years with at least 6 months duration from debut. Use 'off label' device, informed consent. Control at baseline, 3.6 and 12 months after implantation voluntary use. Cost for families. Variables HbA1c, hypoglycemia events/month (moderate, requiring intervention), hyperglycemia/month (>250 mgr/dl) Study comparativo. IBM Stastistics SPSS 19.0., Nonparametric paired samples $n<30$. Health Survey Questionnaire SF-36 (Spanish and summarized). **Results:** Twelve children (7♂), mean age 10.5 to (8–15.5). Previous HbA1c (DCA): 8.1% (6.4–8.8) needs: 0.72 IU/kg per day (0.45–0.88), sensitivity 168 mgr/dl per IU (135–280) and Survey 7.2 points (6–8). Hypoglycemic events/month 6.8,2 (5–15) hypoglycemic events/month 12 (10–32). After 3 months of use HbA1c (DCA): 7.7% (6.8–7.9) *P*: 0.38, hypoglycemic events/month 4.9 (3–8) Events hipeglucemia/month 8 (7–20) difference *P*: 0.03 95% CI (0.12–0.48). After 12 months of use HbA1c (DCA): 6.8% (5.2–7.5) *P*: 0.38, hypoglycemic events/month 2 (1–5) Events hipeglucemia/month 5 (4–8) differences *P*: 0.001 95% (0.001–0.1) Enc 8.5 points (7–9). **Conclusion:** Improving quality of life perceived by parents, improved metabolic control, together with the relatively low cost of the measure defines the potential of this device, allowing even a medium-term decline in consumption of test strips.

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Permanent Neonatal Diabetes by Gene Mutation KCNJ11. Evolution and Treatment after Three Years with Sulphonylureas

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Background: Permanent neonatal diabetes (PND)with heterozygous mutations of KCNJ11, respond to treatment with sulphonylureas. We report a case of PND in a baby, and mother previously mis-diagnosed with Type 1 DM. Both were switched from insulin to oral sulphonylureas. We evaluate the response and evolution. **Case report:** A male newborn at 37 weeks' gestation, with a birthweight 2750 g (40^{th}C) and length 48 cm (40^{th}C), was admitted for glycemic monitoring. He presented with hyperglycemia in the first week, requiring insulin infusions during his first month 0.2–0.5 U/kg per day. Family history: Parents non-consanguineous. Mother on CSII diagnosed with Type I DM from the third month of life, having presented with severe ketoacidosis and dehydration. Currently: HbA1C: 9%. Initial

laboratory evaluations in baby showed, blood glucose: 320 mg/dl, HbA1C:3.5%, no ketonuria, C-peptide:0.22 ng/ml, Insulin:3.2 mU/ml, with negative diabetes antibodies in mother and baby (Anti-GAD, Islet, insulin autoantibodies). Genetic testing undertaken simultaneously on both (at baby age 3.8 months) revealed heterozygous mutation in exon1 KCNJ11 (p.Arg201His,c.602G > A). Following gradual transition from insulin, at 3.8 months the patient was successfully shifted to sulphonylurea therapy, requiring at the beginning 0.45 mg/kg per day, decreasing to 0.2 mg/kg per day from the 4th month until 2.6 years, requiring 0.15 mg/kg per day currently. We evaluated pancreatic insulin reserve and glycemic control prior to transition, HbA1c, fasting insulin and c-peptide over successive years. As result, the glycemic control and the pancreatic reserve were improved in both. Evolution HbA1c: 5.2–5.7% throughout the treatment time. Two years since starting sulphonylureas: fasting insulin 3.9 mU/ml and C-peptide 0.7 ng/ml; 3 years since starting; fasting insulin: 10 mU/ml and C-peptide: 2.88 ng/ml. **Conclusion:** Although the clinical onset of patients with mutations in Kir6.2 is typically described from the first month of life, our case suggests that the blood glucose levels are already affected from birth. This case shows that earlier treatment with sulphonylureas improves pancreatic reserve increasing the c-peptide leading to lower doses being required. We will re-evaluate the diagnosis of patients with early onset Type 1 DM.

P2-P286

Atypical Cystic Fibrosis Adolescent Case Study (with Normal Sweat Test) Referring with Diabetes Mellitus Symptoms Found to Carry Homozygous R352Q Mutation

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Background: Cystic fibrosis is an autosomal recessive genetic disorder affecting typically the lungs, the pancreas, the gastrointestinal tract and tissues that produce mucus secretion, such as sweat glands. Impaired glucose tolerance and cystic fibrosis-related diabetes are the most common complications of cystic fibrosis. Cystic fibrosis-related diabetes is another type of diabetes mellitus and carries some of the characteristics of type1 and type2 diabetes. **Objective and hypotheses:** We hereby present an atypical cystic fibrosis case who is referred to our center as diabetes mellitus. **Method:** Fifteen year old, male referred to our center with symptoms of drinking too much water, peeing more often and losing weight. He had reported oily stool since 1 year of age. This has been analysed in other centers, but found to have no specific reason. His parents were first degree relatives/cousins. In his physical examination, his weight was: 45.5 kg (10–25th percentile), height was: 165 cm (75th p), and puberty was inline with Tanner stage 5. In his laboratory test; serum glucose: 497 mg/dl, HbA1c: 12.7%, C-peptide: 1.04 ng/ml (0.9–7.1), pH: 7.39, HCO3: 22.7 mmol/l, vitamin A: 367 ng/ml (400–1500), vitamin D: 9.1 ng/ml (20 <), vitamin E: 2.5 μg/ml (5–16), steotocrit in gaita: negative, sweat test found to be normal. Fecal elastase: 35 μg/dl (<100: exocrine pancreatic insufficiency). Insulin adacık antibodies (−), glutamic acid decarboxilase antibodies (−), MODY gene was negative. **Results:** With cystic fibrosis prediagnosis, homozygous R352Q mutation has been found on exon 8, in CFTR Full Sequence Analysis. This mutation has already been described in former cystic fibrosis cases. **Conclusion:** Cystic fibrosis coupling with diabetes is rarely seen in childhood. Such a case study, having been presented with diabetes symptoms, and found to be diagnosed as atypical cystic fibrosis has not been presented in the literature, so far.

P2-P287

Diabetic Ketoacidosis Risk Factors in the Initial Presentation of Type 1 Diabetes Mellitus in Children and Adolescents

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Background: Diabetic ketoacidosis (DKA) is the most serious acute complication of type 1 Diabetes mellitus (T1DM). It is important to know the factors associated with the development of DKA and elaborate preventive strategies to reduce their prevalence. **Objective and hypotheses:** To identify DKA predictive risk factors in the initial presentation of T1DM in children and adolescents. **Method:** We conducted a retrospective study, by analyzing the medical records of children/adolescents diagnosed with T1DM between 2000 and 2015, followed in our hospital. We have made a descriptive analysis of demographic and clinical variables, the occurrence of DKA in the initial presentation and a comparative analysis between the groups with and without DKA. Statistical analysis was performed with SPSS. **Results:** A total of 205 children/adolescents were diagnosed, but 50 were excluded due to incomplete data. Of the 155 evaluated, the majority were male (58.1%), with an average age 7.8 ± 4.1 years. In the inaugural episode of T1DM 61 cases (39.9%) of DKA were documented (19 cases (12.4%) had severe DKA). The most common symptoms were polyuria (96.5%), polydipsia (90.3%) and weight loss (61.1%). The DKA was significantly more frequent in cases with a duration of symptoms ≥15 days (46.0% vs 28.3%; $P<0.05$, OR 2.2), initial HbA1c ≥10% (52.2% vs 8.0%; $P<0.001$, OR 12.5) and C-peptide <1.0 ng/ml (40.6% vs 5.9%; $P<0.05$ OR 10.9). The DKA was less frequent in the presence of family history of T1DM (17.4% vs 42.5%; $P<0.05$, OR 0.285). We did not

observe differences in the occurrence of DKA in relation to the following variables: age at diagnosis, gender, parents' education level, month of diagnosis, presenting symptoms and presence of autoantibodies. **Conclusion:** The DKA as the initial presentation of T1DM in pediatric population was high, above the international average that is around 30%. Were identified as risk factors: symptoms that persist longer than 15 days, initial HbA1c $\geq$10% and C-peptide $<$1.0 ng/ml and as a protective factor the family history of T1DM. It is necessary to strengthen the public education in order to reduce the time between the onset of symptoms and the diagnosis of T1DM.

P2-P288

Prevalence of Polycystic Ovary Symdrome and its Clinical Profile in Young Females with Type 1 Diabetes Mellitus

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Background: The non-physiological ways and supraphysiological doses of insulin required for good glycemic control in patients with type 1 diabetes right from onset exposes them to effects of hyperinsulinism. In addition insulin resistance may be seen because of glucose toxicity and abnormal fat mass gain during puberty Insulin acts synergistically with luetinizing hormone to facilitate androgen production by theca. **Objective and hypotheses:** To investigate the prevalence of polycystic ovary syndrome and its clinical profile in females with type 1 diabetes. Exogenous hyperinsulinism and insulin resistance may cause a polycystic ovary like profile in predisposed T1DM women. **Method:** In this cross-sectional study 65 T1DM patients underwent clinical examination, hormonal evaluation for hyperandrogenemia and ultrasonography of the ovaries in the follicular phase of their menstrual cycle. **Results:** Median age and duration of diabetes were 20 (range 11–40) and 6 (range 1.5–27) years respectively. Median glycosylated haemoglobin was 7.15 (range 6.45–11.06). Thirty eight subjects (63%) had pre-pubertal onset of diabetes. Eighteen of 60 patients (30%) satisfied the Rotterdam criteria for PCOS and 7(11%) the NIH criteria, prevalence which is much higher than 3.6% reported by us earlier in young women (18–24 years age) from Lucknow. There was no difference in the clinical, anthropometric and biochemical parameters in patients with or without PCOS. In the subgroups of pre pubertal or post pubertal onset of diabetes, there were no difference in the levels of glycosylated haemoglobin, sex hormone binding globulin, and free androgen index, between the two groups, but the daily insulin dose in U/kg was higher in the post-pubertal group (1.05 ± 0.21 in pre-pubertal vs 1.45 ± 0.61 in post-pubertal; P value $= 0.051$). **Conclusion:** Patients with type 1 diabetes have a high prevalence of menstrual irregularities, hyperandrogenism and PCOS which is not related to metabolic control or age of onset of diabetes.

P2-P289

The Frequency of Diabetic Ketoacidosis in Children and Adolescents with Newly Diagnosed Type 1 Diabetes Mellitus: A Single Centre Experience in Turkey

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Background: Diabetic Ketoacidosis (DKA) is a serious complication of type 1 diabetes mellitus (T1DM) that require prompt recognition, diagnosis and treatment. There is wide geographic variation in the frequency of DKA at onset of diabetes. **Objective:** To determine frequency of DKA in children and adolescents with newly diagnosed type 1 diabetes admitted to a tertiary care hospital in Turkey. **Methods:** A retrospective study was undertaken including patients who diagnosed with T1DM in our paediatric endocrinology clinic, between June 2013 and February 2016. Data from medical carts of 93 children and adolescents (49 female) with T1DM were analysed. DKA was defined in patients based on laboratory test results; hyperglycemia (blood glucose $>$200 mg/dl) and venous pH $<$ 7.30 and/or bicarbonate $<$15 mmol/l and ketonemia. DKA was classified as mild, moderate and severe based on venous pH, 7.20–7.30, 7.10–7.20 and $<$7.10 respectively. **Results:** DKA was determined in 41.9% (39/93) of patients in the sample. The mean age of patients with DKA at the time of diagnosis was not significantly different from patients without DKA (8.7 ± 5.2 vs 9.8 ± 4.6 years). There were significant differences in HbA1c, C-peptide levels between the groups. The frequencies of mild, moderate and severe DKA were 20.4, 6.5 and 15.1%, respectively. **Conclusion:** High frequency of DKA has been determined in our cohort. Community-based education programs could be helpful to increase awareness of diabetes in childhood period, in this way; the frequency of DKA can be reduced in patients with newly diagnosed T1DM.

P2-P290

Wolcott-Rallison Syndrome: Clinical Case Presentation

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Wolcott-Rallison syndrome (WRS) is a rare autosomal recessive disease characterised by neonatal/earlier-onset non-immune insulin –requiring diabetes associated with skeletal dysplasia and growth retardation. WRS is caused by mutations in the gene encoding eukaryoutic translation initiation factor 2 a kinase (EIF2AK3), which plays a key role in translation control during the unfolded protein response. In the endocrinological department of Ternopil Childrens' Hospital diabetic boy was admitted for usual checkup. He is full-term child from II physiological pregnancy and delivery, birth weight 2500 g. Neonatal period and family history are unremarkable. In age 2 mo he was

hospitalized due to moderate dehydration and intoxication syndromes. Capillary blood glucose was 22 mmol/l, Hb1Ac = 9.662%, C-peptide =0.27 ng/ml and manifestation of neonatal DM had been diagnosed. General condition of the child quickly proofed by combined insulin therapy. By genetic DNA analysis of parents and child blood novel EIF2AK3 gene missense mutation of exon 15 was revealed, which confirm the clinical diagnosis of WRS. Child growths and develops properly, but in age of 1 year was hospitalized to the resuscitation department due to development of acute liver failure and anasarca. He was treated for 3 weeks and recovered without defects. Now child is 1 year 10 mo. Physical development is proportional. He is on persistent insulin therapy by Actrapid and Protaphane 4 injection per day in dally dose 1.75 Units. Hb1Ac =8.32%. Blood analyses without pathological symptoms. For that moment signs of skeletal dysplasia are not remarkable. WRS should be suspected in any infant who presents with permanent neonatal diabetes associated with episodes of acute liver failure. Early diagnosis is recommended by molecular genetic testing, in order to ensure rapid intervention for episodes of hepatic failure, which is the most life threatening complication.

P2-P291

The Story of a *de novo* Heterozygous HNF1A Mutation

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Background: MODY is characterised by an early onset of diabetes and a positive family history of diabetes with an autosomal dominant mode of inheritance. We report a 15 year girl with a HNF1A mutation who presented with MODY without a positive family history. **Objective and hypotheses:** HNF1A-MODY is often misdiagnosed as type 1 or type 2 diabetes. Genetic confirmation of MODY in insulin-treated patients helps in making changes in the treatment modality as illustrated below. We tested our patient for HNF1A mutation as she showed features of not being insulin dependant – not developing ketoacidosis in the absence of insulin, good glycaemic control on a small dose of insulin and detectable C-peptide measured when on insulin. **Method:** A 15 year old presented with fainting episodes and feeling thirsty. Her blood glucose was noted to be 12 mmol/l. She was admitted for further investigation and management.Her blood glucose levels remained between 7 and 12 mmol/l and she had no ketonuria. Her OGTT showed a fasting glucose of 6.7 mmol/l and 14.9 mmol/l at 120 min. Her haemoglobin A1c was elevated at 64 mmol/mol. Her blood glucose levels persistently remained between 8 and 12 mmol/l. She was commenced on MDI with Levemir as basal and Novorapid as bolus at 0.25 units/kg per day. Her ICA and GAD antibodies were negative. Her C peptide was 522 pmol/l reflecting intrinsic insulin secretion. There was no family history of diabetes. She tested positive for heterozygous HNF1 A mutation. Insulin was stopped and she was started on sulphonylureas. **Results and conclusion:** The molecular diagnosis of MODY is important to classify the diabetes, predict prognosis and screen asymptomatic family members. Genetic testing of MODY could be considered for carefully selected individuals without a family history of diabetes.

P2-P292

Use of Continuous Glucose Monitoring Helps Selecting Insulin Therapy in Thalassemic Adolescents with Glycemic abnormalities

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Background: Continuous Glucose Monitoring (CGMS) is a useful method to detect the variability of glucose fluctuations and offers the opportunity for better assessment of glucose homeostasis in TM patients and response to therapy. **Objective and hypotheses:** Does real-life monitoring of blood glucose add to the therapeutic approach to patients with TM who have glycemic abnormalities? **Method:** In two thalassemic adolescents with glycemic abnormalities we tested the benefit of monitoring blood glucose to support the therapeutic decision. **Results:** A 15 year old male with TM presented with nocturia. His FBG was 5.6 mmol/l and OGTT showed a BG level at 2 h of 8.5 mmol/l. His CGMS showed a diabetic range of BG after dinner and overnight. Based on this tracing, a basal insulin (Glargine) was prescribed at night. A satisfactory response was recorded by CGMS. In addition, a 14 year old girl with TM with no symptoms related to glycemic abnormalities. Her FBG was 4.9 mmol/l and an OGTT showed a BG level at 2 h of 6.9 mmol/l (IGT). CGMS tracing showed prolonged persistent hyperglycemia after lunch suggesting a need for prandial insulin to cover her carbohydrate load. Insulin aspart before lunch properly controlled her glycemia. **Conclusion:** Our results demonstrate that the CGMS is a useful method to detect the variability of glucose fluctuations and offers the opportunity for better assessment and control of glucose homeostasis in TM patients.

P2-P293

Impact of Demographic Factors on Diabetic Ketoacidosis Occurrence at Type 1 Diabetes Onset in Childhood

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Background: Diabetic Ketoacidosis (DKA) in newly diagnosed children with Type 1 Diabetes (T1D) has been associated in previous studies with several factors, such as age or season of

diagnosis. **Objective and hypotheses:** The aim of the present study was to assess the impact of age, gender, birth order and seasonality in DKA occurrence in newly diagnosed T1D pediatric patients. **Method:** Data of children aged 0–14 years newly diagnosed with T1D between January 2010 and December 2015 were analyzed according to age, gender and seasonality of date of diagnosis and birth using both univariate and multivariate logistic regression analysis. DKA diagnosis and its severity were classified according to ISPAD guidelines 2014. **Results:** Hundred and fifty nine newly diagnosed T1D children in the years 2010–2015 were recorded and 89 (55.9%) presented with DKA (severe DKA in 23.59%, moderate in 43.82%, and mild in 32.58%). In univariate logistic regression analysis neither age (Exp(B):0.930, 95% CI: 0.859–1.006, $P=0.072$) nor the season of birth exhibited any significant effect (Exp(B):1.405, 95% CI: 0.748–2.639, $P=0.290$) on DKA occurrence, while male sex was negatively associated with DKA at T1D diagnosis (Exp(B):0.482, 95% CI: 0.254–0.915, $P=0.026$). Furthermore, diagnosis during the cold months (fall-winter) was borderline negatively associated (Exp(B):0.536, 95% CI: 0.284–1.014, $P=0.055$) with DKA, while the order of birth (1st born children vs other) had no impact on DKA occurrence (Exp(B):1.122, 95% CI: 0.598–2.106, $P=0.720$). In multivariate logistic regression analysis only male gender (Exp(B):0.470, 95% CI: 0.246–0.901, $P=0.023$) and the diagnosis during fall-winter (Exp(B):0.521, 95% CI: 0.272–0.997, $P=0.049$) were statistically negatively associated with DKA occurrence at T1D diagnosis. **Conclusion:** Male gender and diagnosis during the cold months are less associated with DKA at T1D onset.

P2-P294

Differences in Hba1c among Different Ethnicities; Is it just a Matter of Mean Glycaemia?

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Background: Several studies have described ethnic differences in HbA1c. Non-Caucasian patients have been found to have an higher HbA1c than the Caucasian ones. These differences have often been attributed to disparities in access to medical care or quality of the care. **Objective and hypotheses:** Differences in Hba1c among the ethnicities could be related not only to mean glycaemia. The aim of our study was to observe if, at the same level of mean glucose, the HbA1c of Non-Caucasian patients was higher than the Caucasian ones. **Method:** We enrolled patients with type 1 and 2 diabetes, who checked the glycaemia at least twice a day. From each patients' history we chose an Hba1c value and starting from the date of that value we selected on the Diasend the three previous months. We then collected the mean glucose for this periods and matched it with the correspondent Hba1c to observe if there was a disparity in this correspondence among the different races. **Results:** We enrolled 227 patients from three different hospitals of London (63 black, 117 white, 24 mixed and 23 of any other ethnicity). On a mean glucose between 6.1 and 8 mmol/l the mean Hba1c for blacks was 7.33%, 7.13% for whites, 6.46% for mixed, 0 for any other; on a mean glucose between 8.1 and 10 it was 8.86% for blacks, 8.21% for whites, 7.93% for mixed and 7.61% for any others; on a mean glucose between 10.1 and 12 it was 8.74% for blacks, 8.08% for whites, 8.94% for mixed and 8.24% for any others; on a mean glucose above 12 it was 10.13% for blacks, 9.05% for whites, 9.28% for mixed and 11.23% for any others. **Conclusion:** Among all the patients, on a same level of mean glucose the Hba1c of blacks was higher that the other ethnicities and the higher was the mean glucose the wider was this difference.

P2-P295

Ischemic Intestinal Necrosis as a Rare Complication of Diabetic Ketoacidosis in a Child with New-Onset Type I Diabetes: A Case Report

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Background: Diabetic ketoacidosis (DKA) is the leading cause of morbidity and mortality in children with type 1 diabetes (T1DM). Although dehydration and electrolyte imbalance can be present in patients with DKA and T1DM, gastrointestinal tract complication remains unusual, especially in children. We report a child case of newly onset T1DM who developed acute ischemic intestinal necrosis with severe DKA combined with hypernatremic hyperosmolarity. **Case report:** A 13-year-old previously healthy Asian girl presented with vomiting and progressive lethargy lasting 3 days. She had a 1-month history of polyuria and polydipsia and a 13 kg weight loss over a period of 1 month. Over the 1-month, the patient had intermittent episodes of vomiting but she did not visit hospital. She only treated with intermittent medication for acute gastritis. Initial laboratory findings were as follows: serum glucose, 1330 mg/dl; serum sodium, 162 mEq/l; serum osmolarity, 441 mOsm/l; pH, 7.15; base excess 24, respectively. Despite intensive fluid resuscitation and insulin infusion, her consciousness level was rapidly worsened and abdomen wall was distended with rigidity. Emergent abdominal computed tomography showed necrotizing enterocolitis with pneumatosis intestinalis. Twenty hours after admission she died of ischemic intestinal necrosis induced shock. **Conclusion:** DKA and hyperosmolar hypernatremia predispose the patient to develop thrombosis. Hypovolemia and hypernatremic hyperosmolarity in childhood DKA can lead to poor tissue perfusion and subsequent bowel ischemic necrosis. A high index of suspicion of intestinal ischemia as a potential complication of childhood DKA is critical factor influencing survival.

P2-P296

Diabetes – a Rare Complication of Ataxic Telangiectasia Presenting in Childhood

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Case: A South Indian boy diagnosed with ataxic telangectaisa(AT) since aged 5 years (homozygous mutations for *ATM* gene at C1966A>C and 1968-X.delI), presented with type 2 diabetes (T2DM) aged 15.9 years. There was a 4-week history of polyuria and polydipsia without weight loss. Investigations showed fasting glucose 11.5 mmol/l, insulin 209 pmol/l, HbA1c 103 mmol/mol, negative glutamic acid decarboxylase and islet cell antibodies, and urinary C-peptide 2.84 nmol/mol. Intellectually he is normal and attends mainstream school with physical assistance. His father and five paternal siblings were diagnosed with T2DM aged <50 years. On examination, he was Tanner stage 5 and non-obese (BMI 23.2 kg/m^2, SDS 1.15). There were no signs of acanthosis nigricans. Telangiectasia were present on his sclerae and he was ataxic with limited mobility with a mild scoliosis. Metformin 500 mg once daily was started and he responded well with fasting glucose maintained between 5 and 6 mmol/l most days and achieved an HbA1c of 47 mmol/mol 1 year after diagnosis. Screening for coeliac disease, thyroid dysfunction, diabetic nephropathy and retinopathy were negative. However, mildly raised total cholesterol 5.3 mmol/l and triglyceride 2.7 mmol/l, and low HDL 0.9 mmol/l were noted. He also has raised transaminase (ALT 209 U/l) and ultrasound findings of hepatic steatosis. **Discussion:** T2DM is a rare complication in patients with AT which usually presents in adulthood. It is characterised by hyperinsulinism, negative antibodies and liver dysfunction, without clinical obesity and responds well to metformin. It has been proposed that mutations of the *ATM* gene in AT leads to disruption of the downstream signalling pathways in the insulin-stimulated glucose transport at the skeletal muscles, and hence glucose clearance. Our case demonstrates that diabetes and metabolic complications in AT can present in the paediatric age range, and screening should be part of the follow-up of AT from childhood.

P2-P297

Clinical and Demographic Characteristics of Patients with Type 1 Diabetes Mellitus and correlation with risk factors: A South Indian Database

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Background: Type 1 Diabetes (T1DM) is one of the most common paediatric endocrine disorders in India, but diagnosis is often delayed. Moreover, systematized data about symptoms, presentation, management and follow-up of T1DM in India is lacking. Absence of such data makes formulation of uniform region and nationwide protocols for diagnosis, management and follow-up of T1DM patients difficult. **Objective and hypotheses:** To generate data about presentation and management of T1DM, to identify risk factors for delayed diagnosis of T1DM, identify other chronic conditions associated with T1DM and to focus on prevailing socio-economic factors which could have an impact on T1DM management. **Method:** A retrospective analysis of all children attending the pediatric endocrine unit at a tertiary level hospital from April 2014 to March 2016. Detailed questionnaire was administered to the patients and their parents and anthropometric measurements obtained from the patients along with physical examination. **Results:** 221 children were included, of whom 118 were girls and 103 were boys. Mean ± S.D. – age of diagnosis was 9.2 ± 4.3 years. The commonest symptom was polyuria (95.7%), followed by weight loss (80.3%). Commonest mode of presentation was with osmotic symptoms (52.5%), followed by diabetic ketoacidosis (45.5%). Winter was the commonest season of diagnosis (49.3%). The commonest associated autoimmune disorder was hypothyroidism (8.1%). The commonest insulin regimen was split mix regimen using regular insulin thrice a day and intermediate insulin twice a day, before meals (48.5%). There were no differences between sexes for any of these findings. **Conclusion:** Winter was the commonest season for diagnosis. Diabetic ketoacidosis is no longer the commonest mode of presentation. Commonest symptom is polyuria. Hypothyroidism was the commonest associated disorder and there did not seem to be any gender bias in presentation.

P2-P298

Insulin Response at Standard Glucose Load in Children With Normal, Low and Excessive Body Mass

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Background: Obesity epidemic is associated with diabetes and it's complications at young age. Meanwhile, there is no recommendation concerning stratification as a risky for the overweight without dysglycemia by WHO criteria. **Objective and hypotheses:** Insulin response during OGTT might be dependent on BMI and can reflect preclinical stage of dysglycemia **Method:** 72 otherwise healthy adolescents aged 13.56 ± 2.47 y.o. were examined with standard 2-hrs oral glucose tolerance test (OGTT). Subjects were grouped by BMI Z-score: − <1 S.D. low weight (LW, $n=11$), ±1 S.D., normal weight (NW, $n=16$), +1–2 S.D., overweight (OW, $n=14$), +2.1–3.0 S.D., obese (OB 1, $n=18$), + >3 S.D., obese (OB2, $n=13$). **Results:** Dysglycemia by the WHO standards was registered in 37.09% of subjects with excessive body mass: 24.19% of IFG (OW, OB1, OB2), 6.4% IGT (OB 2) and 6.4% IFG + IGT (OB 1, OB 2). It's about 51.11% of total overweight.

All of them were insulin resistant. No one case of diabetes revealed. Fasting insulin was gradually increasing from group to group (6.91; 10.17; 25.84; 30.71; 41.23 μIU/ml; $P<0.01$) as well as HOMA-IR (1.75; 2.69; 5.62; 6.85; 8.56; $P<0.01$) and average insulin concentration during the test ($P<0.01$). Peak insulin response was registered in LW at 30 min and in NW, OW, OB1 and OB2 at 15 min. Afterwards insulin levels were decreasing in LW and NW. Meanwhile it was tendency for insulin level to grow up in all overweight and obese. Insulin dropped down in all subjects at 120 min. Simultaneously, insulin at 120 min was higher than fasting at 387% in LW, 67% in NW, 156% in OW, for 100% in all obese ($P<0.01$). Insulin dynamic demonstrates high variability in LW and OW together with least result in OB2. **Conclusion:** There is a linear dependence of fasting and average insulin concentration on BMI. There is a strongest response in LW and NW subjects during the first phase of insulin response and in OW and OW during the second one. It reveals a necessity to stratify subjects with low variability during OGTT and absent decrease of insulin level after 30 min. as risky even despite of absent diabetes and dysglycemia.

P2-P299

Initial Presentation of Subjects with Type 1 Diabetes: A Change in Spectrum

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Background: The classical presentation of type 1 diabetes mellitus is as diabetic ketoacidosis. As health awareness and access to healthcare improves, more subjects with type 1 diabetes are diagnosed early and present with less severe forms of hyperglycaemia. India accounts for most of the children with type 1 diabetes in South East Asia, but studies on the initial presentation is lacking from India. **Objective and hypotheses:** The aim of the study was to analyse the initial presentation of subjects with type 1 diabetes attending outpatient department. Subjects with other forms of diabetes were excluded. **Method:** The initial presentation of type 1 diabetes was classified arbitrarily into four types. Data was collected by referring to previous discharge summaries and patient histories from file. Type A: Classical diabetic ketoacidosis (DKA) requiring admission. Type B: Probable DKA. Type C: Severe hyperglycaemia requiring admission. Type D: Hyperglycaemia and/ketonuria managed as outpatient. Descriptive statistics were used and SOFA (Open Source) was used for statistics. **Results:** There were 102 patients in the group. Mean age: 11 years (0.6–30 years, 48M, 54F). Majority of the patients were diagnosed in the 6–12 age group (35, 34.5%) followed by 13–18 years (27, 26.6%). 40% (39) of subjects did not require admission for management. In younger children (<6 years), all children were admitted at diagnosis (Type A: 25, Type B: 1). In the older group (>13 years), most patients were managed as outpatient (Type A: 1, Type D: 40). More subjects diagnosed after 2011 were managed as outpatient. **Conclusion:** 40% of subjects with type 1 diabetes, did not require admission at presentation. Admission was more common among younger patients and those patients presenting before 2010.

P2-P300

Evaluation of the Epidemiological, Presenting and Follow-up Characteristics and their Impacts on the Glycemic Control in a Large Cohort of Pediatric Type 1 Diabetes Mellitus Patients from Southeastern Anatolian Region of Turkey

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Background: Type 1 diabetes mellitus (T1DM) is one of the most common chronic disease in childhood. Evaluation of the factors that have impact on the glycemic control and developement of complications would help to develop preventive strategies for management of this group of patients. **Objective and hypotheses:** To evaluate epidemiological, presenting and follow up characteristics and their relationship with glycemic control in pediatric T1DM patients from Southeastern Anatolian Region of Turkey. **Method:** Hospital records of pediatric T1DM patients being followed at Diyarbakir Children's State Hospital and Diyarbakir Gazi Yasargil Training and Research Hospital were retrospectively reviewed. **Results:** Number of patients recruited was 538 (292 female, 246 male). Mean age of diagnosis was 8.2 ± 4.3 years. The frequency of presentation with diabetic ketoacidosis (DKA) was 51.9% with no gender discrepancy (Presentation with DKA:54.1% vs 49.1%, $P=0.303$), while patients with diabetes history at their families had lower rate of DKA at presentation (The rate of DKA: 47.3% vs 58.7%, $P=0.040$). Mean HbA1c level of female (9.6 ± 2.2) and male (9.2 ± 2.2) subjects at last follow-up visit was not different ($P=0.079$). While, HbA1c levels in prepubertal patients was significantly lower than those of pubertal group (Mean HbA1c: 8.9 ± 1.6vs.9.7 ± 2.2, $P=0.000$). Glycemic control for patients who were living at rural or urban area were also not statistically different (Mean HbA1c: 9.5 ± 2.4 vs 9.4 ± 2.2, $P=0.616$). Maternal and paternal education status was not found related to glycemic control (P value: 0.267 and 0.087). Celiac disease was associated to T1DM in 40 out of 375 (10.7%) and Hashimoto's thyroiditis in 30 out of 463 (6.5%) patients. Diabetic nephropaty was the most common chronic complication detected in 24 out of 212 (11.3%). Rate of diabetic nephropaty for prepubertal and pubertal subjects was not different ($P=0.169$). **Conclusion:** In our cohort about half of patients was presented with DKA which was lower in cases with history of diabetes at their families. Puberty was related to poor glycemic control, while rate of complications did not differed with regard of pubertal status.

P2-P301

HbA1C and IGF-1 Levels in Diabetic Children Treated with Vitamin D

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Background: Diabetes mellitus type 1 (T1DM) is the most common chronic diseases in children. Studies show that the prevalence of vitamin D deficiency is higher in this group of patients. **Objective and hypotheses:** The aim of this study was evaluation HbA1C and IGF-1 levels in children with T1DM that receiving vitamin D supplement. **Method:** A total of 30 diabetic children 5–15 years with 25(OH) D levels lower than 74 nmol/l (29 ng/ml) were selected. Vitamin D supplement were given to patients for 8 weeks. Concentrations of serum 25(OH) D, IGF-1 and HbA1c were compared between baseline and after treatment. **Results:** The mean concentrations of serum 25(OH) D and IGF-I were significantly increased from 16.27 ± 6.56 and 245.57 ± 108.9 at baseline to 40.80 ± 1.17 and 264.46 ± 104.30 respectively. The mean concentrations of HbA1c were significantly decreased from 8.89 ± 1.39 to 8.60 ± 1.23 ($P = 0.047$). Serum HbA1c correlated negatively with Serum 25(OH)D ($r = -0.40$, $P = 0.05$) and IGF1 ($r = -0.69$, $P < 0.001$). **Conclusion:** Treatment with vitamin D improved glycemic control in children with T1DM. This study showed that serum IGF1 related to glucose homeostasis in this patients.

P2-P302

Long-Term Follow-Up of Non-Diabetic Obese Children and Adolescents Treated with Metformin

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Introduction: Childhood obesity is an important public health problem with increasing prevalence. Type 2 diabetes (T2DM) is strongly associated with obesity and metabolic syndrome. Adressing obesity and insulin resistance by drug treatment represents a rational strategy for the prevention of T2DM. **Aim:** The aim of our study was to evaluate the one year metformin treatment's long-term effectiveness in children and adolescent. **Method:** Patients who were diagnosed with obesity (VKİ $> +2$ SDS) and found to have insulin resistance (total insulin at OGTT > 300 mIU/ml and homa-IR > 3.4), aged between 10 and 18 years, treated with metformin in addition to lifestyle change for a year and with regular follow-up for a minimum of 2 years after metformin treatment in our clinic were included in the study. **Results:** A total of 12 cases including eight girls with a mean age of 13.2 ± 2.1 years and mean follow-up duration of 3.9 ± 1 years were included in the study. While the BMI of the cases at presentation was 31.2 ± 5.6 kg/m^2 and BMI-SDS was 2.7 ± 0.7, the BMI-SDS value after one year of metformin treatment was found to have regressed to 1.9 ± 1 ($P = 0.04$), and the BMI-SDS value 2 years after the interruption of metformin treatment had increased to 2.1 ± 1.04 but was not as high as the period before metformin treatment ($P = 0.033$). **Conclusion:** One-year metformin treatment improved the BMI-SDS values of the obese children and this improvement decreased but continued in the second year after the discontinuation of the treatment.

P2-P303

Understanding the Molecular and Genetic Basis of Complex Syndromes of Diabetes Mellitus

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Background: The two most commonly known types of Diabetes Mellitus (DM) are DM type 1 and DM type 2, characterized by insulin deficiency and insulin insensitivity, respectively. DM can also be associated with rare mutlisystemic syndromes such as Alstrom, Bardet-Biedl, Wolfram and pigmentary hypertrichosis insulin dependent diabetes (PHID) syndromes. **Objectives:** To understand the genetic and molecular basis of syndromic DM in a large cohort of patients. **Methods:** Homozygosity mapping, followed by confirmation using Sanger sequencing were used to find novel and rare mutations. Protein expression was then studied using Western Blots. **Results:** So far, five patients from Turkey have been identified to have novel causes of Wolfram Type 1, which is a progressive disorder characterized by diabetes insipidus (DI), diabetes mellitus (DM), optic atrophy (OA) and deafness (D) and is known as DIDMOAD. Western Blots show no protein expression. Moreover, 1 patient from Turkey has been identified to have Wolfram Type 2, which differs from Wolfram Type 1 by the absence of DI. Also, 2 siblings from Turkey have been found to have novel variances in the untranslated regions of the gene responsible for the pigmented hypertrichosis insulin dependent diabetes (PHID) syndrome uncovering a novel molecular mechanism for this condition. **Conclusion:** This study so far identified novel causes of Wolfram Type 1 and PHID syndrome. Further work is ongoing to understand the molecular and genetic mechanisms of these and other rare DM syndromes.

P2-P304

Cardiovascular Risk and Long Term Follow-up of Turkish Children with Type 2 Diabetes: Single Center Experience

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Background: Type 2 diabetes (T2DM) increases in parallel with obesity in childhood. T2DM can be associated with cardiovascular risk (CVR) even childhood. **Objective:** To investigate the presence of CVR criterions in children with T2DM and to detect CVR as the earliest age as possible. **Method:** This study enrolled 84 (58 Girls) children with T2DM. OGTT was performed in 47 children. Biochemical and hormonal analyses were performed in fasting state. The presence of hepatosteatosis, polycystic ovaries and microvascular complications were investigated. At admission, atherogenic index of plasma (AIP) and atherosclerosis-index (AI) were calculated. **Results:** Mean age was 13.4 ± 2 years. Clinical features are given in Table 1. 55.1% of girls were obese and 80.7% of boys were obese. 35 patients had been followed for 24 months. The youngest patient with high AIP (> 0.21) was 8.9 year-old girl and the youngest patient with high AI (> 3.1) was 10.6 year-old boy. AIP was high in 90% of patients and high AI was found in 38% of them. 81.5% of them had hepatosteatosis. Autoantibodies were detected in 15 of 60 patients. 65.4% of patients had ≥3 cardiovascular risk criterions. Significant differences were found in BMI between at admission and at 3 rd, at 6 th and at 12 th months ($P=0.001$, $P=0.024$, $P=0.049$, respectively). There was a difference in HbA1c between at admission and at 12th months ($P=0.021$). BMI-at admission was correlated with systolic-blood-pressure (SBP) (0.488), diastolic-BP (r:0.450), HOMA-IR (r:0.307), Quicki (r:−0.307), FGIR (r:−0.336), AST (r:0.268) and ALT (r:0.348). AIP was positively correlated with BMI-SD at-admission (r:0.231), SBP (r:0.259), ALT (r:0.380), AST(r:0.298) and microalbuminuria (r:0.315). BMI-at admission is the determining factor on AIP ($P=0.005$). **Conclusion:** Cardiovascular morbidity is high in T2DM. Children with T2DM have increased CVR even if younger than age of 10. BMI is the most important determining factor of CVR. AIP and AI might be useful for early diagnosis in clinical practice.

Table 1.

	Total *n*:84	**Girls** *n*:58	**Boys** *n*:26
BMI SDS	2.3 (0.6)	2.15 (0.75)	2.4 ± 0.4
SBP, mmHg	121 ± 16	119 ± 15	127 ± 16
DBP, mmHg	78 ± 13	77 ± 13	82 ± 14
HbA1c-0, %	8.4 ± 2.8	8.1 ± 2.6	9.2 ± 3
HOMA-IR	5.62 (15.5)	7.45 (6.9)	6.29 (8.4)
Quicki	0.28 ± 0.03	0.28 ± 0.03	0.28 ± 0.03
FGIR	5.3 (7.41)	7.2 (14.2)	16.4 (19.5)
AIP, log (Triglyceride/HDL)	0.58 ± 0.33	0.59 ± 0.25	0.57 ± 0.46
AI, (LDL/HDL)	2.9 ± 1	2.9 ± 1	2.8 ± 1.1

P2-P305

Thiamine Responsive Megaloblastic Anemia Due to *SLCA19A2* Gene Mutation: Another Cause of Neonatal Diabetes with Succesfull Switch from Insulin to Thiamine

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Itroduction: Thiamine responsive anemia (TRMA) known as Rogers syndrome; is an early-onset, autosomal recessive disorder characterized by diabetes mellitus, megaloblastic anemia and sensorineural deafness. Diabetes in this condition is well described in infancy but has only very rarely been reported in association with neonatal diabetes. **Case:** 3-months old male patient with neonatal diabetes was admitted to our outpatient clinic because of uncontrolled hyperglycemia under insulin treatment. History revealed parental consanguinity, he was born 2000 g at 32nd week of gestation. He was operated on the second day of life due to prenatal diagnosis of duodenal atresia. During hospitalization in intensive care unit, hyperglycemia and supraventricular tachycardia had been detected. Insulin, propranolol and amiodarone was started and the patient was discharged 20 at day of life. The patient was hospitalized for glycemic regulation. On admission he was 56 cm (3 p.), 3.4 kg (< 3 p.); head circumference was 38 cm (3 p.). Physical examination was normal and neuromotordevelopment was consistent with age. He had been on NPH insulin 0.18 mg/kg per day-divided into two doses. HbA1c level was 7.2%, blood glucose was 277 mg/dl, C-peptide level was 0.28 mg/dl. Diabetes autoantibodies were negative. He had frequent hyper andhypoglycemias during the day. Blood glucose levels improved after switching toinsulindetemir three times a day. RFX-6 mutation was examined owing to associated duodenal atresia, was found negative. The patient also had anemia (Hb:8.2 g/dl, MCV:84, MCHC:35.7, ferritin 69 ng/dl, Vitamin B12: 168). Replacement therapy for vitamin B12 deficiency was given. Homozygous frame shift mutation (c.242 dup; p.Y81X) on exon 2 of *SLCA19A2* gene; previously identified on Iranian patients; was detected with next generation sequencing method. Thiamine replacement was started intramuscularly at first (2 × 100 mg/day, five times in total) and then continued as 30 mg/kg per day per oral (divided into two doses). After thiamin replacement, insulin requirement decreased gradually, and insulin therapy was stopped at the end of the first week. Ketosis and hyperglycemia were not observed on the follow-up. He was discharged with oral thiamine. At the end of 3 months his HbA1c level was 6%.

P2-P306

Maturity-Onset Diabetes of the Young (MODY): Tracking and Clinical Follow-up

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Background: Maturity-onset diabetes of the young (MODY) is a monogenic form of diabetes, with an autosomal dominant mode of inheritance and high penetrance. To this date, it is known 13 subtypes of MODY with different genetic etiologies. It is characterized by high incidence in the family, an early onset and primary defect in pancreatic β-cell function. **Objective and hypotheses:** The primary objective of this study is to identify patients with MODY and detect the MODY subtypes prevalence among the study subjects. The confirmation of the MODY diagnosis often results in a personalized treatment for the patient and for the family members that also have diabetes, along with genetic counselling for all the subjects with MODY. **Method:** This is a cross-sectional study, with a quantitative approach that includes the genetic analysis of all the possible MODY patients. The study takes place in the Alcides Carneiro University Hospital (ACUH) of the Federal University of Campina Grande -Paraíba – Brazil (UFCG), in the Endocrinology Clinics of the Hospital. Patients diagnosed with diabetes mellitus type 1 (DM 1) were interviewed and, if they matched our study inclusion criteria, a blood sample was taken for the genetic analysis of MODY mutations. **Results:** A total of 565 patients diagnosed with DM 1 had medical appointments at least once in the ACUH endocrinology clinics. To this date, 67 patients were interviewed and six of those filled our study inclusion criteria, with the genetic analysis of four patients confirmed the diagnosis of 2 MODY2 and 2 MODY3 subjects. The medical records analysis of DM 1 patients revealed 18 possible MODY subjects and interviews will be scheduled. **Conclusion:** MODY represents around 2% of all diabetes cases in the world, and in Brazil about 280 000 have one of the MODY subtypes. The diagnosis is important to personalize treatment according to the MODY subtype and identify family members with the mutations.

P2-P307

Evaluation of Autoimmune Thyroiditis Development on Onset and During Follow Up in Cases with Type 1 Diabetes Mellitus

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Background: Type 1 diabetes mellitus (T1DM) is the most common endocrine disease in children and adolescents. **Objective and hypotheses:** It was aimed to evaluate the frequency of autoimmune thyroiditis (AT) and the possible risk factors for AT at diagnosis and at follow up of T1DM patients. **Method:** T1DM patients who were admitted to Trakya University Medical Faculty Pediatric Department, Pediatric Endocrinology Outpatient Clinic between January 2006 and September 2013 were evaluated. **Results:** The mean age of 134 (63 M, 71 F) cases was 11.3±4.6 years, mean diagnosis age of diabetes was 8.1±3.9 years and mean diabetes duration was 3.1±2.4 years. Most of the cases were diagnosed at spring and winter, and most common administration reason was diabetic ketoacidosis (52.7%). At the diagnosis of T1DM, mean HbA1c was %12.3±2.7 and mean C-peptide was 0.43±0.39 ng/ml. Glutamic acid decarboxylase, anti-insulin and islet cell antibodies were positive in 47.4%, 1.7% and 0.9% of the cases, respectively. AT was found in 19 (5 M, 14 F) out of 134 cases (%14.2). The mean age of these cases was 13.9± 3,6 years and diabetes duration was 4.2±2.9 years. At the diagnosis of AT 68,4% of cases were between ages 10 and 15 years and 78.9% were pubertal. All cases were euthyroid at diagnosis but six of them then developed subclinical hypothyroidism. Sex, age, puberty, anthropometric measures, clinical and laboratory findings at the time of diagnosis of T1DM were similar in AT positive and negative cases. The mean age was higher and number of pubertal cases was more in T1DM cases with AT. **Conclusion:** In conclusion, AT incidence is high in T1DM cases, especially at puberty. At the time of diagnosis, cases with AT are mostly euthyroid but because thyroid dysfunction may be seen in the feature, close follow up is crucial. Therefore, T1DM cases should be assessed for thyroid autoantibodies and thyroid hormones annually.

P2-P308

The Autoimmune Hypothesis for Acute Bilateral Cataract in Type 1 Diabetes

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Background: Cataract as a chronic complication of diabetes is well established in the literature and the risk factors are also well known. However, rare cases of acute bilateral cataract have been reported, all of them happening relatively shortly after diagnosis in T1DM. While the pathophysiology of this phenomenon remains unclear – as a lot of different theories proposed so far with the most accepted being the osmotic stress induced oxidative damage – fail to explain adequately the acuteness of bilateral cataract formation - there have also been reports of acute bilateral cataract as the first presentation of T1DM. **Objective and hypotheses:** We have recently published a case of acute bilateral cataract in a paediatric patient with T1DM manifested 3 months after presentation with severe diabetic ketoacidosis and initiation of insulin treatment. **Method:** The cataract being completely

liquefied; no lens tissue could be sent to immunopathology in either of the two operations. The only remarkable change to his biology and autoimmune status were the previously negative at presentation of T1DM, now clearly elevated insulin autoantibodies (IAA): 1.4 (<1.1). **Results:** Our 'autoimmune hypothesis' proposes that the timing of the cataract formation – usually few weeks or months after onset of insulin treatment, as in our case-suggests an autoimmune response. More specifically, the IAA became positive within 3 months after the beginning of insulin treatment and this period coincides with the cataract formation. Unfortunately, we were unable to measure the IRA, which might have strengthened the autoimmune hypothesis, as decreased immunoreactivity for the insulin receptor has been found in the lens when cataract is detected. The timing of the occurrence of acute bilateral cataract in patients with good metabolic control, who do not carry the burden of a chronic diabetic decay, clearly implies an autoimmune mechanism on the grounds of a possible genetic predisposition for cataract formation. **Conclusion:** While previously reported theories fail to explain the acuteness of the phenomenon, there are indications to suggest a possible autoimmune mechanism for acute bilateral cataract in diabetes that warrants further investigation. Elucidation of a possibly autoimmune underlying mechanism could result in early detection and development of prevention strategies to avoid such a stressful complication.

P2-P309

Clinical Characteristics of Latent Autoimmune Diabetes in Youth (Type 1.5 DM)

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Background: Diabetes mellitus (DM) in childhood was mostly type 1 DM (T1DM), but sometimes it is not easy to classify, especially in the case having both type 2 clinical phenotype and autoantibody positivity. It is named as latent autoimmune diabetes in youth or type 1.5 DM (T1.5DM). **Objective and hypotheses:** This study was designed to evaluate the clinical characteristics of T1.5DM who had autoantibody positivity with clinical phenotype of T2DM. **Method:** Ninety five subjects who were diagnosed as having DM between 2001 and 2015 were enrolled in the study. Subjects with fulminant diabetes or less than 6 months of follow-up, or no assessment of autoantibody status were excluded. Study subjects were classified into type 1, 1.5, and 2 DM. Clinical features as well as laboratory findings were compared between groups. **Results:** Among 95 subjects, type 1.5, 1, and 2 DM were 11 (11.6%), 51 (53.7%), and 33 (34.7%), respectively. In T1.5DM, age at diagnosis and BMI *Z* scores were significantly higher compared to T1DM, and there was no DKA at initial presentation. Serum c-peptide levels were higher compared to those in T1DM (2.28 ± 1.42 ng/ml vs. 0.52 ± 0.44 ng/ml, $P < 0.001$). The titers of anti IA-2 autoantibody were significantly lower in T1.5DM compared to T1DM (4.86 vs. 45.95 U/mL, $P < 0.001$). During mean follow-up of 3.22 years in T1.5DM, 27% turned autoantibody negative, and 25% of the subjects who had persistently positive autoantibody needed intensive insulin treatment of more than 0.5 U/kg per day. **Conclusion:** In T1.5DM, it may be necessary to recheck autoantibody, especially in patients who initially had weakly positive autoantibody titer. It is important to closely monitor patients with T1.5DM because they might need intensive insulin treatment within several years.

P2-P310

Diabetic Ketoacidosis: Clinical Features and Precipitating Factors at DEMPU

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Background: Diabetic ketoacidosis (DKA) is an acute complication of type 1 diabetes mellitus (T1DM) that can be fatal if not properly managed. DKA is a leading cause of mortality in these children, early recognition and prompt treatment should substantially reduce childhood mortality in children with T1DM. **Objective and hypotheses:** We aimed to identify the risk factors and the most common clinical features of newly diagnosed diabetes in children, in addition to the factors related to delayed diagnosis or mismanagement in these children. **Method:** Over a 3 month period, 99 patients newly diagnosed with T1DM; 53 (24 females and 29 males) of which had DKA and 46 (23 females and 23 males) were hyperglycemic with mean (S.D.) age of 6.89 (3.63) and 6.75 (3.53) were recruited from the inpatient department of the Diabetic, Endocrine and Metabolic Pediatric Unit (DEMPU), New Children Hospital, Cairo University. **Results:** Polyuria, polydipsia and weight loss were the most common symptoms preceding the diagnosis (93.8%, 92% and 80.8% respectively). Delayed diagnosis occurred in 98.1% and 58.7% of DKA and hyperglycemic groups respectively. 69.8% of the DKA group were misdiagnosed as respiratory problems, gastroenteritis and urinary tract infections. Mismanagement was detected in 28.3% of DKA group. Multivariate analysis to predict the most significant risk factor(s) associated with the development of DKA at the time of diagnosis of T1DM showed delayed start of insulin therapy was the most significant risk factor associated with development of DKA with (OR = 1.267, *P* value = 0.023). **Conclusion:** Increased awareness of the health care professionals to start insulin therapy appropriately and early is needed to reduce the frequency and severity of ketoacidosis.

P2-P311

Diabetes Distress in Adolescents and Young Adults with Type 1 Diabetes

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Background: Age and gender are important factors in adjustment and psychological well-being in patients with chronic physical illness. **Objective and hypotheses:** To determine whether diabetes distress varies by age and/or gender in type 1 diabetic (T1D) patients. **Method:** Diabetes distress was compared in 255 adolescents and 283 young adults with T1D using Problem Areas in Diabetes Scale. **Results:** High diabetes distress level was found in 22.8% of participants. Lack of confidence in self-care (6.8 ± 5.6 vs 4.8 ± 5.3, $P = 0.001$), negative emotional consequences (11.5 ± 9.3 vs 8.8 ± 9.4, $P = 0.003$), overall score (22.9 ± 17.9 vs 17.0 ± 17.7, $P = 0.001$) were higher in adult than in adolescent males. There was a trend towards higher prevalence of negative emotional consequences in adult compared to adolescent females (14.2 ± 11.0 vs 11.5 ± 8.8, $P = 0.052$). Lack of confidence in self-care (6.8 ± 5.3 vs 4.8 ± 5.3, $P < 0.001$), negative emotional consequences (11.5 ± 8.8 vs 8.8 ± 9.4, $P = 0.001$), overall score (22.9 ± 16.9 vs 17.0 ± 17.7, $P < 0.001$) were higher in adolescent females compared to males. Negative emotional consequences score was higher in adult females compared to males (14.2 ± 11.0 vs 11.5 ± 9.3, $P = 0.041$). **Conclusion:** In conclusion, our findings add to evidence suggesting the importance of addressing diabetes distress in clinical care and the necessity of wider picture beyond the physical manifestation of diabetes to be taken into consideration.

P2-P312

A Novel Glucokinase Gen Mutation: Mody Type-2 Case

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Background: Maturity-Onset Diabetes of the Young (MODY) is a rare monogenic form of diabetes that result in β-cell dysfunction. MODY accounts for 2–5% of all diabetes cases. We presented here a family with MODY2 caused by a novel heterozygous p.L164I (c.490 C > A) mutation of the GCK gene. **Case:** A 15,5-year-old girl was admitted to our department because of fasting hyperglycemia. She had no polyuria, polydipsia and weight loss. Parents had no consanguinity. Her mother was 26 years old with a diagnosis of gestational diabetes in her second pregnancy, used metformin for eight years after having been diagnosed as diabetes. It was learned that her aunt and grandmother had diabetes and her cousin had gestational diabetes. On physical examination body mass index was 23.7 kg/m^2 (83p). She did not have acanthosis nigricans. Pubertal assessment revealed Tanner V. Blood glucose level was repeatedly checked and showed fasting hyperglycemia (114 mg/dl) as well as a mildly elevated hemoglobin A1c level 5.56%; and in the analysis of urine glucose and ketone were negative. Autoantibodies of diabetes were negative. A standard oral glucose tolerance test with 75 g of glucose equivalent was performed with a fasting glucose of 103 mg/dl and a 2-h glucose of 153 mg/dl. The fasting insulin concentration was 4.23 μU/ml and 20.88 μU/ml after 2 h. Considering the clinical and family history, mutation analysis of the GCK gene was performed. In the fifth exon of GCK gene of the patient's, mother, aunt and cousin, a previously unidentified heterozygous p.L164I (c.490 C > A) mutation was found. **Conclusion:** MODY should be suspected in children who is found to have a random rise of blood sugar and has a family history of diabetes. Cases and individuals who have a family history of diabetes should be screened respectively for mutation.

P2-P313

Congenital Hyperinsulinism in a Resource Limited Setting: Overcoming Barriers towards a Survival Path

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Background: Congenital hyperinsulinism is genetic disorder characterized by dysregulation of insulin secretion and it is the most common cause of persistent hypoglycaemia in infancy. The incidence in individuals of northern European extraction is approximately 1:30,000 live births. Published data on the diagnosis and management of congenital hyperinsulinsim in resource limited setting is scarce. **Objective and hypotheses:** To describe the clinical presentation, diagnosis and management of congenital hyperinsulinism in resource limited setting. **Method:** We report on an 18 months old boy who presented in the new-born period with history of poor suck and recurrent hypoglycaemic seizures. He was born by spontaneous vaginal delivery weighing 2.6 kg. The full septic work for possible infection was unremarkable. He was managed with recurrent oral feeds and intravenous dextrose infusion. To maintain euglycaemia, he required intravenous dextrose solution at 10 mg/kg/min. Critical blood samples taken during hypoglycaemic episode. **Results:** The results of the critical sample taken during a hypoglycaemic episode revealed; Blood glucose 0.02 mmol/l (range: 3.5–7.0 mmol/l), growth hormone 22.2 mIU/l (range: 0.2–13 mIU/l), insulin 22.8 mIU/l, C-peptide 1086 pmol/l (range: 364–1655), cortical 6147 nmol/l (range: 55–304 nmol/l), total cholesterol 3.3 mmol/l, triacylglycerides 0.78 mmol/l, high density lipoproteins 1.62 mmol/l, low density lipoproteins 0.6 mmol/l and no urine ketones. In view of the inappropriately elevated insulin levels in the presence of very low blood glucose, the diagnosis of congenital hyperinsulinism was made. He was commenced on oral diazoxide and frequent oral

feeds with polycose. He continued to develop recurrent hypoglycaemic episodes despite the treatment. Following 3 weeks of oral diazoxide therapy with no response, he eventually underwent partial pancreatectomy. The hypoglycaemic episodes resolved following that and he was discharged home. **Conclusion:** The diagnosis and management of congenital hyperinsulinism is feasible in resource limited setting. Congenital hyperinsulinism should be considered in the differential diagnosis of children presenting with recurrent hypoglycaemia at any age.

P2-P314

Vitamin D Levels and Relations with Clinical and Laboratory Findings in Children with Newly Diagnosed Type 1 Diabetes

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Background: Vitamin D deficiency (VDD) is common in the general pediatric population of the world. Some studies reported that low vitamin D levels with an increased risk of diabetes. **Objective and hypotheses:** VDD can be more common in children with type 1A diabetes (DM1A) than those with type 1B diabetes (DM1B). To evaluate 25OHD levels in children with newly diagnosed DM1A and DM1B patients and investigate any relation with clinical and laboratory data at diagnosis. **Method:** Forty-five children (25 girls) with newly-diagnosed DM1 were included in the study. Levels of 25(OH)D, hemoglobin A1c (HbA1c), venous pH and bicarbonate, diabetes-related autoantibodies (islet autoantibody, GAD65, and IAA) were measured at diagnosis. VDD was defined as 25(OH)D level <15 ng/ml. Serum 25(OH)D were assessed by high-performance liquid chromatography. **Results:** Mean $\pm$ standard deviation 25(OH)D levels were 17.0 ± 15.7 ng/ml and age was 8.4 ± 4.3 years. The frequency of VDD was 56%. No gender and age differences were noted between the vitamin D deficient ($n=25$, 65% girls) and non-deficient children. In those with VDD had lower pH and bicarbonate than that of non-deficient ($P<0.05$). The majority of the children (73%) were diabetes-related autoantibody positive (DM1A) and 27% was negative (DM1B). 25(OH)D levels were 14.9 ± 12.3 ng/ml in DM1A patients and 22.5 ± 22.2 ng/ml in DM1B patients ($P>0.05$). HbA1c was lower in DM1A patients than DM1B patients (11.1 ± 2.0 vs 13.4 ± 3.0; $P<0.01$). There was no correlation between 25(OH)D and HbA1c or age. **Conclusion:** VDD is common at onset of DM1 patients. Although we did not establish significantly decreased 25(OH)D levels in children with DM1A when compared with DM1B, we did establish that more severe clinical presentation in patients with VDD. It is obvious that avoiding VDD in children at risk of developing diabetes should be advocated. Supplements of vitamin D can improve insulin sentitivity in patients with DM1.

P2-P315

Lipid Profile, Lipid Per-Oxidation and Trace Elements Status in Libyan Males with Type II Diabetes Mellitus

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The metabolism of several trace elements is altered in diabetes mellitus (DM). The present study investigates serum levels of lipid profile and lipid per-oxidation as well as levels of Mg, Cu, Ni, Co, Mn, Cr, Se, V and Zn, in 72 males with non-insulin-dependent DM (T2DM) and 21 non-diabetic healthy control subjects using inductively coupled plasma optical emission spectrometry (ICP-OES). The results showed highly significant increase in serum concentrations of LDL-C, TG and cholesterol in T2DM patients in comparison with non-diabetic subjects ($P<0.001$). The levels of Zn, Mg and V in male diabetic patients showed significant decline as compared to controls ($P<0.001$). Also serum Cr and Co showed a significant decrease between non-diabetic subjects and T2DM patients ($P<0.05$), whereas Ni, Mn and Se showed no significant differences between the control and T2DM patients. The serum Cu level revealed a substantial increase in T2DM patients compared to non-diabetic individuals ($P<0.001$). Therefore, deficiencies in trace elements and high level of lipid per-oxidation products appear to be possible additional risk factors in the some pathogenesis of type-2 DM and its complications. In addition, they could be used as markers to evaluate the glycemic control and the lipid status of diabetic patients.

P2-P316

Cystic Fibrosis Related Diabetes

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Background: Cystic fibrosis-related diabetes (CFRD) is the most common co-morbidity in association with cystic fibrosis. Cystic fibrosis related diabetes is predominantly an insulin deficiency state it shares features of both type 1 and type 2 diabetes, yet there are important differences, which necessitate a unique approach to diagnosis and management. Development of cystic fibrosis related diabetes is associated with a worse lung function, poorer nutritional status, and more chest infections. **Method:** This is a retrospective study at KFSH & RC 300 Cystic fibrosis patients were reviewed including 173 females, and 127 males**. Results:** At KFSH & RC 300 Cystic fibrosis patients were reviewed including 173 females (58%), and 127 males (42%). 35 (12%) patients had CFRD, 12 males (9%), 23 females (13%). 64% had developed DM before the age of 15 years. Oral glucose tolerance test (OGTT) was performed as a screening test in patients above the age of 10 years. The majority of tests were done in the years of 2014 and 2015 including 26 (8.6%) patients. 9 (34%) patients had CFRD, 9 (34%) had impaired glucose tolerance, 8 (31%) had normal glucose tolerance. **Conclusion:** CFRD appeared to be more common in females than males. The onset of CFRD is very early in the studied population. Physicians started

performing oral glucose tolerance test (OGTT) to screen Cystic fibrosis patients. One third of the population screened had CFRD. More studies need to be done to identify the incidence and the prevalence of CFRD among CF patients.

P2-P317

Type 1 Diabetes in Childhood: An 8-year Experience

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Background: Type 1 diabetes mellitus (DMI) is a chronic disease that requires frequent visits in outpatient pediatric endocrine clinics in order to rearrange their new lives. **Objective and hypotheses:** A retrospective study of patients with DMI was performed during 2008–2015, assessing epidemiological and clinical data, treatment and subsequent course. **Method:** We analyzed the incidence, age and gender of 75 patients at the disease's onset, the HbA_1c at first admission, 2, 4, 6 and 8 years of treatment and the type of insulin received. Statistical analysis was performed with SPSS. **Results:** The average age of DMI onset was 7.82 ± 3.56 years and two seasonal peaks were observed, mainly in January (33%) and April (30.6%). Initial signs were ketoacidosis (61.3%), ketosis (28%) and hyperglycemia as an incidental finding (10.7%). One single case of severe ketoacidosis was reported and no acute complication occurred during DKA treatment. The average HbA_1c at the onset was $12.3 \pm 2.08\%$ and no significant difference was found between the age groups, although all younger patients presented moderate ketoacidocis. Two years after the first diagnosis HbA_1c was reduced. However, there has been an increase of HbA_1c through the years, especially in puberty. The majority of patients received insulin glargine and lispro. The last year, five patients (>14 years old) started treatment with TRESIBA, as basal insulin, and five teenagers put insulin pumps, with no significant difference in their metabolic control, but with an improvement in their quality of life. Finally, after 8-year follow-up, no complication occurred. **Conclusion:** The type of insulin therapy has no big effect on the diabetic control, but the proper psychological support and the education in order to deal with their new way of life is more important.

P2-P318

A Rare Reason of Type 2 Diabetes: Alström Syndrome

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Background: Alström Syndrome (ALMS), occurred due to mutations in ALMS1 gene, is a rare otosomal ressesive disorder. Seven hundred cases have been reported so far. Main clinical findings are rod con dystrofy, neurosensorial deafness, obesity and type 2 diabetes. Hypogonadism, hypothyroidism, growth hormone deficiency, hipertryglyceridemia, cognitive dysfunction, cardiomyopathy, renal, hepatic and pulmoner disorders could also be seen. **Objective and hypotheses:** Herein, we report a patient with ALMS who experienced both type 2 diabetes and hepatic disorder. **Method:** A 15-year-old boy was referred to Pediatric Endocrinology outpatient department because of hyperglycemia. He was born at 40 weeks after a normal pregnancy as a son of consanguineous family and his birth weight was 3600 g. It was learned that he encountered visual problems when he was 1 and moderate deafness when he was 6 years old. The patient presented with truncal obesity, achantosis nigricans, moderate deafness, visual problems and nystagmus. His height was 163 cm (SDS: -1.03) and weight was 76.8 kg (SDS: 1.45). Fasting blood glycemia was 255 mg/dl, insülin 86.5 mikroIU/mL, ALT 113 U/L, AST 75 U/L and triglyceride level was 238 mg/dl. Abdominal ultrasound revealed grade 1 steatohepatitis. Rod con distrofy was detected. **Results:** Due to type 2 diabetes accompanied with rod con distrophy, deafness and high transaminase levels, ALMS was considered. Homozygote c.10975C>T mutation was detected in ALMS1 gene. At first, life style changes were advised as the treatment of type 2 diabetes. However hyperglycemia continued. Because of high transaminase levels glargine insülin was initiated instead of metformin. **Conclusion:** First choice in treatment of type 2 diabetes are life-style changes and metformin. Metformin is a hepatotoxic drug. We thought that if there is a suspicion of hepatic pathology metformin should not be considered as a first line therapy.

P2-P319

The Relationship among Cardiac T2*, Liver T2* and Abnormal Glucose in Patients with Thalassemia Major

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Background: Abnormalities in glucose homeostasis are fairly common complications in thalassemia major (TM) patients. Previous studies had shown associations between some endocrinopathies and iron overload of the myocardium, liver as assessed by MRI techniques. This study aimed at determining the relationship among cardiac T2*, liver T2* and abnormal glucose in TM patients. **Objective and hypotheses:** A total of 34 (27 male) transfusion-dependent TM patients were included. **Method:** The fast blood glucose (FBG) and insulin level, serum ferritin (SF), cardiac T2*, liver T2* were evaluated in all subjects. Insulin resistance index (IRI) and β cell function index were also estimated. **Results:** The mean age was 11.17 ± 4.27 years. The mean SF level was 3795.93 ± 2764.81 ng/ml. The mean cardiac T2* was 21.51 ± 12.46 ms. There were 41.17% of patients with cardiac T2* <20 ms. The median liver T2* was 1.62 (0.53–18.52) ms. Only 2.94% of patients with liver T2* $>$ 6.3 ms. 14.7% of patients had insulin resistance (IR); 23.53% had impaired fast glucose; 5.9% had got diabetes mellitus. The incidence of abnormal glucose patients were lower with cardiac T2* >20 ms than those whose

cardiac T2* were less than 20 ms ($P=0.006$). There were no statistical differences between liver T2* and the incidence of abnormal glucose. The liver T2* was well correlated with FBG, insulin and IRI. The result of logistic regression analysis indicated that the cardiac T2* was a significant predictor for the incidence of abnormal glucose in TM patients ($P=0.035$; odds ratio = 1.182%; 95% CI = 1.048–1.332). **Conclusion:** The iron overload was much severer in TM patients of our centre, especially the liver iron overload. Liver T2* may have a relationship with insulin resistance and cardiac T2* was the independent risk factor of the incidence of abnormal glucose in patients with TM.

P2-P320

Hyperglycaemia in a Boy of 13 years old: Not always Type 1 Diabetes Mellitus. A Case Report

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Background: Type 1 diabetes (T1D), the most frequent type of diabetes in paediatrics, can be easily misdiagnosed presenting with hyperglycaemia due to monogenic diabetes. **Objective and hypotheses:** We report a 13-year-old boy with monogenic diabetes, initially diagnosed and treated as T1D. **Method:** The patient presented at 7.5 years of age with a febrile illness and mild hyperglycaemia. An oral glucose tolerance test (OGTT) then was normal, HbA1c 6.3% (45 mmol/mol). Slowly progressing T1D was diagnosed; he stayed under follow-up with routine BMstix measuring at home (max blood glucose (BG) 153 mg/dl (8.5 mmol/l). A repeat OGTT at the age of 9 years showed BG 127 mg/dl (7.1 mmol/l) at 0' and 258 mg/dl (14.3 mmol/l) at 120', HbA1c 6.7% (50 mmol/mol). He started on small doses of insulin. His glycaemic control was excellent; he remained on small doses of insulin (0.1 U/Kg/d) for 4 years. The patient discontinued insulin without medical advice. Six months later, he had mild fasting hyperglycaemia, (BG 107–148 mg/dl (6–8 mmol/l)), HbA1c 6.2% (44 mmol/mol); Anti-GAD, ICA and IA2 were negative. OGTTs were normal for father and younger sister aged 2 years. His mother, 37 year old, had gestational diabetes, her OGTT showed BG 147 mg/dl (8.2 mmol/l) at 0' and 121 mg/dl (6.7 mmol/l) at 120', HbA1c 6.4% (46 mmol/l); negative anti-IA2 antibodies. DNA analysis was carried out for the presence of mutations in HNF1A and GCK genes employing bidirectional sequencing of the coding regions of the two genes. MLPA was employed to search for deletions in the genes *GCK, HNF1A, HNF4A, HNF1B.* **Results:** Point mutations were not detected in the genes *GCK* and *HNF1A*. The MLPA revealed that the patient and his mother were heterozygotes for *GCK* gene deletion (exons 1–10). **Conclusion:** MODY2 is a form of monogenic diabetes resulting in β-cell dysfunction, characterized by mildly elevated fasting blood sugars and HbA1c ranging from 5.6–7.6% (38–60 mmol/mol). It is frequently unrecognized or misdiagnosed as T1D or T2D, resulting in unnecessary insulin treatment.

P2-P321

Achievement of Metabolic Parameter Goals in Children and Adolescent with Type 1 Diabetes According to the Latest ADA/ISPAD Standards of Medical Care in Diabetes in a Pediatric Diabetes Clinic in North Greece

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Background: Blood glucose control in children and adolescents with type 1 diabetes (TD1) is the most important goal in order to reduce potential complications. Following up these patients frequently and recording the relative metabolic parameters on a regular basis is necessary. **Objective and hypotheses:** The aim of the study was to compare the level of metabolic control in the children and adolescents with TD1 that are followed up in our Pediatric Diabetes Clinic with the targets set by the latest ADA/ISPAD Standards of Medical Care in Diabetes. **Method:** Seventy-four children and adolescents (38 boys, 36 girls), aged 12.6 ± 3.9 years old, suffered from TD1 for 5.8 ± 4.1 years, met the criteria (< 18 years old, > 1 year from TD1 diagnosis, > 3 visits per year) for participating in the study. 61% of the patients had normal weight, 25% were overweight and 14% obese. Fifty of the patients were under multiple insulin injections and 24 on insulin pump. For all patients metabolic parameters (HbA1c, BMI, Blood Pressure, LDL, HDL, Triglycerides) were recorded and they compared with the goals set by ADA (HbA1c < 7.5%, LDL < 100 mg/d, HDL > 35 mg/dl, TG < 150 mg/dl, BMI < 85th centile, BP < 90th centile). **Results:** In total, 62% of patients achieved HbA1c target (7.4 ± 0.8). There was no difference between patients on multiple insulin injections or insulin pump (7.3 ± 0.8 vs 7.4 ± 0.9, respectively). When the patients were categorized by age (< 12 and > 12 years old), it was found that 65% of the patients over 12 years old and 54% of those below 12 years old had HbA1c < 7.5%. Lipid profile targets for HDL (58 ± 15 mg/dl), LDL (98 ± 28 mg/dl), TG (70 ± 33 mg/dl), were achieved by 97, 54, 97% of all patients respectively. In total, 97% of the patients had normal BP. **Conclusion:** Regular monitoring (at least three visits per year) of TD1 patients can lead to a better glucose control, thus reducing the potential for future health complications.

P2-P322

Clinical and Laboratory Characteristics of Children and Adolescents with Type 1 Diabetes Mellitus

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Background: Prevelance of type 1 Diabetes Mellitus is increasing world wide and it is associated with multiple factors. **Objective and hypotheses:** We aimed to evaluate the clinical and laboratory characteristics of patients with type 1 DM. **Method:** Clinical records of 184 patients with diabetes (0–18 years) admitted between January 2010 and January 2014 were analysed retrospectively. Age and season at admission, type of admission, anthropometric measurements, pubertal status, laboratory tests including, blood glucose, electrolytes, gases, HbA1c, insulin, c-peptide levels, thyroid function tests, lipid profile, thyroid and pancreas autoantibodies were recorded. **Results:** Among the patients 53.9% ($n=99$) were girls. Mean chronological age at admission was 8.28 ± 4.28 years. Short stature was observed in 3.2, 1.6% were overweight. More patients were prepubertal (58.1%) ($P=0.019$). Family history was positive for type 1 DM and type 2 DM in 9.78 and 44.6% of the patients. History for an infectious disease 3 months prior the onset of diabetes was observed in 20.4%. Type 1DM was most frequently diagnosed in fall (30.4%) and winter (30.4%), ($P<0.05$). In both genders age distrubution showed peak intervals between 8 and 12 years. Age distrubution didnot differ between genders. Presentation was with diabetic ketoasidosis (DKA) in 37.5% ($n=69$). There was no difference in gender distribution, chronological age and anthropometric measurements between the patients presenting with and without ketasidosis. Fasting c-peptide level was lower in the patients with DKA ($P=0.019$). Subclinical hypothyroidism was observed in 2.2 and 7.3% of the patients with and with out DKA respectively. None of the patients had overt hypothyroidism. Hashimato thyroiditis was determined in 10.3%. In 71.1% of the patients at least one antibody was positive among three (anti-GAD, ICA, AIA) pancreas antibodies. **Conclusion:** Incidence of type 1 DM seems increased in relatively cold weather. Although there is no mechanistic relationship, family history for type 2 DM is high, that should be further investigated. Presentation with DKA is high, that makes relevant recognizing symptoms early.

P2-P323

Prevalence of Acute Metabolic Complications in Children with Type I Diabetes Admitted to the Children Hospital in Qazvin, Iran (2005–2014)

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Background: Type 1 diabetes (T1D) is one of the most common chronic diseases in childhood and adolescence. Diabetic ketoacidosis (DKA) and severe hypoglycemia are complications of T1D and are associated with significant morbidity and mortality. **Objective and hypotheses:** The aim of this study was to determine the prevalence of acute metabolic complications in children with T1D admitted to the children hospital in Qazvin during 2005–2014. **Method:** In this cross sectional study, data were collected from health profiles of 228 patients that were hospitalized with acute complications of T1D during 2005–2014. The measurement tool was a datasheet including demographics, signs and symptoms of T1D, characteristics at the onset of disease, and characteristics during the hospitalization period. Data were analyzed using descriptive statistics. **Results:** Of 228 patients, 70.2% were female. The mean age at onset of disease was 7 years and 1 month. The incidence of diabetes was increased from four cases per year in 2005 to 21 cases per year in 2014. The onset of T1D was diagnosed by DKA and hyperglycemia in 94.7 and 5.3% of patients, respectively. 0.9, 28, and 71.1% of the new cases of T1D had mild, moderate, and severe DKA, respectively. Seven percent of patients were <2 years old, 20% were 2–5 years old, 22.6% were 5–8 years old, and 50.4% were ≥ 8 years old. The peak incidence was found to be in autumn. Of 228 patients, 50% had an infection. Mean blood glucose was 513.28 ± 159.65 mg/dl and mean body mass index was 17.03 kg/m^2. **Conclusion:** A greater incidence of diabetes in females is because of their risk factors for autoimmune diseases. The high incidence of DKA at the onset of disease in the present study compared to the previous studies indicates the delay in diagnosis of T1D.

P2-P324

Glargine versus Detemir Insulin During the Honeymoon Phase in a Child with Type1 Diabetes Mellitus

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Background: The honeymoon period of type 1 diabetes mellitus (DM1) is characterized by reduced insulin requirements to <0.5 Units/kg per day while maintaining good glycaemic control. **Case study:** Seven years old boy who was diagnosed with type 1 diabetes mellitus presented with history of polyuria, polydipsia and weight loss for 3 weeks duration. His random Blood glucose $=408$ mg/dl with initial HBA1C 12.7%. Family history was unremarkable for diabetes or other autoimmune diseases. He had normal growth with no goitre or acanthosis nigricans. Systemic exam was unremarkable. He had low insulin level of 1.5 μu/ml and C peptide $=0.27$ ng/ml and normal thyroid function. AntiGAD antibodies were 12.6 IU/ml. Hamad was started on multiple daily injection of insulin glargine seven units in the evening + insulin Aspart before meals (using carbohydrate count

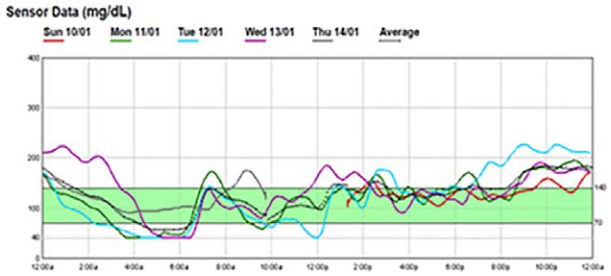

Figure 1. CGMS 1: Sever frequent hypoglycaemia.

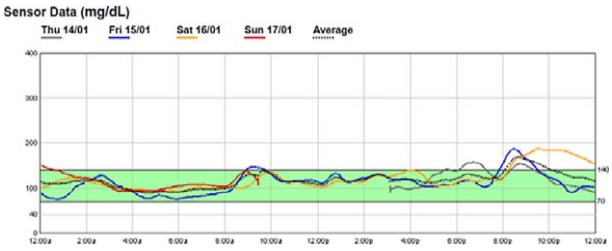

Figure 2. CGMS 2: No hypoglycimia.

(1 Unit/25 g) and BG correction (1 unit/for 50 mg/dl). After 2 weeks he developed frequent hypoglycaemias that required decreasing total insulin dose to 0.2 unit/kg per day (honey mooning). The dose of Glargine was decreased to 3 units/day at night and prandial Aspart discontinued as he was developing sever postprandial hypoglycaemia. In spite of that, hypoglycemia continued to occur. Continuous glucose monitoring (CGM) for 4 days showed severe hypoglycaemia reaching 40 smg/dl almost daily from 0330 h to 0630 h (Fig. 1). Glargine was discontinued and Detemir insulin given on two divided doses 2 units AM and 1 unit PM. CGM displayed no attacks of hypoglycaemia with highest blood glucose of 180 mg/dl and lowest of 85 mg/dl (Fig. 2). **Discussion:** The ongoing debate comparing Glargine and Detemir insulins is over which insulin has a flatter pharmacodynamics profile and longer duration of action is still there. In this patient, Detemir insulin appears to be better in avoiding hypoglycemia between 0330 h to 0630 h probably due to the prolonged effect of Glargine and overlap of its doses. **Summary:** Some patients of DM1 develop hypoglycemia during their 'honeymoon period' in which the symptoms remit and the patient requires little or no insulin. In our patient CGM monitoring showed that low doses of Detemir successfully abolished hypoglycemia. CGM proved to be a good method for managing this patient with frequent hypoglycemia.

P2-P325

Diabetic Ketoacidosis and Multiple Organ Failure Syndrome: A Case Study

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Background: Multiple organ failure syndrome (MOFS) can occur in diabetic ketoacidosis (DKA). **Objective and hypotheses:** A 6-year old female child had DKA and MOFS. **Method:** We presented a case study of a child with DKA and MOFS. **Results:** A 6-year old female child had 1-week history of excessive thirst, polyuria, polydipsia, and weight loss. One day before coming to Vietnam National Hospital of Pediatrics (NHP), she had tiredness, multiple vomiting, lethargy, and she was required to give IV 1000 ml of normal saline in a local hospital and transferred to NHP. On admission to NHP, she had tachypnea, unconsciousness with Glasgow score of 6, severe dehydration, hypovolemic shock. In term of investigation, glucose lever was 32.2 mmol/l; metabolic acidosis with pH of 6.8; hypernatremia with sodium level of 162 mmol/l; ketonuria and glucosuria; HbA1C of 12.1%; low C-peptide of 0.001 ng/ml; increased liver enzymes with GOT and GPT of 470 and 188 U/l, respectively; renal failure with urea and creatinine of 27.9 and 318 mmol/l, respectively; rhadomyolysis with CK of 29642 U/l; myoglobinuria. She was diagnosed of DKA, DM1, and MOFS. Besides DKA treatment, she was in continuous veno-venous hemodialysis for 11 days and in intermittent veno-venous hemodialysis for 5 days. DKA and MOFS were cured. Renal function and liver enzymes were recovered. She was discharged from hospital without neurogenic sequalae. **Conclusion:** Hemodialysis is an appropriate treatment for a combination of DKA and MOFS.

P2-P326

Neonatal Diabetes Associated with Transaminitis in a Growth Retarded Infant

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Background: A neonate, born at 34 weeks gestation by caesarean section for foetal distress, was severely growth retarded at birth. Deranged liver functions were noted at birth with (alanine transaminase (ALT), aspartate transamninase (AST) and gamma-glutamyl transfererase (GGT) recorded as 102, 228 and 1078 U/l respectively. The GGT rose to a peak of 3877 U/l at 6 months of age. The clinical course of the neonate was associated with failure to thrive and intermittent hyperglycaemia (although keto-acidosis was not observed early in the phase of the disease). The insulin and C-peptide levels were <0.5 and <0.1 U/l respectively. A trial of glibencamide failed to control the hyperglycaemia. Investigations for inborn errors of metabolism were normal. **Objective and hypotheses:** It has been postulated that insulin deficiency in utero contributes to growth retardation. Wide fluctuations of the blood glucose and poor weight gain characterized the post natal course. As there was scanty subcutaneous tissue, continuous intravenous insulin infusion was instituted resulting in better weight gain. **Method:** A review of the clinical case record. Permission was obtained from the parent to use the clinical records for presentation. **Results:** A liver biopsy revealed marked glycogen deposition. **Conclusion:** The association of neonatal diabetes with growth retardation suggests that insulin deficiency in utero may have contributed to the growth retardation. Although glycogen deposition in the liver may occur with insulin deficiency, the reasons for the markedly elevated liver enzymes are not fully understood.

P2-P327

Benefits of Switching Insulin from Twice Daily to Multiple Daily Injections on Glycaemic Control in Children with Type 1 Diabetes Mellitus in Sri Lanka at the Lady Ridgeway Hospital, Sri Lanka

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Introduction: Intensive insulin therapy with multiple daily injections (MDI) gives better glycaemic control than conventional biphasic insulin regimen in children with type 1 Diabetes mellitus. Though MDI regimen is widely practiced in other countries, this is not so in Sri Lanka. **Objective:** Effect on glycaemic control and BMI of children with TIDM after the change of insulin regimen to MDI from twice daily insulin regime. ***Methodology***: Longitudinal observational study at the Lady Ridgeway hospital. Eligible children who were on twice a day insulin regimen were switched to MDI regimen and compared glycated haemoglobin (HbA1c) values before and after the regimen change at three monthly intervals for 6 months. BMI of the study sample was compared at the initiation and after 6 months of the study. **Results:** Sample size 40. 37% male. Mean age was 9 years 3 months (range 2 years 3 months–14 years 8 months). There were no major hypoglycaemic events during the study period. Mean HbA1c at the start of the treatment was 9.815 which falled to 8.66 and 8.32 respectively at 3 and 6 months following treatment. The change in HbA1c from the baseline to 3 months and 6 months was significant with a P value of < 0.01. Between 3 months and 6 months there was no significance difference as the P value was 0.211. There was no significant difference in the BMI at the initiation of MDI therapy and after 6 months. **Conclusions:** Change in insulin regime from twice daily to multiple daily insulin resulted in significant improvement in glycaemic control over 3 months and 6 months.

P2-P328

Rapid Acting Insulin Analogue Treatment in Children and Adolescents with Type 1 Diabetes Mellitus; Insulin Glulisine Experience

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Background: The main purpose of insulin analogue treatment is mimicking physiologic insulin secretion and accomplishing a good glycemic control without having late hypoglycemia in patients with diabetes mellitus. **Objective and hypotheses:** In this report, 24 weeks follow-up results of newly diagnosed type 1 DM patients treated with insulin lispro and insulin glulisin is discussed. **Method:** Twelve patients diagnosed with type 1 DM patients in between 4 and 16 years were involved in the study. Patients were put on Insulin glarjine plus insulin glulisin (IG, Group I) or insulin lispro (IL, Group II) treatment. Patients were followed up with 1/3 month intervals. Fasting blood glucose (FBG), postprandial blood glucose (PBG), 03 AM blood glucose (03 BG) recordings of the patients, Hba1c levels and clinical evaluation of the cases were compared. **Results:** Anthropometric parameters, HbA1c and blood glucose levels of the cases were evaluated. Postprandial asymptomatic hypoglycemia was observed in two patient in Group I and three patients in Group II. None of the patients had symptomatic hypoglycemia. 24 weeks follow-up results of the groups were compared. FBG and 03 BG levels of Group I was statistically lower than Group II. **Conclusion:** In children and adolescents, the long interval between insulin injection and food consumption makes adaptation of daily life harder. In this study, the efficacy of insulin glulisine was found at least as good as insulin lispro. We think that the ability of application of insulin glulisine just after meals is a benefit for pediatric age group.

P2-P329

The Prevalence of Dyslipidemia and Associated Factors in Children and Adolescent with Type I Diabetes

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Background: Dyslipidemia increases the frequency and severity of micro- and macro-vascular complications of type 1 diabetes. **Objective and hypotheses:** The present study aims to determine the prevalence of dyslipidemia and its association with clinical and laboratory findings in diabetic children and adolescents. **Methods:** The study included 202 children and adolescents with type 1 diabetes. Demographic data and laboratory findings were obtained from patient's files. **Results:** Dyslipidemia prevalence was found as 26.2%. Hypercholesterolemia (15.8%) and hyperglyceridemia (12.9%) were most common findings. Age, BMI, HbA1c and poor metabolic control was significantly higher in cases with dyslipidemia. Smoking rate was 14.1% in the pubertal group. Poor metabolic control and dyslipidemia was found higher among smokers ($P<0.05$). **Conclusion:** Blood lipid levels should be monitored regularly and nutrition education should be repeated periodically to prevent and control dyslipidemia in patients with type 1 diabetes. Smoking-related risks should be a part of patient education in the pubertal period.

P2-P330

Lipid Metabolism in Children with Diabetes Mellitus Type 1

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Objective and hypotheses: To study the lipid metabolism in children with diabetes type 1. **Method:** It was included 44 children (33 girls), the average age – 10.2±3.3 years. Patients were divided: group 1 (less than 5 years) – 23 children (17 girls), mean age 9.8±3.6, the average length of diabetes 2.08±1.5 years. The second (over 5 years) – 21 children (16 girls), mean age of 11.6±2.4, the average length – 7.5±1.6 years. **Results:** The average content of lipids was: cholesterol 4.51±0.92 mmol/l, β-lipoproteins – 46.16±15.23 IU, HDL – 1.43±0.63 mmol/l, LDL – 2.72±0.98 mmol/l. Elevated cholesterol occurred in 13.6% (6/44), β-lipoproteins in 25% (11/44), LDL in 2.3% (1/44). Reduced HDL cholesterol was observed in 11.4% (1/44) of patients. No differences were found between the groups in the cholesterol (4.28±0.69 vs 4.77±1.08 mmol/l), β-lipoproteins (47.61±13.65 vs 47.43±18.56), LDL (2.59±0.8 vs 2.87±1.15 mmol/l), HDL (1.29±0.54 vs 1.29±0.67 mmol\l), atherogenic index (3.03±2.3 vs 3.3±1.6). It is not revealed differences in the incidence of pathological content of β-lipoprotein (17.3% (4/23) vs 33.3% (7/21)), HDL cholesterol (8.7% (2/23 vs 14.3% (3/21)) and LDL (0% vs 4.7% (1/21)). The tendency for a greater frequency of hypercholesterolemia in a group 1 (23.8% (5/21) vs 4.3% (1\23), $P=0.150$) A direct correlation relationship between the HbA1c and cholesterol ($r=0.384$, $P=0.01$), and LDL cholesterol ($r=0.311$, $P=0.04$). **Conclusion:** The tendency of the relationship between diabetes duration and frequency of hypercholesterolemia. A direct relationship between the degree of compensation and LDL cholesterol disease.

P2-P331

Prevalence of Celiac Disease in Children and Adolescents with Type 1 Diabetes Mellitus

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Background: Owing to a common genetic background, patients with type 1 diabetes mellitus (T1DM) are at high risk of developing other autoimmune disorders. Celiac disease (CD) is the next in frequency after hashimoto's Thyroiditis in these patients. **Objective and hypotheses:** This study was undertaken to investigate the prevalence of CD in diabetic children and adolescent. **Method:** 87 patients (44 female, 43 males) aged 2–18 years, with type 1 DM were subjected to screening for CD with tissue transglutaminase antibody (t TG-IgA) testing. **Results:** The prevalence of CD in patients with T1DM was 3.4%. Diabetic patients with CD were significantly youngers, had an earlier onset of diabetes, had a lower height and weight standard deviation score and poorer glycemic control compared with diabetics without CD ($P<0.05$). We failed to show any significant correlation between tTG- positivity and duration of diabetes. **Conclusion:** The results suggest tTG positivity to be a good immunological marker for use in screening for CD and such screening to be justified in all patients with T1DM regardless of diabetes duration.

P2-P332

Evaluating the Impact of the Diagnosis and Management of a Child with Type 1 Diabetes on Parents

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Background: Glycaemic control is adversely affected by family conflict derived from the psychological impact of the disease upon parents. **Objective and hypotheses:** To identify parental psychological stressors and thus interventions deemed useful to provide parental support. **Method:** 252 diabetic children were identified and PIP questionnaires were sent to each household to assess parental stress. Two parental focus groups were held to discuss the areas of concerns raised in the questionnaire. **Results:** The emotional distance questionnaire category scored the highest scores. Focus groups highlighted the pressure of providing 24-h care for their diabetic children. **Conclusion:** Caring for a child with diabetes has a psychological impact on parents.

P2-P333

Association Between Socioeconomic Status and Glycemic Control in Type 1 Diabetes Mellitus

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Background: Socioeconomic status (SES) is inversely associated with many chronic diseases, with disadvantaged individuals faring worse than the others. In diabetes mellitus, however, studies evaluating the relationship between SES and the glycaemic control have shown variable results. **Objective and hypotheses:** To understand the effect of SES on the long term glycemic control in children with type 1 diaebtes mellitus (T1DM) at a tertiary centre in India. **Method:** In this restroective study, clincial data was collected from 78 children with T1DMand their SES calculating using widely accepted modified Kuppuswamy scale (2012). **Results:** The mean age at diagnosis of T1DM was 7.09 (±3.7) years. The mean HbA1c concentration on admission & subsequent follow up were (12.12±2.69%) and (9.09±2.05%) respectively. Majority (88.31%) of the children were on mixed split regimen and only nine patients (11.69%) were on basal bolus regimen. The mean HbA1c in children using mixed split regimen was 9.10 (±2.12) %, and it was 9.58 (±1.84) % for those on basal bolus ($P=0.111$). As per modified Kuppuswamy scale, the number of children in class 1, 2, 3 and 4 (class 1 being the upper SES) were 6 (10.1%), 19 (32.2%), 17 (28.81%) & 17 (28.81%) respectively. Mean HbA1c for SES class 1, 2, 3 & 4 were 8.15, 8.84, 9.66, 9.54 respectively (using Independent samples 't' test, no significant difference in HbA1c was noted between the upper (class 1& 2) & lower (class 3 & 4) socio-economic groups ($P=0.64$). There was

no significant corelation between SES and HbA1c on follow up by using Pearson's test of Linear corelation ($P=0.10$). **Conclusion:** In our study, we did not find any evidence to suggest that the glycaemic control in T1DM is influenced by SES in Indian population. Further studies are needed to understand the other factors that impact on the long term glycaemic control.

P2-P334

Minimally Invasive Surgical Interventions in the Treatment of Primary Persistent Hyperinsulinemic Hypoglycemia of Infancy

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Case Report: Hyperinsulinemia, diagnosed by laboratory tests, should be diagnosed and treated as soon as possible to prevent fatal complications such as neurological damage. Patients who are resistant to medical therapy should be treated surgically. Minimally invasive surgery, a newly developed approach, is a good choice among surgical procedures to avoid unnecessary extensive pancreatectomy. Here, a 12-year-old boy is presented with diagnosis of hyperinsulinemic hypoglycemia who had recurrent attacks of hypoglycemia and seizures from infancy. Because of his unresponsiveness to medical therapy and his family's preference, he underwent laparoscopic pancreatectomy to reduce morbidity and hospital stay. Two years postsurgical follow-up revealed a normo-glycemic state.

P1-P335

Complete Androgen Insensitivity Syndrome Caused by a Deep Intronic Pseudoexon-Activating Mutation in the Androgen Receptor Gene

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Background: Androgen insensitivity syndrome (AIS), ranging from complete (CAIS) to partial (PAIS) and to mild (MAIS) forms of androgen resistance, is caused by mutations in the X-linked *AR* gene that encodes the androgen receptor. Some cases, however, remain without a molecular genetic diagnosis that would confirm the diagnosis especially in cases that have phenotypic similarities with other 46,XY disorders of sex development. **Objective and hypotheses:** The objective of this study was to identify the genetic cause of complete AIS in two siblings without identified mutations in the *AR* coding region or in the conserved splice sites. **Method:** Whole-genome sequencing of the two siblings and their healthy father was performed at BGI, and the sequencing data was searched for candidate causal variants outside the *AR* coding region. RNA was extracted from the patients' genital skin fibroblasts and the *AR* cDNA was analysed by PCR. The amount of AR protein was also studied by immunoprecipitation and western blot. **Results:** Analysis of the cDNA revealed aberrant splicing of the *AR* mRNA caused by a deep intronic mutation (c.2450-118A>G) in intron 6. The mutation creates a de novo 5' splice site and a putative exonic splicing enhancer motif, leading to the preferential formation of two aberrantly spliced mRNAs (predicted to include a premature stop codon) and significant reduction of normal mRNA levels. Patient fibroblasts showed similar levels of *AR* mRNA when compared to controls but no detectable AR protein. **Conclusion:** This is the first reported case of *AR* pseudoexon activation leading to androgen insensitivity syndrome. Similar deep intronic mutations that can lead to pseudoexon activation may underlie AIS in cases where routine genetic screens reveal no mutations in the coding region nor in the conserved splice sites.

P1-P336

Polycystic Ovary Syndrome in Adolescence: New Therapeutic Approach with Inositol and Alpha-Lipoic Acid

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Background: Polycystic Ovary Syndrome (PCOS) is characterized by clinical and/or biochemical hyperandrogenism, oligo-anovulation and/or ultrasound finding of polycystic ovaries. Insulin-resistance represents the etiopathogenetic key of PCOS: a deficit of Inositol's tissue availability seems to be responsible for this clinical picture. Hyperglycemia resulting insulin-resistance, determines a state of chronic inflammation, which increases oxidative stress. **Objective and hypotheses:** To evaluate the efficacy of a new therapeutic approach of PCOS, based on Alternative Insulin Sensitizers as Inositol and α-Lipoic Acid (natural antioxidant, which reduces oxidative stress) dose 400 mg +1000 mg, twice daily, for 6 months of treatment, in a group of PCOS adolescents, followed at the Pediatric Endocrinology and Adolescentology Clinic of L'Aquila. **Method:** Our study considered 10 female adolescents (14.6±2.8 years). Anthropometric data were assessed both at baseline time (time 0) and after therapeutic intervention (time 1) together with oral glucose tolerance test (OGTT), luteinizing hormone releasing hormone

stimulation test (LHRHT) and hormonal profile. **Results:** Weight and BMI undergo an improvement with therapy. Significant are the improvement of level of Testosterone and Cholesterol and serum LH concentration after LHRHT, with 6 months of treatment, as well as glycaemia and insulin sensitivity. We also demonstrate a positive correlation between the decrease of LH levels and the improvement of Testosterone, DHEAS, D4-Androstenedione and Total Cholestero. Moreover all teenagers show various degree of improvement of hirsutism and acne and regularization of the menstrual cycle (Table 1). **Conclusion:** PCOS treatment based on Alternative Insulin Sensitizers as Inositol and α-Lipoic Acid represents the most suitable choice for adolescent patients instead of classic insulin sensitizer, such as Metformin, often burdened with numerous side effects.

Table 1.

	Time 0	Time 1	*P*
Weight	64.06 ± 18	63.7 ± 16.6	NS
BMI	26.1 ± 5.5	24.5 ± 5.8	NS
LH Peack	53.34 ± 27.9	23.89 ± 21.9	0.01
Testosterone	0.61 ± 0.3	0.31 ± 0.2	0.02
Cholesterol Tot.	182.90 ± 25.4	152.00 ± 23.4	0.01
Glicemic Peack	133.40 ± 19.7	112.70 ± 14.7	0.01
Insulin Peack	100.3 ± 29.1	72.70 ± 28.0	0.04

P1-P337

46,XY Partial Gonadal Dysgenesis Caused by an Xp21.2 Interstitial Duplication that Does not Encompass the *NR0B1* Gene

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Background: A portion of 160 kb on Xp21.2 is defined as dosage sensitive sex reversal, including *NR0B1*, which is considered the most likely candidate gene involved in XY gonadal dysgenesis if overexpressed. The excess of *NR0B1* gene product seems to disturb testicular development by down regulating *NR5A1*, *WT1*, and *SOX9*. Xp duplication causes insufficient SRY expression leading to testis development failure. However, *NR0B1* single duplication associated with XY gonadal dysgenesis is still to be demonstrated as an evidence of its direct involvement in this condition. **Objective and hypotheses:** To describe the duplication of ≈277 kb at Xp21.2 excluding *NR0B1*, in a girl with 46,XY partial gonadal dysgenesis. The patient was referred in the first month of life due to genital ambiguity. She was the first child of unrelated parents, and pregnancy was uneventful. She had a 0.5-cm phallus, a single perineal opening, partially fused labioscrotal folds and nonpalpable gonads (EMS = 4). Karyotype was 46,XY[50] and FISH showed no 45,X cell line. Histopathological analysis of gonads revealed no gonadal tissue with mullerian and wolffian derivatives on the left and dysgenetic testis on the right. Mutations on *SRY*, *WT1*, *DMRT1*, *NR5A1* and *SOX9* were not identified. **Method:** MLPA and aGH (Affymetrix® 750K) assays were performed. **Results:** MLPA revealed the duplication of *CXorf21* probes at Xp21.2 [30,595,621-30,615,321] (arr[hg19]), but signals for *NR0B1* were normal. aGH showed ≈277 kb duplication at Xp21.2 (arr[hg19] Xp21.2(30,580,693-30,857,187)x2), thereby *GK* gene is present in an extra dose and *TAB3* and *CXorf21* are partially duplicated. **Conclusion:** To our knowledge this is the first description of Xp21.2 duplication resulting in gonadal dysgenesis with normal *NR0B1*. This study questions the well-accepted theory that *NR0B1* is responsible for sex reversal in DSS region. Further studies are required to understand the roles of *GK,* CXorf21 and *TAB3* on sex reversal.

P1-P338

Primary Ovarian Insufficiency in Childhood Cancer Survivors: A Report from the St Jude Lifetime Cohort (SJLIFE)

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Background: Primary Ovarian Insufficiency (POI) and infertility are common concerns of female Childhood Cancer Survivors (CCS) and are known to impact their quality of life. Increased availability of fertility preservation techniques mandate a better understanding of risk factors for POI in this population. **Objective and hypotheses:** To describe the prevalence of and risk factors for POI in a cohort of adult CCS. **Method:** Cross-sectional study of clinically assessed participants in an established cohort. POI was defined by delayed or interrupted puberty or persistent amenorrhea 5 years after the completion of cancer treatments (acute ovarian failure (AOF)) or menopause at age < 40 years (premature menopause (PM)). Patients with hypogonadotropic hypogonadism, bilateral oophorectomy, Turner syndrome and those whose ovarian function could not be evaluated were excluded. Multivariable logistic regression was used to study associations between demographic and treatment-related risk factors and POI. Exposure to alkylating agents (AA) was quantified using the validated cyclophosphamide equivalent dose (CED). **Results:** 921 patients (median age 31.7 years, range 19.0–60.6) were evaluated at a median of 24.0 years (range 10.2–48.1) after cancer diagnosis; 153 were treated with pelvic radiotherapy (PRT) and 546 with AA. 100 patients had POI (prevalence 10.9%);

58 had AOF and 42 PM. Factors independently associated with POI were: age >25 years at study (OR 7.2; 95%CI 3.0–17.6), exposure to any PRT (dose <10 Gy (OR 26.8; 95%CI 12.6–57.0); dose ≥10 Gy (OR 208.6; 95%CI 88.6–491.0)) and CED 8000–11999 mg/m^2 (OR 4.7; 95%CI 1.3–16.9) or ≥12 000 mg/m^2 (OR 9.5; 95%CI 3.0–30.2). **Conclusion:** POI is frequently seen in female CCS. The risk of POI increases with age and AA dose; PRT at any dose is associated with the highest risk. Patients should be counselled regarding their risk of POI; those at highest risk should be offered fertility preservation whenever feasible.

P1-P339

Global and Sexual Quality of Life in Patients with Rokitanski Syndrome: A Comparative Study Between Surgical vs Non Surgical Management of Vaginal Agenesis in a French Cohort of 130 Patients

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Background: Vaginal agenesis (VA) in MRKH syndrome can be managed either by surgery or autodilatations. **Objective and hypotheses:** To compare different managements of MRKH-VA in terms of quality of life, sexual function, anatomical results and complications. **Method:** National Multicentric observationnal study including 130 patients older than 18, at least one year after completing VA management, from October 2012 to April 2015. 84 had a surgical intervention (SG), 26 autodilatations (DG) and 20 spontaneous intercourse (IG). All had medical evaluation including normalized pelvic exam, and filled WHOQOL-BREF (General QOL), FSFI and FSDS-R (Sexual QOL) scales. Data were compared using ANOVA, Student, Kruskal-Wallis, Wilcoxon and Student's exact tests. **Results:** Mean age was 26.5 years (18–41). Delay between management and first intercourse was 6 months (NS). In SG 40% (N=34) had complications, requiring 20 secondary surgeries. In DG, 13 (50%) needed maintenance dilatations. Median vaginal depth was shorter ($P=0.039$) in DG (9.25 cm, Sd 1.88) compared to SG (11 cm, Sd 1.7) and IG (11 cm, Sd 1.67), but not between surgeries. 70 patients (53%) had dyspareunia (NS). In all groups, WHOQOL scores were similar to the general population except for a lower Social Interaction dimension score. Global FSFI scores showed similar significant sexual dysfunction in the SG and DG (respectively 25.95 and 24.5), but not in the IG (30.2, $P=0.04$), who had a higher score only in the Satisfaction dimension ($P=0.004$). However, the scores in other dimensions of FSFI were similarly low in all groups. The FSDS-R scores were respectively 17, 20 and 10 in the SG, DG and IG (NS), with a sexual distress in 71% of patients. **Conclusion:** Surgery is not superior to dilatation in term of sexual function, bears more complications, and therefore is not advisable as a first line treatment. Psychological counselling seems essential at diagnosis and during therapeutical management.

P1-P340

Intrauterine Growth Restriction Affects Postnatal Testis Maturation in Rats

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Background: The influence of intrauterine life on long term health is supported by a wealth of epidemiological and experimental studies. A low oxygen and/or nutrient supply to the fetus, resulting in intrauterine growth restriction (IUGR), may affect gonadal development of the offspring, with a potential impact on fertility. Data derived from animal models of placental insufficiency are very limited. **Objective and hypotheses:** To investigate the effects of placental insufficiency induced by uterine artery ligation (UAL) on postnatal rat testis gene expression and testosterone production. **Method:** Sprague-Dawley pregnant female rats underwent UAL at day 19 of gestation to generate IUGR offspring, while *sham* operation was performed for the controls. Offspring were sacrificed at 5, 20 and 40 days *post-partum* (d*pp*). At sacrifice, testes were excised and weighed. Gene expression was analyzed by TaqMan® Low Density Array (TLDA). Intratesticular testosterone (ITT) and serum gonadotrophins were assessed by ELISA. **Results:** Testis weights normalized to body weights were significantly reduced at 5 d*pp* and 20 d*pp* in IUGR rats, with catch-up at 40 d*pp*. The expression of 30 genes among the 90 investigated, involved in regulation of cell cycle, metabolism, angiogenesis, and markers of testicular somatic and germ cells, was dysregulated in IUGR rat testis compared to controls at all time points. At 20 d*pp* ITT was significantly increased in IUGR rats, whereas serum gonadotrophins levels were comparable between the two groups. **Conclusion:** Different genes involved in fundamental processes within the testis were affected by fetal hypoxia up to pubertal age, suggesting that long term alterations occur as a consequence of IUGR. Moreover, testosterone production was increased in the pre-pubertal rats, as putative catch-up growth mechanism. Further analyses are needed to elucidate later consequences of IUGR on testis function.

P1-P341

Application of on Line Learning in Assessment of Competencies of Fellows Pediatric Endocrinology

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Background: The European Society for Paediatric Endocrinology (ESPE) developed an interactive e-learning portal for pre- and postdoctoral training: (www.espe-elearning.org). **Objective and hypotheses:** The aim of the study was to evaluate the role of e-learning in the formative assessment of competencies (medical expert, communicator) of fellows in pediatric endocrinology in informing patients and parents with a difference in sex development (DSD) about diagnosis and management and to assess religious, regional and cultural aspects. **Method:** Sixty-two fellows and 32 experts with global distribution participated in the study. Fellows answered on line Multiple Choice (MC) and open questions of two clinical interactive problem solving cases. Experts provided anonymously feedback on line, using prepared response elements. Evaluation followed by online questionnaires and acknowledgements. All answers of the fellows were evaluated on completeness and wording. A subset of 10 answers of both cases was evaluated by 20 experts on wording and completeness. **Results:** 50% of fellows achieved the correct answer on the first attempt on the MC questions. They answered only 50% of the key elements on the open questions. The evaluation of the subset of 10 answers by 20 distinct experts showed great inter-observer variability. Personalized feedback from various experts was highly appreciated by the fellows. The cultural, religious and regional items most frequently mentioned by the experts were fertility and role of the family. Fellows did not mention any but acknowledged their importance. **Conclusion:** The ESPE e-learning portal offering direct interaction between trainee and trainer is applicable in on line formative assessment of trainees.

P1-P342

Genotype-phenotype Analysis of NR5A1/SF1 Mutations by Functional in vitro Studies

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Background: The steroidogenic Factor 1 (SF1, NR5A1) is one of the key factors involved in gonadal and adrenal development and steroidogenesis. Until now, over 50 mutations were described in different phenotypes of XY disorders of sex development (DSD) such as complete gonadal dysgenesis, severe and mild partial gonadal dysgenesis, hypospadias, infertility and bilateral anorchia. So far, no genotype-phenotype correlation could be demonstrated. **Objective and hypotheses:** To investigate genotype-phenotype correlation SF1-mutations by functional *in-vitro* studies. **Method:** Investigation of the transcriptional activity of different SF1 missense mutations on central promoters of gonadal development in a homogeneous experimental set up by Dual-Glo luciferase assays in HEK and Sertoli cells. Mutations of different structural region from patients with phenotypes ranging from infertility to complete gonadal dysgenesis were chosen. TESCO, the initiator of testis determination and the promoters of CYP11A1, reflecting steroidogenesis and Leydig cell function and AMH representing Sertoli cell function were used as reporter. **Results:** SF1 missense mutations in the DNA-binding (p.E35G, p.R62C) and ligand-binding domain (p.L376F) leading to partial and complete gonadal dysgenesis showed a significant reduced ability to activate TESCO and the CYP11A1 promoter. SF1 mutations in the hinge-region (p.P131L, p.P191C) leading to infertility showed only moderate reduced ability to activate TESCO and minor reduced activation of the CYP11A1 promoter. None of the mutations did show significant reduction of transcriptional activity of the AMH promoter. **Conclusion:** The transcriptional activity of the different SF1 mutations on the TESCO and CYP11A1 promoter reflect the severity of clinical expression of gonadal dysgenesis and steroidogenic function *in-vitro*. Functional studies of SF1 mutations using TESCO and the CYP11A1 promoter can be helpful predictive models for phenotypes *in-vitro*.

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Evolution of Bone Mass and Body Composition in Gender Dysphoric Adolescents Treated with Progestins to Suppress Endogenous Hormones

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Background: In gender dysphoric (GD) adolescents with advanced pubertal development, psychological relief can be attained with progestins, which are much cheaper and easier to administer than GnRHa. Moreover, use of GnRHa has been shown to interfere with pubertal bone mass accrual. To date, few data exist on the effects of progestins on body composition (BC) and bone parameters in this population. **Objective and hypotheses:** To explore the effects of pro- and antiandrogenic progestins on muscle strength, BC and bone mass in mid- and late pubertal GD female to male (FtM: lynestrenol) and male to female (MtF: cyproterone acetate) adolescents respectively. **Method:** Grip strength, DXA (spine, hip, whole body) and pQCT (radius, tibia) measurements were prospectively performed at start of treatment and before association with cross-sex hormones in

48 GD adolescents (median age: 16.3 years (11.9–18.4 years); 33 FtM; 15 MtF). Statistical analysis: paired Student-*t* or Wilcoxon signed-ranks test (as appropriate). *Z*-scores of the biological sex were used. Vitamin D supplementation and calcium-enriched diet was advised in all participants. **Results:** Mean treatment duration was 11.5 months. In FtM, lean body mass (LBM) and grip strength increased. Waist and hip circumference increased, waist-hip ratio (WHR) remained unaltered. Bone mineral content (BMC), density (BMD), trabecular and cortical bone increased at all sites; mean BMD *Z*-scores did not change significantly (WB: −0.813 to −0.813). In MtF, LBM and WHR decreased, fat mass increased; grip strength remained constant. Bone area and BMC increased; however, BMD remained constant and BMD *Z*-scores decreased (WB: −1.280 to −1.587, $P=0.017$). Trabecular bone decreased, cortical bone increased. **Conclusion:** Treatment with pro- and anti-androgenic progestins results in body composition changes towards the desired sex. Lynestrenol did not affect bone mass accrual, while Cyproterone acetate was associated with a stagnating bone mass accrual, similar to GnRHa. Preventive measures are warranted, especially in MtF adolescents.

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Sertoli Cell Function During Chemotherapy in Pediatric Patients with Acute Lymphoblastic Leukemia

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Background: Most reports on gonadotoxicity associated with chemotherapy of acute lymphoblastic leukemia (ALL) comes from studies in adults, and they are mainly focused on the sensitivity of testicular germ cells. Little attention has been placed on Sertoli cells in prepubertal patients, even though Sertoli cell function is essential for adult spermatogenesis. **Objective:** To evaluate Sertoli cell function in prepubertal boys who receive chemotherapy for ALL. **Materials and methods:** A prospective study including prepubertal male patients with ALL. Main outcome measure was serum AMH level after each phase of chemotherapy and 1 year after treatment completion. Secondarily, FSH levels were measured. Results are expressed as medians (range). **Results:** Twenty-six boys with ALL were included: 24 had LLAB and 2 LLAT (four standard, 14 medium and eight high-risk ALL), age at diagnosis was 4.2 year (0.4–14.3). Serum AMH was: at diagnosis, 605 pmol/l (152–1333); at the end of induction ($n=19$), 833 (170–1697) = 143% of pre-treatment level (92–274); after intensification (*n*: 23), 742 (240–1660) = 138% (58–251); after Phase 1 ($n=14$), 644 (265–1095) = 112% (53–150); prior to start of maintenance ($n=16$), 674 (351–1300) = 109% (67–199); at 6 months of maintenance ($n=11$), 695 (312–1386) = 104% (63–215); at the end of treatment ($n=7$), 817 (523–1563) = 131% (87–291); and 3 months after the end of treatment ($n=5$), 738 (396–1336) = 107% (75–123) of pre-treatment AMH level. Serum AMH decreased below 70% of pre-treatment level during chemotherapy in six of eight patients with high risk ALL, in 1 of 14 with medium risk and in none with standard risk. Only six patients (23%) had a transient mild FSH elevation. **Conclusion:** These preliminary results showed that Sertoli cell function is not affected by chemotherapy in prepubertal boys with standard or medium risk ALL, but is at least transiently affected in those with high risk LLA.

P1-P345

Accuracy of Pelvic MRI in Evaluating Internal Genitalia in Patients with Disorders of Sex Development

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Background: Patients with disorders of sex development (DSD) require multidisciplinary team management for etiology identification and gender assignment. Identification of mullerian structures is an important part of the evaluation process. Ultrasonography remains the first-line imaging modality to delineate mullerian structures; while the importance of magnetic resonance imaging (MRI) is insufficiently studied. **Objective and hypotheses:** To evaluate the diagnostic accuracy of MRI in the assessment of internal genitalia in patients with DSD and at least one palpable gonad at diagnosis. **Method:** Retrospective comparative single-center study (2008–2014) of DSD patients with at least one palpable gonad, who had benefited from pelvic MRI and surgical management. Clinical, biological and cytogenetic data were evaluated. A radiologist reviewed imaging blindly and pelvic MRI findings were compared to pelvic ultrasound and to cystoscopy whenever performed during surgery. **Results:** Forty-six patients were included: 46,XY ($n=41$), 45,X/46,XY ($n=3$), 46,XX ovotestis ($n=1$) and 46,XX testicular DSD ($n=1$). Only one patient was reared as a female. Thirty patients (65.2%) were seen during the neonatal period (2 ± 2.1 days), with severe hypospadias (95.6% of cases), and mean genital bud length of 20.1 ± 5.8 mm. Urethroplasty was performed at a mean age of 15.1 ± 4.1 months. Pelvic ultrasound was done in 41 patients (89.1%) and peroperatory cystoscopy in 13 patients (28.2%). Pelvic MRI was concordant with pelvic ultrasound outcomes in identifying retro-urethral cavity and

retro-bladder cavity in 75.6 and 97.5% respectively. Eight patients had retro-urethral cavity seen on MRI but not on ultrasonography; in contrast its morphology was better described on ultrasonography in five patients. In only one patient, ultrasound showed a retro-bladder cavity which was not seen on MRI. **Conclusion:** Pelvic MRI evaluation for internal genitalia appears complementary to ultrasonography in the neonatal period only for retro-urethral cavity. Thus, the cost effectiveness of this expensive technique in the evaluation of DSD patients should be reviewed to reduce costs on public health.

P1-P346

Using Public Databases, 'Virtual Controls' and Geolocalization to Search for Environmental Correlates of Hypospadias

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Background: Incidence of hypospadias varies considerably across countries, ranging from 4 to 43 cases per 10,000 births. Environmental factors might explain these differences. The classical approach is to use case-control studies to identify these factors. However, this approach suffers from the unavoidable arbitrariness of the definition of controls, and of recall bias. **Objective and hypotheses:** To identify environmental markers of the place of birth of children with hypospadias. **Method:** 8766 patients were recruited by 15 surgical centers. Addresses at birth were geolocalized using ArcGIS 9.3.1. This was used to map the addresses of the patients i) with socioeconomic variables available from INSEE and anonymous public databases (spatial resolution:1 km.) ii) with the land cover characteristics assessed with satellite imaging (resolution: 250 m, database: Corine Land Cover). Then 100 sets of 8766 matched virtual controls were chosen randomly on the map thanks to the pps software and provided the reference environmental values. Bonferroni correction for multiple comparison was used to assess test significance. **Results:** Overall, a significant positive association was found with urbanization. When restricted to the 2279 patients whose residence was >10 km from their recruiting surgical center, more hypospadias were found in places close to non-irrigated arable lands, complex cultivation patterns, and broad-leaved forests. A residence close from vineyards was not found predictive of hypospadias. **Conclusion:** Few environmental correlations, none of which being associated with pesticides, were found with our approach, which relies on an objective and unbiased assessment of environmental exposures, but may still lack spatial and temporal resolution.

P1-P347

The International AGD Consortium: A Multi-center Study of 3939 Infants and Children with Anogenital Distance Measurements

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Background: The anogenital distance (AGD) is considered a valid marker of altered androgen action in utero. Recently, reduced AGD has been shown in males with hypospadias, cryptorchidism, reduced semen quality and infertility. It has also been proposed as a new marker to be used by clinicians when managing patients with Disorders of Sex Development. However, little normative data exist and measurement methods vary. **Objective and hypotheses:** We established the International AGD Consortium (IAC), hosted by EDMaRC (www.edmarc.net), with the primary aim of creating an international database for AGD. The aims are to: 1) Generate normative data for AGD in infancy and childhood. 2) Explore the variability in AGD related to age, sex, body size, ethnicity and measurement method. 3) Promote and facilitate AGD-related research by providing access to a large international data set of AGD measurements and relevant covariates. **Method:** Anonymized data on measurements of AGD, relevant anthropometric data, age, genital phenotype and background data including birth weight, gestational age, ethnicity and measurement method will be included in the database. Normative data for the different types of AGD will be generated using the Lambda-Mu-Sigma (LMS) method. **Results:** The IAC database has been developed, validated and registered (www.clinicaltrials.gov #NCT02497209). At the time of writing, it includes data from The Odense Mother-Child Cohort (DK), The Cambridge Baby Cohort (UK) and The Infant Development and the Environment Study (TIDES) (US). A total of 3939 children aged 0–67 months with 9084 examinations have been included. Two different methods of AGD measurement have been used. **Conclusion:** The IAC database has been created and currently includes data from 3939 children. Principle investigators from all published studies on infant/child AGD will be invited to join IAC. Further analyses including the creation of normative AGD values according to gender, age, ethnicity and method will subsequently be carried out.

P1-P348

Exonic Splicing Mutations by Silent Nucleotide Variation in the Androgen Receptor Gene Causes Androgen Insensitivity Syndrome

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Background: Androgen Insensitivity Syndrome is a common form of 46,XY DSD. In the literature, 85–90% of patients with complete form of Androgen Insensitivity (CAIS) and 30% of patients with parcial form (PAIS) have the AR gene mutation identified, In most cases are found a missense mutation with aminoacid change. Mutations without aminoacid changes (silent mutations) are rarely related to human diseases and have never been identified in patients with CAIS. **Objective and hypotheses:** To describe two different silent mutations in the AR exonic region causing a splicing alteration and a premature stop codon in AIS patients without others mutations identified in the AR gene. **Method:** We sequenced the whole coding region of the AR gene including all exon/intron boundaries after amplification by PCR in 14 segments using primers derived from published sequences. All mutations, included silent mutations identified were analysed by prediction tools: Netgene2 and Human Splicing Finder. For new mutations considered deleterious in predictive sites by splicing alteration we performed a sequencing of partial AR cDNA, flanking the mutation region. **Results:** We found two silent mutations in two families with AIS. The first mutation (p.S889S) in exon 8 of AR was found in a patient with atypical genitalia raised in male social sex. The second mutation (p.S510S) was found in a family with three affected 46,XY patients with normal female external genitalia, primary amenorrhea and inguinal hernia. Both mutations were classified as deleterious by predictive tools. Silent mutations creating an alternative splicing was described in only one patient with PAIS but this mutation has not been described in the complete form of AIS. A sequencing of partial cDNA, flanking the mutation region, in patient's AR mRNA (p.S510S) showed a lost around 90 bp at the end of exon 1 leading to a premature stop codon. **Conclusion:** Silent mutations creating an alternative splicing and a premature stop codon can be associated with both partial and complete form of AIS. This is the first description of silent mutation in the AR causing splicing alteration in CAIS.

P1-P349

Severe 5 Alpha Reductase 2 Deficiency with Aphallia is Caused by p.Y91H SRD5A2 Mutation and is Responsive to Dihydrotestosterone Administration During Childhood

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Background: 5-alpha-reductase-2 (5α-RD2) deficiency is an autosomal recessive 46,XY disorder of sexual development, characterized by undervirilized prepubertal males with ambiguous genitalia. The pubertal rise in testosterone and 5α-RD1 isoenzyme activity causes virilization, often resulting in gender assignment change. Early precise diagnosis which anticipate adult function is critical for treatment and gender assignment. **Objective and hypotheses:** To elucidate the genetic cause and the optimal treatment for a unique 46,XY DSD patient. **Method and results:** Consanguineous Palestinian parents requested a change to male gender assignment in their 2.5 year old girl. The girl had labial embedded testis, aphallia, high anogenital ratio (0.78) indicating testosterone responsive genitalia. Laboratory examinations revealed XY karyotype, normal basal and ACTH stimulated glucocorticoids levels, high HCG stimulated testosterone and a testosterone/androstenedione ratio of 2.4. Given the high testosterone and the high anogenital ratio, we sequenced the SRD5A2 gene and found a new 271T > C, Y91H mutation, in an exon encoding 5α-RD2 transmembranal domain. Urinary steroid metabolites profile showed a dramatically decreased ratio between 5alpha/5beta metabolites of corticosteroids indicating a decreased function of the mutated 5α-RD2 in this case. The rare phenotype of absence of clitoromegaly and complete aphallia with seemingly impossible surgical penile reconstruction, complicated the adherence to the parents' request for male gender assignment. A 3 months trial of daily local dihydrotestosterone administration resulted in dramatic enlargement of the rudimentary clitoris to a phallus of > 2 cm length enabling reconstruction urological surgery. **Conclusion:** The new Y91H mutation in SRD5A2 gene, causing a severe reduction in 5α-RD2 activity as reflected in urine metabolites, results in a rare XY-DSD phenotype with complete aphallia. The prepubertal use of local dihydrotestosterone may alleviate the conflict between male gender assignment and a complete female phenotype. Further studies correlating quantitative SRD5A2 enzymatic activity to genotype and phenotype may contribute to early comprehensive decisions regarding gender assignment.

P1-P350

Clinical History and High Prevalence of Gonadal Tumor in 14 Patients with 46 XY Pure Gonadal Dysgenesis

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Background: Pure gonadal dysgenesis 46 XY is a rare form of sexual differentiation disorders. **Objective and hypotheses:** This study describes the diagnosis circumstances, clinical, biological and radiological presentation, and genetic aetiology of 14 patients with a 46 XY pure gonadal dysgenesis. **Method:** It is a retrospective descriptive multicenter study from Necker Hospital (Paris) and Lille university hospitals. **Results:** The patients were diagnosed between prenatal period and 21 years, the median age of diagnosis was 16. Nine of the 14 patients had primary amenorrhea, leading to the late diagnosis. Six of the nine patients aged 10 years and older had already breast development, without any functional gonad; all of these patients had gonadal tumor, gonadoblastoma and/or dysgerminoma. One patient was diagnosed because of abdominal pain due to a tumoral syndrome. Eight of the 13 operated patients (61%) had a gonadal tumor (two gonadoblastoma and six dysgerminoma). Six of the eight gonadal tumor (75%) were malignant, all of those patients were asymptomatic. The median age of tumor's diagnosis was 15 years, and the youngest patient was 2 years 11 months old. Mutation or deletion was found for 5/10 patients, 3/10 (30%) in the coding sequence of the SRY gene, one in the SF1 gene, and one deletion including DMRT1 and DMRT2 genes in the chromosome 9. **Conclusion:** Sixty-one percent of the operated patients had gonadal tumor (gonadoblastoma or dysgerminoma), which is more than literature data. Breast development, even normal appearance, is often due to a tumoral hormonal secretion. We should not delay ablation of the gonads in patients with 46 XY pure gonadal dysgenesis. All primary amenorrhea have to be investigated, and a caryotype must be done, even if it seems isolated with a late Tanner stage.

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Abstract withdrawn.

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A Multicenter Study on Long-Term Outcomes in 56 Males with 45,X/46,XY Mosaicism

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Background: 45,X/46,XY mosaicism is a rare karyotype with a broad phenotypic variation. In patients with a male or predominantly male phenotype, impaired genital development and statural growth have been observed, but little is known about long-term outcomes. Larger multicenter studies are needed. **Objective and hypotheses:** The aim of this study is to investigate long-term outcomes, namely gonadal function, growth and co-morbidities, in a larger group of males with 45,X/46,XY mosaicism. **Method:** Using the I-DSD Registry, all centers with males with 45,X/46,XY mosaicism were invited to participate in this multicenter study. Only post-pubertal patients that had reached adult height were included. At the time of writing, inclusion is still ongoing. **Results:** In total, 22 centers were invited. Thus far 18 centers have responded positively and 16 centers have supplied data on a total of 56 males. Age at the last evaluation was 26.6 years (13.4–70.2 years). External masculinization score (EMS) at time of diagnosis was 8.5/12 (2–12). Nine (23.7%) patients had a score of 12 (complete external virilization). 38 patients (77.6%) entered puberty spontaneously. 15 (34.1%) had received testosterone treatment. Final height was 157.0 cm (141.1–184.0 cm). 17 patients (38.6%) had received growth hormone. Six patients (11.8%) had renal disease/abnormalities and 10 (19.2%) had congenital cardiac malformations. One patient (2.3%) had a gonadal tumor and 6 (18.2%) had precursor lesions. **Conclusion:** These preliminary data show that patients with 45,X/46,XY have varying phenotypes reflected by the EMS. Most of the patients spontaneously entered puberty indicating good Leydig cell function, although 15 did receive testosterone. Patients have short adult stature. The prevalence of gonadal neoplasia *in situ* and renal and cardiac co-morbidities appears to be high. The study is ongoing, but final data analyses will be presented. It can, however, be concluded that recruiting centers through the iDSD Registry was successful.

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Familial Testotoxicosis: Outcome and Possible Relation to Testicular Malignancies

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Background: Testotoxicosis or familial male-limited precocious puberty (FMPP) is a rare disease caused by an autosomal dominant activating mutation of the luteinizing hormone receptor gene, leading to early gonadotrophin-independent precocious puberty. Phenotypic expression is limited to males. Treatment evolved over the last decades and nowadays consists of a combination of a potent anti-androgen agent and a third-generation aromatase inhibitor. Since the identification of etiologic gene mutations in 1993, pre-symptomatic genetic testing provides the opportunity of early diagnosis and treatment without diagnostic delay. **Objective and hypotheses:** Evaluation of clinical course and outcomes in FMPP families. **Method:** Nine affected males; two generations in four families were evaluated. Information was gathered on clinical course, therapy and mutation analysis. **Results:** All four affected fathers were diagnosed based on clinical symptoms. One of them remained untreated and reached a final height of 165 cm. Three others were treated and attained normal final heights (183, 187 and 189 cm). Regarding their offspring, one family opted for pre-symptomatic genetic testing, revealing FMPP in two brothers. Early onset of treatment (age 1.5 years) resulted in a final height in the lower part of target height range. In three other families, diagnosis of FMPP in offspring was made after onset of clinical symptoms at the age of 3–5 years. Treatment was started subsequently. These boys have not yet reached final height, however treatment resulted already in a decrease of both growth rate and skeletal maturation rate. Two affected adults developed testicular cancer in their twenties (embryonal carcinoma and non-seminoma). **Conclusion:** In these families, pre-symptomatic genetic analysis has not led to increased final height. Furthermore, concern is raised by the fact that 50% of adults developed testicular malignancies. We therefore suggest surveillance of adult FMPP patients after treatment in childhood.

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Psychological Impact in Young Women of Announcement of a Utero-Vaginal Malformation (Mayer-Rokitansky-Küster-Hauser – MRKH Syndrome) and its Treatment

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Background: Few studies have addressed the question of psychological impact and long term outcomes in MRKH patients. **Objective and hypotheses:** Our national multi-centric study aimed to assess MRKH patients' experience concerning diagnostic announcement, treatment perception, impact on psychic functioning, socio-professional integration, affective and sexual life and quality of life. **Method:** First 40 MRKH patients aged 19–34 recruited from 137 included and who accepted this protocol which included a semi-directive interview and two projective tests (Rorschach and TAT). **Results:** Diagnosis was made at 15.2 but understood at 16.8. Medical management took place at 17.6. 75% had surgery and 25% vaginal dilatations. Before medical treatment, 20% underwent one or more psychotherapy session(s). 30% stated diagnosis had an impact on school life; 100% displayed depressed mood and disruption of social and family life. 50% had feelings of shame, and 'fear of being discovered' and unaccepted during an intimate encounter with a man. 100% were heterosexual but with complaints (desire, pleasure and pain) despite a normal gynecological examination. 77.5% were in couple, 15% were single and 7.5% had never had love relationships. 87.5% revealed desire for children, with one adoption and four currently in adoption processes. Interviews underline different issues: i) long wandering before diagnosis; ii) trauma to the announcement; iii) feelings of being different; iv) frequency of eating disorders in immediate post-announcement (12.5%); v) reasons for medical treatment decision: 'to get rid of the syndrome', 'be normal' or 'have sex'. **Conclusion:** We suggest a psychological treatment just after the announcement (to prevent eating or others psychopathological disorders), to avoid rapid surgical correction and favor dilatations, and wait for the young woman's demand for treatment fueled by her desire for a romantic and sexual life. ClinicalTrials.gov Identifier: NCT01911884 AP-HP: AOM11168-P110124.

P1-P355

Mutations at the SF-1 Ligand-Binding Domain Can Lead to Different Effects on DNA Binding: Report of Two Novel Mutations

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Background: Steroidogenic factor-1 (SF-1), denominated as nuclear receptor subfamily five group A member 1 (NR5A1), is an orphan receptor that regulates several steps of adrenal and gonadal development. Mutations in its gene are responsible for different phenotypes of disorders of sex development (DSD). **Objective and hypotheses:** To study the functional impact of two novel *NR5A1* mutations, the p.C247* and p.K396Rfs*34, both identified within the ligand-binding domain (LBD). **Method:** In order to evaluate the impact of those mutations at the protein function, normal and mutated SF-1 were expressed in HeLa cells and the expression efficiency was monitored using Western blot. Their transactivation abilities were tested *in vitro* using *AMH* and *STAR* promoter containing luciferase reporter genes and electrophoretic mobility shift assays (EMSA). **Results:** Luciferase reporter gene expression was reduced for both p.C247* and p.K396Rfs*34 when tested with either promoters. Whereas the transactivation activity for p.K396Rfs*34 was completely null, p.C247* retained a very low activity. Western blot showed that normal and mutant proteins were expressed in similar amounts. EMSA was also performed to analyze if those mutations would disturb SF-1 DNA binding ability. Results showed that the mutation p.K396Rfs*34 abolished the ability to bind DNA, whereas the formation of a protein-DNA complex was still observed for p.C247*. **Conclusion:** It is already known that, mutations at SF-1 LBD, may result in variable effects depending on their location and alterations in the ligand specificity/recognition. This was also observed here, once both mutations localized in the LBD had completely different effects on DNA binding. However, both patients present partial gonadal dysgenesis, suggesting that the genotype-phenotype correlation, especially for mutations within the LBD, remains elusive. SF-1 function/regulation is very complex and must be increasingly studied, mainly because the number of different phenotypes correlated with mutations on this gene has been constantly increased.

P1-P356

A New International Registry Highlights the Differences in Practice for Reaching a Diagnosis of CAH – On Behalf of the I-CAH/I-DSD Registry User Group

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Background: Following the 2010 CAH consensus, the need for genetic confirmation of diagnosis remains uncertain and variation in practice is unclear. **Methods:** This variation was assessed by using the International CAH(I-CAH) Registry which was developed using the same platform as the I-DSD Registry. **Results:** After the development of the I-CAH Registry in October 2014, the rate of addition of CAH cases increased from 2/month to 14/month. Of a total of 2061 cases in the I-DSD/CAH Registry in Mar 2016, there were 560 cases of CAH, which had been added by 27 centres in 13 countries from four continents. The median year of birth of cases in the Registry was 2002 (range, 1937, 2015) and 224 (40%) were over 16 years old. The median age at first presentation was 4 months ($<$ 1.48) and the aetiology of CAH was 21-hydroxylase deficiency in 404 (93%). Of the 560 cases, 259 (60%) were 46,XX and 8 (3%) of these cases were raised as boys. The median age at presentation of these eight cases was 2 months ($<$1.18). Of the 433 cases, where information was available, the basis of diagnosis was available in 206 and of these cases, the diagnosis had been confirmed by a combination of biochemistry and DNA analysis in 126 (61%). In 71 (34%), the diagnosis had been reached on biochemistry alone, in 7 (3%) the diagnosis was reported to have been based solely on clinical features and in 2 (1%) the diagnosis had been confirmed by genetics alone. The median year of birth of those cases where the diagnosis was based on genetic vs solely biochemical confirmation were 2007 (1975, 2015) and 1999 (1964, 2014), respectively ($P<0.0001$). **Conclusion:** The quick adoption of the I-CAH Registry clearly demonstrates user acceptability of this new Registry and its use reveals a temporal shift in diagnostic practice towards the use of molecular genetics. **Acknowledgements:** Funded by MRCUK-G1100236, EUFP7-201444, EUFP7-281654.

P1-P357

Changes in Adrenal Steroids During Puberty Suppression and Cross Sex Hormone Treatment in Gender Dysphoric Adolescents

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Background: Current guidelines recommend that gender dysphoric adolescents be treated with puberty suppression using gonadotropin releasing hormone analogues (GnRHa) followed by cross sex hormones. However limited data are available on the safety and side effects of this treatment. In adults changes in adrenal steroids have been observed during cross sex hormone treatment. **Objective and hypotheses:** We aimed to investigate the effect of GnRHa and cross sex hormones on adrenal steroid levels in gender dysphoric adolescents. **Method:** 54 male-to-females (MtFs) and 73 female-to-males (FtM) were treated with triptorelin 3.75 mg i.m. every 4 weeks and from the age of 16 years testosterone or 17beta-oestradiol was added at increasing doses. Serum DHEA-S and androstenedione levels were measured every 6 months. **Results:** Baseline androstenedione was above the reference range in 5/67 FtMs and in none of the MtFs. All individuals had baseline DHEA-S within the reference range. During GnRHa treatment DHEA-S increased in FtMs, but in those aged 12–14 years at start DHEA-S levels after 2 years of treatment were comparable to baseline levels of those aged 14–16 at start. During cross sex hormone treatment DHEA-S levels did not change in either sex. Androstenedione decreased during GnRHa treatment in FtMs whereas levels in MtFs did not change. Testosterone treatment induced a rise in androstenedione in FtMs whereas oestradiol treatment in MtFs had no effect. **Conclusion:** The increase of DHEA-S during GnRHa treatment in FtMs may be physiologic and unrelated to treatment or could imply stimulation of adrenal activity by GnRHa treatment. However, androstenedione levels decreased, probably due to decreased ovarian androstenedione production. The increase in androstenedione during testosterone treatment might be caused by direct conversion or alternatively through an effect on adrenal steroidogenesis although DHEA-S did not change. The clinical implications of the changes that were observed are still unclear.

P1-P358

Do the Anti-Mullerian Hormone Levels of Adolescents with Polycystic Ovarian Syndrome (PCOS), Those Who Are at Risk for Developing PCOS, and Those Who Exhibit Isolated Oligomenorrhea Differ from those of Adolescents with Normal Menstrual Cycles?

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Background: An elevated anti-Müllerian hormone (AMH) level might serve as a noninvasive screening or diagnostic test for PCOS in adolescents. **Objective and hypotheses:** We explored whether the AMH levels of adolescents with PCOS, 'at-risk-of-PCOS', and isolated oligomenorrhea, differed from those of adolescents with normal menstrual cycles, and we identified an AMH level that was potentially diagnostic of PCOS. **Method:** A diagnosis of PCOS was based on the 2012 Amsterdam (ESHRE/ASRM) criteria. The PCOS group consisted of individuals meeting all three diagnostic criteria ($n=21$); those in the 'at-risk-of-PCOS' group met two of the criteria ($n=20$). The OM group consisted of those with isolated OM who did not satisfy the other PCOS diagnostic criteria ($n=21$). Thirty adolescent girls with regular menstrual cycles (21–45 day) (NMC) were recruited for study. **Results:** The AMH levels in the PCOS group were similar to 'at-risk-of-PCOS' group but significantly higher than in the OM and NMC groups. The AMH levels in the 'at-risk-of-PCOS' group were similar to the OM group and significantly higher than in the NMC group. They were also significantly higher in the OM group than in the NMC group. The sensitivity and specificity of each serum AMH concentration for identifying PCOS and 'at-risk-of-PCOS' subjects were determined by ROC curve analysis. The specificity at a cut-off value of 7.25 ng/ml was 83.3%, and the sensitivity was 58.5%. The positive and negative predictive values of this cut-off were 82.8% and 59.5%, respectively. **Conclusion:** An AMH cut-off of 7.25 ng/ml can assist in PCOS diagnosis in adolescents. However, before this criterion is used routinely, larger populations should be studied. OM subjects should be monitored for the development of PCOS.

P1-P359

Feasibility Study for Avoiding Early Surgery in Girls with 21-Hydroxylase Deficiency (21OHD)

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Background: Genital surgery in disorders of sex development (DSD) has been an area of debate over the past 20 years. One can question and even defy the routine practice to surgically align genitalia to the sex of rearing, as early as possible. However, despite multitude of data showing detrimental effects to genital sensation and sexuality, few patients born with ambiguous genitalia have remained unoperated into adolescence. **Objective and hypotheses:** To assess the feasibility of following up 21OHD non-operated patients into adolescence, so as to determine changes in genital morphology and acceptability among patients and parents of such an approach. **Method:** Parents were offered to delay genital surgery until adolescence. All were clear about their decision to defer surgery and fully aware of the pros and cons based on current evidence. We collected data on control, growth, size of the clitoris and subjective measures of adjustment or concerns among parents and patients. **Results:** After observing a 'pilot patient', we left six other patients with 21OHD and Prader 3–4 at birth (clitoris 20–26 mm, testosterone 6–15 ng/ml) unoperated and treated with 50 mg hydrocortisone and 50 μg fludro per m^2.day. Testosterone became <0.02 ng/ml in all. Clitoral size decreased both in true and relative terms as the child grows, to reach 5–15 mm at last exam at 1.5–8 years of age. Child and parents seemed to live non-intervention without specific psychological difficulties regarding genital ambiguity. **Conclusion:** Our data so far suggest that it is acceptable to defer genital operation. Surgery will be performed by a gynecologist with experience in vaginal reconstructive surgery. Ultimate outcome measures will be adaptation, sexual function and satisfaction in late

adolescence and adulthood, using qualitative data similar to those previously used by our team to assess comparable 21OHD women operated in childhood (Gastaud F, 2007).

P1-P360

A Novel Familial Androgen Receptor Mutation (W752G) in Complete Androgen Insensitivity Syndrome: Use of *in vitro* Study According to the Nature of Amino Acid Substitution

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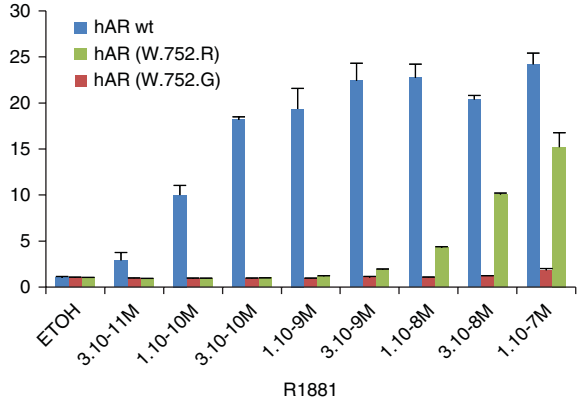
Background: Androgen receptor (AR) gene mutations are the most frequent cause of 46,XY disorders of sex development and are associated with a variety of phenotypes, ranging from phenotypic women (complete androgen insensitivity syndrome) to milder degrees of undervirilization (partial and mild forms). **Aims and objectives:** To specify how a phenotype-genotype correlation can be refined by *in vitro* study based on the nature of amino acid substitution. **Patients and methods:** We report a 2-month-old girl who was admitted to the Pediatric Surgery Unit of the University Hospital of Montpellier for inguinal hernia. Inguinal gonads were present, whereas no uterus was identified at ultrasonography. Karyotype was 46,XY. Inguinal surgery was performed and the gonads were reintegrated in the abdominal position. Family questioning revealed that one of the mother's sisters was infertile. AR gene analysis found a new W752G AR mutation. We performed *in vitro* study of this new mutation and the only other reported W752R mutation. **Results:** Transfection studies confirmed the decrease in AR transactivation despite increased androgen concentration, whereas for the other p.W752R AR mutation previously reported in two sisters with ICA, transactivation increased only at androgen concentrations above 10–8 M. **Discussion and conclusions:** Although newborns diagnosed as CAIS carriers are always raised as females, the time of gonadectomy tends to be later today than it was some years ago. This later gonadectomy timing allows spontaneous puberty, but it raises questions about potential pubertal virilization and male identity in cases of the persistence of residual AR activity. Through this report of a new W752G mutation of the AR gene in a CAIS patient, we underline the usefulness of *in vitro* study to better understand the virilization defect and thus better organize the follow-up of these patients based on the nature of the amino acid substitution.



P1-P361

Partial and Mixed Gonadal Dysgenesis Cannot be Distinguished by Histological Picture: Clinical Evaluation, Histological Differences and Long-Term Follow up of 61 Brazilian Patients

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Background: Differential diagnosis between XY partial (PGD) and mixed gonadal dysgenesis (MGD) was initially established by histological evaluation; however, when there is a 45,X lineage there are differences not only in clinical aspects but also in prognosis. **Objective and hypotheses:** The aim of this work was to analyze clinical picture of patients with genital ambiguity due to testicular dysgenesis, with and without a 45,X lineage, and compare these conditions in terms of phenotype and prognosis. **Method:** All patients with a diagnosis of testicular dysgenesis who were seen in our service between 1989 and 2013 were selected. Patients were divided in two groups (with and without a 45,X cell line), which were compared in regard to gonadal histology, anatomy of external and internal genitalia, gonadal hormone function; growth, puberty and fertility prognosis. Our sample included 61 patients, 25 with mosaicism (MGD) and 36 with an homogenous 46,XY karyotype (PGD). **Results:** There were no differences between the groups in terms of age at the first visit, gestational and family history, degree of external virilization, position and histology of gonads, gonadal hormone function, spontaneous pubertal development and need for hormonal replacement, presence of associated conditions and fertility prognosis. There were significant difference regarding sex of rearing (more often female in MGD); presence of uterus (more common in MGD); higher maternal age (in PGD); lower birth weight and length (in MGD) and short stature (more frequent in MGD). **Conclusion:** PGD and MGD were indistinguishable in terms of gonadal histology and function and genital features, except for the higher frequency of uterus in MGD. They did differ in terms of pre and post-natal growth; in this regard, patients with MGD require specific therapeutic measures. Therefore, the old classification based on histological findings should be abandoned in favor of that based on chromosome constitution, and screening for a 45,X lineage should be thorough in all patients with 46,XY testicular dysgenesis.

P1-P362

Aromatase Activity is Disrupted by Mutations in P450 Oxidoreductase

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Background: The steroidogenic enzyme aromatase (CYP19A1) is a protein located in endoplasmic reticulum (ER) that catalyzes the conversion of androgens to estrogens. Both deficiency and excess of aromatase activity lead to disease states implicating its role in human biology. Cytochrome P450 (CYP) enzymes in ER use reduced nicotinamide adenine dinucleotide phosphate through cytochrome P450 oxidoreductase (POR) for their metabolic activities. Mutations in POR cause disorders of sexual development due to the deficiencies in several steroid metabolizing enzymes like CYP17A1, CYP21A2 and CYP19A1. The effect of POR mutations on different P450 activities depends on individual partner proteins. So each P450-POR mutant combination should be studied individually. **Objective:** Study the impact of mutations in the flavin binding domain of POR (A115V, T142A, P284L, P284T and Q153R) on CYP19A1 activity, which can potentially influence the estrogen metabolism. **Method:** The WT and mutant human POR proteins were expressed in bacteria and membranes were isolated. Human CYP19A1 was produced as His-tag recombinant protein and purified by Ni^{2+} metal chelate chromatography. POR variants were characterized by standard cytochrome *c* reduction assay and flavin content of proteins was analyzed. Bacterial membranes containing WT or mutant POR along with CYP19A1 were reconstituted into liposomes and the aromatase activity was determined by tritiated water release assay using radiolabeled androstenedione as substrate. Kinetic parameters (Km, Vmax) were calculated for each mutant and compared with WT POR. **Results:** Mutations in the flavin binding domain of POR alter the cytochrome c reduction rate. We found severe effect of POR mutation on CYP19A1 enzyme activity. The POR mutants P284L, P284T, A115V and T142A showed less than 20% activity in supporting CYP19A1 reactions. Interestingly, the POR variant Q153R showed 50% higher activity than WT. **Conclusion:** Our study suggests that alteration in aromatase activity may have an impact on estrogen metabolism. Lower aromatase activities due to POR mutation might affect the fetal androgen metabolism, especially in pregnant women with a male child.

P1-P363

Mosaic Xq Partial Duplication Leading to Virilisation of an Adolescent Female

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Background: We present a 17-year-old female who presented with a 1 year history of hirsutism, male pattern baldness, marked cystic acne and mild cliteromegaly. She had her menarche at the age of 15 years and continued thereon to have a regular menstrual cycle. She was pubertal on examination (B3, P5, A5) with no neurological deficit. **Objective and hypotheses:** This female presented with marked clinical hyperandrogenism. We initially suspected polycystic ovarian syndrome (PCOS) given her phenotype. Through investigation and characterisation she has been found to have an unusual genetic mutation which we hypothesise is causative of her symptoms. **Method:** Our case had blood taken for baseline endocrinology, genetic testing, provocation testing, 24 h urine for steroid profiling, and an ultrasound scan of her abdomen/pelvis. She was commenced on treatment for PCOS with Yasmin which she has not shown an early response to. **Results:** She was found to have a normal pubertal ultrasound scan, normal baseline endocrinology, normal provocation testing and a normal 24 hour urinary steroid profile. Her microarray revealed she carries a 46XX/47XX+ mosaic karyotype with a supernumerary marker chromosome which was shown to be derived from the long arm of the X chromosome. This additional genetic material contains the androgen receptor gene but does not include the XIST gene and therefore genes present in this marker chromosome would not be subject to x-inactivation. This was found to be a de novo mutation. **Conclusion:** We present a novel case of a de novo genetic mutation that we hypothesise has led to overexpression of the androgen receptor leading to her having increased sensitivity to normal levels of circulating androgens. The resulting severe phenotype mimics PCOS in appearance but with normal blood biochemistry, urinary steroid profile and ultrasound.

P1-P364

Genotyping Patients with Differences of Sex Development: 25 Years of Investigation of an Italian Population of 308 Cases (194 46,XY and 114 46,XX)

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Background: Differences of sex development (DSDs) (conditions with atypical development of chromosomal, gonadal or anatomic sex) are classified into three groups: sex chromosome DSD, 46,XYDSD and 46,XX DSD. Around 1 newborn in 5000 presents ambiguous genitalia with a major challenge for male or female assignment. The identification of a genetic cause can contribute to a correct diagnosis and to optimize both management and genetic counselling. **Objective and hypotheses:** To describe the results of the diagnostic activity on a large cohort of cases (chromosomal DSD excluded), mostly from the Nord-Est Italian regions referring to our centre in the period 1991–2016. **Method:** Hundred and ninety-four cases with 46, XY DSD and 114 cases of 46,XX DSD where analysed by Sanger sequencing and/or MLPA for the major candidate genes/regions for the specific DSD condition. **Results 46, XY DSD:** A genetic cause was identified in 14 out of the 27 Gonadal dysgenesis **(A)**; in 85 out of

the 133 defects of androgen synthesis or action **(B);** in 11 (9 AMH) out of 14 **PMDS;** in 1 (**MAMLD1**) out of 20 isolated ipospadias. **46, XX DSD:** a genetic cause was identified in 4 **(SRY+)** out of 7 testicular DSD; in 100% of 107 virilized females with androgen excess **(C). Conclusion:** The mutation detection is: 57.2% in 46, XY DSD (111/194) with gonadal dysgenesis and isolated hypospadias as the less characterized; 93.9% (107/114) in 46, XX DSD, confirming both the large prevalence of defects of adrenal steroidogenesis and the lack ok knowledge for testicular DSD. A panel of a limited n. of genes is sufficient to obtain a good mutation detection for group B.

A

SRY	5
NR5A1	2
DUP DAX1	2
DEL DMRT1	1
DEL ENH SOX9	2
WT1	2

B

CYP17A1	1
HSD3B2	1
HSD17B3	6
NR5A1	12
SRD5A2	15
AR	50

C

CYP21A2	101
CYP11B1	6

P1-P365

Functional Studies of a New Mutation in the LH/CG Receptor Gene Identified in 2 Sisters with 46,XY DSD

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Background: Disorders (or differences) of sex development (DSD) are rare congenital conditions in which the development of chromosomal, gonadal, or anatomical sex is atypical. The luteinizing hormone/chorionic gonadotropin receptor (LHCGR) is important for male sex development. *LHCGR* mutations can cause Leydig cell hypoplasia, which is an autosomal recessive disorder. **Objective and hypotheses:** We found two heterozygous mutations in the LHCGR, a new p.F138S mutation in combination with the previously described c.580A>G mutation in exon 6A in two sisters with 46,XY DSD and complete inconspicuous female appearance. Deleterious effect of the p.F138S mutation was assessed by functional analysis. **Methods:** Expression vectors containing LHCGR mutation were generated an employed for functional assay by cAMP RIA, cAMP-responsive element containing reporter genes (pCRE-Luc) and cAMP binding luciferases (GloSensor). Localisation was analysed by immunoimaging and glycosylation was studied by glycosidase F treatment and immunoblot. **Results:** The three different cAMP assays demonstrated a complete loss of function of the p.F138S mutant. Immunoimaging showed that the mutant receptor is expressed internally, but did not reach the membrane surface. Treatment with glycosidase F and subsequent immunoblot revealed an incomplete glycosylation of the receptor. Compound heterozygosity was proven by long range PCR and subcloning of the fragment containing both mutants. **Conclusion:** The mutation p.F138S in Exon 5 leads to a loss of function of LHCGR. Together with the second previously described mutation in cryptic exon 6A these compound heterozygous mutations explain the autosomal recessive disorder. The functional data fully support the observed clinical phenotype.

P1-P366

Consecutive Lynestrenol and Cross-Sex Hormone Treatment in Biological Female Adolescents with Gender Dysphoria: A Retrospective Analysis

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Background: Progestins such as lynestrenol (L) can be used in female to male (FtM) adolescents with gender dysphoria (GD) who have advanced pubertal development to reduce the psychological burden of menstruation. L can later be combined with cross-sex hormones (testosterone esters) (L+T). L is much cheaper and easier to administer than GnRHa. To date, few data exist on the (side) effects of progestins for this indication. **Objective and hypotheses:** To report the effects of consecutive L (5 mg) and L+T in FtM adolescents with GD on antropometrics, biochemical, hormonal parameters and side effects. **Method:** Retrospective analysis of clinical and biochemical data in 45 FtM adolescents treated with L monotherapy for 12.6 months and L+T for 11.4 months. Statistical analysis: McNemar's, paired Student-*t* or Wilcoxon signed-ranks test (as appropriate). All participants were advised to take vitamin D supplements (25,000 U/ml) and a calcium-enriched diet. **Results:** Metrorrhagia of variable intensity and acne were most pronounced during the first months of monotherapy and combination therapy respectively and decreased thereafter. Headaches, hot flushes and fatigue were the most reported side effects. During treatment, a gradual increase in musculature, hemoglobin, hematocrit, creatinine and liver enzymes was seen, progressively sliding into male references. Lipids shifted to a more unfavourable HDL/LDL ratio; glucose metabolism was not affected. SHBG, total testosterone and estradiol levels decreased and free testosterone slightly increased

during monotherapy. Total and free testosterone increased significantly during combination therapy. Gonadotropins were only fully suppressed during combination therapy. AMH remained stable. Most changes occurred in the first six months of the respective treatment phases and remained stable thereafter. **Conclusion:** Treatment with L is effective, safe and inexpensive. However, suppression of gonadotropins is incomplete. Higher doses may be needed to obtain immediate and full suppression of menstruation.

P1-P367

Ovarian Reserve Assessment in Girls and Women after Hematopoietic Stem Cell Transplantation Treatment Underwent in Childhood

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Background: Hypogonadism is one of the most frequent endocrine complication after hematopoietic stem cell transplantation (HSCT). In some patients hypogonadism could be transient, but very often coexists with prematury ovarian failure. Classical methods used in the diagnostics of hypogonadism have limitations for the prognosis of ovarian reserve. **Objective:** The aim of the study was to assess ovarian reserve in patients after HSCT using evaluation of anti-Muellerian hormone (AMH) with comparison to classical hormonal methods. **Methods:** Twenty-eight patients, median age 15.8 years, after allogeneic (19) and autologic (9) HSCT and 28 healthy age-matched controls were included in the study. Fasting blood samples for the measurement of FSH, LH, estrogens, PRL, SHBG, TSH, fT4, AMH, and Inhibin-B, if possibly in 3–5th day of the menstruation cycle, were taken. Hormones were measured by immunochemistry. Statistical analysis was performed using *t*-Student test. **Results:** AMH and inhibin-B levels were significantly lower ($P<0.001$) and FSH and LH levels were significantly higher in patients after HSCT than in controls ($P<0.01$). In 20/28 patients AMH level was below 0.08 ng/ml as postmenopausal, only 2/28 have normal AMH values. Hypergonadotropic hypogonadism was observed in 21/28 patients, 7/28 patients have normal values of sex hormones (3/7 prepubertal). Patients with normal AMH, have normal other hormones and normal menstruation cycles (severe aplastic anemia). Six patients (Fanconi anemia 3, solid tumors 3) with AMH levels 0.08–1 ng/ml presented with prepubertal status with low FSH (3) spontaneous puberty (1) and normal menstruations (2). Their inhibin B level was within normal ranges. **Conclusion:** Patients after HSCT have impaired ovarian reserve. The ovarian reserve is mostly related to the conditioning therapy before HSCT. AMH as well as Inhibin-B and FSH are specific and good markers for the assessment of ovarian function. AMH seems to be more sensitive test than other markers in the evaluation of ovarian reserve after HSCT.

P1-P368

Precocious/Early and Accelerated Puberty in a Boy with a Homozygous R192C Mutation in *CYP19* (Aromatase) Gene

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Background: Aromatase deficiency is a rare autosomal recessive disorder produced by *CYP19* gene mutations. 46XX affected patients presented with ambiguous genitalia leading to early identification. Most 46XY affected patients presented normal external genitalia and the condition often remains undiagnosed until late puberty. Information on pubertal development in affected boys is scarce since to the present date only two patients, younger than 4 years of age, without long-term follow-up, had being reported. **Objective and hypotheses:** We report the clinical phenotype and hormonal studies of a 46,XY aromatase deficient boy. **Results:** Molecular analysis revealed a previously reported homozygous mutation (R192C) in the CYP19 gene, predicted to compromise enzyme function. The patient was the oldest brother of a 46XX affected sister. Maternal virilisation was present during both pregnancies. First evaluation at 7.9 years: 3 years delayed bone age was the only remarkable finding observed. Laboratory tests showed normal prepubertal basal serum gonadotropin (including an adequate GnRH stimulation test), inhibin B, AMH, testosterone and androstendione levels. OGTT was normal as well as bone mass, assessed by DEXA. The patient was lost in follow-up and returned at 11.3 years of age with signs of advanced puberty (Tanner stage IV, testicular volume 12/15 ml). Bone age was 2 years delayed. Laboratory tests revealed normal pubertal basal and GnRH stimulated gonadotropin levels and increased serum testosterone (5.9 ng/ml, male reference range for Tanner IV: 1–5.4 ng/ml). **Conclusion:** Normal pubertal development was referred in adult men with aromatase deficiency. Interestingly our patient presented with precocious/early and accelerated puberty and apparently normal pituitary gonadal function. Estrogen restrain on gonadotropin secretion has been demonstrated in animal and human models of estrogen deficiency operating since early phases of puberty in males. This human model of nature suggests that aromatase activity at hypothalamic level is required to define pubertal tempo and/or the time of puberty onset in boys.

P1-P369

Long-Term Follow-Up of Patients with 46,XY Partial Gonadal Dysgenesis Accordingly Gender Assignment

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Background: Studies on the follow-up of 46,XY partial gonadal dysgenesis (PGD) patients till adulthood are scarce and it is important to provide information to parents on the prognosis of gonadal dysgenesis. **Objective and hypotheses:** To analyze the long term outcomes of 46XY PGD patients in both social sexes regarding testosterone production, social sex adaption and genotype. **Method:** Retrospective longitudinal study conducted at Hospital das Clinicas of São Paulo. We followed up 28 patients (11 assigned in the female and 17 in the male social sex) during a range of 2.7–26 years. Molecular diagnosis was performed by Sanger method and MLPA. **Results:** At first evaluation, in the female social sex group, 5/9 patients had preserved testosterone production (3 came after puberty). In the male group, 8/14 patients had preserved testosterone production and 5 of them developed spontaneous puberty. Three prepubertal patients lost the capacity to produce testosterone during childhood. At adulthood, 3/5 patients maintained testosterone levels. Social sex change was observed in only two patients, one of each social sex group. There was no difference between social sex at adulthood and testosterone production. All patients were well adapted to social sex (64% had a steady partner and 76% had complete sexual intercourses). Gonadal tumor was observed only in patients gonadectomyzed after puberty (2 of 10 patients, one due to Frasier Syndrome and another with intra-abdominal gonad). Molecular diagnosis was possible in 11/28 cases: mutations were found in *SRY*, *SF1*, *WT1*, *CBX2.2*., *MAPK3* and *FGFR1*. **Conclusion:** Patients with 46XY PGD were well adapted to both social sexes at adulthood; testosterone production at puberty was preserved in 50% of the cases. Gonadal tumor was only observed after puberty (20%) in patients with additional factors for the development of gonadal tumor. Molecular diagnosis was reached in 37% of the patients by Sanger method.

P1-P370

45,X/46,XY Chromosomal Disorders of Sex Development: Experience from a Cohort of 50 Patients Followed in One Single Institution

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Background: Disorders of sex development (DSD) are those congenital conditions in which development of chromosomal, gonadal, or anatomical sex is atypical. 45,X/46,XY mosaicism results in a large clinical spectrum of DSD including from female patients with Turner's syndrome to normal appearing males. **Objective and hypotheses:** The main aim of this study is to review the clinical and gonad histological findings in a cohort of chromosomal DSD patients followed between January 1/2000 and January 1/2016 at our institution. **Method:** We analyzed the records 50 patients with 45,X/46,XY karyotype or variants. Patients were divided according to external genitalia into two groups (Gr): normal female phenotype (Turner syndrome, n18, Gr1), and atypical genitalia (n32, Gr2). We also identified one patient with normal male phenotype evaluated because of short stature that was not included in the analysis. **Results:** Gr2 was more prevalent than Gr1 (64% vs 36%, *P* 0.009). Male assigned patients in Gr2 (n22, 69%) presented higher mean external masculinization score than female assigned ones (8.2 ± 0.9 vs 5.6 ± 1.6 S.D. respectively, *P* 0.0017). In all male assigned patients in Gr2 that have reached pubertal years, spontaneous pubertal development was observed (n9). Gonadal neoplasia was found in 5/34 gonads from Gr1 (15%, chronological age at diagnosis 15–18 years), and 2/50 gonads from Gr2 (4%, 3 years). Adult height was available from 18 patients and it was significantly lower in Gr1 vs Gr2 (145.3 ± 5.1 cm vs 151.81 ± 5.1 cm, respectively, *P* 0.016) even though in Gr1, 55% (6/11) received rhGH treatment vs only 30% in Gr2 (2/7). **Conclusion:** In our cohort of 45,X/46,XY chromosomal DSD patients atypical genitalia was the most frequent phenotype. A tendency to a higher gonadal malignancy risk was observed in Turner syndrome patients. External genital phenotype might be a useful predictor for adult height.

P1-P371

Androgen Profile Differs to Adults in Adolescent Girls with Polycystic Ovary Syndrome

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Background: Diagnostic criteria for polycystic ovarian syndrome (PCOS) are well established in the adult population, but may not be appropriate for adolescent girls. Clinical and/or biochemical hyperandrogenism is one important diagnostic criterion. Screening for hyperandrogenism is often restricted to measurements of testosterone in adult practice. It was our impression that this strategy would under-diagnose PCOS in our adolescent population. **Objective and hypotheses:** To describe androgen profiles in adolescent girls presenting with clinical features of PCOS, to identify the most sensitive marker of hyperandrogenism in adolescent PCOS. **Method:** A retrospective case review was undertaken of patients with clinical characteristics of PCOS (clinical hyerandrogenism plus oligomenorrhoea/ primary or secondary amenorrhoea, with or without polycystic ovaries on ultrasound) attending a single centre between 2005 and 2015. **Results:** Data are reported as median (range). Data were collected from 40 patients, age 15.49 (11.84–18.02) years. BMI-SDS was 2.42 (-1.25–3.91), and 25/40 (62.5%) were overweight/obese

(BMI SDS >1.75). Androgen profiles and sex hormone binding globulin levels at presentation are given in Table 1. **Conclusion:** In this population of girls, with clinical feature of PCOS, hyperandrogenism would not have been diagnosed in 60% of patients if only testosterone was measured. No patient, in whom androstenedione was elevated, had normal testosterone levels. These novel data suggest that the most sensitive marker of PCOS in adolescent girls is androstenedione.

Table 1. Androgen and sex hormone binding globulin levels in 40 patients.

Biochemical marker (normal range)	**Number of patients with abnormal level** (%), **median level** (range)
Testosterone (0–3.5 nmol/l)	2 (5%), 1.7 (<0.7–4.7)
DHEAS (1.6–7.8 umol/l)	11 (28%), 5.7 (1.8–14.9)
Androstendione (2–5.4 nmol/l)	26 (65%), 6.6 (1.3–18.2)
SHBG (25–145 nmol/l)	20 (50%), 24.5 (9–200)
LH: FSH ratio (<2)	14 (35%), 1.71 (0.1–5.8)
Free Androgen Index (0.5–6.5)	19 (48%), 5.99 (0.72–33.5)

P1-P372

Effects and Side Effects of Cyproterone Acetate Alone and in Combination with Estrogens in Natal Male Adolescents with Gender Dysphoria

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Background: Male to female (MtF) gender dysphoric adolescents with advanced pubertal development can be treated with antiandrogenic progestins such as cyproterone acetate (CA). CA is much cheaper and easier to administer than GnRHa and can later be combined with cross-sex hormones (17β-estradiol) (CA + E). To date, few data exist on the (side) effects of progestins for this indication. **Objective and hypotheses:** To report the effects of consecutive CA and CA + E in MtF adolescents on antropometrics, biochemical, hormonal parameters and side effects. **Method:** Retrospective analysis of clinical and biochemical data in 27 MtF adolescents treated with CA monotherapy for 11 months and CA + E for 12 months. Statistical analysis: Shapiro-Wilk, paired Student-T or Wilcoxon signed-ranks test (as appropriate). All participants were advised to take vitamin D supplements and a calcium-enriched diet. **Results:** Most patients reported a reduction in facial shaving (CA:54.2%, CA + E:62.5%). Breast development was induced by CA monotherapy in 28% (B2-3), reaching B3-4 in 77.8% during CA + E. Side effects (breast tenderness, emotionality, fatigue, flushes) were reported during CA in 36% and during CA + E in 66.6%. Hemoglobin, hematocrit and creatinin levels reached the female reference range under CA and remained stable thereafter. Transient (limited) elevation of liver enzymes was noted in four adolescents. HDL/LDL ratio became more unfavourable during CA, but restored with addition of E; glucose metabolism was unaffected. Androgens (total and free testosterone, DHEAS, androstenedione) decreased under CA, with a further decrease during CA + E. Estradiol, SHBG and inhibine B decreased during CA but increased during CA + E. Prolactin levels increased under CA. **Conclusion:** CA is effective in suppressing endogenous hormones and initiating feminisation within the first six months of treatment. Furthermore, it is safe and inexpensive. Addition of estrogens are needed for further feminisation.

P1-P373

Compound Heterozygous *C10orf2* Mutations in a Japanese Patient with 46,XX Ovarian Failure and Deafness

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Background: Perrault syndrome is a rare autosomal recessive disorder characterised by sensorineural hearing deafness in both sexes and primary ovarian failure in 46, XX karyotype females. *HSD17B4, HARS2, LARS2, CLPP and C10orf2,* which associated mitochondrial function, are reported as causative genes. **Objective and hypotheses:** Here we reported on a Japanese patient who identified *C10orf2* mutation with the fourth patient in Perrault syndrome. **Method:** The patient was referred to our hospital due to short stature at the age of 12 years old. She showed proportionate short stature with a height of 129.6 cm (−3.1 S.D.) and exhibited hearing difficulty at school medical check-up. Her growth hormone and thyroid functions were normal, however LH and FSH levels were unusually elevated. Her karyotype was 46, XX. She was diagnosed with ovarian failure and sensorineural hearing deafness, namely Perrault syndrome. She has been treated with estrogen replacement therapy since 13-year-old, and her height finally reached 160 cm. **Results:** Molecular analyses identified compound heterozygous *C10orf2* mutations consisting of c.1172G>A (p.Arg391His) on the maternal allele and c.1136G>A (p.Gly379Glu) on the paternal allele, and no pathologic mutations were detected for *HARS2, LARS2,* and *CLPP*. The former mutation was previously reported in a Japanese patient, and the latter novel mutation, which is located in linker domain, might be pathogenic mutation based on the *in silico* analyses. **Conclusion:** *C10orf2* mutations should be considered in patients for ovarian failure with the sensorineural deafness. This is the first report of a mutation at linker domain in Perrault syndrome.

P1-P374

GATA Transcription Factors in Testicular Adrenal Rest Tumours

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Background: Testicular Adrenal Rest Tumours (TARTs) are benign tumours that frequently occur in male patients with congenital adrenal hyperplasia. They exhibit both testicular and adrenal characteristics, but their aetiology is unknown. Additionally, TART resembles Leydig cell tumours (LCTs), while no marker exist to discriminate between these testis tumours. GATA transcription factors play an important role in eukaryotic development and are expressed in foetal and adult adrenal gland and gonads. **Objective and hypotheses:** To determine if GATA transcription factors can discriminate between TART, testis and LCT. **Method:** Gene expression analysis was performed for *GATA 1, 3, 4,* and *6* in TART ($n=12$), adult testis tissue ($n=8$), and adult adrenal tissue ($n=12$). Expression levels were compared and tested with Kruskal-Wallis-test followed by Dunns test ($P<0.05$). Receiver operating characteristic (ROC) curve was used to determine discriminative properties. Protein expression in TART ($n=16$) and LCTs with accompanied normal testis tissue ($n=7$) was tested using immunohistochemistry (IHC). **Results:** *GATA4* gene expression was significantly higher in TART compared to adrenal ($P<0.001$), while gene expression of *GATA3* and *GATA6* were significantly higher in TART compared to testis (both $P<0.05$), with ROC areas under the curve of 0.979 and 0.906, respectively. GATA3 protein expression was undetectable in TART as well as LCT. In both TART as well as LCT, GATA6 showed nuclear or cytoplasmic staining patterns, ranging from weak to strong staining intensity. **Conclusion:** Our study shows that both *GATA3* and *GATA6* mRNA expression is higher in TART compared to adult testis tissue with good discriminative potential between TART and testis. However, GATA3 and GATA6 protein expression could not discriminate between TART and LCT.

P1-P375

Can we Standardize Sex Assignment in 45,X/46,XY Mixed Gonadal Dysgenesis?

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Background: Patients with 45,X/46,XY mixed gonadal dysgenesis (MGD) have variable phenotypes leading to both male and female sex assignments. A multidisciplinary team should guide the process of sex assignment, however a standardized approach may provide objective guidance for the team as well as a tool for settings without such resources. One of the most important considerations for sex assignment is the hormonal production, which often determines the degree of virilization. Therefore, the first step to standardization is to establish a virilization score. **Objective and hypotheses:** To develop a virilization score for sex assignment in patients with 45,X/46,XY MGD. **Method:** Using the external genitalia score previously published by Ahmed et al, we developed a compounded virilization score with nine parameters describing external genitalia, internal structures and gonads. The score was applied retrospectively to 22 patients with 45,X/46,XY MGD and abnormal external genitalia from one institution and validated with 8 patients from a second institution. ROC curves were used to establish a cut off value above which the patients were more likely to be assigned male and a logistic regression model was used to determine the importance of its components. **Results:** Eighteen of the 30 included patients received male sex assignments. The percentages of Y containing cell lines were similar in patients with either sex assignment. ROC analysis showed an AUC of 0.995. When using 9 as the cut off value, the score matched the current sex assignment in 29 out of the 30 patients (96%, 95% CI: 0.83–0.99). All the components were important, with urethral position being the most significant. **Conclusion:** Sex assignment for individuals with 45,X/46,XY MGD is complex. However a virilization score may be used to simplify, standardize, and reduce variability within this process. Prospective studies using a larger sample are needed to validate its utility.

P1-P376

Intratubular Large Cell Hyalinizing Sertoli Cell Tumor of the Testis Presenting with Prepubertal Gynecomastia: A Case Report

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Background: Intratubular Large Cell Hyalinizing Sertoli Cell Neoplasia (ITLCHSCN) resulting from Sertoli cells of the testis are mainly reported in young adults and these are rarely seen in childhood. **Objective and hypotheses:** In this case report, an eight-and-a-half-year old case presenting with complaint of bilateral gynecomastia since two years, showing no endocrine abnormality in laboratory during 2-years of follow-up, determined to have progression in bilateral gynecomastia, increase in testicular volumes, advanced bone age, increase in growth velocity in the clinical follow-up. **Method:** A six-and-a-half-year old male presented with complaint of pain, induration and enlargement of his breasts for three months. Hormonal values were determined as in normal range (prepubertal). Tumor markers were negative. Bone age was consistent with 6 years of age. The scrotal sonography showed hyperechogenicity consistent with testicular microlithiasis in bilateral testes. An increase in the size of his gynecomastia was detected during two years of follow-up. His bone age was consistent with 9 years of age while chronological age was eight-and-a-half-year of age. At the second year of his following, since basal LH value was detected to be higher and an increase was determined in testicular volumes, LH-RH test was performed. The results were consistent with prepubertal response.

Results: Due to determination of increase in growth velocity, advanced bone age and progression in gynecomastia, a testicular biopsy was performed due to suspicion of malignancy. Pathological examination was reported to be consistent with ITLCHSCN. **Conclusion:** Progression of gynecomastia in a boy with increase in growth velocity, advanced bone age, increase in testicular volume as well as presence of microlithiasis in the testicles should suggest Sertoli Cell Tumors (SCTs).

P1-P377

Effect and Safety Aspects of Percutaneous Administration of Dihydrotestosterone in Children with Micropenis with Different Genetic Background

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Background: Micropenis may result from different aetiology and therapy data are still scarce. **Objective and hypotheses:** To investigate the effect and safety of dihydrotestosterone transdermal gel in children with micropenis. **Method:** Totally 23 agnogenic micropenis children with 46,XY karyotype were recruited to participate a perspective study. SRY, AR and SRD5A2 gene were sequenced. 2.5% DHT gel was applied individually based on the serum DHT level for at least three or six months. The changes of stretched penile length (SPL), serum biochemical indexes including sex hormone profile, height, weight and bone age were evaluated. **Results:** There were two patients with AR mutation and five patients with SRD5A2 mutation. The average stretched penile length of 23 participants was 1.68 ± 0.6 cm prior the treatment and the ΔPL-SDS was -1.13 ± 0.47 cm after 6 months therapy. 61% patients reached the standard (>2.5 SDS), 13% withdrawal the medication. Hepatorenal function, CBC, height, weight, bone age and testis volume analysis showed no statistical difference compared with the data prior the treatment at 1, 3, 6 months after therapy. **Conclusion:** Three to six months' small dose of DHT therapy in micropenis children resulted in significant improvement of penis growth without evident side effects.

P1-P378

Randomized Controlled Study Comparing Vitamin D and Omega 3-Fatty Acids Supplementation in Adolescents with Polycystic Ovary Syndrome

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Background: Polycystic ovary syndrome (PCOS) is a complex endocrine genetic disorder, which is associated with increased metabolic and cardiovascular morbidity. Vitamin D or omega-3 fatty acids supplementation may alleviate the metabolic and reproductive complications of PCOS. **Objective and hypotheses:** To compare clinical, psychometric, biochemical, endocrine, bone and sonographic markers in vitamin D sufficient adolescents with PCOS, pre- and post- 6 month intervention with vitamin D or eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) supplementation. **Method:** Adolescents aged 14–18 years with PCOS diagnosed according to Rotterdam criteria, who were Vitamin D sufficient (serum 25OHD ≥ 30 ng/ml), were studied prospectively. Exclusion criteria included severe chronic disease, chronic medication and use of contraceptives or dietary supplements. Both at baseline and post-intervention, participants underwent detailed clinical, biochemical, endocrine, sonographic and psychometric evaluation, as well as measurement of their bone density and body composition by DEXA. Subsequently, they were randomized into 3 groups: vitamin D (D) group received 2000 IU D3 daily, omega-3 fatty acids (Ω3) group received 1 g EPA&DHA daily and control (C) group received no treatment. **Results:** Thirty adolescents (mean age 15.7 ± 2.1 years), 11 in D-group, 10 in Ω3-group and 9 in C-group were included in the study. No statistically significant differences were noted in adolescents' BMI, body composition, blood pressure and perceived stress scale-14 score among groups. Post-intervention and compared with the control group, subjects in the D-group had significantly increased serum DHEA ($P=0.044$), DHEAS ($P=0.017$) and endometrial thickness ($P=0.002$), while subjects in the Ω3-group had significantly decreased serum 25OHD ($P=0.007$) and PTH ($P=0.043$) and increased LDL ($P=0.046$), ApoB ($P=0.023$) and number of menses ($P=0.046$). **Conclusion:** In adolescents with PCOS, improvement of the menstrual cycle was noted in the group treated with omega-3 fatty acids. There was no improvement in the metabolic profile of patients in either group.

P1-P379

Health-Related Quality of Life and Psychological Wellbeing in Adults with Diverse Sex Development

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Background: Rare congenital conditions with incongruence of chromosomal, gonadal, and phenotypic sex have been summarized as disorders of sex development (DSD). Included in DSD are conditions with diverse genetic etiology, varying levels of prenatal androgen effects, phenotypes, and subsequently, different medical treatments. Quality of life (QoL) and psychological wellbeing are indicators of successful psychosocial adaptation to the conditions. Studies addressing these issues in individuals with DSD vary greatly. **Objective and hypotheses:** This multicentre clinical evaluation study was part of a German network related to DSD funded by the German Ministry of Science and Education (BMBF 2003–2007). **Method:** To assess health-related quality of life (HRQoL), as well as psychological wellbeing, the Short Form Health Survey (SF-36) and the Brief Symptom Inventory (BSI) were used. **Results:** Participants included 110 adults with DSD. Participants were classified into five groups: f-CAH, f-XY-pa, f-XY-na, m-XY-pa, and other gender. We found a trend of lowered mental HRQoL and significant higher physical HRQoL for participants as compared to a norm. The high physical HRQoL especially applied to females with androgen effect and XY Karyotype. Participants reported significantly higher psychological distress compared to the norm. Forty-seven participants (43%) reported distress in a clinically relevant range on the BSI. **Conclusion:** Although there is a high physical HRQoL participants reported significant impaired psychological wellbeing. However, a selection bias cannot be ruled out and social desirability bias must be considered. Specialized interdisciplinary care should focus in particular on psychological issues to ensure overall good health and well-being.

P1-P380

Association of Genetic Polymorphisms Around the LIN28B Gene and Idiopathic Central Precocious Puberty Risks Among Chinese Girls

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Background: Genome-wide association studies have identified rs314276, rs314263, rs7759938 and rs314280 in or near the LIN28B gene as associated with age at menarche. To date, the effect of polymorphisms in this gene on idiopathic central precocious puberty (ICPP) in Chinese girls have not been reported. **Objective and hypotheses:** The aim of this study was to evaluate the association of the four loci with ICCP in Chinese girls. **Method:** In this study, we conducted a case–control study including 502 girls with ICPP and 489 controls. Four single-nucleotide polymorphisms (SNPs) were genotyped in both groups using an improved multiplex ligation detection reaction (iMLDR) technique. **Results:** Of the 4 SNPs of the LIN28B analyzed, 3 SNPs, rs314276, rs7759938 and rs314280, were associated with ICPP risk at $P<0.05$. The association of rs314276, however, was no longer significant after adjustment for multiple testing. Compared with rs7759938 TT or TC genotype, decreased ICPP risk was associated with CC (OR = 0.527, 95% CI: 0.329–0.843) genotype ($P=0.008$). Compared with rs314280 GG or GA genotype, decreased ICPP risk was associated with minor allele carrier (AA) genotype (OR = 0.538, 95% CI: 0.337–0.858, $P=0.009$). The two identified variants showed the same association signals for ICPP. **Conclusion:** In conclusion, common genetic variations (rs7759938 and rs314280) of LIN28B may contribute to ICPP susceptibility in Chinese girls.

P1-P381

Psychological Outcomes and Quality of Life of Patients with Non-CAH DSD

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Background: Evidence based treatment of patients with Disorders of sex development (DSD) is challenged by a dearth of outcome studies. **Objective and hypotheses:** To study the quality of life and the psychological outcomes of children with DSD other than congenital adrenal hyperplasia (CAH) and to identify relevant risk factors. **Method:** Patients with DSD other than CAH aged between 6 and 18 years. Control subjects were matched for age and gender. Study tools were the Paediatric Quality of Life (PedQOl) and the parent reports on the Child Behaviour Checklist (CBCL). Patients were grouped by karyotype and sex of rearing/recent gender. **Results:** 30 patients with 46XY-Male ($n=21$), 46XY-Female ($n=6$), 46XX-Male ($n=2$) and 46XX-Female ($n=1$). Median age of this population was 12 years [8–14]. The total PedQOL score was significantly lower in the patient group than in the control group ($P<0.05$) In subgroup analysis this difference was reflected ($P<0.05$) in the social and schooling fields. The patient group also had a significantly higher (more pathological) CBCL score as compared to the control group in the internal and external score realms and also in most domains namely affective, anxiety, attention deficit and conduct problems ($P<0.05$). In addition among the 46XY DSD group the patients who were raised female had significantly lower quality of life especially in the social and schooling fields as compared to their female counterparts. Males with 46 XY DSD had significantly higher internalizing behaviour problems as compared to their male control counterparts. Further analysis revealed that the degree of virilisation at birth did not significantly influence the PedQOl or CBCL scores. **Conclusion:** The present study revealed an overall reduction in quality of life scores and a higher degree of psychological distress in patients with DSD. Early identification and referral for psychological support should be an integral part of the management of these patients.

P1-P382

Normalization of Ovulation Rate in Adolescent Girls with Hyperinsulinemic Androgen Excess

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Background: Oligo-ovulatory androgen excess in women (polycystic ovary syndrome (PCOS) by NIH definition) is a major cause of subfertility and relates to hepatic steatosis, independently of obesity. **Objective:** To test whether early treatment of PCOS affects subsequent ovulation rate. **Method:** Adolescent girls with hyperinsulinemic androgen excess – a subgroup of PCOS – (mean age 16 year; BMI 23.7 kg/m^2) randomly received standard treatment (oral contraceptive; OC; $n=17$) or a low-dose combination of spironolactone (50 mg/d), pioglitazone (7.5 mg/d) and metformin (850 mg/d) (SPIOMET; $n=17$) for 12 months, with follow-up for 6 months. **Results:** Both interventions reduced androgen excess without changing body weight, lean mass or total fat (by DXA), but SPIOMET was accompanied by loss of hepatic and visceral fat (by MRI) toward normal. Ovulation rates (assessed by salivary progesterone, 3–6 months post-treatment) were 2.5-fold higher after SPIOMET than after OC (with normovulation in 94% vs 29%), and they associated closely to on-treatment loss of hepatic fat. **Conclusion:** Early in hyperinsulinemic androgen excess, normalization of central fat was followed by a normal ovulation rate.

P2-P383

Thyroid Autoimmunity in Adolescent Girls with Polycystic Ovary Syndrome – Pilot Study

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Relationship between polycystic ovary syndrome (PCOS) and thyroid autoimmunity has been recently suggested by several authors. Autoimmune thyroiditis (AIT) is the most prevalent autoimmune disease and link between AIT and PCOS has been reported in adult women. There is a hypothesis that functional autoantibodies could contribute to the development of PCOS. The aim of the study was to evaluate the prevalence of thyroid autoimmunity in adolescent girls with PCOS. Forty five adolescent girls with diagnosis of PCOS (study group – SG) (chronological age: 16.9 ± 1.3 year, age of menarche: 12.2 ± 1.4 year, BMI: 25.4 ± 7.9 kg/m^2) and 31 regularly menstruating girls (chronological age: 17.0 ± 1.9 year, age of menarche: 11.8 ± 1.9 year, BMI: 24.5 ± 7.0 kg/m^2) (control group – CG) were recruited to the study. In all participants metabolic and hormonal tests were done and ultrasound of pelvis was performed. Thyroid function and morphology were evaluated by measurement of thyroid stimulating hormone (TSH), free thyroxine (fT_4), antiperoxidase antibodies (anti-TPO Ab), antithyreoglobulin antibodies (anti-Tg Ab) and ultrasound (US) of the thyroid gland. All the participants were euthyroid (TSH <5 mIU/ml), however in six (13%) girls from SG and in two (6.5%) form CG levothyroxine treatment was introduced by the family doctor before. The indices of thyroid autoimmunity (elevated anti-TPO Ab, anti-Tg Ab, hypoechogenic US pattern of thyroid) was detected in 10 (22.2%) girls form SG and in three (9.7%) from the CG. Anti-TPO Ab alone was elevated in eight (17.8%) girls from SG and two (6%) girls from CG, anti-Tg AB in three (6.7%) and one (3%) girls and hypoechogenic US pattern of thyroid in seven (15.6%) and two (6%) girls, respectively. No significant associations were found between antibodies, hormones level and volume and pattern of the ovaries. The study does not confirm the relationship between PCOS and thyroid autoimmunity in adolescent girls, however high prevalence of anti-TPO Ab and anti-TG Ab in euthyroid patients with PCOS may suggest that further monitoring of their thyroid function is warranted.

P2-P384

The Efficacy and Safety of Gonadotropin-Releasing Hormone Analogue Treatment to Suppress Puberty in Gender Dysphoric Adolescents

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Background: Puberty suppression using gonadotropin releasing hormone analogues (GnRHa) is recommended by current guidelines. Although GnRHa have long been used to treat children with precocious puberty there are few data on the outcome of this treatment in gender dysphoric adolescents. **Objective and hypotheses:** We aimed to evaluate the efficacy and safety of triptorelin to suppress puberty in a cohort of gender dysphoric adolescents. **Method:** Fourty-nine MtFs (male-to-females) and 68 FtMs (female-to-males) treated with triptorelin were included. During treatment physical examination including assessment of Tanner stage took place every 3 months and regular blood samples were taken to determine gonadotropins, sex steroids, renal and liver function. Body composition was assessed using dual energy X-ray absorptiometry. **Results:** Median Tanner B/G stage at the start of treatment was 4. Testicular volume decreased in 43 of 49 MtFs. Menses ceased in postmenarcheal FtMs. Breast development completely regressed in 1 of 4 FtMs with Tanner stage B2 at baseline. After three months gonadotropins and sex steroid levels were suppressed. No sustained abnormalities of liver enzymes or

creatinine were observed. Alkaline phosphatase decreased which may be related to decreased growth velocity, as height SDS decreased in both sexes. Lean body mass percentage significantly decreased in both sexes, whereas fat percentage significantly increased. **Conclusion:** Puberty is adequately suppressed with GnRHa in gender dysphoric adolescents. Routine monitoring of gonadotropins, sex steroids, creatinine and liver function as suggested by current guidelines does not seem necessary during treatment with triptorelin. Further studies are needed to determine if the changes in height SDS and body composition that were observed during GnRHa treatment can be reversed with cross sex hormone treatment.

P2-P385

A Familial form of DSD due to NR5A1 Mutation in a Father and His Son

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Background: NR5A1 mutations in 46,XY patients lead to various degrees of disorders of sex development (DSD). Familial cases have been described where the mother (heterozygous for the mutation) presented primary ovarian failure. Little is known about testicular function at puberty but most patients have biological markers of gonadal dysgenesis, raising fears of infertility. **Objective and hypotheses:** To describe a familial form of DSD due to NR5A1 mutation transmitted by the affected father. **Method:** Case report. **Results:** The index case presented at birth a 25 mm penis with perineal hypospadias and bifid scrotum containing two testis. At minipuberty (7 weeks), the hormonal exploration showed: testosterone = 3.42 nmol/l with normal precursors, LH = 7.3 UI/l, FSH = 3.3 UI/l, AMH = 475 pmol/l. After hCG test (six injections of 1500 U every 2 days), testosterone raised to 4.9 nmol/l and AMH decreased during childhood (209 pmol/l at 4 years) suggesting partial testicular dysgenesis. He needed testosterone therapy for increasing penile length and hypospadias surgery. The right testis was brought down at 4 years for secondary ascension. His father presented a perineal hypospadias operated during the childhood but no micropenis. Puberty occurred spontaneously and he had no testosterone treatment. His wife became twice pregnant without medical assistance. At 35 years, leydig function was normal (testosterone = 17 nmol/l, LH = 4 U/l) but FSH and inhibin B suggested a partial balanced Sertoli dysfonction (Inhibine B = 85 nmol/l, FSH = 10 UI/l). Father and son were heterozygous for c.269delG mutation of NR5A1. They had no adrenal insufficiency. **Conclusion:** NR5A1 mutations may be transmitted by the affected father. Gonadal dysgenesis is variable and spontaneous puberty and fertility is possible in some cases.

P2-P386

High Prevalence of SGA in Patients with Disorders of Sexual Development, Especially Idiopathic 46,XY DSD

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Background: Disorders of sex development (DSD) are a group of rare conditions characterized by variable discordance between chromosomal, gonadal and phenotypic sex. An association between smallness-for-gestational age (SGA) and DSD is already recognised, but few studies have investigated this in detail. **Aim of study:** To evaluate the prevalence of SGA, among patients with DSD and to establish a correlation with the different types and causes of DSD. **Patients and methods:** All patients referred for DSD to our endocrine clinic from December 2007 to December 2015 were included. They were investigated to determine the type of DSD (46,XY; 46, XX; or sex chromosome DSD) and where possible the precise aetiology based on clinical assessment, and hormonal, radiological and genetic investigations. SGA was defined as birthweight (BW) or length (BL) $<$10th centile according to the Audipog database. Statistical analysis was made using Epi-info7 and BiostaTGV. **Results:** During the study period, 237 patients were referred with DSD, median (range) BW, BL and gestation: 3.1 (2.66–5) kg, 49.5 (38–57) cm and 40 (25–42) weeks. SGA was present in 83 (35%) infants, 45 (54%) of whom had BW $<$2500 g. The prevalence of SGA was higher in the groups with 46,XY DSD (47%) ($n = 48$) and with sex chromosome DSD (44%) ($n = 7$), than in the 46,XX DSD group (23.5%) ($n = 28$) ($P < 0.01$). In the 46,XY DSD group, the prevalence of SGA was particularly high in patients with syndromic DSD (89%) ($n = 8$) and AR mutation-negative partial androgen insensitivity syndrome (54%) ($n = 27$) ($P < 0.05$). Within this latter group there was no difference in the prevalence of SGA according to the EMS score. **Conclusions:** This study confirms the association between SGA and DSD, which appears especially strong in patients with idiopathic 46,XY DSD. The question remains as to whether there is a common genetic mechanism causing both DSD and SGA in 46,XY patients; or if the defect in prenatal exposure to androgens *per se* affects intrauterine growth.

P2-P387

Questionnaire Surveys Targeting Japanese Pediatric Endocrinologists Regarding Reproduction in Pediatric and Adolescent Cancer Patients

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Background: While existing guidelines recommend long-term follow-up of childhood cancer survivors (CCS), their fertility has not been clarified in Japan. **Objective and hypotheses:** To address this issue, we organized a working panel to compile evidence from CCSs. The team consisted of various medical specialists in foundation hospitals. **Method:** We had conducted the questionnaire surveys targeting pediatric endocrinologists regarding reproduction in pediatric and adolescent cancer patients in collaboration with the CCS committee of the Japanese Society for Pediatric Endocrinology (JSPE). The first survey was sent to 178 JSPE-certified councilors who were asked to self-evaluate their medical examinations (*Clin Pediatr Endocrinol* 2016). The second survey was sent to the physicians who had answered the experience with childbirth of their patients during the follow-up or fertility preservation before cancer therapy. **Results:** A total of 151 responses (85%) were obtained in the first survey. A quarter of the respondents experienced some issues with gonadal and reproductive examinations. In the second survey response rate was 100% (39 respondents). A limited number of councilors had experience with childbirth of their survivors (27 answers: 16 male CCSs, 22 female CCSs). A few cases with premature birth or delivery problems were reported. There were 25 answers of experience with fertility preservation for 21 male and 17 female patients. Sixteen respondents had experience with sperm cryopreservation, and 10 respondents had experience with gonadal shielding before radiotherapy for male patients, whereas nine respondents had experience with gonadal shielding before radiotherapy for female patients. A few respondents had experience with ovarian cryopreservation ($n=3$), testicular ($n=2$) or ovarian tissue cryopreservation ($n=4$), ovarian transposition ($n=4$), or use of GnRH analog ($n=7$). These preservations were proposed from the physicians (21), parents (1), patient (1), and not available (4). **Conclusion:** In this nationwide questionnaire survey, Japanese pediatric endocrinologists mentioned the necessity for inter-disciplinary communication among healthcare providers and the need for long-term follow-up study of reproduction in CCSs.

P2-P388

Fertility Outcomes after Childhood Onset Hypothalamic Hypogonadism

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Background: Childhood onset (CO) hypogonadotrophic hypogonadism (HH), congenital or acquired after midline tumours and their treatment, is reported to have significantly poorer outcomes, in terms of adult spermatogenesis induction and duration of treatment to conception, compared with HH of post pubertal onset. A mixed cohort (youngest aged 26 years) reported median time to conception of 28 months.[1] Use of hCG and FSH in adolescence is reported to result in spermatogenesis after 6–9 months of combined treatment.[2] Presence of other pituitary hormone deficiencies did not alter outcomes. Little data exist regarding fertility outcomes for this group. A recent report confirmed a poorer fertility outcome in men with CO HH, particularly Kallman syndrome, with absent spontaneous puberty, testicular size before treatment correlating with time to fertility, with 8 conceptions, 3/8 requiring ICSI. Birth rate was not reported.[3] **Objective and hypotheses:** To report adult outcomes for a cohort of 14 men with congenital HH. **Method:** Three had past pubertal induction with hCG/FSH, 11/14 used testosterone alone. Age at first adult use of hCG and FSH for fertility induction ranged from 26–32 years. All achieved adult range testosterone levels within 3–4 months. Eight have sought fertility using FSH to date. **Results:** Time to spermatogenesis for first induction: median 9 months (9–36 months), mean sperm numbers: 1.78×10^6 ($1000\text{-}4\times10^6$). Time to first fertility: mean 28 months (9–51 months, IVF/ICSI needed in one), with live births in all. Second round fertility induction was undertaken by 3, mean time to sperm 3.5 months, time to fertility 8 months, all with live births. A total of 9 live normal births is reported. **Conclusion:** These men with CO HH demonstrate similar characteristics to earlier reports, with more rapid onset of spermatogenesis in second round induction. Nine normal live births, for men with CO HH,only one needing ICSI is the largest cohort so far identified. **References:** 1. Liu PY, Baker HW, Jayadev V, Zacharin M, Conway AJ, Handelsman DJ. *J CEM* 2009;94(3):801–8. 2. Zacharin M1, Sabin MA, Nair VV, *Dabadghao PAndrology*. 2016;4(1):87–94. 3. Rohayem J, Sinthofen N, Nieschlag E, Kliesch S, Zitzmann M. *Fertil Steril*. 2012;98(4):836–42.

P2-P389

Persistent Mullerian Duct Syndrome with Transverse Testicular Ectopia: A Novel AMH Receptor Mutation

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Background: Persistent Mullerian duct syndrome is the result of either anti-Mullerian hormone (AMH) deficiency or AMH receptor resistance. While the external genital structure is that of a normal virilized male, fallopian tubes and a uterus are observed in the internal genital structure. We present a case referred to our clinic because of female internal genital structure at laparoscopy during a surgical procedure performed due to undescended testes. **Objective and hypotheses:** A long tubular structure (testis/?) was palpated during the physical examination of a 13-month-old male patient who admitted because of bilateral undescended testes. No testicular structure was found on the left scrotum and in inguinal canal and scrotum by ultrasonography. On the right, two structures thought to be testes, 12×8 mm and 11×7 mm in size, were determined proximally to the inguinal canal and in the middle section. The image was interpreted as transverse testicular ectopia on the right. Structures suggestive of ovaries, a uterus and fallopian tubes were observed during laparoscopic examination of the ectopic testis. Gonad biopsy was performed, and the patient was referred to the Pediatric Endocrinology Department for advanced investigation with a preliminary diagnosis of a disorder of sex development. First-degree consanguinity was present between the parents. In physical examination his weight was 10.2 kg (SDS: −1.06), height; 81 cm (SDS: −0.39) and BP was 98/60 mm/Hg. He was prader stage 5, the testes were impalpable and the phallus was 3.5 cm long. In the laboratory examination, karyotype was XY, SRY (+), FSH: 0.44 mIU/l, LH: 0.27 mIU/l, free testosterone: 0.3 pg/ml, total testosterone: 0.1 ng/dl, E2: <20 ng/ml, and AMH:>22 ng/ml. Immature seminiferous tubular structures were observed in gonad biopsy specimens. AMHR2 gene sequence analysis performed with a preliminary diagnosis of AMH receptor resistance revealed a previously unreported homozygous c.24G>A(p.W8X) mutation. The mother and father carried the same mutation in heterozygous form. The case was assessed as one of AMH receptor resistance. Orchiopexy was performed. **Conclusion:** AMH receptor defect is a rare cause of 46 XY disorder of sex development. The condition should particularly be considered in virilized males with a normal external genital structure and persistent Mullerian structures.

P2-P390

Three Cases of NR5A1 (SF1) Gene Mutations in DSD Patients

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Background: NR5A1 mutations in DSD patients result in a wide range of clinical manifestations. **Objective and hypotheses:** To evaluate the clinical variability of ambiguous phenotypes and the gender assignment in DSD patients with SF1 mutations. **Method:** Clinical examination, hormonal tests, ultrasound, laparoscopy and molecular analyses, including direct and parallel sequencing. **Results:** Case 1. A girl, aged 18 months with female phenotype and Prader II clitorophallus. A small testis was detected in the right labioscrotal fold. The karyotype was 46,XY. Hormonal tests showed LH 0.25 IU/l, FSH 12.9 IU/l and testosterone after hCG stimulation test – 0.3 nmol/l. Pelvic ultrasound and laparoscopy showed the uterus, fallopian tubes and a dysgenetic abdominal gonad on the left side. Bilateral gonadal disgenesis was diagnosed. Molecular analyses detected the nonsense mutation c.256delA of NR5A1. Case 2. A boy, aged 5 months, with ambiguous genitalia. The left testis was found in labioscrotal fold and the right testis was not palpable. The patient had perineal hypospadias and a small phallus 1.5 cm. Hormonal tests showed testosterone – 5.6 nmol/l, LH 2.2 IU/l, FSH 5.0 IU/l and AMH – 43.8 ng/ml. Pelvic ultrasound detected no uterus and found urogenital sinus. As a result of examination, 5ARD2 deficiency was supposed. However, it was not proved by molecular analyses. The following test revealed the heterozygous p.R313C mutation of NR5A1. Case 3. A 46,XY boy, aged 16 month with similar phenotype was examined. Small testes were palpable in bifid scrotum. Uterus not found during pelvic ultrasound. Heterozygous p.S303R mutation of NR5A1 was detected. **Conctusion:** Clinical manifestation of DSD caused by SF1 mutations are characterized by phenotype variability.

P2-P391

Sertoli-Leydig Cell Tumor as a Rare Cause of Hirsutism in a Young Adolescent

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Background: Sertoli-Leydig Cell Tumors (SLCT) account only for 1% of all ovarian neoplasia, occur more commonly in the second or third decade of life and seldom secrete tumor markers. The experience in adolescence is limited. **Objective and hypothesis:** To report the hormonal and biological profile of a SCLT in a young adolescent. Ovarian tumor markers as well as FDG-PET scanning might be helpful in diagnosing ovarian malignancy in case of normal ultrasound imaging. **Results:** Mildly elevated androsteendion (4.35 ng/ml) and 17 hydroxy progesteron (4.6 ng/ml), but a markedly elevated testosterone (425 ng/dl), but normal cortisol (12 μg/dl), SHBG (27 nmol/l)), LH (7 U/l), FSH (4.9 U/l) and estradiol (40 ng/ml) were measured in a 13 years old girl (A3P6M5) with increasing hirsutism, slight acne, voice deepening and menses irregularity, but without male pattern baldness or cliteromegaly at examination. ACTH testing showed a normal cortisol and androgen response. Ultrasound of the adrenals and ovaries were normal. Hormonal re-analysis confirmed the elevated testosterone concentration by LC MSMS (222 ng/dl), but showed normal 17 OH progesterone, DHEAS and androstenedion concentrations. A search for ovarian tumor markers showed an elevated AMH 17.4 mcg/l and a markedly

elevated Alfa fetoprotein (268 mcg/l), but a normal inhibin B and b hCG concentrations. A FDG PET CT scan showed an oval mass with sharp borders (3.1×2.4 cm) with high peripheral uptake in the right ovary. Histopathologically and histochemically the diagnosis of SLTC was confirmed. **Conclusion:** In testosterone producing SLCT, non suppressed gonadotropin levels, probably by a low degree of aromatization to estradiol, as well as elevated alfa fetoprotein concentrations can be observed. FDG-PET scanning might be helpful in diagnosing ovarian malignancy when ultrasound imaging is normal.

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Identification of an *AR* Mutation in Klinefelter's Syndrome during Evaluation for Penoscrotal Hypospadias

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Background: Klinefelter's syndrome (KS) is the most prevalent chromosomal abnormality and clinically characterized by oligo-azoospermia, hypergonadotropic hypogonadism, gynecomastia and infertility in adults. Genital malformations in KS have rarely been reported. **Objective and hypotheses:** To investigate the etiology of penoscrotal hypospadias in a 14-month-old boy. **Method:** The patient was born from a healthy 23-year-old mother after in-vitro fertilization. Prenatal screening tests were normal, no chronic illness present and no drug used. Parents were no relatives. Thirty three-year-old father had subclinical hypothyroidism and azoospermia. Physical examination of the case revealed a height of 82 cm (S.D. score 1.50), weight 16.2 kg (S.D. score 3.4), penoscrotal hypospadias, and ventral chordee abnormality with bilateral normal testes (2/2 ml). **Results:** Laboratory studies showed normal biochemistry, follicle stimulating hormone 1.37 mIU/ml (normal range, 0.3–4.6 mIU/ml), luteinizing hormone $<$0.2 mIU/ml (normal range, 0.04–0.42 mIU/ml), total testosterone $<$0.1 ng/ml (normal range $<$0.2 ng/ml). Pelvic ultrasonography revealed no ovarian and uterine tissue. Following human chorionic gonadotropin administration, total testosterone increased to 1.32 ng/ml indicating normal androgen synthesis. Chromosomal analysis revealed 47,XXY karyotype. Further genetic investigation disclosed a known missense mutation in *AR* (p.p392S, c.1174C$>$T). Results of genetic analyses of the parents are pending. **Conclusion:** Although KS is suggested to be in the differential diagnosis of penoscrotal abnormalities, mutations in genes involved in androgen synthesis or responsiveness should also be investigated.

P2-P393

Assessment of Sexual Identity in Patients with Congenital Adrenal Hyperplasia

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Background: Congenital adrenal hyperplasia (CAH) is caused by different enzyme deficiency in the pathway of corticosteroid synthesis resulted in disorder of sex development (DSD) and may affect sexual identity in patients. **Objective and hypotheses:** To assess gender identity in patients with CAH. **Method:** In this study, 51 patients with CAH [21 children (5–14 years) and 30 adolescents and adults (15–37 years) were assessed using sexual identity questionnaires based on the criteria of Diagnostic and Statistical Manual of Mental Disorders, 5th edition, (DSM-5), separately for children and adults. The reliability of the questionnaires was determined acceptable by the Cronbach's alpha (α) score of 0.955 for adults and 0.726 for children. **Results:** In the children group, compatibility was seen between sexual identity and rearing gender. In adult group, there were three cases of mismatching between sexual identity and gender assignment composed two females (genitoplasty was done in infancy), one of them was in poor control; and one male with 21-hydroxylase deficiency. The parents and children did not agree for changing the gender in two 6-year-old girls with 11-hydroxylase deficiency (11-OHD) who had been reared as boy. One of them is 36 years old now and is depressed and unsatisfied of her gender. One 34-year-old woman with 11-OHD who had complete virilization but uterus and ovaries were saved until 12 years of age agreed for changing of gender to female after appearance of pubertal signs. She got married, has two children and is satisfied with her gender. **Conclusion:** In CAH patients with DSD, gender identity disorder is a rare finding and more than 90% of patients have sexual identity compatible with gender assignment according to their karyotype except males with complete lipoid adrenal hyperplasia and 17-hydroxylase deficiency who have to be female.

P2-P394

Duct Ectasia, a Rare Complication of Gynaecomastia

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Background: Mammary duct ectasia is a bening breast condition which affects primarily middle-aged to elderly women. However, it can occurs wherever there is breast ductal epithelium.

Case presentation: A 9-years-old boy was referred to the regional paediatric endocrine clinic from the General Practicioner due to gynaecomastia. Pubic hair development started at the age of 8. Personal and family history were unremarkable except for a history of coping with potential distress caused by his breast condition. His mother noticed bilateral breast enlargement at the aged of 6. No discharge from the nipples since then. On examination: normal height (p79) and weight (p56), Tanner stage 1 and bilateral gynaecomastia with no signs of inflammation. Genitalia: normal male configuration. In particular, no stigmata of liver disease. Rest of the general examination was unremarkable. Initial investigations: liver, kidney and thyroid function test were within normal range. Testosterone 0.16 ng/ml [1.8–8], oestradiol 9 pg/ml [<25], prolactin 8.7 ng/ml [3–27], LH 0.06 UI/L [<0.3] and FSH 0.9 UI/L [<3] and human chorionic gonadotropin (hCG) <1.2 mUI/ml [0–5]. Karyotype 46XY. Mammography was reported as compatible with gynaecomastia. Normal scrotum ultrasound scan. Diagnosis: idiopathic gynaecomastia. Follow-up (6 months later): he complaint about breast pain and redness. On the examination: left mobile, tender and fluctuate on palpation mass under the nipple and redness, no discharge. Second mammography: complicated breast cyst (8.8 × por 43.6 × 42.7mm). After surgical resection, anatomo-pathological features revealed the diagnosis of left duct ectasia (estrogen receptors: positive 10%). Secondary diagnosis: duct ectasia in a boy with gynecomastia self-limiting. **Conclusion:** We described one of the few cases reported of duct ectasia in a 9-year-old male. It is well known that in the vast majority, gynaecomastia is self-limiting, however it is necessary to be aware of its posible complicactions in order to avoid mistakes and familial stressed as mammary duct ectasia can mimic invasive carcinoma clinically.

P2-P395

Evaluation of Anti-Mullerian Hormone (AMH) Assay Roche® on Umbilical Cord Blood: Determination of Reference Values in Girls and Boys Newborn

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Background: Anti-Mullerian hormone (AMH) concentration is now well studied for prepubertal boys (Plotton, 2009, 2012) or women in reproductive medicine, but there is few data about reference value in newborns. This dosage could be helpful for the management of disorders of sex development. **Objective:** The objective was to determine reference values of AMH on umbilical cord blood and to compare the values to DSD new born diagnosed during the evaluation. **Material and method:** We analyzed venous umbilical cord blood of 192 males and 33 girls between the 13 of May 2015 and the 4 of February 2016, after approval of the ethics committee. AMH were analyzed by using an automated assay ECLIA (Cobas Roche®). Heparin syringes withdrawn systematically after births for blood gas were collected after approval of French ethical board. In parallel, we collect clinical data gestational age and history of syndromic malformation or urogenital anomalies like cryptorchidism, hypospadias or micropenis diagnosed on the clinical exam made systematically 3 days after birth. We eliminated samples of boys presenting genitourinary abnormalities. During this period we also determined AMH concentrations on serum samples for 3 boys with clinical presentation evocative of defective androgen action (DA) and three others presenting testicular dysgenesis. **Results:** Twelve of the 192 boys and 5 of the 33 girls were preterm birth. We analyzed the results (pmol/l) and the mean ± 1 S.D. (min-max) were for boys born at term 268.8 ± 117.5 (58.5–724.3); pre term boys 244.6 ± 63.8 (166.8–367.4); girls at term 2.4 ± 3.1 (0.3–12.3); pre term girls: 1.1 ± 0.9 (0.5–2.6). Reference values between boys and girls are significantly different ($P < 0.0001$). In case of DSD, AMH value (mean ± S.D.) were found at 357.8 ± 123.8 for DA; and 115.8 ± 60.7 for testicular digenesis. **Conclusion:** These preliminary data of normal values on venous umbilical cord blood appear to be useful for the management of DSD at birth.

P2-P396

Hypogonadotropic Hypogonadism in a Girl with 2p11.2–2q12.1 Duplication

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Background: Patients with chromosome 2 pericentromeric duplication are rarely reported in literature. **Objective and hypotheses:** To describe a young girl with a congenital malformations syndrome, hypogonadotropic hypogonadism and impaired bone quality associated with a chromosome 2 pericentromeric duplication. **Results:** The proposita was born at 37th weeks of gestation from a twin pregnancy with a cesarean delivery presenting low birth weight for gestational age. She showed an aneurysm of the Galeno vein, a delayed psychomotor development, hiatal hernia, vernal keratoconjunctivitis and paroxysmal supraventricular tachycardia. The proposita also showed many facial and body dysmorphisms and a severe growth failure. The molecular karyotyping performed by array-CGH highlighted a chromosome 2-pericentromeric duplication of approximately 14 Mbp (2p11.2–2q12.1). At the age of 17 years and 9 month, she was evaluated for delayed puberty and primary amenorrhea. Tanner stage was B3 PH4 AH3. GnRH stimulation test revealed hypogonadotropic hypogonadism (LH peak 5.67 mIU/ml). Oestrogen level was very low, as well as inhibin B and anti-Mullerian factor levels. The pelvic ultrasound showed normal uterus and ovaries with reduced volume. Furthermore, blood tests showed vitamin D deficiency, a low total and ionized calcium levels and a high level of parathyroid hormone. The ultrasound bone densitometry revealed a very low bone mineral status (*Z*-score corrected for height = −3.8 SDS). The patient have spontaneous menarche at 18 years with secondary amenorrhea. **Conclusion:** We suggest that this may be a new congenital syndrome associated with hypogonadotropic hypogonadism. The role of specific genes associated with 2p11.2–2q12.1 duplication must to be evaluated.

P2-P397

A Nonvirilized form of Classic 3β-Hydroxysteroid Dehydrogenase Deficiency Due to a Homozygous S218P Mutation in the HSD3B2 Gene in a Girl with Classic Phenylketonuria

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Background: 3β-hydroxysteroid dehydrogenase (3βHSD) deficiency is a rare form of congenital adrenal hyperplasia (CAH) and caused by loss of function mutations in the HSD3B2 gene. In classic form, affected patients have salt wasting early in infancy and may have ambiguous genitalia in both sexes. Herein we report a nonvirilized female patient with classic form of 3βHSD deficiency due to homozygous S218P mutation in the HSD3B2 gene and classic phenylketonuria. **Case report:** A female neonate was born after uneventful pregnancy by spontaneous vaginal delivery. The parents were first degree cousins. Phenylalanine level was elevated in newborn screening so she was diagnosed with classic phenylketonuria and was put on phenylalanine restricted diet at 7 days of age. At one month of age she was found to be lethargic and dehydration, she failed to gain weight. Laboratory results showed severe hyponatremia (Na: 119 mEq/l), hyperkalemia (K:7 mEq/l), normal glucose level. ACTH was 926 pg/ml, cortisol: 7.3 μg/dl, renin: 1205 pg/ml, aldosterone: 1089 pg/ml, testosterone: 216 ng/dl; androstenedione: >10 ng/ml; 17OHP: 105 ng/ml; 11 deoxycortisol: 132 ng/ml; DHEAS: 1387 μg/dl so she was diagnosed with CAH. In spite of dramatically elevated androgen levels she did not have any sign of virilisation. The karyotype was 46,XX. Pelvic ultrasonography revealed normal female internal genitalia. Mineralocorticoid and glucocorticoid replacement was started. Genetic tests confirmed the diagnosis of 3βHSD deficiency due to homozygote mutation in the HSD3B2 gene (S218P). CYP21A2 and CYP11B1 genes were normal. **Conclusion:** Homozygous S218P mutation in the HSD3B2 gene was associated with nonvirilization of external genitalia in our patient. Previously a compound heterozygous Y190C and S218P mutations has been reported in a girl with moderate virilization. Data is not sufficient for a genotype-phenotype correlation for the current mutation yet.

P2-P398

Nonclassic Congenital Adrenal Hyperplasia and Functional Ovarian Hyperandrogenism Diagnosed During the Transition Period: Differences in Clinical, Hormonal and Metabolic Aspects

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Introduction: Hyperandrogenism is a common presenting complaint during the transition period; however, clinical, hormonal and metabolic parameters in these patients have not been yet adequately characterized. **Objective:** To evaluate the disease-related history, clinical presentation and biochemical parameters in patients diagnosed during this period with nonclassic congenital adrenal hyperplasia (NCCAH) due to 21α hydroxylase deficiency and patients with functional ovarian hyperandrogenism (FOH). **Method:** We retrospectively evaluated 28 patients with NCCAH (confirmed by mutations in CYP21A2) and 28 patients with FOH who presented at the age of 15–25 years. The following aspects were analyzed: age at menarche, BMI, menstrual disorders, hirsutism, acne, increased sweating, premature pubarche, androgenic alopecia, testosterone, androstenedione, dehydroepiandrosterone-sulfate, 17α hydroxyprogesterone (17OHP), LH, FSH, insulin, blood glucose and lipid profile. **Results:** Significant differences were found in the age at menarche: NCCAH 11.7 years (9–14), FOH: 13 years (11–18) ($P<0.002$). Only the NCCAH group showed premature pubarche ($n=4$), sweating ($n=3$), alopecia ($n=4$). In the FOH group, a higher tendency to acne was observed ($P=0.09$); with no differences in menstrual disorders and hirsutism. The NCCAH group showed higher levels of 17OHP (ng/ml): NCCAH 13.3 (2.3–54), FOH 1.45 (0.35–4.0) ($P< 0.0001$) and the FOH group, showed a tendency towards higher levels of LH (mIU/ml): NCCAH 6.4(2.0–21.6), FOH 9.1(1.6–24.4) ($P=0.054$). No significant differences were found in the metabolic parameters evaluated. **Conclusions:** During the transition period, the time of onset and clinical manifestations in hyperandrogenic patients, in addition to 17OHP and LH measurements, may provide better guidance regarding etiology. The NCCAH group was characterized by earlier clinical manifestations, perhaps related to the pathophysiology of this condition, as hyperandrogenism would be present since earlier stages. No differences were found in the metabolic profile regardless of etiology, suggesting that metabolic aspects could be influenced by hyperandrogenism rather than by the underlying condition.

P2-P399

Diagnosis of PCOS in Adolescents Using MRI

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Background: Polycystic ovarian syndrome (PCOS) diagnosis includes ovarian morphology using transvaginal ultrasound (US). However transvaginal US cannot be used in virginal girls and transabdominal US is not optimal particularly in obese patients. **Objective and hypotheses:** To evaluate the validity and reproducibility of ovarian morphology measures using MRI for the diagnosis of PCOS in adolescents. **Method:** This case-control study (2006–2015) included 128 pubescent girls aged 11–18 who underwent pelvic MRI. Cases had a high suspicion of PCOS ($n=45$, hyperandrogenism, oligo-amenorrhea), intermediate ($n=8$, hyperandrogenism) or low ($n=7$, oligo-amenorrhea). Controls ($n=68$, no clinical hyperandrogenism nor oligo-amenorrhea). Using the high suspicion of PCOS vs controls as the reference, we assessed the validity (sensitivity, specificity, area under the ROC curve (AUC)) of follicle number per ovary (FNPO) ≤ 9 and ≤ 5 mm, ovarian volume (OV), sphericity index, peripheral distribution of follicles and absence of dominant follicle. Two radiologists independently measured these criteria in 50 girls with a suspicion of PCOS selected at random, to assess reproducibility (kappa, intraclass correlation coefficient (ICC)). **Results:** All criteria but sphericity index were significantly associated with the level of suspicion of PCOS (P for trend <0.05). AUC of FNPO ≤ 9 mm (0.81; 95% CI: 0.73–0.89), FNPO ≤ 5 mm (0.76; 0.67–0.85) and OV (0.78; 0.70–0.87) were significantly higher than 0.5, contrary to sphericity index (AUC = 0.58; 0.47–0.68). The sensitivity and specificity of peripheral distribution of follicles were 37.8% (23.8–53.5) and 95.6% (87.6–99.1). For absence of dominant follicle, they were 93.3% (81.7–98.6) and 23.5% (14.1–35.4), respectively. The reproducibility was almost perfect for OV (ICC = 0.88), substantial for absence of dominant follicle (kappa = 0.73), moderate for FNPO ≤ 9 mm (ICC = 0.54) and FNPO ≤ 5 mm (ICC = 0.60), fair for peripheral distribution of follicles (kappa = 0.39) and slight for sphericity index (ICC = 0.14). **Conclusion:** The most accurate diagnostic criteria by MRI were FNPO ≤ 9 mm, OV and peripheral distribution of follicles; the most reliable criterion was OV. MRI is a valuable tool to confirm PCOS in adolescent girls based on clinical and hormonal characteristics when transvaginal US cannot be performed.

P2-P400

Novel CYP17A1 Mutation and CYP21 Mutations in Two Siblings

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Background: 17 hydroxylase deficiency is a rare form of congenital adrenal hyperplasia resulting from loss-of-function mutations involving the *CYP17* gene. It is characterized by decreased production of glucocorticoids and sex steroids and increased synthesis of mineralocorticoid precursors. **Objective and hypotheses:** We aimed to identify genetic cause of lack of puberty in a girl and the cause of ambiguous genitalia in her sibling. Fourteen-year-old girl presented with lack of telarche. Parents were first degree cousins. On physical examination, weight was 37 kg (−2.8 SDS), height was 152.5 cm (−1.3 SDS), puberty was Tanner stage 1. Blood pressure was 120/90 mmHg. Bone age was 10 years. Laboratory results were as follows; serum Na: 140 mmol/l, K: 3.6 mmol/l, glukoz: 95 mg/dl, FSH: 94 ıu/l, LH: 63 ıu/l, estradiol: 11.8 pg/ml, PRL: 9.3 ng/ml, ACTH: 1250 pg/ml (0–46), cortisol: 0.5 μg/dl, total testosteron: 10 ng/dl, progesteron: 12.7 ng/ml, pH: 7.34, HCO3: 26.4 mmol/l. Uterus and ovaries were not visualized. Chromosomal analysis was 46 XY. Her newborn sibling was consulted for ambiguous genitalia. Phallus was 2.5 cm with no palpable gonads. Laboratory results showed 17 hidroksi-progesteron:215 ng/ml, total testosteron: 245 ng/dl, 1–4 androstenedion >10 ng/ml. Chromosomal analysis was 46 XX. **Method:** Gene analysis was undertaken as described before. **Results:** CYP17A1 gene analysis showed novel homozygous c.617_618delTA mutation in exon 3. Parents and siblings were heterozygous. Gene analysis of her newborn sibling showed homozygous CYP21 c.293-13A/C>G (In2G) mutation. **Conclusion:** 17 hydroxylase deficiency causes ambiguous genitalia in 46 XY individuals while sexual infantilism is seen in 46 XX patients secondary to decreased production of sex steroids. Different types of congenital adrenal hyperplasia can be seen in the same family specially in areas where consanguineous marriages are frequent.

P2-P401

Aetiology of 46,XY DSD in Algeria; Putative Modifier Role of pV89L Polymorphism in the SRD5A2 Gene in Androgen Receptor Mutation-Negative Subjects

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Background: 46,XY DSD is a heterogeneous group of pathologies characterized by a wide spectrum of phenotypes and aetiologies. While advances in molecular genetics have permitted discovery of numerous genes implicated in testicular development, the diagnosis still remains uncertain for most patients with 46,XY DSD. **Objective:** To identify the aetiologies of 46,XY DSD in Algerian patients. **Methods:** We conducted a multicentre prospective study. All patients referred for DSD (excluding Turner and Klinefelter syndromes) were investigated and classified as 46,XX DSD; sex chromosome DSD and 46,XY DSD. In this last group, clinical, ultrasonography, MRI, genitography and hormonal analysis helped sub-classify the patients as having: disorders of androgen synthesis or action, gonadal dysgenesis, persistent Müllerian duct syndrome (PMDS), ovo-testicular DSD or syndromic DSD. Mutational analysis was performed for patients with disorders of androgen action (*AR* gene and *SRD5A2* gene, *MAMLD1*) and gonadal dysgenesis (*SRY, NR5A1, WT1*).

Results: Of 237 patients in the study 119 had 46, XX DSD (due to congenital adrenal hyperplasia in 92), 102 had 46,XY DSD and 16 had sex-chromosome DSD. Aetiology among the patients with 46,XY DSD was disorder of androgen action (52), defective androgen synthesis (7), varying degrees of gonadal dysgenesis (31), PMDS (2), ovo-testicular DSD (1) and syndromic DSD (9). Mutational analysis revealed two different mutations in two pairs of siblings in the *NR5A1* gene (including one new mutation), one new mutation in the *SRD5A2 gene*, one mutation in the *AR* gene and one new mutation in *MAMLD1*. Furthermore, V89L polymorphism in the *SRD5A2* gene was found in eight patients with androgen resistance, and the p.Gly146Ala polymorphism in the *NR5A1* gene was found in four patients. Genetic analysis was negative and cause of DSD unknown in 33/83 patients (77.11%). **Conclusion:** Disorders of androgen action were the most frequent cause of 46,XY DSD in this large series, but a mutation of the AR gene itself was rarely found. However, pV89L polymorphism in the SRD5A2 gene is not rare in our patient population. This finding is in keeping with the hypothesis that functional polymorphisms may play an important role in complex conditions such as DSD, with several factors contributing to the defect.

P2-P402

Children with 46,XY DSD: Etiology, Clinical Profile, Socio-Demographic Details and Sex of Rearing

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Background: Disorders of sex development (DSD) is a group of uncommon birth defects. Androgen excess in genetic females and androgen deficiency in genetic males can result in DSD. A child with ambiguous genitalia could be a virilized female or an under-masculinized male. Presented here is the socio-demographic profile, age at diagnosis, clinic 351al profile and etiology of patients with 46,XY DSD who are on follow up at our hospital. **Objective and hypotheses:** Children with DSD are usually diagnosed and treated during infancy However in resource poor countries (where all deliveries are not conducted by medical or paramedical people), many of these children remain undiagnosed/ untreated for long periods. This has given us an opportunity to learn the natural history of this disorder, particularly gender identity in the absence of medical intervention. Here we present. **Method:** All patients underwent detailed medical history including parental consanguinity, clinical evaluation, hormonal profile, karyotyping and imaging for gonads and mullerian structures. Children >6 years old underwent detailed psychological evaluation. **Results:** Ninety five 46,XY DSD patients were enrolled in a period of 3 years. Age at initial evaluation ranged from newborn to 31 years (11.4 ± 7.7). 88 patients had ambiguous genitalia, four presented with primary amenorrhea and three with labial swelling. Among 88 children with ambiguous genitalia, parents of only 31 were informed about this at birth. 50 of the 95 children were given female gender assignment at birth. 21 of these were subsequently re-assigned male gender. 30 cases were diagnosed with 5αRD, 31 patients had AIS and 19 cases were diagnosed with gonadal dysgenesis. **Conclusion:** There was delay due to socio-economic reasons and lack of information related to DSD and its management in children, who did not receive treatment during infancy/early childhood. AIS and 5αRD were the most common causes for 46,XY DSD.

P2-P403

Endocrine Risk Factors of Testicular Cancer of Children and Teenagers with Testicular Microlithiasis

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Objective and hypotheses: To evaluate endocrine risk factors of testicular cancer of children with testicular microlithiasis. **Method:** Under research were 74 patients with testicular microlithiasis (average 11.41 ± 4.02). Heredity, case history, endocrine diseases, anthropometric indicators, ultrasound of the scrotum were evaluated. **Results:** At 20 of 74 (27%) children microlithiasis was combined with strong risk factors of testicles cancer – cryptorchism and disorder of sex development (DSD) (50%, 10/20), 54 (73%, $P=0.002$) children had isolated microlithiasis. One-sided cryptorchism detected in 60% (6/10), double-sided in 40% (4/10) of children. 20% (2/10) of patients with cryptorchism had obesity, one case within the Prader-Willy's syndrome. Atrophy of the gonads had 50% (5/10) patients. Among 60% (6/10) in patients with DSD were verified the following diagnoses: partial gonadal dysgenesis – 20% (2/6), mixed gonadal dysgenesis – 20% (2/6), partial androgenic insensitivity syndrome – 20% (2/6). Additional testicular cancer risk factors had 22% (12/54) patients with isolated testicular microlithiasis: heredity – 1.8% (1/54), germ-cell tumors of other location – 1.8% (1/54), leydigoma – 1.8% (1/54), obesity – 7.4% (4/54), testicular atrophy – 3.7% (2/54) , irregular puberty syndrome – 3.7% (2/54), congenital adrenal hyperplasia (21 – hydroxylase deficiency), salt-wasting with TART syndrome – 1.8% (1/54). Conditional risk factors had 16.6% (9/54) of patients: pubertal gynecomastia in 11% (6/54), varicocele in 5.5% (3/54). Among patients with isolated testicular microlithiasis three additional testicular cancer risk factors had 1 (1.8%) teenager, two factors – 4 (7.4%), one factor – 7(13%) children. **Conclusion:** Every third child with testicular microlithiasis had severe testicle cancer risk factors (cryptorchism, DSD). Every 4th patient with isolated microlithiasis had additional endocrine risk factors of testicular cancer; each 12th patient had a conditional risk factor.

P2-P404

Case Report of a Girl with Secondary Amenorrhea Associated with Aurantiasis Cutis

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Background: Aurantiasis cutis is a condition of yellowish or golden skin discoloration that can result from eating excessive amounts of foods containing carotene leading to hypercarotenemia, described causing secondary amenorrhea. **Objective and hypotheses:** Hypercarotenemia can cause secondary amenorrhea without overconsumption of excessive quantities of carotene. **Method:** A 16-year-old girl presented to our endocrine outpatient clinic with a 2-year history of varying yellow discoloration of her skin and secondary amenorrhea. The findings from the general physical examination were normal, but there was a marked yellow discoloration of the palms, soles, and nasolabial folds. A dietary history revealed a low carotene diet, but also a low carbohydrate diet. BMI was 19.9 kg/m^2 (-0.2 SDS) without signs of anorexia. **Results:** See Table 1. **Conclusion:** In this girl we observed hypercarotenemia associated with secondary non-hypothalamic amenorrhea in absence of excess external intake of carotenes. This suggests an intrinsic reason due to a polymorphism in ß-carotene 15,15′-monooxygenase (BCO), an enzyme breaking down carotenes to vitamin A. Phenotype-genotype association studies are needed to confirm this hypothesis.

Table 1.

Laboratory findings	Units	Reference range
ß-carotin	2230 µg/l	(235–1040)
Bilirubin (total)	0.4 mg/dl	(0.2–1.0)
GOT (AST)	26 U/l	(15–41)
FSH	7.0 IU/l	(2.2–10.1)
LH	4.2 IU/l	(1.0–52.2)
Estradiol-17ß	49.4 ng/l	(16.1–238,3)
17-OH-Progesterone	0.73 µg/l	(0.1–2.2)

P2-P405

Maternal Ovarian Luteoma Causing Complete Virilization of a Female Fetus

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Background: Maternal ovarian luteoma is a rare condition that may cause virilization of female fetuses. **Case presentation:** We present the case of a baby born at 29 weeks gestational age to a 20 yo mother with history of two spontaneous abortions and no live births. Physical exam after birth revealed ambiguous genitalia, with a stretched phallic length of 1 cm with hypospadias on the ventral surface of phallus and complete fusion of rugated labioscrotal folds. No palpable gonads in the folds or inguinal canal. Mother denied any medications during pregnancy. Mother was noted to have a low pitch voice and hirsutism. She reported that 3 months into her pregnancy, she noticed the appearance of facial hair and increased clitoral size. No family history of ambiguous genitalia. Baby had a 46,XX female karyotype and negative SRY. A pelvic ultrasound showed normal uterus and ovaries. Baby's testosterone at birth was 71.6 ng/dl and at 2 weeks of age it was 32.6 ng/dl. Her 17 hydroxyprogesterone was high initially and later normalized. Her androstenedione was normal. Right after delivery, maternal testosterone was markedly elevated at 1867 ng/dl. Normal estradiol and DHEAS. Maternal pelvic US and MRI showed multiple leiomyomas and an oval shaped solid mass 31×41 mm within right adnexa with a cystic 19×24 mm lesion medial to the mass suggestive of a tumor. The mother was temporarily lost to follow-up. She returned for follow up two months after delivery. At that time her repeat testosterone was 13.7 ng/dl. Her hirsutism had improved and clitoral size had returned to normal. **Discussion:** We present the case of a female baby with complete virilization of the genitalia due to a presumed maternal ovarian luteoma. There are only other three cases reported, two of them twins, that presented with complete virilization. i) and ii) Other reported cases have partial virilization. The incidence of hyperandrogenism during pregnancy is low. Hyperandrogenism and virilization during pregnancy are usually the result of a disorder arising during gestation, as hyperandrogenism in a non-pregnant female frequently causes infertility. Fetal conditions causing virilization, such as congenital adrenal hyperplasia, are more common than maternal disorders. Two of the most frequent causes of hyperandrogenism during gestation are luteomas and theca-lutein cysts of the ovary. iii) A luteoma is a rare ovarian mass that appears during gestation and regresses and disappears after delivery. About 25% of them secrete androgens. Many luteomas may be subclinical. Diagnosis is made only when the luteomas are large or cause virilization. iv) Maternal virilizing symptoms and signs may be present in approximately 35% of reported cases of pregnancy luteoma, and around 80% of female infants born to virilized mothers are virilized. v) The degree of fetal virilization depends on the timing of the increased maternal androgen production and severity. Early gestation androgen exposure is needed for severe virilization, as in our case.

P2-P406

The Experience of GAIA (Abuse Childhood and Adolescence Group) – AOU Meyer

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Background: GAIA is a health service of Meyer Children Hospital composed of a multidisciplinary team specialized in the management of children victims of child abuse. Sexual abuse occurs when a child is engaged in sexual activities that cannot comprehend, for which the child is developmentally unprepared and cannot give consent, and/or that violate the law or social taboos of society. The sexual activities may include all forms of oral-genital, genital, or anal contact by or to the child, or nontouching abuses. **Objective and hypotheses:** The aim of the

study is to describe our experience about children seen for suspected sexual abuse. **Methods:** Retrospective review of medical records over a 5-year period, from 2011 to 2015. **Results:** We evaluated 385 cases of child abuse of which 96 was suspected sexual abuse. The age ranged from 3 months to 17 years, with an average of 8.29 ± 4.44 years. 70 cases were female (72.9%) and 26 were male (27.1%). Where a perpetrator was described, 52.1% was intrafamilial with no statistically significant difference between cohabitant or non-cohabitant members. 35.4% of offenders were extrafamilial but only in 10 cases (10,4%) were strangers. In 46.8% of cases the physical examination was perfectly normal and in 49% we found nonspecific symptoms like erythema or increased vascularity of the genital tissues. Medical findings diagnostic of sexual abuse were found only in 4.2% of cases: three adolescent girls with hymen transection and an adolescent boy with anal bleeding and bruise. **Conclusion:** Our data are concordant with the literature. In particular females are more likely to be abused and the most affected age group is the pre-pubertal one (5–9 years). In most of 90% cases (95.8%) physical examination revealed no specific signs of sexual abuse.

P2-P407

State of Knowledge of Late Endocrinological Effects of Hematological Patients Who Has Undergone Chemotherapy

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Introduction: Medical advances result in cure and life extension. Modern methods of oncological treatment lead to late endocrinological side effects. **Objective of the study:** The aim of the study was to assess the patients' knowledge of possible result of chemotherapy and its long-term effects linked to gonadal dysfunction. **Materials and methods:** The survey covered a group of 92 (62 women) patients with hematologic neoplasms at the age of 26 ± 8.9. Patients were asked about a disease, treatment and knowledge of side effects, the plans and procreation potentials. **Results:** 78% of patients were informed about the possible fertility decline as a treatment effect. 28% of them assessed this result as serious and/or the worst side effect. 60% of patients planned to enlarge family. More than 1/3 of the men did not know about the possibility to deposit semen, while 36% wished to use such a possibility, if they had been informed of this before. 47% of men have this awareness, but for various reasons did not make use of it. 17% of interviewees banked their semen. 7% of men have a sperm viability test after the treatment. 58% of women permanently stopped menstruating as a result of treatment. Only four women have received hormone replacement therapy. Before treatment, 76% of respondents menstruated regularly, and the age of menarche was 13 ± 2 years. Under the care of a gynecologist and/or endocrinologist is 60% of the patients. 92% of young women have symptoms of iatrogenic menopause. **Conclusions:** Problems of male infertility and premature menopause after hematological treatment, indicate the need of specialist care of patients both before and after cancer therapy. Care about patients' possibility of procreation is insufficient. Patients should be informed about all methods of fertility securing.

P2-P408

Disorders of Sex Genitalia in Yaounde: Difficult Questions, Which Answers?

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Background: Disorders of sex genitalia are a large group of genetic disorders whose management is still unaffordable in many countries in sub Saharan Africa. In Cameroon, although many collaborative initiatives of management are developed, little data are available. **Objectives:** Describe epidemiological clinical, aetiologies and management aspect of DSD in a developing country. **Patients and methods:** This is a 5 years retrospective study. All patients referred for DSD in the single paediatric endocrinology service of the Mother and Child Centre of Chantal Biya Foundation was reviewed. Socio epidemiological variables, external genitalia were described as so as internal sex organs and tanner stage. 17 hydroxyprogesterone, sexual steroids were measured, when possible caryotype and gene sequencing were done. **Results:** We included 65 patients with a median age at consultation of 2.6 years. No consanguinity was found. Sex assignment was already done in 89.2% of them. After hormonal assay and genetic testing (when available) congenital adrenal hyperplasia was found in 26 (40%), gonadal dysgenesis in 14 (21%), 7 (10.5%) ovotestis, were main diagnosis. There was a wrong initial sex assignment in 20% of patients with CAH leading to extreme management difficulties. **Conclusion:** CAH is the main aetiology of DSD in this single pediatric endocrinologic center. There is a wrong sex assignment in many cases leading in extreme management difficulties questioning the issue of midwives training and neonatal screening in our setting.

P2-P409

Analysis of Clinical Manifestations and Gene Mutations of 5α-Reductase Type 2 Deficiency in 16 Cases

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Background: 5α-reductase type 2 deficiency is a rare autosomal recessive hereditary disease. SRD5A2 gene defects lead to dysfunction of 5α-reductase type 2, that impair the conversion of testosterone to dihydrotestosterone and cause clinical features. **Objective and hypotheses:** To analyze the clinical manifestations and gene mutations of 5α-reductase type 2 deficiency in childhood. **Method:** The clinical features, laboratory tests and gene mutational analysis of 16 cases of 5α-reductase type 2 deficiency in our hospital were analyzed retrospectively. **Results:** In 15 of 16 cases with gender as male, one case of gender as female. All had genital dysplasia in clinical history and ambiguous genitalia in physical examination, including microphallus, penile curvature, hypospadias, bifid scrotum and clitoridauxe, etc. The test of hCG stimulation suggested the existence of testicular tissue and the function of secretion of testosterone. Ten mutations in the SRD5A2 gene were detected in 16 patients, including c.282-1G>C, c.586G>A,p.(Gly196Ser), c.680G>A,p.(Arg227Gln), c.159G>A,p.(Trp53X), c.607G>A,p.(Gly203Ser), c.650C>A,p.(Ala217Glu), c.665G>A,p.(Cys222Tyr), c.196G>A,p.(Gly66Arg), c.656delT,p.(Phe219fs) and c.560C>T,p.(Thr187Met). The most common detected mutatons was c.680G>A,p.(Arg227Gln), that 13 out of 16 patients carried the mutation, including five homozygous and eight heterozygous. The second most common one was c.607G>A,p.(Gly203Ser), that four out of 16 cases were detected, including two homozygous and two heterozygous. **Conclusion:** Patients of 5α-reductase type 2 deficiency in childhood had clinical features of genital dysplasia. The test of sexual hormone and hCG stimulation helped to estimate the function of testicular tissue, and SRD5A2 gene mutational analysis was necessary for precise diagnosis. This study found that the mutatons of c.680G>A,p.(Arg227Gln) and c.607G>A,p.(Gly203Ser) may be the hotspot mutations in Chinese patients of 5α-reductase type 2 deficiency.

P2-P410

Unusual Differential Diagnosis of Hyperandrogenism in Adolescent Female Treated for Polycystic Ovarian Syndrome

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Background: Polycystic ovarian syndrome (PCOS) is the most common cause of oligomenorrhea and hyperandrogenism. Diagnostic criteria for PCOS includes ovarian dysfunction and clinical or biochemical evidence of hyperandrogenism. The differential diagnosis includes congenital adrenal hyperplasia as well as steroid producing tumors. **Case presentation:** 18-years-old female presented to establish care with a history of PCOS diagnosed at the age of 11 years. She reported thelarche at 9, adrenarche at 9 and menarche at 11 years with subsequent oligomenorrhea. She reported acne, hirsutism and occasional right lower quadrant pain. She was started on insulin-sensitizers, spironolactone and oral contraceptive pills at age 11. She had been off treatment for one year, without spontaneous resumption of menses. She continued to struggle with hirsutism. On physical exam: weight 99%, height 97% and BMI 98%. Blood pressure was elevated. She was proportionally obese, had acanthosis nigricans and hirsutism. Tanner stage V breast and pubic hair. Her clitoris was 2 cm length and 1 cm width. Laboratory evaluation: BG 91 mg/dl, TSH 0.89 μIU/ml, morning 17OHProgesterone 1261 ng/dl, DHEAS 202 μg/dl, Testosterone 359 ng/dl (12–60), free Testosterone 14 ng/dl (0.3–1.9), FSH 2.0 mIU/ml, Prolactin 12 ng/ml. Midnight salivary cortisol <50 ng/dl (<100), normal morning Cortisol and ACTH. ACTH stimulation test revealed a 60 min 17OH Progesterone 1270 ng/dl, normal values of 11-Deoxycorticosterone. Karyotype 46,XX. Computerized tomography of the adrenals was normal. There was a 3.2×2.0×2.8 cm hyper-enhancing lesion with central hypodensity on the right ovary, unchanged with follow up ultrasound. The decision was to perform a laparoscopic right salpingo-oophorectomy. Pathology was consistent with steroid cell tumor, not otherwise specified. Hormonal levels normalized after resection. **Conclusion:** Virilizing tumors are a very rare cause of hyperandrogenism in adolescents. Appropriate initial assessment of hyperandrogenism and irregular menstrual cycles can lead to early diagnosis and appropriate intervention.

P2-P411

Phenotypic and Hormonal Variability in 46,XY Subjects with SF-1 Mutations

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Background: 46,XY patients with SF-1 mutations have sex reversal or ambiguous genitalia (with or adrenal insufficiency) due to dysgenetic testis. In most cases, a severe defect in testosterone (T) production has been found. We described here 3 cases showing the variability in T production. **Results:** *Case 1*: A was seen at the age of 17 years for primary amenorrhea. Tanner stage was B2PH3. External genitalia were normal. FSH was 55 IU/l, LH 17 IU/l, inhibin B <10 pg/ml, AMH <0.1 ng/ml, testosterone 0.22 ng/ml, E_2 <10 pg/ml, and DHEA-S 2.4 mg/l. Pelvic ultrasound showed a

small uterus, and gonads with no follicles. Karyotype was 46,XY, and a p.Arg362X NR5A1 mutation was found. *Case 2*: B was born at term with microphallus (L 2.5 cm), penoscrotal hypospadias, and scrotum with two palpable gonads. Karyotype was 46,XY. T at d13 was 4.5 nmol/l, increasing to 11.8 nmol/l upon hCG stimulation. FSH was 2.9 IU/l, LH 1.6 IU/l. He was raised as a boy. At the age of 14 years, testis length was 3.5 cm, and phallus length 5.5 cm. T was 21 nmol/l, FSH 19 IU/l, LH 10 mIU/l, INHB 65 pg/ml, and AMH 1.7 ng/ml. A p.Val83Met NR5A1 mutation was found. *Case 3*: C was born at term with DSD (genital tubercle 10 mm, fused genital swellings with two palpable gonads, and one orifice). Karyotype was 46,XY, T 0.35 nmol/l increasing to 1.5 nmol/l upon hCG stimulation, AMH 7.2 ng/ml, and at 0.5 months FSH was 5 mIU/L, LH 0.7 mIU/l. C was raised as a girl and gonadectomy and feminizing genitoplasty were performed at 2 months. At the age of 11 years, ACTH was 191 pg/ml and cortisol 1.3 μg/dl, indicating adrenal insufficiency. A p.C422X NR5A1 mutation was found. **Conclusion:** SF1 mutations showed large phenotypic and hormonal variability.

P2-P412

Towards the Roles of Kisspeptins in the Control of Gonadotropic Axis: Focus on Peripheral Signaling in Androgen-Dependent Tissues in the Experimentally Induced Model Hypogonadotropic Hypogonadism in Male Rats

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Background: Recently kisspeptins are considered as a key gatekeepers of the regulation of the gonadotropic axis. **Objective and hypotheses:** To investigate the impact of experimentally induced hypogonadism on kisspeptins signaling in androgen-dependent tissues and blood. **Method:** Wistar male rats (29 in total) were used. Rats were divided into four groups. Group 1 (control, prepubertal rats aged 2 months, $n=7$). Group 2 (control, pubertal rats aged 4 months, $n=6$). Group 3 (unilaterally gonadectomized (ULG) in neonatal period). Group 4 (ULG treated with testosterone (T) propionate 5 mg/kg per day for 10 days). In all groups the density of GPR54 in testes, muscle as well as serum kisspeptin and T levels were examined. The data was expressed as median values (Me) that were compared by Wilkokson criterion. **Results:** Density of GPR54 in gonads in group 3 was lower than in group 2 (Me 0.88 ng/mg vs 1.13 ng/mg, $P<0.05$) and similar to group 1(Me 0.92 ng/mg). Unlike above, density of GPR54 in muscle in groups 1,2,3 there were not any differences (Me 0.1; 0.12; 0.13 ng/mg, $P>0.05$). Generally, density of GPR54 in group 2 in gonads was significantly higher than in the same group in muscle (Me 0.784 ng/mg vs 0.114 ng/mg, $P<0.01$). In the group 3 a significant decrease in serum levels of T (Me 15.39 ng/mg) in comparison with group 2 (Me 20.02 ng/mg, $P<0.01$) was detected. Serum levels of kisspeptins in both groups were the same (0.27 ng/mg and 0.26 ng/mg, $P>0.05$). Treatment with testosterone propionate of group 4 rats lead to increase of serum level of T (from 15.39 ng/mg to 26.26 ng/mg, $P<0.01$), but did not modify the density of GPR54 in gonads (Me 0.79 ng/mg). **Conclusions:** Hypogonadism lead to decrease of kisspeptins signaling in peripheral androgen-dependent tissues. Serum level of kisspeptins is physiologically low and it probably can not be used as a marker of kisspeptin system activity. Testosterone treatment is not effective enough; new therapeutic methods are required.

P2-P413

Two Patients Presenting the Extremes of the Phenotypic Spectrum of 5 alfa Reductase Deficiency: One with at New Mutation

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Background: The large phenotypic spectrum of Disorders of Sex Development are caused by mutations in many different genes, but a large phenotypic spectrum of sexual disturbancies may also be seen with different mutations in the same gene. **Objective and hypotheses:** To report on one new mutation in the 5 alfa reductase (SRD5A2) gene, and describe the extremes of the phenotypic spectrum of 5 alfa reductase deficiency presented in two patients. **Method:** Patient one was admitted 4 days old due to a micropenis. Parents were non-consanguineous healthy Somalians. Birthweight was 3820 g and birth length was 54 cm at term. Patient two was admitted for suspicion of clitoromegali 6 months old. Parents were non-consanguineous healthy Danes. Birthweight was 1322 g, birthlength was 42 cm at gestational age of 33 weeks. The children had hormonal, chromosomal and genetic analysis. The second child also had an abdominal ultrasound. **Results:** Patient one had a penis length of 2.1 cm with urethral orifice at the top of glans penis and retention of testes at the left side, normal testes at the right side and normal scrotum. The second child had a clitoris length of 1.5 cm with an urethral orifice in the normal female position, bilateral gonads in labia majora but a female like vaginal opening. Both children had the male karyotype 46,XY and normal hormonal axis. Testosterone/dihydrotestosterone ratio was 75 (HCG stimulated) in patient one and 15 (unstimulated) in patient two. Abdominal ultrasound of patient two was without Müllarian structures. Genetic analysis of the SRD5A2 gene: Patient one was homozygous for a novel mutation c.682G>A (p.Ala228Thr), patient two was homozygous for c.692A>G (p.His231Arg). **Conclusion:** We report a new disease-causing mutation in the SRD5A2 gene, c.682G>A, and underline the very heterogenous phenotype in patients with 5 alfa reductase deficiency, examplified by two patients.

P2-P414

Disorders of Sex Development 45,X/46,XY: Clinical and Laboratory Characteristics of Patients

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Objective: To study clinical and laboratory characteristics of patients with disorders of sex development (DSD) 45,X/46,XY. **Subjects and methods:** It was included 248 patients with genital ambiguity, which were divided into groups based on cytogenetic survey. All children with mosaicism 45,X/46,XY evaluated the structure of the external genitalia on the external masculinization score (EMS, range 0–12), ultrasound examination, the definition of anti-Mullerian hormone (AMH, $n=15$), basal and stimulated human chorionic gonadotropin (HCG) testosterone (T, $n=12$). There was removed from seven gonads of 11 patients. **Results:** The structure of patients with DSD showed 46,XY DSD – 48.4% (120/248), 46,XX DSD – 37.5% (93/248), 14.1% (35/248) – sex chromosome DSD. With mosaicism 45,X/46,XY was 21 patients, the sex of rearing was male in 81% (17/21) and female in 19% (4/21) cases. Mediana EMS was 3 [1÷11]. Range of EMS of 17 male patients was from 1 to 11, female patients were 1. Mullerian remnants were revealed in 85.8% (18/21). Gonadal examination of seven gonads showed classical picture of mixed gonadal dysgenesis had just 28.5% of cases (2/7). 52.2% children (11/21) had growth retardation, 35% (7/20) had renal malformation, and 82% (9/11) – congenital heart defects. During hormonal evaluation was detected positive correlation between basal T in mini-puberty and range EMS ($n=8$, $r=0.9$, $p=0.01$). There was a trend to higher frequency low AMH compared to the frequency poor T response to the test with HCG ($p=0.17$). **Conclusion:** The group of patients with DSD 45,X/46,XY was heterogenous in structure of external genitalia, internal genitalia and degree of gonadal dysgenesis. In most cases patients had low levels of AMH, which is a more significant marker of testicular dysgenesis than ΔT. We detected positive correlation between basal T in mini-puberty and range EMS.

P2-P415

Reproductive Function of Central Precocious Puberty in Girls: A Systematic Review

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Background: GnRH analogues are the treatment of choice for central precocious puberty. It has been proven beneficial effects on final adult height, but the reproductive function has many debate especially about PCOS. The criteria used for the diagnosis of PCOS can be more difficult to judge because it is not uniform between the studies. **Method:** The Medline, Cochrane, EMBASE, Web of Science, SCOPUS data bases were searched for studies published up to January 22, 2016 using key phrases 'precocious puberty/early puberty', and 'GnRH analogue'. We were unified in 2003 Rotterdam criteria to the diagnostic criteria for PCOS. **Results:** The initial literature search yielded 3254 articles after the removal of duplicates. Of these, 3223 were excluded as not meeting inclusion criteria or non-relevant, leaving 31 reports for full-text review to assess eligibility. **Conclusion:** Based on the studied literature, CPP patients with GnRH analogue treatment has a regular menstrual cycle at 80.5%. The available evidence supports little confidence regarding the impact of CPP with or without GnRH analogues on the develop of PCOS but suggests that early puberty in girls may increase the risk of PCOS. In order to increase the strength of the results, well-designed cohort studies with large sample size should be performed in future.

P2-P416

Cytogenetic Variability and Phenotypic Findings in Patients with Ovotesticular Disorder of Sex development

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Background: Ovotesticular disorder of sex development (OT-DSD) is a very rare disorder characterized by the presence of both ovarian and testicular tissue in the same individual. It has an approximate incidence of less than 1/20 000.The patients usually present with ambiguous genitalia and the majority show a 46,XX karyotype, with absence of the SRY sequence. **Objective and hypotheses:** The study reports the cytogenetic variability and gonadal histological findings in nine patients with OT-DSD and different phenotypic features. **Method:** Patients were subjected to clinical and genital examination, anthropometric measurements, pelvic sonography and genitography. Laparoscopy with gonadal biopsy was performed to determine gonadal histopathology and to exclude the presence of gonadal tumors. Conventional cytogenetic analysis and Fluorescence *in situ* hybridization (FISH) were used for precise detection of chromosomal abnormalities. In addition FISH on gonadal tissue biopsies were performed in three patients. **Results:** Eight patients presented with ambiguous genitalia and one male patient was diagnosed after presenting with pubertal breast development. Five patients had 46,XX karyotype, one patient had a chimeric 46,XX/46,XY karyotype, two patients had isodicentric (Yq) abnormality and one patient had a complex mosaic karyotype with X;Y translocation. **Conclusion:** The study empathize the importance of cytogenetic and histological investigations in DSD patients and extends the cytogenetic spectrum of OT-DSD patients.

P2-P417

Cytogenetic Study of Sex Chromosomal Abnormalities in Egyptian DSD Patients

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Background: Sex chromosome DSD constitute an important category in the definition of DSD. **Objective and hypotheses:** The study included 379 patients comprising a wide spectrum of presenting features, associated with different arrays of chromosomal abnormalities aiming at. Studying the prevalence of Sex chromosomal abnormalities among DSD patients. **Method:** Patients were subjected to detailed clinical examination, pubertal staging, cytogenetic and FISH analysis. Laparoscopy with gonadal biopsy and FISH on gonadal tissue cells were done when indicated. **Results:** Abnormal sex chromosomal constitution was found in 188 patients (49.6%). They included both numerical and structural sex chromosomal abnormalities. The most common numerical abnormality was 47,XXY followed by 45,X. Structural sex chromosomal abnormalities showed a wide range of variability. The most common structural abnormality was iso(Xq), which was detected among 31 patients. Isodicentric Y abnormality was detected in nine patients. testicular DSD with SRY translocated to the Xp was found in four patients. **Conclusion:** This study confirms the dosage effect of sex chromosomes on somatic development and the phenotypic diversity of their presentation among different age groups.

P2-P418

Phenotype, Genotype and Gender Identity in Pubertal and Post-Pubertal Patients with Androgen Insensitivity Syndrome

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Background: Androgen insensitivity syndrome (AIS) is a rare disease due to end organ resistance of androgens. AIS is commonly caused by the mutations of androgen receptor (*AR*) gene located on chromosome Xq11-12. The mode of inheritance is hemizygous, where males get severely affected and females remain as carriers. **Objective and hypotheses:** Here, we describe the Phenotype–Genotype correlation and gender identity of pubertal and post pubertal patients with AIS. **Method:** Records of patients attending the endocrine clinic of our tertiary care hospital and new patients with diagnosis of AIS were compiled. All patients had detailed history, physical examination, chromosomal analysis and hormonal studies done. Chromosomal analysis was carried out on G-banded metaphases obtained from 72-h cultures from peripheral blood. The genotype of the patients was analysed for *AR* and *SRD5A2* gene mutations. LH, FSH, T were estimated by Electrochemiluminiscence using commercially available kits from Roche, Germany. DHT and androstenedione (A) were extracted from plasma by diethyl ether and separated from other androgens by Celite-chromatography and estimated by radioimmunoassay (Immunotech, DSL9600i, Czech Republic, Prague). DNA was isolated from the blood samples, quantified and subjected to PCR amplification using specific primers for *AR* and *SRD5A2* gene. **Results:** Clinical diagnosis of AIS was established in 32 patients. Out of these, 20 patients presented in pubertal and post-pubertal age group (10–20 years). The mean age of presentation was 18.3 ± 4.5 years and the present age of the patients was 19.2 ± 4.3 years. 12 patients (60%) sought medical attention with the complaint of primary amenorrhoea and were initially reared as females. Gender (re) assignment was done in three patients and nine patient continued as female. All patients had normal 46, XY karyotype. Mean LH was 20.9 ± 11.3 mIU/ml, FSH was 9.7 ± 5.7 mIU/ml, Testo was 8.45 ± 5.0 ng/ml, DHT was 746.8 ± 449.4 pg/ml, T/DHT was 10.0 ± 5.8, A was 1.85 ± 0.95 ng/ml and T/A was 5.13 ± 3.8. The molecular analysis of *AR* gene showed the presence of mutant alleles in 15 patients. We found two novel mutations p.T105R and p.P133A in exon 1. One patient had an inherited hemizygous *AR* mutation along with the de novo homozygous mutation in the *SRD5A2* gene. No mutation was present in five clinically established patients with PAIS.Among these five children, four were initially reared as female and two had male gender re-assigned during childhood. None of them had gender dysphoria. **Conclusion:** No specific genotype–phenotype correlation could not be established in our patients but confirming the diagnosis of AIS with assessment of *AR* and *SRD5A2* gene may help in better management.

P2-P419

XLAG Syndrome Case Accompanying a New ARX Mutation and has a Interhemispheric Cyst

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Background: X-linked lissencephaly with ambiguous genitalia (XLAG) syndrome which is a clinical spectrum of ARX mutations is presented with severe growth deficiency, abnormal genitalia and resistant seizures in neonatal period. We present a XLAG case which was formed due to a new ARX mutation and has an appearance of a huge interhemispheric cyst different from classic neuroradiological imagings. **Case:** The case which was diagnosed with prenatal hydrocephalus and had prematurity, low birth weight and respiration problem was taken to the newborn intensive care unit. In the physical examination, hypotonic, spontaneous movements were very few in macrocephalic appearance and the patient had highly arched palate and the face was dysmorphic (hypertelorism, micrognathia, long filtrum, thin upper lip, low ear). Fallus height was measured 1.1 cm in the genital inspection, ventral hypospadias was present and the gonads

were inpalpable. Starting from the postnatal second day, cyclic movements in facial muscles and multifocal clonic seizures began. Serological tests were negative when TORCH infections were considered. Uterus and gonad were not observed in pelvic ultrasonography. Corpus callosum agenesis, gigantic interhemispheric cyst, lissencephalia and olfactory gyrus absence were detected in brain magnetic resonance imaging. Karyotype analysis 46XY was found. A new homozygote p.Thr357Asnfs*175 (c.1068_1069dupA) mutation was detected in DNa sequence analysis. **Conclusion:** While karyotype is 46XY in ARX mutations, external genital abnormalities can change between hypoplastic penis or undescended testicle and complete female appearance. So genital examinations of lissencephalic cases should be made carefully, clinical spectrums of ARX mutations should be considered in the presence of indefinite genitalia.

P2-P420

Congenital Adrenal Lipoid Hyperplasia in a 30-Year-Old Female with a Tall Stature

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Background: Congenital lipoid adrenal hyperplasia is an autosomal recessive adrenal and gonadal steroidogenesis disorder usually caused by a genetic abnormality in the *STAR* gene encoding the steroidogenic acute regulatory protein (StAR). For 46,XY cases, sex steroid hormone replacement therapy must be initiated together with glucocorticoid and mineralocorticoid treatment. **Objective and hypotheses:** We present the case of a 30-year-old female with a tall stature and 46, XY congenital lipoid adrenal hyperplasia. **Method and results:** The phenotypically female infant was born at term via normal delivery and weighed 4000 g. She exhibited skin pigmentation over her entire body and developed spasms due to low plasma glucose levels 24 h after birth. Although a chromosome study revealed a 46,XY pattern, she presented with female-type external genitalia and was assigned the female gender. At 2 months of age, an ACTH-Z loading test revealed no reaction with 17-OHCS and 17KS. Therefore, the patient was diagnosed with congenital lipoid adrenal hyperplasia and began corticosteroid replacement therapy. Gonadectomy was performed at 6 years of age, after which only prescribed therapy was continued. At 25 years of age, she was recommended to visit a gynecologist, but she refused because of a long distance. She consulted a pediatric endocrinology clinic at 30 years of age. Her height and weight were 189.5 cm and 107 kg, respectively, and she presented with Tanner stage 1 breast development and a bone age of 12 years. A previously reported homozygous A218V mutation was confirmed through *STAR* gene analysis. Oral estrogen therapy was initiated, and after 6 years her height and weight were 193.5 cm and 90 kg, respectively; closure of the epiphyseal line was confirmed, and her bone age was 17 years. An orthopedic physician prescribed bisphosphonate because of osteoporosis. **Conclusion:** It is necessary to initiate estrogen replacement at an appropriate age to ensure closure of the epiphyseal line in individuals with hypogonadism. In this case, osteoporosis was attributed not only to delayed estrogen replacement, but also to an excessive steroid dose.

P2-P421

Onset of Puberty in Healthy Boys is Associated with a Decreased BMI Compared to Values Prior to the Onset of Puberty

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Background: In several studies it has been shown that BMI influences the timing of puberty, mostly in girls, but has not been a consistent finding in boys. **Objective and hypotheses:** To investigate the association between BMI and timing of pubertal onset in a population based sample of Turkish boys. **Method:** Data on growth and pubertal development were collected by biannual visits to six primary and secondary level schools in Istanbul city. Of a total of 2016 boys, data of 1208 boys aged from 8 to 18 years evaluated. Over time, measurements were repeated on these same children, but other children were also included in the study to provide adequate numbers for the older age groups. Our sample consists of a mixture of children followed longitudinally over different periods of time. Measurement of testicular volume (TV) using a Prader orchidometer, was performed by one observer (RB) throughout the study. Evaluation of pubertal stages was also done at 6 monthly intervals. Attainment of a testicular volume of 4 ml was accepted as the onset of puberty. The data were entered in a FoxBase program and analyzed by using SPSS-PC. **Results:** The results of only the longitudinally followed children are given here. In this subsample of 227 boys, who were followed longitudinally, age at onset of puberty was 10.9 ± 1.0 (9–13.8) years. Mean BMI-SDS was 0.09 ± 1.2 during prepubertal time before the onset of puberty and mean BMI-SDS at onset of puberty was 0.02 ± 1.3, significantly lower than the prepubertal period ($P = 0.0001$). In this subsample of boys the mean delta BMI-SDS was -0.07 from the time testes volume 2 ml to the time of testes volume 4 ml. **Conclusions:** The onset of puberty is associated with a lower BMI in healthy boys.

P2-P422

Late Clinical Presentation, Biological Assessment and Management of PAIS in a Developing Country

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Background: Partial androgen insensitivity syndromes (PAIS) are rare 46,XY DSD (disorder of sex development). **Objective and hypotheses:** Three families with PAIS (six patients) are reported, focusing on their phenotype and treatment depending on sex of rearing. Biological investigations and surgical management are described. **Method:** Between 2009 and 2015 a consultation for uro-genital malformations in pediatric patients was set up in Yaoundé (Cameroon). Data on patients with PAIS were retrospectively reviewed. **Results:** Six patients from three families were referred for genital anomalies. Mean age at the first consultation was 19 years [14–25 years]. Gender assignment was attributed by parents in the neonatal period without any investigation (three males, three females). At presentation the patients had breast development, variable degree of genital masculinisation and palpable testes. All patients were 46,XY on lymphocyte karyotypes. Hormonal screening and subsequently hormonal therapy (hormonal substitution for girls) was done once the biomolecular diagnosis of PAIS with AR mutation was confirmed. All the patients requested surgery supporting of sex of rearing. Four out of six underwent genital surgery (two girls and two boys). The surgical treatment consisted of feminising genitoplasty or vaginal dilatation and orchidectomy for girls and mastectomy, masculinising genitoplasty and orchidopexy for boys. **Conclusion:** The management of PAIS patients requires an experienced multidisciplinary team to allow a full clinical and biological assessment. Corrective surgery was performed using actual standards. There was no dysphoria and all patients regretted the late diagnosis and late surgical correction. The potential of sexuality and fertility for the boys need to be assessed.

P2-P423

Sisters with 46XY Gonadal Dysgenesis and Gonadoblastoma

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Background: 46XY DSD with female phenotype is classified as complete gonadal dysgenesis (46XY CGD) if a uterus is present or a disorder of androgen synthesis or action if a uterus is absent. The genetic causes of 46XY CGD are not fully clarified. Less than 15% of the cases were found to carry mutations of the sex determining region Y gene (SRY). **Purpose:** The description of the rare case of two sisters affected of 46XY CPD and gonadoblastoma with SRY mutations. **Patients and methods:** An 11-year old-girl was referred after she palpated an abdominal mass. She was born to non-consaguinous parents and her past medical history was unremarkable. On physical exam she had normal external female genitalia, breasts Tanner I axillary and pubic hair Tanner II. Ultrasonography revealed a right adnexal mass, which was surgically removed and pathology was consistent with gonadoblastoma. Karyotype was 46,XY. A left ovariectomy was performed and she underwent chemotherapy. Her sister's karyotype analysis was also XY. She was closely monitored with pelvic ultrasounds every 3 months and an engorgement of the right ovary was appreciated a bilateral gonadectomy was performed. The result of the histopathological analysis revealed a dysgerminoma on the ground of gonadoblastoma. She also underwent chemotherapy. A molecular analysis revealed a deficit at the HMG region of the Y chromosome, in both sisters, which constitutes a rare observation. At present, both of the girls are in a good health receiving hormonal substitution. **Conclusion:** SRY gene is an essential factor to initiate testicular development from a bipotent gonad. Mutations of the SRY gene are responsible for a number of patients affected with 46XY gonadal dysgenesis and should be investigated.

P2-P424

Follow-up to Adulthood of Two 46,XY Siblings with 5-alpha Reductase Deficiency and Different Sex of Rearing

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Background: 46,XY patients with 5α-reductase deficiency (5-ARD), reared from birth as girls, are reported to self-reassign as boys subsequent to a masculinizing puberty; whether this holds true in cases of early orchidectomy is less well documented. **Objective and hypotheses:** Prepubertal orchidectomy reduces the likelihood of gender self-reassignment. **Method:** Presentation, management and outcome of two siblings with 5-ARD with narrative analysis of interviews with the mother. **Results:** Sib 1 had typical female external genitalia at birth, but palpable gonads, 46,XY karyotype and absent uterus on ultrasound. Complete Androgen Insensitivity Syndrome (CAIS) was diagnosed and gender of rearing was female. Sib 2 had microphallus with chordee, proximal hypospadias, bilaterally palpable gonads and no Müllerian structures on ultrasound. Karyotype was 46,XY. Testosterone enanthate was given (50 mg then 100 mg), resulting in a phallic size of 3.0×1.4 cm and leading to a male gender rearing. Due to of Sib 2's presentation, Sib 1's diagnosis was revised to partial AIS. She was gonadectomized at 5 years and started estrogen replacement at 11. When they were 16 and 13 years, respectively, both sibs were found to be compound heterozygotes

for mutations in SRD5A2 (Patients 50 and 51 in JCEM 96:296, 2011). At age 22, Sib 1 reported satisfactory peno-vaginal intercourse. Sib 2 entered puberty at age 11 and was G5P5 (penis 8×2 cm) at age 18. By age 18, both siblings were fully informed of their diagnosis. At ages 28 and 25, respectively, they are both living in a heterosexual relationship without apparent gender dysphoria. **Conclusion:** Sib 1 had typical female external genitalia at birth, but palpable gonads, 46,XY karyotype and absent uterus on ultrasound. CAIS was diagnosed and gender of rearing was female. Sib 2 had microphallus with chordee, proximal hypospadias, bilaterally palpable gonads and no Müllerian structures on ultrasound. Karyotype was 46,XY. Testosterone enanthate was given (50 mg then 100 mg), resulting in a phallic size of 3.0×1.4 cm and leading to a male gender rearing. Due to of Sib 2's presentation, Sib 1's diagnosis was revised to partial AIS. She was gonadectomized at 5 years and started estrogen replacement at 11. When they were 16 and 13 years, respectively, both sibs were found to be compound heterozygotes for mutations in SRD5A2 (Patients 50 and 51 in JCEM 96:296, 2011). At age 22, Sib 1 reported satisfactory peno-vaginal intercourse. Sib 2 entered puberty at age 11 and was G5P5 (penis 8×2 cm) at age 18. By age 18, both siblings were fully informed of their diagnosis. At ages 28 and 25, respectively, they are both living in a heterosexual relationship without apparent gender dysphoria.

P2-P425

Constitutional Delay of Puberty: Clinical and Hormonal Characteristics of Patients

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Objective and hypotheses: To examine anthropometric, hormonal characteristics and their relationship in boys with constitutional delay of puberty (CDP). **Method:** The study included 47 boys older 13.2 year old with CDP. It evaluated anthropometric indicators, bone age and hormonal status. **Results:** The patients were divided: the first group consisted of 25.5% (12/47) of boys with pathological growth (Median/ Me Ht-SDS = −2.3). Of them, a normal BMI was 83.4% (10/12), deficiency weight and obesity by 8.3% (1/12).The second group of patients with low normal growth (Me Ht-SDS = −1.6) was 32% (15/47). Of them, normal BMI was 47% (7/15), 40% (6/15) – a overweight/obesity and 13.3% (2/15) – a deficiency weight. The third group of patients with normal growth (Me Ht-SDS = −0.1) was 42.6% (20/47). Of them, overweight/obesity was 70% (14/20), 30% (6/20) – a normal BMI. The pathological delay of bone maturation in first group was 75% (9/12), in second group, 46% (7/13), in third group −18.8% (3/16). Overweight/obesity were encountered significantly more frequently in boys normal growth ($P=0.04$) than with pathology growth. The delay of bone maturation in patients with normal growth encountered less frequently than in patients with pathological growth ($P=0.07$). The hormonal characteristics was no differences between boys with the pathological and normal growth, such as inhibin B, AMH, LH, FSH, estradiol, cortisol, prolactin, IGF-1, insulin. In boys with normal growth, testosterone was lower (Me 1.2 vs 5.7 nmol/l, $P=0.01$), DHEAS was higher (6.1±2.5 vs 2.3±0.8 mcmol/l, $P=0.012$) than in boys with delayed growth. **Conclusion:** The CDP in boys is heterogeneous and only in half the cases is accompanied by growth retardation. In contrast to boys with pathological growth, in boys with normal growth, CDP is associated with overweight/obesity, with a mean value of bone maturation, higher levels of DHEAS and lower levels of testosterone.

P2-P426

Comparison between Serum Vitamin D Levels in Precocious Pubertal Girls and Normal Girls

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Background: Vitamin D deficiency has been associated with chronic diseases, such as diabetes mellitus, obesity and auto-immune disease. However, There are only a few studies about the correlation between Vitamin D levels and precocious puberty in girls. **Objective and hypotheses:** In the previous study, vitamin D levels may be associated with precocious puberty. We also aimed to re-evaluate the relationship between serum 25-hydroxyvitamin D (25(OH)D) and precocious puberty in girls. **Method:** A total of 155 girls with central precocious puberty (CPP) and 45 control girls were enrolled. Anthropometric measurement and serum level of 25(OH)D were estimated for all subjects. **Results:** Mean 25(OH)D level of CPP group was 17.3±5.6 ng/ml, which was lower than the control group (19.0±5.3 ng/ml). There was significant difference in the mean serum 25OHD concentration between the precocious puberty group and the control group ($P=0.042$). After 25(OH)D levels be classified by month(season), Significant difference in the mean serum 25(OH)D concentration between the two groups was only winter (December–February). 113 of the 155 girls with CPP (72.9%) had 25(OH)D deficiency (defined as serum 25(OH)D <20 ng/ml) and 38 (24.5%) had 25(OH)D insufficiency. Of the 45 girls in the control group, 25(OH)D deficiency was seen in 24 subjects (53.3%), 20 subjects (44.4%) had 25(OH)D insufficiency, and 1 subjects (2.2%) had sufficient serum 25(OH)D (defined as serum 25(OH)D > 30 ng/ml). The prevalence of 25(OH)D was significantly higher odds ratio (OR, 2.35; 95% CI, 1.18–4.66, $P=0.017$) among CPP group than controls. **Conclusion:** Our results showed that vitamin D level was significant association with precocious puberty. We also recommend further studies are required to identify the correlation vitamin D levels and precocious puberty.

P2-P427

Complete Virilization without Salt Wasting in a 7-year-old Haitian Child with Congenital Adrenal Hyperplasia

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Background: Genetic females with congenital adrenal hyperplasia (CAH) from severe 21-hydroxylase deficiency may be declared at birth as cryptorchid boys. Neonatal salt wasting leads to early reassignment but in its absence, the condition may go unrecognized. **Case presentation:** A term newborn with non-palpable gonads but a penile urethra was declared as boy. At 4.8 years, the child presented with sexual precocity. Height was +2.3 S.D., penile length 9 cm, gonads not palpable, and pubic hair stage 3. Bone age was 12 years. On ultrasound, no uterus was identified and a gonad was described as a testicle. Serum 17-hydroxy-progesterone was 7440 ng/dl, DHEAS 139 mcg/dl, testosterone 224 ng/dl, LH < 0.1 and FSH 0.49 mIU/l. Karyotype analysis is unavailable in Haiti. With a diagnosis of CAH, treatment with prednisone was started. Thelarche developed 1 year later, progressed to stage M4, followed by monthly urethral bleedings lasting 3–4 days. Repeat ultrasound at age 6.9 years showed a pubertal uterus and ovaries. Upon informing the mother, she stated that she had known all along that her child was 'female inside and male outside', and she did not consider sex reassignment. Prednisone was discontinued in an attempt to stop menstruation and reduce breast development. **Conclusions:** Term newborns with a male phallus but non-palpable testes should undergo pelvic ultrasound. While the neonatal uterus, stimulated by maternal estrogens, should be visible, it may become hypoplastic from gonadotropin suppression and thus missed in older genetic females with CAH. When karyotype analysis is unavailable, the search for a Barr body should be considered; indeed, our observation has led to this technique being introduced in Haiti. Late sex reassignment is often unacceptable to the parents and needs to be viewed in the cultural context. Long-term follow-up of this patient to adulthood with a focus on psychosexual development is planned.

P2-P428

Hematocolpos Revealed by Non-cyclic Lower-back Pain in a Pre-menarcheal Girl

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Background: Hematocolpos is a rare condition in young girls that can be caused by imperforated hymen or vaginal agenesis. It is usually diagnosed at early puberty with cyclic abdominal pain and amenorrhoea. Menarche is usually observed two years after the start of puberty; sometimes pre-menarcheal bleeding can occur, ranging from isolated premature menarche to spotting in course of puberty. In case of imperforated hymen or vaginal anomaly, a pre-menarcheal uterine bleeding can cause hematocolpos, making diagnosis difficult. **Objective and hypotheses:** We describe here the clinical case of a 12.8 years old teenage girl who experienced hematocolpos in the course of her puberty. **Method:** Complete clinical history, clinical and biological phenotypes were collected. **Results:** Patient described recurrent episodes of very intense lower-back pain that started 3 months before, lasting few hours, 3 days a week, every week. She never had any genital bleeding. She was Tanner stage III. Abdominal palpation found a pelvic mass. Vulvar inspection revealed an imperforated and tensed but not bulging hymen. Ultrasound imaging and magnetic resonance imaging showed a 45×25 mm uterus without malformation, a 6.5-mm thick endometrium with a 6.4-mm hematometra, 4.8 and 6.0 ml ovaries and no hematosalpinx. A collection of 111×76×78 mm filled the vagina. There were two normal kidneys. Gonadotropins were in the normal range for mid-puberty (FSH 3.73 UI/l, LH 1.22 UI/l, estradiol (E2) 23 pg/ml). The GnRH hormone test showed ongoing physiologic central puberty. Surgery (radial hymenotomy) confirmed the diagnosis of hematocolpos (aspiration of 400 ml of old blood). Additional hysteroscopy found no uterine or vaginal malformation. **Conclusion:** Hematocolpos should be considered even with non-typical symptoms in a pre-menarcheal girl, and can be the consequence of uterine pre-menarcheal bleeding.

P2-P429

Novel AMH and AMHR-II Mutations in Two Egyptian Families with Persistent Mullerian Duct Syndrome

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Background: Anti-Mullerian hormone (AMH) is produced by Sertoli cells and signals through two transmembrane receptors (AMHR), specific type II and type I, leading to regression of Mullerian ducts (uterus and fallobian tubes) during fetal male sex differentiation. Mutations of AMH and AMHR-II genes lead to persistence of Mullerian ducts in males. These conditions are transmitted in a recessive autosomal pattern and are symptomatic in 46,XY phenotypic males. **Objective and hypotheses:** Studying molecular pattern of 46,XY DSD wit persistent mullerian ducts. **Method:** The entire coding regions of *AMH* and *AMHR-II* were amplified by PCR and directly sequenced in both directions.

Results: Two Egyptian 46,XY DSD patients presented with bilateral cryptorchidism, otherwise normal male external genitalia, and both had persistent mullerian ducts. A novel frameshift mutation in *AMH* gene was identified in the first patient, c.203delC (p.L70Cfs*7). On the other hand, sequencing the two genes in the second patient revealed a novel missense mutation in *AMHR-II* gene, c.767A > C(p.H256P). **Conclusion:** Persistent mullerian ducts should be included in differential diagnosis of cryptorchidism.

P2-P430
Study of Genetics of Human Disorders of Sexual Development. Research Project.

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Disorders of sex development (DSD) are a group of congenital developmental disorders in which the chromosomal, gonadal, or anatomical sex is atypical. The clinical diagnosis and management of DSD are difficult and complex because of the various aetiology and diverse manifestation. The project 'Genetics of Human Disorders of Sexual Development' is funded by Swiss National Science Foundation and fulfilled by the University of Geneva Medical School (Switzerland), the Medical Centers from Armenia, Poland and Ukraine. The goal is to identify mutations underlying unresolved DSD phenotypes – in novel DSD genes, or regulatory regions that lead to atypical gene expression. Identification of new genes involved in human sex determination and differentiation is carried out through exome sequencing and CGH microarray in parallel. Armenian partner is participating in all stages preceding the exome sequencing:clinical data collecting (caryotype, family history, physical examination, ultrasound, hormonal status, surgery, histology), caryotyping, DNA samplings (proband, parents, siblings), SRY gene deletion detecting and SRY, SOX9, WT1, SF1, LHX9, RSPO1, FOXL2, WNT4, DMRT1, DMRT2 genes Sanger sequencing. During 2 years Armenian part collected 25 DNA samples from 25 DSD cases – 4 patients with 46,XY complete sex reversal and ovarian development, 13 patients with 46XY partial gonadal disgenesis, 4 patients with ovotestes and and 4 of 46,XX DSD male. We also collected DNA samples from parents. We expect the research will provide the opportunity to develop new genetic tests for DSD diagnosis and to improve understanding of the molecular mechanisms of ovarian and testicular differentiation. The results on the cohort will be discussed in details.

P2-P431
46XX Male Syndrome

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Background: The XX male syndrome – Testicular Disorder of Sexual Differentiation (DSD) is a rare condition characterized by a spectrum of clinical presentations, ranging from ambiguous to normal male genitalia. The project 'Genetics of Human Disorders of Sexual Development' is funded by Swiss National Science Foundation and fulfilled by the University of Geneva Medical School, the Medical Centers from Armenia, Poland and Ukraine. The goal is to identify mutations underlying unresolved DSD phenotypes – in novel DSD genes, or regulatory regions that lead to atypical gene expression. During 2 years Armenian part collected four patients with SRY-positive 46,XX. The physical examination included the measurement of height, potential gynecomastia and the inspection of external sex organs. Bilateral volume was calculated as the sum of the volume of both testes. Serum levels of testosterone and anti-Müllerian hormone (AMH) were assessed. Genomic DNA from peripheral blood of the patients using QIAamp DNA Blood Kits was extracted. The three discrete regions, AZFa, AZFb and AZFc, located on the long arm of the Y chromosome, were performed by multiplex PCRs amplification. The set of PCR primers for the diagnosis of microdeletion of the AZFa, AZFb and AZFc region included: sY84, sY86, sY127, sY134, sY254, sY255, SRY and ZFX/ZFY. **Results:** Our research reported that four patients had a female karyotype but were phenotypically male (46,XX males) and two of them were twins. They had normal external genitalia and masculinization, all males were SRY-positive, which translocated on the short arm of X chromosome, and absent of the spermatogenic factors encoding gene on Yq, such as AZFa, AZFb and AZFc region in Y chromosome. Endocrinological data indicated that the patients had a lower testosterone and a low level of AMH. **Conclusion:** Our reports adds cases on the four new 46,XX male individuals with sex reversal and further verifies the view that the presence of SRY gene and the absence of major regions in Y chromosome should lead to the expectance of a completely masculinised phenotype, abnormal hormone levels and infertility.

P2-P432
45,X/47,XYY Chromosomal Mosaicism as a Cause of 46,XY Disorder of Sex Development

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45,X/47,XYY mosaicism is quite rare, and, like 45,X/46,XY, it can be associated with mixed gonadal dysgenesis, Turner syndrome or apparently normal male/female phenotype. An infant aged 16 days, born full-term via spontaneous vaginal delivery to a 32 year-old G1P1 woman. His pregnancy and perinatal period were both uncomplicated except for maternal long QT syndrome. There was third degree cousin consanguinity between the parents. There was no any virilizing drug use and no maternal virilization during pregnancy. Physical examination was normal except for genital examination which revealed a 3.3 cm phallic structure, with an opening on its ventral side. The labia

majora were posteriorly fused and rugated, and gonads were 1 ml and palpable bilaterally. His height was 56 cm, weight 4600 g, and head circumference 37 cm. His pulse rate was 120/min and blood pressure 80/50 mmHg. Laboratory examination showed normal gonadotropin levels consistent with mini-puberty as FSH: 3.9 mIU/ml (N, 1.37–13.5), LH: 6.2 mIU/ml (1.14–8.75) and total testosteron: 1.8 nmol/l. His serum adrenal androgens were in normal range (androstenedione: 25.9 ng/dL (normal, 5–45 ng/dl), 17-OH progesterone: 5.1 ng/ml (normal, <10 ng/ml)). There was no mullerian structure on pelvic ultrasonography. Chromosome analysis from peripheral blood cells revealed 45,X/47,XYY (80%–20%, respectively) karyotype. Fluorescence *ın situ* hybridization (FISH) revealed a similar karyotype as 45,X (77%)/47,XYY (223%) in 200 cell. Because of the 45,X/47,XYY karyotype, the patient was evaluated for Turner syndrome features and no any abnormalities could not be demonstrated. The patient was reared as male. In conclusion, karyotype analysis is an important diagnostic tool in DSD patients. A 45,X/47,XYY mosaicism should be kept in mind in DSD patients and needs a careful evaluation because of its phenotypic heterogenity.

P2-P433

46,XY Complete Gonadal Dysgenesis with Late Diagnosis

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Background: 46,XY Complete Gonadal Dysgenesis (Swyer Syndrome) is a rare cause for DSD with incidence $\approx$1:80000. It is characterised by defective formation of the gonads as a result of structural anomalies in the sex chromosomes or mutations in specific genes. In 20% of the patients deletion/mutation in SRY can be found. Mutations, deletions or duplications in other genes (NRD5A1, DHH, DAX1, WNT4, DMRT, etc.) are also reported. The phenotype is completely female and the diagnosis is usually made at puberty because of primary amenorrhoea. Early diagnosis is important because of increased tumor risk in the dysgenetic gonads. **Objective and hypotheses:** To present a case of Swyer Syndrome with late diagnosis. **Method:** We present an 18 y 11 m old girl. At the age of 16 she was evaluated by a gynecologist because of primary amenorrhoea and treatment with oral contraceptive pills was started. At the age of 18 because of poor treatment results she was consulted by another gynecologist and a karyotyping was performed. The karyotype was 46,XY with no significant chromosomal rearrangements. The patient was referred to the multidisciplinary DSD team at our institution. **Results:** Hormonal investigations revealed hypergonadotropic hypogonadism and low levels of AMH and InhB. On US and MRI hypoplastic uterus was found. The presence of Y-chromosome was confirmed by QF-PCR analysis. No mutations of the coding regions and exon/intron boundaries in *SRY* and *NRD5A1* genes were detected. Next, MLPA tests are planned (for deletion/duplication screening in *DMRT1*, *NR5A1,* etc.). Laparoscopy for detection and removal of the dysgenetic gonads is underway. Adequate hormone replacement therapy was initiated. **Conclusion:** Management of patients with DSD should be performed in centres with adequate diagnostic and therapeutic potential. Exact genetic diagnosis is not always feasible and new techniques like whole exome sequencing analysis could be considered for clarifying the genetic basis in such cases.

P2-P434

Diagnosis, Treatment and Gene Mutation Analysis of the Case with Steroid 5α-Reductase Type 2 Deficiency

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Background: To explore the reason of children on the 46,XY DSD. **Objective and hypotheses:** To analyze the clinical characteristics, diagnosis and management of a case with steroid 5α-reductase type 2 deficiency (SRD5A2) and perform related gene mutation analysis with a view to raising awareness of this disease. **Method:** A 2 year old 5 months child came with abnomal vulval shape. Karyotype was analyzed by chromosome cultivation. GnRH and HCG stimulation test were measured. Bone age assessment, MRI and pelvic ultrasonography including uterus and ovary were performed for this patient. The nucleotide sequencing of the SRD5A2, SRY and AR gene was determined by the dideoxy chain termination method. The same gene mutations of SRD5A2 were detected in the patient's parents. 2% DHT gel was used for external application. **Results:** The karyotypes analysis revealed 46,XY karyotype. The level of AMH was 22.97 ng/ml and Inhibin B was 274.4 pg/ml. The LH and FSH were 0.07 mIU/ml and 0.39 mIU/ml respectively. The peak of LH and FSH were 1.39 mIU/ml and 2.63 mIU/ml respectively 30 min after GnRH stimulation. And the ratio of T to DHT was 51.72. MRI of pelvis revealed uterus and bilateral ovarian-like structures were not visualized. Two ovate isoecho masses which were considered to be testicular tissue with clear boundary were visualized through ultrasound. One with bore diameters of 17.3×8.7 mm was detected in the left labia minora and the other one with bore diameters 15.5×7.4 mm was under the right groin. A negative result from the SRY gene and AR gene mutation analysis of the leukocyte DNA was obtained only from the patient and positive results from SRD5A2 gene mutation were obtained from all members of the family. The length of penis grew up 2 cm after 4 months when treated with 2% DHT gel in its root skin. **Conclusion:** The diagonosis of SRD5A2 was mainly based on the elevated ratio of T to DHT. The detection of pathogenic mutation of SRD5A2 was helpful for confirming the case. And it need to be differentiated from CAIS. The external application with 2% DHT gel revealed a good curative effect.

P2-P435

An Infant with 49XXXXY Syndrome: A Case Report from Sri Lanka

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Introduction: 49XXXXY syndrome is the rarest X chromosome aneuploidy with an approximate incidence of 1: 85 000–100 000 male births. The classic triad of symptoms include mental retardation, hypogonadism and radioulnar synostosis along with congenital heart diseases; Patent Ductus Arteriosus being the commonest defect reported, Distinct facial features, skeletal defects, cerebral and renal defects. To the best of our knowledge this is the first reported case of 49XXXXY syndrome in Sri Lanka. **Case presentation:** This, day 10 old neonate who was born in a tertiary care center was referred to the paediatric Endocrinology unit of Lady Ridgeway due to detection of ambiguous genitalia at birth. He was the first child born to non consanguineous healthy parents. His 31 years old mother had an uncomplicated antenatal period with normal ultra sound scans. He was born at term via normal vaginal delivery with a birth weight of 2.385 kg. The baby sucked well and did not observed any hypoglycaemia or alteration in basic biochemical investigations. On examination child had hypertelorism, upslanting palpebral fissures, flat occiput and mild webbing of neck. System examination was normal. Genitalia examination revealed bifid scrotum, perineal urethra, 2 cm phallus and bilateral testis *in situ*. The hormonal analysis including DHEAS, Testosterone and 17-OHP levels were normal except for an elevated level of FSH indicating gonadal dysgenesis. USS abdomen detected testis located at bilateral inguinal canal and no mullerian structures were visible. Echocardiography showed a small patent foramen ovale with otherwise normal heart. Chromosome analysis turned out to be 49XXXXY syndrome. **Conclusion:** Knowing the associations of 49XXXXY syndrome, diagnosing this syndrome in this child with ambiguous genitalia is beneficial as a multidisciplinary approach can made for further management to ensure quality of life.

P2-P436

Mixed Gonadal Disgenesia: Patients of Instituto da Criança, HC-FMUSP

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Background: Mixed gonadal dysgenesis (MGD) is a heterogeneous group of gonadal, chromosomal and phenotypic abnormalities. The diagnosis is based on the presence of testicular tissue and streak. **Objective and hypotheses:** Casuistics description of patients with MGD in our hospital. **Method:** A retrospective analysis of medical records. **Results:** We studied 15 patients. The age at first visit ranged from two weeks to 14.1 years, mean 19.9 months. Birth weights ranged from 1705 to 3400 g. Seven patients had no definite sex at first visit, four were female and four male. Of these, one patient was created in female sex. Among those of indeterminate sex, six were created as females and one as male. The karyotypes were: 45,X/46,XY in five patients, 45,X/46,X + marY in two patients, in addition to other mosaiscismos. The presence of Mullerian derivatives was reported in 14 patients. Upon examination of the external genitalia, 14 patients had perineal urethra. Falus size ranged between 1.5 and 3 cm, with presence of palpable gonads in four patients. The average response of testosterone after hCG stimulation was 409.5 ng/dl. **Conclusion:** The DGM should be considered among the etiologies of genital ambiguity, despite the rare occurrence.

P2-P437

Primary Amenorrhea as Alarm Manifestation in a Oligosymptomatic Girl with Xq Deletion and Turner Syndrome

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Background: Turner syndrome (TS) affects about one in 2500 liveborn females. It results from the loss of all or part of X-chromosome and has a variable phenotype. The classical form is characterised by short stature, skeletal abnormalities, lymphedema, renal and cardiac anomalies, webbed neck, peculiar neurocognitive profile and gonadal dysgenesis. While loss of up to 2/3 of the X chromosome short arm is compatible with normal fertility, chromosome deletions involving Xq are often associated with abnormalities of menstrual cycles and fertility. A large critical region for normal ovarian function has been located between Xq13 and Xq28 and deletions in these regions have been reported in women with premature ovarian failure. **Case report:** We present the case of a 17-year old girl who was referred to our Unit of Pediatric Endocrinology for primary amenorrhea. On physical examination showed: height 143.8 cm (−2.9 SDS), maternal height 147.0 cm (−2.5 SDS), mid-parental height 151.2 cm (−2.0 SDS), BMI 18.5, sitting height/height = 0.528, Tanner stage B5, P5, no dysmorphic features. Laboratory investigation showed elevated levels of FSH (237 mIU/ml) and LH (111 mIU/ml), low levels of estradiol (< 5 pg/ml) and Inhibin B (3.7 pg/ml) and pelvic ultrasound showed infantile uterus (longitudinal diameter 36 mm) and small ovaries (1 cc) without follicles. Although clinical phenotype was not typical of TS we performed a karyotype analysis that pointed out a large Xq deletion: 46,X del (Xq1.2). The investigation were completed, and all autoimmune diseases as well as renal and cardiac malformations were excluded. Replacement treatment with estroprogestins was started. **Conclusion:** Our case

confirms that TS patients with large deletions of Xq may exhibit a mild phenotypic expression, characterised by only menstrual disorders and short stature.

P2-P438

Hypogonadotropic Hypogonadism in a Patient with Vanishing Testis Syndrome – Case Report

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Vanishing testis syndrome leads to hypergonadotropic hypogonadism. We report the case of a 28-years-old patient, who was diagnosed with bilateral cryptorchidism and phymosis at birth. At one, three and seven years-of-age orchidopexy was unsuccessfull to find testicular tissue. Meanwhile one cure of human chorionic gonadotropin (hCG) therapy was applied, without success. Endocrine investigation was continued just in 2011, at 24 years-of-age, when infantile external male genitalia without male secondary sexual characters were recorded. Surprisingly, low free testosterone level (1.64 pg/ml, normal: 5.5–42) with very reduced LH (0.13 mIU/ml) and FSH (0.7 mIU/ml) were detected, with normal hypothalamic-pituitary system on MRI. Abdominal and pelvic MRI detected hypoplastic prostate and seminal vesicles, the gonads were not found. The karyotype is 46,XY. Because of a reduced compliance the boy returned to endocrinology evaluation just in February 2016 with intense hypogastric pain. The urological exam diagnosed a severe phymosis with chronic incomplete urinary retention and frequent urinary infections. After circumcision was performed, urinary complains ceased. Hormonal assessment: TSH: 1.23 mIU/l, free-T_4: 1.10 ng/dl (0.7–1.48), basic morning cortisolaemia: 12.8 μg/dl, PRL: 5.46 ng/ml, LH: 0.03 mIU/ml, FSH: 0.13 mIU/ml, Total testosterone: 37.3 ng/ml (142.39–923.1), Free-testosterone: 0.15 ng/ml, SHBG: 20.8 nmol/l (13.5–71.4), DHEAS: 370.5 μg/dl (167.9–591.9), Androstenedione (1.92 ng/ml, normal: 0.6–3.1), AMH: 2 ng/ml (1.43–11.6). Repeated total testosterone (0.26 ng/ml, normal: 2.41–8.27) and dihydrotestosterone (DHT: 67 ng/l, normal: 250–1000) at baseline were almost undetectable, without any response to hCG stimulation (1500 IU/m^2): stimulated total testosterone 0.30 ng/ml and DHT 61 ng/l. This confirmed a bilateral anorchia, but associated with hypogonadotropic hypogonadism. Replacement therapy with testosterone undecanoate im. was recommended. **Conclusion:** We report a case with bilateral anorchia associated with deficient secretion of gonadotropines. The occasional coexistence of correlation of these two etiologies need to be studied, in the literature have not been reported such case.

P2-P439

17 Alpha Hydroxylase, 17–20 Lyase Deficiency, a Case with Hypocalcemic Symptoms

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17 alpha hydroxylase, 17–20 lyase deficiency is an autosomal recessive inherited congenital adrenal hyperplasia type which is due to mutation in CYP17A1 gene and characterized with adrenal and gonadal sex steroid deficiency, delayed puberty in girls, XY sex development disorder in boys and hypergonadotrophic hypogonadism in both gender. **Case:** 15 year old girl referred to our clinic with vomiting, fatigue and muscle spasms. In her physical examination weight was 25–50 centile, height was 75–90 centile, The patient's blood pressure was 120/70 mmHg, Her breast development was at Tanner stage 1. The bone age was determined 11 years. There was no axillary or pubic hair. The patients laboratory results were glucose: 98 mg/dl K: 2.1 mEq/l, Na: 142 mEq/l, Ca: 9.3 mg/dl, iCa: 0.94 mmol/l (1.16–1.34 mmol/l), FSH: 59.2 mIU/ml, LH: 64.4 mIU/, E2: <5 pg/ml, total testosterone: <0.025 ng/dl, cortisol: 4.59 μg/dl, ACTH: 129 pg/ml, renin: 2.05 ng/ml per h (0.98–4.18), aldosterone: 11.01 ng/dl (4–48 ng/dl), 17 OH progesterone: 0.43 ng/ml, DHEA-S: 1.4 μg/dl, TSH: 0.61 μIU/mL, free T_4: 1.49 ng/dl, prolactin: 13.79 ng/ml, progesterone: 2.79 ng/ml, 11 deoksikortisol: 0.81 ng/ml), the blood gases examination results were ph: 7.60, HCO3: 37.3 mmol/l, PCO2: 57.1 mmHg, and base excess: 14. In the suprapubic ultrasonography of the patient, there were no mullerian or wolfian duct. Karyotype was 46XY and SRY(+). Treatment with hydrocortisone at a dose of 15 mg/m^2 per day was started. Hormone replacement therapy and laparoscopic gonad examnination was planned. We are waitig for genetic examination result about 17 alpha hydroxylase, 17–20 lyase deficiency. **Discussion:** 17 alpha hydroxylase, 17–20 lyase deficiency is a rare congenital adrenal hyperplasia type which presents with hypertension, hypokalemia and hypogonadism. But this case was referred our clinic with hypocalcemic symptoms due to metabolic alkalosis.

P2-P440

An Uncommon Case of Adolescent with POF

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Background: Premature ovarian failure (POF) is uncommon in pediatrics and when occurs during the adolescence is typically iatrogenic or due to chromosomal anomaly. Also many genes have been identified that contribute to the development of POF, and most of these mutations are extremely rare. **Objective:** We describe a case of 15 years old female presented short stature and secondary amenorrhea, after a normal puberty but without peak height velocity. She was well being with no history of illness, drugs or radiation and no family history of ovarian insufficiency.

Results: Clinically besides short stature (−2 SDS), we highlighted an involution of secondary sexual characteristics with very small mammary gland (4 cm). Laboratory findings revealed eleveted gonadotropins (LH 65 U/l, FSH 185 U/l) confirmed by LHRH test (peak LH >250 U/l, peak FSH >200 U/l) that allowed to diagnose an hypergonadotropic hypogonadism. Kariotype was normal and adrenal and ovaries antibodies were negative. Pelvic imaging by tras-abdominal ultrasound and MRI showed a very small ovaries and uterus. We started with estrogen replacement therapy, until the dose of 10 μg/die. She had regular mestrual bleending and an adult development of uterus and mammary gland. She received a GH replacement therapy to improve the final height and she catch her target height. Nevertheless the last abdominal MRI failed to identify the ovaries. **Conclusion:** Probably a genetic etiology, maybe a gonadotropic receptor dysfunction, is implicated but the certain cause still remain not known.

P2-P441

Trisomy 9 Syndrome in an Infant with Ambiguous Genitalia

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The pericentric inversion of Chromosome 9 is one of the most common chromosomal abnormalities, which could be associated with various manifestations in some cases. Herein, a patient is presented with ambiguous genitalia that karyotyping revealed 9 inv (p12q13). Trisomy 9 syndrome could be considered in the list of differential diagnosis of those with ambiguous genitalia, while chromosomal karyotype and culture could be recommended in children with ambiguous genitalia. **Keywords:** trisomy 9, chromosomal structural abnormalities, ambiguous genitalia.

P1-P442

Placental and Cord Blood DNA Methylation Profiling in Small-for-Gestational-Age Newborns from Uncomplicated Pregnancies: Relationship to Prenatal Growth and Postnatal Body Composition

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Background: Fetal growth is partly regulated by epigenetic factors, such as DNA methylation. Altered methylation status in placental genes relates to gestational diabetes, preeclampsia and prematurity. However, the epigenetic mechanisms underlying fetal growth restraint in uncomplicated pregnancies remain unknown. **Objective and hypotheses:** We aimed at identifying new candidate genes related to fetal growth, by assessing DNA methylation profiling in placenta and cord blood -as well as expression levels of differentially methylated genes- in newborns born appropiate- (AGA) or small-for-gestational-age (SGA). **Method:** Placentas and cord blood samples were collected from uncomplicated pregnancies delivering term AGA (birthweight, between −1.1 and 1.1 S.D.; $n=30$) or SGA (birthweight, <-2 S.D.; $n=21$) newborns. Placental methylation profiling was performed using Agilent DNA Methylation array design to detect CpG sites located within promoter regions of 14.475 genes. Results were validated by bisulfite pyrosequencing (BSP). Differentially methylated genes ($n=39$, all $P<0.009$) were also analyzed in cord blood by BSP. Placental and cord blood expression of four out of such 39 genes was assessed by real-time PCR. Body composition was assessed by absorptiometry at age 15 days. **Results:** SLC13A5, NKX6-1 and ATG2B -related to hepatic steatosis, insulin production and autophagy – were hypermethylated in placenta and cord blood from SGA newborns ($P=0.02$ to $P<0.0001$ vs AGA), whereas GPR120 – related to free fatty acid regulation – was hypomethylated in placenta ($P=0.0006$) and hypermethylated in cord blood ($P<0.0001$). Expression levels of these genes were opposite to their methylation status. Both methylation and expression levels in placenta and in cord blood correlated with birthweight and with total and abdominal fat at age 15 days. **Conclusion:** Epigenetic modifications of genes involved in the regulation of energy metabolism in placenta and in cord blood contribute to explain fetal growth restraint and postnatal fat mass gain in SGA newborns from uncomplicated pregnancies.

P1-P443

The Collapse of the BDNF/POMC System in the Hypothalamus is Responsible for the Extreme Obesity with Hyperphagia Observed in Female Heterozygous MeCP2 Null Mice

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Objective and hypotheses: The aim was to elucidate the mechanism underlying the extreme obesity observed in female heterozygous MeCP2 null mice fed a high-fat diet. **Method:** We examined the molecular biology and physiology of female heterozygous MeCP2 null mice ($Mecp2^{tm1.1Bird/J}$, $MeCP2^{+/-}$ mice) fed a high-fat diet (HFD) for 12 weeks since 4 weeks of age using analytical tools. C57/BL6 mice were used as controls.

Results: MeCP2$^{+/-}$ mice fed with HFD (MeCP2$^{+/-}$ +HFD mice) showed extreme obesity with hyperphagia since 7 weeks of age. However, O_2 consumption and locomotor activity was not different between the MeCP2$^{+/-}$+HFD mice and the controls fed a HFD (HFD mice). The amount of subcutaneous and visceral white adipose tissue was higher in the MeCP2$^{+/-}$+HFD mice than in the HFD mice. Further, UCP1 mRNA and PGC1a mRNA expression in the brown adipose tissues was not different between the two groups. Serum leptin was higher in the MeCP2$^{+/-}$+HFD mice than in the HFD mice. A dietary preference test revealed that the MeCP2$^{+/-}$+HFD mice greatly preferred HFD than the HFD mice. AgRP mRNA and Ghrelin mRNA expression in the hypothalamus was higher in the MeCP2$^{+/-}$+HFD mice than in the HFD mice. POMC mRNA expression in the hypothalamus was lower in the MeCP2$^{+/-}$+HFD mice than in the HFD mice. Interestingly, mRNA and protein levels of BDNF in the hypothalamus were upregulated in the HFD mice, but downregulated in the MeCP2$^{+/-}$+HFD mice. In addition, the phosphorylation of JAK2/STAT3 and Foxo1/AMPK in the hypothalamus was similar between the two groups. **Conclusion:** The collapse of the BDNF/POMC system in the hypothalamus could lead to extreme obesity with hyperphagia in the MeCP2$^{+/-}$+HFD mice. Epigenetic pathogenesis rather than disturbances in cell signaling appears to be the mechanism underlying the hyperphagia with leptin resistance observed in the MeCP2$^{+/-}$+HFD mice.

P1-P444

Neonatal Overfeeding Alters Hepatic Insulin Sensitivity During Lactation and Leads to Long-term Insulin Resistance and Fatty Liver in Mice: Key Role of *Mogat1*

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Background: Excessive energy intake and rapid weight gain early in life are associated with obesity, type 2 diabetes, hepatic steatosis and other features of the metabolic syndrome. The monoacylglycerol acyltransferase (MGAT) is an enzyme involved in an alternative pathway for triglyceride (TAG) synthesis and storage. It has been recently proposed to have potential implications in the pathogenesis of hepatic insulin resistance (IR). **Objective:** To understand the mechanisms that contribute to i) the development of early IR and ii) the long-term programming of metabolic disease in a mouse model of childhood obesity. **Method:** Here we used a mouse model of model of neonatal overnutrition (ON) and accelerated growth that develops obesity, IR, glucose intolerance and hepatic steatosis with aging. To gain insight about the mechanisms that lead to IR and steatosis, we performed gene expression profiling (Affymetrix) in livers from Control and ON Mice. **Results:** Gene expression profiling uncovered that the Ontology with highest significance was the Lipid Biosynthetic Pathway. Strikingly, Mogat1 ranked with highest significance in this list. We confirmed Mogat1 up-regulation in liver samples from 4–6 month old ON mice. Importantly, Mogat1 was already elevated in livers of lactating 15-day-old ON mice. Furthermore we found no changes on other pathways that could contribute to lipid synthesis and storage in the liver (synthesis *de novo*, oxidation or VLDL transport). Mogat1 catalyzes the conversion of Monoacylglycerol to DAG, which activates PKCε that in turn contributes to IR. In agreement, we found that Mogat1 over expression resulted in DAG hepatic accumulation and higher PKCε activation in ON mice. **Conclusion:** Mogat1 might be a key player in the development of IR and hepatic steatosis. Therefore, targeting MGAT activity in the liver might be a novel potential strategy to improve hepatic insulin sensitivity.

P1-P445

The Impact of Activating PIK3CA Mutations and PTEN Haploinsufficiency on Human Adipocyte Phenotype and Biology

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Background: The phosphatase and tensin homolog (PTEN) /phosphatidylinositol-3-kinase (PI3K)/AKT signaling pathway is central for cell cycle control, differentiation, migration, and metabolism. Unrestricted growth of adipose tissue in particular is frequently seen in humans with germline PTEN and mosaic activating PIK3CA mutations, respectively. **Objective and hypotheses:** We assume that adipocytes from affected tissue show hyperproliferation and modified differentiation ultimately leading to adipose tissue overgrowth. We aimed to study preadipocytes *in vitro*, which were derived from affected regions of pediatric mutation carriers. Moreover, we established a PTEN knockdown in SGBS preadipocytes to mimic hyperactive PI3K/AKT signaling. **Method:** We used paraffin embedded lipoma tissue samples for histological analysis. Size of adipocytes was measured using automated image analysis. After cell culturing of mutant preadipocytes, AKT- and p70S6-kinase phosphorylation was determined by western blot analysis. Oil-Red-O-staining of cellular lipids was followed by a photometric quantification. Gene

expression was analyzed using qRT-PCR. PTEN knockdown was performed using siRNA. **Results:** Adipocytes from PTEN or PIK3CA mutation carriers ($n=6$) were found to be significantly larger compared to controls ($n=5$). Contrary to expectation, cell proliferation was not enhanced, despite higher basal AKT (Ser473) and p70S6-kinase phosphorylation. We found an increase of lipid accumulation and PPAR-gamma mRNA expression in PIK3CA mutant adipocytes during differentiation, which was absent in PTEN mutant or PTEN knockdown adipocytes. **Conclusion:** Mutations in PTEN or PIK3CA lead to hypertrophic adipocytes with constitutive phosphorylation of AKT, but no increase of proliferation.

P1-P446

Bioinactive Leptin is not Frequently Detected in Severe Early Onset Childhood Obesity

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Background: Rodent models of leptin inactivity show progressive obesity due to exaggerated food intake. In humans, only rare monogenic cases of leptin deficiency and almost absent circulating leptin levels have been identified. Recently, two cases of children with early onset massive obesity due to biofunctionally inactive leptin in the face of normal total levels have been identified. **Objective and hypotheses:** Here we aimed to identify leptin inactivity in obese children through decreased proportion of bioactive leptin. **Method:** Seventy probands with severe early-onset non-syndromic obesity (age of obesity onset <3 years and BMI SDS >3 SDS at the age of 1–4 years) were selected from a large Leipzig childhood obesity cohort ($n=1377$) for the leptin measurement. Serum concentrations of whole and bioactive leptin were measured with enzyme-linked immunosorbent assays. Proportion of bioactive leptin was evaluated as percentage from the whole leptin levels. Sanger sequencing of the leptin gene was performed in probands with proportion of bioleptin $<90\%$. **Results:** In 70 selected probands the mean levels of bioactive and whole leptin were 37.4 ± 24.1 ng/ml, and 32.0 ± 20.6 ng/ml, respectively. The corresponding proportion of bioactive leptin was $122.3\pm26.2\%$ (47.5–188.3%). We identified five probands suspicious for impaired leptin activity (bioactive leptin $<90\%$). However, DNA analysis of the leptin gene did not confirm causal mutations. **Conclusion:** In our sample selected for severe early onset childhood obesity, we did not identify leptin gene mutations leading to decreased proportion of bioactive leptin.

P1-P447

Neonatal Overnutrition Causes Sex and Age Dependant Long-Term Effects on Body Weight, Body Composition and Serum Triglyceride and Free Fatty Acid Levels

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Background: Neonatal over-nutrition (NON) can increase the propensity to become overweight and develop associated metabolic disturbances in later life. Moreover, some of these long-term effects are sexually dimorphic. **Objective and hypotheses:** We aimed to determine how NON affects body weight (BW), body composition and triglyceride (TG) and non-esterified fatty acids (NEFA) levels. We hypothesized that the effects would be both age and sex dependant. **Method:** At birth, Wistar rats were organized into litters of four (NON) or 12 (CT) pups (equal number males (M)/females (F)) and killed on postnatal days (P) 10, 50 or 150. BW, subcutaneous adipose tissue (SCAT) and visceral adipose tissue (VAT) mass and serum levels of TG and NEFA were measured. **Results:** At P10, BW was greater in NON rats of both sexes ($P<0.0001$), continuing until approximately P50. This effect on BW then dissipated and reappeared at P90, but only in M ($P<0.0001$). At P10 and until weaning (P21) SCAT was increased by NON, with F more affected than M ($P<0.0001$). At P150, NON M again had increased SCAT. At weaning NON increased VAT ($P<0.001$) and M had more VAT than F ($P<0.0001$). Serum levels of TG were unaffected by NON at P10 and P50, but were increased at P150, with NON M having higher levels than NON F ($P<0.03$). Serum NEFA levels were unchanged at PND10. At P50, NON F had lower levels than CT F and NON M, while NON M tended to have increased NEFA levels compared to CT M. At P150, NEFA were increased in NON M compared to CT M ($P<0.05$). **Conclusions:** i) Early over nutrition affects males and females differently, even prepubertally. ii) The long-term effects of neonatal overnutrition are both age and sex dependant. iii) Neonatal overnutrition could possibly affect the aging of metabolic homeostasis.

P1-P448

Laparoscopic sleeve gastrectomy in adolescents with morbid and dynamic obesity. A controlled monocentric study.

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Background: Following years of dietary and lifestyle intervention (DLI) as the only therapeutic option, reports of bariatric surgery are emerging in adolescents with morbid obesity. We present herein preliminary results of our 4-yr sleeve gastrectomy study. **Objectives and hypotheses:** To compare the effects of laparoscopic sleeve gastrectomy (LSG) and intensive DLI in adolescents with morbid obesity (ie BMI >4 DS) and extremely active weight gain (i.e. >0.6 kg/month). **Patients:** 45 patients (mean age 17.3 ± 1.6 years, BMI 45.5 ± 8.4; *z*-score 4.6 ± 0.8) underwent LSG and were followed for 25 ± 12 months (6–48 months) while a control group of 100 patients received intensive DLI (mean age 15.5 ± 1.9 years; BMI 38 ± 4; *z*-score $+4.4\pm0.6$). LSG was systematically preceded by a 12-month period of intensive DLI. Insulin resistance (IR) was estimated using HOMA-IR. **Results:** Patients who underwent LSG lost 33.2 ± 8.2% of their initial body weight (98 ± 2% of excess body weight) i.e. a total of 40.4 ± 5 kg over the whole period of observation: 29.6 ± 8.7% one year post-surgery (-3 ± 0.6 kg/mo); 30.2 ± 6.5% at the end of the 2nd year (-0.6 ± 0.2 kg/month) and 33.3% (-0.41 ± 0.2 kg/month) at the end of the 3rd year. In comparison, the control group lost little weight (0.5 ± 0.3 kg/month) and only in the 1st year, a rate observed in patients the year before LSG (0.6 ± 0.4 kg/month) and after the 1st post-surgical year. Durable improvement of IR, glucose tolerance, serum lipids, arterial pressure, QoL were observed in all patients following LSG, but did not correlate with the magnitude of weight loss. **Conclusion:** While classical LDI had almost no effect on severe obesity in morbidly obese adolescents, preliminary results support important and durable benefits of LSG.

P1-P449

Efficacy, Safety and Metabolic Effects of Carbohydrate Restriction in the Treatment of Obese Adolescents

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Background: Dietary carbohydrate restriction in the treatment of obese adolescents could cause a substantial shift in the substrates used as an energy source, inducing changes on body composition and metabolism, but experience in this age range is limited. **Objective:** We assessed the influence of 6 months of dietary carbohydrate restriction on body composition and lipid and carbohydrate metabolism in obese adolescents. **Method:** Thirty-six (15.8 ± 1.5 years; 22 girls/14 boys) obese ($+4.72\pm2.80$ BMI-SDS) Caucasian adolescents were recruited and analyzed monthly. Two nutritional interventions with similar caloric content (1500 kcal/day) were compared: limited carbohydrates (CH-L, $n=19$, 10% carbohydrates for 4 months and 30% later) vs. unrestricted carbohydrate diet (CH-N, $n=17$, 52% carbohydrates). Patients were studied at recruitment (R) and after 3 (3M) and 6 months (6M). BMI, body composition (BIA, Tanita® BC-420MA), glycemia, insulinemia, HOMA, lipid profile, uric acid and serum 25[OH]vitamin-D levels were recorded. **Results:** Both groups reduced their BMI-SDS at 6M ($P<0.001$), with this being greater in the CH-L group (-1.70 ± 0.98 vs -0.80 ± 1.09 in the CH-N; $P<0.05$) due to a larger reduction in the first 3 months (-1.41 ± 0.71 vs. -0.62 ± 0.78 in the CH-N; $P<0.001$) as the BMI-SDS evolution between 3 and 6 months was similar. This loss in BMI was due to a decrease in fat mass. A transient rise in uricemia was observed in the CH-L group at 3M ($P<0.01$), which normalized at 6M. HOMA improved exclusively in the CH-L group at 6M (-1.75 ± 1.48 vs. $+0.15\pm1.25$ in CH-N; $P<0.001$). No significant differences within or between groups were observed in the evolution of the lipid profile, but both groups showed an increase in vitamin-D levels at 6M after weight loss ($P<0.001$). **Conclusion:** Diet carbohydrate restriction results in a more intense weight reduction and insulin resistance improvement in obese adolescentes after 6 months of treatment.

P1-P450

Severe Hypertriglyceridemia in Pediatric Oncology Patient

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Background: Severe Hypertriglyceridemia (HTG) defined as triglycerides (TG) in blood plasma higher than 1000 mg/dl is a rare condition in childhood. Its causes are classified as primary and secondary and among these last they include pharmacological causes. Steroids associated with some chemotherapy drugs, particularly asparaginase (Asp), are a combination with special risk. **Objective and hypotheses:** Describe the evolution of lipids profile in LLA patients, treated with Steroids-Asp. **Method:** Retrospective descriptive study of cases of severe HTG in patients with acute lymphoblastic leukemia (ALL) treated in a tertiary hospital in 2010–2015. We have studied the prevalence of this disorder and its characteristics. Patients were treated on the LLA SHOP-2005 or LLA SHEOP-PETHEMA 2013 with an average of 23 dose of intramuscular Steroids-Asp (prednisone 60 mg/m^2 per day, or dexamethasone 8 mg/m^2 per day)/patient and distributed

Table 1. (for abstract P1-P450)

Patient	Age (years)	TG (mg/dl)	Treatment	TG 3 days (mg/dl)	TG 1 week (mg/dl)	TG 3 months (mg/dl)
A	14.5	>7.000	Bezafibrate (6 mg/kg/día)	2,836	244	NA
B	7.7	6.280	Bezafibrate (10 mg/kg/día)	323	123	91
C	5.9	2.200	None	252	340	314
D	3.5	3.799	None	771	522	171

in three blocks of treatment (induction, intensification or re-induction, and maintenance). **Results:** 45 patients were diagnosed with ALL (mean age 5 years old, male/female: 1.5/1). Protocols: ALL SHOP-2005 (49%) and ALL SHEOP-PETHEMA 2013 (51%); 102 estimated blocks with Steroids-Asp administration. It was found severe HTG in four patients with steroid-Asp (prevalence of 4%). The mean age was 7 years. Three were high-risk ALL. No relationship with other medications received was found. The evolution of HTG was adequate regardless of the therapeutic approach. No acute clinical complications. The medium-term evolution was (Table 1): **Conclusion:** The Asp and steroids can produce a transient severe HTG. Its management is based on dietary modifications +/− lipid lowering agents, and close monitoring without altering chemotherapy. No serious acute complications observed in any case.

P1-P451

The Frequencies of 5-HTTLPR Locus in Promotor Part of Serotonine Transporter Gene (SLC6A4) Polymorphism in Children with Different Forms of Obesity

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Background: Serotonine transporter gene (SLC6A4) polymorphism is one of genetic aspects of appetite and mood disorders. **Objective and hypotheses:** To determine the frequencies of 5-HTTLPR locus in promotor part of serotonine transporter gene (SLC6A4) polymorphism in children with different forms of obesity. **Method:** We examined 191 pubertal obese children. Patients were divided: Group 1 (simple obesity) 143 children, 14.3±1.8 years, 30.6±2.8 kg/m^2; group 2 (severe obesity) 48 children, 15.2±1.8 years ($P=0.3$), 39.7±4.2 kg/m^2 ($P=0.0001$). Control 80 children, 14.4±2 years ($P=0.5$), 14.4±2 kg/m^2 ($P=0.0001$). Serotonin levels, genotyping on 5-HTTLPR locus in serotonine transporter gene (SLC6A4)) promotor part were determined. Psychological testing using DSRS scales were used. Statistics was performed using SPSS.18. **Results:** Genotype 5-HTTLPR-SL determined in 57.1% cases in severe obese children compared to simple one (34.0%), 5-HTTLPR-SS genotype 7.1% and 20.0%, respectively ($\chi^2=6.0$; $P=0.05$). There was no ($\chi^2=5.0$; $P=0.7$) significant differences between groups with obesity and control in the frequency of 5-HTTLPR-SS, 5-HTTLPR-SL, 5-HTTLPR-LL genotypes occurrence. We found more frequent depression occurrence in obese children and the presence of SS (40%) genotype compared to SL (4.5%) and LL (30%) ($\chi^2=6.0$ $P=0.05$). Serotonin levels were significantly higher in severe obese children and SS genotype 654.0 (425.0; 654.0) comparison to SL (315.6 (257.7; 403.7) ng/ml genotype ($U=2.0$, $P=0.04$). Significantly higher values of BMI were in group with severe obesity and SS genotype (44.7±2.0 kg/m^2) than LL (38.5±3.0) ($P=0.01$) and SL (40.5±4.9) ($P=0.04$) genotypes. Children with simple obesity and SS-genotype (33.2±0.8) had higher BMI than with LL (31.7±3.2) ($P=0.04$) and SL (31.2±2.4) ($P=0.003$) genotypes. **Conclusion:** Genotype 5-HTTLPR-SL were more often in severe obese children (57.1%) compared to simple one (34.0%) ($P=0.05$). Severe obese children with SS had higher BMI compared to LL ($P=0.01$) and SL ($P=0.04$) genotypes. Serotonin levels were higher in severe obese children with SS compared to SL genotype ($P=0.04$).

P1-P452

High Predictability of Impaired Glucose Tolerance by Combining Diagnostic Parameters in Obese Children

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Background: Current guidelines suggest to test obese subjects with impaired fasting glucose (IFG) by oral glucose tolerance test (OGTT) for the presence of type 2 diabetes. This strategy, however, misses most cases of impaired glucose tolerance (IGT). **Objective and hypotheses:** To investigate whether combining risk factors improves predictability of IGT in OGTT. **Method:** In this observational study of 145 overweight children, aged 2.5–17.3 years, an OGTT was performed in all obese subjects. We determined the association of anthropometric and laboratory parameters with IGT. Furthermore, we analysed whether a combined model of associated parameters improved sensitivity of screening for IGT. **Results:** Out of 145 patients (53% female, 66% Caucasian, mean age 11.3 years, mean BMI SDS 3.4) IGT was present in 11 patients, of whom 2 had IFG. Hypertension ($P=0.025$) and elevated liver enzymes ($P=0.003$) were associated with IGT, whereas IFG was not ($P=0.067$). The presence of one or more abnormal screening parameters predicted IGT with a high sensitivity of 1.00 (95% CI 0.74–1.00), and a number needed to screen of 5.7. **Conclusion:** Combining IFG, presence of hypertension and elevated liver enzymes, into a model significantly increases predictability of IGT compared to using IFG alone.

P1-P453

The Effect of Subclinical Hypothyroidism (SH) and Treatment of SH with L-T4 on Basal Metabolic Rate in Obese Children: A Prospective Study

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Introduction: Subclinical hypothyroidism (SH) is reported up to 20% of obese population and thyroid hormone replacement in these individuals are controversial. In this study, we aimed to determine the effect of thyroid hormones on basal metabolic rate (BMR) in obesity and, thyroid hormone replacement on BMH and weight in obese patients with SH. **Method:** The study was conducted in 31 obese children (15 of them had subclinical hypothyroidism) admitted to our clinic between the February 2015 and February 2016 in a prospective manner. L-T4 replacement was started in SH group. As a control group, 12 healthy children with similar age and sex distribution were included. In the first and final evaluation of patient groups, anthropometric measurements, serum TSH and f-T4 and BMR measurements are performed in obese group but also body composition and BMH were also compared with control group. **Results:** BMI *z*-scores of children with obesity (*n*: 16), SH obesity (*n*: 15) and control groups were 2.32 ± 0.35; 2.31 ± 0.32; 0.80 ± 0.59, respectively. BMI *z*-scores were similar in two obese groups and which were higher than the control group. BMR and %BMR were similar in all three groups. TSH levels of obese and obese SH groups were significantly different (2.8 ± 1.13 vs 6.60 ± 1.44; $P < 0.001$). After 6 weeks of L-thyroxin treatment TSH levels were significantly decreased (6.60 ± 1.44 vs 4.5 ± 0.9; $P < 0.0001$), but, f-T4 levels remained unchanged (0.83 ± 0.1 vs 0.83 ± 0.14; $P > 0.05$) in obese SH group. Additionally, no significant change has been detected in BMR, %BMR, BMI z-score and percentiles after L-T4 treatment ($P > 0.05$). **In conclusion:** BMRs were similar in obese children to healthy non-obese children. We found no effect of SH on BMR and degree of obesity. Normalization of TSH with L-T4 replacement also had no effect on BMR and weight in obese children with SH.

P1-P454

Influence of Television Viewing During Meals on Eating Patterns

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Background: Recent studies show negative impact of the use of television while having food on the eating patterns. **Objective and hypotheses:** Our goal is to use cluster analysis to evaluate this influence in children. **Method:** In 895 Spanish children and adolescents (47% male and 53% female), from 3 to 18 years of age (10.25 ± 2.67 years), a validated food frequency and food consumption habits questionnaire (CFCA) is performed. Three cluster eating patterns based on healthy eating recommendations are established. Each cluster consists on daily consumption of dairy, fruit and vegetables, cereals and olive oil, weekly consumption of meat, eggs, fish and legumes and occasional consumption of sugar, snacks sweet, salty snacks, sugary drinks, processed foods, meats and fats. K-means analysis is performed by using SPSS19 statistical program. **Results:** 31.9% ($n = 188$) of children have Cluster 1 (daily: -0.724; weekly: -0.727; sporadic: -0.749) not fulfilling any of the recommendations. 31.8% ($n = 187$) have cluster 2 (daily: 0.248; weekly: -0.380; sporadic: 0.956), applying the recommendations for the consumption of sporadic food but avoiding them in the consumption of weekly food. 36.3% ($n = 214$) have cluster 3 (daily: 0.445; Weekly: 0.936; sporadic: -0.252), applying the recommendations for the consumption of daily and weekly food and avoiding them in the consumption of sporadic food. A higher percentage of children and adolescents who eat in front of the television, have an eating pattern Cluster 1 (43.9 vs 38.6%) and Cluster 3 (25 vs 20.3%) ($P = 0.043$). Both cluster are characterized by non-compliance with the recommendations of food intake sporadic type. **Conclusion:** No child or adolescent meets all recommended food consumption daily, weekly and sporadic. Eating in front of the television has a negative influence on dietary patterns, especially when consuming sporadic food. Cluster analysis is a good tool for establishing food strategies both for intervention and prevention.

P1-P455

Seven-year Follow-up of Mothers from a Randomized Controlled Trial of Exercise in Pregnancy and their Offspring

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Background: We have previously shown in a randomised controlled trial that moderate-intensity exercise over the last 20 weeks of gestation in healthy nulliparous women led to a birth weight reduction of approximately 250 g. **Objective and hypotheses:** We aimed to assess the long-term effects of exercise in pregnancy on anthropometry and body composition in mothers and offspring 7 years after the intervention. We hypothesized that

women who exercised in pregnancy would have lower adiposity than control mothers, and that children born to exercisers would be leaner than controls. **Method:** Of the initial 84 women and their offspring who participated in the randomised controlled trial, follow-up data were available on 57 mothers (33 exercisers, 24 controls) and 57 children. On average, assessments were carried out 7.6 years post intervention. Mothers and children underwent assessments of anthropometry and body composition (DXA scans). **Results:** There were no differences in maternal outcomes between exercisers and controls. However, compared to pre-pregnancy, weight (−4.3 kg; $P=0.006$) and BMI (−1.56 kg/m^2; $P=0.008$) were reduced among exercisers, but total body fat was reduced in both groups (Exerciser = −4.2%; Control = −3.2%). At a mean age of 7.6 years, girls exposed to antenatal exercise had greater percentage body fat ($P=0.028$) and increased abdominal adiposity ($P=0.019$) than controls. Anthropometry and body composition were similar among exerciser and control boys, although boys of exercisers had higher diastolic blood pressure ($P=0.041$). **Conclusion:** There was a reduction in adiposity in both groups of mothers, but a positive effect was more marked amongst exercisers, who were also significantly lighter and leaner compared to pre-pregnancy. However, the data suggest that the exercise intervention may be associated with adverse effects in the offspring of both sexes. Larger follow-up studies are required to investigate the long-term effects of exercise in pregnancy.

P1-P456

E-Health: A National Registry and Therapeutic Algorithm for the Prevention and Management of Overweight and Obesity in Childhood and Adolescence in Greece

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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. In Greece, more than 35% of children and adolescents are currently overweight or obese. **Objective and hypotheses:** To develop a National e-Health System for General Pediatricians and General Practitioners for the prevention and management of overweight and obesity. Specific aims included: i) Development of a 'National Registry for the Prevention and Management of Overweight and Obesity in Childhood and Adolescence' and ii) Guidance and Training of General Pediatricians and General Practitioners as to how to manage an overweight or obese child or adolescent. **Methods:** Using information and communication technologies (ICT), we developed a web application supporting interoperability with other National infrastructures (i.e. ePrescription) and multi-layered security spanning preventive, detective, and administrative controls. This includes transparent data encryption, data redaction, data masking, privileged user controls, privilege usage analysis, conditional auditing and real application security. The Patient Summary Dataset includes information on the present and past medical history, family history, medications, immunizations, clinical examination and laboratory findings, and appointment booking service. Based on the data that the doctor is registering, the system calculates a personalized therapeutic algorithm that provides information on diet, physical exercise and sleep, as well as guidance on laboratory investigations and referral to specialized centers. **Results:** The application was launched in September 2015 and is accessible by the following URL: http://app.childhood-obesity.gr/. A pilot study performed in 1000 children and adolescents indicated that using this system resulted in a reduction of obesity rates by 30% and overweight rates by 35% within 1 year. **Conclusion:** This National e-Health System appears to be effective in the management of overweight and obesity in childhood and adolescence.

P1-P457

Premature Adrenarche and Metabolic Risk: Differences by Gender

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Background: Premature adrenarche (PA) has been considered a benign condition. Recently, associations with an increased metabolic risk have arisen. This risk may depend on ethnic background and infancy weight gain, which could be different by gender. **Objective and hypotheses:** To determine whether PA in children at pubertal onset (TII) determines a higher metabolic profile. **Methods:** 1190 children (49.9% female) from the longitudinal cohort (Growth and Obesity Cohort Study) were followed from 2006 and undergone every 6 months a clinical evaluation and a complete metabolic profile. PA was defined by DHEAS (RIA, μg/dl) >75th percentile for each gender (girls>

Table 1.

	Girls PA+	Girls PA−	Boys PA+	Boys PA−
Height_SDS	0.3±0.9**	0.05±1.0	0.4±0.9**	0.03±1.0
BMI_SDS	1.1±1.1**	0.8±1.1	1.6±1.1**	1.1±1.2
Leptin (ng/ml)	12.9±8.9	12.7±8.1	15.3±8.7**	12.2±8.6
IGF-I (ng/ml)	243±62*	233±70	209±59	200±58

a*$P<0.05$
b**$P<0.01$

42.0 and boys > 45.1 at age 6.8 ± 0.6 year). TII was defined by telarche in girls and testicular volume ≧3 cc in boys. Statistics: Generalized linear models and survival analysis were used to assess the relation between PA and anthropometric and metabolic profile at TII, adjusting by chronologic age at DHEAS sampling and BMI. **Results:** At TII, children who developed PA (PA+) were taller and had higher BMI vs without PA (PA-). Boys PA+ had higher leptin levels (Table 1). In girls, higher DHEAS levels were associated with higher IGF-I levels ($P < 0.05$). No differences were observed in insulin, glycemia, adiponectin, lipid profile, usCRP and visfatin. **Conclusions:** Children with PA were taller and had higher BMI; boys had higher leptin levels and girls higher IGF-I, but not to a disadvantageous metabolic profile at TII. Follow-up of this cohort is necessary to address prospectively the interrelationships of PA, early growth and adiposity as markers of metabolic risk (Fondecyt 1140447 & 1120326, WCRF:2010/245).

P1-P458

Association of miR-34a and mir-149 with Obesity and Insulin Resistance in Obese Children and Adolescents

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Background: Obesity is a major public health problem and its rate is increasing worldwide. Obesity accompanies perturbations in metabolism, conferring substantial excess risk for insulin resistance and Type 2 diabetes. Various genetic and epigenetic factors contribute to the development of obesity. MicroRNAs (miRNAs) are short noncoding RNAs involved in posttranscriptional regulation of gene expression and influence many cellular functions including glucose and lipid metabolism and adipocyte differentiation. miRNAs have been shown to be involved in obesity but their role in this regard is not clearly defined. **Objective and hypotheses:** The aim of this study was to evaluate the levels of miR-34a and miR-149 and their association with metabolic parameters in obese children and adolescents. **Method:** Seventy children (35 obese and 35 control) (8–18 years) were included in the study. The miRNA fractions were isolated from plasma and elongated by poly A tailing using *E. Coli* poly A polymerase. The resulting miRNA was reverse transcribed into cDNA, amplificated by Real time PCR using miRNA-specific primers and detected by SYBR green. Data were normalized with cel-miR-39 and compared with ΔΔCt method. Concentrations of visfatin and insulin in plasma were measured by ELISA method. Glucose and lipid profile were determined colourimetrically. HOMA-IR was calculated and used as an index of insulin resistance. **Results:** There was an inverse relationship between miR-34a levels and both insulin and HOMA-IR. On the other hand, miR-149 was significantly correlated with visfatin. There was no significant difference in miR-34a and miR-149 between obese and normal weight subjects. Visfatin was significantly elevated in obese children compared to control subjects and was correlated with glucose, insulin and HOMA-IR. **Conclusion:** miR-34a is associated with insulin and HOMA-IR and thus seems to be involved in insulin resistance. miR-149 is inversely associated with visfatin levels which could be indicative of anti-inflammatory effect of this miRNA.

P1-P459

Erythropoietin Activates Classical Brown Adipose Tissue Through the Erythropoietin Receptor/STAT3 Pathway, Improving Obesity and Glucose Homeostasis in High Fat Diet-induced Obese Mice

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Background, aims and objectives: We hypothesized that classical brown adipose tissue (cBAT) could play a crucial role in the anti-obesity effects of erythropoietin (EPO). Our study highlights the mechanism in which EPO treatments could upregulate energy expenditure and improve glucose homeostasis through cBAT in obese mice fed with a high-fat diet (HFD). **Method:** C57BL/6J mice had been fed with HFD since the age of 4 weeks (HFD mice). We administered recombinant human EPO (200 IU/kg) to some HFD mice intraperitoneally, three times per week for 4 weeks (HFD+EPO mice). Blood glucose, serum insulin and FGF21 were monitored and an intraperitoneal glucose tolerance test (IPGTT) was performed on the two groups. We analyzed the interscapular BAT (iBAT) and the liver harvested from both groups using molecular biology and physiological methods. **Results:** Body weight, blood glucose and serum insulin were decreased in HFD+EPO mice compared with HFD mice. Serum level of FGF21, interscapular surface temperature and oxygen consumption were higher in HFD+EPO mice in comparison with HFD mice. The IPGTT showed that the levels of blood glucose were lower in HFD+EPO mice than in HFD mice. The weight of iBAT was larger in HFD+EPO mice than in HFD mice, whereas that of white adipose tissue was decreased in HFD+EPO mice than in HFD mice. The mRNA and protein levels of UCP1, beta3ADR, PRDM16, PPARα and FGF21 in the iBAT were higher in HFD+EPO than in HFD mice. However, the mRNA and protein level of FGF21 in the liver was similar between the two groups. EPO treatment significantly stimulated phosphorylation of EPO receptor (EpoR)/STAT3 in the iBAT in a HFD condition. **Conclusion:** The activation of EpoR/STAT3 pathway in the cBAT by extrinsic EPO could be an underlying mechanism of the upregulation of energy expenditure and the improvement of glucose homeostasis by upregulating the secretion of FGF21 on the cBAT in HFD mice.

P1-P460

The Association between Insulin Resistance and Lower Extremity Muscle Strength, Static and Dynamic Standing Balances in Obese Adolescents

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Background: Obesity is characterized by insulin resistance of target tissues, such as skeletal muscle, adipose tissue and liver. Skeletal muscle tissue is responsible for approximately 75% of whole body insulin-stimulated glucose uptake. Previously, it has been shown that skeletal muscle strength is significantly associated with insulin resistance in type-2 diabetics and non-diabetics. **Objective and hypotheses:** To examine the relationship between insulin resistance with isokinetic muscle strength, static and dynamic standing balances in obese adolescents. **Method:** 192 obese (12–17 years old) adolescents and age-matched 75 healthy controls were recruited in this study. The isokinetic test protocol for measuring the strength of knee flexion-extension muscle groups was performed by using the Biodex System 3 Pro isokinetic dynamometer. In addition, dynamic and static standing balances were detected with Biodex® Balance System. HOMA-IR was calculated in all subjects. In patient group BMI, fasting insulin and HOMA-IR values were higher than controls. **Results:** At all velocities, the isokinetic muscle strength of knee extensors and flexors were significantly higher in obese group without insulin resistance ($P<0.05$), but were lower in obese group with insulin resistance ($P<0.05$). Knee extensor peak torques bilaterally were positively correlated with BMI and age, but negatively correlated with insulin and HOMA-IR in both obese groups. Static standing balance was better in patient group than controls, but dynamic standing balance was worse in both patient groups and negatively correlated with insulin and HOMA-IR. **Conclusion:** İsokinetic muscle strength was lower in obese adolescents with insulin resistance than those of controls and obese adolescents without insulin resistance, but dynamic standing balance was worse and both parameters were negatively correlated with insulin resistance in both obese groups. It was thought that insulin resistance can lead to impair the dynamic standing balance and muscle strenght.

P1-P461

Adiponectin and IL-6 in Simple Childhood Obesity with and without Hepatic Steatosis

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Background: Non-alcoholic fatty liver disease (NAFLD) represents a spectrum of clinicopathological conditions frequently discovered in obese patients and characterized by multifactorial pathogenesis. Hypoadiponectinaemia and higher interleukin (IL)-6 levels has been related to NAFLD, even if some contradictory findings have emphasized our incomplete understanding of the role of the cytokines in NAFLD. **Objective and hypotheses:** To investigate the relationship between adiponectin and IL-6 in the hepatic steatosis (HS) and insulin resistance mechanisms in a cohort of obese children. **Method:** Thirty-five children with simple obesity, considered as subjects with a body mass index (BMI) over the 95th percentile obese according to Italian centiles, and 29 controls were recruited. Serum adiponectin and IL-6 levels were determined and an oral glucose tolerance test and a hepatic ultrasound were performed in the two groups. The Homeostatic model assessment of insulin resistance (HOMA-IR) and the whole body insulin sensitivity index (WBISI) were calculated. **Results:** IL-6 serum levels were significantly higher ($P=0.03$) and serum adiponectin levels were significantly lower ($P=0.04$) in the obese children than in the controls. The serum adiponectin level was significantly inversely correlated with BMI in both groups (obese $P=0.01$; controls $P=0.04$). The BMI values were significantly higher ($P=0.0002$), and adiponectin levels were significantly lower ($P=0.01$) in obese children with hepatic steatosis than in those without, whereas IL-6 serum levels were not statistically different. HOMA-IR and WBISI were significantly correlated with adiponectin, but not with BMI, HS or IL-6. **Conclusion:** Hypoadiponectinaemia plays a more precocious role than IL-6 in the development of hepatic steatosis and insulin resistance in obese children.

P1-P462

Determinants of Advanced Bone Age in Childhood Obesity

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Background: Childhood obesity is associated with advanced bone age (BA), leading to an altered growth pattern. Previous results of studies suggest that androgens, estrogens, sex hormone binding globulin (SHBG) and insulin are responsible for this phenomenon, but results are contradictory and might be biased by confounders. **Objective and hypotheses:** To investigate the independent effects of estrogens, androgens, SHBG and insulin parameters on BA advancement in children and adolescents with obesity. **Method:** We performed a correlation analysis of BA standard deviation score (SDS) with androgens, oestrogens and indicators of insulin secretion derived from oral glucose tolerance testing, in a group of obese children and in subgroups according to sex and pubertal status. For oestradiol, testosterone, SHBG and dihydroepiandrosterone sulphate (DHEAS) we calculated age and sex specific SDS. A multivariate analysis was performed to investigate which parameters were independently predictive of BA SDS. **Results:** In this cohort ($n=101$; 47% female; 56% pubertal; mean age 10.9 years; mean BA 11.8 years; mean BMI

SDS 3.4 kg/m^2), BMI SDS was significantly correlated to BA SDS ($r=0.55$, $P<0.001$). In a regression analysis in the total cohort ($B=0.27$, $P<0.001$), as well as in females ($B=0.34$, $P=0.042$), males ($B=0.31$, $P=0.006$) and pubertal children ($B=0.32$, $P=0.046$), DHEAS showed a positive, independent association with BA SDS. In prepubertal children, SHBG showed an independent negative association with BA SDS ($B=-0.41$, $P=0.013$). No association with insulin, insulin resistance or insulin secretion was found. **Conclusion:** Increased DHEAS has a central role in advanced BA in obese children.

P1-P463

Exposure to Phthalates Is Associated with Overweight or Obesity in 4-Year-Old Children

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Background: Childhood obesity is a major health concern. Exposure to environmental chemicals may play a role in childhood obesity. **Objective and hypotheses:** We investigated whether urinary phthalate metabolite concentrations was associated with overweight or obese status in 4-year-old children. **Method:** Forty-hundred thirteen children born as term, appropriate-for-gestational-age infants (226 males) were included in this study. BMI was calculated based on height and weight at the visit. Children were classified into lean ($n=366$) and overweight or obese ($n=47$, $\geqq$85th BMI percentile). Birth weight, parental BMI, breastfeeding, daily calorie intake, and weekly exercise hours were investigated. Urinary mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono-(2-ethyl-t-oxohexyl) phthalate (MEOHP), and mono-n-butyl phthalate (MnBP) were measured at ages 4. Urinary phthalate metabolites were ln-transformed (ln-MEHHP, ln-MEOHP, and ln-MnBP) for statistical analysis. **Results:** The proportion of overweight or obese children was higher in girls than boys (15.5% vs 8.0%, $P<0.05$). Overweight or obese children showed lower hours of weekly exercise ($P=0.03$), and higher concentrations of MEHHP (mean 78.0 vs 62.7, $P=0.034$) and MEOHP (mean 58.8 vs 48.3, $P=0.044$) than lean children, respectively. No significant differences in birth weight, paternal obesity, exclusive-breastfeeding, daily calorie intake, and levels of ln-MnBP were found between the two groups. No interaction of sex on the relationship between urinary phthalates and overweight or obesity was found. In multivariable models after adjusting for sex, birth weight, weekly exercise hours *(including significant covariates in univariate analysis)*, each ln unit increase in MEHHP and MEOHP was associated with increased odds of overweight or obesity (OR=1.95 for MEHHP and 2.04 for MEOHP, $P<0.05$ for both). After additional adjustment for exclusive breastfeeding, parental obesity, parental college graduate, and daily calorie intake *(including all previously well-known covariates)*, each ln unit increase in MEHHP and MEOHP was significantly associated with increased odds of overweight or obesity ($P<0.05$ for both). **Conclusion:** This study suggests positive relationships between urinary concentrations of MEHHP and MEOHP and overweight or obese status in 4-year-old children, even after adjusting for genetic and environmental confounders.

P1-P464

Central Obesity among European Preschool Children: The ToyBox-Study

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Background: Waist circumference (WC) reflects the fat distribution and the degree of central adiposity in children, which is specifically associated with cardiovascular risk factors and useful as a component of metabolic syndrome definition in children. **Objective and hypotheses:** To evaluate the distribution of WC measures among preschool children aged 3.5–5.5 years from six European countries. **Method:** Cross-sectional study of a representative sample of 7527 children from six European countries (Belgium, Bulgaria, Germany, Greece, Poland and Spain) (52.0% boys), aged 3.5–5.5 years (2012). Body weight, height and WC were measured using standard procedures and BMI and waist-to-height ratio (WHtR) were calculated. The overweight/obesity prevalence for each age group both for boys and girls was estimated using IOTF reference. Percentile values were defined for each age group within sex. A standardized questionnaire was used to collect information on SES and demographic data. **Results:** Mean WC was 52.2 ± 4.1 cm, significantly increasing with age as its mean values were higher in males compared to females (52.4 ± 3.9 vs 52.0 ± 4.2 cm, $P<0.001$). Greek and Spanish children had the highest WC measures, while the lowest values were found among Bulgarian preschoolers ($P<0.001$). Children from the lowest SES group had significantly higher WC and WHtR values compared to those with highest SES (52.7 ± 4.1 cm and 0.484 ± 0.034 vs 51.8 ± 4.0 cm and 0.477 ± 0.033, respectively, $P<0.001$). Abdominal obesity with WHtR above 0.5 was found in 23.6%

(21.7% boys vs 25.7% girls, $P<0.001$). The 90th percentile value for WC was higher in girls compared to boys (57.4 vs 57.1 cm). The prevalence of overall overweight/obesity was 14.4%, with 16.3% in the low SES group vs 12.9% for the high SES. **Conclusion:** The ToyBox study adds data to our knowledge on abdominal obesity among preschoolers in Europe, highlighting the need to identify new strategies to decrease it.

P1-P465

Changes in Waist-to-Height Ratio during Preschool Years Differ between Children being Obese or Overweight at Five Years of Age Compared with not Overweight Children

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Background: Growth patterns in early childhood are important for predicting adult overweight or obesity. BMI is the most widely used measure. However BMI does not reveal much regarding the distribution of fat, for example the visceral fat that in adults is highly correlated with metabolic risk. Waist-to-Height Ratio (WtHR) is in adults a better measure for visceral fat and studies indicate that the same applies to children. **Objective and hypotheses:** To study changes in WtHR during preschool years in children being obese, overweight or not overweight at five years of age according to ISO-BMI cut-off values. **Method:** Longitudinal study of 2666 children participating in the Halland Health and Growth Study, followed from 0 to 5 years. Measurements of weight, waist circumference and height were made at 0, 3, 6, 12, 18, 24, 36, 48 and 60 months. Children were classified as obese, overweight or not overweight at 60 months according to ISO-BMI cut-off values. **Results:** Overweight boys had higher WtHR at every measure point compared with not overweight boys, exemplified by; 0 m, 0.70 vs 0.68, $P<0.001$, 24 m, 0.57 vs 0.55, $P<0.001$ and 60 m, 0.51 vs 0.48, $P<0.001$. Overweight girls had higher WtHR, except at birth; 0 m, 0.69 vs 0.68, $P=0.07$, 24 m, 0.58 vs 0.56, $P<0.001$ and 60 m, 0.51 vs 0.48, $P<0.001$. Obese boys had higher values compared with not overweight boys, except at birth, however only significant after 18 m; 0 m, 0.68 vs 0.68, $P=0.95$, 24 m, 0.58 vs 0.55, $P=0.02$ and 60 m, 0.53 vs 0.48, $P<0.001$. Obese girls had higher values at every measure point compared with not overweight girls; 0 m, 0.69 vs 0.68, $P=0.19$, 24 m, 0.60 vs 0.56, $P<0.001$, 60 m, 0.56 vs 0.48, $P<0.001$. **Conclusion:** Obese or overweight children at five years of age could be identified by higher WtHR during first five years compared with not overweight children.

P1-P466

Remarkable Increase in the Prevalence of Overweight and Obesity among School Age Children in Antalya, Turkey, between 2003 and 2015

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Background: The prevalence of childhood obesity is increasing all over the world and leading to an increase in obesity-related health problems such as adult obesity, cardiovascular diseases, type 2 diabetes and depression. There is no nationwide systematic study investigating obesity trends in Turkish children. **Objective and hypotheses:** The aim of this study is to determine the prevalence of overweight and obesity among school age children, to compare the data with those of 2003 and to observe the change in BMI in Antalya, Turkey. **Method:** The study included 58 schools from 124, throughout the city centre of Antalya, Turkey during the period March-April 2015. A number of 1687 school children (boys 873, girls 814) aged 6–14 years were chosen from 61,092 children, using a population based stratified cluster sampling method. BMI was calculated by measuring the weight and standing height. Overweight was defined as BMI between 85th and 95th percentile, and obesity as BMI above the 95th percentile. **Results:** The overall prevalence of obesity was 9.8% while overweight was 23.2%. There was no significant difference between boys and girls for overweight prevalence. However obesity prevalence was higher in boys (11.3%) than girls (8.1%) ($P<0.05$). Comparing with 2003 data, the values of BMI were found to be increased in all age groups (Figure 1). The prevalence of obesity and overweight showed an

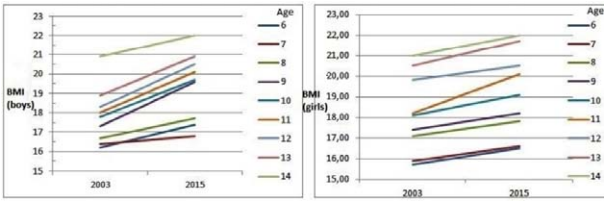

Figure 1 Comparison of the value of BMI among 6–14 years old school children in different ages and genders between 2003 and 2015.

Table 1. The comparison of 6–14 years old school children in Antalya, between 2003 and 2015.

	2003	2015	*P*
Number	1775	1687	–
Age (year)	6–14	6–14	–
Gender (girls/boys)	867/908	814/873	>0.05
Obesity (OB) (%)	3.4	9.8	0.0001
Overweight (OW) (%)	14.6	23.2	0.0001
OB + OW (%)	18	33	0.0001

increase up to 2–3 times from 2003 to 2015 (Table 1). **Conclusion:** The prevalence of obesity is increasing rapidly in Antalya, Turkey. Because obesity is a major health problem, determination the prevalence of obesity and overweight at regular intervals and taking measures in this regard is critical.

P1-P467

The Peculiarities of Neurotransmitters Levels in Children with Obesity and Different Genotypes of COMT Gene

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Background: Polymorphic genes Val158Met gene catechol-O-metiltrasferaz (COMT) are used to be responsible for less neurotransmitters utilization. **Objective and hypotheses:** To determine the peculiarities of neurotransmitters levels in children with obesity and different genotypes of COMT gene. **Method:** We examined 191 pubertal obese children. Patients were divided: Group1 (simple obesity) 143 children, 14.3 ± 1.8 years, 30.6 ± 2.8 kg/m^2; group2 (severe obesity) 48 children, 15.2 ± 1.8 years ($P=0.3$), 39.7 ± 4.2 kg/m^2 ($P=0.0001$). Control 80 children, 14.4 ± 2 years ($P=0.5$), 14.4 ± 2 kg/m^2 ($P=0.0001$). Dopamine, serotonin levels were determined. Genotyping was performed on polymorphic genes COMT. Statistical analyse was using SPSS.18. **Results:** We determined more frequent occurrence of GA (Val/Met) genotype COMT gene in children with severe obesity (54.3%) compared to simple disease (32.7%) ($\chi^2=6.9$; $P=0.03$). AA genotype frequency was 21.7% in patients with severe obesity, 45.5% and simple one which were higher than control (16.6%) ($\chi^2=14.6$; $P=0.006$). We revealed significantly higher BMI in children with severe obesity and the presence of GA genotype (41.3 ± 4.5 kg/m^2) compared to GG (37.4 ± 3.1) ($P=0.006$) and AA (38.6 ± 2.8) ($P=0.04$) genotypes. We did not find any significant differences in BMI values between children with simple obesity and GG, GA, AA genotypes. A statistically significant difference between dopamine levels were in patients with simple (8.8(4.8; 20.7)) and severe obesity (48.8(29.8, 163.9)) ng/ml and AA genotype ($P=0.05$). We found a significant increase in serotonin levels in patients with severe obesity and the presence of GA ($P=0.02$) and AA ($P=0.01$) genotypes compared with GG. There were no significant differences in the concentration of serotonin in children with simple obesity with different genotypes. **Conclusion:** A large frequency of AA genotype were found in children with severe and simple obesity. Higher BMI levels were in children with severe obesity and genotype GA. A significant serotonin increasing levels were in patients with severe obesity and the presence of GA and AA genotypes.

P1-P468

Association of Fasting Triglycerides to High-Density Lipoprotein Ratio with Risk for Metabolic Disorders in Children

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Background: Atherosclerosis begins in childhood and progresses silently. Triglycerides/HDL ratio(TG/HDL) is a risk factor for cardiovascular diseases. **Objective and hypotheses:** To investigate TG/HDL as possible predictive factor for metabolic disorders in children. **Method:** Descriptive correlation, with 110 children (6–12 years old) in Sparta, Greece. Anthropometric and biochemical analyzes were performed. **Results:** 17.27% of children had predisposition for metabolic syndrome (MetSyn). ROC analysis showed that the TG/HDL has a high sensitivity (73.7%) and specificity (68.1%) for diagnosing MetSyn with 1 as a cutoff point. For the total population, the relative probability that a child suffers from MetSyn with a TG/HDL ≥ 1 is almost six times greater than when a child has TG/HDL <1 (OR = 5.986; 95% CI = 1.968–18.205). TG/HDL is positively correlated with cholesterol ($P=0.006$), LDL ($P=0.001$), ALT/SGPT ($P=0.033$), γGT ($P<0.001$) and the cholesterol/LDL(CAD) ratio ($P<0.001$). Multivariate analysis showed that children with TG/HDL ≥ 1 had a 1.4 times greater odds for increased levels of cholesterol (OR = 2.411; 95% CI = 0.713–8.158), 2.6 times greater odds for increased LDL (OR = 3.614; 95% CI = 1.561–8.365), and 58.5% greater odds for increased ALT/SGPT (OR = 1.585; 95% CI = 0.215–11.698). In children without predisposition for MetSyn it comes out that as the TG/HDL increases so does the body weight ($P=0.035$), uric acid levels ($P=0.002$), and CAD ($P<0.001$). In this category, children with TG/HDL ≥ 1 had 3.5 times greater odds for increased value of uric acid (OR = 4.519; 95% CI = 0.393–51.988). In children with predisposition for MetSyn it comes out that the TG/HDL is positively correlated with CAD ($P<0.001$). **Conclusion:** Atherosclerosis is associated with TG/HDL due to the high concentration of both triglycerides and very low-density lipoprotein in plasma which leads to the production of small, dense LDL particles during the lipolysis. Previous studies report that the TG/HDL >4 in adults is a powerful predictive factor for the coronary disease. Interestingly, the current study showed that children may be affected for metabolic disorders when TG/HDL >1.

P1-P469

Assessment of Adherence to Mediterranean Diet during a Weight Loss Intervention in Children with Cardiometabolic Risk

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Background: Dietary patterns have notably changed in Mediterranean countries during the last decades. Mediterranean diet (MeDiet) is associated with lower prevalence of cardiometabolic diseases. **Objective and hypotheses:** To assess adherence to MeDiet in children and adolescents with abdominal obesity during a comprehensive weight loss intervention. **Method:** Children and adolescents with abdominal obesity (waist circumference $>$p90) were enrolled in a randomized study during 8 weeks. Participants were divided into a control group ($n=17$) and an intervention group ($n=46$) according to a 1:3 relation. Conventional nutritional and lifestyle recommendations based in National Health System guidelines were explained to control participants. The weight loss program for the intervention participants consisted of a moderate calorie-restricted diet calculated according to children's obesity degree. The degree of adherence to MeDiet was evaluated using the KIDMED index which categorized the quality of Mediterranean Diet as high (≥ 8 points), medium (4–7points) and poor ($\leq$ 3 points). Statistical analyses (paired *t*-test) were performed in software STATA 12.0, and results are expressed as mean and SD. **Results:** Sixty-three participants (45 girls) aged between 7 and 17 years (11.12, 2.47) were assessed. The weight loss in the intervention group was statistically significant (ΔBMI-SDS: -0.53, 0.43; $P<0.001$). A medium adherence to MeDiet at baseline was found in all the subjects (KIDMED $\text{score}_{\text{control}}$ 5.64, 1.57, KIDMED $\text{score}_{\text{intervention}}$ 5.97, 2.03). Furthermore, after 8 weeks of intervention, 89% of participants of the intervention group had a significant higher KIDMED index 8.80, 1.37 ($P<0.001$). Moreover, at the end of the weight loss program, 98% of intervention participants had daily breakfast ($P_{\Delta}=0.017$), and 91.3% reported to consume fish at least 2–3/week ($P_{\Delta}<0.001$). **Conclusion:** In children with high abdominal obesity a reduction - in BMI-SDS improvement during a weight loss intervention was accompanied by an increase in adherence to MeDiet pattern.

P1-P470

Brain Structure, Executive Function and Appetitive Traits in Adolescent Obesity

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Background: Children with obesity show differences in brain structure, executive function and appetitive traits when compared to lean peers. Results of imaging studies, however, have been contradictory. **Objective and hypotheses:** To investigate whether childhood obesity is associated with differences in brain structure and whether differences associate with executive function and appetitive traits. **Method:** A cross-sectional case-control study among 23 obese and 19 lean control subjects, aged 12–16 years, was conducted. Brain structures were measured by MRI using cortical thickness and subcortical volumes. Appetitive traits were measured by the Child Eating Behavior Questionnaire and executive function by a Stop Signal Task and a Choice Delay Task. Associations between brain structures and appetitive traits or executive function tests were investigated using linear regression analysis. **Results:** Obese adolescents had larger volumes of the pallidum; 1.78 ml (SE 0.03, $P=0.014$), when compared to controls; 1.65 ml (SE 0.02). In the obese group, increased pallidal volume was positively associated with the ability to delay reward in the Choice Delay Task ($P=0.012$). **Conclusion:** The positive association of pallidal volumes and Choice Delay Task found in obese adolescents supports the hypothesis that the pallidum plays an important role in executive dysfunction described in obese children.

P1-P471

Improved Clinical and Laboratory Changes after 12 Months of Use of Metformin in Obese Insulin Resistant Children and Adolescents

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Background: Childhood obesity is one of the most prevalent and challenging health care concerns. In this context, insulin resistance (IR) is an important disorder with strong association

with metabolic (type 2 diabetes, hypercholesterolemia) and cardiovascular (hypertension, atherosclerosis) outcomes. Clinical trials have been showing Metformin as an effective drug on reducing the IR and BMI. However, there is little data on use of metformin in children. **Objective and hypotheses:** The aim of this study is to evaluate our experience on use of metformin in obese children and adolescents with IR, and determine the benefits in weight loss after 12 months of treatment. Other clinical and biochemical variables were described. **Method:** Retrospective study of 50 children and adolescents followed in the Pediatric Endocrinology Clinic ICR-FMUSP, due to obesity and IR, at baseline and after a year of use of metformin. Exclusion criteria: T2DM, Neurological disorders with or without mental impairments and use of other weight related medications. Clinical (age, gender, weight, height, waist circumference, BMI, pubertal stage) and biochemical (fasting glucose, insulin, lipid profile) data were analyzed. IR was measured by HOMA-IR. **Results:** Mean age 12.4 ± 2.2 (8–17 years), without gender predominance. At baseline and 12 months after metformin's introduction, statistical analyses of the studied variables were respectively: HOMA-IR: 4.7 ± 2.5, 3.56 ± 1.8 ($P = 0.005$); fasting insulin 23 ± 9.5, 17.3 ± 9.1 ($P < 0.001$); BMI score Z 3.2 ± 0.67, 2.9 ± 0.58 ($P < 0.001$). There was a statistical improvement in fasting glycemia ($P = 0.002$) and cholesterol ($P = 0.041$). There were no significant differences in outcomes between others variables. **Conclusion:** Metformin increased insulin sensitivity, and provided a statistically significant, but very modest reduction in BMI. This poor alteration in BMI makes our results arguable. Further researches are needed to prove if there is a substantial clinical benefit on using metformin in children and adolescents.

P1-P472

Risk factors for Atherosclerosis after Anticancer Treatment in Childhood: The Assessment of Lipid Parameters and Indicators of Susceptibility to Atherosclerosis in a Group of Pediatric Patients after Anticancer Treatment

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Introduction: Lipid disorders are a common complication of anticancer therapy. These disorders may be included in both the metabolic syndrome or also may be associated with increased risk of cardiovascular disease. The aim of our study is to evaluate lipid profile in children after anticancer treatment. **Materials and methods:** Study group consisted of 44 patients (aged 3.25–16 years) with solid tumors, at least one year after cessation of anticancer treatment. Group was compared with a control group (31 healthy children). Following parameters were evaluated: cholesterol SDS, triglycerides SDS, LDL-C SDS, HDL-C SDS, weight SDS, height SDS, BMI SDS. Statistical distances (τ-risk factors of dyslipidemia, $\tau = ([(E_i - O_i)^2] \times 100)/E_i$, wherein E_i = median of the control group; O_i = median in the study group) for lipids parameters between study group and the control group were calculated. Indicators of susceptibility to atherosclerosis were calculated. **Results:** Following abnormal lipid parameters were found: hypercholesterolemia in 45.46% elevated TG SDS in 25%, elevated LDL-C SDS in 20.45%, low HDL-C in 6.82% of cases. Patient in study group were at higher risk of lipid disorders (sum of $\tau = 150.98$) for cholesterol SDS ($\tau = 180.3$), LDL-C SDS ($\tau = 8.82$) and TG SDS ($\tau = 10.03$) than in control group. In children with cancer was observed lower risk of reduced HDL-C SDS ($\tau = -48.17$), compared to healthy children. Elevated values of susceptibility to atherosclerosis were found: for index Castelli in 11.36%, for ratio cholesterol C/HDL-C in 11.36%, for ratio LDL-C/HDL-C in 29.55% of children with cancer. Overweight or obesity were found in 30.24% of children with cancer. **Conclusions:** Children after anticancer treatment are exposed to disorders of lipid metabolism. The role of these disorders and their impact on health in adult life requires further study and long-term follow-up.

P1-P473

Inherited Duplication (X) (p11.4) Associated with Obesity, Autoaggressive Behaviour and Delayed Speech Development

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Background: Obesity is a major feature in several syndromes. In patients with early-onset severe obesity, 7% harbour a single locus mutation. **Objective and hypotheses:** We report a 3.11 year old male patient with early onset obesity (BMI 29.9 kg/m^2 $>>$ P97), ongoing excessive weight gain, autoaggressive behaviour, and delayed speech development. No growth retardation or further dysmorphic signs. Early postnatal feeding difficulties required tube feeding. Hyperphagia began at the age of 6 months resulting in excessive weight gain. Delayed speech development, currently babbling without specific words and autoaggressive behaviour occurred. Laboratory examination showed insulin resistance with elevated HOMA-index of 10.5. Prader-Willi-Syndrome was suspected. Non-consanguineous parents of Turkish origin, obesity of the father and the sister, otherwise unremarkable family history. **Method:** Molecular genetic testing for PWS was performed, subsequently an array CGH analysis. **Results:** Unremarkable Prader-Willi genetic results on chromosome 15. In the array CGH analysis, a duplication was found at Xp11.4. Within this region the *ATP6AP2*-gene is located. Point mutations in this gene are associated with X-linked mental retardation and obesity. A gene duplication of *ATP6AP2* has not been reported so far, however, we assume that this may cause of the patient's clinical symptoms. Genetic analysis of the mother has been performed demonstrating maternal X-linked inheritance. **Conclusion:** Early onset and rapidly progressive obesity in early childhood should raise the suspicion of a genetic/syndromic

origin, especially if there are further associated clinical symptoms such as developmental delay. Here, array CGH revealed a duplication of Xp11.4 in a patient with Prader-Willi-like phenotype which is suspected to be the cause the syndromic disease.

P1-P474

Switching Patients with Congenital Hyperinsulinism from Standard Octreotide to Long-Acting Release Octreotide Preserves Blood Glucose Control and Improves Quality of Life of Their Caregivers

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Background: Congenital hyperinsulinism (CHI; MIM #256450) is the most common cause of persistent hypoglycaemia in children. Recessive inactivating mutations in K_{ATP} channel subunits, encoded by *ABCC8 and KCNJ11* genes, are the most common cause of CHI. Mutations of these genes usually cause forms of CHI which in the vast majority of patients are unresponsive to first line medical treatment with diazoxide. Multiple daily standard octreotide injections combined with diet are second line treatment and may permit to avoid near-total pancreatectomy. Treatment with long acting release (LAR) octreotide has been reported as efficient and well tolerated in children affected by CHI. Nevertheless, experience in younger patients is yet poor. We here report two 2-year-old children affected by CHI who were switched from standard octreotide to LAR octreotide treatment. **Aim:** The objective was to evaluate the blood glucose control and the quality of life of the families before and after the therapy change. **Method:** Standard octreotide therapy was changed to LAR octreotide therapy in 3 months. Blood glucose control was assessed by premeal glucometer measurement and by 7-day continuous glucose monitoring before and after the therapy change. Parents self-reported Paediatric Quality of life was evaluated with a questionnaire before and after the change of therapy. **Results:** Blood glucose control did not show significant variations and hypoglycaemic episodes remained rare and isolated. No side effects were observed during a follow up of six months. QoL questionnaire, completed separately by patient's mother and father, revealed a clear improvement in psychosocial health with agreement between the parents. **Conclusions:** LAR octreotide therapy seems to be effective and safe also in young patients affected with CHI. Because LAR octreotide simplifies the medical care of children with CHI, it improves also the quality of life of their caregivers.

P1-P475

Reduction of Body Mass and Change in Body Composition of the Participants of the PoZdro! – Programme for Prevention of Diabetes and Civilisation Diseases by Medicover Foundation – Preliminary Results, after the First Year of Interventions

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Background: Lifestyle interventions are basic tool to treat obesity in the youth. They prevent from civilisation diseases. Globally, there are many programmes including regular meetings with dieticians, exercise specialists, and others. Results are promising, although there's no consensus regarding one model of recommended diet, exercise's intensity and frequency of interventions. **Objective and hypotheses:** Assessment of preliminary results of 'PoZdro!'. Analysis of factors affecting reduction of body mass and change in body composition in programme participants. **Method:** 870 adolescents with excessive body mass (BMI $\geq$90 pc), age 13.8$\pm$0.7 years, 388 (44.6%) girls, 482 (55.4%) boys were included in a two-year programme of lifestyle interventions. During the first year 6 interventions were realised, everyone included meeting with physician, dietician, exercise specialist, and psychologist, at six-week intervals at the beginning, and at three-month intervals in later period. Healthy diet, especially reduction of simple carbohydrates and regular exercises of moderate intensity were recommended. Laboratory tests (OGTT, HOMA-IR, lipid parameters, ALT) were performed at the beginning. Anthropometric parameters (height, mass, WHR, body composition) were evaluated during each intervention. **Results:** 870 participants started programme, 125 (14.4%) have already had six interventions. Significant decrease in BMI and WHR was observed at each visit. BMI fell down from 26.77$\pm$3.06 to 25.97$\pm$3.06 at six visit, and WHR from 0.96$\pm$2.49 to 0.87$\pm$0.07. Reduction of body fat percentage (BFM (%)) from 30.07$\pm$7.67 to 27.5$\pm$7.84 and absolute body fat mass (BFM (kg)) from 22.79$\pm$7.75 to 21$\pm$7.15, increase in absolute muscle mass (MM (kg)) from 49.9 to 52.16$\pm$8.71 were stated. Decrease in BMI centile (pcBMI) at the last visit was observed in 311 (49.9%) participants, no changes in 175 (28.1%), and increase in 137 (22%). Change in BMI correlated inversely with baseline pcBMI ($r=-0.102$, $P=0.011$) and baseline MM (kg) ($r=-0.116$, $P=0.004$). Change in BFM (%) was inversely correlated with the baseline BFM (%) ($r=-0.262$, $P<0.001$) and positively correlated with baseline MM (kg) ($r=0.081$, $P<0.001$). Change in MM (kg) correlated positively with baseline WHR ($r=0.120$, $P=0.003$) and BFM (%) ($r=0.156$, $P<0.001$). **Conclusion:** PoZdro! programme resulted in significant reduction of BMI and WHR and improvement in body composition. Participants with higher baseline BMI and MM (kg)

achieved greater decrease in BMI. Changes in body composition were greater in more obese adolescents.

P1-P476

Polysomnography in Obese Children with and without Prader-Willi

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Background: Several studies found a high prevalence of sleep disorders in PWS patients. It is assumed that Prader-Willi Syndrome (PWS) patients are at a high risk of sleep disordered breathing, such as obstructive sleep apnea (OSA), because of their childhood obesity, associated with muscle hypotonia, leading to upper airway collapse. **Objective and hypotheses:** We studied a group of PWS children (genetically confirmed, non-GH-treated) who performed complete sleep studies and compared to a group of non-PWS obese children (OC) matched for sex, age and BMI. **Method:** All patients underwent overnight polysomnography. Data are reported as medians (interquartile range), Manne–Whitney test was used for between-group. **Results:** We did not find a statistically significant difference in the prevalence of OSA between obese PWS and OC (58.8% vs 50%, $P=0.64$) (Table 1). **Conclusion:** There is a high prevalence of OSA in PWS children, but it's not higher than in simply obese pediatric patients. However, PWS patients were found to have distinctive polysomnographic features – the significantly shortened REM latency vs non-PWS children, suggesting possible dysregulation of sleep-wake cycle. Further research is necessary to clarify the mechanism of sleep related disorders in PWS.

P1-P477

Renal Involvement ın Obese Children and Adolescents

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Background and aim: Epidemiologic studies have been shown that obesity increases the risk of renal disease and it impact on prognosis. In this study, we aimed to investigate both glomerular and tubular involvement in asymptomatic obese children and to investigate the association of metabolic-anthropometric parameters with renal parameters. **Material-method:** Children with BMI $\geq$95th percentile and diagnosed as primary obesity ($n=43$) were included to this study. Also, sex and age matched healthy control subjects ($n=43$) with BMI $<$85th percentile were also included. Anthropometric parameters of all subjects were evaluated, and blood creatinine and sistatin C, 24h urine microalbumin, protein, N-asetil-β-D glucoseaminidase (NAG), sodium and transphorming growth factor-beta (TGF-β) levels were measured. Glomerular filtration rate (GFR) was calculated according to Schwartz formula. Renal structure and volumes were calculated by ultrasonography. **Results:** Waist to hip ratio, both systolic and diastolic blood pressures, 24 h protein, microalbumin and sodium excretion and renal volumes were higher in obese children than control subjects ($P<0.05$). There was no difference between the groups for serum sistatin C and creatinine, GFR, 24 h TGF-β and NAG levels. There was positive correlation between BMI and systolic-diastolic blood pressure, GFR, microalbumin-sodium excretion and renal volumes in obese children. Beside, waist to hip ratio was positively correlated with systolic and diastolic blood pressure, 24 h microalbumin and sodium excretion in control subjects. **Conclusion:** Obesity seems to effect glomerular and tubular functions negatively.

P1-P478

BMI Correlates Positively with Hair Cortisol, whereas Excessive Body Fat Correlates Positively with Hair Cortisol: Salivary Cortisol and Fasting Insulin Concentrations in Prepubertal Girls

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Table 1. Polysomnography characteristics of PWS and non-PWS obese children (for abstract P1-P476)

	PWS ($n=23$)	**OC** ($n=8$)	***P***
Age (years)	9.9 [6.9÷13.9]	9.15 [6.85÷13.0]	$P=0.98$
Boys/girls	14/9	3/5	$P=0.4$
BMI SDS	3.16 [2.2÷ 4.53]	2.9 [2.79÷ 3.4]	$P=0.7$
Tonsillar hypertrophy	30.4% ($n=7$)	25% ($n=2$)	$P=0.73$
Adenoidal hypertrophy	52.1% ($n=12$)	62.5% ($n=5$)	P=0.36
REM latency (min)	81.75 [63.0÷143.25]	160.5 [125.75÷205.50]	$P=0.01$
Apnea-hypopnea index	3.5 [0.6÷9.2]	1.7 [0.3÷8.1]	$P=0.61$

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Background: Chronic stress and increased adiposity have been associated with each other in children. Further studies are needed, however, to evaluate both the directionality of this association and the mediating metabolic mechanisms. **Objective and hypotheses:** This study investigates the interrelations between BMI, body composition parameters, indices of the stress response, such as hair and salivary cortisol levels, and, metabolic mediators, such as insulin. **Method:** 26 obese prepubertal girls (BMI 24.7 ± 3.4 kg/m^2) and 24 normal weight prepubertal girls (BMI 16.9 ± 1.7 kg/m^2), aged 5-10 years, were studied. Anthropometrics were obtained, conducted alongside with body composition analysis using an advanced bioimpedance apparatus (BIA-ACC, Biotekna, Venice, Italy). Scalp hair samples from the posterior vertex were collected to measure hair cortisol concentrations. Cortisol was extracted overnight in methanol, followed by solid phase extraction. Quantification of cortisol was performed using a Waters Xevo TQ-S LC-MS/MS system. Five serial saliva samples over a weekend day (0830, 1200, 1500, 1800, 2100 h) were also collected for cortisol measurements. **Results:** Body fat mass as an absolute value in kg was positively associated with morning fasting insulin ($P<0.01$) and serial salivary cortisol excretion (computed as the area under the curve (AUC), $P<0.01$) while body fat mass (Kg) also correlated positively with hair cortisol ($P<0.05$). Skeletal muscle as a percentage (%) of total body mass was positively associated with morning fasting insulin ($P<0.01$) and serial salivary cortisol excretion (computed as the AUC, $P<0.01$) but not with hair cortisol. **Conclusion:** The positive correlations between total body fat mass and hair and salivary cortisol suggest that long-term activation of the hypothalamic–pituitary–adrenal axis is associated with excessive fat mass accumulation and elevated fasting insulin levels in prepubertal girls.

P1-P479

Hepatic Steatosis and Cardiovascular Risk in Overweight Children: Preliminary Results of the Study EFIGRO

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Introduction: The accumulation of fat in the liver is a serious complication of childhood obesity seems to be associated with cardiometabolic risk. **Objective:** To examine the association between fat accumulation in the liver and cardiovascular risk factors in overweight children. **Material and methods:** In the study 68 children/as (51.4% girls) were overweight or obese (defined according to the classification criteria of the International Federation of Obesity, IOTF) between 9 and 11 years they participated Vitoria-Gasteiz. liver fat (nuclear magnetic resonance), total and abdominal fat (dual absorptiometry X-rays), blood pressure and blood levels of fasting glucose, insulin, total cholesterol, HDL and LDL, triglycerides were measured, alanine transaminase (ALT), GGT (gamma-GT), aspartate transaminase (AST) and uric acid. **Results:** A total of 16 children/as (23.5%) had hepatic steatosis (>4.85% fat in the liver). No significant differences in body mass index, the percentage of obesity, and glucose levels, total cholesterol, HDL and LDL among children with and without hepatic steatosis were found. However, the

Table 1. Differences in body composition and cardiovascular risk factors in children aged 9–11 years overweight (>4.85% hepatic fat) without non-alcoholic fatty liver disease

	Control ($N=52$)	Hepatic Steatosis ($n=16$)	*P*
Age (years)	10.4 (1.0)	10.4 (0.9)	0.822
Girls (N, %)	28, 53.8	7, 43.8	0.480
BMI (kg/m^2)	25.3 (3.2)	26.7 (4.1)	0.252
Overweight/obesity/ obesity II	21, 27, 4	3, 10, 2	0.329
Fat mass (%)	39.7 (4.8)	42.5 (4.6)	**0.046**
Level of fat mass (kg/m^2)	10.1 (2.3)	11.3 (2.9)	0.089
Free of fat mass (kg)	30.5 (5.1)	32.2 (5.1)	0.270
Abdominal fat R1 (g)	1569 (607)	2087 (859)	**0.036**
Abdominal fat R2 (g)	2041 (793)	2653 (1030)	**0.041**
Abdominal fat R3 (g)	2545 (1038)	4422 (5026)	**0.014**
Hepatic fat (%)	2.9 (1.0)	10.4 (6.7)	**<0.001**
Systolic P (mm Hg)	96.5 (12.1)	103.1 (2.8)	**0.042**
Dyastolic P (mm Hg)	62.7 (5.8)	68.6 (9.0)	**0.003**
Glucose (mg/dl)	86 (5)	86 (6)	0.749
Insulin (μU/ml)	11 (3)	15 (5)	**0.033**
A.uric (mg/dl)	4.5 (0.7)	5.2 (1.1)	**0.030**
Colesterol total (mg/dl)	168 (29)	181 (32)	0.165
Colesterol-HDL (mg/dl)	51 (10)	50 (14)	0.712
Colesterol-LDL (mg/dl)	102 (25)	110 (27)	0.300
TAG (mg/dl)	74 (31)	104 (52)	**0.043**
ALT (U/l)	18 (6)	29 (16)	**0.024**
Gamma-GT (U/l)	16 (4)	22 (5)	**<0.001**
AST/ALT	1.342 (0.282)	0.950 (0.302)	**<0.001**

percentage of total abdominal fat ($P<0.05$), systolic blood pressure ($P=0.042$) and diastolic ($P=0.003$) insulin concentrations ($P<0.05$), triglycerides ($P=0.024$), uric acid ($P=0.030$), ALT ($P=0.024$) and gamma-GT ($P<0.001$) were significantly higher and the rate of AST/lower ALT ($P<0.001$) in children/as with hepatic steatosis. The percentage of fat liver showed significant associations with total fat ($\beta=0.24$, $P=0.048$) and abdominal ($\beta=0.26$; $P=0.025$) and plasma insulin levels ($\beta=0.24$; $P=0.041$) regardless of age and sex. **Conclusion:** Children with overweight and fatty liver disease are at increased cardiometabolic risk than having overweight or obese do not have an excessive accumulation of fat in the liver. The percentage of fat in the liver is associated with adiposity and total abdominal with insulin resistance.

P1-P480

Associations of Different Appetite Hormones with Physical Activity and Cardiorespiratory Fitness in Adolescent Boys with Different BMI Values

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Background: Higher physical activity (PA) attenuates the health risks of obesity and has positive effects on body weight reduction. The results of our recent longitudinal study showed that PA, especially vigorous PA (VPA), is an important factor for predicting overweight in boys during puberty (Lätt *et al.*, 2015). **Objective and hypotheses:** The aim of this study was to examine the associations of fasting serum acylated and des-acylated ghrelin, peptide YY (PYY) and leptin levels with PA and cardiorespiratory fitness (CReF) parameters in adolescent overweight (OWB) and normal weight (NWB) boys. **Method:** Fasting blood samples of 55 OWB (BMI >85th percentile) and 154 NWB (BMI <85th percentile) aged 12–16 years were collected to measure serum acylated and des-acyl ghrelin, PPY, leptin, testosterone, glycose, and insulin levels. Total PA was measured by 7-day accelerometry (counts/min) and CReF by direct measurement of peak oxygen consumption (VO_2 peak/kg). **Results:** No differences were seen in serum PYY, acylated or des-acylated ghrelin levels, while mean leptin (11.6 ± 10.6 vs 2.0 ± 2.7 ng/ml) and insulin (18.1 ± 8.7 vs 11.0 ± 6.2 mU/l) were significantly higher ($P<0.05$) in OWB compared to NWB. CReF was significantly lower in OWB compared to NWB (39.7 ± 8.7 vs 50.5 ± 6.8 ml/min per kg; $P<0.05$). Leptin was negatively correlated with CReF in both groups ($r=-0.43$; $P<0.05$) and des-acylated ghrelin with CReF only in OWB ($r=-0.36$; $P<0.05$). In OWB leptin was negatively correlated with total PA ($r=-0.32$; $P<0.05$) and positively with sedentary time of PA ($r=0.35$; $P<0.05$). In NWB 28.1% of the variability of CreF was determined by leptin and insulin resistance index (HOMA-IR) whereas in OWB 71.9% was determined by trunk FM and BMI. **Conclusion:** Serum leptin concentration is inversely associated with CReF in adolescent boys independently of their BMI value while serum des-acyl ghrelin may be involved to determine the CReF level in OWB. Low PA in OWB is associated with high serum leptin level.

P1-P481

The Relation of Glycaemic Variability Obtained by Continuous Subcutaneous Glucose Monitoring with IL-6 and Adiponectin Levels in Obese Children with Metabolic Syndrome and Insulin Resistance

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Background: Increased glycaemic variability (GV) (short-term fluctuations in blood glucose level) is associated with increased oxidative stress, vascular complications and mortality in diabetic and prediabetic patients. **Objective and hypotheses:** To investigate the relationship between GV and inflammatory markers in obese children with metabolic syndrome (MS) and insulin resistance (IR). **Method:** Fifty obese adolescents with insulin resistance were included in the study. Insulin resistance was diagnosed according to the results of oral glucose tolerance test (OGTT). All patients underwent anthropometric measurements, body fat analysis and subcutaneous continuous glucose monitoring (SCGM) for 24 h. Serum lipid, adiponectin and interleukin-6 (IL-6) levels were measured. Glycaemic variability coefficient (GVC) was calculated using the standard deviation and the average glucose value obtained by SCGM. MS was diagnosed according to the modified World Health Organization and the International Diabetes Federation criteria. **Results:** Twenty-seven of the patients had MS and the remaining had only IR. Body fat mass, HbA1c and peak insulin levels in the OGTT were significantly higher in patients with MS than the group without MS. IL-6 levels were significantly higher in the group with MS, but there was no difference in adiponectin levels. There was a significant positive correlation between GVC and HOMA-IR; fasting, peak and total insulin levels. When ROC analysis was used to determine the best sensitivity and specificity value for IL-6 and adiponectin in the diagnosis of MS, the best sensitive (70.4%) and specific (82.6%) value for IL-6 was 1.41 (pg/ml×2) but there were no significant expression of adiponectin values. **Conclusion:** This

study suggests that there may be a relationship between GV and insulin resistance parameters such as HOMA-IR, fasting insulin, peak and total insulin values in OGTT. IL-6 levels are higher in obese children with MS than without MS.

P1-P482

Changes in Urine and Plasma Metabolomics Profiles after a Lifestyle Intervention Program in Obese Prepubertal Children

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Background: Obesity is one of the major risk factor for metabolic and cardiovascular disorders, and its global prevalence has increased exponentially in the last decades. Excessive weight gained during early childhood increases long-term risk; however, reversing this condition during early-life reduces risk, improving children's quality of life. **Objective and hypotheses:** We hypothesized that a lifestyle intervention in obese prepubertal children would result in differential metabolic signatures, in parallel to improvements in BMI. Our aim was to determine the changes in the urine and plasma metabolomics profiles induced by the intervention program. **Method:** Longitudinal prospective study of obese (BMI > 2SDS) prepubertal children ages 7–10. The lifestyle intervention was primarily educational, focused on children and family for 6 months. Untargeted metabolomics was applied to analyze urine (nuclear magnetic resonance) and plasma (liquid chromatography-mass spectrometry) samples to obtain a comprehensive metabolic profile at baseline and after intervention from 35 subjects. **Results:** The intervention decreased BMI z-score (3.5 ± 0.1 vs 3.1 ± 0.1, $P < 0.001$), waist-circumference (83.4 ± 1.6 cm vs 81.6 ± 1.6 cm, $P < 0.0019$), and HbA1c levels ($5.35 \pm 0.03\%$ vs $5.22 \pm 0.03\%$, $P < 0.0004$) using two-tails paired student *t*-test. Urine metabolomics identified 33 metabolites. Trimethylamineoxide (TMAO) levels, were significantly lower after intervention (0.72 ± 0.19 vs 0.33 ± 0.07, $P = 0.019$). Plasma metabolomics identified 2566 features, and principal component analysis was applied to consolidate them into principal factors. Factor 1 differed between pre- and post-intervention ($P < 0.001$, significance was maintained after adjusting for multiple comparisons); factor 1 was characterized by lipid metabolites, including triacylglycerols, diacylglycerols and ceramides. **Conclusion:** A 6-month lifestyle intervention able to reduce BMI *z*-score changes the urine and plasma metabolome. In particular, the intervention reduced TMAO levels, a major cardiovascular risk factor, and a number of lipid metabolites, including proinflammatory signals. Together, these data suggest that the intervention improves the cardiovascular and metabolic risk profiles in prepubertal obese children.

P1-P483

The Effectiveness of a Stress Management Intervention Program in the 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. In addition to the increased consumption of calories and lack of exercise, accumulating evidence suggests that childhood obesity is strongly associated with prolonged and excessive activation of the stress system. **Objective and hypotheses:** The aim of our study was to assess the effectiveness of a stress management intervention program, which included progressive muscle relaxation, diaphragmatic breathing, guided imagery and cognitive restructuring, in overweight and obese children and adolescents. **Methods:** Forty-nine children and adolescents (mean age $\pm$ S.E.M.: 11.15 ± 1.48 years) were prospectively recruited to participate in this randomized controlled study. Of those, 23 participants were assigned in the intervention group, while 26 participants represented the control group. Anthropometric measurements were recorded at the beginning and at the end of the study, and participants were asked to complete the Screen for Child Anxiety Related Disorders (S.C.A.R.E.D.), the Child Depression Inventory (C.D.I.), the Child Behavior Checklist (C.B.C.L.) and the Youth Self Report (Y.S.R.). **Results:** The applied stress management methods resulted in a significant reduction in the body mass index (BMI) in the intervention group compared with the control group (ΔBMI = 1.18 vs 0.10 kg/m^2 ($P < 0.001$)). In addition to BMI, these methods ameliorated depression and anxiety, and reduced the internalizing and externalizing problems in the intervention group. **Conclusions:** Our study demonstrated that the application of an 8-week stress management intervention program could facilitate weight loss in Greek overweight and obese children and adolescents. Further studies with a larger sample size are required to evaluate the effectiveness of stress management methods in overweight and obese subjects.

P1-P484

Fetuin-A as an Alternative Marker for Insulin Resistance and Cardiovascular Risk in Prepubertal Children

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Background: Fetuin-A plays a role in insulin resistance and cardiovascular disease. **Objective and hypotheses:** The aim of present study was to determine the relation between fetuin-A levels and caridiometabolic risk factors and to investigate effect of serum fetuin-A to insulin sensitivity indices for determining whether fetuin-A is additional marker of insulin resistance in prepubertal children. **Method:** Ninety-nine prepubertal Korean children (59 males) with ages ranging from 6.0 to 10.0 years were included in this study. Subjects were divided into groups as normal-weighted and overweight/obese groups. Serum fetuin-A levels were measured using an enzyme-linked immunosorbent assay. **Results:** Serum fetuin-A concentrations were significantly elevated in overweight/obese children ($P=0.029$). Serum fetuin-A were significantly positively correlated with BMI SDS ($r=0.239$, $P=0.017$), TG ($r=0.285$, $P=0.004$), insulin ($r=0.377$, $P<0.001$), HOMA-IR ($r=0.365$, $P<0.001$), systolic blood pressure (BP) ($r=0.018$, $P=0.006$) and diastolic BP ($r=0.018$, $P=0.006$) and were significantly inversely correlated with HDL cholesterol ($r=-0.256$, $P=0.019$). When adjusted for age, sex, BMI and lipid profiles in multivariate linear regression analysis, fetuin-A was significantly positively associated with homeostasis model assessment of insulin resistance (HOMA-IR) ($P=0.048$), and was marginally inversely associated with QUICKI ($P=0.054$). **Conclusion:** Our results suggested that fetuin-A can be an alternative marker for insulin resistance and cardiovasucular risk in prepubertal children.

P1-P485

What are Early Predictors of Impaired Glucose Tolerance in Children Born SGA?

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Background: Subjects born small for gestational age (SGA) were shown to be at higher risk to later metabolic consequences but early prediction factors of changes in glucose metabolism are not clearly known. **Objective and hypotheses:** We aimed to investigate glucose tolerance and insulin resistance in adolescents born SGA or appropriate for gestational age (AGA) and their relationship with perinatal and postnatal factors. **Method:** A prospective cohort of 48 SGA and 98 AGA children was followed-up from birth to adolescence (75 boys, 71 girls). At the time of study subjects were 11–15 years old (mean 13.1 ± 1.4; SGA 12.3 ± 1.1; AGA 13.5 ± 1.4 years). 14.6% of SGA children did not show catch-up growth. Statistical analyses were adjusted for sex, age, pubertal stage and BMI SDS. **Results:** SGA children without catch-up had higher glucose concentration 30 min. after glucose load than those with catch-up growth or AGA (9.03 ± 0.61 vs 7.38 ± 0.23 ($P=0.01$); 7.2 ± 0.15 mmol/l ($P=0.005$), respectively). In both SGA groups 120 min. postload glycemia was higher than in AGA, but the difference was more pronounced between AGA and SGA without catch-up growth (AGA 5.81 ± 1.13; SGA with catch-up growth 6.37 ± 1.07 ($P=0.04$); SGA without catch-up growth 7.43 ± 2.01 mmol/l ($P=0.01$)). The differences in insulin levels and HOMA-IR were not significant between groups. Higher 120 min. glucose concentration was related with lower birth weight and length ($r=-0.222$, $P=0.008$; $r=-0.169$, $P=0.046$), birth weight and length SDS ($r=-0.283$, $P=0.001$; $r=-0.215$, $P=0.011$), birth BMI ($r=-0.199$, $P=0.018$) and faster prepubertal BMI growth rate ($r=0.267$, $P=0.012$). Fasting insulin and HOMA-IR correlated directly with height growth velocity during first month after birth ($r=0.252$, $P=0.018$; $r=0.237$, $P=0.027$), height and weight gain during first 6 years of life ($r=0.419$, $P=0.021$; $r=0.408$, $P=0.025$). **Conclusion:** Small size at birth, higher prepubertal BMI gain and absence of postnatal catch-up growth are related to higher posprandial glucose levels at puberty.

P1-P486

Multidisciplinary Intervention Programme in Childhood Obesity- Review of Service

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Background: A multidisciplinary team (MDT) intervention may improve severe obesity in children through education and life-style change. **Objective and hypotheses:** MDT intervention leads to improvements in clinical measures of obesity. **Method:** Participants were selected by criteria: <16 years old; BMI > 3.5SDS or BMI >2.5 SDS with obesity-related co-morbidity. Children and their families, attended intervention sessions over 10–13 weeks. Height, weight and resting heart rate (RHR) were measured at beginning (T1) and end of the intervention (T2). Participant records were examined for anthropometric measures at referral (T0) and the most recent (T3) date available. Scottish Index of Multiple Deprivation (SIMD) was used to assess socio-economic status of families. BMI SDS was calculated using UK 1990 data. **Results:** Of 174 children referred to the service, 32 fulfilled the criteria. F:M ratio was 24:8 and T1 median (range) age was 8.25 (2.0–15.42) years. 20/31 (64.5%) families came from the most deprived quintile and >80% came from the lower two quintiles, this was similar to those referred to the service but not suitable for the intervention. Median (range; n) BMI SDS was T0-3.67(2.5–5.3; 32), T1-3.58 (2.14–4.7; 18), T2-3.51(1.78–4.84; 18) and T3-3.62(3.3–4.3; 15). Although BMI SDS was not different at T2 ($P=0.7$) it had improved or remained stable in 16/18 (89%) while two participants increased BMI SD (0.18, 0.41), maternal

BMI also improved in 6/10. The rate of change in BMI SDS improved in patients completing the programme compared to the interval preceding the programme from −0.16 to −0.31 although not significant ($P=0.13$). Comparing the programme completors to non-completors there was no significant difference in change in BMI SDS from the start of the programme to T3 ($P=0.8$). However median (range) RHR changed significantly from 115(90–148) to 91(72–152) over the same period ($P=0.01$). **Conclusion:** Deprived areas seem to be at greatest need of childhood obesity management and MDT interventions have a role. Short term programmes may not reduce BMI SDS, but improvements in RHR suggest improvements in cardiovascular risk.

P1-P487

Hypercholesterolemia in Childhood: How the Response to Diet could Lead to Diagnosis. Lesson from a Case-Report

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Background: Sitosterolemia is a rare autosomal recessive disorder characterized by intestinal hyperabsorption and decreased biliary excretion of dietary plant sterol, due to mutations in adenosine-triphosphate (ATP)-binding-cassette (ABC) transporter family (ABCG8 and ABCG5). **Case report:** A 7.86 years old boy was referred to the Childhood Lipid Clinic due to incidental finding of hypercholesterolemia: total cholesterol 524 mg/dl (13.54 mmol/l), LDL-cholesterol 412 mg/dl (10.65 mmol/l), HDL-cholesterol 52 mg/dl, triglycerides 55 mg/dl, ApolipoproteinA 104 mg/dl and ApoB100 253 mg/dl. Parents were unrelated. Family history was positive for obesity and hypertension. Only his father presented a mild hypercholesterolemia (total cholesterol 242 mg/dl). Anthropometric parameters were: height-SDS −2.02 and BMI-SDS −1.40. He was prepubertal and no xanthoma and/or xanthelasma, arcus corneae or splenomegaly were detected. Apolipoprotein E genotyping was E3/E3. Thyroid, liver and renal function results and echocardiography were normal. He was started on diet according to Therapeutic Lifestyle Changes (from National Cholesterol Education Program ATP III). First genetic analysis did not detected mutations on ARH and LDL-R genes. Meanwhile, his lipid profile showed an impressive improvement within 6 months of cholesterol-lowering diet: total cholesterol decreased to 203 mg/dl (5.25 mmol/l) (−39%) and LDL-cholesterol to 141 mg/dl (3.64 mmol/l) (−34%). Because of the degree and speed of his response to diet, sitosterolemia was suspected. Genetic analysis confirmed the presence of two non-sense mutation of ABCG8 gene (exon 3: c.320C>G, p.Ser107* and exon 7: c.1083 G>A, p.Trp361*) configuring our patient as a compound heterozygous. **Conclusion:** Sitosterolemia shares clinical and biochemical features with homozygous familial hypercholesterolemia. Nevertheless, it is impressively responsive to cholesterol-lowering diet. In our report, we demonstrate a rapid reduction of severe hypercholesterolemia in response to dietary restriction in a young patient leading to the diagnosis of this rare disease. Early identification and treatment may prevent premature atherosclerosis.

P1-P488

Glucose Metabolism In Children with Prader-Willi Syndrome: The Effect Of Gh Therapy

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Background: Numerous studies have shown that PWS patients demonstrate the preservation of insulin sensitivity despite severe obesity. Data about insulin secretion in PWS however, are still conflicting. Other reports showed that PWS subjects and simple obese controls had similar insulin levels and were both insulin resistant. These discrepancies could be due to the different clinical characteristics of the study groups, including age, weight excess levels and the presence/absence of GH therapy. **Objective and hypotheses:** In this study we compared measures of insulin secretion and glucose levels in PWS children with those in BMI-, gender- and age-matched obese controls (OC), highlighting the influence of GH therapy on glucose metabolism. **Method:** Three groups of children were studied: i) 12 PWS (eight males, median age 12.9 years and BMI-SDS: 3.37) on treatment with GH (PWS-GHT); ii) 8 PWS (two males, median age 13.1 years and BMI-SDS: 3.25) without GH therapy (PWS-noGHT); iii) 40 OC (21 males, median age 13.1 years and BMI-SDS: 3.7). All subjects underwent a standard OGTT, and the following parameters were evaluated: ISI, QUICKI, HOMA-IR, insulinogenic index (InsIn), and the area under the curve of insulin (In) and glucose (G). Diagnosis of altered glucose metabolism was defined according to the ADA criteria (2016). **Results:** Impaired glucose tolerance was detected in 1 PWS-GHT (7%), 2 PWS-noGHT (25%) and 6 OC (15%). The more relevant findings are reported in the Table 1. **Conclusion:** Our data support the relative hypoinsulinemia and greater insulin sensitivity in obese children with PWS compared to OC. To be noted, GHT does not seem to negatively affect glucose and insulin homeostasis in PWS subjects.

Table 1.

	G 0'	In 120'	ISI	InsIn
PWS-GHT	76.7±7.9*	64.6±30.8+	3.81±2.37	2.1±0.91
PWS-noGHT	73.2±8.5*	75.0±45.4	6.05±5.44§	1.17±0.83°
OC	82.1±6.9	141.9±90.8	2.63±2.60	2.63±1.43

*p<0.05 vs OC; +p<0.02 vs OC; § p<0.03 vs OC; °p<0.02 vs OC

P1-P489

Impact of a Group-based Treatment Program on Adipocytokines, Oxidative status, Inflammatory Cytokines, and Pulse Wave Velocity in Obese Children and Adolescents

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Background: The link between obesity and dysregulation of adipocytokines, inflammatory cytokines, and oxidative status has been found to underline the pathogenesis of obesity-related complications, such as cardiovascular disease and type 2 diabetes. **Objective and hypotheses:** The objectives were i) to evaluate the effect of a group-based lifestyle modification program on adipocytokines, inflammatory cytokines, oxidative status, and brachial-ankle pulse wave velocity (ba-PWV) in obese youths and ii) to determine the relationship between changes in obesity, insulin resistance, cytokines, oxidative status, and ba-PWV. The hypothesis was weight reduction would result in improvement of adipocytokines, inflammatory cytokines, oxidative stress, and arterial stiffness. **Method:** The 1-year weight reduction program included 126 obese youths. The intervention involved initial hospitalization and five out-patient group-based sessions for instruction on healthy lifestyle living. Measurements included anthropometric data, blood tests, body composition, and ba-PWV pre-and post-intervention. **Results:** The study was completed by 115 participants. Percentage weight for height and percentage total fat decreased significantly (both $P<0.001$). High molecular weight (HMW) adiponectin increased ($P<0.001$), while leptin, interleukin 6 (IL-6), and high sensitivity C-reactive protein decreased significantly (all $P<0.001$). No significant change in oxidative status was detected. The ba-PWV decreased from baseline ($P<0.001$). Even participants without weight reduction had decreased levels of leptin ($P=0.021$), IL-6 ($P=0.019$), and ba-PWV ($P=0.031$). Change (Δ, before-after) in percentage weight for height was positively correlated with Δleptin ($r=0.624$, $P<0.001$) and Δhomeostasis model assessment of insulin resistance (HOMA-IR) ($r=0.230$, $P=0.021$). Change in HMW adiponectin was negatively correlated with Δpercentage total fat ($r=-0.289$, $P=0.003$). Changes in ba-PWV were positively correlated with Δplasma malondialdehyde ($r=0.233$, $P=0.036$) and ΔHOMA-IR ($r=0.253$, $P=0.025$). **Conclusion:** A group-based healthy lifestyle program for obese youths had beneficial effects on adipocytokines, inflammatory process, and arterial stiffness. Participants without change in weight status also benefited. These improvements may reduce the risk of obese youths developing obesity-related complications.

P2-P490

Matsuda Index in Correlation with Clinical Indicators of Insulin Resistance in Children and Adolescents

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Background: Obesity-related insulin resistance is present in obese children and Matsuda index is a method proposed to evaluate insulin resistance, using data obtained from the oral glucose tolerance test (OGTT). **Objective and hypotheses:** To investigate whether the clinical indicators of family history of obesity and/or Type II diabetes, acanthosis nigricans, and increased waist circumference are associated with insulin resistance, as calculated by the Matsuda index and if they could be used as selection markers for patients to undergo OGTT. Moreover, the correlation of insulin resistance with the coexistence of metabolic syndrome. **Methods:** Data from 95 overweight and obese children (47 boys and 48 girls) with mean age 10.7 ± 2.2 years were analyzed. Student's *t*-tests were used for the comparison of means and Pearson correlation coefficients were used to explore the association of two continuous variables. **Results:** Insulin resistance was found in 39.1% of the children. The mean MATSUDA index was 3.4 (S.D. = 1.9). The mean AUC for glucose was 14211.3 (S.D. = 2016.5) and for insulin 13484.2 (S.D. = 11985.3). Matsuda index was significantly lower in cases with acanthosis nigricans ($P=0.007$), in those with metabolic syndrome and in puberty. Additionally, Matsuda index was significantly correlated with waist circumference ($r=-0.40$, $P=0.006$). The proportion of those with insulin resistance was similar in boys and girls and greater in puberty. AUC for insulin was significantly greater in cases with acanthosis nigricans ($P=0.007$) or metabolic syndrome ($P=0.006$). Waist circumference was also predictive for AUC for insulin ($r=0.30$, $P=0.044$). **Conclusion:** Family history of obesity and diabetes, acanthosis nigricans and increased waist circumference are associated with insulin resistance and can be used as clinical markers to indicate that a patient should undergo OGTT. In addition, increased insulin sensitivity is associated with better metabolic profile as reflected by lower levels of triglycerides, LDL and higher HDL.

P2-P491

Anthropometric, Biological and Imagistical Methods For Assessing the Cardiovascular Risk in Obese Children

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Background: Pediatric obesity has increased worldwide over the last decades, being diagnosed at ever-younger ages. **Objective and hypotheses:** Evaluation of clinical and biological parameters and changes that occur in children with obesity; metabolic syndrome (MetS) identification in the studied groups; identification, evaluation, analysis and correlation of the adipogenic factors with the carotid intima media thickness (CIMT). **Method:** A cross-sectional study was conducted over a period of 1 year (April 2014–April 2015). 68 obese patients with mean age 11.83 years were included, distributed as follows: 17 (25%) were aged between 5 and 9, 35 (51%) between 10–14 and 16 (24%) between 15 and 18. Blood pressure, lipids, glucose, leptin, adiponectin and high sensitive CRP were determined. Oral glucose tolerance test was performed in all children. Insulin resistance (IR) was assessed by HOMA. CIMT was measured in all patients. **Results:** MetS was present in 18 patients (26.14%), with a higher prevalence among the 15–18 age group (11.76% vs 22.85% vs.50%). A strong correlation between CIMT and other metabolic factors has been observed ($r=0.83$). Lower levels of adiponectin, higher levels of leptin, high sensitive CRP and CIMT values have been observed in the 15–18 age group. **Conclusion:** Metabolic risk increases with age. There is a correlation between CIMT and adiponectin, leptin, high sensitive- CRP. CIMT is a known marker for subclinical atherosclerosis, it is a cheap and noninvasive method. Extensive population studies are required to establish threshold values for CIMT in children.

P2-P492

Trends of Nutrition of Ukrainian Children from Kharkiv Region: Tendency to Overweight, Dehydration, Impaired Social Adaptation

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Background: Diabetes, acute cardiovascular events and lifelong psychological problems reflect the obesity burden. Nutrition is a key point in prophylaxis and management of overweight and there is important to know trends of nutrition to build interventional strategies. **Method:** There are 1021 healthy lean (LH) and 372 obese (OW) adolescents aged 10–17 y.o. were survived with original questionnaire, which also included social and psychological (Beck-Youth) determinants of background. **Results:** Regular planned meals are present in 82% of lean vs. 59% of overweight. 12% LH and 64% OW skip their breakfasts and 18% and 43%, respectively, skip their lunch. At the same time total number of meals approximately the same ($P=0.006$) and they are shifted to the night. The interval between dinner and bedtime is $2.99+0.84$ hours in LH and $3.5+0.41$ h in OW ($P< 0.001$). At the same time 82% of children without group difference are prone to the snacks after dinner. And the interval between evening snacks (last meal) and bedtime statistically less in OW ($2.05+1.15$ h. vs. $1.25+0.57$ h, $P< 0.001$). Overweighs more prone to consume dairy (more than two times per day) than meat or fish, less prone to veggies (with exclusion potato) and prefer to consume fruits instead of meals as well as skipping breakfasts and lunches ($P<0.01$ for all). Average fluid consumption is 1.74 l in LH vs. 1.88 l in OW ($P=0.03$) with preferences to tea or coffee in 50.4%, juices or soda in 48.6%, water in 1% with no difference in groups. Irregular meals revealed association with anxiety level ($r=0.53$) and low self-esteem ($r=-0.67$). It was established that just 19.5% of children were able to impact the choice of meal and only 8.51% of parents are prone to support their children with healthy eating. **Conclusion:** Style of nutrition of modern population of Eastern Ukrainian children reflects a tendency to overweight and dehydration due to imbalanced diet, not planned meals and insufficient support of healthy eating by parents. On addition to this, there is a tendency to impaired social adaptation due to hyperdominant parental behaviour. So, social strategies together with family oriented psychological interventions are necessary for the healthy lifestyle promotion at the population level to prevent risks and improve social adaptation.

P2-P493

Melanocortin-4 Receptor Gene Mutations in a Group of Turkish Obese Children and Adolescents

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Background: Melanocortin-4 receptor (MC4R) mutations are the most common known cause of monogenic obesity but there is no data for Turkish children. **Objective:** To determine the prevalence of *MC4R* mutations in a group of Turkish morbid obese children and adolescents. **Method:** *MC4R* gene was sequenced in 47 consecutive morbidly obese children and adolescents (28 girls and 19 boys, aged 1–18 years) who presented during a 1-year period. Inclusion criterion was a BMI $\geq$120 percent of the 95th percentile or ≥ 35 kg/m^2. Those with chronic diseases, Cushing syndrome, hypothyroidism, or suspected syndromes that could cause obesity were excluded. Onset of obesity was before the 10th year of life in all subjects. **Results:** Mean values of age of all patients was 13.2 ± 4.1 years, age at onset of obesity 5.1 ± 2.1 years, height SD score 1.21 ± 0.93, BMI 40.0 ± 8.8, BMI SD score 2.72 ± 0.37. One novel (c.870delG) and two

previously reported (c.496 G>A, c.346_347delAG) mutations have been found in four (8.5%) obese children and adolescents. The novel mutation (c.870delG) was predicted to be a disease-causing frame-shift mutation using *in silico* analyses. Fasting glucose and lipid levels of the patients with *MC4R* mutation were normal but insulin resistance was present in two of them. Six more individuals with MC4R mutation (one child, five adults) were detected following analyses of the family members of affected children. **Conclusion:** This study is the first to report the prevalence of Turkish children and adolescents with morbid obesity. *MC4R* gene mutations are frequently found in morbid obese Turkish children and adolescents as well.

P2-P494

Comparison between CDC (Centers for Disease Control and Prevention) and Italian Growth Charts in the Characterization of Pediatric Obesity

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Background: The use of international or local growth charts for the definition of pediatric obesity is still debated. Inappropriate reference standards may lead to under/over-estimation of the prevalence and consequently of the number of patients to be included in diagnostic work-up. **Objective and hypotheses:** To define the differences between patients considered obese according to either CDC or Italian growth charts. **Method:** A single-centre cohort of 177 children was studied: all children (mean age 12.85 ± 1.94 years) underwent clinical and anthropometric assessment by the same pediatric endocrinologist. BMI SDS were calculated by both CDC and local growth standards. Obese (>95th percentile) and overweight (>85th percentile) patients, according to local BMI SDS, underwent oral glucose tolerance test (OGTT), blood tests for metabolic and endocrine evaluation, and DEXA scan to define body composition. **Results:** According to the CDC growth charts, 84 out of 117 patients (71.8%) were considered obese (BMI ≥2 SDS); this percentage decreased to 62.4% (73/117 patients) when national BMI SDS were used. No significant differences in the distribution of patients according to sex (males: 58.3% in CDC growth charts vs 52.1% in local growth charts) and puberty (prepubertal: 20.2% vs 16.4%) were found. The comparison between patients considered obese only for CDC growth charts and patients considered obese for both growth charts showed that the first were younger ($P<0.001$) and had lower abdominal ($P<0.001$), waist ($P<0.001$) and wrist circumference ($P=0.002$), abdominal circumference/height ratio ($P<0.001$) and triglyceride concentrations ($P=0.032$), higher HDL cholesterol ($P=0.028$) and lower percentage of fat mass ($P=0.001$). **Conclusion:** Local growth charts showed lower BMI SDS than CDC growth charts. The use of CDC growth charts could result in an earlier identification of patients with anthropometric and radiological characteristic of obesity, before biochemical alterations can be detected.

P2-P495

The Cutoff Values of Indirect Indices for Measuring Insulin Resistance in Korean Children and Adolescents

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Background: With the use of insulin resistance (IR) as a cause of metabolic syndrome (MetS), it is possible to screen the risk group of childhood MetS. Indirect index of IR can be estimated thru homeostasis model assessment (HOMA) of IR. Another index of triglyceride and glucose (TyG) were evaluated and equally effective in some adult studies. However, we do not have consistent prevalence rate and percentile distribution of MOMA-IR and TyG index in children and adolescent population. **Objective and hypotheses:** To investigate the prevalence rate of MetS, the distribution of HOMA-IR and TyG index, and cutoff values of these indices to screen high risk group of MetS in Korean children and adolescents. **Method:** Data from 3313 Korean subjects (1756 male, 1556 female) were included from Korean National Health and Nutrition Examination Survey conducted during 2007–2010. With three different criteria of MetS, we calculated the prevalence rate of MetS. The cutoff values of indirect index of IR were obtained from the receiver-operation characteristic (ROC) curves. **Results:** The prevalence rate of MetS in male and female by three different criteria were 13.9% and 3.6%, 4.6% and 3.6%, and 1.4% and 1.6%, respectively. The cutoff values of HOMA-IR and TyG index were 2.94 and 8.41, 3.29 and 8.48, and 3.54 and 8.66, respectively. The cutoff values by three different criteria were equivalent to 50th–75th percentile, 75th percentile, and 75th–90th percentile of the distribution of HOMA-IR and TyG index in Korean children and adolescents, respectively. **Conclusion:** The prevalence rate of MetS and cutoff values of indirect indices of IR by three different criteria were ranged widely. Further studies need to be performed to validate these cutoff values of indirect indices of IR to screen high-risk group of MetS.

P2-P496

Intensive Exercise Intervention for Long-term Adolescent and Young Adult Survivors of Oncology-Related Cranial Insult: A Pilot Study

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Background: Survivors of childhood cancer are at increased risk of cardiovascular morbidity and mortality in later life. Although the brain is known to be involved in control of metabolic functions including appetite regulation and energy expenditure (1), little data are available relating to the risk of metabolic dysfunction secondary to cerebral injury. Several studies have attempted to investigate the impact of exercise on physical and psychosocial parameters in survivors of childhood cancer, however most involved exercise durations of less than 12 weeks. It is therefore unknown whether intensive, prolonged exercise intervention is safe and tolerable for young adults and adolescents with cerebral injury due to tumours or cancer therapy or if it is beneficial from a metabolic perspective. **Aim:** To expose 20 adolescent and young adult survivors of cerebral injury due to brain tumour or cancer therapy, to a supervised, tailored exercise program of 6 months duration in order to determine whether an intensive exercise regimen is safe and tolerable for this cohort. Further, to explore the impact on their metabolic profile and body composition. **Methods:** Adolescents and young adults aged 15–23 with a past history of brain tumours or cranial irradiation, were recruited from the Princess Margaret Hospital Oncology database. Baseline testing included auxology, body composition using DXA, oral glucose tolerance testing and lipid and hormone profiling. Subjects were re-tested after a non-intervention control period of six months and then commenced the intervention program. All tests were repeated upon completion of the intervention, which consisted of thrice weekly small-group, tailored supervised exercise sessions over a six month period. **Results:** Twenty out of 87 possible candidates were recruited from the PMH oncology database. All underwent testing at baseline and after the 6 month control period. Two dropped out prior to commencement of the intervention program, three decided to pursue a home-based program and three pulled out of the intervention early on due to other commitments. No significant variation occurred in body composition, BMI, lipid profile, insulin or glucose levels during the control period ($n=20$). Twelve participants completed the intervention phase; nine participated in more than 20 exercise sessions and three participated in more than 40 sessions. No difference ($P>0.05$) was seen in their BMI or metabolic profile after the intervention regardless of the extent of their compliance, however improvement in body composition was noted: total fat percentage decreased from 36.2% to 34.5% ($P=0.024$) and trunk: total mass ratio dropped from 0.51 to 0.48 ($P=0.014$) indicating reduction in central adiposity. During the intervention, there was one fall. No other adverse events were identified. Of those who completed the intervention, 91% indicated that they enjoyed it and would consider participating in further tailored programmes. **Conclusion:** Small-group based exercise is acceptable, safe and enjoyable for young adult and adolescent survivors of childhood cancer. Although metabolic benefit was not evident in the small group who completed the intervention, body composition improved. Participant's enthusiasm for the program and desire to continue exercising, indicate that this form of intervention may be sustainable in the long term and requires further, larger scale investigation.

P2-P497

Cardiometabolic Effect of Sugar-Sweetened Beverages Reduction in Obese Children

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Background: The excessive consumption of sucrose, primarily used in sweetened beverages, has been considered an important inducer of cardiometabolic diseases. Besides the association between metabolic syndrome and fructose found in animal models, literature is lacking prospective studies in humans, especially in paediatric ages. **Objective and hypotheses:** We assessed the effect of sugar-sweetened beverages reduction on markers of metabolic syndrome in obese children. **Method:** This was a prospective analysis of the first 200 pre-pubertal patients admitted to our hospital-based obesity clinic, during 2015 (mean BMI z-score 3.41 ± 0.54). To access dietary intake, children were asked to make a three 24 h-recall weekly. Sugar-added beverages were quantified as number of servings, and sucrose intake was calculated. During the first 4 weeks, patients had their usual diet. For the next 24 weeks, they were asked to restrict sugar-added beverages to one serving a week, keeping everything else as previously. **Results:** At baseline, mean daily sucrose intake was 219 ± 62 g, of which 144 ± 14 g (about 66%) from sugar-sweetened beverages; mean systolic and diastolic BP z-scores were 1.8 ± 0.6 and 1.7 ± 0.4 respectively; median HOMA-IR was 3.57 (1.34–6.43); mean uric acid was 4.1 ± 1.9 mg/dl; median triglycerides was 132 (72–201) mg/dl. After adjustment for potential confounders, the reduction of beverages to one serving a week was associated to a decrease of: 0.5 (95% CI, 0.3–0.7) and 0.4 (95% CI, 0.2–0.6) in systolic and diastolic BP z-scores correspondingly; 1.7 mg/dl (95% CI, 1.0–2.2) in uric acid; 44 mg/dl (95% CI, 21–55) in triglycerides; 19 mg/dl in apolipoprotein B (95% CI, 13–25); 41.9 μUI/ml (95% CI, 27.3–56.5) in insulin at 30′ of OGTT; 2.2 ng/ml (95% CI, 1.3–3.1) in leptin. No association was found for HOMA-IR. **Conclusion:** Our results provide additional evidence supporting a positive relationship between sugar-sweetened beverages reduction and the improvement of important markers of metabolic syndrome. Therefore, controlling its consumption by children is an efficient and urgent measure of public health worldwide.

P2-P498

A Comprehensive and Multidisciplinary Management Plan is Extremely Effective at Reducing the Prevalence 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. In Greece, more than 30–35% of children and adolescents are overweight or obese. **Objective and hypotheses:** To investigate the effectiveness of a comprehensive and personalized multidisciplinary management plan in reducing the prevalence of overweight and obesity in childhood and adolescence. **Methods:** One thousand two hundred and seventy children and adolescents (mean age $\pm$ S.E.M.: 10.06 $\pm$ 3.29 years; 573 males, 697 females; 608 prepubertal, 508 pubertal) 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 personalized advice on diet and exercise. Psychologic assessment and management was included when required. Endocrinologic and biochemical investigations were performed at the beginning and at the end of the study. The study was approved by the Committee on the Ethics of Human Research, and written informed consent was obtained by all parents. **Results:** At initial evaluation, 60.2% of subjects were obese, 28.4% overweight and 11.4% of normal BMI. A higher number of boys were obese compared with girls (68.5% vs. 53.3%, $P < 0.001$), while a higher number of girls were overweight (30.7% vs. 25.6%, $P < 0.001$). The onset of weight gain had been observed beyond the age of 5 years and was progressive throughout childhood and adolescence. Following one year of the multi-disciplinary management interventions, the prevalence of obesity was decreased by 30%, the prevalence of overweight was decreased by 35%, normal BMI increased by 8%, and the cardiometabolic indices improved substantially. **Conclusions:** A personalized multi-disciplinary management plan is extremely effective at reducing the prevalence of obesity in childhood and adolescence.

P2-P499

Multidisciplinary Care Management of Pediatric Obesity and Factors Associated with Better Outcomes

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Background: RePPOP Aquitaine (network of prevention and treatment of pediatric obesity in southwest France) has developed a multidisciplinary approach to treat childhood obesity based on multicomponent lifestyle interventions and family-based actions. **Objective and hypotheses:** This study assessed the impact of the care management proposed by RePPOP Aquitaine and investigated factors associated with better outcomes. **Method:** The impact of RePPOP care management was assessed by changes in BMI *Z*-score between baseline and the end of care management among 982 overweight or obese children. A multivariate analysis examined independently factors significantly associated with better outcomes at the end of care management. **Results:** At the end of care management, 75.5% of children had decreased their BMI *Z*-score. Initial characteristics significantly associated with better outcomes at multivariate analysis were: age at baseline (5–15 years old), practice in sports club, length of follow-up by RePPOP (>10 months), no parental obesity and having no academic difficulties. **Conclusion:** This study confirms that several social and individual factors affect the efficiency of pediatric obesity care management but highlights that multidisciplinary treatment has a significant positive effect on body weight and the importance of organizing care within the family and the health professional community.

P2-P500

Prevalence and Characteristics of Polycystic Ovary Syndrome in Obese Adolescents

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Background: Polycystic ovary syndrome (PCOS) in adolescence has a challenging diagnosis and therefore has raised intense discussions. Its prevalence in childbearing age women ranges from 5 to 10%. However, the prevalence in obese adolescents has not yet been reported. Besides, the relationship of PCOS with metabolic and cardiovascular disorders in this specific population has not been established. **Objective and hypotheses:** We aimed to assess the prevalence and characteristics of PCOS in a population of obese adolescents treated at a quaternary hospital. The hypotheses was that PCOS was frequent in obese adolescents. **Method:** We performed a cross-sectional study with 49 postmenarcheal obese adolescents with a mean age of 14.7 years. Anthropometric assessment and review of medical records were performed. Clinical and laboratory hyperandrogenism were quantified using Ferriman-Gallwey index and androgenic dosage, respectively. The ovarian morphology was evaluated by suprapubic ultrasound. All patients had their metabolic profiles evaluated. **Results:** The prevalence of PCOS in obese adolescents, according to the new guideline for PCOS in adolescence of the American Pediatric Endocrinology Society, was 18.4%. When assessed by the Rotterdam, the Androgen Excess and PCOS Society and the National Institute of Health criteria, the prevalence

of PCOS was 26.4, 22.4 and 20.4%, respectively. Menstrual irregularity was found in 65.3% of the patients. Clinical hyperandrogenism was observed in 16.3 and 18.4% had total testosterone concentrations above the normal range. Ultrasonography revealed that 18.4% had polycystic ovaries. Obese adolescents with PCOS had higher prevalence of metabolic syndrome. **Conclusion:** The prevalence of PCOS in obese adolescents is high compared to that observed in the literature.

P2-P501

Efficacy of the Treatment for Childhood Obesity in Specialist Care: Age Over 10 Years at Baseline and Acanthosis Nigricans Predict a Worse Outcome

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Background: Treatment of pediatric obesity is challenging and especially the long-term outcome has been modest in many previous studies. **Objective and hypotheses:** We wanted to evaluate the efficacy of obesity treatment in specialist care and to find out factors, which have a major impact on the outcome. **Methods:** A total of 654 children (302 girls) aged 2–18 years treated for obesity between 2005 and 2012 in three specialist clinics covering whole Eastern Finland were included. BMI-SDS based on the national growth references before the treatment, at baseline, and up to 3 years after baseline were recorded. The change in BMI-SDS and potential factors influencing the outcome (age and BMI-SDS at baseline, sex, presence of acanthosis nigricans (AN), psychiatric disturbances, parental obesity, motivation for treatment, and adherence to the protocol) were explored with mixed model analyses. **Results:** BMI-SDS increased during the year before the baseline (mean difference 0.13 (S.D. 0.14); $P<0.001$), and decreased from the baseline (at 0.5 year -0.07 (0.01); at 1 year -0.10 (0.01); at 2 years -0.09 (0.02), all $P<0.001$, and at 3 years -0.06 (0.02) $P=0.005$). The presence of AN or age >10 years at baseline attenuated the treatment outcome and the long-term outcome was negligible. Children aged <10 years and those without AN had a significant and long-lasting decrease in BMI-SDS (at 3 years -0.27 (0.04), $P<0.001$ and -0.14 (0.04), $P<0.001$, respectively). In addition, motivation for treatment, adherence to the protocol, and BMI-SDS at baseline affected the outcome, whereas sex, psychiatric disturbances, or parental obesity had no impact on it. **Conclusions:** Treatment of pediatric obesity is most effective when started at a younger age. The association of AN with a poor treatment outcome is a novel finding and suggests a link to insulin resistance. This warrants further studies.

P2-P502

Metabolic Syndrome in Prepubertal Obese Children: Inclusion of the Triglyceride/Hdl Ratio as an Alternative Diagnostic Criterion

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Background: Although a large number of publications show a high prevalence of Metabolic Syndrome (MS) during childhood, to date, there is no uniform definition for evaluating this condition in children and adolescents. In the pediatric population, there are difficulties for characterizing this condition and the various criteria used might lead to underdiagnosis. In recent years, the triglycerides/HDL (TG/HDL) ratio has been proposed as a new marker. **Objective and hypotheses:** To analyse the prevalence of MS using Cook's diagnostic criteria and to evaluate the inclusion of the TG/HDL ratio as an alternative criterion for MS characterization in obese prepubertal children. **Method:** 111 obese prepubertal children (BMI >95th percentile), aged 5–13 years (72 boys; 39 girls) were included. A TG/HDL $\geqq 2$ was considered abnormal. Insulin was measured for HOMA-IR calculation. **Results:** 16 (22.2%) boys and 16 (41.0%) girls met at least 3/5 Cook's criteria. The TG/HDL ratio was found to be abnormal in all these subjects. Of the remaining children, 28 boys and 11 girls met 2/5 Cook's criteria; 78.6% boys and 63.6% girls of these subjects showed elevated TG/HDL ratio, while the HOMA-IR was abnormal in only 46.7% boys and 25% girls of this subgroup. The inclusion of the TG/HDL parameter would increase the prevalence of MS to 52.8% and 59.0% in the obese boys and girls evaluated, respectively. **Conclusion:** In this study, using Cook's criteria, 29% of obese children had a diagnosis of MS; however, 35% (39 out 111) children included had only two components of MS. Based on our findings, we suggest including, as an alternative diagnostic criterion in the latter subgroup, the TG/HDL ratio for reducing underdiagnosis in MS in prepubertal patients of both genders. The lower detection of MS using classical criteria may underestimate cardiometabolic risk in children and delay the strengthening of preventive measures.

P2-P503

The relationship between Subclinical Hypothyroidism and Iodine Deficiency, Serum Leptin Levels and Metabolic Syndrome in Obese Children

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Background: Subclinical hypothyroidism (SH) has an incidence of 3.2–22.2% in obese children. The etiology of increased prevalence of SH is still unclear in obese individuals. **Objective and hypotheses:** To investigate the relation of SH with iodine deficiency, serum leptin levels and metabolic parameters in obese children and adolescents. **Method:** One hundred and fifty nine obese and 54 healthy children and adolescents were included in the study. Anthropometric measurements, biochemical and thyroid function tests were performed. Insulin resistance was diagnosed according to the results of oral glucose tolerance test (OGTT). Thyroid autoantibodies, leptin and urinary iodine levels were measured. Patients with a diagnosis of autoimmune thyroiditis were excluded from the study. Metabolic syndrome (MS) was diagnosed according to the modified World Health Organization and the International Diabetes Federation criteria. The iodine deficiency was defined with the urinary iodine levels <100 μg/l. **Results:** In the study group, MS was detected in 37 (24.2%), SH in 22 (14.4%) and iodine deficiency in 56 (36.6%) patients. In the control group none of the patients had SH, although 22 (40.7%) patients had iodine deficiency. Mean urinary iodine concentrations and iodine deficiency rates were not different between the groups. There were no significant difference between obese patients with or without SH for age, gender, BMI-SDS, body fat mass, HOMA-IR, urinary iodine levels, iodine deficiency rates and serum leptin levels. SH rates were similar in obese patients with or without IR. SH rate was significantly higher in obese patients with MS than those obese without MS. **Conclusion:** SH was detected in 14.4% of obese children and adolescents, but it was not associated with iodine deficiency or increased leptin levels. However, since SH rate was significantly higher in obese patients with MS than without MS, we suggest that SH may play a role in MS development or vice versa.

P2-P504

Analysis of Circulating miRNAs in Obese Children Born Small for Gestational Age

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Background: Children born small for gestational age (SGA) are at increased risk of coronary heart disease and type 2 diabetes in adulthood, due to reprogramming of endocrine and metabolic functions. Dysregulation of specific miRNAs in response to genetic and environmental factors contribute to aberrant gene expression patterns underlying metabolic dysfunction. **Objective and hypotheses:** We aimed to identify miRNAs associated with increased risk of obesity in SGA children. We hypothesized that circulating miRNA expression profiles vary according to differences in BMI and circulating miRNAs may reflect metabolic dysfunction. **Method:** We recruited 4 SGA obese children (BMI-SDS 2.41 ± 0.72, 11.96 ± 1.76 years) and 4 appropriate for gestational age (AGA) obese children (BMI SDS 2.38 ± 0.57, 13.61 ± 0.5 years), with their respective controls matched for sex and age. Small RNAs have been extracted by serum and sequenced by miSeq Illumina sequencer. miRNA-Seq data has been analyzed throughout a customized bioinformatics pipeline in order to detect and quantify miRNA profile in the groups analyzed. The results have been validated by RT-qPCR. **Results:** We identified four down regulated and ten up-regulated miRNAs in the group of obese SGA, among which four shared with AGA obese children, compared to AGA controls. Specific miRNAs, such as miR-486-3p, miR-122-5p, miR-16-5p, miR-532-5p, miR-425-5p and miR-16-2-3p appeared specifically correlated with the obesity in SGA children. We used mirTarBase (miRNA-target interactions database) to search experimentally validated mRNA targets. A functional analysis of these genes in DAVID database showed a significant statistical enrichment in 'regulation of cell proliferation' and 'regulation of metabolic process'. **Conclusion:** We identified new serum molecular biomarkers which may be useful for cardiometamolic risk prediction in SGA children.

P2-P505

Irisin and Abdominal Obesity in Preschool Age

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Background: Since its discovery in 2012 the 'browining' adipokine irisin is known to lead to increased thermogenesis and energy expenditure. Studies in children are scarce, with results similar to most studies in adults. **Objective and hypotheses:** To establish a link between total and abdominal fat mass, physical activity and irisin in preschool age. **Method:** Height, weight and waist circumference (WC) of 40 healthy pre-pubertal city children were measured at mean age of 5.31 ± 0.74 years. Normal weight, overweight and obesity were defined by BMI values compared to the age and sex specific CDC2000 reference, while abdominal obesity was defined as WC $>$ 90th percentile, according to own published reference. Blood for testing was taken after 12 h of overnight fasting. Children wore pedometers to measure physical activity (PA). A DXA scan was performed to determine and validate abdominal obesity. **Results:** With obesity were 17.5% of

the participants. Only 9.7% of all met the minimum recommendations for PA during week-days and 16.1% at weekends. Total fat mass (FM) by DXA correlated significantly with BMI and WC ($P<0.001$). The mean irisin level was 0.95 ± 2.39 μg/ml, withiout significant sex difference ($P=0.451$). Irisin serum levels correlated with total FM ($r=0.406$; $P=0.039$), without significant correlation with BMI or WC. Children with WC>90th percentile had significantly higher values of irisin ($P=0.025$). Irisin levels were also higher in children, covering minimum requirements for PA (at least 10 000 steps per day). When analyzing the factors with a potential influence on serum concentrations of irisin (age, sex, indicators of obesity, body composition, PA), only WC proves to have a positive significant effect ($\beta=1.333$; $P=0.025$). **Conclusion:** This study finds a significant association between total fat mass, abdominal fat, waist circumference and irisin in healthy children. Irisin is definitely an interesting biomarker for studing the interrelations between fat mass and muscle.

P2-P506
Long Term Outcomes after Hospital Based, Life-Style Weight Loss Intervention During Childhood

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Background: Weight loss interventions for obesity have shown variable short-term effects in adolescents and children, but data on longer-term benefits are sparse. **Aim:** To describe longer-term impact of lifestyle weight loss interventions in adolescent obesity. **Method:** Obese subjects previously underwent lifestyle weight loss interventions at a hospital-based clinic were invited to participate in metabolic re-assessment. Outcome measures included: blood pressure (BP), BMI-Z, lipid profile, alanine aminotransferase (ALT), fat% from bioimpedance and oral glucose tolerance tests (OGTT). Data were compared by Mann-Whitney *U* tests at 5% significance and reported in median (ranges). **Results:** 25 (M=10) subjects were recruited. Median age was 14.1 (9.5–17.6) years at the beginning of intervention and 18.2 (16.1–24.8) years at re-assessment. With lifestyle interventions, after 3.5 (1.4–14.1) years, 28% (7/25) had BMI-Z reduction of >0.25 from baseline (responders). Responders demonstrated significant reduction in BMI-Z (2.98 vs 3.36, $P=0.017$), total fat% (35.1 vs 46.2, $P=0.003$), systolic BP (115 vs 136 mmHg, $P=0.007$) and glucose area-under-the-curve from OGTT (11.7 vs 15.2, $P=008$) at re-assessment compared with baseline. Non-responders showed significant increases in total fat% (47.2 vs 40.2, $P=0.03$) and trunk fat % (44.9 vs 33.7, $P=0.03$). At re-assessment, responders compared with non-responders showed significant differences in BMI-Z changes (-0.4 vs 0.36, $P=0.034$), BMI-Z (2.98 vs 3.34, $P=0.034$), total fat% (35.1 vs 47.2, $P=0.001$), trunk fat % (34.2 vs 44.9, $P=0.005$), 120 min insulin from OGTT (16.3 vs 92.4 mU/l, $P=0.029$), ALT (26 vs 34 U/l, $P=0.041$), and better insulin sensitivity ($ISI_{comp:}$ 3.81 vs 1.73, $P=0.021$). There were no differences in diastolic BP or lipid profile. **Conclusion:** These data suggest that slightly >1/4 obese adolescents benefit in the longer term after lifestyle modification interventions with associated improvements in body composition and metabolic parameters in young adulthood. Whilst, by no means ubiquitous in effect, a simple intervention that improves the anthropometrics and metabolic health in the longer-term of one in four obese adolescents undergoing therapy is encouraging given the pandemic of adult obesity.

P2-P507
Implications of Insulin Resistance in Obese and Overweight Children: A Cohort Analysis

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Background: Rising trend of both type 2 diabetes and obesity observed in adult and pediatric Indian population. Imperative to evaluate insulin resistance among overweight and obese children. **Objective and hypotheses:** To examine insulin resistance and associated co-morbidities in overweight and obese children. **Method:** Hospital based Cross sectional study 50 overweight and obese 5–18 years (BMI ≥90th centile WHO Charts). Weight, height, waist circumference, BMI, clinical and biochemical evaluation of fasting plasma glucose (FPG) and insulin, 2 hour post glucose load plasma glucose (FPPG) and insulin and lipid profile measured. Homeostasis Model assessment index (HOMA-IR) calculated and uniform HOMA value >3.5 defining Insulin Resistance (IR) taken as cutoff. In view of wide variability in cut offs of HOMA used, a Receiver Operating coefficient (ROC) curve in study population, predicting occurrence of metabolic abnormalities and value of 2.91 obtained. **Results:** Of 50, 22(44%) prepubertal, 28 (56%) pubertal mean age, BMI and WC were 10.76 ± 2.48 years, 24.18 ± 3.12 kg/m^2 and 72.55 ± 9.12 cm. Fasting plasma glucose (FPG-82.7+7.2 mg/dl), post prandial plasma glucose (PPPG112.3+11.6 mg/dl), fasting insulin (15.95+4.83 uU/ml), normal limits and mean HOMA 3.29+1.19. Abdominal obesity, hypertension, dyslipidemia, insulin resistance, metabolic syndrome, fatty liver in 33(66%), 15(30%), 15(30%), 18(36%), 9(18%), 9(18%) respectively. Pubertal children had higher hypertension (39.3% vs 18.2% $P=0.03$) and metabolic syndrome (28.6% vs 4.5% $P=0.03$). 18/50 children of IR (HOMA>3.5) had higherWC (76.02+8.07 vs 70.6+9.21 $P=0.04$), FPG (86.6+7.1 vs 80.6+6.4 $P=0.00$), PPPG (117.3+13.4 vs 109.5+9.6 $P=0.02$), fastinginsulin (21.45+2.32 vs 12.86+2.57 $P=0.00$), postprandialinsulin (25.69+4.02 vs 17.30+3.76), HOMA (4.58+0.82 vs 2.56+0.59 $P=0.00$). Abdominal obesity, hypertension, dyslipidemia, metabolic

syndrome, acanthosis nigricans, fatty liver found in 16(88.8%), 8(44.4%), 9(50%), 7(38.8%), 3(16.6%), 9(50%). HOMA values correlated with total cholesterol ($r=0.28$), postprandial insulin ($r=0.79$), PPPG ($r=0.46$). At HOMA 2.91, 30(60%) Insulin resistant vs 20 non insulin resistant weight, BMI and systolic blood pressure of the insulin resistant subjects were significantly higher and 21(70%) were pubertal ($P=0.02$) with hypertension (12/30, 40%), dyslipidemia (12/30, 40%), and fatty liver (9/30, 30%) significantly higher. WC higher (74.52±9.44 vs 69.5±7.94 cm), FBS (85.1±6.2 vs 79.2±7.3), fasting insulin (19.11±3.44 vs 11.2±1.65 $P=0.00$), postprandialinsulin (23.58±4.56 vs 15.4±2.52), HOMA (4.03±0.05 vs 2.19±0.37 $P=0.00$) significant. **Conclusion:** Obese children showed metabolic derangements as early as 10years, Insulin resistance (HOMA>3.5) observed 18(36%), significantly more at pubertal mean age 12.54±1.65 and with associated comorbidities hypertension, dyslipidemia, fatty liver. In this cohort ROC of 2.91 predicted metabolic abnormalities with 30/50 (70%) being insulin resistant. Early evaluation of insulin resistance and metabolic derangements mandatory for sensitization and interventions.

P2-P508

Effects of Highly Mineralized Water on Weight and Metabolism – A Randomized Controlled Blinded Trial in a Pediatric Hospital Staff

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Background: The role of calcium in cardiovascular and metabolic risk is controversial. **Objective and hypotheses:** To examine the effect of highly mineralized natural water in lowering body weight, blood pressure, cholesterol and blood sugar and to assess health behaviour of the staff of a pediatric hospital. **Method:** Out of 650 pediatric hospital staff members, we examined 161 healthy subjects, aged 28–64 years, 77.5% women, two drop-outs, in a randomized, placebo-controlled blinded trial. After randomization, 77 drank 1.5 l of mineral water (Ca 519, Mg 117, Sulfate 1445 and $HCO3^-$ 278 mg/l) and 82 natural water (40, 5, 6.2 and 10 mg/l, resp.) during 3 weeks. Before and at the end, we assessed nutrition and activity by standardized questionnaires, weight, height, blood pressure, waist and hip circumference, hydration by bioimpedance as well as fasting morning serum calcium, sodium, total-, LDL-, HDL-cholesterol, triglycerides, glucose, creatinine and calcium/creatinine ratio in the 2nd morning spot urine. **Results:** BMI was 23.5±3.2 kg/m^2, 26% were overweight and 6.8% obese (Swiss average of 33 and 11%, resp.) and did not change significantly, same as blood pressure, triglycerides, serum and urinary calcium. Most importantly, glucose (4.95±0.6) decreased by 10%, as did waist circumference, creatinine, total (5.4±0.95; 5.1±0.95) and HDL-cholesterol (1.73±0.45;1.62±0.4), although less markedly. Water intake (initially 0.8±0.3 l), BIA-phase-angle and LDL-cholesterol increased slightly, but significantly. Physical activity of 4.0 h/week was above national recommendation (3.5 h). **Conclusion:** Pediatric staff participating in this RCT may be a particularly healthy role model population. While the higher mineral content of water did not induce significant changes during this study and the variations in cholesterol levels were unexpected, the decrease of waist circumference as well as of glucose levels points to favourable effects of drinking water. This is supported by epidemiological findings of higher type 2 diabetes prevalence in restricted fluid intake.

P2-P509

Which Marker is the Most Reliable One for the Detection of NAFLD in Outpatient Clinic?

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Background: Non-alcoholic fatty liver disease (NAFLD) has become a public health issue because its incidence increased threefold during the last 3 decades among children and adolescents. Although liver biopsy is the gold standard to determine NAFLD, its applicability is low in childhood. Thus, some noninvasive markers are being used more commonly. **Objective and hypotheses:** We aimed to find the most reliable marker to detect NAFLD in routine examination. **Method:** We included 367 obese children and adolescents with or without NAFLD in our study. We used BMI percentile to determine obese patients. Bloood glucose, insulin, liver enzymes, blood lipid profile, uric acid and thyroid hormone levels were analysed. Abdominal ultrasonography was performed in all patients by the same radiologist, and steatosis was graded. Homeostasis model of assesment was used to determine resistance to insulin. Patients were classified according to their steatosis findings as Group1 and Group 2. **Results:** A total of 367 patients were analysed. 198 patients were female and 169 were male. The mean age of the cases was 11.9±3.18 years (6.0–17.9), and their mean birthweight was 3,252±688 g (650–6000 g). Hepatosteatosis was detected in 41%. Grade 1 steatosis was present in 80% of subjects. Hyperinsulinism was found in 39% of patients. There was a significant difference between the two groups regarding the age, sex, BMI and finding of hyperinsulinemia ($P<0.05$). Uric acid, AST, ALT, HDL, TG, VLDL, insulin and Homa-IR were also different between the groups ($P<0.05$). Sex, BMI, HDL were found to be of higher predictive value. Being female was shown to increase the risk of having NAFLD 0.47 times. Besides, 1 unit increase in HDL and BMI increased the risk of NAFLD development 0.97 and 1.10 times, respectively. **Conclusion:** Male sex, low HDL and high BMI levels seem to be associated with hepatosteatosis, and these factors should be taken into consideration when evaluating patients in outpatient settings.

P2-P510

Nonalcoholic Fatty Liver Disease: Evolution after 1 year of Follow-Up with Different Therapies

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Background: Fatty liver disease is diagnosed increasingly in obese children, which pathophysiology remains unexplained. Risk factors as insulin resistance, evolution of steatosis and hypertriglyceridemia, should be taken into consideration in its development. **Objective and hypotheses:** To analyse the prevalence of hepatic steatosis identified by ultrasound, as well as features and anthropometric data in our population divided into 2 groups: with steatosis and without steatosis, to assess the risk factors. To determine the influence of those risk factors and assess the evolution of them, one year after diagnosis in patients divided into 2 groups(treated with diet and exercise vs treated with diet, exercise and metformin). **Method:** In this cross-sectional study, 190 children aged 5–14 with BMI >2 S.D. were evaluated from 1st January 2012 to 31st May 2015. Anthropometric data, family history, biochemical parameters as fasting glucose, fasting insulin, lipid profile, index (HOMA-IR) and liver profile were evaluated. Liver ultrasound was performed to grade the presence of hepatic steatosis. All patients underwent to OGTT. The identification of hepatic steatosis was evaluated after one year. Metformin was given to patients with the criteria: Age >11 years, HOMA >3.5 and/or index glucose: Insulin >0.6 at $120'$ in OGTT. Statistical analysis was performed by SPSS16.0 program. **Results:** In the cohort of 190 patients, 70 presented within hepatic steatosis. They were divided into two groups of treatment(30 treated with diet and exercise vs 40 treated with diet, exercise and metformin). The mean age was (12 ± 0.8 years vs 13.5 ± 0.9 years). The prevalence of steatosis, after one year was (7.5% vs 2.5%) $P<0.05$. Fating insulin (16 ± 3.5 mIU/ml vs 13 ± 3.8 mIU/ml) $P<0.05$ and triglycerides (98 ± 3.4 mg/dl vs 90 ± 2.8 mg/dl) $P<0.05$. There was no significant difference in the BMI, abdominal circumference, total cholesterol and the hepatic transaminases. **Conclusion:** In our study the prevalence of fatty liver is high, related with obesity and insulin resistance. Although weight loss contributes to reverse steatosis, patients treated with metformin get better results and evolution.

P2-P511

Lifestyle Survey of Doctors, Medical Residents and Medical Students in Latvia

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Background: According to World Health Organization, balanced diet and regular physical activity is the key to maintaining a healthy lifestyle. **Objective and hypotheses:** The aim of this study was to evaluate lifestyle habits of the healthcare personnel in Latvia. **Method:** Data about eating habits, physical activity, duration of sleep and other lifestyle factors were collected from medical students, medical residents and specialized doctors working in Latvia. **Results:** The study included 727 participants, 445 (61.2%) of them specialized doctors, 190 (26.1%) medical residents and 92 (12.7%) medical students. Only 72.1% doctors, 60.8% residents and 65.6% of students reported having balanced diet. Significant portion of respondent groups reported sleep <7 h (41.6%, 44.7% and 71.4% respectively). Only 3.9% doctors, 7.4% residents and 6.5% students observed the recommended frequency of moderate intensity physical activity of five times a week. The amount of respondents taking part in three times weekly high intensity physical activity was 10.1% of doctors, 14.2% residents and 15.2% students. BMI of doctors, residents and students was 25.90 ± 4.07, 22.74 ± 3.55, and 22.03 ± 3.48 respectively, the BMI of doctors being significantly higher than that of other groups ($P<0.001$). The prophylactic visit to their general practitioners was attended by 56.0% of doctors, 67.2% residents and 64.1% students. **Conclusion:** Medical personnel in Latvia often fail to maintain adequate diet, duration of sleep and physical activity. The study reported a tendency of Latvia's doctors to be overweight. The low prophylactic health examination attendance rates display lack of care about their own health in a significant proportion of the healthcare personnel in Latvia.

P2-P512

Weight Status in Children at 8 Years: A Prospective Cohort Study

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Background: Prevalence of childhood obesity represents a major public health concern, given the tracking of body weight from childhood to adult age and its health sequelae. **Objective:** To describe prevalence of overweight (OW) and obesity (OB) in children at 8 years and investigate the relationship with pre-pregnancy maternal weight and weight status at 4 years. **Methods:** 485 pregnant mothers recruited between 2004 and 2007 and 409 children from a population-based cohort study. Research protocol was approved by the Ethics Committee. We analysed maternal BMI, BMI at 4 and 8 years and prevalence of OW/OB according to IOTF. At 8 years, we also measured waist circumference and body composition (by electrical bioimpedance). **Results:** 319 (169 boys) were studied, aged (mean (S.D.)) 8.26 (0.28) years. Table 1 shows anthropometric characteristic for the total and by sex. 4.6% mothers were underweight (BMI less than 18.5 kg/m^2), 68.8% normal weight (BMI 18.5–24.9 kg/m^2), 18.7% had OW (BMI

25–29.9 kg/m^2) and 7.9% OB (BMI equal or more than 30 kg/m^2). 20.2% children had OW or OB at 4 years. At 8 years, one to three children had OW or OB. There is positive relation between pre-pregnancy BMI and BMI at 4 and 8 years (*P*-trend <0.001). **Conclusion:** High prevalence of overweight and obesity at 8 years were found, even more that at 4 years. There is a positive correlation between offspring's weight status and pre-pregnancy maternal weight. Childhood obesity prevention should be started from pregnancy and infancy.

Table 1.

		Boys *N* (%)	Girls *N* (%)	Total *N* (%)
BMI	Normal	118 (69.8)	97 (64.7)	215 (67.4)
	Overweight	37 (21.9)	38 (25.3)	75 (23.5)
	Obesity	14 (8.3)	15 (10.0)	29 (9.1)
Waist circumference	<P90	134 (79.3)	96 (64.0)	230 (72.1)
	>=P90	35 (20.7)	54 (36.0)	89 (27.9)
Waist circumference/ Height	Normal	44 (26.0)	28 (18.7)	72 (22.6)
	Overweight	77 (45.6)	58 (38.7)	135 (42.3)
	Obesity	48 (28.4)	64 (42.7)	112 (35.1)
% Body fat	<25%	105 (70.5)	90 (66.7)	195 (68.7)
	>=25%	44 (29.5)	45 (33.3)	89 (31.3)

P2-P513

Low Birth Weight is not Associated with Increased Risk of Metabolic Syndrome in Obese Children and Adolescents

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Background: Children born small for gestational age (SGA) are at risk for metabolic syndrome (MetS) as adults and show a higher prevalence of MetS components. **Objective and hypotheses:** To define the association between low birth weight and the presence of MetS in a cohort of obese Italian children and adolescents. **Method:** The presence of MetS was studied in a cohort of obese (BMI >90th centile) children and adolescents consisting of 281 subjects with birth weight >2500 g (130 F/151 M, mean age 12.8 ± 1.9, group 1) and 25 subjects with birth weight ≤2500 g (12F/13M, mean age 12.5 ± 1.9, group 2). 22 subjects were defined as SGA (8F/14M, mean age 12.8±2.4, group 3). MetS was defined according to IDF criteria. Chi-square test was used to establish the relationship between birth weight and MetS and odds ratios were calculated. **Results:** MetS was present in 41 subjects (14.6%) of group 1, in 4 subjects (16%) of group 2 and in four SGA patients (18.2%). No significant differences in MetS prevalence were found between groups. Compared to normal birth weight, neither a birth weight ≤ 2500 g (odds ratio 1.1; 95% CI: 0.3–3.4) nor SGA status (odds ratio 1.3; 95% CI: 0.4–4) were significantly associated with increased risk of MetS. **Conclusion:** Low birth weight is not associated with increased risk of MetS in obese children and adolescents. Therefore, routine evaluation of metabolic parameters is not justified in children and adolescents born SGA.

P2-P514

Prader Willi Syndrome in Brazil: 6 months Follow-up in a Reference Center

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Background: Prader–Willi syndrome (PWS) patients have been followed in our country in different ways but without a reference center. In January 2015, we started a PWS reference center in Sao Paulo University to promote a better care for patients and families and to support them with a multidisciplinary team, including pediatric endocrinologist, dietician, nurses, neurologist specialized in sleep disorders and otorhinolaringologist. **Method:** Forty-two patients, between 2 and 21 years old, were followed for 6 month in our PWS clinic. The following items were compared before and after 6 month of follow-up: i) BMI-SDS, ii) use of growth-hormone, iii) metabolic profile: LDL, triglycerides, glycated hemoglobin (HbA1c), fasting glucose and insulin levels and iv) polysomnography. All patients received orientation in diet (900 calories/day independent of weight), physical activity and behavior. **Results:** The mean age was 9.8±5.2DP. BMI-SDS at the first visit was 2.8±1.9DP and after 6 months 2.41±1.8DP. Metabolic profile showed that 21.6% patients had high LDL-c level (LDL-c> 130 mg/dl), 48.6% had low HDL-c level (<40 mg/dl), 18.6% had hypertriglyceridemia (>150 mg/dl), 23.5% had high A1c (≥5.8%) and 44.8% had insulin resistance. Only 12 patients used rhGH at the first visit and at the latest we had 29 (69%) patients on rhGH use. Thirteen patients were not in use of rhGH due to polysomnography alterations and need of surgery or CPAP. Polysomnography revealed that 47.8% patients had an apnoea-hypopnoea index >5 events/hour, 20.8% had O2 saturations under 92 and 56.5% had reduced sleep efficacy. **Conclusion:** Most of our patients lost weight with the correct approach in diet, behavior and physical activity. The use of rhGH was increased after the beginning of the clinic. Alterations in polysomnography were a major problem revealed in the follow-up and the correct approach of the multidisciplinary team is essential to support this disorder.

P2-P515

Early Blood Pressure Abnormalities Related to Cardiovascular Risk in Obese Children and Adolescents

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Background: Emerging data suggest that ambulatory blood pressure (BP) monitoring for 24 h may be efficient in the diagnosis of hypertension in adults, children and adolescents. Additionally, in adults, it may predict the existence of some early BP abnormalities related to cardiovascular risk: (a) elevated BP load (>25%) and (b) non-dipping (BP decrease in night-time <10%). **Objective and hypotheses:** To evaluate the presence of early BP abnormalities related to cardiovascular risk in obese children and adolescents. Contrast its prevalence with non-obese counterparts. **Method:** Case-control study of 41 obese boys/36 obese girls (BMI $\geq$ 30 kg/m^2 for age and sex according to IOTF, 2000); mean age 11.5 $\pm$ 2.1 S.D. It was selected a homogeneous control group (BMI from 18.5 to 25 kg/m^2; IOTF, 2000) matched by sex, age and Tanner stage. Patients were monitored for 24 h BP (WatchBP 03). Parameters calculated: (a) BP load = percentage of readings above the ambulatory BP 95th percentile (AHA 2014). Calculated for the entire 24-h day, daytime and night-time periods. Abnormal if >25%. (b) Nocturnal BP decrease = (daytime mean of BP- night-time mean of BP)/daytime mean of BP $\times$ 100. Abnormal if <10%. **Results:** The percentage of individuals who had an abnormal BP load was generally higher in obese. In the 24-h-systolic BP register this difference was significant: 22.1% of obese vs 6.5% of non-obese ($P<0.05$). The mean value of SBP dipping was significantly more acute in non-obese compared to obese: 12.1% vs 9.8% ($P<0.05$). Non-dipping was present in up to 54.5% of the obese in the systolic register compared to 35.1% of controls ($P<0.05$). **Conclusion:** The current study shows a high prevalence of early BP disturbances in obese children and adolescents. It would be interesting to extend the study; adding analytical markers related to cardiovascular risk and echocardiography evaluation.

P2-P516

4G Polymorphism of Plasminogen Activator Inhibitor-1 (PAI-1), PAI-1 Plasma Levels, and Lipid Profiles in Overweight/Obese Children and Adolescents

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Background: Studies have shown that *PAI-1 4G* polymorphism is related to increased plasma PAI-1 levels, obesity, dyslipidaemia and cardiovascular disease (CVD) in adults. Few studies have explored that relationship in overweight/obese (Ow/Ob) children/adolescents. **Objective and hypotheses:** We investigated the relation between plasma PAI-1 levels, PAI-1 4g polymorphisms and lipid profiles in Ow/Ob children/ adolescents - compared with healthy normal body mass index controls. **Method:** A total of 193 children/adolescents aged 2.2–17.4 years old (99 Ow/Ob, 93 controls) participated in the study. Anthropometry, BMI, PAI-1 plasma levels, fasting total cholesterol (TCh), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglycerides (Tg), apolipoproteins A and B (ApoA, ApoB) and lipoprotein (a) (Lp(a)) were measured. PCR-restriction fragment length polymorphism was performed for the 4G/4G, 4G/5G και 5G/5G PAI-1 polymorphisms in 89 Ow/Ob (89.9%) and 88 (94.6%) controls. IBM Statistics SPSS 20.0, $P<0.05$ were used. **Results:** Mean age (y) for Ow/Ob group was 10.1y (9.9 $\pm$ 2.8), for controls 10y (10 $\pm$ 2.1). TCh, ApoA, PAI-1 plasma levels were statistically significantly higher in controls ($P<0.007$ and $P<0.001$ respectively), as LDL-C and Lp(a) (non-significant). Tg were significantly higher in the Ow/Ob group ($P<0.001$). HDL-C and ApoB were significantly lower in the Ow/Ob group ($P<0.001$ and $P<0.026$ respectively). In controls: compared to Ow/Ob higher mean values PAI-1 were observed in relation to genotypes 4G/4G, 5G/5G and 4G/5G ($P=0.011$, 0.008 and >0.05 respectively), 4G/4G genotype and PAI-1 levels correlated negatively to BMI, TCh, LDL- C, and Lp(a), 4G/5G correlated positively with Apo(B). Genotype 5G/5G was commonest (38.6%, $P<0.05$). In the Ow/Ob group: 4G/4G genotype was more prevalent (40.4%, $P<0.05$) and correlated positively to BMI and Tg. **Conclusion:** Although, in conflict with previous studies, PAI-1 levels were higher in greek controls. 4G genotype was mostly noted in the Ow/Ob and associated with TCh and Tg, thus indicating a possible positive correlation with metabolic syndrome and CVD in that risk group. However, further studies are needed in children/adolescents.

P2-P517

Polycystic Ovarian Syndrome in a Population of Obese Adolescents

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Background: Polycystic ovarian syndrome (PCOS) is the most common endocrine disease among women of reproductive age with a prevalence of about 8% according to the Androgen Excess Society (AES) criteria. The pathophysiology of PCOS is not well understood and it is associated with a high prevalence of metabolic disorders. During puberty, irregular menses and acne are common, thus making the diagnosis of PCOS in adolescence challenging. **Objective and hypotheses:** To study the prevalence of PCOS among obese teenage girls referred to the Obesity Unit at CHUV Hospital and characterize the clinical, endocrine and metabolic profiles of these obese teens. **Method:** 1-year prospective observational study of obese girls (BMI > +2 SDS) from menarche or after age 15 in cases of primary amenorrhea. Exclusion criteria were hyperprolactinemia, hypothyroidism, pregnancy and every other cause of hyperandrogenemia. Endocrine and metabolic profiling and pelvic ultrasound were performed. **Results:** In total, 21 patients (11–17 years old) were included – none of whom had been previously diagnosed with PCOS. According to AES criteria (hyperandrogenism, oligomenorhea, PCO morphology on pelvic US) the 43% of this cohort presented with PCOS. By definition, total testosterone and androstenedione were significantly higher in the PCOS group. This group exhibited higher LH, (10.6 vs 5.3 mUI/l, $P=0.029$), inhibin B (108.3 vs 57.5 pg/ml, $P=0.023$) and AMH (35.16 vs 16.6 pM, $P=0.05$), and had higher total cholesterol levels (4.1 vs 3.6 mM, $P=0.05$). Yet no other differences in metabolic parameters. Interestingly, lumbar bone mineral density was significantly lower in PCOS teens. **Conclusion:** PCOS among obese adolescent is extremely frequent. Moreover, this prevalence is probably underestimated given the poor sensitivity of trans-abdominal ultrasound to detect PCO morphology in these teens. No significant differences were observed in terms of prediabetes/diabetes among these obese teens – potentially due to the limited sample size. Further imaging using pelvic MRI is ongoing and will enable a more precise diagnosis of PCO morphology.

P2-P518

Vitamin D Deficiency in Obese Children and the Relationship with Insulin Resistance and Metabolic Syndrome

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Background: Vitamin D is a pleiotropic hormone the deficiency of which is related with extraskeletal manifestations such as insulin resistance and cardiovascular risk disease. **Objective and hypotheses:** To investigate the levels of Vitamin D in a sample of children with obesity and to evaluate the relationship between carbohydrate metabolism and metabolic syndrome (MS). **Method:** In this prospective cross-sectional study, 189 children aged 5–14 years, with BMI > 2SD, were evaluated from 1 January 2012 to 31 May 2015. Anthropometric data used: weight, height, BMI, abdominal circumference and blood pressure. Serum 25-hydroxyvit D, was measured. For lipid metabolism, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglyceride levels were determined. For glucose metabolism, fasting plasma glucose levels and insulin were measured after 12 h of fasting performing an oral glucose tolerance test. Serum 25-hydroxyvit D levels were considered: appropriate values > 30 ng/dl, deficiency < 29 ng/dl and insufficiency levels < 20 ng/dl. Classification of MS was accordance with that of the International Diabetes Federation. A multiple regression analysis was performed. **Results:** A total of 189 patients were included (48% male; 33.4% prepubertal), with a mean age 11.1 years (CI 9.8–12.5). 36 patients presented within MS (21%). We found higher incidence of deficiency and insufficiency VitD levels in pubertal children than in prepubertal (25 and 48% vs. 10 and 26% respectively) $P<0.001$. Prepubertal children (50%) presented HOMA > 2.5 and pubertal children (73.4%) within HOMA > 3 was found ($P<0.05$). 78% of children with VitD insufficiency presented HOMA > 3 and only 22% had HOMA < 3 ($P=0.0001$). 15% of patients with at least three criteria of MS (36/169), had levels of 25-hydroxyvit D > 30 ng/dl. We found a negative correlation between HOMA and 25-hydroxyvit D among prepubertal and pubertal children ($P=0.01$). **Conclusion:** Our data support that serum 25-hydroxyvit D level may be inversely associated with insulin resistance. Also patients within MS criteria have significantly lower levels of 25-hydroxyvit D.

P2-P519

Dietary Habits of Children and Adolescents Attending an Out-Patient Clinic for the Prevention and Management of Overweight and Obesity in Greece

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Background: Obesity in childhood and adolescence represents a major health problem and its management requires a multidisciplinary approach. **Objective and hypotheses:** To assess the main eating habits of children and adolescents attending an Out-patient Clinic for the Prevention and Management of Overweight and Obesity in Greece, as recorded before implementing any intervention. **Method:** We studied 1005 children and adolescents [age range 1–18 years old, 45% boys, 55% girls, 52.4% prepubertal, 47,6% pubertal], who attend our Out-patient Clinic. According to their BMI, subjects were classified as obese, overweight or of normal BMI. On their first Clinic visit, patients and/or their parents completed the semi-quantitative food frequency questionnaire 'ToyBox', which records the frequency and the habitual amount of consumption of the main food groups, as well as the breakfast eating habits. The mean daily consumption of each food group was then estimated. **Results:** 12% of children and adolescents had normal BMI, 27% were overweight and 61% were obese. Overweight children consumed more sugary cereals ($P=0.038$), while obese children ate more meat products ($P=0.004$) and fries ($P=0.001$). Boys drank more soft drinks daily and ate more sugary cereals, white and brown bread, meat and cold cuts ($P<0.05$), while girls drank more milk ($P<0.001$). Consumption of soft drinks, chocolate and savory snacks increased with age ($P<0.05$), however, the opposite was observed for milk ($P=0.029$). Adolescents consumed more treats, sugary cereals, bread, meat and cold cuts ($P<0.05$). Finally, a statistically significant association was observed between the BMI of the child or adolescent and the BMI of their parents ($P<0.001$). **Conclusion:** The eating habits of children and adolescents attending our Out-patient Clinic for the Prevention and Management of Overweight and Obesity were associated with BMI, gender and age group. The expected effect of parental BMI on children's BMI is worth noting.

P2-P520

Preliminary Findings on Nutrition Care Competence in Health Care Professionals Using a Standardized Questionnaire NUTCOMP Korean Version

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Background: It is well known that obesity, diabetes or chronic disease are related with nutrition. However it has not been known whether health providers have concepts or competence about counseling of nutritional support in clinical practice basis. There is rare of information about differences among types of profession jobs. **Objective and hypotheses:** We investigated a survey with standardized questionnaire tool among different types of profession jobs doctors, nurses, dieticians with modified Korean version from original NUTCOMP (nutrition care competence) tool by Lauren Ball. Evaluation items to assess nutrition care competence are confidence in knowledge about nutrition and chronic disease, confidence in nutrition skills, confidence in communication and counselling about nutrition, attitudes towards nutrition care. **Results:** Total 67 participants, 36 doctors, 18 nurses and 13 dieticians were enrolled as pilot sample populations. For validation of Korean version questionnaire, linguistic validation and cultural validation by two bilingual experts were taken. Reliability of Korean version NUTCOMP was tested as Cronbach's coefficient ($\alpha=0.934$). Current job duration was 7.25 ± 6.42 (year, mean $\pm$ S.D.). Completion of a program that included some nutrition content was 49.3% ($n=33$) and no previous engagement in continuing education on the topic of nutrition was 68.7% ($n=46$). Agreement with need of further nutrition education was 53.7% ($n=36$) and strong agreement was 20.9% ($n=14$). Nutrition care competence between doctors, nurses and dieticians ($n=67$) about knowledge, skill, counselling & communication, attitude were significantly different except category of attitude. Doctors and nurses have less competence in three categories than dieticians ($P<0.001$). Factors influencing the nutrition care competence in health care providers were previous nutrition education ($\beta=0.272$, $P=0.018$) and continuing education on the topic of nutrition ($\beta=0.506$, $P<0.001$). **Conclusion:** The NUTCOMP Korean version is valid tool to assess nutrition care competence in the Korean health care providers and nutrition education experiences are important to affect confidence about nutrition care.

P2-P521

Construction of Remote Monitoring System of Children with Tall or Short Stature and Overweight or Poor Weight Gain from the Elementary School Health Checkup Data

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Background: A school nurse and a school physician do screening of short stature and overweight by height and weight measured in the school health examination. Furthermore, in the municipality, practitioners are doing medical examination to preventing for children's unhealthy lifestyle to applicants. However the pediatric endocrinologists of the ward sometimes examine the first visit patients with short stature, highly obese or type 2 diabete patients who have passed a few years from the onset. **Objective and hypotheses:** To reveal how many children who have the extent physique problems from height and weight data obtained from school health check of the ward there are. To build a regional cooperation system not to miss the patients who hospital

consultation from the onset becomes too late. **Method:** We analyzed the height and weight data which had been input to the academic affairs system and which were the total of 11 times in the school medical examination from September 2012 to April 2014. Sharing the results with the Medical Association, the Board of Education and school nurse, we talked about future challenges. **Results:** We were able to obtain the data of 10,022 children to sixth graders from fourth graders who belonged to the public elementary school of the ward. Height analysis subjects 9511 patients (94.9%), degree of obesity analysis subjects were 9837 patients (98.2%). 254 students with tall stature (Total 2.67%: 4th Grade 2.55%, 5th 2.79%, 6th 2.36%), 147 students with short stature (Total 1.55%: 1.27%, 1.58%, 1.59%), 740 obese students (Total 7.52%: 7.50%, 7.58%, 7.54%), 560 slimming students (Total 0.17%: 0.06%, 0.18%, 0.27%). According to '2014 School Health Survey' conducted by the Ministry of Education, Culture, Sports, Science and Technology, percentage of obesity trend students was 8.88% (8.14%, 9.07%, 9.44%), that of slimming trend students was 2.55% (1.92%, 2.68%. 3.05%). **Conclusion:** Unlike propotion of the tall stature, that of short stature was about 1.6% not follow a normal distribution. According to the school year it goes up, because the students that have problems in physique (poor weight gain, obesity, short stature) was observed tends to increase, there is a need for early intervention.

P2-P522

The Effect of Demographic and Lifestyle Factors on One-year BMI Increments in 776 Norwegian Children Aged 6–15 Years

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Background: There is limited information on the ability of demographic or lifestyle factors to predict short term changes in weight status during childhood. **Objective and hypotheses:** To study the effect of parental (educational level, BMI status and perception of child's weight status) and childhood factors (eating habits, sedentary behaviour and physical activity), on 1-year BMI increments by the use of BMI, BMI SDS and BMI SDS conditional gain. **Method:** With data from the Bergen Growth Study the relations between demographic and lifestyle factors and one-year BMI increments were explored. Each of the three BMI measures (changes in BMI and BMI SDS, and BMI conditional gain) was analysed separately as a dependent variable with linear regression models. Adjusted regression models were estimated for each BMI measure separately, including all the statistically significant variables from the unadjusted models. **Results:** In the unadjusted models, 1-year changes in BMI were correlated to maternal BMI, parental perception, irregular meals and screen time. Changes in BMI SDS were only correlated to irregular meals and screen time. Changes in BMI SDS conditional gain were correlated to maternal BMI, parental perception and irregular meals. In the fully adjusted model raw BMI increments were correlated to parental perception, irregular meals and screen time, BMI SDS increments to irregular meals and BMI SDS conditional gain to parental perception and irregular meals. **Conclusion:** Parental perception of child's weight status, irregular meals and screen time can predict higher 1-year BMI increments. BMI SDS conditional gain adjusts for regression towards the mean, and might therefore be the preferred measure.

P2-P523

Body Image Perception Changes in Obese and Lean Children

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Background: Body image (BI) is subjective picture of one's own physical appearance established both by self-observation and by noting the reactions of others. Different BI scales used for screening of the Binge Eating symptoms that strongly linked to obesity. **Objective and hypotheses:** We supposed to get differences in the own body image perception in overweight and lean children. **Method:** BI questionnaire (BIQ) and own body satisfaction scale (OBSS) were answered by 47 children with simple obesity (BMI SDS >2.0) (1st group) (f/m $=20/27$) and 30 children with normal weight (BMI SDS <1.0) (2nd group) (f/m $=16/14$). Children BMI were standardized according to national reference data. BIQ, OBSS, head, trunk and lower body satisfactions cores (HSS, TSS and LBSS) were used for estimate the BI construct. Statistical analysis were performed by means of SPSS 21.0 ($P<0.05$). **Results:** Girls were 15.2 (13.3–16.1) and 15.5 (15.0–16.9) years old in the 1st and 2nd groups, boys – 14.8 (13.0–16.1) and 16.1 (14.7–17.1) accordingly ($P>0.05$). BMI, waist circumference (WC) were higher in the 1st group irrespective of gender ($P=0.0001$). The most negative BI perception was in obese girls (22 points (16–25)) compare to lean ones (eight points (3.5–12.8)), $P=0.0001$, according to BIQ scale. Obese girls had disturbed whole body perception ($P=0.002$), trunk ($P=0.003$) and lower body satisfactions ($P=0.002$) according to OBSS, TSS and LBSS. These patterns of relationships were similar in obese boys with accent on changed trunk image perception. Correlations between BMI, BMI SDS and BIQ scores were stronger in girls ($r=0.6$ and $r=0.6$, $P=0.0001$) than in boys ($r=0.4$, $P=0.02$ and $r=0.4$, $P=0.03$). BMI and BMI SDS positively correlated with OBSS, TSS and LBSS scores ($r=0.5$, $r=0.5$, $P=0.004$, $r=0.5$, $P=0.003$ and $r=0.5$, $r=0.5$, $r=0.5$, $P=0.01$) in obese girls. Overweight boys had less strong correlations in the same parameters ($r=0.4$, $P<0.05$). Girls had positive correlations between WC, OBSS, TSS and LBSS scores($r=0.5$, $P=0.01$, $r=0.5$, $P=0.004$ and $r=0.5$, $P=0.01$) as opposed to boys ($P>0.05$). **Conclusion:** Negative perception of body image with dissatisfaction of whole body, trunk and lower body part increase in line with

BMI and waist circumference raise. Body image perception depends on gender and more negative in girls compare to boys.

P2-P524

Non-Alcoholic Hepatic Steatosis in Obese Children and the Relationship with Insulin Resistance

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Background: Hepatic steatosis is common in obese children. The pathophysiology remains unexplained but it is known that insulin resistance and hypertrilycerdemia are involved in its development. **Objective and hypotheses:** To analyse the prevalence of hepatic steatosis identified by ultrasound, as well as features and anthropometric data in our population divided into two groups: (with steatosis and without steatosis) to assess the risk factors. **Method:** In this cross-sectional study, 190 children aged 5–14 with BMI > 2SD were evaluated from 1st January 2012 to 31st May 2015. Anthropometric data, family history, biochemical parameters as fasting glucose, fasting insulin, lipid profile, index (HOMA-IR) uric acid and the presence of acanthosis nigricans were evaluated. Liver ultrasound was performed to divide into two groups. All patients underwent to OGTT. Statistical analysis was performed by SPSS13.0 program. **Results:** 190 patients (51% male and 49% female). We found (36.84% had steatosis vs 63.15% without steatosis). Subjects with hepatic steatosis had mean age (13 ± 1.7 years vs subjects without steatosis 10.4 ± 1.4 years) $P < 0.05$. The prevalence of family history of obesity in subjects with steatosis was higher (60% vs 44%) $P < 0.05$, as well as BMI (31.7 ± 2.2 vs 26.7 ± 1.3) $P < 0.05$, abdominal circumference (100 ± 8 cm vs 90 ± 15 cm) $P < 0.005$, fating insulin (17.5 ± 3.5 mIU/ml vs 14 ± 5.5 mIU/ml) $P < 0.05$, (HOMA-IR) (3.8 ± 1.5 vs 2.8 ± 1.1) $P < 0.05$, triglycerides (123.1 ± 6.4 mg/dl vs 74.4 ± 5.3 mg/dl) $P < 0.005$, GOT (40 ± 4.7 U/L vs 26 ± 2 U/L) $P < 0.005$ and GPT (49 ± 3.8 U/L vs 37 ± 1.5 U/L respectively) $P < 0.05$. High-density lipoprotein cholesterol was lower in subjects with steatosis compared to those without (39 ± 4 mg/dl vs 48.8 ± 3.8 mg/dl respectively) $P < 0.003$. There was no significant difference in total serum cholesterol. **Conclusion:** The prevalence of hepatic steatosis in our population is higher than other published reports. Our results show that hepatic steatosis is related with increased BMI, abdominal circumference, hypergtriglyceridemia and (HOMA-IR) Furthermore these parameters could be used to assess the risk of developing steatosis.

P2-P525

Prevalence of Melanocortin 4 Receptor Mutations in Turkish Obese Children

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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 analyzed in molecular genetic obesity research. MC4R dysfunction in humans causes hyperphagia, impaired satiety and obesity. **Objective and hypotheses:** To identify MC4R mutations prevelance in Turkish obese children and adolescents. **Method:** Ninenty three pediatric and adolescent patients aged between 1.3 and 15 years old with early onset obesity (45 female/48 male) were enrolled. Obesity was defined as a body mass index (BMI) standart deviation score (SDS) of +2.0 according to the Turkish Population. Children with genetic syndromes associated with obesity or mental retardation, or taking drugs that promote changes in eating behavior or weight were excluded. Coding region of the MC4R gene was sequenced by Illumina MiSeq Next Generation Sequencing System. **Results:** The mean age of the patients was 7.3 ± 3.7 years and mean BMI was SDS 3.7 ± 0.7SD. Seventy nine patients (85%) were prepubertal, and 14 patients (15%) were pubertal. We identified four different mutations in eight patients, giving a mutation detection rate of 8.6%. Of these, three were previously identified missense mutations p.N274S, p.S136F and p.V166I). One was a novel homozygous mutation p.I291SfsX10 (c.870delG) detected in a severely obese 2-year-old boy. 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. **Conclusion:** MC4R gene mutations is quite common in childhood obesity in Turkish population. Investigating the mutations in MC4R gene in patients with severe childhood-onset obesity is necessary.

P2-P526

Prevalence of Overweight and Obesity in Children and Adolescents in Izmir, Western Turkey

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Background: Although the highest prevelance rates of childhood obesity and overweihgt have been observed in developed countries, its prevelance is reported to be increasing in developing countries as well. Prevelance of obesity and overweight in different regions of Turkey ranges between 1.6–7.8 and 9.9–17.6 respectively. **Objective and hypotheses:** The purpose of this study was to investigate the prevelance of obesity and overweight among students between the ages of 5 and 20 in rural and urban areas of İzmir, Western Turkey. **Method:** This population-based cross-sectional study was conducted in 36 schools (12 primary, 12 secondary, and 12 high schools) in rural and urban areas of İzmir between September 2015–February 2016. A total of 2447 children and adolescents in 5–20 age range were involved in the study. BMI of the participants were compared using the BMI references for Turkish children and adolescents. **Results:** The mean age was 12.43 ± 3.32; 52.7% of the children

were female and 47.3% of them were male. It was identified that 16% of all children were obese and 12.1% were overweight. This findings revealed that the prevelances of overweight and obesity in children and adolescents were higher than a previously conducted study in İzmir (obesity 6.3%, overweight 9.9%). There was no statistically significant prevalence difference between age, gender, school level, rural and urban areas. The prevalence of obesity according to gender was 16.3% for girls and 15.8% for boys ($P>0.05$). There was significantly important difference between the prevelance of obesity and overweight among the families of obese and over weight children ($P<0.001$). **Conclusion:** Obesity and overweight are concerns for children and adolescents in both rural and urban areas. Having obese parent(s) appears to be a risk factor for obesity in childhood. Further studies investigating the etiopathology of the corresponding disorders in the region is being conducted.

P2-P527

Arbitrary Cutoffs Lead to Underestimation of Metabolic Abnormalities in Obese Children: The Value of Age- and Sex-adjusted Normative Values

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Background: Metabolic syndrome and insulin resistance are well recognized in adult obesity. Their criteria and prevalence and are still controversial in children. **Objective and hypotheses:** To evaluate the prevalence and natural history of clinical and biological parameters of the metabolic syndrome in a pediatric cohort of obese subjects. To identify metabolically healthy subjects and the persistence of this phenotype over time. **Method:** Prospective longitudinal, observational, single-center study on children monitored for overweight or obesity. Data collection was done yearly from 2007. Metabolic syndrome parameters were expressed in SDS for age and sex, using reference curves obtained from an independent representative healthy cohort of children in France, using the the same biological assays (Mellerio *et al*, Pediatrics 2012). Results are expressed as median (IQR). **Results:** 533 children and pre-teens were enrolled between 2007 and 2015. They ranged in age from 5 to 13 years at baseline (9.2, 8–10.2), had a BMI of +3.8 SDS (3.1–4.3). The results are shown on the table. Metabolic abnormalities were detected in 90% of children initially and during follow up, and only 10% could be considered metabolically healthy. **Conclusion:** The prevalence of metabolic abnormalities is higher than expected in obese children and early adolescents when appropriate reference values are used.

Table 1.

	Waist circumference	Fasting plasma glucose	Fasting plasma insulin	Triglycerides	HDL cholesterol
Median (IQR)	+2.8	+1.5	+0.7	+0.7	−0.7
% > +2 S.D.	85%	24%	11%	13%	11%

P2-P528

Breasts Diseases in Adolescent Girls With Obesity

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Background: Obesity is associated with increased risks of the disease of the reproductive organs (including breasts). Several studies mentioned correlation between obesity and increased risks for breast cancer. **Objective and hypotheses:** To study the frequency and peculiarities of breasts diseases in adolescent girls with obesity. **Method:** The study included 2369 adolescent girls (aged 11–19 years). Gils were subjected to the clinical examination, ultrasound examination of the breast. The nonparametric method of correlation analysis by Spirmen was studied. **Results:** The investigation shows that 145 (6%) girls had obesity with BMI 30–39 kg/m^2 and 37 (2%) patients had morbid obesity (BMI $\geq$ 40 kg/m^2). The macromastia was found in 19 (51%) adolescent girls with morbid obesity. The dysplasia of mammary glands (mastopathy) was diagnosed in all patients with macromastia. In half girls with obesity with BMI 30–39 kg/m^2 (rs = 0.45) and in all the girls with morbid obesity was diagnosed fibrous mammary dysplasia (rs = 1). **Conclusion:** This study has shown that breast disorders have been diagnosed in every second adolescent girls with obesity (BMI 30–39 kg/m^2) and all the girls with morbid obesity. The obesity in adolescents is indication for mammary observation.

P2-P529

Insulin Resistance Correlates to Cognitive Fatigue Dimensions in Non-diabetic Obese Children

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Background: Alterations in endocrine functions and low-grade systemic inflammation represent fundamental characteristics of obesity. These biological systems have been repeatedly

linked to fatigue symptoms. **Objective and hypotheses:** The aim of the study was to assess the relationship between fatigue symptoms and metabolic/inflammatory markers in a sample of non-diabetic obese children. **Method:** The study was conducted in 41 obese (median BMI-SDS 4.2 (25–75th percentiles: 3.6–5.1)) children, median aged 12 (9–15) years, recruited in a pediatric tertiary center. Three dimensions of fatigue were assessed using the Pediatic Quality of Life Inventory Multidimentional Fatigue Scale: general fatigue, sleep/rest, cognitive fatigue. Moreover, a principal component analysis extracted relevant additional symptom dimensions (concentration, energy, self-perceived cognitive efficiency, sleep/rest and motivation/anhedonia). **Results:** Cognitive fatigue dimension and reduced motivation/anhedonia dimension were both associated with BMI, independently of sex and age. Cognitive fatigue was correlated to insulin concentration and HOMA. Reduced motivation/anhedonia was correlated to insulin concentration, HOMA, uric acid and hs-CRP concentrations. The association with insulin concentration and HOMA persisted when BMI was taken into account. **Conclusion:** Among several fatigues dimensions, specific dimensions of cognitive fatigue and reduced motivation/anhedonia relate to insulin resistance in non-diabetic obese children.

P2-P530

Vascular Endothelial Growth Factor as The Predictor Microangiopathy in Obese and Diabetic Children

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Background: Vascular endothelial growth factor (VEGF) is a signal protein produced by cells that stimulates vasculogenesis and angiogenesis. It is part of the system that restores the oxygen supply to tissues when blood circulation is inadequate. Serum concentration of VEGF is high in bronchial asthma and diabetes mellitus. Overexpression of VEGF can cause vascular disease in the retina of the eye and other parts of the body. **Objective and hypotheses:** The aim of this study is comparison between circulating VEGF levels in children with diabetes type 1, obese and healthy children. **Method:** The study concerned 90 children with diabetes type 1, 60 children with obesity without diabetes and 60 healthy children. The blood has been taken fasten from peripheral vein. The VEGF was checked by ELISA in all children. **Results:** The VEGF mean levels were highest in children with obesity 356.55 pg/ml (S.D. 169.44 pg/ml). In children with DM1 mean VEGF was 254.88 pg/ml (S.D. 167.89 pg/ml). The lowest levels of VEGF was observed in group healthy children: mean 188.75 pg/ml (S.D. 144.88 pg/ml). We noticed statistic significant differences between group of diabetic and obese children and healthy children. The results were correlated with BMI. **Conclusion:** High levels in peripheral blood – marker of vasculogenesis VEGF is more connected with obesity then with diabetes type 1.

P2-P531

Associations of Serum 25-Hydroxyvitamin D and Components of the Metabolic Syndrome in an Egyptian Cohort

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Background: Vitamin D deficiency may be associated with increased risk of metabolic syndrome. **Objective and hypotheses:** We aimed to assess the relation between 25-hydroxyvitamin D (25(OH) D) with the different metabolic syndrome components in overweight and obese subjects. **Method:** Ninety eight subjects ($\geq$85th percentile for age and sex) recruited from the Diabetes, Endocrine & Metabolic Paediatrics Unit (DEMPU), Cairo University, were evaluated with blood pressures, anthropometric measurements, fasting measurements of serum lipid profile, insulin, blood glucose (FBS), 25(OH) D, calcium, phosphorous, and alkaline phosphatase. Homeostasis Model Assessment Method-Insulin Resistance (HOMA-IR) and Quantitative Insulin Sensitivity Check Index (QUICKI) were calculated. **Results:** Among 98 subjects, 29 (29.9%) were vitamin D insufficient, 64 (65.3%) were vitamin D deficient and only 5 (5.1%) had normal level of vitamin D. On correlating 25 (OH) D with metabolic and anthropometric variables, 25 (OH) D was inversely associated with both of FBS ($r=-0.343$, $P=0.001$) and weight standard deviation score (Wt SDS) ($r=-0.216$, $P=0.033$), while no correlations were detected between 25 (OH) D and each of BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), high density lipoproteins (HDL), triglycerides (TG), HOMA-IR and fasting insulin. Regression Multivariate Analysis was applied on 25 (OH) D after adjustment of age and sex, showing that Wt SDS, waist circumference (WC), hip circumference (HC), waist/hip ratio (W/H ratio), FBS, Fasting Insulin, HOMA-IR and QUICKI had significant relations with vitamin D ($P=0.038$, 0.025, 0.036, 0.015, 0.019, 0.007, 0.02 and 0.04, respectively). **Conclusion:** Hypovitaminosis D is prevalent in obese and overweight Egyptian subjects. Significant relationship between 25 (OH) D and each of Wt SDS, WC, HC, W/H ratio, FBS, Fasting Insulin, HOMA-IR and QUICKI were suggestive of possible adverse influences of vitamin D.

P2-P532

Retrospective Evaluation of the Efficiency of Metformin Therapy in Obese Children with Insulin Resistance

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Background: Prevalence of obesity has been rising throughout the world. Dyslipidemia, hypertension, insulin resistance, and type 2 diabetes mellitus (DMT2) (metabolic syndrome) are frequently observed serious complications of obesity. The primary approach in the treatment of metabolic syndrome is improving insulin resistance. Metformin is considered as an option for treatment in children with insulin resistance. During the last decade, numerous studies have been published demonstrating that metformin delays the risk of DMT2 in obese adolescents through overcoming insulin resistance. In this study, it was aimed to retrospectively evaluate the subjects who used metformin treatment due to insulin resistance and exogenous obesity in our clinic and assess the effects of metformin on anthropometric and metabolic variables. **Method:** The medical records of the 36 patients, who were started metformin therapy due to obesity and insulin resistance and were followed-up in Dokuz Eylül University Faculty of Medicine, Department of Pediatric Endocrinology between 2005 and 2015, were retrospectively evaluated. The anthropometric and metabolic variables of the obese individuals at the sixth month of treatment who received metformin were compared with basal values. **Results:** Statistically significant decrease was detected after 6 months of metformin treatment in weight SDS, BMI, and BMI SDS of individuals. A mean reduction of 2.41 ± 1.93 kg/m^2 in BMI values of study subjects was present ($P < 0.001$). Statistically significant reductions in post-treatment fasting insulin, fasting glucose/insulin ratio, HOMA-IR, and Quick were index values were found. **Conclusion:** Metformin is one of the treatment options in obese adolescents with insulin resistance. In our study, it was observed that improvement in anthropometric measurements and metabolic parameters was achieved without any serious side effects in who received metformin treatment.

P2-P533

Parental Obesity can Trigger Obesity in Children

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Background: Obesity is a disease (2) which is associated with increased morbidity and mortality rate (3) and needs extensive preventive procedures and effective interferences. Children with obese parent are in danger of becoming obese in their adolescence and adulthood even when trying to keep their weight stable. **Objective and hypotheses:** We aimed to investigate whether parental obesity can trigger obesity in children or not. **Method:** This is an analytic cross sectional study which was conducted on 12 years old students from different area in Rasht, north part of Iran. The checklist included demographic characteristics such as age, maternal age during childbirth, student and maternal height and weight, child rank. Data were analyzed by Pearson correlation analysis, paired *t*-test and ANOVA test and χ^2 in SPSS Software 19.0. A *P*-value less than 0.05 were considered statistically significant. **Results:** Results showed significant correlation between students' BMI and parental BMI and father weight. ($r = 0.304$, $P < 0.0001$) ($r = 0.257$, $P < 0.0001$) ($r = 0.249$, $P < 0.0001$) ($r = 0.166$, $P = 0.019$). Also, there was significant correlation between students weight with parental BMI and father weight and birth rank. **Conclusion:** This study shows that mother's and father's BMI and birth order are the factors that can predict children obesity and these variables could have major role in predicting 14.4% of high BMI cases. The role of family in changing nutritional habits of children must be considered, because through parental education and changing their perceptions we can prevent at least 14% of cases.

P2-P534

Value of BMI-SDS, Waist Circumference-SDS and Waist-to-Height Ratio in the Identification of Obese Children and Adolescents at an Increased Risk for Cardio-Metabolic Complications

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Background: Determination of obese children/adolescents at an increased risk of cardio-metabolic complications is of paramount significance for early intervention. **Objective and hypotheses:** To determine the value of simple anthropometric measures of obesity (BMI-SDS, waist circumference (WC)-SDS, waist-to-height ratio (WHR)) in the determination of individuals at an increased risk for selected cardio-metabolic complications (impaired glucose metabolism, dyslipidemia, increased blood pressure). **Method:** 395 obese children and adolescents (212 females; age mean(SD) 12.4(3), BMI-SDS 2.8(.6), WC-SDS 3.2(.6), WHR .61(.06)) were studied. Body weight, height, WC and blood pressure were measured by a trained medical professional in the morning in a fasting state and were standardized according to the UK-WHO references. A standard 2-h OGTT was performed in all. HOMA-IR and Matsuda index were calculated. Spearman's correlation was used to determine associations between parameters. Regression analysis with stepwise selection of parameters was used to calculate prediction models for selected cardio-metabolic complications. **Results:** Several significant correlations between BMI-SDS, WC-SDS, WHR and selected cardio-metabolic complications were determined (Table 1). Correlations were not determined for total cholesterol, LDL and A1c . However, using regression analysis we determined that analyzed anthropometric measures of obesity alone describe only a small proportion in the variability of HOMA-IR (20%), HDL (6.2%), Tg (8%), SP (10%),

DP (8%). WHR had the highest impact in regression analysis models except for HDL (BMI-SDS). **Conclusion:** Several significant correlations between simple anthropometric measures of obesity and selected cardio-metabolic complications were determined. These measures however seem to have only a limited value in the prediction models for selected cardio-metabolic complications, WHR having the highest impact.

P2-P535

Thyroid Dysfunction and Formation of Dyslipoproteiniaemias: Gender Differences in Children with Obesity

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Background: Thyroid dysfunction plays an important role in formation of dyslipidemia during obesity while thyroid pathology (TP) is one of the most common endocrinopathies associated with obesity. Among adults existence of gender differences has been proven in formation of a dyslipoproteiniaemias and thyropathies; the presence of such changes in obese children requires clarification. **Objective and hypotheses:** To explore the details of blood lipids in children with obesity depending on the functional state of the thyroid and sex. **Method:** In 187 children with obesity, age 6–18 years (105 boys, 82 girls) the following blood lipids indicators were studied – total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides (TG). Data were analyzed according to gender and the presence of hypothyroidism, taking indicators of thyroid hormones into account (1gr – TSH > 4.0 mIU/ml, 2 gr – TSH < 4.0 mIU/ml). **Results:** Atherogenic lipid level changes were detected more frequently in patients of 1gr (increase of TG level in 35.7%, reduction of HDL level in 42.8% of patients) compared to 2 gr (16.7% and 22.2% respectively, $P < 0.05$). These results were confirmed by the difference between average rates of TG (1.15 ± 0.37 mmol/l in 1 gr vs. 1.07 ± 0.31 mmol/l in 2 gr) and LDL (2.72 ± 0.48 mmol/l in 1 gr vs. 2.51 ± 0.43 mmol/l in 2 gr), $P < 0.05$. In the 1 gr such shifts were more typical of boys than girls: TG – 1.23 ± 0.58 vs. 1.08 ± 0.48 mmol/l, LDL – 2.93 ± 0.61 vs. 2.55 ± 0.43 mmol/l, $P < 0.05$. In 2 gr such differences have not been identified and changes in average HDL levels were less pronounced. **Conclusion:** Formation of atherogenic dyslipidemia in children with obesity is closely associated with hypothyroidism, especially in boys. This requires particularly careful monitoring of thyroid hormone indicators and blood lipids in this group of patients.

P2-P536

How Early is Insulin Resistance in Our Pediatric Population with Metabolic Syndrome

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Background: Childhood critical period for onset/continuity of obesity with development of significant clinical and metabolic changes, impairing health in adulthood. Metabolic syndrome on rise both in adult and pediatric obese Indian population. Development of impaired glucose tolerance and progress to insulin resistance and other metabolic alterations like hypertension, dyslipidemia, Non alcoholic fatty liver disease are important. **Aim:** Evaluate insulin resistance and associated comorbidities among children with Metabolic syndrome. **Materials and Methods:** 50 overweight and obese 5–18years (BMI $\geq$90th centile WHO Charts) evaluated – weight, height, waist circumference (WC), BMI, clinical and biochemical. Fasting plasma glucose and insulin, 2 h post glucose load plasma glucose and insulin and lipid profile measured. Metabolic syndrome (MS) defined in children >10 years International Diabetes Federation guidelines, central obesity WC >90th percentile (ethnicity-specific values) AND any two-Raised triglycerides $\geq$150 mg/dl (1.7 mmol/l), reduced HDL $\leq$40 mg/dl (1.03 mmol/l), hypertension, Elevated FPG $\geq$100 mg/dl. Homeostasis Model assessment index (HOMA) calculated >3.5 taken as cutoff for insulin resistance. Cutoffs of BMI, WC, HOMA-IR which best predicted occurrence of metabolic syndrome by plotting ROC were 24.1 kg/m^2, 74.7 cm, and 3.48 respectively. Further, ROC analysis plotting HOMA is 3.48 predicting occurrence of MS with sensitivity and specificity of 77.8% and 78%. **Results:** Metabolic syndrome in 9/50 (18%), mean age $11.46 + 1.59$ years. Calories consumed and duration of physical activities did not differ among MS and non MS but with MS increased screen time $3.6 + 0.8$ h vs $2.6 + 1.2$ ($P = 0.02$). Being in puberty higher rate of MS (71.4%). Mean WC $80.8 + 5.3$ vs. $70.7 + 8.77$ cm $P = 0.00$ and systolic BP ($118 + 7.2$ vs $111.5 + 9.5$ mmHg $P = 0.05$), FPG ($88.1 + 9.4$ vs. $81.6 + 6.1$ mg/dl $P = 0.01$), PPPG ($125.4 + 12.7$ vs $109.4 + 9.2$ mg/dl $P = 0.00$), fasting insulin ($19.2 + 5.6$ vs $15.2 + 4.4$ μU/ml $P = 0.02$), HOMA index ($4.17 + 1.35$ vs $3.10 + 1.07$ $P = 0.01$) and TGL ($164.6 + 29.8$ vs $117.4 + 19.2$ mg/dl $P = 0.00$) significantly higher in MS. Abdominal obesity (100%), hypertension (44.4%), insulin resistance (77.7%), acanthosis nigricans (44.4%), dyslipidemia (77.7%) higher in MS. **Conclusions:** Though MS established in (18%) of overweight/obese, comorbidities identified in significant number by simple clinical examinations and biochemical measurements, confirms disturbed glucose and lipid homeostasis starts early, increases likelihood of type 2 diabetes and cardiovascular disease at young

Table 1. (for abstract P2-P534)

	HOMA-IR	Matsuda	HDL	Tg	SP-SDS	DP-SDS
BMI-SDS	0.18*	−0.10	−0.23*	0.27*	0.28*	0.15*
WC-SDS	0.07	−0.02	−0.19*	0.23*	0.21*	0.16*
WH ratio	0.28*	−0.25*	−0.20*	0.35*	0.17*	0.20*

SP, systolic pressure; DP, diastolic pressure. *$P < 0.001$.

age and need for early screening. HOMA-IR valuable tool (>3.5) useful for early evaluation identifying insulin resistance and metabolic syndrome have long-term benefit of preventive and diagnostic as well as therapeutic intervention.

P2-P537

Insulin Resistance for Adolescents with Obesity in Latvia

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Background: Insulin resistance for adolescents with obesity takes up a central role in the development of metabolic comorbidities, especially of type 2 diabetes. **Objective and hypotheses:** The aim of this study was to compare anthropometric data, apolipoprotein B, glucose, insulin level and HOMA-IR coefficien between genders. **Method:** Data about anthropometric parameters, blood samples, 6-min walk test (6MWT), eating habits and physical activities was collected and analyzed by a multidisciplinary team in Children's Clinical University Hospital (Riga, Latvia). **Results:** 60 children participated in study, 25 girls and 35 boys. Mean age (years $\pm$ S.D.) was 13.3 ± 2.5, weight (kg $\pm$ S.D.) 86.9 ± 23.7, height (cm $\pm$ S.D.) 165.9 ± 12.4, BMI (kg/m^2 $\pm$ S.D.) 31.1 ± 5.2, waist circumference (cm $\pm$ S.D.) 104.5 ± 14.1. Analyzing possible gender differences in obesity-related complication development, there was found statistically significant higher waist circumference for boys (cm $\pm$ S.D.) 113.5 ± 19.19 compared to girls (cm $\pm$ S.D.) 97.3 ± 9.3 ($P=0.037$). Insulin level was statistically significant higher for boys (μU/mL $\pm$ S.D.) 22.0 ± 11.3 compared to girls 10.4 ± 6.4 ($P=0.014$). Boys had statistically significant higher Apo B level in blood serum (mmol/l $\pm$ S.D.) 1.0 ± 0.2 compared to girls Apo B level 0.8 ± 0.1 ($P=0.049$). Calculated HOMA-IR coefficient was (value $\pm$ S.D.) 4.8 ± 2.6 for boys and 2.3 ± 1.7 for girls – significant gender differences was found ($P=0.019$). **Conclusion:** It is possible that there is gender predisposition to obesity-related complication development. Further research should be done to extend the study population and to assess factors that may have had effect on the result (birth weight, duration of exclusive breastfeeding, negative family history) for boys and girls.

P2-P538

Parental Obesity can Trigger Obesity in Children

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Pediatric Growth Disorder Research Center, 17 Shahrivar Hospital, Shahid Siadati St, Rasht, Iran

Background: Obesity is a disease which is associated with increased morbidity and mortality rate and needs extensive preventive procedures and effective interferences. Children with obese parent are in danger of becoming obese in their adolescence and adulthood even when trying to keep their weight stable. **Objective and hypotheses:** We aimed to investigate whether parental obesity can trigger obesity in children or not. **Method:** This is an analytic cross sectional study which was conducted on 12 years old students from different area in Rasht, north part of Iran. The checklist included demographic characteristics such as age, maternal age during childbirth, student and maternal height and weight, child rank. Data were analyzed by Pearson correlation analysis, paired *t*-test and ANOVA test and χ^2 in SPSS Software 19.0. A *P*-value less than 0.05 were considered statistically significant. **Results:** Results showed significant correlation between students' BMI and parental BMI and father weight. ($r=0.304$, $P<0.0001$) ($r=0.257$, $P<0.0001$) ($r=0.249$, $P<0.0001$) ($r=0.166$, $P=0.019$). Also, there was significant correlation between students weight with parental BMI and father weight and birth rank. **Conclusion:** This study shows that mother's and father's BMI and birth order are the factors that can predict children obesity and these variables could have major role in predicting 14.4% of high BMI cases. The role of family in changing nutritional habits of children must be considered, because through parental education and changing their perceptions we can prevent at least 14% of cases.

P2-P539

Cerebrotendinous Xanthomatosis: A Case Report of Rare Lipid Storage Disorder

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Background: Cerebrotendinous xanthomatosis (CTX) is a very rare autosomal recessive lipid storage disorder affecting bile acid biosynthesis. It is manifested by subtle neurological and non-neurological symptoms due to abnormal tissue lipid deposition. Usually, the diagnosis is delayed but early diagnosis and replacement therapy can prevent devastating neurological sequelae. **Objective and hypotheses:** To diagnose and manage a case of cerebrotendinous xanthomatosis. **Method:** A 15 years old Asian Indian female presented with complaints of swellings behind both the ankles and in front of both the knees for last 2 years. Patient had history of bilateral cataract surgery 1 year back. On examination, patient had firm, non-tender, fusiform swellings over bilateral tendoachilles (Right: 10 cm $\times$ 4.5 cm, Left: 8 cm $\times$ 3 cm) and bilateral infra-patellar tendons (Right: 2 cm $\times$ 1.5 cm, Left: 1.5 cm $\times$ 1.2 cm). General and systemic examination was unremarkable except bilateral pseudophakic eyes. Her hemogram, renal and hepatic function tests, serum electrolytes and fasting lipid profile were within the normal limits. Serum cholestanol level was 4.27 mg/dl. X-ray both legs revealed soft tissue thickening in bilateral ankle posteriorly and overlying right tibial tuberosity. magnetic resonance imaging (MRI) brain revealed T2 and FLAIR (Fluid-attenuated inversion recovery)

hyperintense signals in the region of Dentate nucleus of both the cerebellar hemispheres with high choline and low N-acetylaspartate (NAA)/Creatine peaks on magnetic resonance spectroscopy (MRS). Patient underwent excisional biopsy revealed foamy cells admixed with inflammatory cells and giant cells surrounding cholesterol clefts. **Results:** On the basis of above findings the diagnosis of cerebrotendinous xanthomatosis was made and the patient was started on replacement with chenodeoxycholic acid 250 mg three times a day, Ursodeoxycholic acid 300 mg three times a day and Atorvastatin 10 mg at bedtime and patient improved after 1 year follow up. **Conclusion:** CTX is a rare lipid storage disorder which is easily misdiagnosed and leads to devastating complications but a timely diagnosis and management can prevent these.

P2-P540

Analysing Child Obesity Risk Factors: Adenotonsillectomy

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Background: Adenotonsillectomy is one of the most common surgical procedure performed in children in Romania. Child obesity also, seems to follow the same trend of increasing prevalence as worldwide. **Objective and hypotheses:** To determine if there is a relationship between adenotonsillectomy and postoperative weight gain in children. **Method:** The retrospective four year study included 235 children. After applying the exclusion criteria, data from 209 children with mean age of 11.5 $\pm$ 3.29 years old was analysed. The first evaluation included a complete clinical exam with anthropometric measurements, biochemical tests and a Standard risk factors questionnaire. **Results:** Only 13.39% of children had adenotonsillectomy. Three smaller groups were formed: 1st: children that had excess weight before surgery ($n=7$), 2nd: children that gain weight after surgery and parents identified adenotonsillectomy as the cause of obesity ($n=13$), and the 3rd group: children that gain weight after surgery and parents could not identify adenotonsillectomy as the cause of obesity ($n=8$). So 10.04% of all children gain weight after the surgical procedure. Children in the second and the third group had no or maximum one or two other known obesity risk factors analysed (parents with obesity, diabetes or cardio-vascular diseases, birth weight, type of milk used in the first year of life, age of introduction of the solid food or the introduction of the cow milk into alimentation). **Conclusion:** Educating the parents and general practitioners about the possibility of weight gain after adenotonsillectomy could be useful in fighting obesity epidemic. For children undergoing surgery, adding simple dietetic habits and exercise guidelines for to the existing Post-operative recovery recommendation would be beneficial. The postoperative follow up, including anthropometric measurements, should be done for at least 2 years period.

P2-P541

Non-Medicament Treatment of Severe Obese Children, Using the One-Year Courses

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Background: It is hard to treat severe obese children only with diet and physical activity, psychological interventions are need. **Objective and hypotheses:** To examine the differences between courses of non-medicament treatment of severe obese children. **Method:** We examined 32 pubertal severe obese children BMI 31.2 $\pm$ 0.8 kg/m^2, 13.5 $\pm$ 0.3 years. The newel (in Belarus) course of non-medicament treatment of obesity (diet, physical activity, psychological treatment) in groups was proposed to children and their parents. According to children's and parent's motivation were divided: group 1 19 patients underwent the whole course with their parents (four times with 3 month intervals between them). The first part group1 include: four lectures for parents with endocrinologist (children's diet, physical activity), two lectures for parents with psychotherapeutist (children's psychoemotional problems), four lectures for children with endocrinologist (diet, physical activity) and four lectures for children with psychotherapeutist (motivation for losing weight). Another three parts include four lectures for children with psychotherapeutist and one lecture for children with endocrinologist. Group 2 13 children underwent only the first part of treatment without parents. Weight (W) and BMI were collected before treatment (W1, BMI1), 1 months after the first part (W2, BMI2), after the last (W3, BMI3). **Results:** We found the decreasing of W and BMI of group1 (W1 87.2 $\pm$ 4.6 vs W2 84.4 $\pm$ 4.5 kg ($P=0.03$)), BMI1 31.3 $\pm$ 1.1 vs BMI2 30.3 $\pm$ 1.2 kg/m^2 ($P=0.01$)) and group2 (W1 81 $\pm$ 4.6 vs W2 80.7 $\pm$ 4.6 kg ($P=0.04$)). Without differences in group 2 BMI (BMI1 312. $\pm$ 1.3 vs BMI2 30.8 $\pm$ 1.3 kg/m^2 ($P=0.1$)). After the last part we determined the decreasing W and BMI in group1 comparison to the initial results (W3 83.4 $\pm$ 5.5 kg ($P=0.03$)), BMI3 29.4 $\pm$ 1.4 kg/m^2 ($P=0.002$)). Group2 showed statistical increasing of W without any significance of BMI (W3 86.9 $\pm$ 4.1 kg ($P=0.05$)) BMI3 32.8 $\pm$ 1.8 kg/m^2 ($P=0.6$)). **Conclusion:** Command treatment (intense course with endocrinologists, psychotherapeutist and parents) showed a success in decreasing of weight and BMI in obese children.

P2-P542

Obstructive Sleep Apnea Syndrome in Early Childhood: Case Report

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Background: Obstructive sleep apnea syndrome (OSAS) in children is a common medical disorder, often associated with

adenoid and tonsil hypertrophy. The prevalence of OSAS has been increasing due to alarming rates of obesity in childhood. This is a very concerning subject since there is a higher risk of cardiovascular outcomes in patients with elevated BMI and OSAS. **Objective and hypotheses:** The aim of this study is to report a hazardous case regarding childhood obesity and its association with OSAS. **Resumed report:** Two and half years-old girl followed in the pediatric endocrinology clinic, due to obesity (weight: 38 kg ($Z = +7.63$) and BMI: 39.5 kg/m^2 ($Z = +8.57$)), and other complications, such as: high blood pressure with microalbuminuria, retinopathy with arteriolar narrowing, insulin resistance, dyslipidemia, moderate concentric hypertrophy of the left ventricle and hepatic steatosis. She had lethargy and daytime somnolence, snoring and night apnea, needing emergency care in one of the apnea episodes. An overnight polysomnography was requested, revealing an apnea-hypopnea index of 23.9/hour, and an oxygen-desaturation average 81.9%. The diagnosis of severe OSAS was made, and adenotonsillectomy indicated, but due to no clinical conditions to a surgery procedure, ventilator support (BIPAP) and weight loss were proposed. Polysomnography under BIPAP use was normalized and patient evolved with clinical and life quality improvement. **Conclusion:** Even in early childhood obesity could be associated with severe apnea. A precocious diagnose and approach could change life quality and prevent sudden death risk.

P2-P543

25-Hydroxyvitamin D Concentrations in Pubertal Children with Obesity

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Background: The prevalence of childhood obesity has been rapidly increasing worldwide and the last report of World Health Organisation define it as epidemic and one of the most serious global public health challenges for the 21st century. Obese children and adolescents are at an increased risk of developing various health problems including type 2 diabetes mellitus, hypertension, osteoarthritis, cardiovascular disease. Obesity is a risk factor for vitamin D deficiency. Vitamin D deficiency is associated with variability in the insulin resistance (IR) and the peripheral insulin sensitivity. **Objective and hypotheses:** The aim of the study was to assess the relation between obesity, IR and vitamin D status in obese pubertal children. **Method:** We studied 30 children (17 male and 13 female, aged 10–17 years) with body mass index above the 97th centile and no other co-morbidities. We used serum 25-Hydroxyvitamin D (25(OH)D) as known to be the better marker of vitamin D status. The insulin resistance we measured with the homeostatic model assessment (HOMA) as a method for assessing β-cell function and IR from basal (fasting) glucose and insulin concentrations. **Results:** The results showed vitamin D insufficiency in all patients. Twelve children (8 male and 4 female) had mild (50-80 nmol/l) and 18 children (9 male and 9 female) had moderate vitamin D insufficiency. There were no vitamin D deficient patients. Increased insulin resistance as HOMA-IR > 2.5 we found in 18 patients. **Conclusion:** In the analysed cohort we found lower level of the serum 25(OH)D as confirmed in many studies. Our results did not confirm insulin resistance in all patients but in the majority the high levels of HOMA-IR correlated with low levels of 25(OH)D as per the moderate vitamin D insufficiency. Prospective studies on a large group of individuals need to be done to confirm the findings.

P2-P544

Management Preschool Children of Prader–Willi Syndrome

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Background: The symptoms of Prader–Willi syndrome are likely due to dysfunction of a portion of the brain called the hypothalamus. Children of Prader–Willi syndrome want to eat constantly because they never feel full hyperphagia and usually have trouble controlling their weight. **Objective and hypotheses:** Genetic syndromes with obesity and delayed altered intellectual development as a major part of the phenotype include Prader–Willi syndrome, Albright hereditary osteodystrophy, Alstrom syndrome, Bardet-Biedl syndrome, Borjeson-Forssman-Lehmann syndrome, Cohen syndrome and fragile X syndrome. Chromosomal conditions, including Down, Klinefelter and Turner syndromes, also have an increased prevalence of obesity. **Method:** Children patients with Prader–Willi syndrome may require the support of the following specialists: geneticist for initial diagnosis and counseling, developmental pediatrician for stimulation programs, endocrinologist for management of hypogonadism, nutritionist for dietary counseling, ophthalmologist for management of strabismus, pulmonologist for management of sleep apnea, psychiatrist, psychologist, or both for management of behavioral issues and gastroenterologist for GI issues. Authors have had six children preschool patient during last two decade. **Results:** Babies with Prader–Willi syndrome commonly gain weight more slowly than other babies. Based on these guidelines, authors had made the diagnosis of Prader–Willi syndrome is highly likely in children younger than three years with five points (three from major criteria) or in those older than three years with eight points (four from major criteria) in six preschool children. Additionally ten minor criteria and five criteria we had described

during twenty years in the most cases of Prader Willi syndrome depends from child and level of disease. **Conclusion:** Prader–Willi syndrome is a rare genetic disorder characterized by hypothalamic-pituitary abnormalities with severe hypotonia during the neonatal period. Prader–Willi syndrome is the most common genetic cause of obesity in children.

P2-P545

Prevalence of Acanthosis Nigricans and Related Factors in Iranian Obese Children

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Background: Obesity is one of health problems worldwide. Acanthosis nigricans has been considered as a symptom of hyperinsulinemia in children. **Objective and hypotheses:** We designed this study to evaluate and compare clinical and laboratory findings in Iranian obese children with and without acanthosis nigricans. **Material:** Seventy-one obese children enrolled. Fasting blood sugar, total cholesterol, triglycerides, alanine aminotransferase, aspartate aminotransferase (AST), alkalinephosphatase (ALP), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C), insulin, TSH, and free thyroxine (fT4), calcium, phosphorus and 25- hydroxyvitamin D (25[OH]D) were measured with routine techniques. Collected data compared between cases with and without acanthosis nigricans. **Results:** Seventy-one children who were considered as obese were enrolled in this study. Twenty-five were female (35.2%) and 46 (64.7%). In 20 cases (28.2%) HOMA-IR was less than 2.5 and in 51(71.8%) HOMA-IR was more than 2.5. Forty-eight had acanthosis nigricans (67.6%). Mean BMI (24 in without acanthosis vs 27, $P=0.002$), insulin (14 vs 27, $P<0.001$), HOMA-IR (3.2 vs 6.2, $P<0.001$), TG (116 vs 156), and AST(24 vs 30, $P=0.01$) levels were significantly higher in cases with acanthosis nigricans. **Conclusion:** Obese children with acanthosis nigricans are at risk of developing diabetes. So, identification of this symptom and precise evaluation of children with this symptom is recommended. It is better to screen obese children with acanthosis nigricans for predisposing factors of diabetes and pay attention to risk factors of this disease.

Keywords: obesity, children, acanthosis nigricans, BMI, insulin.

P1-P546

Higher Risk of Low Birth Weight and Multiple Nutritional Deficiencies in Neonates from Mothers after Gastric Bypass: A Case Control Study

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Background: Maternal bariatric surgery is associated with increased risk of small-for-gestational-age infants. Risk of nutritional deficiencies in neonates of mothers with prior gastric bypass (GBP) is unclear. **Methods:** This study compared the clinical and cord blood biological characteristics of 56 newborns of GBP mothers and 56 newborns of healthy mothers, in the Obstetrics Department of Angers University Hospital between 01/03/2008 and 31/10/2012. After GBP, the women took multivitamin and trace element supplements. They had blood drawn at delivery for nutritional assessment. **Results:** GBP mothers lost 18.1 ± 6.3 kg/m^2 of BMI in the 11–69 months between surgery and pregnancy onset, reaching BMI of 30.1 ± 6.0 kg/m^2 compared with 22.3 ± 4.0 kg/m^2 in the controls ($P<0.05$). Birth weight was 0.34 kg lower in neonates born to GBP mothers ($P<0.01$), and 23% were small for gestational age vs. 3.6% in control group (odds ratio 8.2, 95% CI 1.7–38.1, $P<0.01$). Cord blood mean concentrations were significantly lower for Ca, zinc, and vitamin A ($P<0.05$). OR for cord blood concentrations below the 2.5th percentile were significant in GBP neonates for calcium [4.3 (1.3;14.1)], zinc and iron [3.8 (1.0; 14.8)], and vitamin A [OR 3.5 (1.1;11.8)]. In contrast, the OR for cord blood concentrations over the 97.5th percentile were significant in GBP neonates for Mg [OR 4.3 (1.1;16.4)] and vitamin E [OR 4.6 (1.2;17.3)], owing to maternal supplementation. Birth weight was related to variation in BMI between surgery and pregnancy ($r=0.45$, $P<0.01$) and unrelated to time between surgery and pregnancy, BMI at pregnancy onset, and weight gain during pregnancy. A significantly higher percentage of GBP mothers than expected displayed concentrations <2.5th percentile for calcium (13%), phosphorus (18%), zinc (21%), vitamin A (18%), and IGF-1 (28%) ($P<0.05$). **Conclusion:** Neonates from GBP mothers showed nutritional deficiencies. The long-term consequences remain to be explored.

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Laboratory Findings of 302 Patients with Hyperinsulinemic Hypoglycemia at Hypoglycemia

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Background: It is critically important to correctly diagnose hyperinsulinemic hypoglycemia (HH) to avoid neurological sequelae. However, the diagnosis is not always easy in the critical care setting since some patients present with atypical biochemical profiles. **Objective and hypotheses:** To delineate the range of biochemical data of HH patients at hypoglycemia to help establish a better diagnostic criteria. **Method:** Biochemical data (blood glucose, insulin, β-hydroxybutylate, free fatty acids, ammonia, lactate, and pyruvate) at hypoglycemia (<3 mmol/l) were collected from 302 patients with HH (167 transient, 135 persistent). Of these, 127 were obtained from the datasheets for mutational analyses conducted in our laboratory and other 175 were obtained from the national survey we conducted in Japan. As a control, we collected similar data from 29 non-HH patients who underwent controlled fasting tests in our institute. These data were statistically analysed to define the ranges and cutoffs to diagnose HH. In addition, clinical details of atypical patients were obtained from the medical charts. **Results:** Most of the severely affected patients present with typical biochemical profile of HH whereas less severely affected patients or patients with other comorbidities often present with atypical results. Insulin as high as 2–7 μU/ml was observed in non-HI patients. On the other hand, HH patients could present with insulin <0.5 μU/mL, β-hydroxybutylate up to 2.1 mEq/l, and free fatty acids up to 1.7 mEq/l. One of these patients responded dramatically with diazoxide. In addition, a number of patients without GLUD1 mutation initially present with hyperammonemia. **Conclusion:** No single cutoffs can diagnose all patients with HH especially when they present with mild symptoms or they have comorbidities. Initial hyperammonemia should be retested before diagnosing hyperinsulinism-hyperammonemia syndrome. Short trial of diazoxide might be considered in atypical patients.

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Recognition of a Sequence: More Growth before Birth, Longer Telomeres at Birth, More Lean Mass after Birth

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Background: Telomere length at birth is a major determinant of telomere length in late adulthood. However, the prenatal setting of telomere length is poorly understood. Individuals born large from non-diabetic mothers are at lower risk for later-life disorders than those born small, a feature of their longer health span being a higher lean mass that provides more muscle strength and that is already present in infancy. **Objective, hypotheses & methods:** At birth, we studied leukocyte telomere length (by quantitative polymerase chain reaction) in 103 small-, appropriate- or large-for-gestational-age (SGA, AGA, LGA) infants born after uncomplicated, term, singleton pregnancies. All infants were breastfed for ≥ 4 months. At 2 weeks and 12 months, body composition was assessed by dual X-ray absorptiometry. **Results:** Telomere lengths were shorter in SGA newborns and longer in LGA newborns than in AGA newborns ($P<0.001$), also after adjustment for maternal age, pre-gestational body mass index, gestational weight gain, and gestational age. Telomere length at birth associated (all $P\leq 0.001$) to birth weight ($r=0.50$) and to both lean mass ($r=0.43$) and fat mass ($r=0.48$) at age 2 weeks, but only to lean mass at 12 months ($r=0.51$). **Conclusion:** Higher weight and longer telomeres at birth are followed by more lean mass in late infancy.

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Congenital Hyperinsulinism in Infancy: The Profiles of Insulin Secretory Granules are Markedly Different in Focal- and Diffuse β-Cells

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Background: The mechanisms responsible for inappropriate insulin release from β-cells in congenital hyperinsulinism in infancy (CHI) have largely focused upon defects in K_{ATP} channels. Little is known about insulin biogenesis, the profiles of insulin in insulin-containing secretory granules or whether the impact of K_{ATP} channel defects is the same in diffuse- and focal disease. **Objective and hypotheses:** To define the ultrastructural properties of the insulin-containing granules in β-cell different forms of CHI compared to control samples. **Methods:** CHI patients were positive for mutations in the K_{ATP} channel gene *ABCC8* and underwent surgery for the treatment of hypoglycaemia. Morphometric analysis and immuno-gold labelling of insulin (I-Au) was applied to frozen tissue sections of control ($n=4$) and CHI tissues (diffuse-CHI, $n=3$; focal-CHI, $n=3$) and used to identify the insulin-containing granules. Data were acquired using Transmission Electron Microscope from each of the tissue sections; control $n=60$, diffuse-CHI $n=58$ and focal-CHI $n=61$. **Results:** Three profiles were defined: mature, dense-core/crystalline granules; immature secretory granules and secretory granules that were depleted of insulin. Approximately 60% of secretory granules ($n=3428$) were depleted of insulin in focal-CHI compared to around 10% of granules in diffuse- ($n=2258$) and control β-cells ($n=2577$). The percentages of immature granules

were significantly lower in focal-CHI (5.7 ± 1.7%) compared with diffuse CHI (45.5 ± 8.7%) and control samples (31.6 ± 3.7%). In contrast, control β-cells had a higher proportions of crystalline granules (62.9 ± 3.1%) compared with focal- (36.6 ± 3.5%) and diffuse-CHI (42.7 ± 1.9%). We also found a higher incidence of multi-vesicular secretory granule structures in focal- (74.7 ± 3.3%) compared to diffuse-CHI and control β-cells (39.5 ± 6.8% vs 27.8 ± 5.6%). **Conclusion:** Our data also imply that β-cells in focal-CHI have a greater secretory capacity (increased number multi-vesicular secretory granules and depleted granules) than in diffuse disease, despite the fact that both conditions associate with *ABCC8* gene defects.

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Persistent Ketotic Hypoglycemia as an Atypical Presentation of Heterozygous *HNF4A* Mutation

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Background: Heterozygous loss-of-function *HNF4A* mutations are known to lead to monogenic diabetes, and in infants to macrosomia and hyperinsulinemic hypoglycemia. We are reporting a patient with a heterozygous *HNF4A* mutation (c.997C > T p.ARG333Cys) presenting with persistent ketotic hypoglycemia. **Case report:** In a 38 weeks' gestation infant (birth weight 4.1 kg, pregnancy complicated by insulin-requiring gestational diabetes), hypoglycemia developed in the first hours of life. Initially diagnosed with hyperinsulinemic hypoglycemia due to gestational diabetes, treatment with diazoxide 7.5 mg/kg/day was initiated. Hyperglycemia and severe signs of fluid overload requiring intensive care developed and treatment was discontinued. During a lengthy hospitalization, high insulin and concurrently low C-peptide levels in the context of hypoglycemia were suggestive of exogenous insulin administration. A congenital hyperinsulinism genetic panel showed a likely pathogenic variant of *HNF4A*, but was not thought to be relevant in the context of suspected Munchausen by proxy. At age 7 months, the patient presented to our hospital with recurrent ketotic hypoglycemia. Hypoglycemia observed as soon as 1 h post-prandially persisted while hospitalized and while wearing a continuous glucose monitor at home. Critical samples during hypoglycemia showed appropriately low levels of insulin (1.1–5.2 pmol/l), and elevated ketone levels 1.30–2.30 mmol/l). Cortisol and growth hormone were 667 nmol/l and 4.2 mcg/l (maximum value), respectively. Glycemia rose < 1.7 mmol/l in response to glucagon administration. Acylcarnitine profile, glycogen storage disease genetic panel and toxicology screen were negative. Therapeutic trials with corn starch and Octreotide failed. Despite prior side effects, Diazoxide at a dose of 5 mg/kg/day was retrialed in combination with hydrochlorothiazide, and hypoglycemia resolved. **Conclusion:** Heterozygous *HNF4A* mutations may present as ketotic hypoglycemia, and laboratory investigations may not suggest hyperinsulinism. We considered dysregulated insulin secretion, down-regulation of GLUT2 as a result of the known *HNF4A* mutation vs. an additional condition predisposing to hypoglycemia as possible mechanism to explain this presentation.

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Enhanced Mitochondrial Densities Associate with the Pathobiology of β-Cells in Congenital Hyperinsulinism in Infancy

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Background: Congenital hyperinsulinism in infancy (CHI) is associated with inappropriate insulin release from β-cells. This is causally linked to defects in the ion channel genes *ABCC8* and *KCNJ11* regulating insulin, but little is known about the metabolic support for sustained insulin exocytosis. **Objective and hypotheses:** We hypothesised that inappropriate insulin release in CHI would require sustained ATP generation by enhanced mitochondrial activity. To test this we have quantified total mitochondrial volumes in individual islet β-cells and in glucagon-secreting α-cells from in CHI tissue and compared these with control samples. **Method:** Pancreatic tissue was obtained from five patients with CHI following surgery. All patients were positive for *ABCC8* gene defects. Tissue samples were fixed and embedded for use in serial block face-scanning electron microscopy. This was used to generate ultrastructural images of islet cells from serial sections of tissue 100 nm thick. From these images islet cells were digitally reconstructed in 3 dimensions for analysis of mitochondrial volume. Mitochondrial density was calculated by expressing mitochondrial volume as a proportion of total cytoplasmic volume for an individual cell. **Results:** The profiles of mitochondria in β-cells demonstrated higher order organisation and complexity of structures and networks in contrast to those in α-cells. In α-cells the mitochondrial volume was approximately 2% of the cytoplasmic volume, with no difference between CHI and controls; 2.7 ± 0.3% ($n = 3$) vs. 3 ± 0.4 ($n = 3$), respectively. However, in contrast in β-cells there was a 2.5-fold increase in the mitochondrial density in CHI tissue compared to controls; 7.3 ± 0.3% ($n = 6$) and 3 ± 0.2% ($n = 3$), suggesting increased mitochondrial activity sustaining insulin hypersecretion. **Conclusion:** In CHI β-cells we found greater mitochondrial density implying that mitochondrial expansion associates with the pathobiology of islet β-cells providing energy capacity to sustain uncontrolled insulin release.

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Congenital Adrenal Hyperplasia Newborn Screening: Improving the Effectiveness of the Neonatal 17OH-Progesterone and Serum Confirmatory Tests

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Background: Main concerns of Congenital Adrenal Hyperplasia Newborn Screening (CAH-NBS) are the high false-positive results (FPR) rate, low positive predictive value (PPV) and heterogeneity of confirmatory tests. Considering the CAH-NBS implementation in our country, our. **Objectives:** Objectives are to optimize the Neonatal 17OH-Progesterone (N17OHP) cutoffs and to evaluate the best serum confirmatory test. **Methods:** 473 983 newborns were evaluated; N17OHP was measured by IFMA (*AutoDelfia*) and cutoffs (99th and 99.8th) adjusted to birth-weight (BW1: <1500 g; BW2: 1500–2000 g; BW3: 2001–2500 g; BW4:> 2500 g), and to age at sample collection (before/after 72 h of life). For confirmatory tests, 17OHP (RIA and LC-MS/MS) and 21-deoxicortisol (21DF), Δ4 and cortisol (LC-MS/MS) were analyzed. Asymptomatic newborns with persistently increased 17OHP levels had the *CYP21A2* gene sequenced. **Results:** The recall rate was 0.05% using the P99th of N17OHP levels and 0.03% using the P99.8th; PPV increased from 11% (P99th) to 17% (P99.8th). N17OHP cutoffs in samples collected earlier (<72 h) were significantly lower than those collected later; consequently, different N17OHP cutoffs according to BW and age were determined. Twenty-six newborns were diagnosed (22SW/12M), confirmed by sequencing. Confirmatory tests were performed in 149 newborns and FPR persisted in 70% (by RIA) and 13% (LC-MS/MS); PPV of LC-MS/MS methodology was significantly higher than RIA (52 vs 27%). Serum 21DF and steroid ratios (17OHP/cortisol; 17OHP + Δ4/cortisol; 17OHP + 21DF/cortisol) presented similar FPR and PPV values in comparison to 17OHP by LC-MS/MS. Among asymptomatic newborns with persistently increased 17OHP levels, genotype identified 2 with NC-form. **Conclusion:** N17OHP levels adjusted to P99.8th (birth-weight and age) improved the CAH-NBS by reducing the FPR rate without missing the classical form diagnosis. Although serum 17OHP by RIA is widely used as confirmatory test in our country, 17OHP dosage by LC-MS/MS significantly reduced recall rate. The 21DF and steroid ratio measurements did not provide higher accuracy than serum 17OHP by LC-MS/MS. Molecular analysis could be restricted for asymptomatic newborns with persistently increased 17OHP levels.

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Neonatal Diabetes in Ukraine

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Background: We established a neonatal section of the Ukrainian Pediatric Diabetes Registry (UPDR) to identify cases of neonatal diabetes (ND). **Objective and hypotheses:** We investigated the genetic etiology and treatment of patients with ND. **Method:** According to the UPDR the number of children (0–17 y.o) with DM1 in 2015 was 8388 (a prevalence of one in 907), with DM2 – 36 (one in 211519) and with ND – 52 (one in 146436). We studied 48 probands with permanent or transient diabetes diagnosed within the first 6 months of life ($n=27$) and 21 probands with permanent diabetes diagnosed between 6 and 9 months of age. *KCNJ11, INS* and *ABCC8* were sequenced in all patients. For those diagnosed before 6 months who were negative in the initial screening, we also tested for 6q24 and used targeted next generation sequencing (tNGS) to screen other known genes. **Results:** We determined the genetic etiology in 28 of 48 (58.3%) probands diagnosed with diabetes before 9 months: in 88.9% of those diagnosed before 6 months and in 19% diagnosed between 6 and 9 months. K_{ATP} channel mutations were the commonest cause of ND accounting for 50% of cases. All of these patients transferred from insulin to sulfonylureas (SU). After 1 year of SU treatment all had a HbA1c level <48 mmol/mol (<6.5%), $P=0.01$. The daily dose of SU after 1 year of treatment decreased to 0.15 [0.08;0.19] mg/kg per day, $P=0.03$. C-peptide increased from 0.13 [0.06;0.6] to 1.1 [0.5;1.7] ng/ml, $P=0.01$ (Table 1). **Conclusion:** Every child with diabetes onset <9 months should undergo genetic testing for ND. tNGS increased the number of patients with a confirmed genetic etiology of ND.

Table 1. Other genetic causes of ND

	6q24	*INS*	*EIF2AK3*	*GLIS3*	*GCK*	*FOXP3*
Onset <6 months ($n=27$)	11.1%	7.4%	11.1%	3.7%	3.7%	3.7%
Onset 6–9 months ($n=21$)	–	14.3%	–	–	–	–

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Clinical and Molecular Characteristics of Turkish Patients with Congenital Hyperinsulinism: A Single-Center Experience

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Background: Congenital hyperinsulinism (HI) is the most common cause of persistent hypoglycemia which needs a prompt diagnosis and relevant treatment to avoid brain damage. So far, mutations in 11 key genes are known to cause monogenic forms of HI. **Objective and hypotheses:** The aim of this study was to characterize the clinical and molecular features of Turkish congenital HI patients and analyze the genotype/phenotype correlations. **Method:** Fifty-three patients with HI were included from one pediatric endocrinology center in Istanbul, Turkey. Clinical profile, response to treatment and genetic information of patients and their parents were recorded. Genetic analysis was performed in Exeter, UK. **Results:** Mutations were identified in 67.9% (36/53) of all patients. While mutations in *ABCC8/KCNJ11* were the commonest genetic cause with a frequency of 47.2% (25/53), *HADH* and *GCK* constituted 18.9% (10/53) and 1.9% (1/53), respectively. Among 17 diazoxide-unresponsive patients (32.1% of all), 14 had mutations in *ABCC8/KCNJ11* (12 of whom underwent pancreatectomy) and 1 in *GCK*, mutations were not identified in the remaining two patients. K_{ATP} channel mutations in diazoxide-unresponsive patients revealed biparental inheritance in 9 and uniparental inheritance in 5 (all with a paternal origin), while the only mutation in *GCK* was *de novo*. Among the diazoxide-responsive patients, (66.0% of all), 10 had mutations in *ABCC8/KCNJ11* and 10 had mutations in *HADH*, constituting all of the *HADH* mutations in the cohort and all being recessively inherited. **Conclusion:** Mutations in *ABCC8/KCNJ11* genes are the commonest identifiable genetic cause of congenital HI and are followed by *HADH* mutations in Turkish patients from our center. Genetic diagnosis of patients is critical to predict the course of the disease.

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Islet of Langerhans in Congenital Hyperinsulinism in Infancy are Disrupted and with Decreased Expression of Collagen (IV) α1 Chain in Basement Membranes

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Background: Congenital hyperinsulinism of infancy (CHI) is the most common cause of severe hypoglycaemia in children. Although CHI arises from mutations in K_{ATP} channels which lead to inappropriate insulin secretion, CHI it also is associated with marked changes in islet organization. **Aims and objectives:** Our aim was to investigate the structure and composition of the islet capsule in CHI and age-matched control tissue. **Methods:** Pancreata were obtained from CHI patients following surgery and from autopsy specimens of age-matched control infants. Islet capsule and intra-islet blood vessels structures were demonstrated after staining diffuse CHI (CHI-D) tissues and control pancreata with Picro Sirius Red (PSR). Collagen distribution was quantified using a digital macroanalysis after placing the PSR stained slide under polarising microscopy. Then, immunostaining was performed on CHI-D, focal CHI (CHI-F), atypical CHI (CHI-A) and control tissues to examine the expression pattern of collagen (IV) α1 chain (COL4A1) in islets and intra-islet basement membranes. **Results:** PSR staining showed that control islets are surrounded by defined layer of basement membrane (BM). In CHI-D ($n=7$, 2–13 months), 75% of islets were incompletely encapsulated compared to only 22% in control islets ($n=4$, age 7 weeks–10 months). When collagen content was quantified, CHI-D was significantly lower ($P \leq 0.0001$) than control islets and this was found to be associated with a marked decrease in the expression of COL4A1in CHI-D ($n=4$, 2–5 months). **Summary/conclusion:** CHI tissue has disrupted islet architecture and lower collagen content compared to the age-matched control tissues. The decreased expression of COL4A1 supports the involvement of islet matrix in the pathogenesis of CHI.

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Pancreatic Glucagon Secretion is Severely Impaired and Somatostatin Secretion Unchanged in Patients with Hyperinsulinaemic Hypoglycaemia

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Background: Hyperinsulinaemic hypoglycaemia (HH) is a common cause of hypoglycaemia in children. Glucagon is an important counter-regulatory hormone and the role of somatostatin is not known in children with HH. **Objective and hypotheses:** To understand the roles of glucagon and somatostatin in children with HH. **Method:** Children admitted for management of HH in our hospital were included in the study. Plasma insulin, glucagon and somatostatin were collected at the start and end of the fast or at the time of hypoglycaemia. Glucagon and somatostatin were measured by radioimmunoassay. Descriptive statistics mean, S.D. and three quartiles (Q1, Q2 and Q3) were obtained to check normality assumptions for patients with HH and control group respectively. **Results:** There were 26 children with HH and seven children as controls included in the study. Both mean and median were different and hence 50th centile (Q2 or median) is considered for calculation. Among HH patients, median insulin concentration was significantly increased at the start of fast compared to end of fast (P value $= 0.001$). There was

no significant change in glucagon and somatostatin concentration at the start and at the end of the fast (at the time of hypoglycaemia) (P value $>$ 0.05). Among control group, median insulin concentration was significantly decreased and glucagon concentration was significantly increased (P value $<$ 0.05) at the end of the fast respectively. However, there was no significant change in somatostatin concentration at the start and end of the fast (P value $>$ 0.05). **Conclusion:** This study suggests that in HH glucagon secretion is severely impaired from the alpha-cell whereas somatostatin secretion from the delta-cell is unaffected. The mechanisms that lead to impaired glucagon secretion in HH are unknown. Somatostatin does not seem to have any significant role as a glucoregulatory hormone in patients with HH.

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Mutations in MODY Genes: About Four Cases of Congenital Hyperinsulinism

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Background: Congenital hyperinsulinism (HI) is the most common cause of persistent hypoglycemia in infants and children. **Objective and hypotheses:** Recently, mutations in genes usually involved in MODY 1 and 3 have been described in HI. **Method:** We present here six cases of hyperinsulinism associated with MODY1 (one case) and MODY3 (four cases) and one case of HI associated with MODY5 mutation. **Results:** *Case 1*: Girl (BW 3350g, GA 36 weeks) with neonatal hypoglycemia due to congenital HI owing to HNF4a mutation (c.131G$>$C). HI was diazoxide-responsive, and the treatment could be stopped after 3 years. *Case 2*: Boy (BW 3670g, GA 41 weeks) with neonatal hypoglycemia due to transient congenital HI owing to HNF1b duplication (c.1-?-1674+?dup). He required diazoxide for 10 days. His mother has the same HNF1b duplication, and gestational diabetes during a subsequent pregnancy. *Case 3 and 4*: Brother (BW 2990g, GA 39 weeks) and sister (BW 2800g, GA 38 weeks), with neonatal hypoglycemia due to HI owing to HNF1a mutation (c.598C$>$T), requiring diazoxide treatment for a few months for the girl. *Case 5*: 4.8-year-old boy with hypoglycemia (convulsion) due to HI owing to HNF1a mutation (c.502C$>$T), still requiring diazoxide treatment 5 years later. Hypoglycemia was associated with ketonuria, and was initially believed to be secondary to GH and ACTH deficiency. *Case 6*: 5-year-old boy with hypoglycemia due to HI owing to HNF1a mutation (c.77T$>$C), still requiring diazoxide treatment after 1.5 years. Initially, hypoglycemia was believed to be secondary to GH and ACTH deficiency. **Conclusion:** We report the first case of HI associated with HNF1b mutation. HNF4a and HNF1a are recently described causes of HI. Our cases showed that the clinical presentation can be variable, from transient neonatal HI to persistent HI discovered during childhood.

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Cerebral Outcome of Children with Congenital Hyperinsulism

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Background: Congenital hyperinsulinism (CHI) is a rare condition characterized by unregulated secretion of insulin from pancreatic islet β cells. The primary treatment goal is to obtain normoglycemia, since hypoglycemia in the neonatal period can have severe impact on cerebral development. **Objective and hypotheses:** To assess the cerebral function in children with CHI at follow up. **Method:** From an international cohort, 40 children diagnosed with CHI (Russia/Kazakhstan/Belarus, $n=21$, Ukraine, $n=4$, Sweden/Denmark, $n=15$) were examined to assess neurodevelopment. The children underwent a standardized assessment program including Bayley Scale of Infant and Toddler Development, 3rd Edition (age 0–2 years$=10$), DP-3 Developmental Profile (age >2 years$=20$), or Wechsler's Intelligent Scale for Children, 4rd edition (age ≥ 6 years, $n=5$), and Movement ABC to assess motor function (age 3–17 years, $n=10$). Exclusion criteria were gestational age <32 weeks. **Results:** Median (range) age at follow up was 3.4 (102 d–18.5 y) years. The mean (S.D.) lowest recorded blood glucose was 0.9 (0.6) mmol/l, birth weight 3604 (735) g, Apgar score (5 and 10 min) 8.1 (1.2), and 8.6 (0.8). The majority ($n=21$, 52%) had the first recorded hypoglycaemic episode <3 days after birth. Epilepsy was found in 8 (21%). By Bayley III, mean (S.D.) motor function composite score was 76.7 ± 28.6 (26th percentile); cognitive score 73.6 ± 24 (20th percentile); language score 63.4 ± 4 (13th percentile), social-emotion score 75.6 ± 23 (23th percentile) and adaptive score 0.6 ± 28 (15th percentile). Twenty children assessed by DP-3 achieved a mean standard score of 68 (normal score 85–115). Ten children achieved an average Movement ABC score equalling 39th percentile, and five Danish children assessed with WISC-IV had a normal

cognitive development with a mean (S.D.) IQ score of 95 ± 12.4 (40th percentile). **Conclusion:** A high degree of neurodevelopmental delay still occurs in children with CHI, dependent on treatment.

P1-P559

Recognition of the Fetal and Perinatal Features of the Prader-Willi Syndrome is Required to Avoid Delay in Diagnosis

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Introduction: Prompt diagnosis in Prader-Willi syndrome (PWS) is important for counselling the family and thus pre-empt the hyperphagic phase of the condition. **Objectives:** To determine the key diagnostic features of PWS during the perinatal period and hence recommend strategies to ensure early diagnosis. **Study design:** Retrospective case note review with prospective questionnaire survey of birth details for the affected child and healthy siblings in which mothers scored fetal movements on a scale of 1 (low) to 5 (high). **Results:** Between 1991 and 2015 incluive 90 subjects (54M:36F) with PWS were seen in a multidisciplinary clinic. Cause was paternal deletion (56), maternal disomy (26), imprinting centre mutation (2), translocation/deletion (1), mutation-negative (1), tested elsewhere (5). Mean maternal/paternal ages for disomic patients were 34.6/34.6 years, significantly older than for deletion at 26.4/29.6 years ($P < 0.001$ & 0.004). PWS pregnancies featured polyhydramnios in 10/34 (29%), breech presentation in 15/53 (28%), and caesarean section delivery in 38/86 (44%). Median (range) birthweight and gestation for patients cf siblings were 2.76 (1.18–3.99) cf 3.3 (3.1–4.9) kg; and 39 (30–43) cf 40 (33–42) weeks, with prematurity (< 37 weeks gestation) in 21 (23.6%) and low birthweight (< 2500 g) in 28 (32%) of PWS patients. Median (range) fetal movement scores were 1(1–4) ($n = 80$) for PWS cf 3(1–5) ($n = 94$) siblings ($p < 0.001$). Median (range) duration of nasogastric feeding and hospital stay was 30.5 days (2 days–1.3 years) and 27 days (0 days–2 years). Median (range) time to clinical/molecular genetic diagnosis (available ≥ 1991) was 2.5 month (1 day–46 years)/10 month (4 day–46.5 years). Stratifying by year of birth < 1980, 1980–89, 1990–99, 2000–09, and > 2010 showed significant improvement in median time (days) to clinical/molecular diagnosis: 1862/8395, 97/3577, 74/73, 19/60 and 7/14 days ($P < 0.001$). However from 2000–2015 inclusive clinical diagnosis was > 28 days in 11 and > 1 years in five patients. **Conclusions:** Despite the overlap in features with prematurity, diagnosis of PWS can and should be made within days of birth if the key features, mostly hypotonia-related but including cryptorchism in males, are recognised and actively sought. Neonatal paediatricians need to be fully aware of the perinatal features of PWS, including a history of reduced fetal movements, so that unnecessary investigations such as MRI brain scan and muscle biopsy can be avoided.

P1-P560

Congenital Hyperinsulinism Due to Compound Heterozygous Mutation in *ABCC8* and *KCNJ11* GENES: 20 Years Experience of A National Referral Centre

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Background: Congenital hyperinsulinism (CHI) is a condition caused by dysregulated insulin secretion. Compound heterozygous mutations in *ABCC8* or *KCNJ11* genes account for approximately 13% of CHI mutations and have traditionally been associated with diffuse disease unresponsive to diazoxide. **Objective and hypotheses:** To analyse the clinical presentation and response to treatment of patients diagnosed with CHI due to compound heterozygous mutations in the *ABCC8* or *KCNJ11*genes. **Method:** Retrospective review of clinical records of all patients diagnosed in our centre with CHI due to compound heterozygous mutations, between 1994 and 2015. **Results:** 21 patients were included (11 females). The mean gestational age at birth was 38 weeks (35–40 weeks) with an average weight of 4422.9 g (± 660.4 g). Hypoglycaemia was identified within the first 18 h of life in 19 patients. The remaining 2 were diagnosed at 3 weeks and 12 months old respectively. Biochemical parameters of CHI were similar in all subjects. Eight patients (38%) had a 18F-DOPA PET scan that revealed diffuse disease in all cases. Regarding management, six patients (28.6%) responded to pharmacological treatment: one child (4.8%) improved with diazoxide and five patients (23.8%) responded to newer pharmacological agents such as octreotide-lanreotide or sirolimus. 14 patients (66.7%) underwent near total pancreatectomy, from this group, eight patients (57.1%) developed diabetes mellitus, five (35.7%) are currently treated with sirolimus ± lanreotide and one was cured. One baby who did not respond to diazoxide, presented with severe CHI that resolved spontaneously by the age of 8 weeks. Genetic analysis of both *ABCC8* and *KCNJ11* was performed, but only mutations of the former were found, of those, 10 mutations had not been previously described. **Conclusion:** Due to their heterogeneity in terms of clinical presentation and response to medical therapy, patients with compound heterozygous mutations in the *ABCC8* gene, require individualised assessment to achieve the best outcome.

P1-P561

A Case of Hyperinsulinemic Hypoglycemia, Associated with Insulin Autoimmune Syndrome (IAS) in 3.5 Year Old Girl

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Background: Insulin Autoimmune Syndrome (IAS) is a rare cause of hyperinsulinemic hypoglycaemia with only few descriptions in children in the literature. Drugs containing the sulfhydryl group, such as methimazol, are known to be a causative factor of this syndrome. Diazoxide and octreotide are usually ineffective in such patients. **Objective:** We aim to describe a rare case of IAS in a child, with a good response to a short course of glucocorticoid therapy. **Results:** A previously healthy 3.5 year old Caucasian girl presented with hypoglycemic seizures. It is known that she had two courses of Piritinol treatment before the onset of the disease- for 1 month (6 months before) and for 2 weeks (10 days before). On admission blood glucose monitoring showed recurrent episodes of fasting hypoglycemia (1.7–2.8 mmol/l) and postprandial hyperglycemia (11–16 mmol/l), fasting tolerance was no longer than 1.5–2 h. Fasting test revealed non-ketotic hyperinsulinemic hypoglycemia: blood glucose 2.9 mmol/l, insulin >1000 μUn/ml, C-peptide 16.8 ng/ml. OGTT showed hyperglycemia (14.7 mmol/l) at 90 minute, but normal glucose levels at 120 min. (6.9 mmol/l). Based on extremely high levels of serum insulin in the absence of sulfonylurea intake, IAS was suspected. High levels of AIAb (>100 U/ml) and typical HLA alleles (DRB1* 04; DQA1* 0301) confirmed the diagnosis. To suppress autoimmunity, the girl was started on Prednisone 1.4 mg/kg per day. Normoglycemia was achieved in 3 days, but insulin and antibody levels remained elevated. Dose of prednisone was gradually reduced; treatment was stopped in 6 weeks. Follow up 2 months later showed clinical remission with negative fasting test, normalization of insulin secretion, but still mildly elevated AIAb (24.4 U/ml). **Conclusion:** To our knowledge this is a first description of IAS in children in Russian Federation. We suspect that the likely trigger factor of the disease in this case was treatment of Piritinol, which has a disulfide bond, although we have not found information about the same cases in the literature. A short course of glucocorticoid treatment was effective in our case and might be recommended as an immunosuppressive therapy to achieve the remission rapidly.

P1-P562

Effectiveness of Calcium Channel Blocker Nifedipine in Children with Hyperinsulinaemic Hypoglycaemia Due to Genetically Proven Mutations in the *ABCC8/KCNJ11/GCK* Genes

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Background: Several previous publications have documented the usefulness of Nifedipine for treating hyperinsulinaemic hypoglycaemia (HI). These reports include transient and persistent forms of HI, with and without known genetics, used in monotherapy or in combination with other drugs, and demonstrate various outcomes. **Objective and hypotheses:** To systematically trial Nifedipine in children with known HI mutations and diazoxide unresponsive, assessing glycaemic control. **Method:** Nifedipine was administered according to our hospital's protocol for HI management. Two hourly blood glucose determinations were performed whilst on this medication. The dose of Nifedipine was withheld should the systolic blood pressure be under the 5th percentile for gender and age. Information regarding birth and HI presentation characteristics, family history, associated illnesses, genetic result, PET scan/histology report, surgery and other HI medication, and maximum dose of Nifedipine administered were collected. **Results:** Ten patients were recruited (six females) with ages ranging from 1 month to 14 years. The genetics were: homozygous *ABCC8*, compound and paternally inherited heterozygous *ABCC8*, heterozygous *KCNJ11* and paternally inherited *GCK*. All of them were diffuse HI disease. The median maximum dose of Nifedipine received was 2.5 mg/kg per day. Three subjects had Nifedipine in monotherapy, whilst four also received octreotide, one octreotide + glucagon, one octreotide + diazoxide and one octreotide + sirolimus. After a median of 7 days of trial none of the patient's demonstrated improvement in glycaemic control, hence it was discontinued in all cases, and their blood glucose concentrations were subsequently stabilised with other medications. **Conclusion:** Children with HI due to mutations in *ABCC8, KCNJ11* and *GCK* genes do not respond to therapy with Nifedipine. This is the first study to systematically assess the effectiveness of Nifedipine in children with genetic causes of HI.

P1-P563

Hyponatremia in Infants Under 100 Days Old: Frequently Overlooked and Multifactorial

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Background: Hyponatremia is one of the most common electrolyte disorders in hospitalized children and early diagnosis and management are crucial to prevent morbidity and mortality. Because of the physiological resistance to aldosterone under 3 months of age, the mechanisms leading to hyponatremia are often misunderstood. **Objective and hypotheses:** To assess the prevalence of hyponatremia in hospitalized infants younger than 100 days and evaluate the mechanisms leading to water and sodium imbalance. **Method:** The database of a large paediatric hospital was searched for hyponatremia occurring in infants younger than 100 days hospitalized in 2012. The charts were analyzed to evaluate the origin, evaluation and management of hyponatremia. **Results:** 86 patients (4.3% of hospitalized children younger than 100 days) were included. The median age at identification of hyponatremia was 19.5 days (IQR 9.25–44.75). 77

patients (89.5%) had hospital-acquired hyponatremia. Iatrogenic mechanisms were involved in 25 cases (29%). The cause of hyponatremia was SIADH in 12 patients (14%), transient or constitutional abnormality of the mineralocorticoid pathway in 28 patients (32.6%), digestive origin in three patients (3.5%), acute renal failure in three patients (3.5%) and heart failure in one patient (1.2%). Abnormality of the mineralocorticoid pathway included functional tubulopathy of prematurity (20 patients; 23.3%), physiological resistance to aldosterone compounded by a severe sepsis (one patient), pseudohypoaldosteronism secondary to pyelonephritis or uropathy (four patients; 4.7%) and constitutional genetic deficiency in the mineralocorticoid pathway (three patients). In 24 patients (27.9%) the etiology of hyponatremia was considered as multifactorial, including iatrogeny (11 patients; 12.7%). **Conclusion:** Hyponatremia is a frequent electrolyte disorder in the neonatal pediatric population. Iatrogenic causes played a major role in the occurrence of hyponatremia. Genetic abnormalities of the mineralocorticoid pathway, considered as extremely rare were relatively prevalent and might be otherwise underdiagnosed. We conclude that hyponatremia in infants should be thoroughly analyzed and managed.

P1-P564

Long-Term Effects of Differences in Fetal Environment: Endocrine Influences on Cognitive Function and Personality in Teen Monozygotic Twins

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Background: Low birth weight and unfavourable intrauterine conditions are associated with long-term effects on life. **Objective and hypotheses:** In a longitudinal study, we followed genetically identical twins with intra-twin birth-weight (bw) differences due to twin–twin transfusion syndrome from birth until after puberty. We propose that differences in birth weight lead to differences in hormone levels with effects on personality and cognitive function. **Method:** 43 pairs of monozygotic twins with intra-twin bw-differences were seen at birth, 2.8 and 15.0 years, 28 of these pairs were also seen at 17.6 years. Auxiological data were collected at all occasions; we differentiated between donators (lower birth weight) and acceptors (higher birth weight). At 15 years, fasting blood was drawn to measure levels of gonadotropins, steroids, adrenal and thyroid hormones. Additionally, two psychological questionnaires were issued: the Strength and Difficulties Questionnaire (SDQ-self and -parent) and the Kidscreen-52 (Health Related Quality of Life). At 17.6 years an IQ-Test (WAIS-IV, Wechsler Adult Intelligence Scale) was administered. **Results:** Endocrine parameters did not differ significantly in-between twin-pairs. Preliminary results of 26 subjects (13 pairs) showed no significant differences for cognitive function between donators and acceptors. FSH-levels at 15 years of age were positively correlated with perception-linked logical thinking at 17.6 years, while IGF-1 was negatively correlated with speech comprehension and working memory. Testosterone concentration was negatively correlated with emotional problems and positively with quality of self-perception, while Estradiol conc. was positively connected to prosocial behaviour. While T4-levels were also positively correlated with prosocial behaviour, they were negatively associated with parent-observed hyperactivity. TSH on the other hand was positively correlated to perceived autonomy and relationships to family members. **Conclusion:** Endocrine parameters are closely linked to differences in personality and quality of life in adolescent monozygotic twins. Preliminary results also suggest an impact on cognitive function. If these differences can actually be associated with birth weight differences has yet to be determined, further analyses will be performed on the presented sample.

P1-P565

Different Long-term Neurodevelopmental Outcomes in Very Preterm Versus Very-low-birth-weight Infants

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Background: Birth weight (BW) is often used as a proxy for gestational age (GA) by studies on preterm birth. Recent data indicate that the terms very-low-birth-weight (VLBW; BW <1500 g) and very preterm (VP; GA <32 weeks) birth are not equivalent with regard to perinatal outcomes and postnatal growth up until final height. It is unknown whether the differences between these terms could be extended to long-term neurodevelopmental outcomes. **Objective and hypotheses:** To compare neurodevelopmental outcomes at age 19 years between VP and VLBW infants. **Method:** VP and/or VLBW subjects from the Project On Preterm and Small-for-gestational-age infants cohort were classified as i) VP+/VLBW+ ($n=354$), ii) VP+/VLBW- ($n=144$) or (3) VP-/VLBW+ ($n=207$), and compared with regard to: intelligence quotient (IQ) assessed with the Multicultural Capacity Test-Intermediate Level; neurological functioning using Touwen's examination of mild neurologic dysfunction; hearing measured with audiometry; behavior assessed with the Young Adult Self Report (YASR) and the parent-reported Young Adult Behavior Checklist (YABCL); achieved education and occupation; and self-assessed health using the Health Utilities Index and the London Handicap Scale. **Results:** At age 19 years, VP+/VLBW- infants exhibited a 3.5 (95% CI: 0.2–6.8) higher IQ score, a 1.5 (95% CI: 1.01–2.1) increased odds of higher education, 3.2 (95% CI: 1.1–5.3) dB better hearing, and lower scores on anxious behavior, attention problems and internalizing behavior as measured with both the YASR and YABCL compared to VP+/VLBW+ subjects, after adjusting for gender. Additionally, VP-/VLBW+ infants

reported a 1.8 (95% CI: 1.2–2.6) increased odds of poor health compared to VP+/VLBW+ subjects. **Conclusion:** At age 19 years, infants born VP+/VLBW+, VP+/VLBW- or VP-/VLBW+ have different neurodevelopmental outcomes, hence the terms VP and VLBW are not interchangeable. We recommend, at least for industrialized countries, to base inclusion for future studies in preterm populations on GA instead of BW.

P1-P566

Challenging Management of Costello Syndrome with Severe Congenital Hyperinsulinaemic Hypoglycaemia

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Background: Costello syndrome may be associated with Hyperinsulinaemic Hypoglycaemia (HI), but this is usually a mild medically-responsive form. **Objective and hypotheses:** To describe the clinical characteristics, biochemical findings and challenging management of a case of Costello syndrome with severe HI. **Method:** Review of the patient's medical records. **Results:** Male, born to non-consanguineous healthy parents, at term with birth weight of −0.45 S.D. with good Apgar scores, after a pregnancy complicated with polyhydramnios. He developed hypoglycaemia, feeding intolerance and tracheomalacia since day 1 of life. Subsequently found to have failure to thrive, biventricular hypertrophy with pulmonary stenosis and gastroesophagic reflux disease with possible abnormal gastric emptying, requiring gastrostomy feeds. The phenotype includes weight and height on the 0.4th centile, macroglossia, low set ears, deep palmar and plantar creases and abdominal distension (normal genitalia). Hypoglycaemia persisted despite continuous feeds and investigations were consistent with HI, with no hypoglycaemia being triggered by protein load or oral glucose tolerance test. Genetics were negative for the known HI, BWS, *PTPN11* genes and a novel *de novo* mutation was found in the *HRAS* gene. He was tried on diazoxide, chlorothiazide, octreotide and sirolimus without achieving glycaemic control, hence a 95% pancreatectomy was performed which did not identify histologically abnormal pancreatic tissue. Despite surgery, hypoglycaemia persisted requiring the addition of octreotide injections to the continuous enteral feeds; unfortunately he developed tolerance to increased doses of octreotide. Aiming to avoid further surgery and considering the likelihood of increased insulin sensitivity, he was started on prednisolone (dose equivalent to 4 mg/m^2 per day of hydrocortisone) combined with continuous feeds (8.2 mg/kg per min of glucose) achieving satisfactory blood glucose concentrations. **Conclusion:** Costello can present with severe medically and surgically unresponsive HI. In view of possibly increased insulin sensitivity in some of these patients the use of steroids might help to avoid further surgery.

P1-P567

Risk Factors and Clinical Features of a Large Cohort of Patients with Transient Hyperinsulinemic Hypoglycaemia

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Background: Transient hyperinsulinemic hypoglycaemia (THH) is associated with risk factors such as prematurity, maternal diabetes mellitus, perinatal hypoxia, small for gestational age (SGA) and syndromes like Beckwith Wiedemann syndrome (BWS). **Objective:** To present the features of a large cohort of patients with THH managed at a Quaternary referral centre. **Method:** Patients who had neonatal onset HH that resolved before the 2nd birthday were considered to have THH. Retrospective data was collected over a period of 6 years to the identify risk factors, medications used and duration of treatment for THH. **Results:** Out of the 85 THH patients (59 males), 27 (31%) were born preterm. 10/27 of the preterm infants (37%) and 15/60 of the term infants (25%) were SGA. Two preterm (7%) and two term (3%) infants had BWS. Three patients (3.5%) with confirmed hyperinsulinism resolved without medical treatment. The table gives risk factors, medications used and duration of treatment. **Conclusion:** Prematurity and SGA are the major risk factors for THH. There is no difference in the total duration of treatment between the preterm and term infants. Whilst almost half the preterm infants had three risk factors or more, nearly 30% of term infants had no identifiable risk factor that potentially trigger the unregulated insulin release leading to severe hypoglycaemia.

P1-P568

A Rare Case of Neonatal Hypothyroidism

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Case study: Baby A, a boy was delivered at 33 weeks gestation (birth weight 1.545 kg, 9th centile) by emergency caesarean section following maternal preeclampsia. He did not require any resuscitation at birth. He is the second baby of non-consanguineous Asian parents with no family history to note. Both parents are healthy and there was no history of maternal medication use. Baby A experienced respiratory distress syndrome and suspected sepsis. He developed a heart murmur, confirmed by echocardiography to be a ventricular septal defect and atrial septal defect. After initial intravenous fluids he was established on expressed

breast milk by nasogastric tube. As he was failing to thrive, Baby A's feed was switched to high-calorie formula and there was a brief period where his weight seemed to be improving. Around this time he also developed symptoms of gastroesophageal reflux disease and was commenced on Ranitidine and Gaviscon. His vomiting and weight gain failed to improve. Furthermore he required continued nasogastric feeding, out of keeping for his prematurity. Investigations included a metabolic screen. Surprisingly, in-spite of a normal newborn screen, his thyroid-stimulating hormone (TSH) was extremely high at 340 mU/l with free-T_4 at 4.0pmol/L. An urgent radioisotope scan revealed a bulky thyroid. We also looked for rarer causes of hypothyroidism including iodine exposure and initial urinary iodine/creatinine ratio was high at 2361 nmol/mmol (50–360 nmol/mmol). Repeat results as well as maternal urinary iodine are pending. We are continuing to investigate how this baby has been exposed to iodine. Levothyroxine was commenced at 25 μg and adjusted as shown in the table below (Table 1). **Conclusion:** This case highlights the importance of further investigations into hypothyroidism when initial screening results are normal, especially to exclude exposure of the baby to excess iodine.

Table 1.

Day of life	63	71	79	84	89	99
TSH (mU/l)	340	44.47	2.36	0.57	2.63	2.73
T4 (pmol/l)	4.0	13.7	25.0	27.4	21.3	14.8
Levothyroxine (μg)	25	25	25	25	15	15

P1-P569

Maternal Nutritional Risk Factors Associated with Neonatal Hyperinsulinism

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Background: Neonatal hyperinsulinism is the most frequent cause of neonatal recurrent hypoglycaemia. The persistent form can be explained by mutations of genes involved in beta cell function, whereas the transient form can occur in case of prematurity, low birth weight, macrosomia, perinatal hypoxia, and maternal diabetes. **Objective and hypotheses:** As we observed an increase in the incidence of neonatal hyperinsulinism, we hypothesized that potential maternal nutritional risk factors could be associated with this pathology. **Method:** Questionnaire relative to dietary habits during pregnancy in mothers of children followed for a transient or persistent neonatal hyperinsulinism compared to mothers of control newborns matched for gestational age and birth weight. **Results:** 61 newborns with hyperinsulinism (HI) and 100 controls (C) were included. The occurrence of gestational diabetes was similar between groups. We observed less frequent consumption of low-fat dairy products ($P<0.05$), fresh legumes ($P<0.05$), fruits and fruit juice ($P<0.05$) in mothers of child with HI. They also tended to consume more frequently industrial meals reheated in microwave in their original plastic packaging ($P<0.10$). We noted a greater gestational weight gain in this group ($P<0.05$), whereas birth weight was comparable (2870 ± 612 g). **Conclusion:** A 'less healthy diet', qualitatively richer in lipids and industrial meals in plastic packaging, and poorer in fresh fruits and legumes, associated with a greater gestational weight gain, was more frequently found in mothers of newborns with HI, in comparison to controls.

P2-P570

Genotype and Phenotype of 99 Vietnamese Patients with Congenital Hyperinsulinism

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Background: Hyperinsulinemic hypoglycemia (HH) is a consequence of unregulated insulin secretion by pancreatic β-cells. Congenital HH is caused by mutations in genes involved in regulation of insulin secretion (*ABCC8*, *KCNJ11*, *GLUD1*, *CGK*, *HADH*, *SLC16A1, HNF4A* and *UCP2*). Severe forms of congenital HH are caused by inactivating mutations in *ABCC8* and *KCNJ11*, which encode the two components of the pancreatic β-cell ATP-sensitive potassium channel. **Objective and hypotheses:** Our aim is to identify mutations in the *ABCC8* and *KCNJ11, HNF4A* and *GLUD* genes, and to describe genotype and phenotype correlations of Vietnamese children with congenital hyperinsulinism. **Method:** A prospective study was conducted on 99 cases with congenital hyperinsulinism diagnosed and treated at Vietnam National Children's Hospital from January 2007 to March 2016. Patients were selected by using inclusion criteria of Hussain K (2008). All exons of *ABCC8; KCNJ11*, *HNF4A* and *GLUD1* were amplified from genomic DNA and directly sequenced. **Results:** Mutations were identified in 50 cases (50.5%) including mutations of *ABCC8* gene (44 cases; 44.4%), Among these cases 25 with homozygous/compound heterozygous of *ABCC8* and 19 cases with one paternal/maternal mutation of *ABCC8* gene); *KCNJ11* (five cases; 5.1%), *HNF4A* (one case; 1.0%). 100% of cases with homozygous/compound heterozygous recessive mutations or one paternal dominant mutation of *ABCC8* gene did not respond to diazoxide treatment and required 95% pancreatectomy or octreotide injection. Other cases without identified mutations responded to diazoxide and/or glucose infusion. **Conclusion:** Children with congenital hyperinsulinism should be performed mutation analysis which helps in making diagnosis and treatment decision. Families of children with congenital hyperinsulinism should be given genetic counseling. Prenatal diagnosis should be performed as well as follow-up and treatment should be given to children with congenital hyperinsulinism immediately after birth.

P2-P571

The Effects of Serum Insulin, Leptin, Ghrelin, Adiponectin and Resistin Levels on Early Postnatal Growth in Small for Gestational Age Newborns

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Background: Adipose tissue acts as an endocrine organ, secreting biologically active molecules in response to external stimuli or lipid overloading. These adipose tissue-derived signaling molecules include adipokines such as leptin, adiponectin and resistin (4). On the other hand, ghrelin is the hunger hormone and an endogenous growth hormone secretagogue. **Objective and hypotheses:** This study aimed to investigate the relation between weight gain and serum insulin, leptin, ghrelin, adiponectin and resistin levels in small for gestational age newborns during neonatal period. **Method:** Newborns whose weight was lessthan the 10th percentale for gestational age were classified as small for gestational age newborns. Asymetrical SGA newborns were included in this study. All newborns were term. **Results:** Biochemical parameters were similar for two groups ($P > 0.05$) except for serum resistin levels at the birth. At the birth serum resistin levels were significantly lower in SGA group ($P < 0.01$). At the end of the first month there was no difference between biochemical parameters for two groups ($P > 0.05$). Δweight gain were negatively correlated with serum ghrelin ($p < 0.01$) and resistin ($P < 0.05$) levels of birth in SGA group. In control group, there was positively correlation between Δweight gain and serum insulin levels of birth ($P < 0.01$). **Conclusion:** Our results indicates that serum ghrelin and resistin levels negatively affect early posnatal growth in SGA newborns. On the other hand serum insulin levels were important in healthy newborns during early postnatal weight gain.

P2-P572

Sirolimus Therapy in Infant with Congenital Hyperinsulinemic Hypoglycemia Unresponsive to Diaxoside

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Background: Hyperinsulinemic hypoglycemia (HH) is the most common cause of severe, persistent neonatal hypoglycemia. Treatment of diffuse forms that is unresponsive to diazoxide and octreotide is near total pancreatectomy. **Objective:** To describe the clinical characterization of a newborn with congenital HH due to a diffuse pancreas lesion and unresponsive to diaxoside. **Case report:** Preterm term male of 33 weeks born to non-consanguineous Chilean parents at normal delivery. Birth weight 3030 g (>90th ce), length 44.5 cm (50th ce) and HC 34 cm (>90th ce). Apgar scores was 8 at 1 min and 9 at 5 min. He was non-dysmorphic and systemic examination was unremarkable. At 5 h of life his blood glucose level it was 20 mg/dl, concomitant insulin was increased (36 uU/ml) and ketone bodies are negative. HH was suspect. He was treated with i.v. glucose infusion (up to 19 mg/kg per min and s.c. glucagon 5 μg/kg per h but remained hypoglycaemic, so glucagon was increase up to 8 μg/kg per h. The patient was started on diazoxide (with hydrochlorothiazide) at 10 mg/kg per day on day 3 and then increased to 20 mg/kg per day but continued requirement of high glucose load and glucagon to maintain normal glucose levels. Ten days of life the patient failed to respond to diazoxide and sc octreotide was started (5 μg/kg per day to 25 μg/kg per day) with a good response. Sequence analysis for the ABCC8 and KCNJ11 gene showed no mutation. 68Ga dotatate PET/CT shows a diffuse compromise of the pancreas. 30 days of life the patient present and acute cholecystitis, so suspension of octreotide was decided. Glucose load and glucagon must be recommence. So the patient failed to respond to maximal dose of diazoxide and have major side effect with octreotide. At 2 month age, before to decide surgery of near total pancreatectomy, we decide treatment with Sirolimus an Mtor pathway inhibitor at of 0.5 mg/m^2 of body-surface area per day orally. The dose was gradually increased with the goal of reaching a serum trough level of 5–15 ng/ml. Over a period of 1 month the patient maintained stable blood glucose levels. Glucose infusion and glucagon were then gradually discontinued. The patient discharge at 3 month of age, with enteric feeding every 4 h, without hypoglycemia and sirolimus doses of 1 mg/m^2 of body surface and plasmatic levels of 5 ng/ml. **Conclusion:** We present a case of a newborn with congenital hyperinsulinism due to a diffuse compromise of the pancreas without response to maximal dose of Diaxoside. We decide to try with oral sirolimus. The patients had a good glycemic response to sirolimus. There were no adverse events during 10 month of follow-up.

P2-P573

IPEX Syndrome Caused by A Novel Mutation in Foxp3 Gene: A Case Report

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Background: Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome is a rare and life-threatening primary immunodeficiency characterized by wide-spread autoimmunity. Mutations in the *FOXP3* gene have been identified as the cause for IPEX syndrome. **Objective and hypotheses:** To describe clinical characteristics and genetic finding in the first Vietnamese patient with mutation of *FOXP3* gene. **Method:** Clinical features, biochemical finding, mutation analysis in a 12 day-old-boy were studied. Based on analysis of a 12 day-old-boy's clinical symptoms associated with biochemical examination, the diagnosis of IPEX was therefore confirmed. Genomic DNAs were extracted from peripheral blood leukocytes of proband and her parents with their informed consent for

genetic studies. Analysis of the coding regions and conserved splice sites of the *KCNJ11*, *ABCC8*, *INS*, *INSR*, *EIF2AK3*, *FOXP3*, *GATA4*, *GATA6*, *GCK*, *GLIS3*, *HNF1B*, *IER3IP1*, *PDX1*, *PTF1A*, *NEUROD1*, *NEUROG3*, *RFX6*, *SLC2A2*, *SLC19A2*, *WFS1* and *ZFP57* genes was performed using targeted next generation sequencing. Mutation in exon 11 of *FOXP3* was confirmed using Sanger sequencing. **Results:** The patient had gestation age of 41 weeks, birth weight of 2400 g. He was admitted with prolong jaundice and suspected hypothyroidism in the results of newborn screening. On admission, he presented with diarrhea, jaundice, vomit, dehydration. After one day, he presented with the features of diabetic ketoacidosis with pH of 6.95; HCO_3^- of 1.5 mmol/l; BE of −28.9 mmol/l; Investigation showed: blood glucose level 91.31 mmol/l; HbA1C 3.5%; total bilirubin level 274.4 μmol/l; direct bilirubin level 18.17 μmol/l; AST 40.6 U/l; ALT 18.4 U/l; T_3 0.4 nmol/l; T_4 24.39 nmol/l; TSH 764.2 mUI/ml, urea 28.14 mmol/l; creatinine 179 μmol/l; Na^+ 164 mmol/l, K^+ 4.7 mmol/l, Cl^- 146 mmol/l. WBC 4.97 G/l, NEU 3.89 G/l, LYM 0.63 G/l. Sanger sequencing analysis showed hemizygous for a novel *FOXP3* missense mutation, p.Pro378Leu from affected mother. He was treated with insulin infusion, adjustment of electrolyte and renal failure. **Conclusion:** We reported a classical case of IPEX syndrome in a boy with severe DKA and hypothyroidism in the second week of age. The identification of a *FOXP3* mutation in this family was important to predict prognosis for the child and risk for future offspring and enabled prenatal diagnosis.

P2-P574

Use of a Cord Blood F-Dex Monocyte Binding Assay to Study the Glucocorticoid Sensitivity in Premature 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 (GS) in this population would be helpful, especially in the preterm population, to determine optimal steroid treatment for better lung outcomes. Few groups have characterized the glucocorticoid receptor and its sensitivity using cord blood monocytes. Our pilot studies looking at term neonates born to mother without complications demonstrated that cord blood monocytes could be used as a non-invasive way to measure glucocorticoid sensitivity using a Fluorescein labelled dexamethasone (F-Dex) monocyte binding assay in this population. **Objective and hypotheses:** We propose to use cord blood monocytes to characterize glucocorticoid sensitivity in preterm neonates using a Fluorescein labelled dexamethasone (F-Dex) monocyte binding assay. We also propose to determine what factors can effect GS in neonates. **Method:** 25 cord samples were collected for neonates in the following cohorts: five from mothers with GDM, five from mothers with infection, five from mothers who smoke, five from mothers with pre-eclampsia and five from IUGR infants. We compared F-Dex binding in these groups to 25 term healthy neonates born without any complications that served as controls. **Results:** Preliminary results so far show that the F-Dex binding in these cohorts were similar to that in the control neonate populations. **Conclusion:** Our preliminary results show that factors such as gestational diabetes, maternal smoking, infection, pre-eclampsia and IUGR does not effect F-Dex binding in neonate cord blood monocytes. We will need to collect more sample to examine these factors and others further.

P2-P575

Persistent Hyperinsulinemic Hypoglycemic of Infancy

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Background: Persistent Hyperinsulinemic Hypoglycemic of Infancy (PHHI) is a clinically and genetically heterogeneous disorder with familial and sporadic form due to dysregulation of insulin secretion, PHHI is a severe disease that leads to brain damage. In diffuse type near total pancreatectomy has become the mainstay of surgical therapy for patients with PHHI who did not respond to medical therapy. **Objective and hypotheses:** To early detected cases of PHHI, try to differentiate between focal and diffuse types to manage them accordingly. As well as the importance of genetic analysis to identify genetic changes. **Method:** We have reviewed 14 infants (nine male and five female) who presented with severe recurrent nonketotic hypoglycemia in the period between (1996–2013), the mean age of presentation 3 weeks (2 days–3 months) except one patient was diagnosed at 6 years of his age, they came from different parts of Libya, they were managed at our center. The diagnosis of primary form of congenital hyerinsulinemic hypoglycemia was confirmed by laboratory investigations. Analysis of data regarding the time and mode of presentation, birth history, family history, consanguinity, genetic analysis was available for one patient, management and outcome of the patients were studied. **Results:** All patients showed persistent hypoglycemia in spite of normal to high insulin levels which inappropriately high for the blood glucose levels (Insulin: glucose ratio >0.3). Other causes of hypoglycemia were excluded. Eight patients with birth weight range from (2.9 kg–5.7 kg), they were found to have diffuse hyperplasia of the Beta cells of their pancreases. Two male infants presented with severe form of hypoglycemia earlier age 1–7 days of life with blood sugar 2–4 mg% and had greater birth weight (4.5 kg and 5.7 kg) their mothers were not suffering from gestational diabetes, they did not respond to medical therapy they found to have had multifocal adenomatosis in their pancreases. Four patients presented at <7 days with blood sugar <20 mg% had focal lesions of their pancreases. 13 patients under went near total

pancreatectomy. Unfavourable neurological outcome in 2 pts post pancreatectomy. Unfavourable neurological outcome in 2 pts due late intervention, because their family rejected operation. Diabetes mellitus developed in 2pts post pancreatectomy with mean age (5 years). Two patients died with fulminate infection. **Conclusion:** Early recognition, diagnosis and treatment of the condition are necessary to prevent or minimize neurologic damage. Preoperative investigations to identify a focal lesion of the pancreas can lead to a limited pancreatectomy and minimize the post operative complications such as development of diabetes, genetic analysis should be available for all patients.

P2-P576

The Postnatal Effect of Serum Vitamin D Binding Protein on Serum Vitamin D Level

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Background: It is not an uncommon situation that newborns have normal serum Ca, P, Mg, ALP, and PTH levels despite low vitamin D. Serum vitamin D binding protein (VDBG) may play a role for this situation. However, there is no any study investigated the relationship between serum vitamin D and VDBP in postnatal period. **Objective and hypotheses:** The aim of this study is to examine the relationship between serum vitamin D level and VDBP in neonates who have normal serum Ca, P, Mg, ALP, and PTH levels despite low vitamin D and investigate the effect on serum vitamin D level of prophylactic vitamin D dose (400 unite/day). **Method:** Mothers and their newborn, whose serum Ca, P, Mg, ALP, and PTH levels were normal, were separated into two groups by their serum vitamin D level (group A, low vitamin D; group B, normal vitamin D). VDBP level was measured in both group. Mothers and their newborn in group A were given 400 unite/day vitamin D. Serum Ca, P, ALP, Mg, PTH, vitamin D, and DVBP levels in group A were re-measured on the postnatal 45–60th days. **Results:** Both group A and group B had 30 mother-newborn pairs. There was no difference between group A and B in terms of serum Ca, P, Mg, ALP, and PTH levels of mothers and their newborn, whereas mothers and their newborn in group A had significantly lower vitamin D ($P=0.000$ and $P=0.000$, respectively) and higher VDBP ($P=0.04$ and $P=0.004$, respectively). On the 45–60th days, mothers' serum Ca and vitamin D levels significantly increased ($P=0.000$; $P=0.000$, respectively), whereas there was no difference in DVBP level. Newborns' vitamin D level significantly increased ($P=0.000$), however DVBP level significantly decreased ($P=0.004$). A negative correlation was found between serum vitamin D level and VDBP in both mothers and newborns ($P<0.048$, $r=-0.239$ and $P<0.002$, $r=-0.401$, respectively). **Conclusion:** Serum Ca, P, Mg, ALP, PTH, and vitamin D levels should be evaluated in both mother and their newborn. If serum vitamin D level is inconsistent with other parameters, this situation may be related to high VDBP level. In that case, prophylactic vitamin D dose should be preferred instead of high dose vitamin D therapy.

P2-P577

Endocrinologists Have A Role in Moderating Adverse Metabolic Consequences of Early Over Feeding of Children Born IUGR

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Background: Intra uterine growth retardation (IUGR) is well recognized to result in infants born small for gestational age (SGA). Early morbidity is followed by increased lifetime risks for health problems, particularly in the 10% of IUGR infants who fail to catch up. Risks include metabolic syndrome with obesity, insulin resistance, abnormal glucose metabolism, hypertension, dyslipidaemia, T2DM. Rapid weight gain in infancy is associated with increased incidence of later obesity, premature adrenarche and PCOS, as precursors of metabolic syndrome. Insulin resistance may be evident by the second year of life. In hospital settings, early care of SGA/IUGR infants is usually provided by neonatologists and general paediatricians. Early gastroenterologic referral for apparent failure to thrive is common. Use of percutaneous gastrostomy is utilized, aiming to improve weight gain. Endocrinology referral is usually later, for poor linear growth and consideration for growth hormone. **Objective and hypotheses:** Over feeding of IUGR infants and young children increases linear growth at the expense of signs of early metabolic syndrome. We aimed to provide evidence of adverse metabolic consequences of early over feeding of IUGR children. **Method:** Observation of growth parameters, weight distribution and metabolic parameters of 4 PEG fed children, aged 2-4 years with a history of IUGR, referred to an endocrine service for slow linear growth. **Results:** Severe central adiposity, buffalo hump and accelerated weight gain far exceeding increase in linear growth was seen in all. Glucose, insulin, lipids, liver function remained in normal ranges. **Conclusion:** Extreme caution should be undertaken before PEG feeding of IUGR infants and young children is considered. Careful monitoring is required to prevent onset of features of early metabolic syndrome. Ongoing surveillance is essential as children with rapid weight gain are those at greatest future and long term risk of dyslipidaemia, T2DM, ischaemic heart disease and stroke. It is a responsibility of endocrinologists to adequately inform their colleagues of cautions and special needs of IUGR children.

P2-P578

Primary Hyperparathyroidism in Children and Adolescents: About a Series of Ten Patients

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Background: Primary hyperparathyroidism (PHPT) in children and adolescents is rare. Sporadic forms are more frequent and correspond, usually, with an adenoma (73%). Most rare familial forms (7%) are related to hyperplasia. They may be isolated or integrate with multiple endocrine neoplasia (MEN). The PHPT is revealed mostly by chronic bone pain increased by pressure, walking and exercise, arthralgia, growth failure and nonspecific late deformities. **Objective and hypotheses:** Report clinical and paraclinical features of the HTP in children and adolescents. **Method:** This is a retrospective study of ten patients with PHPT identified in 20 years. All underwent clinical examination and paraclinical assessment looking for aetiology of PHPT (cervical ultrasound ± MIBI scintigraphy), bone repercussion (SKELETAL radiography, BMD), cardiac repercussion (ECG, cardiac Doppler ultrasound), renal repercussion (ultrasound) and the genetic study of the locus of menin. **Results:** Mean age at diagnosis was 15 ± 0.8 years (10–17). The sex ratio F/G was 4. The reason for consultation are: bone pain and muscular fatigability (70%), bone deformities (10%), pseudomyopathie (10%), systematic research in the case of NEM (10%). Clinical presentation was symptomatic in all cases: anorexia, constipation, abdominal pain, bone pain, short stature: Average height (-2.5 DS/M SEMPE; -2/TC), drowsiness, behavioral disorders and memory disorders with reduced performance school and bone deformity. A waddling gait was observed in one case. Biological assessment was characteristic: calcemia average 115 ± 1.5 mg/l (100–120), PTH average 80 ± 0.6 pg/ml (65–120). Radiological investigation showed adenoma in 70% and hyperplasia in 30%. He did not repercussion, There was an exception in cases of osteoporosis. The search for MEN 1 was positive in three cases. **Conclusion:** PHPT is rare in children. Sporadic or familial, or genetic or not, it must be detected before any clinical abnormalities suggestive. Its management must be early to prevent complications.

P2-P579

The Effects of Serum Leptin, Ghrelin, Adiponectin and Resistin Levels on Early Postnatal Growth in Infants of Diabetic Mothers

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Background: The exact mechanisms on growth are not fully eluciated, but they involve insulin resistance, fetal hyperleptinemia, hypothalamic changes. The adipose tissue-derived signaling molecules include adipokines such as leptin, adiponectin and resistin. On the other hand, ghrelin is the hunger hormone and an endogenous growth hormone secretagogue. **Objective and hypotheses:** This study aimed to investigate the relation between growth and serum insulin, leptin, ghrelin, adiponectin and resistin levels in infants of diabetic mothers during neonatal period. **Method:** The mothers were diagnosed as having gestational diabetes by an oral glucose tolerance test (OGTT) performed between 24 and 28 gestational weeks. Mothers were controlled by appropriate diet. Newborns of these mothers were included into the study. **Results:** Mean HbA1c level between well controlled diabetic and control mothers were not significantly different. There was no significant difference between antropometrical measurements (weight, length, head circumference and mid arm circumference) at the birth. Also, biochemical parameters were similar for two groups ($P > 0.05$). At the end of the first month there was no significant difference both antropometrical measurements and biochemical parameters for two groups ($P > 0.05$). Δweight gain was not correlated with serum leptin, ghrelin, adiponectin and resistin levels in two groups. Δweight gain was positively correlated with serum insulin levels at the birth in controls (< 0.05). While there were positively correlations between Δweight gain and head circumference (< 0.01), mid arm circumference (< 0.01) of first month in infants of diabetic mothers, there was just positively correlation between Δweight gain and, mid arm circumference (< 0.01) of first month in controls. **Conclusion:** Our results indicates that serum leptin, ghrelin, adiponectin and resistin levels do not affect early posnatal growth both in healthy newborns and in infants of diabetic mothers. In healthy newborns early postnatal weight gain is related to serum insulin at the birth.

P2-P580

Newborns of Mothers Affected by Autoinmune Thyroid Disease

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Background: Monitoring of thyroid function in neonates born from mothers affected by autoinmune thyroid disease is not perfectly established. The influence of etiology of maternal disease, maternal thyroid peroxidase antibodies (TPOAb) and L-thyroxine therapy during pregnancy on neonatal thyroid function were also investigated. **Method:** 194 term neonates were tested for thyroid function by measurement of free thyroxine (FT_4), TSH in the 2nd day and one month of life. 167 neonates were born from mothers affected by chronic lymphocytic thyroiditis and 27 from mothers with Grave's disease. TPOAb and thyroglobulin antibodies (TGAb) were measured in all patients, Thyroid Stimulating Inmunoglobulin (TSI) were also measured in newborns from mothers with Grave's disease; periodical control of thyroid function were performed if TPOAb/TGAb were positive until they were negative or they were descended. Etiology of maternal hypothyroidism, maternal TPOAb and TGAb during pregnancy and dose of maternal therapy with L-thyroxine during pregnancy were retrospectively collected. **Results:** 20% neonates showed at least a mild increase of TSH value (more than 6 mcU/ml) at the different determinations. 1.5% were newborns from mothers with

Grave's disease. Only three cases (1.5%) showed an increase of TSH value more than 10 mcU/ml, all of them born from mothers with chronic lymphocytic thyroiditis. In all of them, a spontaneous completely normalisation of TSH value was observed within the next determinations and they did not required L-thyroxine replacement therapy. **Conclusions:** Transient mild elevation of serum TSH above the normal reference value for age is frequently observed in the first months of life in infants born from mothers affected by autoinmune thyroid diseases, but no so many need L-thyroxine replacement therapy. Follow-up is still recommended in these newborns.

P2-P581

Missense Mutation of *GLIS3* Gene Resulting Inneonatal Diabetes and Congenital Hypothyroidism

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Background: Neonatal diabetes, diabetes diagnosed before six months of age, is rare, with incidence of approximately 1:90 000–160 000 live births. In approximately half of cases, neonatal diabetes istransient and usually resolves between 6 and 18 months of life. In the remainder of cases, the diabetes is permanent. Mutations in the GLI-similar 3 (*Glis3*) gene encoding the transcription factor *GLIS3* are a rare cause of permanent neonatal diabetes and congenital hypothyroidism with eight affected cases reported to date.We are reporting first missense mutation in *GLIS3* resulting in neonatal diabetes and congenital hypothyroidism. **Objective and hypotheses:** To evaluate and present non classical situation for a case of neonatal diabetes and. As well as sequence correlation between neonatal diabetes and hypothyroidism in missens mutation in genetic studies. **Method:** One infant Libyan female 6 weeks old, she was presented with hypovolemic shock in ketotic state and markedly raised her blood sugar 1020 mg/dl. the patient was managed according her condition and discharged on basal insulin. Consequently at 5 month of her age developed hypothyroidism. Evaluations the patient clinically and genetic studies was done were found first missens mutation resulting in her condition. **Results:** A Libyan female, was born at full term with a weight of 2.4 kg and head circumference of 34 cm, to non-consanguineous parents. Intrauterine growth retardation was noted during pregnancy. Six weeks after birth, she was admitted to the hospital with hypovolemic shock found to have blood sugar of 1020 mg/dl without significant acidosis or ketosis. Target blood glucoses have been easyto achieve with just intermittent insulin therapy. At five months of age TSH found to be persistently elevated (10.7 μIU/ml) with free T_4 15.9 Pmol/l and started on levothyroxine replacement. Abdominal ultrasound scan performed at age of six months showed normal morphology of the liver, pancreas and both kidneys. The homozygous mutation c.1924A > T (p.Ser642Cys), was identified when the patient was tested for a monogenic etiology by sequencing a panel of 13 genes associated with neonatal diabetes. Patient now is at eight months of age with normal developmental milestones, as well as physical development and requires 0.1–0.2 units/kg per day of basal insulin with HbA1c 6.3%. **Conclusion:** This case extends the clinical spectrum associated with mutations in *GLIS3.* We are describingthe first case of *GLIS3* gene missense mutation c.1924A > T (p.Ser642Cys) resulted in neonatal diabetes and congenital hypothyroidism. Mutations in *GLIS3* should be considered in all children with neonatal diabetes without an established cause, irrespective of reported parental relatedness or insulin requirements.

P2-P582

Birth Chest Circumference Relations to Circulating Insulin-Like Growth Factor-I in the Not-life-threatened Newborn: Relevance of Birthweight to Birth Crown-Heel Length Ratio Beyond The Presence of a Small Birthweight for Gestational Age and of Respiratory Support Measures

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Background: Birth chest circumference (BC) may be related to Insulin-like-Growth-Factor-I blood serum levels (IG1) in the human newborn (NWB). **Objective and hypotheses:** We evaluated the relevance of birth body weight (BW) to birth crown-heel length (BL) ratio (BW through BL, BW/BL) in BC relations to IG1 after control for BW for birth gestational age (GA) < = 10th centile (SGA), respiratory oxygen supplementation (O2S) and assisted ventilation of any kind (AV) in not-life-threatened NWBs. **Method:** NWBs with any among total parenteral nutrition, life-threatening disease, diabetes mellitus (DM), endocrine diagnosis out of DM, malformation, clinically relevant trunk trauma, and mother with DM were excluded. Each of 78 included NWBs had available data for: i) gender (SEX), GA (unit: complete week; range = 28–42), BW (unit:kg; range = 1.200–4.150), BL (unit: m; range = 0.360–0.550), BC (unit: cm; range = 22.0–39.0), BW/BL (unit: kg/m; range = 3.158–8.137), SGA, postnatal age (PNA; unit: day) and ii)same-day records at one of the first 5 postnatal days (x), 5 days after x (y) and 10 days after x (z) for O2S, AV, as well as IG1 RIA measurements (unit: uM/dl)

(male SEX, *n*, 43; birth at GA ≤ 36, *n*, 46; SGA, *n*, 20; O2S, *n*, x = 22, y = 11, z = 1; AV, *n*, x = 8, y = 4, z = 1). Natural log-transformed IG1 (IG1-LN) resulted near-normally distributed. Multiple Linear Regression (MLR) was used (computations; male SEX, SGA, O2S, AV, condition present = 1, condition absent = 0). **Results:** MLR showed a significant partial correlation (PC) coefficient (*r*) of BC PCs with outcomes IG1-LNx-y-z when including as predictors ii) PNA, O2S and AV chronologically corresponding to IG1-LN, SEX, SGA and BC, all together (MLR1;BC vs IG1-LN; x, r : 0.38, *P* : 0.0011; y, *r* : 0.47, *P* < 0.0000; z, *r* : 0.42, *P*: 0.0002) while no significant BC PCs with outcomes IG1-LNx-y-z were found after adding as predictor to MLR1 either iii) BW/BL(MLR2) or ii) BW/BL and GA(MLR3) (R2 of considered MLR models: 0.27–0.52, always significant). **Conclusion:** BW/BL could be involved in BC relations to IG1-LN not explained by SEX, SGA, PNA, O2S and AV in the not-life-threatened NWB.

P2-P583

Neonatal Failure to Thrive and Dyselectrolytemia – Not Always a Congenital Adrenal Hyperplasia

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Background: Pseudohypoaldosteronism (PHA) is a rare entity inducing, in case of late or missed diagnosis, life-threatening clinical and biochemical complications. **Objective and hypotheses:** To report a case of 4-week-old boy with failure to thrive, dehydration, hyponatremia, hyperkalemia, metabolic acidosis. The first diagnosis was congenital adrenal hyperplasia, but in the evolution, the right diagnosis of PHA was retained. **Method:** The baby presented to a general hospital with failure to thrive (actual weight below the weight at birth), clinical sign of dehydration (no vomiting or diarrhoea), dyselectrolytemia (hyponatremia, hyperkalemia) and metabolic acidosis. The first diagnosis was adrenal crisis and intravenous hydrocortisone was started. 24 h later, he was transferred to our Department, with a better clinical appearance, but with persisting hyponatremia and hyperkalemia. He is the second child of non-consanguineous parents. No history of sudden infant death, but a paternal cousin had transient problems with salt in the neonatal period. **Results:** An extensive hormonal profile revealed normal 17 hydroxyprogesterone level, high cortisol, renin and aldosterone levels, high urinary sodium and low potassium, confirming biologically the clinical suspicion of PHA. The sweat test was normal. Neither urinary tract obstruction, no infection. As the clinical evolution, response to hydrocortisone and biological results were suggestive of PHA, hydrocortisone was stopped and normal salt was added into the milk. The clinical and biological course was satisfactory (weigh gain of 50 g/d, stabilized sodium and normal potassium levels). **Conclusion:** Considering the clinical spectrum, family history, favourable response to sodium supplementation and kidney restricted aldosterone resistance (no sodium loss through sweat) we assume that this PHA is a renal type 1. A genetic analysis is under way. Our goal in describing this case is to underline the necessity to have in mind a differential diagnosis for clinical and biological appearance of CAH, notably early in the presentation, when the hormonal profile is not completely available.

P2-P584

A Unique IL2RA Mutation Presenting as Neonatal Diabetes, Congenital Hypothyroidism and Sepsis

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Background: 16 year old female neonate presented with neonatal diabetes, congenital hypothyroidism and sepsis. **Objective and hypotheses:** To evaluate the neonate for a common cause of neonatal diabetes, congenital hypothyroidism and sepsis and to explore for the best modality of management, including a possible role for sulphonylureas. **Method:** The neonate born of 3rd degree consanguinity was admitted and started on insulin infusion and thyroxine supplementation of 25 μg. After stabilisation, she was switched to subcutaneous insulin, but the dose requirements were so low that she needed only 0.3 units of glargine in two divided doses daily for a weight of 5 kg. Thyroxine dose also needed to be enhanced to 50 μg. Ultrasound neck showed normal thyroid morphology. Genetic analysis was sought. **Results:** On Day 52 of life, child developed severe sepsis and expired within 4 days. Targeted next-gen sequencing revealed a homozygous Interleukin2 Receptor Agonist partial deletion c.65-?_819+?del, associated with lymphoproliferation and autoimmunity. Her parents were heterozygous for same mutation and unaffected. She is only the second child to present with IL2RA mutation and diabetes and the first with this unique mutation. **Conclusion:** The IL2RA mutation caused a constellation of features including sepsis, neonatal diabetes and hypothyroidism (? Possibly autoimmune in origin) which culminated in the death of the neonate due to severe sepsis. Since the parents are consanguineous, they have been offered antenatal genetic testing in future pregnancies.

P2-P585

Change Level of TRAb in Newborn Leads to Thyroid Dysfunction – Case Report

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Maternal new-diagnosed Graves' disease is quite rare thyroid dysfunction with an estimated incidence of 0.4–1% of all pregnancies, but only 1–5% of newborns delivered to mothers with Graves' disease develop overt clinical signs and symptoms of hyperthyroidism. Neonatal hyperthyroidism almost always is transient and results from the transplacental passage of maternal thyrotropin (TSH) receptor stimulating antibodies. Neonates born to mothers with Graves' disease are at risk for significant morbidity and mortality and need to be appropriately identified and managed. We present the case of 1-month-old baby, who was diagnosed by hypothyroidism during first week of his life, and after that we observed clinical signs and symptoms of hyperthyroidism. A 3350-g male neonate in a good condition was born at term to a mother with Graves' disease first diagnosed at 13-week gestation. Pregnant woman had high level of TRAb and she was treated with methimazole (MMI) and beta-blockers, obtained euthyroid. During first days in newborn we observed increased level TSH in serum (30. 47 uIU/ml) and normal level of fT4 (0.73 ng/ml) and elevated TRAb (30.36 IU/l), so positive level of TSH- receptor antibodies regarded the newborn as 'at risk' for the development of hyperthyroidism. Development of hypothyroidism was the effect of using antithyroid drugs (ATDs) in his mother. We followed up the baby and we observed changes levels of thyroid hormones and increased serum TRAb. A 8-day-old male had tachycardia without any other physical signs of thyrotoxicosis. TSH – 0.05 uIU/ml; fT3 – 13.21 pg/ml; fT4 – 7.79 IU/l; TRAb – 33.17 IU/l. Because of development of hyperthyroidism we used methimazole (MMI) as the treatment of choice; beta-blockers can be added for sympathetic hyperactivity. A 1-month-old baby taking ATDs became euthyroid without significant side effects and we observed decreased level of TRAb (26.14). **Summary:** 1. Testing for TSH receptor antibodies is useful in pregnant women with Graves' disease to determine the risk of neonatal thyroid dysfunction due to transplacental passage of stimulating or blocking antibodies; 2. Tachycardia in newborn from mother with Graves' usually is a first sign of thyrotoxicosis; 3. Rapid fT4 elevation during the first postnatal week is predictive of hyperthyroidism and warrants ATD therapy.

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Hyperthyrotropinemia of the Preterm Newborn: Treat or Not to Treat?

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Background: It is often difficult to establish whether hyperthyrotropinemia in preterm newborn is a simple physiologic energy sparing phenomenon or a true hypothyroidism requiring replacement treatment. **Objective and hypotheses:** This study aimed to find in what extent thyroid function in the preterm newborn can be influenced by clinical characteristics and complications. **Method:** We studied 35 preterm newborn, gestational age (GA) 32.0 (2.1) weeks, 21 males, 13 small for gestational age (SGA), positive at TSH neonatal screening and with persistent hyperthyrotropinemia during hospitalization. We collected the following clinical data: GA, type of delivery, birth weight (BW), length (BL) and head circumference, clinical complications (RDS, jaundice, infections), time of detection and level of the pathologic TSH value in the dried blood spot (DBS) and in the serum sample, time of starting L-thyroxine and its dosage at steady state. Data are reported as median (IQR). Mann-Whitney test and simple regression were applied for statistical analysis. **Results:** TSH levels and time of detection of pathologic values were not correlated to GA, BW, length and head circumference. SGA showed lower serum TSH levels (14.6 (5.1) μU/ml vs 22.6 (69.9) μU/ml; $P<0.05$). The patients with RDS showed lower TSH levels compared with patients without RDS (14.6 (7.9) μU/ml vs 24.0 (66) μU/ml; $P<0.05$) and required lower L-Thyroxine dosage at steady state (6.6 (4.0) vs 10.0 (2.0) μg/kg per day; $P<0.05$). The starting time of replacement treatment was inversely correlated to BW and BL ($P<0.05$) but was not different in SGA compared to appropriate for gestational age newborns. The patients who received replacement treatment had significantly higher pretreatment TSH in serum (18.11 (65.07) μU/ml vs 11.55 (10.83) μU/ml; $P<0.02$) but not in DBS (10.0 (23.75) μU/ml vs 6.69 (3.05) μU/ml; $P>0.05$). **Conclusion:** Our results support the hypothesis that subclinical hypothyroidism could play a protective effect on growth and respiratory function in the preterm newborn. Further studies are needed to determine whether or not to undertake replacing therapy.

P2-P587

Permanent Neonatal Diabetes Mellitus Due to a G32S Heterozygous Mutation in the Insulin Gene

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Background: Permanent neonatal diabetes mellitus (PNDM) is a rare form of monogenic diabetes with onset less than 6 months of age. Together, activating mutations in KCNJ11 and ABCC8 genes, that encode the Kir6.2 andsulfonylurea receptor 1 (SUR1) subunits, respectively, account for nearly 50% of PNDM cases. **Case report:** We present a case reported a child diagnosed with PNDM resulting from a new mutation in the insulin (INS) gene, leading to severe hyperglycemia and ketoacidosis from 5 month of life. Molecular analyses for KCNJ11, ABCC8, GCK, GLIS3 did not show any mutation. We sequenced the INS gene in the proband and her patents, identified the heterozygous missense mutation G32S (c.94G>A, p.Gly32Ser) in the child with diabetes. It has

been hypothesized that the mutations in the INS gene disrupt the folding of the proinsulin molecule and result in a bad situation causing endoplasmic reticulum stress and pancreatic beta cell apoptosis. Subjects with this form of diabetes will need lifelong insulin therapy. **Conclusion:** Insulin gene mutations appear to be an important cause of neonatal diabetes. We recommend that all the infants with PNDM should undergo genetic analysis before oral sulfonylurea treatment.

P2-P588

Case Report on Hyperinsulinism/hyperammonaemia Syndrome: An Easily Treatable Cause of Postprandial Hypoglycaemia

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Background: Hyperinsulinism/hyperammonaemia (HI/HA) syndrome is associated with postprandial hypoglycaemia and mild hyperammonemia. There is increased insulin release following protein ingestion, which is amenable to diaxozide therapy. While developmental delay and normoglycaemic seizures can also occur, hepatomegaly has not been reported. We report a child with HI/HA and hepatomegaly, mild learning difficulty and obesity, who was initially mistaken to have glycogen storage disease (GSD). **Objective and hypotheses:** The child first presented at 9 months of age with hepatomegaly and hypoglycaemic seizures. Liver biopsy was suggestive of metabolic hepatopathy and he was managed as GSD. Despite frequent feeds and corn starch, intermittent hypoglycaemic seizures continued, and he was re-evaluated at 5 years of age. This time, mild learning difficulty, obesity, and mid-afternoon lethargy/drowsiness and brief normoglycaemic seizures were noted, while hepatomegaly had regressed. His capillary blood glucose levels were relatively low throughout the day. **Method:** The child tolerated a supervised fast for 18 hours, without hypoglycaemia, but subsequently had a hypoglycaemic seizure, an hour after a meal containing rice, dhal and egg. During the in-ward seizure, child had detectable serum insulin and absent urine ketone bodies. HI/HA was suspected and a protein loading test was performed. **Results:** Symptomatic hypoglycaemia occurred within an hour of protein loading, and blood glucose increased by 40 mg/dl with IV glucagon, while serum ammonia was elevated. These results were compatible with HI/HA. Oral dioxide and a low protein (leucine) diet were prescribed, and corn starch and frequent feeding discontinued. **Outcome:** A rapid clinical improvement was seen, with disappearance of lethargy and hypoglycaemia, and improvement in obesity. HI/HA can be biochemically confirmed and managed easily if suspected, emphasising the importance of awareness of this entity. **Conclusion:** The presence of hepatomegaly deterred from the correct diagnosis at presentation. However the correct diagnosis was uncovered by a detailed history, and simple ward procedures. This is an important condition for paedaitrci endocrinologists to be aware of as the diagnosis and treatment can be instituted even in low resource settings without genetic testing facilities.

P2-P589

Severe Systemic Pseudohypoaldosteronism Type 1: 5 Years of Evolution

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Background: Pseudohypoaldosteronism type 1 (PHA1) is a rare syndrome characterized by unresponsiveness or resistance to the action of aldosterone. It manifests with persistent salt loss, resulting in hyponatremia, hyperkalemia and metabolic acidosis. High levels of aldosterone and renin activity, confirms the diagnosis. When the inheritance pattern is autosomal recessive it expresses as a severe systemic disease. Often occurs in the neonatal period and presents with recurrent episodes of salt loss that are life-threatening. **Objective and hypotheses: Method: Results:** Male child with irrelevant gestational history. Ten-year-old sister with Chediak-Higashi syndrome. A recessive form of PHA1 (homozygous mutation of intron 3 of the SCNN1A gene) was diagnosed in the neonatal period (severe hyperkalemia, hyponatremia, dehydration and acidosis). After numerous life-threatening crisis he was discharged at five months-old under fludrocortisone 1.5 mg/day, sodium supplement 33 mEq/kg per day and cation-exchange resin 1 g/kg 5 times/day. He was admitted several times in the emergency room with hypovolemic shock, requiring intensive treatment, increasing of cation-exchange resin and frequently nebulized salbutamol and calcium gluconate. He always maintained tight control of electrolyte balance and therapeutics. Empirically, hydrochlorothiazide was started since eighteen months-old to four years-old (maximum dose 2 mg/kg per day). At this time, fludrocortisone was gradually reduced, and later, cation-exchange resin was also decreased. Sodium supplement ranged from 28 to 55 mEq/kg per day. At 18 months-old, his first seizure occurred in apirexy, the other six were simple febrile seizures. Electroencephalograms were normal. Analytical monitoring showed transient subclinical hypothyroidism, asymptomatic hypoglycemia and normal ACTH, cortisol, C-peptide, insulin and IGF-1. ACTH stimulation test and brain magnetic resonance imaging were normal. Currently, at five years-old, he maintains failure to thrive (height – 2.61 SDS, weight – 3.53 SDS) with regular growth velocity and normal development. He only keeps sodium supplement. **Conclusion:** We report this

severe PHA1 case with poor initial prognosis but with favorable evolution. We discuss hydrochlorothiazide and fludrocortisone use in this pathology, despite the lack of evidence.

P2-P590

Birth Chest Circumference Relations to Circulating Insulin-Like Growth Factor Binding Protein-3 in The Not-Life-Threatened Newborn: Relevance of Birthweight to Birth Crown-Heel Length Ratio After Control for A Small Birthweight for Gestational Age, for Respiratory Support Measures and for Circulating Insulin-Like Growth Factor-I

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Background: Birth chest circumference (BC) may be related to Insulin-like Growth Factor (IGF)-Binding-Protein-3 blood serum levels (IB3) in the human newborn (NWB). **Objective and hypotheses:** We evaluated the relevance of birth body weight (BW) to birth crown-heel length (BL) ratio (BW through BL, BW/BL) in BC relations to IB3 after control for BW for birth gestational age (GA) $<=$10th centile (SGA), respiratory O2 supplementation (O2S), assisted ventilation of any kind (AV) and IGF-I blood serum levels (IG1) in not-life-threatened NWBs. **Method:** NWBs with any among total parenteral nutrition, life-threatening disease, diabetes mellitus (DM), endocrine diagnosis out of DM, malformation, clinically relevant trunk trauma and mother with DM were excluded. Each of the 78 included NWBs had available data for: i) gender (SEX), GA (unit: complete week; range = 28–42), BW (unit: kg; range = 1.200–4.150), BL (unit: m, range = 0.360–0.550), BC (unit: cm; range = 22.0–39.0), BW/BL (unit: kg/m; range = 3.16–8.14), SGA, postnatal age (PNA; unit: day) and ii) same-day records at one of the first 5 postnatal days (x), 5 days after x (y) and 10 days after x (z) for O2S, AV, as well as IG1 and IB3 RIA measurements (unit: uM/dl) (male SEX, *n*, 43; birth at GA $\leq$ 36, *n*, 46; SGA, *n*, 20; O2S, *n*, x = 22, y = 11, z = 1; 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, SGA, O2S, AV; condition present = 1, condition absent = 0). **Results:** MLR showed that the partial correlation (PC) coefficient (*r*) of BC PCs with outcomes IB3-LNx-y–z was significant when including as predictors i) PNA, O2S and AV chronologically corresponding to IB3-LN, SEX, SGA and BC, all together (MLR1; BC vs IB3-LN; x, *r*: 0.38, $P < 0.0000$; y, *r*: 0.50, $P < 0.0000$; z, *r*: 0.62, $P < 0.0000$), or ii) PNA, O2S, AV and IG1 chronologically corresponding to outcome, SEX, SGA and BC, all together(MLR2; BC vs IB3-LN; x, *r*: 0.27, *P* 0.0231; y, *r*: 0.27, *P*: 0.0228; z, *r*: 0.53, $P < 0.0000$) but no significant BC PCs with outcomes IB3-LNx-y-z were found after adding as predictor to MLR1 or to MLR2 either iii) BW/BL(MLR3) or iv) BW/BL and GA(MLR4) (R^2 of considered MLR models: 0.38–0.68, always significant). **Conclusion:** BW/BL may be involved in BC relations to IB3-LN not explained by SEX, SGA, PNA, O2S, AV and IG1 in not-life-threatened NWBs.

P2-P591

Renal form of Pseudohypoaldosteronism Type I in Sucking: Clinical Case

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Pseudohypoaldosteronism is one of the least explored questions in clinical endocrinology. That leads to complexity in diagnosis and differential diagnostics of disease. A boy, aged 13 days was admitted to the hospital with complains: vomiting, low weight gain, constipation. Biochemical blood assay (BBA) and acid-base balance of blood: level of sodium – 127 mmol/l (N 132–145 mmol/l), potassium – 6.6 mmol/l (N 3.1–5.1 mmol/l), chlorine – 94.7 mmol/l (98–107 mmol/l), pH – 7.42 (N 7.35–7.45). Clinical blood analysis, clinical urine analysis, thyroid hormones, coagulation profile were within normal limits. Values of 17-pregnenoldione in blood – 4.09 and 2.57 nmol/l (N 0.7–2.3 nmol/l), adrenocorticotropic hormone (ACTH) – 9.61 pmol/l (N 7.2–63.3 pmol/l), cortisol – 76.5 and 324 nmol/l (N 140–600 nmol/l), dehydroepiandrosteronum-sulfate – 252.1 μg/dl (N 31.6–214 μg/dl). Diagnosis was made: salt-losing form of congenital adrenal cortical hyperplasia. Fludrocortisone and hydrocortisone were given. BBA after treatment: level of sodium – 127 mmol/l and potassium – 6.8 mmol/l. Values of ACTH in blood (34.9 pmol/l), aldosterone (2772 ng/l, N 300–1900 ng/l), renin (128 pg/ml, N 4.66–31.9 pg/ml) were measured. Resistance of electrolyte disturbances was marked on glucocorticoid and mineralocorticoid treatment. The final clinical diagnosis was made: renal form of pseudohypoaldosteronism type I (based on complains, level of sodium and potassium, values of ACTH, aldosterone and renin in blood, resistance of electrolyte disturbances was marked on treatment of glucocorticoid and mineralocorticoid). Gradual dose decline of fludrocortisone and hydrocortisone to full drug withdrawal; solution of Sodium Chloride 0.9% peroral (100 ml within 24 h) were recommended. The child (2 months 13 days) was discharged from the hospital in compensated condition. **Conclusion:** Early diagnosis of pseudo-hypoaldosteronism permits to start treatment timely and to improve prognosis, to reduce the risk of physical and psychomotor retardation.

P2-P592

Neonatal Hyperparathyroidism with Homozygous Missense Mutation in the CASR Gene

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Background: Neonatal hyperparathyrodisim can be caused by homozygous and heterozygous inactivating mutation in the calcium-sensing receptor can cause familial hypocalciuric hypercalcaemia (FHH) or neonatal sever hyperparathyroidism (NSHPTT). NSHPT represents the most sever expression of FHH and courses as life threatening condition. **Objective and hypotheses:** Neonatal hyperparathyrodisim can be caused by homozygous and heterozygous inactivating mutation in the calcium-sensing receptor can cause FHH or NSHPTT. NSHPT represents the most sever expression of FHH and courses as life threatening condition. **Method:** CASR gene mutation analysis performed on genomic DNA of the siblings and their parents. **Results:** A novel homozygous mutation in CASR was identified in the asymptomatic normocalcaemic parents and the symptomatic three siblings (female and 2 male) so confirming the sever neonatal hyperparathyroidism in the sibling. **Conclusion:** The identification of this novel CASR gene mutation established the basis of hypercalcemia in the this family and further management.

P1-P593

The Mechanistic Role of Fibroblast Growth Factor 21 (FGF21) in Growth Hormone Resistance Secondary to Chronic Childhood Conditions

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Background: Both undernutrition and chronic inflammation impair linear growth through resistance to GH. Fibroblast growth factor 21 (FGF21) is known as an important regulator of the metabolic adaptation to fasting. Elevated expression of FGF21, secondary to prolonged undernutrition has been identified to develop GH resistance and subsequent attenuation of skeletal growth and growth plate chondrogenesis in both mice and human. However, the mechanism of FGF21's actions remains largely unknown. Molecular understanding of this process may open avenues for novel therapeutic intervention to enhance linear growth of children with secondary GH resistance. **Objective and hypotheses:** We envisage that elevated FGF21 exposure has a key role in GH resistance by direct action on human chondrocytes. The objective of this study is to unravel the mechanistic interplay of FGF21 in GH-receptor (GHR) signalling. **Method:** Hek-293 stable lines were generated with human/mouse GHR overexpression. Time course evaluation with cycloheximide, without/with; GH and recombinant FGF21 treatment for 1 8 h revealed GHR half-life. Hek-293 human/mouse GHR cells were treated without/with; recombinant FGF21 and GH for 0, 10 or 30 minutes and assessed for signal transducer and activator of transcription 5 (STAT5) and phosphorylated-STAT5 expression. **Results:** Validation of stable lines confirmed the expression of FGF21 receptor complex; FGFR1 iiiC/β-Klotho and the molecular integrity of GHR signalling. We identified two interrelated mechanisms for GH resistance after exposure to FGF21. i) FGF21 significantly reduced GHR half-life overtime. ii) GH induced the activation STAT5 phosphorylation and downstream signalling which was inhibited by FGF21 exposure. Future work will determine the role of FGF21 in GH resistance under chondrogenic differentiation. **Conclusion:** Chronic FGF21 exposure increases GHR turnover and inhibits early upstream in GHR signalling, implicating a fundamental role for FGF21 in GH resistance secondary to chronic childhood conditions.

P1-P594

Somapacitan, a Once-Weekly Reversible Albumin-Binding Growth Hormone (GH) Derivative, Is Well Tolerated and Convenient in Adults with GH Deficiency (AGHD): Results from a 26-Week Randomised, Controlled Phase 3 Trial

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Background: Growth hormone (GH) replacement as daily s.c. injections for patients with adults with GH deficiency (AGHD) can be cumbersome. Somapacitan (Novo Nordisk), a once-weekly reversible albumin-binding GH derivative, has been shown in short-term trials to be well tolerated in healthy adults and in patients with AGHD. **Objective and hypotheses:** This trial was a multinational, multicentre, randomised (2:1), open-label, active-controlled trial (NCT02382939; REAL 2) investigating the safety, tolerability and treatment satisfaction of once-weekly somapacitan versus once-daily hGH (human GH; somatropin) in patients with AGHD. **Method:** Ninety-two patients (diagnosed with AGHD, previously treated with somatropin for $\geq$6 months, male or

female, aged 18–79 years) were randomised to once-weekly somapacitan or once-daily somatropin. During the first 8 weeks, somapacitan and somatropin doses were titrated according to serum insulin-like growth factor-I (IGF-I) SDS levels in order to achieve IGF-I levels within the normal range and preferably between 0 and 2 SDS; a fixed dose was received for the remaining 18-week period. Treatment satisfaction was assessed using the Treatment Satisfaction Questionnaire for Medication-9. **Results:** A similar pattern and rate of adverse events (AEs) and serious AEs was observed with the two treatments. The most frequently occurring AEs for somapacitan and somatropin were nasopharyngitis, headache and fatigue. Mild and transient injection site reactions were observed only in the somapacitan group. After dose titration, the IGF-I levels were maintained in both treatment groups. No anti-somapacitan or anti-hGH antibodies were detected. A statistically significant difference between treatment arms in convenience score was observed with once-weekly somapacitan being more convenient than once-daily somatropin. Effectiveness and global satisfactions scores were similar in both groups. **Conclusion:** Somapacitan was well tolerated and no safety issues were identified. These data indicate that somapacitan may serve as a well-tolerated, once-weekly treatment for AGHD and be more convenient than once-daily treatment.

P1-P595

The Diagnostic Value of IGF-II, IGF-I and IGFBP-3 in Silver–Russell Syndrome

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Background: Recently we described a family with several members having intrauterine and postnatal growth failure as well as signs of Silver–Russell syndrome (SRS) who carried a heterozygote nonsense mutation of IGF2. The patients had low IGF-II serum levels, but normal IGF-I serum levels. **Objective and hypotheses:** We aimed to estimate the diagnostic value of the IGF-II, IGF-I and IGFBP-3 measurements in the assessment of children with SRS. **Method:** We collected data from 52 genetically analysed children with SRS and 113 children with non-syndromic SGA short stature, seen during the last 20 years in our centre. Patients were prepubertal and GH treatment naive. The SRS patients fulfilled ≥ 4 of the following criteria: SGA, failure to thrive, short stature, relative macrocephaly, prominent forehead or skeletal asymmetry. 11p15 loss of methylation (11p15LOM) was present in 22 patients, maternal uniparental disomy of chromosome 7 (UPD7mat) in seven patients and IGF2 nonsense mutation (IGF2mut) in three patients. There were two carriers of structural chromosomal aberrations outside of 11p15 and 18 patients were tested negative (idiopathic). The SRS children were 4.7 ± 2.1 years and the 113 SGA children 5.7 ± 1.8 years of age. IGF-II, IGF-I and IGFBP-3 were measured by the same in-house RIAs during the full study period. **Results:** The median IGF-II SDS values were in the different diagnostic categories in increasing order: IGF2mut -1.75, UPD7mat -1.69, non-syndromic SGA -1.55, idiopathic -0.65, and 11p15LOM -0.61. The median IGF-II to IGF-I concentration ratio was lowest with 2.57 (range; 2.51–2.96) in IGF2mut contrasting to a ratio of 5.44 (3.01–11.20) in 11p15LOM ($P = 0.036$), 7.35 (3.19–13.82) in idiopathic, and 7.98 (5.31–10.52) in UPD7mat. Patients with UPD7mat had significantly lower values of IGF-I and IGFBP-3 than patients with 11p15LOM ($P \leq 0.002$). **Conclusion:** The molecular diagnosis in SRS can be predicted based on IGFs and IGFBP-3.

P1-P596

Functional *in vitro* Characterization of Two Novel Germinal *STAT3* Mutations Associated with Short Stature, Immunodeficiency and Autoimmune Disease

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Background: We have recently reported the molecular diagnosis of two patients with severe growth failure associated with a spectrum of early-onset autoimmune disease and immunodeficiency. Heterozygous *de novo* mutations, c.1847_1849delAAG (p.E616del) and c.1276T > C (p.C426R), in the *STAT3* gene were found. Functional *in vitro* studies of these variants are presented. **Objective and hypotheses:** We aimed to study the impact of p.E616del and p.C426R mutations on STAT3 activity under basal and GH- or IL-6-stimulated conditions. We hypothesised that both variants are activating, since inactivating *STAT3* mutations are associated with hyper-IgE syndrome without growth failure. **Method:** *STAT3* gene variants were generated by site-directed mutagenesis and transfected into HEK293T cells. The effects of IL-6 (20 ng/ml) and GH (200 ng/ml) on expression, phosphorylation and transcriptional activity of WT and mutants STAT3 were studied using a luciferase reporter system and by

Western Immunoblot. **Results:** Under basal conditions, variants p.C426R and p.E616del, presented increased reporter activity compared to WT-STAT3 ($P<0.01$). However, STAT3 mutants were not constitutively phosphorylated. GH stimulation of STAT3 variants induced the luciferase reporter gene 2- and 4-fold for p.E616del and p.C426R, respectively ($P<0.01$). Nonetheless, only variant p.C426R showed increased transcriptional activity under IL-6-stimulation compared to WT ($P<0.05$). WT-STAT3 and the two variants were phosphorylated in response to GH and IL-6, but phosphorylation kinetics was different for each mutant: p.C426R exhibited delayed dephosphorylation only under GH treatment, while p.E616del, only under IL-6-stimulation. **Conclusions:** i) p.E616del and p.C426R STAT3 variants are gain-of-function mutations since they both presented increased basal transcriptional activity; ii) While GH was able to induce the STAT3 responsive reporter vectors for both variants studied, IL-6 does not lead to enhanced transcriptional activity for p.E616del mutant; iii) Further studies are necessary to disclose the underlying molecular mechanisms that mediate the effect of these STAT3 variants on IL-6 and GH action.

P1-P597

Abstract withdrawn

P1-P598

Human Phase1 Clinical Data of ALT-P1 (hGH-NexP) by Healthy Korean Males

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Background: ALT-P1 (CJ-40002) is a long-acting recombinant growth hormone (GH) fused with NexP, which is a long-acting carrier developed by Alteogen Inc. NexP is a protein engineered recombinant alpha1 antitrypsin with further increased in vivo half-life without a native proteinase inhibitor activity. In non-clinical studies of cynomologus monkeys, the extended half-life of hGH-NexP has been successfully proved without side effects in high dose as 20 mg per kg dose. **Objective and hypotheses:** Currently available GH is developed as daily injections which cause inconvenience and poor compliance for patients. ALT-P1 was developed for once-weekly administration in GH deficient adults and children. i) Safety and tolerability, ii) pharmacokinetics and pharmacodynamics of once-weekly s.c. administration of ALT-P1 was evaluated in a phase 1 study of korean healthy male volunteers. **Method:** This phase 1, single-blinded, placebo-controlled, single-dosed, dose-escalated, randomized study was conducted in Yonsei University of Korea. A total of 40 subjects were enrolled and randomized to one of the five dose cohorts: 0.03, 0.06, 0.12, 0.24, and 0.35 mg/kg. In each dose cohort, six subjects were randomized into the test cohort and 2 to the placebo group. The mean age was 25.7 ± 5.1 and the BMI was 22.0 ± 1.7 kg/m^2. **Results:** No safety concerns were shown, including absence of lipoatrophy and anti-drug antibodies. Also there were no drug related severe adverse events. These results demonstrated that ALT-P1 is both non-immunogenic and highly tolerated in healthy, male subjects. Power modelling was adjusted to PK data analysis of AUC and Cmax. The terminal half-life were 19.09 ± 6.66 h (0.12 mg/kg), 26.81 ± 3.31 h (0.24 mg/kg), and 39.50 ± 20.34 h (0.35 mg/kg), respectively. Furthermore, maximal IGF-1 SDS change from baseline of each dose were 1.74 (0.12 mg/kg), 2.05 (0.24 mg/kg) and 3.05 (0.35 mg/kg), respectively. **Conclusion:** In conclusion, s.c. administration of single dose ALT-P1 to healthy male volunteers, demonstrated not only excellent safety and tolerability profile but also increased efficacy which can be injected once per week.

P1-P599

Validation of Prediction Models for Near Final Adult Height in Children with Idiopathic Growth Hormone Deficiency Treated with Growth Hormone for 1 Year

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Background: An accurate prediction of final height after the first year of growth hormone (GH) treatment may help clinicians to give parents and children more realistic expectations. **Objective and hypotheses:** To validate two prediction models (with and without max. GH peak) for near final adult height (nFAH) by Ranke *et al*. **Method:** Height data of 142 (93 male) idiopathic GH deficient (iGHD) children, treated with GH for at least four consecutive years with at least one year before puberty, who attained nFAH, were retrieved from the database of the Belgian Society for Pediatric Endocrinology and Diabetology. Bland Altman (BA) plots were used for validation of prediction models. Clark error grid (CEG) analysis was performed to assess the clinical significance of the differences between observed and predicted nFAH. **Results:** Mean duration of GH therapy was 9.6 years. Mean nFAH for boys was 169.1 cm (-1.76 SD), for girls 157.5 cm (-1.54 SD), mean nFAH minus midparental height SDS

was −0.41, median total height gain was 1.73 S.D. In males, the Ranke nFAH predictions were significantly higher than the observed nFAH (difference: 0.29 S.D. ±0.66; 95% CI 0.14–0.43; $P<0.001$). In females, there was no significant difference. BA: the means of the differences between the observed and predicted nFAH are close, but not equal to zero. There is a proportional bias with an overprediction for the smaller heights and an underprediction for the taller heights. We propose a small correction equation. CEG: 56% of predicted nFAH are in zone A (<0.5 S.D. difference from observed nFAH), 28–31% are in zone B (0.5–1 S.D. difference), 13–16% are in zone C (>1 S.D. difference). In females, 38–40% of predicted nFAH are in zone A, 38–40% in zone B, 22% in zone C. **Conclusion:** Ranke's prediction models for nFAH after first-year GH therapy accurately predict nFAH in females and overpredict nFAH in males by about 2 cm. We propose a small correction equation that should be evaluated in a separate cohort. These prediction models are useful for predicting nFAH after first-year GH treatment in clinical practice.

P1-P600

The Influence of Recombinant Human Growth Hormone Treatment on Very Small Embryonic/ Epiblast Like Stem Cells

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Background: Present knowledge on the effects of growth hormone (GH) on aging and lifespan are controversial. Clinical data indicate that normal or high levels of GH may accelerate aging and increase the risk of cardio-vascular diseases. Very small embryonic-like stem cells (VSELs) are a population of developmentally early stem cells residing in adult tissues, which could have the potential role in aging and organ rejuvenation. **Objective:** The aim of the study was to analyze the effect of GH treatment on VSELs. **Methods:** Twenty-five patients: GH-deficient (20), Turner Syndrome (3), Prader–Willi Syndrome (2), treated with GH, mean age 9.1±2.7 years were included in the study. The mean GH dose was 0.27 mg/kg/week. Fasting peripheral blood samples were taken before the administration of GH, then two-weeks, one-month, three-months and six-months after it. Subsequently, we evaluated by employing FACS changes in the number of small $CD133^+Lin^-CD45^-$VSELs and $CD34^+Lin^-CD45^-$VSELs – that are precursors of long term repopulating hematopoietic stem cells, mesenchymal stem cells (MSCs) and endothelial progenitor cells (EPCs). Statistical analysis was performed ANOVA. **Results:** The administration of GH initially stimulated for a month an increase in number of VSELs, and subsequently the number of VSELs decreased. After six months of treatment the number of circulating in PB VSELs was lower as compared to baseline values ($P=0.026$). The increase in VSELs number paralleled with increase in number of circulating MSCs and EPCs, however two months shift has been observed in case of EPCs. Finally, the number of MSCs and EPCs become lower than before GH treatment. **Conclusions:** The treatment with GH modulates the population of VSELs, MSCs and EPCs circulating in PB. Our data suggests that: 1/VSELs respond to GH treatment, and 2/since the therapy with GH modulates population of VSELs, therefore it could influence life span and organ rejuvenation.

P1-P601

A Lipid-Based System for the Oral Delivery of Growth Hormone

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Background: Bioavailability of peptide/protein – drugs is extremely low after oral administration due to their instability in the gastrointestinal tract or poor absorption. **Objective and hypotheses:** Oral delivery of growth hormone and somatostatin by adding extreme stable lipids. **Method:** A liposomal system based on a combination of standard lipids and membrane spanning tetraether lipids, which are extremely stable biomolecules. The somatostatin analogue Octreotide (Sandostatin) and human growth hormone (hGH) were used as model drugs. The bioavailability of Octreotide and hGH was determined after administration of peptide loaded liposomes to rats via gavage and of peptide alone via i.v. injection. **Results:** The shape of the liposomes was characterized by freeze fracture electron microscopy and light scattering particle size analysis showing an average diameter of 100–150 nm. The release properties and stability of these liposomes was studied after incubation in artificial gastric and intestinal fluids. The liposomes containing tetraether lipids showed a significantly increased stability compared to standard liposomes. Further optimized by incorporation of the liposomes into a jelly matrix generated a solid dosage form being stable for up to 1 year, from which liposomes could be released in the GI-tract. The absolute bioavailability of Octreotide was increased by a factor of 25–30 after administration of tetraether lipid liposomes, the bioavailability of hGH was increased by a factor of 360, both resulting in therapeutically relevant plasma concentrations. **Conclusion:** Formulation of peptides in tetraether liposomes increases the bioavailability of peptidic drugs after oral administration.

P1-P602

Prediction of First Year Response to Growth Hormone Treatment in Neural Network Models

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Background: Accurate prediction of responsiveness to growth hormone (GH) therapy is an important issue. The 1st year response to treatment is regarded as significant predictor of the attained final height. Neural networks are techniques of machine learning which do not require any assumptions and preprocessing of data, contrary to linear regression models. **Objective and hypotheses:** The aim of the study was to predict height velocity (HV) during 1st year of therapy (HV-1) in GH treated children with isolated GH deficiency. **Method:** Our retrospective analysis comprised data of 253 patients, age 11.5 ± 2.8 (2.5–15) years, for whom we tried to predict HV-1 using multilayer perceptron (MLP) and radial basis function (RBF) neural networks. Mean HV before treatment (HV-0) in those patients was equal to 4.2 ± 1.3 cm/year, while during 1st year of treatment 9.6 ± 1.9 cm/year (4.9–17.0 cm/year). As potential predictors of HV-1 we included height and HV-0, parental heights, IGF-I and IGFBP-3 concentrations, chronological and bone age (BA), results of GH stimulation tests with clonidine and glucagon, and patient's gender. **Results:** Best MLP network predicted HV-1 with mean error 1.77 cm/year in learning data and 1.70 cm/year in testing set. It included all predictors with exception of gender. Best RBF network was characterized by averaged error equal to 1.76 cm/year in original data and 1.77 cm/year in testing dataset, but it included only BA, father's height, result of test with glucagon and concentrations of IGF-I and IGFBP-3. **Conclusion:** Models tend to reproduce general, averaged tendencies rather than extreme values for particular patients, thus the range of answers they produced was narrower (e.g. for MLP network 7.4–12.4 cm/year) than in the case of real values. Together with obtained relatively low error this feature may allow us to use such models for identifying patients with poor response to treatment.

P1-P603

Pediatric Phase 2 Data Demonstrate that TransCon hGH Has an Anti-hGH Immunogenic Profile that is Comparable to Daily hGH

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Background: TransCon hGH, is a once-weekly prodrug releasing unmodified hGH, for the treatment of Growth Hormone Deficiency (GHD) in children and adults. To date, TransCon hGH has demonstrated comparable efficacy, safety and anti-hGH immunogenic profile to daily hGH, with no occurrence of neutralizing antibodies. **Objective and hypotheses:** Protein-based therapies may be associated with generation of drug-specific antibodies, which may impact efficacy, particularly if they neutralize the activity of the protein. Patients with neutralizing anti-hGH antibodies may not respond to hGH therapy, and may require initiation of IGF-I therapy to facilitate growth. As daily hGH therapy utilizes the recombinant human protein, the immunogenic potential is low. Sensitive anti-hGH binding and neutralizing antibody assays have been developed, validated and utilized to assess anti-hGH immunogenicity in a Phase 2 clinical study of children with GHD. **Method:** Pre-pubertal, treatment-naïve, children with GHD ($n = 53$) were randomized to weekly s.c. injections of TransCon hGH at 0.14, 0.21 and 0.30 mg hGH/kg per week or daily s.c. injections of Genotropin at 0.21 mg hGH/kg per week for 26 weeks. Serum samples were collected during screening, pre-dose Weeks 1, 5 and 13 and following the last dose at Week 26. Samples were assessed for anti-hGH binding and, if appropriate, neutralizing antibodies. Anti-hGH binding and neutralizing antibodies were detected in serum using validated bridging ELISA and cell-based proliferation assays, respectively. **Results:** Very low levels of treatment-emergent anti-hGH immune response was detected in 1 subject (2.5%), which were confirmed to be non-neutralizing (0.14 mg hGH/kg per week TransCon hGH). There was no impact on the subject's pharmacokinetic (TransCon hGH and hGH) or pharmacodynamic (IGF-I) profiles and the subject demonstrated an annualized height velocity of 19.0 cm. **Conclusion:** Sustained-release TransCon hGH is considered to have an anti-hGH immunogenic profile comparable to that of daily hGH and maintain the same safe and efficacious hGH levels in the body as currently available daily therapies.

P1-P604

The Exon3-Deleted Growth Hormone Receptor Gene Polymorphism (d3-GHR) is Associated with Increased Spontaneous Growth and Impaired Insulin Sensitivity in Prepubertal Short SGA Children (NESGAS)

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Background: A common polymorphism in the growth hormone receptor gene (d3-GHR) was found to be associated with pre- and postnatal growth and GH-induced growth. D3-GHR was associated with glucose metabolism in adults with GHD and acromegaly, but this has not previously been explored in children. **Objective and hypotheses:** We examined the impact of the GHR-exon-3 deletion on glucose metabolism and anthropometrics in short SGA children before and following 1 year of GH therapy. **Method:** The North European Small for Gestational Age Study (NESGAS) is a multicentre study of GH therapy in 96 (57 males) prepubertal short SGA children receiving high-dose GH therapy (67 μg/kg per day) for 1 year. Insulin sensitivity (IS) and disposition index (DI) were estimated from IVGTT. The GHR-exon-3 locus was determined by simple multiplex PCR on isolated DNA. **Results:** D3-*GHR* genotype frequencies were: 54.2% full-length (fl/fl), 38.5% heterozygous (fl/d3) and 7.3% homozygous (d3/d3). The d3-GHR genotype was divided into two groups: fl/fl vs. fl/d3 and d3/d3. Change in spontaneous height gain from birth to baseline was significantly higher in children carrying the d3-allele (fl/fl mean (S.D.) 0.55 SDS (1.97) vs. d3-allele 0.53 SDS (1.27), $P=0.02$). Baseline glucose and c-peptide levels were significantly higher in children carrying the d3-allele and there was a trend towards higher insulin levels in this group. Baseline IS was significantly lower in children carrying the d3-allele (fl/fl mean (SD) 351% (339) vs. d3-allele 248% (182), $P=0.02$), but there was no difference in DI. Following 1 year of GH therapy the change in IS was significantly higher in the fl/fl group compared to children carrying the d3-allele ($P=0.04$). **Conclusion:** Short prepubertal SGA children carrying the exon3-deleted GHR allele had lower insulin sensitivity at baseline, but the change in IS was reduced compared to the fl/fl group. Furthermore, we confirmed a positive effect on postnatal spontaneous growth.

P1-P605

A New Case of Intragenic Deletion in IGF1R with Very Mild Phenotype

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Background: *IGF1R* mutations are characterized by IGF-1 resistance causing impaired fetal and postnatal growth. Several reports in children with heterozygous defects of *IGF1R* have demonstrated a variable phenotype, which can be associated to microcephaly, dismorphic features and mild developmental delay. **Case presentation:** We report of an 8-years-old boy, who came at our observation with short stature (−3.2 SDS) and mild microcephaly. He was born SGA and familial medical history revealed short stature in both parents (target height −2.4 SDS). Psychomotor development was normal. His bone age evaluated by TW2 method was 6 years. His laboratory data excluded a GH deficiency and his IGF1 levels were normal. GH treatment (0.035 mg/Kg per die) was started, but it was interrupted after 1 year of therapy because of elevated IGF-1 levels (>95 th) and no clinical response (−3.1 SDS). Genetic analysis of *IGF1R* revealed an heterozygous deletion of exon 3; the same deletion was found in the father (adult height −2.2 SDS) and in one of the two sisters (born SGA; height −2 SDS; head circumference −2 SDS) of the index case. Both affected relatives had normal psychomotor development. Our patient started GH treatment again at a higher dosage (0.040 mg/kg per die), with good response. **Conclusions:** We expand the phenotypic knowledge of intragenic deletions of *IGF1R* reporting a family with deletion of exon 3, determining a milder phenotype without mental retardation, psychiatric features and dysmorphisms. In fact, only a family with exon 3 deletion has been previously described and dismorphic features, psychiatric phenotypes and mental delay were present in all affected members. The explanation of these differences warrant further investigation. Moreover we confirm the importance of *IGF1R* analysis in SGA patients with short stature and microcephaly poor responsive to GH treatment.

P1-P606

The Role of IGF-1R Gene Polymorphisms with Regard to Susceptibility to Idiopathic Short Stature Risk in the Chinese Population of Jiangxi Area

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Background: Accumulated evidence indicates that the GH-IGF-1 pathway might be one of the crucial mechanisms of ISS. Insulin-like growth factor-1 receptor (IGF-1R) is the effector molecule that regulates the cascade reaction of hormone receptors in the GH–IGF-1 axis. **Objective and hypotheses:** To investigate the role of IGF-1R gene polymorphisms with regard to susceptibility to Idiopathic short stature risk in the Chinese population of Jiangxi area. **Method:** A total of 609 samples (ISS = 295, control = 314) from Jiangxi area were controls were enrolled in this study. The possible associations between 46 tag SNPs and progression risk among 295 patients were investigated using a two-step case-control study with a discovery cohort ($n=100$) and

a validation cohort($n=195$). SNPs (rs2684788) were genotyped using the SNaPshot Multiplex System. **Results:** We found that the rs2684788 in the IGF1R gene is associated with ISS in population of Jiangxi area among allelic model (G vs. A, OR = 1.685, 95%CI = 1.272, 2.233, $P<0.001$), genotypes (GG vs. GA vs. AA, $\chi^2=13.724$, $P<0.001$), dominant model (GG + GA vs. AA:OR = 1.887, 95%CI = 1.352–2.634, $P<0.001$). Notably, for individuals having the rs2684788 with the GG/GA genotype, the magnitude of increased ISS riks for lower IGF-1SDS was significantly elevated ($P<0.004$). **Conclusion:** The results suggested that the human IGF1R gene SNP rs2684788 might be associated with ISS genetic susceptibility in population of Jiangxi area, and might be associated with ISS clinical phenotype.

P1-P607

Effects of the Addition of Metformin to Recombinant Human GH on Bone Maturation and Pubertal Progression in Short Children Born Small-for-Gestational-Age

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Background: Small for gestational age (SGA) children who experience rapid and exaggerated postnatal catch-up are prone to develop insulin resistance and to progress faster into puberty, resulting in a shorter final height. Short, non-catch-up SGA children treated with recombinant human GH (rhGH) may present with the same sequence. In a previous controlled study from our group performed in short SGA children, metformin – added to rhGH therapy – improved endocrine-metabolic parameters without modifying the reponse to rhHG. **Objective and hypotheses:** To describe the effects of the addition of metformin to rhGH in non-catch-up SGA on growth, pubertal timing and endocrine-metabolic variables. **Method:** Retrospective, descriptive study in a tertiary hospital (2010–2015). Inclusion criteria: SGA children (39.5% girls) treated with rhGH only ($n=18$; 0.035–0.04 mg/kg per day) or with rhGH plus metformin ($n=20$; 23–25 mg/kg per day) with either early puberty and/or an advance in bone age >1 year in the previous 6 months. **Results:** The results were analyzed after 28 months (12–55) on treatment, when patients had reached Tanner III–IV stage. At baseline, the rhGH + metformin group had higher growth velocity in the previous year and a more advanced bone age ($P<0.05$ vs the rhGH-only subgroup). In the rhGH + metformin subgroup, bone age progressed less in the second and third year of follow-up in comparison to the rhGH-only group ($P<0.05$). No differences in pubertal timing, age at menarche, growth velocity or analytical parameters were found between subgroups. **Conclusion:** Despite the methodological limitations (observational, not controlled study), these preliminary results show that in those patients with higher growth velocity and an advanced bone age at puberty start, metformin slows down bone maturation, without altering growth rate. Longer follow up will ascertain whether metformin can also modulate pubertal progression and thus improve final height.

P1-P608

Pubertal Height Gain in Females with Isolated Growth Hormone Deficiency Treated with rhGH Alone or in Combination with GnRHan

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Background: A significant component of total linear growth is height gain achieved after the initiation of puberty. Children with Isolated GH Deficiency (IGHD) frequently come for evaluation around the peripubertal stage. Therefore, increasing pubertal height gain in IGHD children entering puberty with a relatively low height is important. Researchers have tried to assess effectiveness of treatment in such patients based on various key measurements and a variety of end-points. **Objective and hypotheses:** To compare the effect of rhGH with or without the use of a GnRHan based on the height gained from puberty initiation (Breast Tanner II) to final height in girls with IGHD. **Method:** We retrospectively analysed pertinent data of females with IGHD receiving either rhGH alone ($n=17$) or rhGH and GnRH ($n=16$). Twenty females with normal growth served as controls. None of the participants had health problems (other than IGHD for patients) that could affect growth potentials. Kruskal–Wallis test used for statistical comparison. **Results:** Pubertal Height gain in girls who received rhGH alone did not differ from controls (21.74 ± 3.11 vs 20.4 ± 3.93 cm, $P=0.21$) whereas Pubertal Height gain (28.44 ± 4.76 cm) of girls that received both rhGH and GnRHan was significantly higher than both controls and girls receiving rhGH alone ($P<0.001$ for both). **Conclusion:** It seems that with rhGH treatment, pubertal gain expected for children with normal growth is achieved. Although groups are not matched for all major parameters, combined rhGH and GnRH treatment seems to significantly increase pubertal gain compared to either normal girls or IGHD girls treated only with rhGH.

P1-P609

Cognitive Abilities and Academic Achievement Among Youths with Short Stature Receiving Growth Hormone Therapy

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Background: Reports suggest that youths with short stature (SS) exhibit academic under-achievement relative to cognitive aptitude and GH treatment diminishes the difference. However,

interpretation of this achievement-aptitude discrepancy is confounded by the use of achievement and intelligence tests normed in different samples. **Objective and hypotheses:** To assess whether reports of academic underachievement in SS samples are partially attributable to choice of tests and whether benefits of GH could be demonstrated using a co-normed psychometric battery. We hypothesized that the achievement-aptitude discrepancy and putative benefit of GH would be diminished through assessment using a co-normed battery (Woodcock–Johnson Battery-Revised; WJ-R). **Method:** Sixty-nine youths ($\bar{x} = 10.2$ years, 64.2% male) with SS prior to initiating GH and 54 untreated average height (AH) youths ($\bar{x} = 9.87$ years, 48.3% male) participated. WJ-R testing occurred at baseline and at 1 year. Participants completed the WJ-R Cognitive Ability tests, yielding a Broad Cognitive Ability (BCA) score and domain-specific academic skills tests. **Results:** *Baseline* – Compared with population norms, SS youth scored lower on BCA and 2 academic domains. SS youth also 'overachieved' relative to their BCA in three domains. *1-Year Follow-Up* – Mean BCA in the SS group was no longer below population norms; two academic skill scores remained below norms. Paired *t*-tests showed 'underachievement' in one domain. *Comparison with AH* – AH youth scored significantly higher than norms on BCA and the majority of academic domains. Paired *t*-tests showed evidence of both over- and under-achievement at baseline and follow-up. **Conclusion:** Significant effects for the SS sample challenge prior research (i.e., overachievement vs underachievement), and it remains open whether these differences are clinically meaningful as all scores were ±1 S.D. of norms. The fact that the AH comparison group did not follow the pattern observed in the GH-treated SS group suggests that observed changes are not due to maturation or practice effects.

P1-P610

One Year Use of Anastrazole Improves the Predicted Adult Height of Male Adolescents with and without Associated GH Therapy

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Background: Estrogen is an essential regulator of bone maturation, growth plate fusion, and cessation of longitudinal growth. Aromatase inhibitors (AI) block the conversion of androgens to estrogens, and can be used to delay bone maturation in males. **Objective and hypotheses:** We sought to determine whether the blockage of estrogen biosynthesis due to the use of the AI Anastrazole increases the Predicted Adult Height (PAH) in boys with short stature. **Method:** Twenty-eight boys (13.6 years), used oral Anastrazole 1 mg/day for 1 year. Eighteen received GH therapy ('GH' group) and 10 did not ('ØGH' group). PAH was calculated based on Bayley/Pinneau formula. **Results:** Basal PAH was statistically below the TH (−2.9 cm, $P = 0.008$), and after 1 year of treatment with Anastrazole it was above the TH (+3.4 cm, $P = 0.008$) and above the Basal PAH (+6.3 cm, $P < 0.001$). For the 'GH' group the increase in PAH after 1 year was +3.6 cm comparing to TH ($P = 0.01$) and +6.3 cm for Basal PAH ($P < 0{,}001$). For the 'ØGH' group, the increase in PAH after 1 year was +3.1 cm comparing to TH ($P = 0.06$) and +6.2 cm for Basal PAH ($P < 0.002$) Table 1. **Conclusion:** One year use of anatrazole in boys with short PAH can improve PAH in 'GH' and 'ØGH' groups. The complete follow up until adulthood will determine if this increase in PAH will reflect in better final adult height.

Table 1. Comparison of TH with basal and one year PAH (cm).

Group	TH (cm)	Basal PAH (cm)	1 year PAH (cm)	P*
'ØGH'	173.7±4.39	170.62±3.9	176.8±3.89	0.003
'GH'	171.48±4.48	168.77±4.1	175.11±4.46	<0.001
Total	172.28±4.50	169.43±4.06	175.71±4.27	<0.001

P1-P611

IGFALS Gene Deletion in a Family with Short Stature

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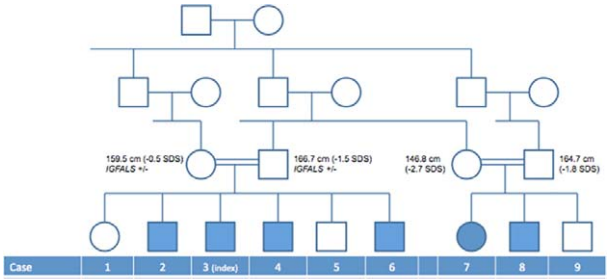
Background: ALS deficiency is characterized by mild short stature, delayed puberty, low serum IGF1, low serum IGFBP3 and undetectable serum ALS levels. **Case:** A 11.3 years old boy presented with short stature. He was born at term to consanguineous parents and the birth weight was unknown. On physical examination, his height and weight were 130.5 cm (−2.33 SDS) and 25.2 kg (−2.36 SDS) and he was prepubertal. The routine laboratory tests were normal, IGF1 level was very low and bone age was delayed (9 years). Since peak GH level in clonidine test was 10.3, IGF generation test was performed and unresponsive to GH (before IGF1:37,IGFBP3:<500, after IGF1:39,IGFBP3:<500). In light of this information, ALS deficiency was thought and the family members were checked



Case	1	2	3 (index)	4	5	6	7	8	9
Age	15.5	13.7	11.3	9	6.8	4.3	9.5	7.1	4.3
Height SDS	-0.87	-2.36	-2.33	-1.76	-1.33	-2.02	-2.93	-3.64	-1.60
Weight SDS	-1.65	-1.78	-2.36	-2.16	-1.53	-2.84	-2.41	-4	-1.1
IGF-1 (ng/ml)	-	41	37	25	-	40	29	<25	51
IGFBP3 (ng/ml)	-	<500	<500	<500	-	1470	<500	<500	1300
ALS (mg/L) (SDS)	13.0 (-1.5 SDS)	1.50 (-3.8 SDS)	1.54 (-3.49 SDS)	1.50 (-3.28 SDS)	10.8 (-0.71 SDS)	5.56 (-2.0 SDS)	1.44 (-6.3 SDS)	1.50 (-3.0 SDS)	4.52 (-2.3 SDS)
IGFALS gene (c.1477del)	+/-	-/-	-/-	-/-	+/+	+/-	-/-	-/-	+/-

Figure The pedigree of family and clinical/laboratory findings of the cases.

(Figure). The short siblings had low IGF1-IGFBP3 levels. *IGFALS* gene analysis identified a homozygous c.1477del (p.Arg493fs) deletion in the index case and short siblings. Also, his short cousins were checked and they had same deletion in *IGFALS* gene. **Conclusion:** Since, patients with ALS deficiency have mild short stature and heterozygous parents have low-normal height, these patients can be diagnosed as familial short stature. Therefore, the physician should be careful at differential diagnosis of short stature.

P1-P612

Adherence with Twice-Monthly, At-Home Dosing Schedule of Somavaratan (VRS-317) Long-Acting Growth Hormone Treatment in Children with Growth Hormone Deficiency (GHD) (NCT02068521)

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Background: Treatment adherence to daily subcutaneous rhGH is a burden for GHD patients, with noncompliance reported in up to 77% of patients and significantly associated with reduced efficacy (Rosenfeld Endocr Pract 2008; Cutfield PLoS One 2011). Somavaratan, a novel rhGH fusion protein with $t_{1/2}$ >100 h, demonstrated clinically meaningful improvements in height velocity and IGF-I in prepubertal children with GH deficiency (GHD) in a multicenter, randomized, Phase 1b/2a study (Moore JCEM 2016). **Objective and hypotheses:** To evaluate treatment adherence to at-home dosing of twice-monthly dosing schedule of somavaratan in an ongoing, long-term extension study. **Method:** 64 subjects were initially randomized to weekly, twice-monthly, and monthly dosing groups for total dose of 5.0 mg/kg per month for 6 months. Sixty subjects enrolled in an extension study; all transitioned to somavaratan 3.5 mg/kg twice-monthly by the start of the 2nd treatment year, based on growth and IGF-I responses observed in the first 6-12 months of treatment. During the extension study, injections were administered at home by caregivers. Treatment adherence was reported by caregivers using an electronic patient-reported outcome diary (eDiary; Bracket, Inc.). **Results:** Mean age at baseline was 7.5±2.3, 8.0±2.4 and 8.0±2.5 for the weekly, twice-monthly, and monthly dosing groups; mean age for subjects enrolled in the extension study was 8.3±2.4 (Day 1). With at-home dosing facilitated with an eDiary system during the initial 18 months and over 1600 doses administered, dosing adherence was 99.6% and injection adherence was 99.4%. Data on dosing and injection adherence during Year 2 will be presented. **Conclusion:** With nearly 100% dosing adherence using the eDiary and the Phase 3 dosing schedule for somavaratan, we present evidence that long-acting rhGH has the potential to improve long-term adherence in children with GHD. A Phase 3 study of 3.5 mg/kg twice-monthly somavaratan using the eDiary to monitor treatment adherence is ongoing (NCT02339090).

P1-P613

Glucose Dysregulation in Children with Growth Hormone Deficiency (GHD), Turner Syndrome (TS) or Born Small for Gestational Age (SGA) Treated with GH: A Report from the NordiNet International Outcome Study (IOS)

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Background: The prevalence of glucose dysregulation in children treated with GH is not well established. **Objective and hypotheses:** To evaluate the prevalence of glucose dysregulation in children with growth disorders (GH deficiency (GHD), Turner syndrome (TS), small for gestational age (SGA)) treated with GH (Norditropin, Novo Nordisk) enrolled in NordiNet International Outcome Study (IOS) (NCT00960128), a non-interventional study evaluating safety and effectiveness of Norditropin in clinical practice. **Method:** Diabetes was identified based on reports of: clinical diagnosis; diabetes reported as an adverse event; treatment with antidiabetic medication. A subgroup of 1659 children without diabetes at baseline was evaluated for ΔHbA_{1c} (2-year change). Data are mean (s.d.). **Results:** Diabetes prevalence in NordiNet IOS was 0.34% (45/13,134 patients): Type 1: $n=29$ ($n=$reported before/after GH): (GHD, $n=15/3$; TS, $n=4/2$; SGA $n=4/1$); Type 2: $n=10$ (GHD, $n=4/3$; TS, $n=0/1$; SGA, $n=0/2$). Unspecified diabetes: $n=6$ (GHD, $n=2/2$, SGA, $n=2/0$). In the subgroup analysis (GHD, $n=915$; TS, $n=191$; SGA, $n=553$) children born SGA were younger (7.7 (3.2) years) and leaner (BMI SDS, –1.06 (1.24)) than children with GHD (9.8 (3.8) years; BMI SDS, –0.21 (1.34)) or TS (8.4 (3.6) years, BMI SDS, 0.33 (1.08)). Mean GH dose (μg/kg per day) over 2 years was lower in GHD, 32.6 (8.3), and higher in TS, 45.0 (10.5) and SGA, 38.6 (10.4). Two patients (GHD, $n=1$; SGA, $n=1$) with normal baseline HbA_{1c} (<5.7%) developed type 2 diabetes, and two patients (GHD, $n=1$; SGA, $n=1$) had HbA_{1c} >6.5% at year 2. Mean ΔHbA_{1c} was 0.08(0.36)% for SGA, 0.06(0.46)% for GHD and 0.05(0.55)% for TS. The proportion of patients with an increase in HbA_{1c} from normal (<5.7%) to prediabetes/high-normal (5.7%–6.5%)) at 2 years was 12.2%, 10.6% and 6.5% for GHD, SGA and TS, respectively. **Conclusion:** With this report we present the prevalence of glucose dysregulation in children with growth disorders before and after short-term GH treatment. These findings warrant further analysis and comparison to measures within population-based diabetes studies.

P1-P614

Serum α-Klotho Levels are not Informative for the Evaluation of GH Secretion in Short Children

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Background: α-klotho is a transmembrane protein which can be cleaved and act as a circulating hormone. Since low α-klotho levels were found in organic GH deficiency (GHD) and high levels in acromegaly, an interaction between α-klotho, GH and linear growth has been suggested. **Objective and hypotheses:** We investigated the role of α-klotho protein as a reliable marker of GH secretion in short children and the factors influencing its secretion. For this purpose, we used the pegvisomant-primed GH stimulation test, since pegvisomant acts as enhancer of GH secretion. **Method:** We enrolled 20 Egyptian short children with reduced GH secretion (GH peak <10 ng/ml) after two pharmacological stimuli (clonidine and insulin tolerance test) and 20 subjects with normal GH secretion. Then, pegvisomant was injected subcutaneously and after three days a GH stimulation test (insulin tolerance test) was performed. The baseline samples obtained before and after pegvisomant were used for measuring IGF-I and α-klotho. α-klotho levels were measured by an ELISA assay, IGF-I and GH levels were determined by a chemiluminescent assay which has no cross-reaction with pegvisomant. **Results:** α-klotho basal levels were not significantly different between GHD and non-GHD children. After pegvisomant priming, a reduction in IGF-I and α-klotho levels was found in both groups. Furthermore, α-klotho basal levels significantly correlated with IGF-I levels in both groups and with the area under the curve of GH secretion (GH-AUC) only in non-GHD subjects. In these children, the reduction of α-klotho depends on the basal α-klotho and IGF-I levels and on the reduction of IGF-I but not on GH-AUC. On the contrary, in GHD children, the correlation with basal α-klotho levels was no longer significant after adjusting for BMI. **Conclusion:** In conclusion, IGF-I and the nutritional status have a role in the regulation of circulating α-klotho. Therefore, α-klotho is not a reliable biomarker for GH secretion in children.

P1-P615

Immunogenicity Results of Once-Weekly Administration of CTP-Modified Human Growth Hormone (MOD-4023): A Phase 2 Study in Children with Growth Hormone Deficiency

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Background: CTP-modified hGH (MOD-4023) has been developed for once weekly administration in GH deficient (GHD) adults and children. Immunogenicity samples of once-weekly s.c. administration of MOD-4023 were detected for the presence of binding and neutralizing anti-MOD-4023 Ab's in pediatric Phase 2 study. **Objective and hypotheses:** During the first year of the study, 53 pre-pubertal GHD children were treated with once-weekly s.c. injections of one of three MOD-4023 doses (42 subjects) vs. daily hGH (11 subjects). Serum samples for immunogenicity analysis were collected at pre-dose, and after 6 and 12 months of MOD-4023/hGH treatment, using the ADA and neutralizing Ab's methods for detection. **Method:** First, each sample was analyzed in screen format. Samples reactive for anti-MOD-4023 Ab's were confirmed for MOD-4023 in specificity format. Samples confirmed positive for anti-MOD-4023 binding Ab's, were titered and analyzed for hGH and CTP specificity format, as well as anti-MOD-4023 and anti-hGH neutralizing Ab's using cell-based assays. **Results:** Immunogenicity data for the first year of Phase 2 in GHD pediatric population present low titers of non-neutralized anti-MOD-4023 Abs at a similar incidence rate as Genotropin; No Ab related AE's were reported during the study. **Conclusion:** Qualitative methods were validated to detect whether binding as well as neutralizing Ab's were developed after once weekly administration of MOD-4023 compared to daily hGH treatment. During the first 12 months of the Phase 2 study in GHD pediatric population, along with previous Phase 2 data in GHD adults, MOD-4023 demonstrated promising immunogenicity profile, with no detection of binding Ab to the CTP moiety nor neutralizing Ab to the drug. The data affirms MOD-4023 has the potential provide promising safety outcome when injected on weekly basis.

P1-P616

Serum IGF-I, IGFBP-3 and Als Concentrations and Physical Performance in Young Swimers During a Training Season

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Background: Exercise programs are related to the anabolic function of GH/IGF-I axis. **Objective and hypotheses:** To analyse IGF-I, IGFBP-3 and ALS serum concentrations in adolescent swimmers at different stages of training season, and compare them with physical performance and body composition. **Method:** Nine male athletes, aged 16–19 years, who trained regularly throughout the season, were studied. IGF-I, IGFBP-3 and ALS were recorded before and after standardized training sessions during different stages of a training season (extensive, intensive, tapering). Aerobic endurance in freestyle, anaerobic fitness in tied swimming (Peak Force and Average Force), weight, fat-percentage and lean body mass were analysed at the different stages of training. **Results:** IGF-I was sensitive to the acute and chronic

effects of training, exhibiting biphasic behaviour throughout the season. Catabolic phase was characterized by reduction in IGF-I levels during the intensive stage (**Δ**IGF-I: -43 ± 47 ng/ml; $P < 0.05$) while anabolic phase was marked by an increase in post-training serum IGF-I levels during the tapering stage following similar basal concentrations at the different stages of training (319 ± 40, 298 ± 36 and 359 ± 94 ng/ml; $P < 0.05$). IGFBP-3 was sensitive to the chronic effects, with reduction in post-training serum levels during the intensive stage and an increase during the tapering stage (4.7 ± 0.7, 4.6 ± 0.4 and 5.0 ± 0.7 mg/l; $P < 0.05$). No difference ($P > 0.05$) was observed between pre-/post-training IGFBP-3 levels (**Δ**IGFBP-3) at the different stages. ALS remained unchanged throughout the season. Peak Force (25.0 ± 6.3, 24.2 ± 5.7 and 28.5 ± 6.5N; $P < 0.05$) and Average Force (10.3 ± 3.6, 8.8 ± 1.8 and 14.7 ± 1.8N; $P < 0.05$) followed IGF-I and IGFBP-3 variations, with a decrease during the intensive stage and an increase during the tapering stage ($P < 0.05$). Body composition and cardiorespiratory condition did not change throughout the season. **Conclusion:** Serum IGF-I and IGFPB-3 concentrations have proven to be sensitive markers of training status and, thus, may be used as guide for the challenging task of modulating training intensity in young athletes.

P1-P617

The Blood Antioxidant System in Adult Growth Hormone Deficient Patients after Concluded Childhood Growth Hormone Therapy

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Background: The antioxidant system that protects tissues from damaging oxidation processes is a universal indicator for metabolic balance. It is known that GH deficiency (GHD) is associated with a high risk of developing metabolic disorders. **Objective and hypotheses:** The aim of this study was to examine the effects of inadequate GH secretion on the markers of the blood antioxidant system in adult GHD patients. **Method:** The study included ten adult patients aged 18–26 years, median age 23 years, with a confirmed diagnosis of GHD since childhood. All patients received hormone therapy in childhood to achieve target height and/or closing of growth plate zones. All of the patients had not received metabolic therapy with GH after the closure of growth plate zones. 15 healthy adult volunteers were included in the control group, aged 22–35 years, median age 26 years. The blood antioxidant system was examined using superoxide dismutase (SOD) and catalase activities; ceruloplasmin (CP) concentrations; total antioxidant capacity (TAC) of plasma; non-protein thiol, and thiobarbituric acid reactive substances (TBARS) levels. **Results:** Elevated TBARS and CP levels (median 5.02 vs 3.15 nMol/ml, 558 vs 387 μkg/ml, correspondingly) in GHD patients vs. healthy subjects was observed. Raised SOD activity in GHD patients (13.4 vs 21.4 a.u./g Hb) was also shown. The present work has demonstrated that parameters of the blood antioxidant system are impaired in adult GHD patients with interrupted GH treatment after having reached target height, which is indicated by oxidative stress development.

P1-P618

Design and Clinical Development of TransCon Growth Hormone for Growth Hormone Deficiency (GHD)

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Background: TransCon GH is designed as a once-weekly sustained-release prodrug of recombinant human GH (hGH, somatropin). Based on the inert TransCon prodrug technology unmodified native hGH is released with a Cmax and AUC comparable to daily therapy. TransCon GH leverages the known pharmacology of daily hGH and is being developed for the treatment of GH deficiency (GHD) in children and adults. **Objective and hypotheses:** Develop a safe and efficacious sustained-release hGH resulting in both hGH and IGF-I serum concentrations within the therapeutic range, leveraging the safety, efficacy, tolerability and immunogenicity of daily hGH, which have been established over decades of use. **Method:** Within the TransCon GH development program a Healthy Volunteer (HV) Phase 1 and two Phase 2 studies in adults and children with GHD were conducted. Daily hGH as comparator was included in those clinical trials to enable comparison of hGH, IGF-I levels and predict auxology in the Phase 2 paediatric trial. **Results:** TransCon GH was shown in HVs and GHD adults and children to be safe and well tolerated; generate predictable and dose dependent serum peak levels and overall exposure (AUC) within the therapeutic range of both GH and IGF-I, and in children to provide comparable height velocity to daily hGH. Immunogenicity was low and comparable to daily hGH, and no neutralizing antibodies have been observed. **Conclusion:** To date, TransCon GH has demonstrated efficacy and safety comparable to that observed with daily hGH. Injection site reactions were generally mild and similar to daily hGH injections, with no nodule formation or lipoatrophy noted. The completed clinical studies supports Phase 3 development.

P1-P619

Mutations in PROP1 Gene in Combination with 47,XYY Karyotype: Case Report

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Background: Mutations in *PROP1* gene are the most common known genetic cause of multiple pituritary hormone deficiency. It

is characterized by somatolactotroph, thyrotroph, gonadotroph and sometimes corticotroph deficiencies and pituitary hyper- or hypoplasia. The karyotype 47,XYY occurrs in 1 in every 1000 live male birth. Some studies report that the phenotype of XYY syndrome includes tall stature, behavioral problems and low fertility. **Objective and hypotheses:** To present the first reported case of *PROP1* mutation and XYY syndrome in one patient. **Method:** We describe the clinical case of 7-year-old boy with short stature and hypothyroidism. **Results:** The boy was born at term from unrelated healthy parents. His birth length and weight were 53 cm and 3950 g respectively. The patient complained about short stature at 2 years old (SDS = −2.75). Karyotype was performed at 5 years old, abnormal chromosome test was received (47,XYY). Very low height (SDS −5.2), overweight (SDS +1.3), dry skin and pastosity were found at physical examinations at 7 years old. Laboratory results showed low level of free T_4 (7.0 pmol/l), normal levels of TSH (1.1 mIU/l), cortisol (537 nmol/l) and prolactin (307 mIU/l), low levels of IGF1 (3 ng/ml). Brain MRI showed anterior pituitary hyperplasia. Genetic analysis revealed compound heterozygous mutations in the *PROP1* gene (c.150delA and c.301_302delAG). The boy was started on growth hormone and levothyroxin therapy. No clinical signs of XYY syndrome were found. **Conclusion:** The unique combination of mutation in *PROP1* gene and 47,XYY karyotype was observed. Further monitoring of the patient is required in order to detect possible abnormalities.

P1-P620

Efficacy of Growth Hormone Treatment in Patients with Type 1 Diabetes Mellitus and Growth Hormone Deficiency

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Background: The combination of type 1 diabetes mellitus (T1DM) and GH deficiency is uncommon. In a previous study (1) we found that in children with T1DM and GHD with adequate adaptation of insulin dosage, the metabolic control of T1DM did not worsen during GH treatment. However, decreased catch-up growth was observed and no data on GH dose was available. **Objective:** To analyse first year treatment growth response and GH dosage in prepubertal patients with T1DM and GHD. **Patients and method:** A total of 69 patients with T1DM and GHD treated with GH have been documented in KIGS (Pfizer International Growth Database). Of these, 24 patients were prepubertal and were included in this analysis. Of 30 570 GHD patients without T1DM, 15 024 were prepubertal and served as controls. **Results:** Patients with combined T1DM and GHD were older at start of GH treatment (median age at start of therapy 10.2 years (S.D. 3.13) compared to 8.42 years (S.D. 3.46) in controls, although statistically not significant, $P=0.14$). Height SDS corrected for mid-parental height SDS at start of treatment was not different between the two groups (−1.62 vs −1.61, $P=0.80$). There was also no significant difference in mean GH dosage (0.24 mg/kg per week vs 0.20 mg/kg per week, $P=0.09$). First year catch-up growth in prepubertal children was comparable within the two patient groups, median first treatment year height velocity 7.54 cm/year (S.D. 3.11) in children with T1DM and GHD compared to 8.35 cm/year (S.D. 2.54) in controls, $P=0.38$. Median height SDS of children with T1DM and GH deficiency improved from −2.62 (mean −2.58, S.D. 1.04) to −1.88 (mean −1.90, S.D. 1.11). **Conclusion:** In KIGS database prepubertal children with T1DM and GH deficiency were treated with adequate GH dosage and demonstrated regular catch-up growth. Therefore taken together with previous data, GH treatment is safe and effective.

P1-P621

Final Height after Growth Hormone Treatment in Children with Chronic Renal Failure

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Background: Growth retardation is seen in about 30% of children with chronic renal failure (CRF). Under-nutrition, anaemia, secondary hyperparathyroidism, acidosis, corticosteroid therapy and abnormalities in the GH/insulin like growth factor system have been implicated. Recombinant GH (rGH) therapy is recommended in children showing failure to maintain a normal height velocity despite optimized primary treatments. **Objective and hypotheses:** It has been demonstrated that rGH treatment stimulates growth in short children with CRF. However, the extent to which this therapy improves final height (FH) has not been clearly defined. **Method:** We followed, from CRF diagnosis until FH, 53 children with height velocity (HV) $<$25th percentile, who were treated with rGH (mean duration of rGH treatment: 5.6 ± 2.1 years). Anthropometric parameters were compared with those of a matched group of 30 children with CRF who did not receive rGH therapy because HV was not $<$25th percentile, or due to contraindications to therapy or refusal of parents. Seventy-one children (85%) underwent renal transplantation during follow up. **Results:** The cumulative height SDS gain in rGH-treated patients was 0.33 ± 0.8. FH SDS and target adjusted FH SDS were not significantly different in rGH treated and control patients. Multivariate analysis showed that rGH therapy and its duration did not affect FH, whereas height SDS at the start of rGH treatment, transplantation and target height SDS positively

	rGH-treated patients	Untreated patients	*P*
FH SDS	−1.32±1.2	−1.04±1.2	0.34
Target adjusted FH SDS	−0.93±1.1	−0.72±1.4	0.21
Age at transplantation (years)	12.5±4.1	12.7±4.9	0.63

influenced FH and target adjusted FH SDS ($P<0.001$). **Conclusion:** rGH-treated patients with HV<25th centile reached a FH not significantly different from that of untreated patient, but probably our rGH-treated children had a more severe clinical phenotype than untreated controls. Current guidelines recommend rGH therapy in all children with CRF and growth retardation, making unfeasible to design a case-control study with a homogeneous untreated population. The comparison with matched untreated historical controls could help to clarify the effect of rGH on FH.

P1-P622

Major Plasma Carotenoids Levels in Growth Hormone Deficient Children

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Background: Carotenoids are potent antioxidants that affect many different metabolic processes. In plasma, carotenoids are transported with lipoproteins. Growth hormone deficiency (GHD) is known to induce oxidative stress and deterioration in the lipid profile, which can change the level and composition of carotenoids. Particularly interesting to measure these parameters in GHD children. **Objective and hypotheses:** The aim of this study is to examine the amount and percentage of main plasma carotenoids in prepubertal treatment-naive GHD children. **Method:** The 13 prepubertal treatment-naive children (two girls, 11 boys; aged 3.5–12.0 years; median 8.0 years) with GHD and seven prepubertal health children (seven boys; aged 6–11 years; median 9.3 years) were included in the study. The levels of total carotenoids, lutein (with zeaxanthin), various forms of lycopene, cryptoxanthin, and α- and β-carotene were measured using HPLC. Total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), and triglycerides (TG) were measured. Activity of antioxidant system was also examined by thiobarbituric acid reactive substances (TBARS), ceruloplasmin and total antioxidant capacity (TAC). **Results:** The level of TBARS, TC and LDL-C in GHD children was higher than in healthy children (median 5.6 vs 3.8 μM/l, 4.00 vs 4.37 and 2.40 vs 2.70 mM/l, respectively), whereas total carotenoid level did not significantly differ. However, content of lutein and cryptoxanthin were significantly lower in GHD children than in control group (2.4 vs 13.5 and 5.0 vs 13.7%, respectively), in contrast to lycopenes and α- and β-carotene (5.6 vs 8.0 and 22.2 vs 28.9%, respectively). At the same time the percentage of undefined substances in GHD children increases (52.9 vs 20.9%). **Conclusion:** We observed a mild oxidative stress and the altered lipid profile in GHD children. Very likely carotenoids protect the lipoproteins from oxidation, which change their composition.

P1-P623

Autosomal Dominant Growth Hormone Deficiency due to a Novel Mutation in the *gh1* Gene

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Background: Familial growth hormone deficiency (GHD) with an autosomal dominant inheritance pattern (isolated GHD type II) due to multiple different mutations in the GH1 gene have been described. **Objective and hypotheses:** Describe the clinical characteristics and mutation analysis of affected individuals in a family with growth hormone deficiency inherited in an autosomal dominant pattern. **Method:** Medical record review. **Results:** GHD was first identified in the female proband at 6 years 1 month, Height SDS – 3.21 with a peak stimulated GH of 4.9 ng/ml. GHD was subsequently identified in her female sibling (6 years 0 month, Ht SDS – 1.67, peak GH 2.9 ng/ml) and female maternal half-sibling (3 years 1 month, Ht SDS – 1.68, peak GH 6.6 ng/ml). The mother had previously been diagnosed with GHD at age 7 years. Due to the family history, sequencing of the GH1 gene was performed and identified a heterozygous change in the *gh1* gene (c.178G>A) resulting change in the GH protein (p.Ala60Thr) in all four affected individuals. This genetic variant has not been recorded in the Broad ExAc dataset representing >60,000 children without severe childhood onset disease. This amino acid is weakly conserved. The amino acid change is not predicted to cause a significant structural change in the protein. However heterozygous mutation of the gene leading to changes in the adjacent amino acid (P59), lead to a bio-inactive GH protein that has lower GHR binding affinity and impaired Jak2-STAT5 signaling. **Conclusion:** The presence of the heterozygous *gh1* gene variant (c.178G>A, p.Ala60Thr) in four individuals with GHD inherited in an autosomal dominant pattern suggests this novel mutation is likely pathogenic and causes GHD. Functional studies of the mutant GH (p.Ala60Thr) are needed to confirm the negative impact of this mutation on protein function.

P1-P624

A Novel GH1 Mutation in a Family with Autosomal-Dominant Type II Isolated Growth Hormone Deficiency

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Background: The familial type of isolated growth hormone deficiency (IGHD) is characterized by a variable degree of growth restriction, low but detectable GH serum concentrations. The recessive type IA and IB, the autosomal-dominant type II, and X-linked recessive type III. Phenotype-genotype correlations are notoriously difficult to be established. Herein, we described the patient who has autosomal-dominant type II IGHD due to a novel GH1 mutation. **Objective and hypotheses:** The proband was fifteen month old girl who presented with short stature at. Her height was 67.3 cm (−3.66 SDS) and her weight was 7.3 kg (−2.77 SDS), MPH was 146 (−2.91 SDS), bone age was consistent with 6 months. She had typically growth hormone deficiency phenotype (baby face, increased truncal adiposity, and shrill voice). In two GH stimulation tests she had low but detectable GH peaks; respectively 5.93 ng/ml (with clonidine) and 4.79 ng/ml (with L-dopa). Other pituitary hormones and magnetic resonance imaging (MRI) of the pituitary region was normal. Patient diagnosed IGHD, but she had also congenital hip dislocation operation history. Growth hormone treatment was delayed up to 2 years and seven month old. The proband received recombinant human GH (rhGH) treatment (28 μg/kg per day) and she grew 2.9 cm in 3 months. Furthermore, patient's father had growth hormone treatment history because of growth hormone deficiency. **Results:** Sequencing of the GH1 gene revealed a novel heterozygous mutation in patient and her father (p.Q110E) (c.424G>C). In silico methods were concluded that, this novel mutation mutation is the cause of disease. **Conclusion:** Establishing the genetic diagnosis of GHD is a challenge but clinical feature exceptions have to be considered.

P1-P625

2nd Year Pharmacokinetic and Pharmacodynamic Modeling of Long-Acting Human Growth Hormone (MOD 4023) in Growth Hormone Deficient Children

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Background: OPKO Biologics is developing MOD-4023, a long-acting growth hormone (GH), intended for weekly dosing for the treatment of idiopathic GH deficiency in children. At ESPE2015, we presented pharmacokinetic (PK) and pharmacodynamic (PD, based on IGF-1) models for weekly MOD-4023 administration in children aged 3–11 years. Those models were based on data collected during the 'PKPD period' (the second steady state dose of MOD-4023) and monthly values during the remainder of the first year of treatment. We now extend those analyses to data collected during the second year of treatment. **Objective and hypotheses:** To evaluate whether the PK and PD models developed from data during the first year of treatment with MOD-4023 apply to data during the second year of open-label treatment. **Methods:** After one year of treatment, children treated with weekly MOD-4023 continued on the same dose of MOD-4023 (0.25, 0.48, or 0.66 mg/kg); children treated with daily Genotropin were reassigned to one of the three weekly MOD-4023 dose levels. Blood was sampled monthly at ∼4 days post-dose to determine concentrations of MOD-4023 and IGF-1. A dataset was assembled that included values through 2 years of treatment. MOD-4023 concentrations were fit to a 2-compartment linear compartmental model. IGF-1 data were fit to an indirect PD model in which MOD-4023 increases input of IGF-1 to plasma, from which there is first-order elimination. We evaluated whether data from the second year was predicted by data from the first year. **Results:** Analyses are not yet complete. **Conclusion:** Clinical data indicate that efficacy of MOD-4023, particularly at the higher dose levels, is preserved through it least 2 years of treatment. The current analysis will evaluate whether PK and PD characteristics predicted from the first year of treatment are preserved during the second year.

P1-P626

Significance of IGF-I Generation Test in Diagnosing Primary and Non-Primary IGF-I Deficiency – Clinical Considerations

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Background: The diagnosis of severe primary IGF-I deficiency (IGFD) in children with normal growth hormone (GH) peak in stimulation tests (stimGH) should be confirmed by IGF-I increase <15.0 ng/ml during generation test (IGF-GT), however the significance of IGF-GT has been questioned by some researchers. **Objective and hypotheses:** Evaluation of the significance of IGF-GT in children with normal stim GH and IGFD, with respect to efficacy of growth-promoting therapies. **Method:** Analysis comprised 110 children with height SDS (hSDS) <−2.0, stimGH >10.0 ng/ml and IGF-I SDS <−1.0, subjected to IGF-GT with daily GH dose 0.033 μg/kg, during 7 days. **Results:** In 24 children with hSDS <−3.0 and IGF-I SDS <−2.5, the increase of IGF-I ranged from 25 to 357 ng/ml (none of them fulfilled the criteria of severe primary IGFD). The patient with IGF-I increase 25 ng/ml was treated with mecasermin up to

final height (FH) with hSDS increase from −3.69 to −1.67. Other 10 of these 24 ones were treated with GH up to FH, with hSDS increase from −3.60±0.41 to −1.26±0.60. In other three patients with hSDS < −3.0 and IGF-I SDS < −1.5, increasing in IGF-GT by 23–39 ng/ml, currently treated with mecasermin, height velocity (HV) increased significantly. In 60 children with hSDS < −2.0 and IGF-I SDS < −1.0 increasing in IGF-GT by 51–514 ng/ml, subjected to GH therapy, HV during 1st year of treatment increased from 3.7±0.9 to 8.7±2.6 cm/year; 55 out of them completed GH therapy with hSDS increase from −3.01± 0.67 to −1.37±0.87. **Conclusion:** The diagnosis of primary IGFD should be confirmed by IGF-GT, as some children with severe IGFD benefit during GH therapy despite normal stimGH that speaks for non-primary IGFD and against GH insensitivity. It seems reasonable to increase cut-off level of IGF-I SDS and of IGF-I response in IGF-GT for qualifying children to mecasermin therapy.

P1-P627

Change of Growth Pattern and Thickness of Epiphyseal Plate in Female Rats According to Injected Estrogen Dosage

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Objective and hypotheses: The purpose was to get the basic data of optimum serum concentration of estrogen in maximizing pubertal growth spurt, and decreasing the acceleration of epiphyseal closure of long bones. **Method:** i) Fifteen female SD rats (13-week aged; post pubertal growth spurt) were randomly divided into three groups. After 1 week, the group 1 were injected subcutaneously with sesame oil, as a control, group 2 were with 10 μg/kg per week of estradiol depo as a low-dose, and group 3 were with 100 μg/kg per week of it as a high-dose for 8 weeks on their posterior neck area. ii) Their crown-lump length, body weight were checked weekly. iii) Serum levels of GH and estradiol were checked with ELISA before and after injections. iv) After 8 weeks of injections, they were euthanized, their proximal tibias and distal femurs were dissected and stained with hematoxylin-eosin. v) The thicknesses of epiphyseal plate including proliferative and hypertrophic zone of the proximal tibias and distal femurs were measured in 20 evenly divided sites with microscope. vi) Statistical analyses were done among the three groups before and after injections using ANOVA with multiple comparisons for auxological data, and Kruskall–Wallis test for seum levels of GH, estradiol levels with SPSS ver.21.0. **Results:** i) There were no significant differences in body lengths and body weights among 3 groups. ii) Serum GH levels were significantly increased in both group 2 and group 3. iii) There is a tendency that epiphyseal plate thicknesses were decreased with high dosage of estrogen, but it is not statistically significant. **Conclusion:** i) Both low and high dose estrogen could increase the secretion of GH. ii) There is a tendency that epiphyseal plate thickness had a negative relation with estrogen dosage, but larger sample studies are needed iii) The effects of estrogen on epiphyseal plate in rodents may be different with human, therefore this kind of studies in animal models other than rodents are necessary.

P1-P628

Height Gain and Safety Outcomes in Growth Hormone (GH)-Treated Girls and Boys with Idiopathic Short Stature (ISS): Experience from the Prospective GeNeSIS Observational Study

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Background: GH treatment for ISS received first approval in the USA in 2003 based on data from two controlled clinical trials. Eligibility is restricted to those with baseline (BL) height standard deviation score (HtSDS) ≤ −2.25; other approvals followed, but not in Europe. **Objective and hypotheses:** To assess outcomes of GH therapy in a large cohort of patients (pts) treated in routine clinical practice. **Methods:** Short-term Ht gain, final height (FHt, defined by ≥1 of closed epiphyses, Ht velocity <2 cm per year, bone age >14 years for girls/>16 years for boys) and safety were assessed using data (mean±S.D. unless stated) collected in GeNeSIS. **Results:** ISS represents 13% of all enrolled pts (2833 of 22 161), 91% were from the USA, ∼81% were Caucasian and 71% male. In 420 pts with up to 4 years of treatment, age at BL was 10.2±2.7 years, HtSDS was −2.4±0.7 and GH dose 0.31±0.08 mg/kg per week; ΔHtSDS was 0.6±0.3 (y1), 0.3±0.3 (y2), 0.3± 0.3 (y3) and 0.1±0.3 (y4). Girls with ISS were younger at BL than boys (9.7±2.3 vs 10.4±2.8 y), shorter (HtSDS −2.7±0.7 vs −2.3±0.6), but had comparable ΔHtSDS (0.6±0.4 vs 0.6±0.3 [y1], 0.3±0.3 vs 0.3±0.2 [y2], 0.3±0.4 vs 0.3±0.3 [y3] and 0.1± 0.4 vs 0.2±0.3 [y4]). FHt was available for 530 pts with age 12.3± 2.5 y, BMI SDS −0.4±1.3 and HtSDS −2.4±0.8 at BL. Age, BMI SDS, FHt SDS and GH duration at FHt were 16.6±1.7 years, 0.2± 1.4, −1.2±0.9 and 4.2±2.4 years, respectively. FHt gain from BL was 1.1±1.0 SDS, with 83% of pts achieving FHt > −2 SDS. FHt was greater for boys (FHt SDS −1.1±0.9, HtSDS gain 1.2±1.0) than girls (−1.4±0.9, 1.0±1.0), but boys had longer duration of therapy (4.6±2.4 vs 3.5±2.0 years). There were no significant

gender differences for BL HtSDS, BMI SDS or GH dose. Of 2632 GH-treated pts with ISS with $\geq$1 follow-up visit (2.9 $\pm$ 2.1 years of follow-up) $\geq$1 adverse event (AE) was reported for 619 (24%). AEs reported for $\geq$2% were headache (3%), ADHD (2%), arthralgia (2%) and scoliosis (2%); 1 death (septic meningitis), three cases of type 1 diabetes and one cancer (malignant nevus) were reported. **Conclusion:** GH-treated pts with ISS had substantial Ht gain, similar to that observed in other studies and in other short stature conditions. Girls received GH less often than boys, but had similar Ht gain. No ISS-specific safety issues were identified.

P1-P629

Treatment of Resistant Paediatric Somatotropinomas due to AIP Mutation with Pegvisomant

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Background: Somatotropinomas are rare in childhood and are frequently associated with genetic mutations. AIP mutations are found in 20–25% cases of sporadic pediatric adenomas and are most commonly associated with GH secreting tumours that are large, aggressive and may be resistant to medical therapy. **Objective and hypotheses:** To assess response to Pegvisomant, a GH receptor antagonist in two children with sporadic somatotropinomas due to AIP mutation, where resistance to somatostatin is a recognized phenomenon. **Method:** We report two children, a 13-year-old boy and a 10-year-old girl who presented with rapid growth and visual compromise and were found to have evidence of GH hypersecretion. MRI confirmed presence of a pituitary macroadenoma with parasellar extension in both cases. Multiple surgical attempts were needed to debulk tumour mass. Residual tumour in cavernous sinus was not amenable to further surgery. Genetic analysis showed deletion in the AIP gene is both cases, patient 1-c.562delC (p.Arg188Glyfs*8) and patient 2- c.140_163del24 (p.Gly47_Arg54del8). They were initially treated with long acting somatostatin analogues (Sandostatin LAR 60 mg/week). Pegvisomant was subsequently started, at 10 mg per day subcutaneously, increased to 20 mg/day. Sandostatin was ceased due to patient intolerance and lack of biochemical control of GH excess. Radiotherapy was administered to both, as definitive treatment, for long term disease management. **Results:** Patient 1 had normalisation of IGF1 to 64.8 nmol/l (20.03–70.98) after 5 months of combined therapy with pegvisomant and cabergoline. Patient 2 was controlled after 2 months of cabergoline and pegvisomant, with normalisation of IGF1 to 34.4 nmol/l (12.14–59.29). Her clinical course was complicated by cholelithiasis and abnormal liver function, induced by somatostatin and which resolved after cholecystectomy. **Conclusion:** AIP mutation associated tumors are resistant to medical management with somatostatin receptor ligands. Pegvisomant can safely used in this situation to normalise IGF1 levels and help in disease control.

P1-P630

GH-Pattern with High Trophs are Often Found after Daily sc rhGH-Injection in Children

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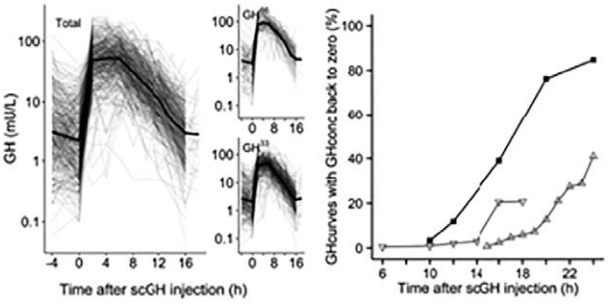
Background: Endogenous GH pattern is characterized by high peaks (growth signal) and low trophs (metabolic signal). Exogenous GH is given by subcutaneous injection (scGH-injection) daily at bedtime. **Objective and hypotheses:** To study the factors influencing intra-/interindividual variation of pharmacokinetics and pattern of scGH-injection in GH treated children. **Method:** One hundred and twenty eight subjects followed yearly $\leq$ 8 years for GH-curves after deep sc 12 mm needles, GH^{33}/GH^{67}µg/kg. EXPerimental setting (59 GH-curves in 15 MPHD patients) and CLINical setting (429 GH-curves in 117 IGHD/ISS patients). T_{max} (h) at maximal GH-concentration C_{max} (mU/l), area under the curve (AUC) mU/l and GH_{peak} width were estimated. **Results:** Interindividual variability, median (coefficient of variance, %), was for C_{max} 71(44), AUC 534(42); intra-individual variability was for C_{max} 71(38), AUC 534(36). A positive GH-concentration dependency 16 vs 4 IU/ml, $P=0.025$ and a GHinj time dependency, evening vs morning ($P=0.0014$) was found. There was a dose-dependency with C_{max} 63(51) vs 103(46), $P<0.001$, and AUC 464(45) vs 865(37), $P<0.001$, GH^{33} vs GH^{67} respectively. Forty-three percent of both C_{max} and AUC-variation could be explained by the GH-dose and indirect measurements of the injection depth ie GH_{peak}width, BMI_{SDS}. Fifteen percent of the EXP-GHcurves and 60% of the CLIN-GHcurves had not returned to zero-level before the next injection. **Conclusion:** The GH pattern of the scGHinj was characterized by a peak around 3 h, higher after a deep evening injection with high GH dose and high GH concentration (signal for growth) with great intra-/interindividual variability that in many of the GH-curves had not returned to undetectable level before the next injection which implies a non-physiological signal for metabolism.



P1-P631

Are the GH Treatment Doses in Use within Secretion Rates of Healthy Children?

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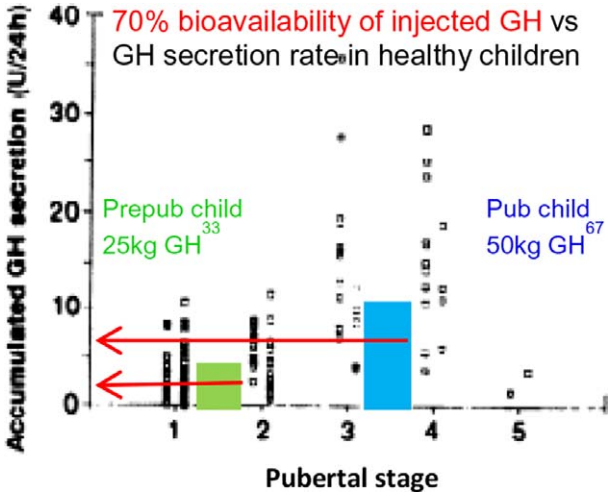
Background: GH-secretion rates for children ranges in pre/early puberty 0.1–11 U/24 h and during mid-puberty 4–40 U/24 h. This can be used to optimize the rhGH treatment doses in children. **Objective and hypotheses:** To calculated the bioavailable rhGH in relation to injected dose and compare this to GH-secretory rate in healthy children; and to investigate factors influencing bioavailability. **Method:** One hundred and twenty eight children were followed yearly ≤8 years for GH-curves after deep sc injection with 12 mm needle, GH^{33}/GH^{67} µg/kg. EXPerimental setting (59 GH-curves in 15 MPHD patients) and CLINical setting (154 GH-curves in 117 IGHD/ISS patients). The cumulative amount of GH was estimated by our formula (1), compared with the injected dose (U) = 100% which gives the bioavailability (%). **Results:** Bioavailability (median %, coefficient of the variation %) in EXP became 84%(35), range 0–100% with positive GH-concentration dependency,16 vs 4 IU/ml, $P = 0.035$. In CLIN, bioavailability was 71(43), range 0–100%, without GH-dose dependency, $P = 0.21$. Twenty-two percent of the variation was explained by the depth of injection estimated by GH_{peak}width, BMI_{SDS} and GH-level at baseline. *Consequence for GH-dosing:* i.e. in a prepubertal 25 kg child GH^{33}gives 2.5 U/24 h (70% = 1.75 U/24 h); in pubertal 50 kg child GH^{67} gives10 U/24 h (70% = 7 U/24 h). **Conclusion:** The uptake of injected GH^{33} GH^{67} was around 70% with great variation influenced by injection-depth. Bioavailable GH will therefore, correspond to secretion rates in lower range of healthy children.



P1-P632

The Influence of Growth Hormone Treatment on Fat-free Mass in Prepubertal Children with Kabuki Syndrome

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Background: The influence of GH on prepubertal children with Kabuki Syndrome (KS) is a novel field of research. KS is a congenital anomaly/intellectual disability syndrome caused by a mutation in the *KMT2D* or *KDM6A* gene. These mutation causes distinct phenotypically features, such as short stature and facial dysmorphology. Earlier studies describe a high incidence of obesity in children with KS. **Aims and objectives:** In this prospective study we investigated the influence of GH on the total energy expenditure (TEE) and fat-free mass (FFM) in genetically proven, prepubertal children with KS. **Methods:** Nineteen children with KS were included, 10 girls and 9 boys with a mean age of 6.87 ± 2.23 year. The total body water (TBW) before start and during GH treatment was measured with double-labeled water (DLW) technique. We used the DLW also to calculate the TEE in kJ/min. The FFM was calculated by dividing the TBW by the water percentage of FFM for children (Lohman *et al.* 1989). **Results and conclusions:** The data from 17 of the 19 children could be used for calculations; the data from the other two children were incomplete. We found that the mean TEE before the start of GH treatment was 3.60 ± 1.39 kJ/min and this increased significantly ($P < 0.0001$) during GH treatment to 5.51 ± 1.91 kJ/min. The FFM was also significantly increased during GH treatment compared to the baseline ($P = 0.014$). The increase of metabolic activity and FFM may decrease the number of obese children with KS and hopefully reduce the chance to develop metabolic syndrome later in life. **Disclosure:** Pfizer sponsors this study.

P1-P633

Evaluation of Prepubertal Patients with Suspected Neurosecretory Dysfunction of Growth Hormone Secretion: Diagnostic Steps and Treatment Response

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Background and aims: Existence and diagnostic procedures of neurosecretory dysfunction (NSD) are still a matter of debate. The aim of the study was to analyse prediagnostic data of short-statured children with pathologic and normal spontaneous GH-secretion and to evaluate the effect of GH-therapy in NSD-patients. **Methods:** Of 90 children aged 3–16 years, in whom 12-hour night profiles for GH-secretion were performed (unicentric), in 49 NSD was diagnosed. Their auxologic data, IGF-I

/IGFBP3-levels, GH-stimulation tests as well as spontaneous overnight GH-secretion were analysed and compared to data from children with normal spontaneous GH-secretion. Additionally, follow-up auxological data of the NSD-patients during GH-treatment were collected. **Results:** Age, prediagnostic auxologic data (height, weight, HSDS, HV, HV-SDS), delay of bone age and IGF-I/IGFBP3-levels did not differ between the two groups. Mean GH-response in clonidine tests was lower in NSD-children, but results widely overlapped (10.58 ± 4.63 ng/ml vs 14.36 ± 8.29 ng/ml). Instead, for all criteria of spontaneous GH-secretion a significant difference was found (number of peaks: 2.90 ± 1.13 vs 3.85 ± 0.99, maximal secretion: 10.23 ± 4.14 vs 18.27 ± 6.58 ng/ml, mean secretion: 2.39 ± 0.54 vs 4.36 ± 0.88 ng/ml) with mean secretion showing no overlap between the two groups. Children with NSD showed a good response to GH-treatment after 1 (ΔHSDS $+0.77 \pm 0.48$, ΔHV-SDS: 4.4 ± 3.51 cm/year) as well as 4 years (ΔHSDS: $+1.51 \pm 0.75$, ΔHV-SDS: 0.77 ± 1.86 cm/year). These results are similiar to those of children with idiopathic GHD and as in these, a significant relation of treatment effect with age was seen. Children diagnosed <10 years showed better responses after the first year although in 40% of the older ones a good benefit was found, too. **Conclusion:** According to our results, analysing overnight GH-secretion remains the only method to identify NSD. Yet, as response to GH-treatment is comparable to results in idiopathic GHD, it is worth to consider this diagnosis.

P1-P634

Four-Year Results from PATRO Children, a Multi-Centre, Non-Interventional Study of the Long-Term Safety and Efficacy of Omnitrope® in Children Requiring Growth Hormone Treatment

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Background: PATRO Children is an international, open, longitudinal, non-interventional study of the long-term safety and efficacy of Omnitrope®, a biosimilar recombinant human GH (rhGH). **Objective and hypotheses:** The primary objective of PATRO Children is to assess long-term safety of Omnitrope® (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. **Methods:** The study population includes infants, children and adolescents treated 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 standard deviation score, height velocity and height velocity standard deviation score are calculated using height measurements and country-specific reference tables. **Results:** As of January 2016, 4675 patients were recruited from 291 sites (14 countries). The mean (S.D.) treatment duration is 30.2 (22.0) months. One case of new-onset type 1 diabetes has been linked to study treatment. No clinically relevant positive anti-hGH antibody titres have been found in patients tested so far. In total, 234 patients (5.0%) have experienced treatment-related AEs and 248 (5.3%) have experienced a serious AE (SAE). SAEs were considered treatment-related in 22 (0.5%) patients. There are 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 all 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 extend the evidence base for Omnitrope®, and rhGH use in general, in the paediatric population.

P1-P635

Glucagon vs Clonidine Stimulation for Testing Growth Hormone Secretion in Children and Adolescents: Which is Better?

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Background: The definitive diagnosis of childhood GH deficiency (GHD) depends on the demonstration of failure to respond to two stimuli. In our center children are allocated to either glucagon-first or clonidine-first according to the preference of the pediatric endocrinologist following the patient. The nursing staff prefer glucagon-first due to patient safety (less pronounced adverse events and faster recovery time). Few studies have addressed which GH stimulation test should be performed first in the evaluation of children with short stature. **Objective:** To investigate the diagnostic value of the glucagon test as compared to the clonidine test in short children. **Methods:** Endocrine nurses performed 1350 stimulation tests (GH, ACTH, LRH, OGTT, water deprivation) in our tertiary pediatric endocrine center during 2015. The primary outcome measures of this retrospective study included prevalence and rate of false positive with glucagon-first as compared to clonidine-first. GH cut-off level was 7.5 ng/ml. **Results:** The studied cohort was comprised of 465 short children [median age 9 years (range 0.8–16 years), 307 (66%) boys]; glucagon-first group ($n=435$) and clonidine-first group ($n=30$). GH stimulation testing flowchart is presented in the attached figure. Glucagon-first was more often prescribed as compared to clonidine-first (93.5 and 6.5%, respectively, $P<.001$). False-positive GH testing was diagnosed in 27.6% of the children (120/435) in the glucagon-first group as compared to 23.3% of the children (7/30) in the clonidine-first group ($P=0.613$). In attempt to overcome the limitation of small sample for clonidine-first group, GH tests from the first half of 2016 will be added to the analysis. **Conclusions:** Although pediatric endocrinologists more commonly prescribed glucagon as the first test in the evaluation of short children, our preliminary findings do not favor one stimulus over the other as the preferred test in the diagnosis of GHD. Future prospective studies are warranted to determine which GH stimulation test should be performed first.

P1-P636

The Use of Tissue Doppler Imaging in Assessing Right and Left Ventricle Diastolic Function in Children with Growth Hormone Deficiency before and after 1-Year Therapy with Growth Hormone

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Background: Growth Hormone (GH) therapy has a positive effect on many parameters including metabolic and physiologic functions as well as its effect on growth. It has also been shown that GH therapy exerts a significant effect on cardiac morphology and function as evidenced by echocardiographic findings. **Aim:** To investigate left and right ventricle (LV, RV) diastolic function by Tissue Doppler imaging (TDI) in pre-pubertal growth hormone deficient (GHD) children before and one year after GH therapy versus the standard M-mode and Doppler echocardiographic imaging techniques. **Patients and methods:** A prospective case–control study performed on 23 pre-pubertal GHD patients and 14 age, sex and body mass index (BMI) matched controls. Anthropometric measurements and TDI were done before and one year after therapy with GH. **Results:** GHD patients showed significant impairment in RV and LV diastolic functions by TDI when compared to controls as shown by lower levels of maximum wave velocity of early filling across tricuspid annulus (E't), and maximum wave velocity of late filling (atrial wave) across tricuspid annulus (A't) ($P=0.00$ and 0.00 respectively) as well as higher ratios of maximum wave velocity of early filling across mitral annulus to maximum wave velocity of late filling across mitral annulus (E'm/A'm) and ratio of maximum wave velocity of early filling across tricuspid valve to maximum wave velocity of early filling across tricuspid annulus (Et/E't) in cases compared to controls ($P=0.0001$ and 0.0001 respectively). One-year therapy with GH significantly decreased both ratios denoting improvement in the net diastolic functions. **Conclusion:** GH improves RV and LV ventricle diastolic functions as shown by TDI.

Key Words: GHD, ventricular function, TDI

P1-P637

Diagnosing GH Deficiency in Children by Arginine Hydrochloride Infusion Test: Relationship between Auxiological Characteristics, Arginine Plasma Profile and Arginine-Stimulated GH Release

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Background: Arginine HCl infusion is commonly used in the diagnostic workup of GH deficiency. There is a paucity of data whether obesity and/or short stature modulate arginine plasma concentration and associated arginine-stimulated GH secretion following a weight-based arginine infusion protocol. **Objective and hypotheses:** To study whether auxiological parameters modulate the arginine plasma concentration profile and associated GH secretion in children undergoing arginine stimulation testing. **Method:** Retrospective analysis, including 35 short-statured children (24 male; age 10.1 ± 3.5 years; height SDS -3.1 ± 0.6, weight SDS -2.5 ± 1.0; BMI SDS -0.81 ± 0.2). Arginine plasma concentration profile, following intravenous infusion of 0.5 g/kg arginine, was measured using a lithium high-resolution column (Biochrom 30 amino acid analyser); hGH concentration was measured by a highly sensitive ELISA (Mediagnost, Germany). **Results:** Peak arginine plasma concentrations were observed 30 min (4980 ± 364 γmol/l) after start of arginine infusion and preceded peak GH concentration (7.5 ± 1.0 ng/ml) at 45 min. Peak arginine plasma concentration correlated both with weight ($r=0.464$; $P<0.01$) and height SDS ($r=0.407$; $P<0.05$). We found no sex-dependant differences in arginine profile or stimulated GH secretion. In linear regression analyses, weight SDS contributed significantly to the variance in peak arginine concentration ($r^2=0.13$). Furthermore, BMI SDS contributed significantly to the observed variance in peak GH concentration ($r^2=0.14$). **Conclusion:** Weight and height are associated with the arginine plasma profile and the stimulated GH response to arginine stimulation testing and thus should be considered in the interpretation of test results.

P1-P638

Retrospective Analysis of Growth Hormone (GH) Treatment Results in Children with Idiopathic Growth Hormone Deficiency (IGHD), Turner Syndrome (TS) and Small for Gestational Age (SGA) using iGRO* in a Pediatric Endocrine Practice

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Background: Quality management of GH treatment in children is important to ensure optimal treatment outcome and to save resources in the health care system. iGRO is a new internet based Medical Device to compare treatment results with predicted results according to published prediction models. **Objective and hypotheses:** Growth data were analyzed by iGRO for 1st and 4th year prediction in comparison to treatment results. All eligible patients of our practice treated with GH between 2009 and 2015 were analyzed to compare results with prediction. **Method:** Growth data were analyzed by iGRO for 1st year treatment results in 55 IGHD patients (age 6.76 ± 2.19 years; $\pm$S.D.), 22 TS pts (age 7.85 ± 3.31 years), and 56 SGA pts (age 5.4 ± 1.79 years). Eighteen, 6, and 14 pts were available for the analysis of the 4th year. **Results:** Of the IGHD, TS, and SGA pts 41.8% ($n=23$), 12.5% ($n=2$), and 29% ($n=14$) did not reach the mean prediction after 1 year of treatment, respectively. Of these low responders, 16, 2, and 5 pts differed more than 1 cm from their individual mean predictions, respectively. The reason for this low treatment response was related to adherence problems in 6, 2, and 5 children and related to a low dose of GH in 3, 0, and 0 children, respectively. Additional reasons for low treatment response were

Noonan syndrome (1), undefined syndromal disease (1), and revision of diagnosis to constitutional delay of growth and puberty (2). In the 4th year of GH treatment 33% ($n=6$), 16.7% ($n=1$), and 50% ($n=7$) of patients in IGHD, TS, and SGA groups did not reach the mean prediction. **Conclusion:** The analysis of treatment response to GH using iGRO showed a high percentage of good responders and only a low percentage of patients missing their prediction by more than 1 cm. In most cases, reasons for a suboptimal response to GH could be found. Thus, iGRO is a valuable and easy-to-use tool in a Paediatric Endocrine Practice to analyze the response to GH treatment in IGHD, TS, and SGA children. For the future iGRO will be used prospectively to optimize GH treatment from the start onwards.
*iGRO is a CE-certified Medical Device, available in EU countries, provided by Pfizer, Inc.

P1-P639

Spanish ECOS Study Analysis: Socioeconomic Data, Adherence and Growth Outcomes with Case Studies

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Background: The ECOS observational study in Spain (NCT01376921) aims to evaluate adherence to r-hGH therapy prescribed via the easypod™ electromechanical auto-injector device and to analyse factors that may influence adherence in paediatric patients. Easypod™ administers pre-set doses of Saizen® r-hGH and stores accurate records of each dose and injection taken, which can then be shared with the HCP for evaluation of the patient's adherence. **Objective and hypotheses:** To assess the use and acceptability of easypod™ and adherence to r-hGH therapy, to highlight individual patients' dosing patterns and growth outcomes and to assess the socioeconomic background of care-givers responsible for administering injections. **Method:** Adherence was determined categorically and also as %adherence over time, defined as the number of days with injections received, divided by the number of days with injections planned. Accurate individual adherence data were transcribed directly from the patients' easypod™ while socioeconomic, demographic, auxological and diagnostic data were obtained from medical notes. **Results:** The Spanish cohort consisted of 280 children, of whom 240 were included in the final analysis set (52% male). The majority were Caucasian (93.8%), with a diagnosis of GH deficiency (GHD, 60.0%), small for gestational age (SGA, 35.8%), Turner Syndrome (TS, 3.3%) or chronic renal failure (CRF, 0.83%). Despite high overall adherence (median 98.8%, mean 94.5% [95% CI 92.8, 96.3]), growth responses varied and patterns of missed doses proved highly individual and, in some cases, fluctuated over time, possibly reflecting changes in caregiver or other life circumstances. Almost 80% of injection-giving carers were employed, while 31.5% had degree level education, 35.0% had only had school level education, 9.5% had 'other' education and 22% had not had this recorded. **Conclusion:** The majority of children adhere extremely well to their treatment regimen using the easypod™ device. Individual cases show distinctive patterns of adherence and growth outcomes.

P1-P640

Analysis of Correlation between Stem Cells ($CD133^+/CD45^+$ and $CD133^+/CD45^-$) and Anthropometric Parameters of Children with Growth Hormone/Primary Insulin-Like Growth Factor 1 Deficiency

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Introduction: Hematopoetic progenitor stem cells (HSCs, $CD133^+/CD45^+$) and very small embryonic-like stem cells (VSELs, $CD133^+/CD45^-$) can differentiate into specific immune cells. Some studies suggest that levels of HSCs and VSELs change during therapy with growth hormone (GH) or insulin-like growth factor 1 (IGF-1). GH deficiency (GHD), an endocrine disease connected with insufficient production of GH by pituitary gland, is treated with synthetic GH. IGF-1 is main growth factor, secreted under the influence of GH. Primary IGF-1 deficiency syndrome (PIGFDS) may be caused by genetic defects and it is treated with IGF-1. **Aim:** The aim of the study was to estimate the concentration 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 or IGF-1. To assess correlation between the level of HSCs and VSELs and anthropometric parameters. **Materials and methods:** Anthropometric parameters (height, weight, BMI) and HSCs and VSELs levels were measured in 32 children with GHD during GH therapy and 4 with PIGFDS during IGF-1 therapy. Mean age 12 years old. The control group comprised 16 healthy, age and sex matched children. HSCs and VSELs levels were determined with flow cytometry. **Results:** Comparing to control group HSCs level increases statistically significant ($P<0,05$) in the group treated with GH but tendency to increase without statistical significance was demonstrated by VSELs in both study groups and by HSCs in IGF-1 treated group. Statistically significant correlations ($P<0,05$) between stem cells levels and anthropometric parameters were observed in both GH (HSCs and weight, VSELs and height) and IGF-1 (VSELs and BMI, VSELs and height) treated patients. **Conclusion:** In conclusion, GH and IGF-1 mobilize stem cells. VSELs and HSCs could be monitoring markers of patients response to therapy.

P2-P641

Hypochondroplasia (HC) Treatment with rGH: Actualization of Pilot Observations

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Background: In patients with HC due to N540K FGFR3 mutations, adult height ranges 138–155 cm (men) and 128–145 cm in women. We have previously reported that a mean 0.075 μg/k.d rGH dose could allow a gain of 1.9 S.D. of height over 6.1 year and could reduce body disproportion in 6 young patients (*Journal of Pediatrics* 2012). **Objectives:** To confirm these results and extend observation of rGH effects. **Patients:** Starting at 1.8–7 year of age, 10 HC patients received cumulative 0.081 ± 0.009 mg/k.d rGH with repeated planned breaks from treatment and frequent measurements of height, body proportions, and serum IGF1. At 10 years of age in 2 girls and 11 in 2 boys, GnRH analogs were used to delay puberty and epiphyseal closure. **Results:** Current duration of treatment ranges 1–10 years. Mean IGF1 values averaged 2.3 ± 0.3 S.D. during rGH treatment. As previously observed, patients treated before 3 yrs gained height actively and stabilized near the −2S.D. height line. Patients treated at an older age showed a more reduced catch-up effect. Despite efficient blockade of puberty, femoral and tibial growth plates underwent a rapid with almost complete closure around 13 years of age; thereafter height started to plateau despite continuing rGH treatment. **Conclusion:** rGH treatment in patients with HC i) show clearcut positive results when started early ii) are more limited if started in mid-childhood iii) cannot maintain growth acceleration at adolescence iv) seems to end its effect around age 13. The current observations are preliminary and should be confirmed in larger studies of this rare chondrodysplasia. However, this report can serve as a warning for an early treatment and for trying to maximize rGH effects in infancy and early childhood.

P2-P642

The Influence of Growth Hormone Treatment on the Basal Metabolism in Prepubertal Children with Kabuki Syndrome

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Background: The influence of growth hormone (GH) on the metabolism of prepubertal children with Kabuki syndrome (KS) was never investigated before. Kabuki syndrome (KS) is a rare syndrome, which is mainly characterized by mental retardation, short stature, specific facial features, obesity and hypotonia. This syndrome caused by a mutation in the *KMT2D* or *KDM6A* gene. **Objective and hypotheses:** In this prospective study we investigated the influence of GH on the basal metabolic rate (BMR) and physical activity in genetically proven, prepubertal children with KS. **Method:** We included 19 KS children, ten girls and nine boys with a mean age of 6.87 ± 2.23 year. The BMR before start and during GH treatment was measured with the ventilated hood (VH) technique. We calculated the BMR by Weirs' formula. The accelerometer was used to measure the physical activity. **Results:** The VH data were useful in 18 of the 19 children, we found that the mean BMR before the start of GH treatment was 3.17 ± 0.52 kj/min and this increased significantly ($P = 0.001$) during GH treatment to 3.70 ± 0.57 kj/min. The children who wore the accelerometer correctly had a mean wearing time of 8.5 days and this resulted in six out of ten in a higher physical activity during GH treatment than before the start of GH. In conclusion, the BMR is significantly higher during GH treatment compared to the baseline value and in the majority of the cases the physical activity raised by GH treatment in children with KS.

P2-P643

An Analysis of the Safety of Childhood Growth Hormone (GH) Therapy: Data from the NordiNet® International Outcome Study (IOS)

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Background: NordiNet® IOS (NCT00960128), a non-interventional study, collects long-term effectiveness and safety data of GH (Norditropin®, Novo Nordisk) treatment in everyday clinical practice. **Objective and hypotheses:** Identify paediatric patients more likely to experience a second adverse event (AE). **Method:** Based on diagnosis at GH treatment start and associated risk for mortality, patients were classified into: low-risk (idiopathic GH deficiency, idiopathic short stature, small for gestational age), intermediate-risk (multiple pituitary hormone deficiency, clinically defined syndromes) or high-risk (malignancy, craniopharyngioma, chronic renal failure) groups. Incidence rates (IRs)/1000 patient-years of exposure (PYE), for adverse drug reactions (ADRs), serious ADRs (SADRs) and serious AEs (SAEs) were calculated. AEs were classified using System Organ Class/MedDRA Preferred Terms. **Results:** Data were analysed for 16 359 patients (mean (S.D.) age 8.7 (3.9) years; treatment duration 4.1 (3.0) years; GH dose 34.2 (10.0) μg/kg per day; low-risk, 62.1%; intermediate-risk, 32.6%; high-risk, 5.3%). 372 patients reported

434 AEs: one AE, 89.8% ($n=334$); two AEs, 8.1% ($n=30$); ≥ 3 AEs 2.2% ($n=8$). IRs/1000 PYE were: ADRs, 3.78; SAEs, 3.84; SADRs 1.11. IRs were significantly higher in the intermediate- and high- versus low-risk group ($P<0.05$). Post-AE, GH dose was unchanged in 54.5 and 37.9% of the low- and high-risk groups, respectively; treatment discontinuation was more common in the high- (39.4%) vs low-risk group (17.4%). Proportions of patients with one AE were: low-risk, 92.6% ($n=138$); intermediate-risk, 88.0% ($n=147$); high-risk, 87.5% ($n=49$). Higher proportions of patients in the intermediate – 10.2% ($n=17$) and high- 8.9% ($n=5$) vs low-risk group, 5.4% ($n=8$) reported two AEs; ≥ 3 AEs occurred in $<4\%$ in any risk group. **Conclusion:** These results are consistent with previous reports from NordiNet IOS and reconfirm the overall favourable safety profile of GH treatment. Patients in the intermediate- and high-risk groups were more likely to have a second AE than those in the low-risk group. A similar low rate for ≥ 3 AEs was reported across all risk groups.

P2-P644

Adverse Effects after Priming with Testosterone in Short Statured Boys before Growth Hormone Stimulation Test

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Background: Current guidelines recommend the priming with low-dose testosterone in prepubertal boys prior to growth hormone stimulation tests. To our knowledge, only few adverse events after low-dose testosterone have been described so far. **Objective and hypotheses:** To assess possible side effects of testosterone priming. **Patients:** We studied 188 prepubertal boys aged between 10 and 15 years (mean $\pm$ S.D.: 11.4 ± 1.25 years), who were primed with testosterone doses between 50 mg ($n=136$) and 125 mg ($n=51$) seven days before the test. One boy accidentally received 250 mg testosterone. We report on three patients who developed priapism and two patients with testicular pain. Serum testosterone levels were measured by LC-MS/MS at the time of the test. **Results:** Two boys (twins aged 12 years) developed severe low-flow priapism 2 weeks after the I.M. injection of 125 mg testosterone. In both cases, decompression of the cavernous bodies by blood aspiration was performed. A 10-year-old boy (50 mg I.M.) suffered from stuttering priapism and testicular pain (5 days after injection). The symptoms were self-limiting within a few days. Two boys (10 years, 50 mg I.M.) only reported on testicular pain. The side effect rate after priming was overall low with 2.7%. Serum testosterone levels (ng/ml) were available in 95 boys without side effects and ranged from 0.38 to 46.1 (mean $\pm$ S.D.: 9.8 ± 7.7, median: 6.2). The testosterone levels of four of the five boys with adverse events (missed: $n=1$) ranged from 4.0 to 26.3 ng/ml and were within the range of the boys without side effects after priming. We found no significant differences between the used doses of 50 and 125 mg testosterone (SI units: ng/ml $\times 3.47 =$ nmol/l). **Conclusion:** Parents and patients should be informed about priapism and testicular pain as rare side effects of testosterone priming.

P2-P645

Effect of One-Year Growth Hormone Therapy on Serum Levels of Ghrelin and Leptin in Children with Growth Hormone Deficiency and their Correlations with Cardiac Functions and Dimensions

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Background: Controversial data on ghrelin and leptin concentrations in patients with growth hormone deficiency (GHD) have been published. Little has addressed the correlation between Ghrelin and leptin with cardiac functions in patients with GHD. **Aim:** To investigate the effect of one year Growth hormone (GH) therapy on serum levels of ghrelin and leptin in children with GHD and to study their correlations with cardiac functions and dimensions in patients with GHD. **Patients and methods:** A prospective case-control study was performed on 23 pre-pubertal growth hormone deficient patients and 14 age, sex and BMI matched controls. Anthropometric measurements, echocardiography (conventional and cardiac tissue Doppler imaging) and measurement of serum levels of ghrelin and leptin were done before and after one-year therapy with GH. **Results:** Untreated GHD patients had significant lower height ($P=0.0001$) when compared to controls. Ghrelin and Leptin levels were comparable between the two groups at baseline and after one year follow up without any statistical significant difference. Ghrelin in visit two correlated negatively with Ratio between maximum wave velocity of early diastolic filling across mitral annulus and maximum wave velocity of late diastolic filling (atrial wave) across mitral annulus by Doppler echocardiography, (Em/Am) in both visits ($P=0.012$ and 0.013 respectively), ejection fraction (EF) in visit two and left ventricular mass index (LVMi) in both visits ($P=0.036$ and 0.009 respectively). Leptin in visit two correlated positively with left ventricular diameter in diastole (LVEDd) in both visits and aortic root diameter in visit 2 (Ao) ($P=0.009$, 0.009 and 0.24 respectively). Neither ghrelin nor leptin showed correlation with other echocardiographic and cardiac tissue Doppler imaging parameters. **Conclusion:** Treated and untreated GHD children did not show any difference in their serum levels of ghrelin and leptin, However Ghrelin correlated with Em/Am, EF and LVMi while Leptin correlated with LVEDd and AO.

Key words: GHD, Ghrelin, Leptin, cardiac

P2-P646

Metabolic Parameters and Glucose Homeostasis in Childhood Onset Growth Hormone Deficiency at Time of Initial Evaluation and Retesting

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Background: It is well known that growth hormone (GH) brings about several effects, involving bone, body composition, lipids and glucose homeostasis. However, the complex interplay between these parameters is rather poorly studied in children with childhood-onset-GH deficiency (CO-GHD). **Objective and hypotheses:** To investigate lipids, adipokines (leptin- adiponectin- resistin) and glucose homeostasis and their relationship with bone and body composition in children and adolescents with CO-GHD at time of diagnosis and retesting at final height. **Method:** A cross-sectional study of children undergoing GH stimulation tests for short stature (total −25, GH deficiency −15, median age (range) 10.9 years (5.6–16.0)) and biochemical revaluation at final height after GH therapy (total – 11, GH deficiency – 7, age 16.7 years (14.9–18.6)). **Results:** At time of diagnosis and retesting, lipid profiles, adipokines and glucose homeostasis in both groups were within the normal range with no differences between those with GHD and those who had normal GH levels. Leptin levels in both groups correlate positively with fat mass ($r=0.9$, $P<0.001$), and with osteocalcin positively at diagnosis ($r=0.5$, $P=0.01$) but inversely at retesting ($r=-0.9$, $P<0.001$). In retesting group, those who were older at the time of diagnosis CO-GHD and had a shorter duration of GH therapy were more likely to have higher cholesterol ($r=0.9$, $P<0.001$), LDL($r=0.9$, $P<0.001$), and leptin ($r=0.8$, $P<0.001$), and lower osteoclacin ($r=-0.7$, $P=0.01$) at final height. **Conclusion:** Metabolic profiles and glucose homeostasis are not significantly different between those with GH deficiency and those with normal GH levels at times of initial evaluation and retesting at final height. Timing and duration of childhood treatment may influence adiposity parameters and bone formation biomarkers seen in adolescents with CO-GHD. Differences in relationship between leptin and osteoclacin at diagnosis and retesting may be related to active growth. Further studies are still required to clarify the relationship between adipokines, bone and CO-GHD.

P2-P647

Final Adult Height (FAH) in Patients with PROR-1 Gene Mutations during GH Long-Term Therapy

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Background: PROP-1 gene mutations are responsible for most of the cases of multiple pituitary hormone deficiencies (MPHD). **Objective and hypotheses:** We performed to evaluate the final adult height (FAH) in a group of patients with a PROP-1 gene mutations. Twenty-five patients (11 males) with a PROP-1 gene mutation, not treated before, were recruited. All the patients had been treated with a fixed rhGH dose (0.033 mg/kg per day) for 10.5 years (7.0–11.45). Fifteen patients (seven males) reachad FAH. At the time of the diagnosis secondary hypothyroidism was revealed in 83.3% of patients, secondary hypocortisolism – in 12.0%. In adult, secondary hypothyroidism was revealed in 100%, secondary hypogonadism in 100% of patients and secondary hypocortisolism in 33.3%. All patients received replacement therapy and were compensated all the time during the rhGH treatment. **Method:** 'Hypopituitarism panel' genes were sequenced using a custom Ion Ampliseq gene panel and PGM semiconductor sequencer (Ion Torrent). **Results:** Baseline characteristics of patients (Table 1): Characteristics at the end of the therapy (Table 2): **Conclusion:** Patients with a PROP-1 gene mutation showed a good response to GH therapy in our study. All patients with a PROP-1 gene mutation reached PAH.

P2-P648

Congenital Hypopituitarism: Genotypic–Phenotypic–Neuroradiological Correlation

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Background: Congenital hypopituitarism is a rare cause of pituitary insufficiency (incidence: 12–42 new cases/million per year; prevalence: 300–455 cases/million). The aetiology remains largely unclear: the most frequently correlated genetic abnormalities are those involving transcription factors implicated in pituitary organogenesis. The phenotype and neuroradiological findings associated with the underlying genotype may be highly variable (from an isolated hypopituitarism to more complex conditions such as septo-optic dysplasia and holoprosencephaly). **Objective and hypotheses:** i) Retrospective analysis of a population of pediatric patients with hypopituitarism in clinical, diagnostic and therapeutic terms; ii) assessment of the phenotypic characteristics and clinical findings in order to highlight common features that may suggest a diagnosis, a most likely genetic mutation and possible genotypic, phenotypic and neuroradiological correlates; iii) evaluation of the therapeutic response to GH replacement. **Method:** Clinical, neuroradiological and molecular data were collected in 31 patients (M/F=15/16) with congenital hypopituitarism, 15 with neonatal diagnosis and 16 with delayed diagnosis, born from 1989 to 2014. **Results:** Eighty-four percent of patients presented symptoms at birth: the most frequent were prolonged hypoglycemia (55%), prolonged jaundice (51%) and respiratory distress (49%). Micropenis and cryptorchidism were present in 47% of male patients. Genetic analysis showed correlated mutations only in 19% of cases (4 patients: mutation in HESX1, microdeletion in PROP1, mutation in GLI2, deletion 1q24.3q31.1 containing LHX4). Brain MRI showed: 84% adenopituitary hypo-aplasia, 77% pituitary stalk hypoplasia/interruption/absence, 74% ectopic neurohypophysis, 22% septo-optic dysplasia,

Table 1. (for abstract P2-P647)

Characteristic	Males ($n=11$)	Females ($n=13$)	Total ($n=24$)
Chronological age at diagnostic (years)	5.0 (5.0 to 6.0)	6.0 (5.0 to 9.0)	6.0 (5.0 to 7.0)
Peak GH level on testing	0.95 (0.2 to 2.5)	0.33 (0.1 to 1.36)	0.5 (0.2 to 1.4)
Height at initiation, SDS	−3.25 (−4.25 to −3.06)	−4.02 (−5.49 to −3.14)	−3.77 (−4.46 to −3.12)

Table 2. (for abstract P2-P647)

Characteristic	Males ($n=7$)	Females ($n=8$)	*P*
Height velocity in the first year, SDS	8.98 (6.85 to 11.25)	8.67 (7.35 to 13.02)	
FAH, cm	176.0 (172 to 181.1)	160.5 (158.05 to 166.15)	
HSDS (FAH)	0.24 (−0.41 to 0.98)	−0.25 (−0.67 to 0.69)	0.61
Predicted adult height (PAH), cm	179.0 (174.5 to 190.5)	162.5 (162.5 to 168.5)	
Predicted adult height, SDS	0.65 (−0.03 to 2.38)	0.08 (0.08 to 1.0)	0.62
Δ PAH − FAH	0.00 (−0.26 to 2.14)	0.50 (−0.75 to 1.75)	

normal in 3%. **Conclusion:** The clinical suspicion should be placed at birth in those symptomatic children. MRI evaluation is fundamental in order to predict the endocrinological phenotype and the underlying genotype. The evidence of common traits in these patients make the hypothesis of a common genetic alteration more likely; however other genes still remain to be identified and other factors (such as environmental) could contribute to the pathogenesis of this complex condition.

P2-P649

A Case of Hypopituitarism in a Patient with Cantù Syndrome

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Background: Cantù syndrome is a rare disorder characterized by congenital hypertrichosis, neonatal macrosomia, a distinct osteochondrodysplasia, and cardiomegaly. Other findings described are vascular abnormalities, pulmonary hypertension, generalized edema, mild learning disability and behavioral problems. Cantù syndrome is related to an heterozygous pathogenic variant in *ABCC9* or *KCNJ8*, which can be inherited in an autosominal dominant manner or due to a *de novo* pathogenic variant. **Objective and hypotheses:** We report a particular case of a 15 years old girl, affected by Cantù syndrome clinically diagnosed (genetic tests are currently being conducted), with hypopituitarism. **Results:** The propositus showed macrocephaly and typical coarse facial features with broad nasal bridge, anteverted nares, enlarged nasal filter, macroglossia and enlarged pinna. She also has widespread hypertrichosis, joint laxity, pectus carinatum and hoarsely voice. The patient also showed bone abnormalities typical of Cantù Syndrome and cardiac involvement represented by a dilated cardiomyopathy. Diagnosis of central congenital hypothyroidism was made at 1 month of life. During the follow-up, diagnosis of GH deficiency and hypogonadotropic hypogonadism was made. MRI showed a hypoplastic pituitary. **Conclusion:** We described the first case of Cantù Syndrome with hypopituitarism, underlying the importance to assess endocrine status at diagnosis and during follow-up in these patients.

P2-P650

Delaying Puberty with GnRHa does not Promote Adult Height in GH Treated Children Who Enters Puberty at Average Age

Felicia Hansson, Peter Bang

Table 1. (for abstract P2-P648)

	Neonatal diagnosis (48%)	Delayed diagnosis (52%)	Peculiar phenotypic traits	%
Median age at diagnosis	0.1 years (1.2 months)	3.16 years	Depressed nasal bridge	26
Hormones deficiency	GH + TSH + ACTH 97% TSH + GH 3%	GH + TSH + ACTH 90% GH + ACTH 7% TSH + GH 3%	Prominent forehead	23
Median cortisol levels (ng/ml)	10	47.5 ($P<0.0001$).	Low-set ear	23
Response to GH replacement (mean dose 0.21 mg/kg per week)	ΔHt after 2 year: +1.6 SDS ΔHt final height: +2.61 SDS	ΔHt after 2 year: +1.79 SDS ΔHt final height: +3.35 SDS	Cleft lip and palate	9
			Polydactyly	9

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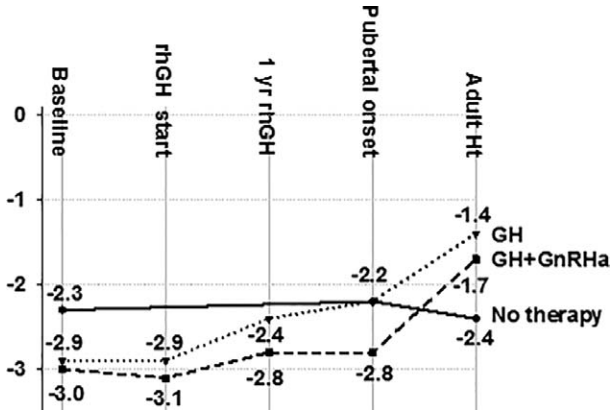
Background: Delaying puberty with GnRHa in an attempt to improve final height in GH treated children is relatively common in clinical practice. Such treatment is only supported by one retrospective study in which pubertal start was relatively early. **Objective and hypotheses:** To retrospectively assess adult height in children with short stature treated with GH and receiving or not receiving GnRHa. We hypothesized that delaying puberty with GnRHa improves adult height. **Method:** We identified 70 children (35 girls) assessed for short stature in our clinic between 2000 and 2009 and in whom we had data on adult height. rhGH monotherapy was given to 27 patients (GH start at mean (S.D.) age 10.1 (2.2) years), rhGH plus GnRHa therapy to 24 patients (GH start at age 10.9 (2.2) years and GnRH start at age 11.9 (2.9) years) and the remaining 19 patients did not receive any treatment (Investigated at age 11.2 (3.7). Patients had diagnosis of IGHD, SGA and ISS. **Results:** Adult mean (S.D.) heights were −1.4 (0.9) SDS in rhGH and −1.7 (0.6) SDS in rhGH plus GnRHa treated patients, significantly higher than −2.4 (0.8) in controls ($P<0.01$ and $P<0.05$, respectively). The gain from baseline to adult height did not differ between patients treated with rhGH or rhGH plus GnRHa but was larger than in non-treated children ($P<0.005$ and $P=0.011$, respectively). The distance from reference mean age at B2 or testicular volume >3 ml to pubertal start was 0.7, 0.3 and −0.3 years, respectively. The most important predictors of adult height were a low baseline height, long distance to MPH and a low GH_{max}. **Conclusion:** This study does not support that delaying puberty with GnRHa promote adult height in GH treated children who enters puberty at average age.



Background: Fibroblast growth factor 21 (FGF21) is a metabolic and growth regulator. The growth-promoting effect of GH in children with GH deficiency (GHD) depends on many factors. FGF21 concentration in and its interaction with growth deficiency and growth response to GH therapy in GHD was not examined. **Objective and hypotheses:** To estimate the FGF21 concentration and its correlation with degree of growth deficiency and growth response in non-obese, prepubertal children with isolated GHD before (GHD before GH) and after 6 months of GH therapy (GHD after 6 m GH). **Method:** The 32 (22 boys, 10 girls) children with GHD (mean height 117.9 cm, −2.77 S.D., mean BMI −0.75 S.D.), mean age 8.87 years. Control group (CG): 18 (11 boys, 9 girls) age matched healthy children (mean height 125.8 cm, −0.93 S.D., mean BMI −0.28 S.D.). Serum fasting FGF21 was measured in all and in GHD after 6 months (m). In GHD IGF1 was measured before and after 3 months (m) of GH therapy. GHD patients were divided into subgroups dependently on degree of growth deficiency before GH therapy: A < median height S.D. and B > median height S.D.. **Results:** The median concentration of FGF21 did not differ significantly between CG, GHD before GH and GHD after 6 m, however in CG it was lower than in GHD (94.1 vs 99.8 before GH and 133 pg/ml after 6 m GH). IGF1 was significantly higher after 3 m of GH than before GH (242 vs 116.4 ng/ml). FGF21 after 6 m correlated with height S.D. after 6 m: the higher FGF21 after 6 m the more profound growth deficiency ($r=-0.50$, $P<0.05$). Stepwise discriminant analysis showed that FGF21 and IGF1 are differentiating features between A and B subgroup (canonical factor: 0.49). In subgroup A FGF21 was higher than in subgroup B. FGF21 before GH was higher in subgroup A than in subgroup B with border significance (median 111 vs 84.5 pg/ml, $P=0.07$) while FGF21 in subgroup A after 6 m of GH was significantly higher (median 174.5 vs 94.1 pg/ml, $P<0,05$). IGF1 was significantly lower in group A than in B both before and after 3 months of GH therapy. **Conclusion:** FGF21 has potential negative impact on stature growth in GHD children.

P2-P651

Estimation of FGF21 Concentration in Prepubertal Children with Growth Hormone Deficiency before and after 6 Months of Growth Hormone Treatment

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P2-P652

Abstract withdrawn

P2-P653

Improving the 'Gold Standard': The Insulin Tolerance Test Revisited

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Background: The optimal method to assess GH status remains controversial. GH provocation tests are used and the Insulin Tolerance Test (ITT) is regarded as the 'gold standard' to

diagnose GH deficiency (GHD). The original selection of 0, 20, 30, 60, 90 and 120 min time points is still used in many protocols worldwide, but variations have evolved. **Objective and hypotheses:** Comparing standard ITT (StdITT) to a revised (RevITT) protocol. **Method:** ITT was performed according to local protocol. StdITT measured GH at −30, 0, 30, 60, 90 and 120 min. RevITT added three additional samples (15, 45 and 75 min). Data are presented as mean±S.D. unless specified otherwise. **Results:** ITT where hypoglycaemia was achieved were included (376/392). 65 were done using RevITT. Median GH levels were highest at 60 min on StdITT and 45 min on RevITT. Peak GH levels were measured (in decreasing frequency) at 60, 30, 0, −30 min on StdITT and 45, 0, 60, 30 min on RevITT but did not necessarily preclude GHD. Using peak GH cut-offs of 7 μg/l for prepubertal children and 5 μg/l for adolescents, 214/311 (68%) of StdITT and 38/65 (58%) of RevITT were abnormal. Analysis of 124 normal tests (97 StdITT and 27 RevITT) identified 51/124 (42 StdITT and 9 RevITT), where a single GH level was above the diagnostic cut-off. The 45 min sample represented the peak GH level in 8/27 normal RevITT and in two tests it was the only level precluding GHD. The 75min sample did not preclude GHD. The 15 min sample represented the peak GH level in 3/27 normal RevITT, but did not preclude GHD on its own in any of these three tests. The −30 min sample precluded GHD in 5/124. **Conclusion:** Early and more frequent sampling are key to diagnosing GHD accurately, precluding GHD in an additional 7.5% (45 min sample) and 4% (−30 min sample). The 120 min can be removed as it does not contribute to GHD diagnostic yield.

P2-P654

Adherence to Growth Hormone Therapy: Comparison of Electronic Auto-Injection to Non-Electronic Injection Devices

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Background: Mean adherence (AD) rates in patients treated with recombinant human GH (r-hGH) using either the easypod™ or a non-electronic (NEL) device have recently been reported. **Objective and hypotheses:** To evaluate AD rates of r-hGH treatment under everyday conditions and to calculate the amount of r-hGH administered using the easypod™ or a NEL device. **Method:** Retrospective, observational, open-label, non-controlled study in patients receiving r-hGH, either by the easypod™ or a NEL device. For patients using a NEL device, AD was calculated from the ratio of provided vials to prescribed dose. The easypod™ device is an automated electronic injection device for r-hGH (Saizen®) delivery that accurately records each dose and injection taken to evaluate AD. **Results:** The mean AD rate was higher in the NEL device patients ($n=348$, mean age 11.2±6.2 years) than in the easypod™ patients ($n=251$, mean age 9.2±3.6 years): 95.6±19.6% vs 89.7±10.1%. Modified analysis according to the criteria of Cutfield et al. indicated that this was due to a higher proportion of over-adherent NEL patients (AD >110%; Table 1). **Conclusions:** The calculated AD rate with NEL devices appears to be higher than the recorded AD rate with easypod. The over-adherence with NEL devices could be interpreted as increased wastage of r-hGH. Further analysis of how to detect mismanagement of prescribed r-hGH is needed.

Table 1. Adherence rates in patients using easypod or NEL devices.

Mean AD rate	Easypod (% of patients)	NEL (% of patients)
>110% (wastage of r-hGH)	0	15.5
85.7–110%	72.5	58.8
57.1–85.7%	26.3	24.6
<57.1%	1.2	1.1

P2-P655

Factors Influencing Peak GH Response During Insulin and Clonidine Stimulation Tests

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Background: Several factors (bone age, BMI, target height, age) have been previously demonstrated to impact on GH response during stimulation tests, none of them proving to be of crucial importance. **Objective and hypotheses:** To analyze the influence of several anthropometric and laboratory parameters on peak GH response during insulin and clonidine stimulation tests. **Method:** Retrospective review of 265 patients who underwent GH stimulation tests with clonidine and/or insulin in two endocrinology centers (Bucharest and Tirgu-Mures) from Romania between 2009 and 2015. Variables: age, sex, height SD score, BMI SDS, and IGF1 SDS. **Results:** Mean ages was 9.4±4.0 years with a sex repartition favoring boys (M: F=1.8:1). 165 subjects were GHD deficient according to the peak GH response (<10 ng/ml). In univariate analysis, BMI SDS was negatively correlated with peak GH during clonidine ($r=(-0.20)$, $P=0.0023$), but not insulin ($r=(-0.13)$, $P=0.1776$). IGF1 SDS correlates positively with both clonidine and insulin GH peak response ($r=0.37$ and 0.30, $P<0.0001$ and 0.0014 respectively). Age, sex and prepubertal status had no significant influence on the peak GH response. In multivariate regression analysis, BMI SDS and IGF1 SDS significantly influenced the peak GH response during clonidine, the whole model explaining 11.3% of the response. For insulin, the model explained 31.5% of the GH variance with age and IGF1 SDS being the significant factors. **Conclusion:** In our study BMI SDS

negatively correlates with GH response during clonidine, but not insulin GH stimulation test. IGF1 SDS is the only factor positively correlated with GH response in both provocative tests analyzed.

P2-P656

Improved Growth Outcomes with Jet Delivery of Growth Hormone in Children are Maintained Over Long-Term Treatment

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Background: We previously reported in a national cohort, that adherence to subcutaneous Growth Hormone (GH) treatment in children is better with jet delivery compared with needle devices (Spoudeas *et al.* Patient Prefer Adherence. 2014;8:1255–1263). We also separately reported that adherent children showed significantly improved height outcomes at one year. **Objective and hypotheses:** To examine the potential influence of adherence and demographic covariates on growth outcomes of children using Growth Hormone (GH) jet delivery beyond one year of treatment. **Method:** A cohort of children aged <16 years treated with GH via jet delivery was identified at a split-site centre (GOSH and UCLH, UK). Adherence and growth parameters were followed-up over a treatment period beyond one year. Adherence was evaluated using the Proportion of Days Covered (PDC) index. Patients with a PDC score >0.8 were considered adherent. Standard deviation scores for Height (HTSDS) and Height Velocity (HVSDS) were primary outcomes compared to pre-treatment and target height. The influence of categorical demographics before treatment was assessed. **Results:** From a cohort of 72 patients, 31 (20M, 11F) were defined as adherent at one year and followed-up for median (range) 3.12 (1.46–4.85) years. Mean$\pm$S.D. HTSDS and HVSDS were significantly improved from baseline at one year and assessment end (-2.03 ± 1.18, -1.34 ± 1.22, -1.02 ± 1.21 and -1.10 ± 2.51, 2.56 ± 2.51, 0.74 ± 3.91, $P<0.001$). HTSDS and HVSDS outcomes at end of treatment were not influenced by thyroxine use, previous irradiation, years before start of treatment, sex and age at onset. **Conclusion:** Jet delivery of GH for a treatment period beyond one year provides children with improved height outcomes which are independent of demographics pre-treatment. High persistence of use with GH jet delivery, as reported earlier, may contribute to these long-term outcome benefits.

P2-P657

Septo-Optic Dysplasia and Excellent Growth with Low Growth Hormone Dose: Our Experience

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Background: Septo-optic dysplasia (SOD) is a congenital, rare anomaly (1:10 000) associated with optic nerve hypoplasia, midline brain abnormalities and pituitary hormone abnormalities. Genetic alterations associated are: HESX1, SOX2 and SOX3. SOD's pattern of growth even without GH treatment has been reported to be often good. **Objective and hypotheses:** Evaluate SOD's growth in patients followed in our Centre. **Method:** See Figure 1. **Results**: All presented severe GH deficiency with low IGF1 levels, hypoglycemia and pathological MRI, therefore started GH treatment before 3 years of age. During GH treatment growth rate was excellent with a starting GH dose of 0.18 mg/kg per week. As IGF1 levels were $>+2$ SDS in each patients at least once, GH posology was reduced to a median of 0.11 mg/kg per week with a normalization of IGF1 levels, nevertheless growth velocity remained good (gv: $+1.02$ SDS), with a currently median height gain of $+2.54$ SDS and a median delta to midparental height of $+1.29$ SDS after almost 10 years of treatment. **Conclusion:** Some SOD, with GH and IGF1 deficiency, present excellent growth during GH treatment even with minimal doses. The mechanism underlying is not clear: high levels of insulin, PRL or leptin may be involved, however no specific cause has been found, therefore more studies are needed to better explain this phenomenon.

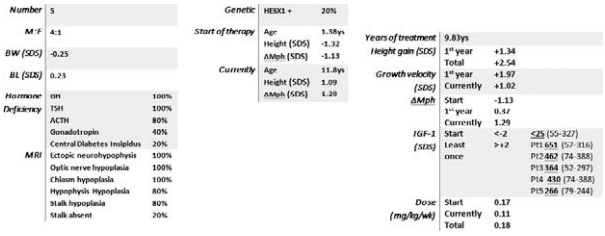

Figure 1

P2-P658

Early Diagnosis and Treatment of a Newborn with POU1F1 Mutation

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Background: POU1F1 encodes a pituitary-specific homeodomain transcription factor that is crucial for development and differentiation of anterior pituitary cell types. Mutations in this gene result in GH, TSH and prolactin (PRL) deficiencies.

Objective and hypotheses: To describe a male newborn of a mother with known dominant p.R271W mutation in the POU1F1 gene. **Methods:** Case report with clinical follow up, endocrine investigations, neuroimaging, and genetic analysis. **Results:** Cord blood analysis suggested central hypothyroidism (TSH: 0.695 mU/l; fT_4: 9 pmol/l), GH deficiency (0.06 nmol/l), and PRL deficiency (2 μmol/l). GH deficiency (0.07 μg/l) was confirmed during symptomatic hypoglycaemia (1.7 mmol/l) at day 2 of life. IGF1 (<32 μg/l) and IGFBP-3 (<0.5 mg/l) where low. MRI revealed a hypoplastic adenohypophysis (height: 1.7 mm). The knee-bone maturation was delayed. Thyroid hormone substitution was initiated at day 2 of life. Early GH treatment starting at 4 days of life (0.025 mg/kg per day) prevented further hypoglycaemias as controlled by continuous glucose monitoring. At the age of 2.5 months (minipuberty) the patient had normal activation of the gonadotropic axis (LH (2.7 UI/l), FSH (1 UI/l), testosterone (7.2 nmol/l), AMH (>210 ng/ml), Inhibine B (790 pg/ml)). Genetic analysis confirmed the p.R271W mutation in the POU1F1 gene. **Conclusion:** The known maternal mutation enabled prompt screening of the newborn. Endocrine testing diagnosed central TSH, GH and PRL deficiencies and allowed early treatment. Genetic testing confirmed the presence of the same mutation as his mother. Early GH substitution prevented repeated hypoglycaemic events and eventual related complications. Long-term follow-up is needed to confirm normal growth and development.

P2-P659

Influences of GHR-Exon 3 and -202 A/C IGFBP3 Polymorphisms on 1 Year Follow-Up Outcome of Growth Hormone Treatment in Korean Children with Growth Hormone Deficiency

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Background: The GHR-exon3 and the -202 A/C IGFBP3 polymorphisms have been suggested to affect responses to recombinant human GH (rhGH) therapy in some individuals with short stature. This study aimed to assess the influences of the two polymorphisms on treatment outcomes in patients with GH deficiency (GHD). **Method:** In 72 (32 girls and 40 boys) children with confirmed diagnosis of GHD, genotyping and serial measurements of auxological and endocrinologicalparameters were performed. Forty-nine patients who remained in the prepubertalstate after 1 year of GH treatment were analyzed. **Results:** Distribution of the GHR-exon3 genotypes was as follows: d3/d3 genotype 2.8%; d3/fl genotype 15.3%; and fl/fl genotype 81.9%. Frequencies of the -202 A/C IGFBP3 genotypes were as follow: A/A genotype 55.5%; A/C genotype 38.9%; and C/C genotype 5.6%. In comparing the d3/d3 and d3/fl group with the fl/fl group, there was no significant difference in first-year height velocity (9.4±2.2 vs 8.1±1.7 cm, $P=0.08$). Likewise, comparing the A/A group with the A/C and C/C group, no significant difference was observed in height velocity (8.3±2.0, 8.3±1.7 cm, $P=0.97$). Combined analysis of the two polymorphisms showed no significant interaction on the first year height velocity. **Conclusion:** Our results suggest that the two polymorphisms are not major factors in the modulation of interindividual growth response to GH therapy in Korean children with GHD.

Keywords: GH deficiency, growth hormone receptor, insulin-like growth factor binding protein 3, polymorphism

P2-P660

Comparison between Effects of Oral Iron and Vitamin A with Oxandrolone upon Height and Puberty of Children with Constitutional Delay of Growth and Puberty

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Background: Constitutional delay of growth and puberty (CDGP) is one of the most common problems of pediatrics. It causes a lot of psychological and social disorders in families. Currently there are a variety of therapies including administration of testosterone enantate, oxandrolone and growth hormone. **Objective:** The aim of this study, which has been performed as the first in Iran and the second in the world, is the comparison between effects of oral iron in combination with vitamin A with oxandrolone in promotion of height growth and bone age of these children. And HSDS, WSDS, BMI, SMR, bone age and serum IGF-1 level are used as milestones of such improvement in this study. **Materials and methods:** This clinical trial has been performed on 85 CDGP boys. After registration of personal identities and taking blood, urine and stool specimens to rule out probable underlying diseases and interfering factors, the children were divided into three groups include control, treated with oxandrolone and treated with oral iron and vitamin A. Data were transferred to SPSS program where the results were analyzed by paired T-, ANOVA, Tukey, and Wilcoxon–Kruskal–Wallis tests. **Results:** There was no significant difference between the treated groups in HSDS (P value $=0.56$) and WSDS (P value $=0.08$), BMI (P value$=0.51$). On the other hand there was a significant difference in SMR (P value < 0.0001) and bone age (P value <0.0001) between them. Eventually there was not significant difference in serum IGF-1 level between two treated groups (P value$=0.98$). **Conclusion:** Iron and vitamin A can be used instead of oxandrolone in CDGP children with the same therapeutic and without the adverse effects seen in oxandrolone administration. In addition, this new therapeutic method has no significant effect on SMR and bone age promotion in contrast with oxandrolone therapy.

Keywords: CDGP, BMI, SMR, bone age, IGF-1

P2-P661

'First Do No Harm': Growth Hormone (hGH) Treatment in a Case of Recurrent Craniopharyngioma

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Introduction: Craniopharyngiomas (CP) are benign, dysontogenic supra or intra-sellar tumours. They are locally aggressive with severe endocrine, neurological and ophthalmological implications. Somatotroph deficiencies rise therapeutic management problems due to increased risk of tumour growth and recurrence. **Case report:** Male patient, aged 18 years 4 months, born naturally, late-term (42 weeks, 3200 g, Apgar 7), third child in a brotherhood of four (apparently healthy parents and brothers), with slightly delayed developmental acquisitions, was firstly evaluated in the Endocrinology Department at age 13 years 6 months for growth retardation. Investigations pleaded for pituitary dwarfism (short stature −2.5 S.D., absence of puberty signs, delayed bone age of 10 years, somatotroph axis: low basal GH with no stimulation to arginine, low IGF-1) and rhGH therapy was initiated. After just 5 months he was admitted to Neurosurgery Department due to severe headache, Jacksonian seizures and optochiasmatic syndrome determined by rapid developing para- and suprasellar compressive craniopharyngioma identified at MRI. Minimally invasive surgery was performed (partial ablation). On follow-up patient sustained panhypopituitarism and received corticoid and thyroid substitutive treatment. The evolution comprised of two other surgeries performed for tumour recurrence and external radiation (54 Gy/30 ft/CTV), associating further ophthalmological complications. At current evaluation, severe growth retardation (−5.11 S.D.), delayed bone age (11 years 6 months, fertile cartilages) and somatotroph deficiency raised the question of usefulness of rhGH treatment. Given frequent tumour recurrences and the presence of tumour residue, the histological type of CP determination becomes crucial for better adjustment in treatment strategy. **Discussions:** Regarding published data on patients treated surgically and with rhGH, CP recurrence is reported at approximatively 4 years after surgery and two after rhGH therapy. Although GH receptors exist in some craniopharyngiomas, many authors consider rhGH safe. We emphasize the importance of close follow-ups of rhGH treatment, given the rapidly evolving tumour in our patient case.

P2-P662

High Efficacy Growth Hormone Therapy in Patient with Homozygous Mutation in Growth Hormone Gene (*GH-1*) During 3 Years

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Background: Mutations in *GH-1* gene is a rare cause of isolated growth hormone deficiency. Main features of this condition include markedly reduced secretion of GH combined with low concentrations of IGF-I leading to short stature. **Objective and hypotheses:** 1.56 years old girl was admitted to our hospital because of short stature. She was born at term from closely related healthy parents. Her birth length and weight were 48 cm (SDS: −1.07) and 3670 g (SDS: 0.75), respectively. Failure to thrive and psycho-motor delay were noted. The karyotype is 46 XX. On examination at 1.56 years her height was 59 cm (SDS: −7.25) and her weight was 4.6 kg, BMI SDS −3.69, she had some mild dysmorphic features (prominent forehead, saddle nose and blue sclera). Laboratory testing revealed low IGF-1 (3 ng/ml), normal random fT_4, cortisol and prolactin levels. Bone age was 8 month. Genetic analysis revealed homozygous GH-1 gene deletions. The girl was started on GH therapy and protein rich diet. **Method:** 'Hypopituitarism panel' genes were sequenced using a custom Ion Ampliseq gene panel and PGM semiconductor sequencer (Ion Torrent). **Results:** For the first year of GH therapy she grew 18.44 cm (SDS height velocity 5.96 cm/year) and showed some improvement in psychomotor development. For the first 2 years of GH therapy she grew 13.26 cm (SDS: 4.23). Now her Δ height is 41 cm, Δ height SDS is 5.53 for 3 years of therapy. **Conclusion:** Mutations in *GH-1* gene is a rare cause of isolated growth hormone deficiency, which may present with extremely short stature and showing a good response to GH therapy.

P2-P663

A Case of GH Deficiency in a Female with 3M Syndrome

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Background: 3-M syndrome is an autosomal recessive primordial growth disorder characterized by severe prenatal and postnatal growth retardation, normal mental development, unusual facial features and skeletal abnormalities. Mutations in the *CUL7*, *OBSL1* and *CCDC8* genes are responsible for this syndrome. In literature a modest response to GH treatment in 3M children is reported without a significant improvement in the final height, suggesting a picture of GH insensitivity. **Objective and hypotheses:** To describe the 1 year results of r-hGH treatment in a patient with 3M syndrome and GH deficiency. **Results:** Here we describe the case of an Italian girl born from non consanguineous parents, full term, small for gestational age (weight 2120 g: <3rd

centile; length 40.5 cm: <3rd centile). She presented postnatal growth retardation, hip dysplasia, hyperextensible joints and normal mental development. Therefore clinical diagnoses of 3M syndrome was suspected and then confirmed by the finding of a *CUL7* mutation in compound heterozygosity (c. 3750delA +3753_3762 del and c.4814delG: this last mutation unreported). At the age of 4 years and 4 months the height was −2.74 SDS, growth velocity −2.60 SDS. GH stimulation tests with arginine and clonidine showed a peak of 5.95 and 4.97 ng/ml, respectively. Not alterations in size, morphology and impregnation of pituitary gland were found at MRI. Therefore r-hGH treatment was started at 0.30 mg/kg per week. After 6 months of therapy we report a significant catch up growth: height −2.16 SDS and growth velocity 0.64 SDS; after 1 year of treatment: height was −1.80 SDS. **Conclusion:** Even if a longer follow up is necessary to confirm this finding, our data may suggest to study GH axis in 3M syndrome for the possibility of an interindividual response to GH treatment in these patients.

P2-P664

Case Report of SHOX Gene Haploinsufficiency Diagnosed in Early Infancy

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Background: SHOX-D is rarely diagnosed in early infancy as cause of short stature. **Objective and hypotheses:** Describe clinical characteristics of two girls with an early diagnosis of Leri-Weill dyschondrosteosis, admitted to our hospital because of severe short stature. **Method:** Mutation screening of SHOX and its regulatory regions was performed by MLPA. Family analysis was undertaken. **Results:** The first 1.3 years girl was born on term, SGA for weight (−1.9 SDS) and length (−1.77 SDS) with a family history of short stature in both parents (T-Ht −2.6 SDS). Physical examination revealed rhizomelic body disproportion, H −3.96 SDS, Span/H ratio 90%, SH/H ratio 63%. Hypochondroplasia was ruled out by Rx vertebral column and limbs, that did not reveal any radiological sign. SHOX gene MLPA in her and her father revealed c.463G>C mutation in heterozygosys, already described in X-chromosome gene database. The second 1.2 yeas girl was born on term, AGA, with a prenatal finding of short femur. Physical examination revealed relative macrocephaly, prominent frontal bossing, depressed nasal root and rhizomelic aspect of upper limbs, L −2.11 SDS, no family history of short stature (T-Ht 0.18 SDS). She undergone FGFR3 analysis which result normal. SHOX gene analysis showed c.728 dup in heterozygosis cause of frameshift mutation. **Conclusion:** *SHOX* deficiency leads to short stature with variable phenotype that is frequently nonspecific in early childhood. There is not consensus on time and auxological criteria to start therapy with GH and if It could affect final height.

P2-P665

Association between IGF-1 (Insulin-Like Growth Factor) SD Levels and Children with Growth Hormone Deficiency with and without Pituitary Morphological Abnormalities

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Background: The diagnostic use of IGF-1 in children suspected of GHD is based on the assumption that a single determination of this parameter reflects the integrated 24-h GH secretion. IGF-1 levels are low in GHD, but a study found a significantly lower sensitivity in children with organic lesions in the brain. **Objective:** The aim of this study was to check if there is a statistically significant relation between IGF-1 values in children with GHD with and without pituitary morphological abnormalities. **Method:** The study was carried out at a Pediatric Endocrinology Center and it used a sample of 125 patients diagnosed with GHD. It was analyzed the IGF-1 SD values and the presence, or not, of pituitary morphological abnormalities. It was taken under consideration gender and the relation between H-SDS and age at the moment of diagnosis, inside each group of children. The medical imaging exams used for pituitary analysis where Magnetic Resonance Imaging (MRI) and/or Computed Tomography (CT-Scan) when available. **Results:** Were analyzed 70 male, 39 (31.2%) presented pituitary abnormalities. There is no difference between IGF-1 SD and morphological pituitary changes, when considering level of IGF-1 values <0 SD. Although when analyzed IGF-1 value <−2 SD the number of patients with morphological pituitary abnormalities were significantly higher than the patients without pituitary abnormalities ($P<0.05$). The relation between H-SDS and age at the moment of diagnosis according IGF-1 <0SD and <−2 SD not presented significant difference in the group with and without pituitary abnormalities. **Conclusion:** According this study patients with IgF-1 <−2 SD showed abnormalities in the pituitary gland.

P2-P666

Usefulness of Growth Hormone Transient Treatment Suspension in Prepubertal Children Treated with Growth Hormone

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Background: The primary goal of treatment is to achieve a final height within the normal range and avoid the physical and

psychological consequences of short stature (SS). If after a time, treatment efficacy criteria are not achieved, it is necessary to revalue its usefulness. There is no consensus about which conduct should be adopted in these cases. An alternative, is the suspension of rhGH treatment and evaluate the clinical and biochemical results to decide to continue or discontinue treatment definitively. This discontinuation of rhGH treatment, we have called 'transient treatment suspension' (TTS). **Objective and hypotheses:** Determine the characteristics of a group of prepubertals patients undergoing TTS with rhGH and establish its usefulness in clinical practice. **Method:** It is a retrospective study of a group of patients, which indicated TTS with rhGH (*n*: 41). **Results:** 78% of patients were male. 70% had diagnosis of IGHD and the remaining SGA. The average age of the onset of treatment with rhGH was 7.4 ± 2.5 years for IGHD and 4.7 ± 1.7 years for SGA. The mean rhGH dose used was 0.22 mg/kg per week. The mean onset of TTS was to 9.5 years. The mean duration of TTS was 11.3 months. Treatment was restored in 76% of patients, because they showed a significant deterioration in their growth during the TTS period respect to Pre-TTS, both in GV, H, and IGF-1 levels. A significant recovery of the three parameters after 12 months of restoration of rhGH treatment was achieved. In the remaining 24%, rhGH was not restarted due to it was not observed significant difference in GV, H and IGF-1, compared to Pre-TTS. Through ROC curve analysis observed that differences in GV (SDS) between Pre-TTS and TTS period is a useful parameter to identify dependent rhGH patients (AUC = 0.876, $P < 0.0001$). A decrease ≥ 0.97 in GV-SDS between the Pre-TTS and TTS period was the best cut-off point associated with the reinstated of treatment (sensitivity 80%, specificity 80%). **Conclusion:** Based on our results, we conclude that TTS may help us to decide to continue or definitively suspend treatment. Thus, the costs and inconveniences caused by the daily administration of an ineffective treatment would be reduced.

P2-P667

Birth Length, Weight and Head Circumference of Neonates with IGF-I Receptor Mutations

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Background: In recent years more and more genetic defects along the GHRH–GH–IGF-I axis have been reported. Those mutations of the IGF-I receptor (R) are a rare abnormality of whom only the heterozygotes progenies survive. **Objective and hypotheses:** To determine the birth length, weight and brain size using head circumference and find out whether these correlate with the type of mutation. **Method:** Collection of data of 65 neonates from published literature. **Results:** Forty-seven different mutations of the IGF-I (R) located on chromosome 15 have been identified. Birth length (BL), available for 28 neonates with a gestational age of 34–41 weeks, ranged between 39 and 49 cm ($m \pm$ S.D. $= 45 \pm 2.7$ cm), one was premature (30 cm at 31 weeks). Birth weight (BW) of 38 neonates ranged from 1400 cm to 2600 g ($m \pm$ S.D. $= 2535 \pm 651$ g). Two premature neonates weighed 650 950 g. The BW correlated with gestational age, not so the BL. The BMI of 27 neonates ranged from 6 to 13. Seven out of 16 mothers were short (133–148 cm). There was no correlation between type of mutation and birth length or weight. In 21 records microcephaly was ascertained or stated. **Conclusion:** Heterozygotes neonates for a variety of IGF-I-R mutations tend to be shorter and more microcephalic than neonates with hGH gene deletions and GH-R defects, (Laron syndrome). They are also less obese than the above diagnostic entities. The below normal head circumference indicates the important role of IGF-I in the intrauterine growth of the brain in addition to that on linear growth.

P2-P668

A Rare Cause of Growth Delay: Jacobsen Syndrome

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Background: Jacobsen syndrome is a rare genetic condition caused by partial deletion of the long arm of chromosome 11 associated with delayed development, distinctive facial features, bleeding disorder, skeletal abnormalities and endocrine disorders. **Case report:** We report a rare case of Jacobsen syndrome in 4 year old boy addressed for short stature. Born at term (36 W) with low birth weight (1780 g) and delayed development, his height at presentation was 86 cm (-3.95 S.D.) and weight 9 kg (-6 S.D.). He presented typical syndromic features: trigonocephaly, craniostenosis, ocular hypertelorism, left palpebral ptosis, strabismus, bilateral epicantus, short nose, micrognathia, small, low set ears, pectus excavatum, lumbar scoliosis, unique palmar crease, multiple toe malformations and cardiac malformations (ventricular septal defect). Clinical examination revealed normal genitalia. The hormonal exploration revealed normal thyroid and adrenal function with altered growth hormone and IGF1 levels. The low height and weight were explored and metabolic causes such as malabsorbtion syndromes, other chronic disease or poor nutrition were excluded. Cerebral MRI revealed small pituitary (7/6/2.5 mm) and hand radiograph showed delayed bone age (3 years). Genetic exploration described 46 XY cariotype with deletion (11) (q23,1qter), consistent with Jacobsen syndrome. Hematologically, he presented slight poliglobulia with normal platelet count. Treatment with recombinant growth hormone was initiated, justified by growth delay, SGA history and low IGF1 levels with good outcome (monthly growth rate of 0.7 cm), height of 93 cm (-3.5 S.D.) and a weight of 11.5 kg at 6 months reevaluation. **Conclusion:** Intensively studied, Jacobsen syndrome is frequently associated with dysmorphic features, multiple complications and short stature. Having into consideration the rarity of the syndrome, there is a sparse number of cases treated with rGH with Jacobsen syndrome with good evolution, as seen in our case. Therefore, growth hormone treatment should be made individually, directed at understanding the risks and benefits unique to this polymorphic condition.

P2-P669

A *GH-1* Mutation Diagnosed in a Preadolescent Obese Girl with Only Mild Reduced Height

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Background: Mutations in *GH-1* are classically associated with autosomal dominant familial isolated GH deficiency (IGHD type II). **Objective and hypotheses:** Here, we report a new case of *GH-1* mutation identified in a preadolescent girl consulting for a mild reduced stature contrasting with obesity. **Method:** The patient was born from non consanguineous French parents. She consulted at the age of 9 for short stature. Her height at −1.5 SDS (regular growth) contrasted with obesity (BMI = +4 SDS) and a genetic target height of +1 S.D. There was no familial obesity. GH stimulation test showed a GH peak at 1.1 mUI/l ($n > 20$ mUI/l). IGF1 was 70 ng/ml (< −2 S.D). Pituitary MRI was normal. **Results:** During the 3.5 years of GH treatment, the height increased to 163 cm (+0.6 S.D), and BMI decreased from +4 S.D to +2 S.D. An heterozygous G6664A mutation in *GH-1* caused Arg183His substitution (R183H) in the GH proteine. **Conclusion:** We confirm here that *GH-1* mutation could be responsible of obesity with mild growth retardation.

P2-P670

A New Reusable Manual Pen Device for Injection of Human Growth Hormone: Results of a Convenience and Functionality Evaluation Study

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Background: This multi-country study, conducted in the USA, is also ongoing in France, Germany, Brazil and South Korea (52 healthcare professionals (HCPs) and 30 patients/caregivers in total). The new device consists of a reusable aluminium body and cap, with a multi-use cartridge system, viewing window, dose-display window, dose-selection knob and injection button. **Method:** Semi-structured 60-min qualitative interviews were conducted in six major US cities with 22 HCPs and five adults with GH deficiency/caregivers administering GH to children. HCPs had to be responsible for training on use of GH devices and to see ≥4 GH patients/caregivers per month, while patients/caregivers had to be responsible for GH administration. **Results:** Eighty-two percent of HCPs described the device as 'simple' or 'easy', and 55% described it as 'sleek'. The aluminium body was perceived as attractive and comfortable to hold and operate, and the ease of preparation and use made it suitable for children and adults. The injection button was considered smooth and easy to press, with a reassuring click, and required less pressure to inject than other devices. Fifty percent of HCPs spontaneously mentioned the ability to dial back the dose, if entered incorrectly, as a major benefit, as other devices need several user steps to reset. Patients/caregivers liked being able to see the plunger move through the cartridge window, providing reassurance that the full dose had been given. Overall, 86% of HCPs and 80% of patients/caregivers would be likely to recommend or request the new device, respectively. Moreover, patients/caregivers rated the device higher than their current reusable pens in terms of ease of learning, preparation, administration and ease of use. **Conclusions:** The new pen device was very well accepted by HCPs and patients/caregivers for ease of use, design and functionality.

P2-P671

Assessing Disease and Treatment Burden for Young Children with Growth Hormone Deficiency (GHD)

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Background: Children with GHD, in addition to short stature, may experience physiological symptoms as well as social and emotional problems. Assessing these impacts is critical for understanding the extent of GHD burden and assessing treatment benefit. Since many children initiating treatment are too young to self-report information, we must rely on adult reporters. However, according to FDA guidelines and established measure development principles, adult reporter information cannot be captured as subjective proxy information as this could bias responses. Thus, it is necessary to develop new methodology to capture objective, observer-reported (ObsRO) information for young children with GHD. **Objective and hypotheses:** Develop methodology to capture reliable and valid data to allow for item development for ObsRO measures of disease and treatment burden for young GHD children. **Method:** Qualitative interviews ($n = 34$) were conducted (USA, Germany, UK) with parents/guardians of children (ages 4 to <13) with GHD. Respondents were instructed to report only what they 'had seen, heard or been told by others'. To confirm their ability to respond objectively to questions about their child, respondents were asked to provide concrete examples of observed events or behaviors to support their assumptions about their child. **Results:** The methodology developed elicited statements from parents/guardians regarding the impact of GHD on their child, which were validated by concrete examples. For example, reported burden of being treated differently by others was supported by parent/guardian observing children throwing a ball to their child with less force than they did to others. Based on qualitative data analysis of the interviews, a conceptual model of the range of GHD burdens for young children and items for ObsRO burden measures were developed. **Conclusion:** Using the ObsRO measures developed for this study will make it is possible to collect reliable and valid disease and treatment burden information for young GHD children.

P2-P672

Long-Term Results of GH Therapy in GH-Deficient Children Treated in Albania

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Background: GH treatments aim to normalize growth, correct health problems associated with GH deficiency, and help patients achieve an adult height in the normal range for the general population and for familial genetic potential. **Objective and hypotheses:** To evaluate the efficiency of recombinant GH (rhGH) for improving adult height in children with GH deficiency (GHD). **Method::** This is an observational follow up study which enrolled all Albanian children diagnosed with GHD and treated with rhGH, who had attained final height. Their treatment started between 2001 and 2015. Main outcome measures are: annual changes in height, change in height between the start of treatment and adulthood height and the importance of the factors that influence on final height. **Results:** Adult height was obtained by 92/176 (52.3%) patients. Male/female ratio was 70/22. The mean age of starting treatment was 13.06 ± 2.61 years (male 13.21 ± 2.53 years and female 12.58 ± 2.87 years). Mean HAZ in the beginning of therapy was −4.28 ± 1.06 (male −4.21 ± .99, female −4.50 ± 1.26). The mean dose of GH at start of treatment was 0.21 IU/kg per week for 29 patients, 0.24 IU/week for 54 patients and 0.27 IU/week for 9 patients. Height gain was 2.18 ± 1.20 *z*-scores during 3.73 ± 2.0 years of treatment, resulting in an adult height of −2.08 ± 1.13 *z*-score (−2.32 ± 1.32 *z*-score for girls; −2.0 ± 1.25 *z*-score for boys). Most of the variation in height gain was explained by regression towards the mean, patients' characteristics, and delay in starting puberty. **Conclusion:** The most of our patients with GHD treated with recombinant GH were able to achieve their genetic height potential. Despite starting treatment late, they managed to gain 2.18 ± 1.20 *z*-scores in height and the final height for majority of them (58.7%) was within the target height range. It was found that the final height had good correlation with the prediction height, HAZ score at beginning of treatment, change of HAZ score during the puberty, duration of treatment with GH, and pubertal stage at the start of therapy.

P2-P673

Abstract unavailable.

P2-P674

Did Growth Hormone Treatment Associated with Psychological Status in Children with Short Stature?

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Background: Short stature is clearly not a disease, but is commonly perceived to be associated with social and psychological disadvantage. **Objective and hypotheses:** To evaluate the psychological changes in children with short stature after growth hormone therapy. **Method:** One hundred and thirty children aged 6–14 years old were diagnosed as short stature (ISS and GHD). And they were divided into intervention group (55 children) and control group (75 children). Children in intervention group were given GH therapy (0.15–0.20 IU/kg.d); kids in control group were followed up for 6 months. Psychological functions were tested in intervention group at baseline, reassessed after 6 months of GH therapy. Psychological functions examinations were tested by Zung Depression Inventory. **Results:** Six months of GH therapy in patients significantly improved psychological status. Slight depression decreased, as well as intensity of interpersonal sensitivity, hostility, paranoid ideation and anxiety. **Conclusion:** Our preliminary data support the necessity of conducting GH therapy induced reduction of depression, intensity of interpersonal sensitivity, hostility, paranoid ideation and anxiety.

P2-P675

The Effects and Safety of Recombinant Human GH (rhGH) Treatment on Growth Hormone Deficiency in Children with Rathke's Cleft Cyst

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Background: Rathke's cleft cyst (RCC) has been reported rarely in children and adolescents. The occurrence of RCC with hypoplastic anterior pituitary can be explained by their common embryologic origin. However, the effects and sfety of recombinant human GH (rhGH) in GH deficient (GHD) children with RCC has not been previously reported. **Objective and hypotheses:** To assess the effects and safety of recombinant human GH (rhGH) in GH deficient (GHD) children with RCC. **Method:** The clinical data of 15 GHD children aged from 5–12 years old, whose radiologic diagnosis showed RCC during Jan 2013 to Dec 2015 in Sun Yat-sen Memorial Hospital, were analyzed retrospectively. rhGH was given subcutaneously to each enrolled child with a night dose of 0.1 IU/kg 6–7 times a week for 12–30 months. The serum biochemical indices as well as endocrine hormone level were detected regularly. The clinical data before and after treatment were compared, including height, weight, growth velocity, height

standard deviation scores (height SDS), insulin-like growth factor 1 (IGF-1), bone age and the magnetic resonance imaging result. **Results:** With rhGH treatment, a significant increase ($P<0.01$) of growth velocity in all 12 children, from 4.06 ± 0.61 to 9.86 ± 4.01 cm, was observed in the first 12 months. Meanwhile the height SDS increased obviously from -3.31 ± 1.47 to -2.63 ± 1.36 ($P<0.01$). In addition, IGF-1 rose from (186.73 ± 73.32) μg/l to (436.78 ± 208.60) μg/l ($P<0.01$), with IGFBP-3 from (4.32 ± 0.96) mg/l to (5.63 ± 1.45) mg/l. The peak values of both IGF-1 and IGFBP-3 were within normal limits. During the treatment and the follow-up period, the biochemical indices were normal and the volumes of the Rathke cysts did not increase. **Conclusion:** The treatment of low level rhGH in GHD children with RCC was demonstrated effective in this study. Moreover, GH treatment is safe when fully evaluated and closely monitored.

P2-P676

Is the Growth Hormone Deficiency the Cause of Short Stature in Floating Harbor Syndrome?

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Background: Floating Harbor syndrome (FGS) is a dominant autosomal genetic disorder characterized by facial dysmorphism, delay in language development and short stature associated with delayed bone age. Currently there are about 100 cases reported worldwide. Although the short stature is one of the main features of the FHS, its etiology is poorly understood. A limited number of cases reported growth hormone deficiency as a cause of short stature in FHS and the evolution during treatment. **Objective and hypotheses:** The aim is to present the evolution during somatropinum treatment of a case with FHS and short stature due to GH deficiency. **Method:** Case report. **Results:** We present the case of a boy aged 9.8 years, followed in our Endocrinological Department since the age of 3.3 years for severe short stature (-4 S.D.) due to GH deficiency (maximum GH during Clonidine stimulation test 8.77 ng/ml and low IGF-I levels) for which he received treatment with somatropinum. The patient presents also with delayed bone age (1.5 years) with particular phenotypic features for FHS, delay in language development, hypospadias and astigmatism. Genetic evaluation showed that patient tested positive for SRCAP mutation. It was established treatment with GH 0.035 μg/day. The initial response to somatropinum treatment (0.035 mg/kgc per zi) was favorable with an increase of 1.7 S.D. during first 2.5 years of treatment. Subsequently the response to treatment decreased and SDS for height did not additionaly improved although the IGF1 levels were increased and IGFBP3 level were at the upper limit of normal values. However the attempt to discontinue the somatropinum treatment was followed by a stationary height. **Conclusion:** This case suggests that growth hormone deficiency may be a cause of short stature in FHS patients. However the response to somatopinum treatment and long-term evolution should by clarified by further study.

P2-P677

LHX-4 Gene Mutation in a Boy with Hypopituitarism and Severe Congenital Myopathy

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Background: *LHX4* mutations are rare in combined pituitary hormone deficiency, and even rarer in isolated GHD. **Objective and hypotheses:** We describe a 14 years old boy who was referred for investigation of short stature. **Methods and Results:** Short stature, convergent strabismus, nystagmus was present. At the age of 5 years his gait was unstable. A progressive myopathy ensued. Tests of pituitary reserve showed partial IGHD (8.2 ng/ml). Other pituitary hormones were within normal range. Muscle biopsy showed congenital myopathy of undefined aetiology. MRI of the brain revealed the empty sella syndrome. Targeted resequencing with a panel containing probe sets for enrichment and analysis of >4800 clinically relevant genes, targeting 12 Mb of the human genome revealed the c.250C>T (p.Arg84Cys) *LHX4* mutation in the propositus. His father is healthy, with no myopathy or pituitary deficiencies, but has the same *LHX4* mutation. **Conclusion:** This report extends the range of phenotypes associated with LHX4 gene mutations. To the best of our knowledge, we are the first to report on congenital myopathy in an *LHX4* gene mutation.

P2-P678

Prevalence and Causes of Short Stature and Impact of GH Therapy among Preschool Children at King Abdul-Aziz Medical City for National Guard in Riyadh, Saudi Arabia

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Background: It is widely assumed that short stature can result in psychological, social, and physical problems. The validity and efficacy of GH in management of short stature is still debated. **Aims:** This study aimed to i) estimate the prevalence of short stature in preschool children (4–6 years), and determine the final diagnosis of abnormality based on different investigations, and ii) assess the impact of intervention for short stature among preschool children at King Abdulaziz Housing city of the National Guard in Riyadh, Saudi Arabia. **Study design:** In a cross sectional study, all preschool children attending the preschool comprehensive screening examination during academic years 2007–2010,

at the school health clinic of the National Guard in Riyadh ($n=5500$), were subjected to: i) Full clinical examination, ii) Estimation of mid-parental height (MPH), iii) Assessment of bone age, and iv) laboratory tests. A prospective study of the impact of GH on short statured children attending the pediatric endocrinology clinic at King Fahad Hospital, KAMC, Riyadh, and their parents ($n=180$). They were assessed prospectively in terms of growth velocity and increment in height and height *Z*-scores, with GH therapy. Individual records of all children with short stature were examined. **Results:** The results of screening for short stature to 4949 preschool and school entrants revealed a prevalence of 3.64%, in the form of familial short stature (30%), constitutional (19%) and GHD (10.4%). The majority of those short children did not need any intervention except assurance, especially that more than 70% were short statured children with normal growth velocity. About 14% of those children were put on GH therapy to be assessed prospectively in terms of growth velocity and increment in height and height *Z*-scores. **Conclusion:** Prevalence of short stature among Saudi preschool children which is comparable to the prevalence figures in other previous studies in the region. The impact of intervention with GH will be determined and a final conclusion regarding the debate in the validity and efficacy of GH treatment will be stated.

P2-P679

Association between Growth Hormone Peak at a Stimulation Test and Pituitary Morphological Findings in Children with Growth Hormone Deficiency

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Background: GH deficiency (GHD) diagnosis includes clinical manifestations, laboratory tests and imaging. There are controversies about the validity of the GH stimulation test. A variety of stimulation tests are used in clinical practice. The biochemical definition of GHD has generally been considered to be a peak stimulated GH concentration <10 ng/ml. **Objective:** The aim of this study was to check if there is a statistically significant relation between GH peak in growth hormone stimulation test and pituitary morphological findings in children with GHD, assessing whether there is difference between GH peak in patients with and without pituitary morphological abnormalities. **Method:** The study was conducted in the Pediatric Endocrinology Ambulatory. The tests were analyzed in 189 patients with GHD. It was analyzed the GH peak in growth hormone stimulation test with clonidine and hypoglycemia and correlate with the presence, or not, of pituitary morphological abnormalities (magnetic resonance imaging and/or computed tomography). **Results:** GH clonidine stimulation test with was conducted in 139 patients and nine patients with GH insulin stimulation test. Thirty-seven patients that realized the test with clonidine had pituitary morphological abnormalities; 26 patients of them were males (70.3%). The peak of GH was higher after 60 min of the stimulus (83 patients) (9.21 ng/ml). There is not a statistic difference between the peak of GH in patients with and without pituitary morphological changes, 8.52 and 9.5 ng/ml, respectively. Comparing H-SDS and chronological age at diagnosis in patients with and without morphological pituitary abnormalities they showed no significant difference. **Conclusion:** There were more morphological pituitary abnormalities in males with GHD. There is not significant difference between GH peak in patients with and without morphological pituitary abnormalities. The presence of morphological pituitary abnormalities may indicate more severe deficiency, therefore it is necessary more discussions about the validity of the GH stimulation tests.

P2-P680

A Case of Growth Hormone Deficiency with Combined Encephalocraniocutaneous Lipomatosis and Jaffe–Campanacci Syndrome

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Introduction: Encephalocraniocutaneous lipomatosis (ECCL) is a rare neurocutaneous syndrome characterized by unilateral lipomatosis and ipsilateral neurologic/ophthalmic malformation. Jaffe–Campanacci syndrome (JCS) is characterized by the association of café-au-lait spots, axillary freckles, multiple nonossifying fibromas of the long bones and jaw. Both of ECCL and JCS was associated neurofibromatatosis type 1. We had a case of GH deficiency with combined ECCL and JCS. **Case report:** The 9-year-old Tadzhikistan girl visited our Center to treat her left hypertrophic leg. Her height was under 3 percentile and weight was in 5–10 percentile. She had incomplete upper eyelids and separated sparse alopecia. She had left hemibody hyperpigmentation and ipsilateral edema of leg. She had 2 years of slow development compare to the same age group. In brain MRI, widening of unilateral ventricular system and extraaxial CSF space of the left hemisphere and posterior fossa were observed. Coarctation of aorta was found by 2D-echocardiogram. Extremity MRI showed a well-defined, elongated cortical bone lesion involving the left proximal humerus with heterogeneous enhancement suggestive of nonossifying fibromata-extraskeletal anomalies, or angiomatosis, and lipomatosis. CT guided biopsy showed suggestive of metaphyseal fibrous defect, focal fatty-vascular tissue proliferation to the bone and suggestive for lipomatosis, fatty tissue proliferation to the soft tissue. To evaluate combined problem, blood test with hormone study was done. Her bone age was 8 years, GH deficiency was noted with insulin and L-Dopa stimulation test. NF1 mutation was not found in her blood and her karyotyping was normal 46, XX. **Conclusion:** To reduce her left leg edema, Z plasty on left ankle was done. After operation, her walking was better than before. To improve morphologic anomaly, upper eye lid plasty was done. GH trial could be helpful for her height growth.

P2-P681

Evaluation of GH Deficient Pre Pubertal Children Treated with Omnitrope® Using the AuxoLog Computer Program

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Background: AuxoLog is a validated computer program that evaluates auxologic parameters comparing them with the Spanish growth charts. It also allocates subjects to the corresponding pubertal development group. **Objective:** To assess the evolution of auxological parameters in GH deficient (GHD) pre pubertal children treated with Omnitrope for a minimum of 2 years prior to puberty. **Method:** This study is non-interventional, retrospective, longitudinal, multicentre study. Patient data was collected from the medical histories of patients and registered in the AuxoLog program. **Results:** Sixteen patients were recruited, with a mean age of 13.2 years. 56.3% (9) were males. The mean age at the beginning of treatment with Omnitrope® was 9.1 ± 0.98 years (9.35 ± 1.08 in males and 8.78 ± 0.8 in females). The HSDS at the beginning of treatment was -2.87 ± 0.4. After the first and second years of treatment the HSDS was -2.08 ± 0.44 and -1.76 ± 0.47 respectively, corresponding to an increase in HSDS of 0.79 ± 0.4 in the first year and 0.32 ± 0.4 in the second year. The Increase in HSDS in the first 2 years of treatment was 1.11 ± 0.4. A similar evolution was observed with height velocity SDS (HVSDS): 4.91 ± 2.17 and 2.07 ± 1.58 at the first and second years of treatment respectively. Similar results were obtained in previous studies concerning the Spanish population. Eleven adverse events were reported, all non-serious and mild to moderate; two possibly related to treatment (headache, lumbar pain). **Conclusion:** Omnitrope® showed efficacy and safety in the treatment of pre pubertal children diagnosed GHD.

P2-P682

Calcaneal Apophysitis (Sever's Disease) Development in a Case Using Growth Hormone

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Background: Orthopedic complications related to the GH are rare and there is no clear pathological association between the use of GH and these complications. Calcaneal apophysitis is an inflammation of the apophysis and is caused by the constant pull of the Achilles tendon. A literature search did not reveal a similar case of calcaneal apophysitis during GH use. **Case presentation:** A 13-year-old male receiving GH treatment for isolated GH deficiency presented outside his routine follow-up schedule with symptoms of pain in both heels and limping for 1 month without a history of trauma. The patient whose annual growth rate was 4.4 cm (-0.87 SDS) was started GH at a dose of 0.03 mg/kg per day with a diagnosis of isolated GH deficiency. He grew 7.4 cm in height in the first year of treatment. There was pain in both heels increasing with palpation. He could not put his weight on his heels when walking. The lateral foot graph revealed a sclerotic and fragmented apophysis. The patient was followed up jointly with the orthopedics department. He was recommended bed rest and nonsteroidal anti-inflammatory drugs in case of excessive pain. The GH treatment he was using was not interrupted. The pain in both heels and limping had regressed at follow-up 3 months later. **Conclusion:** We did not come across any information on a relationship between GH usage and calcaneal apophysitis development. The association can be incidental or may stem from the increased growth rate following GH treatment. However, studies comparing patients treated with GH and healthy controls are required regarding such an association.

P2-P683

Bone Health Index: A Potential Discriminator between Growth Hormone Deficiency and Constitutional Delay in Growth and Puberty in Adolescent Children

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Background: Constitutional delay in growth and puberty (CDGP), the most common cause of short stature in children, is a transient state of delayed growth, skeletal maturation and attenuated pubertal growth spurt. It is not always easy to differentiate from GH deficiency (GHD) even with robust clinical and auxological assessment, measurement of IGF1 and bone age evaluation Bone health index (BHI) is a quantitative measure of bone health calculated from a hand and wrist X-ray using a software programme. **Objective and hypotheses:** To examine whether measurement of BHI aids differentiation between GHD and CDGP during adolescence. **Method:** Retrospective data from 75 patients (43CDGP/32GHD) were analysed. GHD was diagnosed if GH peak was <6.7 µg/l on 2 standard GH

stimulation tests; CDGP was diagnosed on clinical grounds and by exclusion of other pathologies causing growth and pubertal delay. Bone age (BA) and BHI estimation (Tanner–Whitehouse −2, 3) were performed by BoneXpert software. **Results:** Forty-three children (6F, 13.9%), age 14.69±1.29 years, had CDGP and 32 (2F, 6.3%), age 14.20±2.04 years GHD. Mean height SDS was −1.92±0.87 in the CDGP group and −2.41±0.71 in the GHD group. BA was 12.85±1.41 in the CDGP group and 12.78±2.18 in the GHD group. IGF-I SDS was significantly higher in patients with CDGP compared with GHD, −1.33±1.14 vs −2.54±1.22 ($P=0.008$). BHI SDS was also significantly higher in patients with CDGP (0.84±0.99) vs (−1.59±0.96) in the GHD group ($P=0.007$). **Conclusion:** These novel data indicate that BHI, a simple measure obtained at the time of BA estimation, is significantly lower in children with GHD than in those with CDGP. This may be a helpful tool to aid in differentiating CDGP from GHD, which is important as the treatment of each disorder is markedly different. Furthermore, there may be potential to reduce the number of GH stimulation tests unnecessarily performed, in short adolescents.

P2-P684

Growth Effects of Somatropin during the Treatment Congenital Hypopituitarism in Children after the Start of Puberty

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Background: Today the features of GH therapy in children after reaching the beginning of puberty and the necessity of therapy in such age group are discussed. **Objective and hypotheses:** To identify the relationship between the growth increase after the start of puberty (patient's bone age achieved 12–13 years, according to the atlas Greulich) and the individual characteristics of the patients. **Method:** Thirty-four patients with congenital isolated GH deficiency and with multiple pituitary hormone deficiencies were included in the study. All children received GH in the dose of 0.033 mg/kg per day and other hormonal replacement therapy, if it was necessary. Duration of GH therapy varied from 1 year to 4 years after the start of puberty. **Results:** The growth difference between the start of puberty and the patient at the time of the study are significant ($P<0.05$ using the nonparametric Wilcoxon matched pairs test). Growth was increased after the start of puberty, while continuing GH therapy did not depend on the age of initiation of therapy (performed a correlation analysis with the calculation of pairwise Pearson coefficient $r=0.22$, $P=0.2$). **Conclusion:** Our results have shown that growth hormone therapy is necessary after the start of puberty and does not require increasing doses of GH, despite the start of puberty. The growth in patients after the beginning of puberty and growth increase after GH continue therapy is significantly different and the total growth increase in patients treated after the start of puberty not depend on the age of initiation of therapy.

P2-P685

Congenital Hypopituitarism and Giant Cell Hepatitis in a Two-Months-Old Boy

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Background: Congenital hypopituitarism (CH) in the neonate which manifests as the deficiency of one or more pituitary hormones can be presented by a highly variable phenotype. Either as isolated hypopituitarism or with associated developmental defects such as ocular, midline, and genital abnormalities. Mutations in genes encoding for a number of transcription factors have been described in a minority of patients with CH. This indicats that further genes remain to be identified. This is the case of a 2-months-old infant hospitalized for cholestatic jaundice. **Method:** Clinical and anthropometric data were obtained. Biochemical liver function parameters, blood glucose, TSH, free thyroxin (FT_4), GH, insulin-like growth factor-1 (IGF-1), cortisol, ACTH levels were analyzed. Laparoscopic liver biopsy and cholecystocholangiography were carried out. PROP1 gene (exons 1-3), LHX4 gene mutations were investigated by direct sequencing method. **Results:** The boy was carried full term and born a healthy weight and lenght. The patient had craniofacial dysmorphisms and genital abnormality. Jaundice had started during the first week and had a prolonged course. In addition boy had repeated episodes of severe hypoglycemia. At the age of 2-month-old the non-specific giant cell hepatitis was revealed. The diagnosis of congenital hypopituitarism was completed with confirmation of FT_4, ACTH, GH deficiencies. Genetic analyses were negative for y mutation in the PROP1 gene (exons 1-3), LHX4 gene. The boy takes hormone replacement therapy by hydrocortisone and L-thyroxin. As ACTH, FT_4 deficiency were eliminated the hypoglycemic syndrome and hepatitis are disappeared. **Conclusion:** In the case of neonatal liver dysfunction associated with hypoglycemia the diagnosis of CH should be excluded.

P2-P686

Neonatal Characteristics of GH Deficiency in 107 Children

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Background: GH deficiency (GHD) rarely reveals at birth. Pregnancy is proceeding normally. The size and weight are generally normal and the birth occurs at terms. In some cases, neonatal markers and other pituitary deficits are present and allow early diagnosis. **Objective and hypotheses:** Report neonatal characteristics of GHD. **Method:** 107 children GHD were followed. The interrogation noted the progress of pregnancy, childbirth, weight and size and the presence of signs for other hormone deficiencies: hypoglycemia, jaundice, micropenia, cryptorchidism. Clinical examination sought other neonatal GHD markers as midline abnormalities (MA). **Results:** 94.4% are born at term. The percentage of prematurity is not different from general population 5.6% vs 11.2 $P=0.07$. The delivery was normal in 84.1%. Neonatal dystocia was observed in 15.9%. It is not different from general population 15.9 vs 15.34% $P=0.87$. In 47.05% dystocia is associated with a breech delivery. This percentage is not different from general population 7.74% vs 6.29 $P=0.63$. The average size at birth is 50.3 ± 2.05 cm for males 49.7 ± 1.05 cm for girls. It is not different of theoretical normal size for gestational age. It is the same for the average birth weight: 3, 5 ± 0.72 kg and 3, 3 ± 0.75 kg. 57.94% showed signs for a congenital GH deficiency: Abnormalities of the external genitalia in 66.12% of boys : micropenia isolated or associated with cryptorchidism : 24.2%;MA: 37.38%; Craniofacial and visceral malformations : 0.84%. In 7.47%, other anomalies were reported during neonatal period: jaundice ($n=4$) hypoglycemia ($n=4$). **Conclusion:** GHD rarely is rarely revealed to the neonatal period. The existence of signs of other hormone deficiencies and MA should evoke it precociously.

P2-P687

Diagnostic Value of Growth Hormone Stimulation Test for Growth Hormone Deficiency in Short Children

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Background: It is important to find and manage the cause of short stature in children. GH stimulation test is considered as a 'gold standard' for the diagnosis of GH deficiency (GHD), and several pharmacologic agents including insulin, glucagon, L-dopa, or clonidine are used for GH stimulation test (GHST). However, diagnostic value, sensitivity or specificity of each GHST is not clear. **Objective and hypotheses:** This study was designed to evaluate the diagnostic value of GHST by insulin, glucagon, L-dopa, or clonidine for GHD during childhood. **Method:** Subjects who visited the pediatric endocrine clinic for the evaluation of short stature underwent GHST using two or three combinations out of insulin, glucagon, L-dopa, or clonidine. GH deficiency was defined when serum peak GH concentration was less than 10 ng/ml with at least two provocation tests. Clinical data were collected retrospectively from a review of 55 children who performed GHST for the evaluation of short stature between January 2011 and December 2014. **Results:** A total of 38 children (69.1%) were diagnosed with GHD and 18 children (30.9%) were diagnosed with idiopathic short stature. Mean height z score was -2.52. Insulin test, glucagon test, L-dopa teat, and clonidine test were done in 54, 41, 45, and 12 subjects, respectively. In each test, sensitivity for GHD was 100, 65.4, 74.2, and 90%, respectively. Specificity was 56.3, 73.3, 92.9, and 50%, respectively. Positive predictive value for GHD was highest in L-dopa test (95.9%), and negative predictive value was highest in insulin test (100%). There was no serious adverse event during GHST, except for mild hypoglycemic symptoms or transient vomiting. **Conclusion:** Any GHST was relatively safe to perform in short children. Considering the GHST results, we could conclude that combination test using insulin and clonidine is more useful to detect GHD in short children.

P1-P688

Thyrotoxicosis, Nephrogenic Syndrome of Inappropriate Antidiuresis, Tall Stature and Mental Retardation Caused by a Novel *GNAS* Gain of Function Mutation

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Background: Nephrogenic syndrome of inappropriate antidiuresis (NSIAD) is a very rare clinical condition. Patients suffer from hyponatremia, hypo-osmolality with inappropriately elevated urinary osmolality and undetectable AVP levels. Activating mutations of AVPR2, the vasopressin receptor type 2 (V2R), induce a prolonged signaling of the intracellular cAMP/PKA pathway and cause NSIAD in patients. **Objective and hypotheses:** To describe a new phenotype in a patient with symptoms suggestive of the concomitant and inappropriate activity of several GPCRs, a pattern reminiscent of Mc Cune Albright syndrome (MAS), yet with a different phenotype including the phenocopy of the V2R constitutive activation. **Patient:** A 4-years old tall girl had persistent hyponatremia (118–

128 mmol/l) and antidiuresis. Her plasmatic osmolarity was low (260 mOsm/lkg) while the urinary osmolarity was inadequately elevated (1020 mOsm/kg). The AVP level was undetectable. No variant was identified in the AVPR2 gene. She also had symptoms of androgen secretion (mild clitoral enlargement, pubic hair and advanced bone age, slightly elevated testosterone and sDHA levels). Adrenals were of normal size and shape on the CT-scan. At the age of 5 years, she developed a non-immune thyrotoxicosis. At the age of 6, a *café au lait* spot appeared on the tight. We hypothesized that she could have a constitutional activation of the cAMP/PKA pathway and we searched for mutations in candidate genes downstream of AVRPR2 and the TSH receptor. **Results:** We found a de novo S250I mutation in *GNAS*, encoding the alpha-subunit of the stimulatory G protein (Gsα). Transfection of the mutated S250I-Gsα in *Gnas* null cells demonstrated a greater accumulation in cAMP compared to the wild-type Gsa ($P=0.0004$). But a lesser cAMP production than that we observed upon R201-Gsα transfection (the activating mutation responsible for MAS) ($P<0.0001$). **Conclusion:** We describe a novel form of constitutive Gsα activation responsible for NSIAD and thyrotoxicosis.

P1-P689

Novel Germline Mutations in *DICER1* Gene in Patients with Different Pediatric Hereditary Tumors

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Background: Carriers of germline *DICER1* mutations are predisposed to a rare cancer syndrome, the DICER1 syndrome, associated with tumors such as pleuropulmonary blastoma (PPB), ovarian Sertoli-Leydig cell tumors (SLCT), multinodular goiter (MNG), cystic nephroma (CN), embryonal rhabdomyosarcoma (ERMS) or primitive neuroectodermic tumor. DICER1 is involved in the generation of microRNAs (miRNAs), short, double-stranded, non-coding RNAs that modulate gene expression at the posttranscriptional level. Germline mutations in *DICER1* would cause an alteration in miRNAs processing deregulating target oncogenes and leading to elevated risk of tumorigenesis. In most reported cases, there is an heterozygous germline mutation detected and a somatic second hit mutation in the wild type allele. **Objective and hypotheses:** To analyze the presence of *DICER1* germline gene alterations in four patients with pediatric tumors associated. **Method:** Automated sequencing of *DICER1* gene from gDNA extracted from blood of affected subjects and relatives. Clinical Cases: three girls (P1, P2, P4) and one boy (P3), chronological age at diagnosis were: 5, 12, 15, and 2 years, respectively. Pathological studies revealed in P1: bilateral ovarian SLCT, P2: ovarian SLCT and MNG P3: CN and P4; ovarian SLCT and MNG. **Results:** P1, P2 and P3 were found to be heterozygous for the novel p.Trp1098*, p.Phe351fs*1 and p.Asp244Glyfs*27 variations respectively while P4 was found to be heterozygous for the previously described p.D1437Mfs*16 mutation. In P2 and P3 familial molecular studies the same alteration in one parent (father and mother respectively) was detected. It is predicted that these alterations would lead to a truncated protein above the RNAsa IIIa and RNAsa IIIb domains that includes metal-binding sites, and therefore without catalytic enzyme activity if translated. **Conclusion:** We report three novel heterozygous frameshift mutations in the *DICER1* gene. Molecular analysis of *DICER1* gene allows identification of high-risk families, to perfom an early diagnosis and to offer a genetic counselling about familial recurrence risk.

P1-P690

Fludrocortisone: A Treatment for Tubulopathy Post Paediatric Renal Transplantation – A Scottish Study

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Background: Post renal transplantation, tubulopathies may occur as an effect of transplantation itself or secondary to the use

Table 1. (for abstract P1-P690)

Patient	Diagnosis	Fludrocortisone (μg)		$NaHO_3$ (g)		NaCl (g)	
		Initial dose	Max dose	Pre-fludro	With fludro	Pre-fludro	With fludro
1	Congenital renal hypoplasia	100	200	–	–	–	–
2	Congenital nephrotic syndrome	50	75	3.0	0	1.8	1.8
3	Prune belly syndrome	25	100	1.9	0	2.7	1.8
4	Posterior urethral valves	25	150	2.0	0	1.8	0.9
5	Congenital renal hypoplasia	50	150	5.0	0	0.9	4.0
6	Prune belly syndrome	25	150	6.7	0	4.0	0

of immunosuppressive regimes. This often requires administration of large doses of sodium bicarbonate and sodium chloride, resulting in poor compliance. Adult studies have shown the advantages of fludrocortisone in the treatment of severe tubulopathies post renal transplant. There is limited data in children. We report our experience from a tertiary paediatric centre. **Objective and hypotheses:** To evaluate the efficacy of fludrocortisone as a treatment for tubulopathy post renal transplantation in children. **Method:** Retrospective review using data collected from a renal database from December 2014 to January 2016. **Results:** A total of 24 post transplant patients were identified as being on sodium supplements, of which 6 patients were started on fludrocortisone post transplantation. The median patient age was 7.3(4.9–9.9) years. Patients received fludrocortisone 18.5(2–52) months after transplantation and were followed up for 12.5(6–20) months. Following treatment with fludrocortisone, all patients stopped sodium bicarbonate supplements and all patients had a reduction in the total daily doses of sodium chloride. Serum potassium levels were significantly lower on treatment, 5.3 vs 4.5 mmol/l, $P=0.04$. There was no significant increase in systolic blood pressure, 98.5 vs 103.5 mmHg, $P=0.40$. Renal function was unchanged, serum creatinine 57.0 vs 54.5 µmol/l, $P=0.12$. No side-effects of treatment with fludrocortisone were reported in this cohort (Table 1). **Conclusion:** Fludrocortisone is an effective treatment for tubulopathies in children post renal transplantation. It reduces the requirement for sodium bicarbonate and sodium chloride supplementation without a significant effect on renal function or blood pressure. The hypokalaemic properties of fludrocortisone are an added benefit as some patients in this cohort were also on potassium restricted diets. This study adds to the limited evidence in the literature regarding the benefit of fludrocortisone.

P1-P691

Neonatal Diabetes and Congenital Hypothyroidism, a Rare Condition: Report of 2 Cases with Different Genetic Causes

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Background: Neonatal diabetes (ND) is a rare monogenic form of diabetes presenting within the first six months of life. The most frequent causes include mutations in *KCNJ11*, *ABCC8* and *insulin* genes, but up to 40% of patients remain without a molecular genetic diagnosis. **Case presentation:** *Case 1*: a female newborn of non-consanguineous parents, born at 35 weeks, SGA. She presented with hyperglycemia at second day of life and low serum C-peptide 0.1 ng/ml (0.80–4.20); diabetes related autoantibodies were not performed. Congenital hypothyroidism was diagnosed at 10th day of life, thyroid ultrasound revealed severe thyroid hypoplasia and thyroid scintigraphy showed no ectopic or normotopic uptake of radiotracer. She also developed persistent diarrhea and cholestasic jaundice, with normal liver and pancreas on abdominal ultrasound. The patient died at 6 months of life due to persistent pulmonary hypertension after a severe pneumonia. *Case 2*: A 13 years old female, born full term but SGA. She presented with hyperglycemia since first day of life. Congenital hypothyroidism with a normal thyroid ultrasound was confirmed during first week of life. Abdominal ultrasound showed pancreatic agenesis. Nowadays she has normal growth and development. In both cases mutations in *KCNJ11*, *ABCC8* and *INS* genes were excluded, sequence analysis identified a novel *de novo* heterozygous STAT3 missense mutation, c.1928A>G, p.Gln643Arg (case 1) and a heterozygous mutation GATA6 c.1339C>T, p.Cys447Arg (case 2). Molecular genetics laboratory, Exeter University, UK. **Conclusion:** We present two cases of neonatal diabetes associated with congenital hypothyroidism. *GATA6* mutation is a known cause of ND due to pancreatic agenesis associated with congenital hypothyroidism. Mutations in *STAT3* have been recently associated with early-onset autoimmune disease including enteropathy, primary hypothyroidism, fibrotic lung disease, juvenile arthritis and ND. A specific molecular diagnosis has important clinical consequences as it may influence diabetes treatment and define prognosis.

P1-P692

Access to Medicines in Pediatric Endocrinology and Diabetes in Africa: Insights from the WHO and National Lists of Essential Medicines

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Background: Access to essential medicines remains suboptimal in Africa. The World Health Organisation (WHO) maintains two non-binding essential medicine lists (EML) (for children and for adults). Individual countries refer to these lists to prepare national EMLs. **Objective and hypotheses:** To determine which medicines commonly used in pediatric endocrinology and diabetes are included in the WHO and national EMLs in the WHO African region. We hypothesize that significant differences are present between countries, reflecting at least in part differences in Gross National Income (GNI). **Method:** We

compared a master list of medicines with i) the WHO EML for children and adults and ii) The national EML for countries included in the WHO African region. National EMLs were obtained from the WHO website and GNI data from the World Bank. **Results:** Data from 40 of the 47 countries included in the WHO African region was collected. Four countries (=10%) had separate adult and child EMLs and 33 countries (=83%) were classified as low income. Overall, the WHO EMLs included medicines for contraception, Vitamin D deficiency, Type 1 and Type 2 diabetes and diseases of the adrenals, the thyroid and puberty. Calcitriol, diazoxide, growth hormone and bisphosphonates were not included. In African EMLs, all countries included at least one glucocorticoid and 96% included a short and/or long acting insulin. In contrast, fludrocortisone was only present in 11 (=25%) and glucagon in 10 (=23%) of the national EMLs, despite being suggested by WHO. Calcitriol was included by 7% of the countries. Diazoxide was not included in any of the lists. Overall, richer countries had more medicines listed than poorer countries. **Conclusion:** There are significant discrepancies between the content of the WHO and National EMLs. Future research will determine the extent to which the national EMLs reflect availability of the medicines in the country.

P1-P693

Is it Cautious to Wait for Serum Basal Calcitonin Levels Rise in Patients with Ret Codon C634 Mutation?

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Background: 2015 ATA Guidelines for management of medullary thyroid cancer (MTC) include C634 RET codon mutation in 'High risk' group, recomendating prophylactic thryroidectomy before 5 years old based on serum basal calcitonin levels (SBCt). **Objective and hypotheses:** We present 14 pediatric patients with C634 RET codon mutation, who underwent prophylactic thyroidectomy in our center, their clinical and analytical features and anatomopathological findings. **Method:** Preoperative SBCt, thyroid function, parathyroid hormone, urinary cathecolamines, cervical ultrasound were performed, besides physical examination. Surgery was performed at diagnosis, except in youngest patients in whom surgeons preferred to wait until 3–4 years old. **Results:** Mean age of patients at diagnosis was 8.1 years (18 months–16.5 years). Clinical examination showed palpable thyroid nodule in only one of the patients. SBCt was elevated in 7/14 patients. It was moderately elevated in the oldest patients, and extremely elevated (2400 ng/l; NV: <10 ng/l) in patient presenting goiter. Total thyroidectomy was performed to the whole cohort. Only one patient suffered postsurgery complication, a surgical site hemorrhage solved with a Penrose drainage for 24 h. No other postsurgical complications occurred. Histopathologic findings were: 10 C cell hyperplasia (CCH), 3 MTC, 1 normal thyroid. Every MTC patient had elevated SBCt, the same as three patients having CCH. The rest of CCH patients presented normal SBCt, even those having atypias. **Conclusion:** SBCt cannot reliable discriminate between CCH and MTC. Our recommendation is to perform prophylactic thyroidectomy as soon as high-volume surgeons accept.

P1-P694

Abstract withdrawn.

P1-P695

CANDLE Syndrome: A New Autoinflammatory Lipodystrophic Disorder with Challenging Diagnosis and Limited Therapeutic Options

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Background: We present a 3 years old boy born on term from young non-consanguineous parents with negative family history. Shortly after birth swelling of the feet and multiple generalised erythematous cutaneous plaques and nodules gradually appeared. Recurrent fever attacks, hepatosplenomegaly, significant growth delay (height – 4.0 S.D.) and progressive loss of subcutaneus fat tissue followed. **Objective and hypotheses:** Laboratory investigations found anaemia, thrombocytopenia, elevated leucocytes count and CRP levels. Bone marrow samples were not diagnostic and skin biopsy revealed allergic vasculitis. The immunological tests showed slightly elevated pANCA and cANCA, but normal ANA, IgG, IgA, IgM, IgE, C3, C4, AST and WR. **Method:** In the differential diagnosis a list of dermatologic, inflammatory, hematologic, systemic and allergic disorders were taken into consideration. The treatment attempts included the usage of corticosteroids, resorchin, methotrexate, with a little or no effect. **Results:** CANDLE syndrome – a chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature was suspected and later on genetically proven in NIH, USA. This is a newly described autoinflammatory disease with presentation shortly after birth. It is inherited in an autosomal recessive way

and is due, in most cases, to mutations in the proteasome subunit, beta type, 8 (PSMB8) gene (6p21.3) that lead to dysregulation of the IFN pathway. **Conclusion:** The CANDLE syndrome is another example of autoinflammatory disorder affecting the subcutaneous fat tissue. At the moment various treatments have been proposed with dubious effect, but experiments with JAK inhibitors show some promises.

P1-P696

Variable Phenotype and Genetic Findings in a Cohort of Patients with Pseudohypoparathyroidism

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Background: Pseudohypoparathyroidism is a group of rare disorders characterized by tissue insensitivity to PTH and Albright hereditary osteodystrophy (AHO) due to inactivating mutations or epigenetic defects of the GNAS. **Objective and hypotheses:** Clinical features and molecular characteristics of patients with PHP have been examined. **Method:** We included 28 patients from 26 families with PHP1a and 1b. *GNAS* mutation analysis was performed in patients with AHO signs. Clinical data were analyzed. **Results:** The first clinical signs in 20 patients (71.4%) were seizures. 11 of them were misdiagnosed with epilepsy and had been receiving anticonvulsants for 2 month – 7 years before hypocalcemia was revealed. Obesity was the first complain in seven patients, one of them had hypothyroidism manifested before hypocalcemia. One patient had only growth and mental retardation and was examined because of sister's disease. 19 patients had TSH resistance and one had GnRH resistance. AHO features were observed in 13 patients. The most common feature was brachymatecarpia (13 patients), subcutaneous calcifications was seen in eight patients, obesity was seen in seven patients, moon face had five patients, short stature had five patients, mental retardation were observed in six patients. 17 patients had complications of hypocalcemia: Fahr's Syndrome (60.7%), 5 had cataracts (17.8%). Maternally-inherited *GNAS* mutations were identified in two patients (siblings), de novo *GNAS* mutations were identified in five patients with PHP1a. **Conclusion:** Obesity or hypothyroidism can precede hypocalcaemia in PHP. Evaluation of serum Ca is important for all patients with seizures to avoid misdiagnosing. Absence of *GNAS* mutation in patients with AHO indicates overlap between PHPIa and PHPIb. Further investigations including MS-MLPA assay are planned to explore potential phenotype-genotype correlations in PTH.

P1-P697

Contiguous Gene Syndrome Involving *DAX1* Deletion with Congenital Adrenal Insufficiency

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Background: In contrast to monogenic diseases, contiguous gene syndrome (CGS) describes a clinical phenotype caused by a deletion or duplication of several neighbouring genes. Angelman or Williams-Beuren syndrome are examples demonstrating that deletion of several adjacent genes causes a complex clinical syndrome. However, CGS are very rare events in pediatric endocrinology, and require knowledge of clinical associations pointing towards specific potentially affected genes in local chromosomal proximity. **Objective and hypotheses:** A male preterm geminus born at 30 weeks of gestation was admitted to NICU for further treatment. Selective metabolic screening was performed in the second week of life because of persistent hyponatremia and muscular hypotonia. Massive glyceroluria was detected, indicating glycerol kinase deficiency which mostly is clinically subtile and did not explain the clinical presentation. However, other genes in close proximity to the *GK* gene are *DAX1* and *DMD*, which may cause congenital adrenal insufficiency and Duchenne muscular dystrophy. Indeed, during further course, increased ACTH, decreased cortisol, and elevated creatine kinase were found pointing to a CGS involving at least these three putative genes. **Method:** Array-CGH was initiated to confirm contiguous gene deletion. **Results:** Array-CGH showed deletion of *DAX1*, *GK* and *DMD* on Xp21.3. Additionally, *IL1RAPL1* was deleted causing a variable spectrum of mental retardation, and further genes without known clinical association. Fortunately, the neighbouring gene for ornithine carbamoyltransferase (OTC), causing an urea cycle disorder, was not affected. Adrenal hypoplasia was confirmed by non-existent adrenal gland in ultrasound. Hydrocortisone and fludrocortisone replacement treatment was initiated with so far uncomplicated clinical course until the present age of now 9 months. **Conclusion:** Contiguous deletion of x-chromosomal genes leads to a complex disease pattern involving multiple systems. The association of adrenal insufficiency, elevated creatine kinase, glyceroluria, and hyperammonemia in variable combinations strongly indicates a CGS with deletion of Xp21.3.

P1-P698

Clusters of Autoinmune Diseases in Children

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Background: Autoimmune diseases (AIDs) have familial aggregation and frequently share a common genetic background, but few studies have evaluated autoimmune clusters in children with AIDs and their families. **Objective and hypotheses:** To identify clusters of AIDs in children and their first-degree relatives. **Method:** A cross-sectional study was performed in subjects with an AID of pediatric onset (<18 years) recruited at Pediatric Endocrinology, Rheumatology, and Gastroenterology Clinics at the Health Network of the Pontificia Universidad Católica de Chile School of Medicine. Clusters of AIDs were identified by K-means cluster analysis. **Results:** 191 subjects with pediatric AIDs were included, of which 45 (24%) had polyautoimmunity. Mean age was 12.1 years (range 1–19) and 68% were female. Most frequent AIDs were JIA (36%), AITD (25%), T1D (19%), uveitis (8%), celiac disease (6%), and vitiligo (6%). 59% of subjects with pediatric autoimmunity had first-degree relatives with an AID. Five clusters of AID were identified in families of children with autoimmunity (Table 1). Among the 45 subjects with pediatric polyautoimmunity, four clusters of AIDs were identified (Table 2). **Conclusion:** AIDs in affected children and their families may be grouped into well-defined clusters suggesting a common etiopathogenesis among diseases grouped in each cluster.

Table 1. Clusters of autoimmune diseases among children with autoimmunity and their first-degree relatives.

Cluster	Number of cases	**Autoimmune diseases** (Descending order of relevance)
1	94	Juvenile idiopathic arthritis Connective tissue diseases Autoimmune thyroid disease
2	29	Juvenile idiopathic arthritis Psoriasis Autoimmune thyroid disease
3	31	Type 1 diabetes Autoimmune thyroid disease Celiac disease Psoriasis
4	25	Autoimmune thyroid disease Type 1 diabetes Vitiligo Connective tissue diseases
5	10	Celiac disease Autoimmune thyroid disease Type 1 diabetes Autoimmune hepatitis Juvenile idiopathic arthritis

Table 2. Clusters of autoimmune diseases among children with pediatric polyautoimmunity.

Cluster	Number of cases	**Autoimmune diseases** (Descending order of relevance)
1	4	Connective tissue diseases Autoimmune thyroid disease Juvenile idiopathic arthritis
2	11	Type 1 diabetes Autoimmune thyroid disease Celiac disease Inflammatory bowel disease Immune thrombocytopenic purpura
3	10	Autoimmune thyroid disease Vitiligo Juvenile idiopathic arthritis Celiac disease Scleroderma
4	18	Juvenile idiopathic arthritis Uveitis Psoriasis Vitiligo Alopecia Areata Autoimmune Hepatitis

P1-P699

Role of PTPN22 C1858T Gene Polymorphism in Pediatric Polyautoimmunity

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Background: Children with more than one AID (pediatric polyautoimmunity) may have a stronger genetic component than children with a single AID. PTPN22 C1858T SNP has been associated with multiple different AIDs in adults and children. **Objective and hypotheses:** Evaluate the association of *PTPN22* C1858T gene polymorphism with pediatric polyautoimmunity. **Method:** A cross-sectional study was performed in subjects with an AID of pediatric onset (<18 years) recruited at Pediatric, Endocrinology, Rheumatology and Gastroenterology Clinics at the Health Network of the Pontificia Universidad Católica de Chile School of Medicine. The *PTPN22* C1858T gene polymorphism was determined by RT-PCR in subjects with pediatric polyautoimmunity, in subjects with three common AIDs: juvenile idiopathic arthritis (JIA), autoimmune thyroid disease (AITD), type I diabetes (T1D) and in 98 healthy controls. **Results:** Genomic DNA from 128 subjects was evaluated for PTPN22

C1858T gene polymorphism revealing common homozygosity (C/C) in 85.2%, heterozygosity (C/T) in 13.3%, and rare homozygosity (T/T) in 1.6%, in equilibrium with Hardy Weinberg Default ($P=0.4$). 26% of polyautoimmune subjects had the T allele in contrast with 11% of monoautoimmune subjects ($P=0.04$). No significant difference was found in the age of onset of autoimmunity between mono and polyautoimmune subjects ($P=0.44$) or between subjects with C/C genotype vs C/T and T/T genotypes ($P=0.81$). **Conclusion:** A higher prevalence of the *PTPN22* C1858T polymorphism in pediatric polyautoimmunity, suggesting that this variant may be a risk factor for polyautoimmunity in children with AID.

P2-P700

Effects of 2 Years of Growth Hormone Treatment on Glucose Tolerance in Young Adults with Prader-Willi Syndrome

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Background: Growth hormone treatment (GH) in children with PWS results in an improvement in height velocity, body composition and mental and motor development. Discontinuation of GH after attainment of adult height (AH) leads to a decrease in lean body mass and an increase in body fat percentage, which results in an increased risk of impaired glucose tolerance (IGT) and diabetes mellitus type 2 (DM2). Studies in adults with PWS suggest positive effects of GH, but GH is known to induce insulin resistance. Reports on the prevalence of DM2 vary from 7-50% in adults with PWS. **Objective and hypotheses:** To evaluate the effects of GH on glucose metabolism in young adults with PWS who were treated with GH during childhood and recommenced GH in adulthood. Hypothesis: GH lowers insulin sensitivity, but does not significantly alter glucose tolerance. **Method:** In this prospective study 15 patients with PWS (15-20 years) recommenced Somatotropin in a dose of 0.33 mg/m^2 per day, after discontinuation for a median duration of 4 months at attainment of AH. Fat Mass, Lean Body Mass, weight, waist and hip circumference, blood pressure, IGF-I, IGF-BP3 and OGTT were collected at baseline and yearly thereafter. **Results:** There was a significant increase in baseline insulin and HOMA-IR after 2 years of GH ($P=0.011$ and 0.019, respectively), but baseline glucose, glucose and insulin 2 h after glucose load and glucose AUC did not significantly change. One patient had IGT before start of GH and two patients developed IGT during 2 years of GH. None developed DM2. **Conclusion:** Two years of GH in young adults with PWS leads to lower insulin sensitivity without significant changes in glucose levels. Two patients developed IGT during 2 years of GH treatment, but none developed DM2. Thus, GH does influence insulin sensitivity, but did not lead to the development of diabetes in our group of young adults with PWS.

P2-P701

TPIT Mutation may be Involved in Multiple Pituitary Deficiencies

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Background: Congenital isolated adrenocorticotrophic hormone (ACTH) deficiency (IAD) is a rare condition. It is characterized by low plasma and cortisol levels and preservation of all other pituitary hormones (2 cases described with transient partial growth hormone deficiency). The principal molecular cause is identified as TPIT mutation. We present here the case of a neonate with TPIT mutation and ACTH deficiency associated with probable growth hormone and thyrotropin deficiencies. **Results:** The patient was the couple's first child. Parents were first cousins. The boy was delivered at 37 weeks of gestation, with birth weight of 2750 g, from first cousins parents. He had immediate hypotonia, poor feeding, hypoglycemia (blood glucose 1.65 mmol/L), and early jaundice. Transfontanelar ultrasound and electroenkephalogram were normal. Total and direct bilirubin and gamma-glutamyl transpeptidase (GGT) were 300 µmol/L, 260 µmol/L and 186 UI/L respectively. At d12, TSH was 3.1 mUI/L (1–10), FT4 14.40 pmol/L (18–28), suggesting thyrotropin deficiency; IGF1, IGFBP3, and baseline GH were 21 ng/mL (45–150), 0.9 mg/L (1.2–3.0), and 7.60 ng/mL (7–30), respectively, suggesting GHD. ACTH, cortisol, and DHEA-S levels were $<$ 1.0–ng/L (5–49), 1 µg/L (18–252), and 53 ng/mL (360–2000), respectively, indicating corticotropin deficiency. Hydrocortisone, growth hormone, and thyroid hormone treatments were started, which allowed for a rapid improvement of hypotonia, jaundice, and blood glucose. Pituitary MRI was normal. **Conclusion:** Given the apparent multiple pituitary hormone deficiencies, PROP1 and LHX3 genes were first screened for mutation (negative). Eventually, an homozygous TPIT mutation was found (c.383 C$>$A). Multiple pituitary hormone deficiencies may lead to the molecular diagnosis of TPIT mutation.

P2-P702

Clinical Analysis of 24 Cases of Rathke's Cleft Cysts in Children

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Background: Rathke's cleft cysts (RCC) are benign, epithelial lined cystic remnants of the craniopharyngeal duct, and are a common radiological differential for lesions involving the sellar and sellar/suprasellar region. RCC are not very common in children. **Objective and hypotheses:** To investigate the clinical characteristics of RCC in children. **Method:** A retrospective analysis was conducted in 24 patients with RCCs diagnosed between July 2010 and August 2015. Their clinical, hormonal, and imaging findings were reviewed. **Results:** 24 patients with radiologically proven RCCs were lack of headaches, visual disturbances, adrenal dysfunction or hyperprolactinemia. 15 patients (62.5%) got growth retardation, and 7 of them (29.2%) were diagnosed idiopathic short stature, 8 of them (37.5%) were diagnosed growth hormone deficiency (GHD). In all GHD cases, 1 case had both GHD and central diabetes insipidus; 1 case had both GHD and central hypothyroidism. 6 cases had breast development before 8 years old and 3 of them (12.5%) were diagnosed central precocious puberty, Other 3 cases (12.5%) were diagnosed un-completely precocious puberty. 3 cases (12.5%) were obesity. Till February 2016, none of these 24 cases had headache or visual disturbance. All 24 cases were re-examined pituitary magnetic resonance and three of them were self-healing. 2 cases got undertook transsphenoidal pituitary cyst excision and 3 years follow-up, theirs Rathke cysts were not recurrenced. **Conclusion:** RCCs in the pediatric population are known to be an infrequent cause of headaches and visual disturbances, but pituitary dysfunction are most common. Most of Rathke's cleft cysts pediatric patients don't need surgery, a few patients can heal itself.

P2-P703

French National Healthcare Network for Rare Endocrine Diseases (FIRENDO): The First Year of Activity to Monitor Patients with Rare Endocrine Diseases

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Background: Twenty-three national healthcare networks for rare diseases were identified in 2014 as part of the French scheme on rare diseases. The rare endocrine disease national healthcare network FIRENDO (www.firendo.fr) includes six centers of reference with complementary fields of expertise certified between 2005 and 2006, 30 centers of competence covering all French regions, 18 research and 37 diagnostic laboratories, 5 national learned societies and 13 patient advocacy groups. **Objective and hypotheses:** FIRENDO aims at promoting care and research in rare endocrine diseases and also provides epidemiological data on patients with rare endocrine diseases. **Method:** FIRENDO shortlisted 120 rare endocrine disorders, for which surveillance was instituted with a network of clinical research associates located in seven key clinical centers, one in each region of France. Under the impulse of FIRENDO Database management taskforce, data collection procedure has been unified nation-wide. Data are collected using the CEMARA national database developed for rare diseases. **Results:** From September 2015 to March 2016 each of the seven regions started progressively to register in and out-patients with rare endocrine diseases. Up to now a total of 43 departments of adult or paediatric endocrinology units participate in the surveillance protocol. In 6 months a total of 6791 patients were registered. Analysis of the data will be performed annually and the first results will be presented at the meeting. **Conclusion:** The epidemiology of rare diseases is considered crucial to define a consistent healthcare and medical research scheme in France. However, these data are alarmingly lacking for some rare endocrine disorders. FIRENDO should be able to build up a solid epidemiological tool to screen these populations, providing more accurate data in years to come.

P2-P704

Autoimmune Diseases and Metabolic Outcome in Turner Syndrome – Comparison between 45,X0 and other X Chromosome Abnormalities

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Background: Turner syndrome (TS) is a genetic disorder caused by X chromosome monosomy (45,X0) or partial absence of

the second sex chromosome, with or without mosaicism. An increased frequency of autoimmune diseases and metabolic disorders has been observed in Turner patients. **Objective:** To compare Turner monosomy to the other X chromosome abnormalities with regards to occurrence of autoimmune diseases and metabolic disorders. **Methods:** Retrospective study of 103 TS patients followed at the Institute for Endocrinology and Diabetes, SCMCI during 1960–2013. **Results:** Monosomy was diagnosed in 30% of the cohort. The mean age at diagnosis was younger in 45,X0 compared to the other X chromosome abnormalities (6.2 ± 5.5 vs 4 ± 4.8yrs, $P = .004$); duration of follow-up (14.0 ± 8.8 yrs) and age at patient's last visit (21.9 ± 9.6 yrs) were similar. The prevalence of autoimmune diseases [autoimmune thyroiditis (45.6%) and positive celiac serology (7.1%)] and age at onset were similar in both groups. BMI-SDS (TS charts) increased during follow-up; obesity at last visit was more prominent in girls with 45,X0 ($P = .013$). The percentage of patients with impaired glucose metabolism increased during follow-up: IFG (> 100 mg/dL) from 10.6% to 17.9%; IGT (140–199 mg/dl) from 23.8% to 30.5% and elevated HbA1c (> 5.8%) from 12% to 16.7%. At last clinic visit, lipid profile levels were above the 90th centile for TC, LDL-cholesterol and TG in 29.1%, 23.5%, and 30.1% of the patients, respectively; systolic blood pressure was increased in 52.3% and diastolic blood pressure in 18.2% of the cohort. The prevalence of metabolic disturbances (glucose metabolism, lipid profile, and blood pressure) were similar in both groups. **Conclusions:** In TS, an increased risk of autoimmune diseases and metabolic disorders were found regardless of the karyotype. Careful surveillance and early intervention in patients with monosomy and increased weight gain are warranted in an attempt to prevent obesity and thereby the risk for development of metabolic disorders.

P2-P705

Endocrinological Disorders in Children with Neurofibromatosis Type 1 and Optic Pathway Gliomas

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Background: Children with neurofibromatosis type 1 (NF1) have an increased risk of developing optic pathway gliomas (OPGs) during childhood. Although these tumors usually have a benign course, some cases result in significant clinical symptoms, including endocrinological disorders. **Objective and hypotheses:** The aim of this study is to evaluate the endocrinological complications of OPGs involving the chiasm in children with NF1. **Method:** We retrospectively evaluated children with NF1 and OPG involving the chiasm, with (Dodge 3) or without (Dodge 2) hypotalamic involvement seen between 1997 and 2015 at our institution. Details on patient demographics, tumor location, and endocrinological work-up were recorded. **Results:** 28 children (13 F) were identified (mean age at diagnosis of OPG 5.1 years). Patients underwent brain MRI mainly because of ophthalmic problems, 3 because of endocrinological signs. 16 patients showed OPG with chiasm involvement, 12 had a Dodge 3 tumor. Eight patients presented with endocrinological disorders at the time of OPG diagnosis or during follow-up: diencephalic syndrome (two girls of 5.5 and 1.3 years), GH hypersecretion (two girls of 3.9 and 3.8 years) and central precocious puberty (in three boys of 3.0, 7.6 and 8.6 years and one 7.6 years old girl). Debulking surgery was performed in 8/28 patients, while none was irradiated. Two of these experienced endocrinological complications after surgery including: GH deficiency in a 9.8 years old boy; and central diabetes insipidus and anterior pituitary deficiency in a 5.6 years old girl with a previous diencephalic syndrome. **Conclusion:** Our data suggest that endocrinological disorders occur frequently (32%) in children with NF1 and OPG involving the hypotalamic-chiasmatic region, in particular in those with a specific hypothalamic involvement. Herein we report several rare endocrinological disorders such as diencephalic syndrome, GH hypersecretion and male CPP. A careful auxological follow-up is desirable in children with NF1 given endocrine sign may represent the first element of suspicion of OPG.

P2-P706

Nephrogenic Syndrome of Inappropriate Antidiuresis (NSIAD) Managed with Fluid Restriction and Salt Supplementation

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Background: NSIAD is a rare genetic cause of hyponatremia, due to activating mutations in AVPR2 gene, encoding the Arginine Vasopressin Receptor Type 2, and located on Xq28. Of the fewer than 30 reported cases, most have been managed with fluid restriction and urea. **Objective and hypotheses:** Illustration of the presentation of a family with this genetic abnormality and approach to management. **Method:** The clinical, biochemical and genetic findings are presented. **Results:** A previously healthy and developmentally normal 14 month old boy presented with hyponatraemic seizures following increased water intake the previous day. Repeated investigations were consistent with inappropriate antidiuresis (serum Na 114 mmol/L, serum K 3.7 mmol/L, urine sodium 51 mmol/L and urine osmolality 301 mmol/kg); but a vasopressin level associated with hyponatraemia (Na 127 mmol/l) was low (1.7 pmol/l). Thyroid and adrenal function and imaging of the head, chest and abdomen were normal. There was no evidence of intracerebral, respiratory

or renal infection. The child was managed with water restriction and salt supplementation resulting in normal sodium levels over the following four months. Sequencing of the AVPR2 gene found that the child was hemizygous for a c.409C > T missense mutation which results in amino acid substitution p.Arg137Cys, previously described as causing NSIAD. Family history revealed hyponatraemic seizures in a maternal uncle as a child (serum Na 118 mmol/L, urine Na 146 mmol/L, urine osmolality 893 mmol/kg), consistent with X-linked inheritance. He had been misdiagnosed as having inappropriate ADH secretion secondary to seizure activity. **Conclusion:** This case illustrates the importance of considering NSIAD in children with hyponatraemia, with unexplained SIAD. Treatment is possible with water restriction and salt supplementation and the long-term outcome is good.

P2-P707

The Triglyceride to High-Density Lipoprotein Cholesterol Ratio and Non-High-Density Lipoprotein Cholesterol Reference Data for Korean Children and Adolescents: Results of the 2007–2013 Korean National Health and Nutrition Examination Surveys (KHANES)

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Background: Cholesterol levels are variable throughout childhood and adolescence. The attention not only to conventional lipid profiles but also to non-high-density lipoprotein cholesterol (non-HDL-C) and triglyceride to HDL-C ratio (TG/HDL-C ratio) are becoming more apparent in pediatric lipid studies because of their clinical importance. **Objective and hypotheses:** The aim of the present study was to establish age- and gender-specific reference values for serum lipid profiles in Korean children and adolescents. **Method:** A total 6,197 subjects aged 10 to 19 years old from KNHANES 2007–2013 were enrolled. Reference values were developed for the serum lipid levels including non-HDL-C and TG/HDL-C ratio. **Results:** The mean concentration of non-HDL-C was 105.5 ± 25.6 mg/dL in total subjects with significant gender difference; 103.3 ± 26.1 in boys and 107.9 ± 24.7 in girls ($P = 0.028$). The median values for non-HDL-C in boys and girls were 111 and 112 mg/dL in 10-year-old age; 95 and 103 mg/dL in 15-year-old age; and 109 and 103 mg/dL in 19-year-old age, respectively. The mean TG/HDL-C ratio was 1.74 ± 1.22 in total subjects and it was not different between two genders; 1.77 ± 1.25 in boys and 1.72 ± 1.22 in girls ($P = 0.183$). The median values for TG/HDL-C ratio in boys and girls were 1.16 and 1.00 in 10-year-old age; 1.54 and 0.95 in 15-year-old age; and 1.74 and 0.84 in 19-year-old age, respectively. **Conclusion:** Age- and gender-specific reference values for non-HDL-C and TG/HDL-C ratio can provide clinicians with useful information that will allow for the proper care of children and adolescents. Based on the present study results, we cannot overlook the lipid profiles in young children because their reference values are not significantly differ from late adolescents.

P2-P708

Inhibition of NAMPT Increases the Sensitivity of Leukemia Cells for Etoposide

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Background: Cancer cells have a high NAD turnover rate due to their increased cell proliferation and DNA repair. Nicotinamide phosphoribosyltransferase (NAMPT) is the key enzyme of the NAD salvage pathway, a regulator of the intracellular NAD pool and of the activity of Sirtuins (SIRTs), a class of NAD-dependent deacetylases. **Objective and hypotheses:** Cancer cells are highly dependent on NAD and are expected to be more susceptible to an inhibition of NAD synthesis than non-transformed cells. Does an inhibition of NAMPT by FK866 make leukemia cells more sensitive to chemotherapeutic agents? **Method:** Jurkat and Molt-4 cell lines were used as leukemia cell models. Viability was measured using WST-1 assay. Cell death was analysed by propidium iodide staining. NAD levels were measured using HPLC. NAMPT enzymatic activity was measured using ^{14}C-nicotinamide. **Results:** NAMPT expression and enzymatic activity was significantly higher in leukemia cell lines compared to normal PBMCs. Incubation with FK866 [10 nM] for 24 h reduced NAMPT activity by 91.1 ± 3.6% in Jurkat cells and by 97.8 ± 1.2% in Molt-4 cells. NAD levels were reduced by FK866 by 83.9 ± 1.0% (Jurkat) or 79.2 ± 2.8% (Molt-4). The combination of etoposide and FK866 caused increased cell death compared to each substance alone. Apoptosis induction as measured by caspase-3 and -7 activation was not further increased by the addition of FK866 to etoposide. Interestingly, etoposide decreased the expression of the NAD-dependent deacetylases SIRT1 and SIRT2. The acetylation and activation of the SIRT1 target p53 was enhanced after combining etoposide with FK866, which was associated with an increased expression of its downstream target p21. **Conclusion:** The combination of etoposide and FK866 caused increased cell death which was not caspase-mediated, but led to reduced SIRT1 activity as indicated by enhanced acetylation and transcriptional activity of p53. Combining FK866 and etoposide could be a novel therapeutic strategy to enhance the efficacy of etoposide against leukemia.

P2-P709

Neonatal Endocrinological Problems in Collodion Babies

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Background: Collodion babies (CBs) are an inherited group of diseases characterized clinically by diffuses severely dry and scaling skin. Patients are generally born prematurely and/or small for gestational age (SGA). Congenital hypothyroidism is seen together with various congenital anomalies, although the mechanism involved is still unclear. **Objective and hypotheses:** To identify endocrinological problems, and particularly those concerning growth, in 42 CBs. **Method:** Clinically identified newborn CBs were included in the study group (Group 1). Since CBs are generally premature and/or born SGA, control group matched to the patients in the study group in terms of gestational age ($\pm$7days) and birth weight (100 gr $\pm$) (Group 2) was established. Blood specimens were collected between the 3rd and 7th days of life from both groups for thyroid function tests [thyroid-stimulating hormone (TSH), triiodothyronine (T3), thyroxine (T4) and thyroglobulin (TG)] and to measure serum GH, IGF-I and IGFBP-3 levels. **Results:** Group 1 consisted of 42 CBs (25 males and 17 females) with gestational ages between 32 and 42 weeks and birth weights between 1,400 and 4,000 gr. Twelve patients were assessed as premature and 17 as SGA. Serum IGF-I and IGFBP-3 levels were lower and serum GH levels higher compared to the controls. Primary hypothyroidism was diagnosed in 10 patients in the study group, subclinical hypothyroidism in two and central hypothyroidism in one. A statistically significant difference was determined between the groups in terms of primary hypothyroidism ($P=0.01$). Serum GH levels were weakly negatively correlated with birth weight ($r=-0.32$, $P=0.04$) and serum IGF-I ($r=-0.38$, $P=0.001$) and IGFBP-3 ($r=-0.36$, $P=0.002$) levels. **Conclusion:** Premature birth and SGA are more common in CBs. High GH and low IGF-I and IGFBP-3 levels in cases indicate malnutrition-like GH resistance. In addition, the greater prevalence of hypothyroidism in babies is noteworthy.

P2-P710

Endocrine Dysfunction in Children and Adolescents with CHARGE Syndrome

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Background: CHARGE syndrome is a complex of congenital malformations affecting multiple organ systems caused by mutations in *CHD7*. **Objective and hypotheses:** This study was performed to evaluate endocrine dysfunctions including hypogonadotropic hypogonadism, growth hormone deficiency, or hypothyroidism in patients with CHARGE syndrome. **Method:** Eighteen patients (10 males and 8 females) with CHARGE syndrome were included. A diagnosis of CHARGE syndrome was made according to the diagnostic criteria by Verloes. All coding exons and exon-intron boundaries of the *CHD7* were amplified by PCR and directly sequenced in 14 patients. Clinical features and endocrine functions were evaluated by retrospective chart review. **Results:** Nine patients fulfilled the criteria for typical CHARGE syndrome, two patients for partial/incomplete, and seven for atypical CHARGE syndrome. *CHD7* mutations were identified in 12 patients: 11 truncating and one complete deletion mutations. Micropenis was found in all 10 boys, 6 of whom had unilateral or bilateral cryptorchidism. Two females and one male were diagnosed with hypogonadotropic hypogonadism during adolescents. LH responses to GnRH stimulation were prepubertal pattern. Mean height- and weight-SDS were -2.54 ± 1.16 and -2.57 ± 1.86, respectively. Of these, short stature of less than 3rd percentile was apparent in 12 patients (66.7%). One female was confirmed to have growth hormone deficiency by L-dopa and insulin tolerance tests at age 8 years. She was previously diagnosed with hypothyroidism at age 6.7 years and treated with levothyroxine, however, brain MRI did not show abnormalities. **Conclusion:** Hypogonadotropic hypogonadism has been reported as an endocrine defect in CHARGE syndrome. However, endocrinological evaluation is necessary in patients with CHARGE syndrome. As the ages of the patients in the present study were not in the range that would provide useful information concerning gonadotropin secretion, long-term follow-up is needed to assess endocrine functions in these patients.

P2-P711

Growth and Pubertal Patterns in Young Survivors of Childhood Acute Lymphoblastic Leukemia

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Background: Childhood acute lymphoblastic leukemia (ALL) survivors are at increased risk for endocrine late effects. **Objective and hypotheses:** To evaluate growth and pubertal patterns in patients diagnosed with childhood ALL and to identify risk factors for impaired growth and puberty. **Method:** Retrospective chart review with longitudinal assessment of anthropometric measurements and pubertal status of 183 childhood ALL survivors diagnosed between 1985 and 2011 (154 chemotherapy-treated and 29 chemotherapy + cranial radiation-treated; mean age at therapy 6.26 ± 3.8 years and 6.5 ± 4.34 years, respectively). Included in the study were patients aged 8–30 years at data collection, disease-free > one year, who remained in first remission, with $\geq$3 years follow-up. **Results:** Median age at last endocrine visit was 16.1 years (range 8.2–27.6 years); median duration of follow-up was 8.7 years (range 3–21.4 years). Mean age at pubertal onset was normal (girls: 10.3 ± 1.3 years; boys: 12.0 ± 1.3 years); precocious puberty

was diagnosed in 8.7% of patients. Overweight and obesity were found in 22.9% and 9.3% of the cohort, respectively. Patients treated with chemotherapy + cranial radiation as compared to chemotherapy-alone were shorter (mean height-SDS -0.93 ± 0.92 vs. -0.21 ± 1.1, $P = 0.001$), had higher prevalence of adult short stature (13% vs. 2.2%) and had a higher rate of precocious puberty in girls (30% vs. 9.4%) with no difference in age at menarche. Predictors for occurrence of endocrine disorders included: female gender (OR 3.26, 95% CI 1.04–10.1), cranial irradiation treatment (OR 3.96, 95% CI 1.14–13.78) and younger age at diagnosis (OR 0.83, 95% CI 0.68–1.02). Predictors for obesity - a higher BMI-SDS at diagnosis (OR 1.46, 95% CI 1.18–1.81), and for short stature - lower height-SDS at diagnosis (OR 0.35, 95% CI 0.13–0.94). **Conclusion:** Although most patients treated with chemotherapy-alone attained normal adult height & puberty, those treated with adjuvant cranial irradiation are at increased risk for short stature and precocious puberty (in girls). Childhood ALL survivors are also at an increased risk for overweight, especially those with increased BMI at diagnosis. Therefore, clinicians need increased awareness & screen for overweight & its associated health conditions early in survivorship. Interventions as changes in lifestyle habits are required to address weight control early during treatment.

P2-P712

Clinical Assessment of Hypercalciuria and Hypomagnesemia in Patients with Bartter Syndrome and Gitelman Syndrome

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Background: Bartter syndrome (BS) and Gitelman syndrome (GS) have similar clinical manifestations. It's hard to be distinguished by the symptoms and laboratory, even though the genetic analysis cannot identify them precisely. The precise diagnoses associate with the right treatment and prognosis. **Hypercalciuria** usually involved with neonate type Bartter syndrome, and **hypomagnesemia with Gitelman syndrome. Objective and hypotheses:** This study was based on the analysis of clinical data of 72 patients of BS and GS, and tries to find some useful parameters to help to differentiate diagnose. **Method:** To summarize the clinical data, and to analyze the correlation between clinical symptoms with urinary calcium and blood magnesium. **Results:** 72 cases patients aged from 2 months to 15.5 years (median 1.75 years), sex ratio of boy: girl is 52:20. All patients had hypokalemia, metabolic alkalosis, normal blood pressure and the levels of plasma rennin, **argiontensin** and aldosterone elevated.The ratio of urine calcium/creatinine over 0.2 was considered as a mark of hypercalciuria. The age of hypercalciuria group was 2.64 ± 2.95 years old, and that of ratio < 0.2 was 8.26 ± 4.49 years ($P = 0.00$). The SDS of weight was -2.58 ± 1.11 and -1.59 ± 1.26 respectively ($P < 0.005$). The age of patients with hypomagnesemia (serum magnesium < 0.8 mmol/l)was 7.88 ± 4.47 years, and that of normal serum magnesium was 3.78 ± 4.14 years ($P = 0.001$), the SDS of weight were -2.42 ± 1.60 and -1.42 ± 1.13 ($P = 0.005$). Correlation analysis showed that urinary calcium/creatinine ratio positive correlated with serum magnesium ($R = 0.355$, $P = 0.008$). **Conclusion:** The patients with hypercalcinuria were younger than that of normal urine calcium, and coincidently with poor nourished and development. The GS patients with hypomagnesemia usually had mild symptoms. The clinical types and genotypes of BS and GS were often overlapped. Hypercalciuria and hypomagnesemia were a good parameters in the differential diagnosis of BS and GS.

P2-P713

Wolfram Syndrome: Three Cases

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Background: Wolfram syndrome is an autosomal recessive disorder accompanied by diabetes insipidus, diabetes mellitus, optic atrophy and deafness. Mutations in the WFS1 gene are determined in 90% of cases. We present the clinical features of three cases of Wolfram syndrome. **Objective and hypotheses: Case 1:** A 14-year-old girl presented with loss of vision. At the age of 3 years she had been diagnosed with type 1 diabetes mellitus with a blood glucose level of 410 mg/dl and ketone positivity in urine at a center to which she presented with symptoms of excessive water consumption and urination. At the age of 8 the water deprivation test was performed, due to symptoms of polyuria and polydipsia and low urinary specific gravity, although her blood glucose levels were normal. She was started on nasal desmopressin therapy with a diagnosis of central diabetes insipidus. Blurred vision had begun at the age of 8, and cataract was determined in the right eye. Optic atrophy was determined at fundus examination following cataract surgery. No consanguinity was identified between the parents, although they came from a very small village. A brother had died from diabetic ketoacidosis at the age of 4 years, while a 24-year-old sister had been diagnosed with type 1 diabetes mellitus. Weight was 38 kg ($-2{,}3$ S.D.), height 145 cm ($-2{,}3$ S.D.), puberty Tanner stage 3 and blood pressure 110/60. Arthropathy was determined in the fingers. Other system examinations were normal. No loss of hearing was determined at audiometry. Homozygous p.I845N (c 2534T > A) mutation in the WFS1 gene was determined at molecular genetic analysis. The parents were also heterozygous for the same mutation. HbA1c was between 8% and 9% with multiple insulin therapy and exchange list nutrition. **Case 2:** A 7-year-old male patient presented with polyuria and polydipsia. Vision was reported to be poor since babyhood. Birth weight was 3700 gr, and the parents were second-degree cousins. Weight 35 kg (3.3 S.D.), height 115 cm (-1.2 S.D.), BMI 26.4 kg/m^2 (3.2 S.D.) and blood pressure 100/60 mmHg. Central type obesity and constant nystagmus were determined. Vision was at the light perception level. Bilateral optic atrophy and pigmented retinopathy were observed at fundus examination.

Blood glucose 209 mg/dl. Ketone positive in urine. HbA1c was 7%, and 60 dB sensorial loss was determined at audiometry. No mutation was detected at WFS1 gene analysis.HbA1c was between 7.5% and 8.5% with multiple insulin therapy and exchange list nutrition. **Case 3:** A 9-year-old girl presented due to polyuria and polydipsia. Loss of vision was reported to have begun after the age of 3 years. Weight 26.5 kg (−0.8 S.D.), height 126.5 cm (−0.5 S.D.), BMY 16.5 kg/m^2 (0.1 S.D.), puberty stage 1 and absence of vision and light perception were determined. At fundus examination the central area was normal, while abundant salt and pepper pigmentation was observed in the periphery. Other system examinations were normal. The water deprivation test was compatible with central diabetes insipidus. The oral glucose tolerance test was normal. HbA1c was 4.8%. Total block of transmission (complete blindness) was determined with VEP and ERG. No hearing loss was determined at audiometry. The patient was started on desmopressin nasal spray with a diagnosis of central diabetes insipidus and placed under monitoring. Genetic analysis could not be performed. **Conclusion:** Clinical features may differ in presentations of Wolfram syndrome. The syndrome may emerge during monitoring even if not all the features are present concurrently at presentation.

P2-P714

Autoimmune Hypoparathyroidism and Celiac Disease: A Rare Paediatric Association Outside an Autoimmune Polyglandular Syndrome

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Background: The association between primary hypoparathyroidism and celiac disease (CD) is uncommon in paediatrics, even more if they are not part of an autoimmune polyglandular syndrome (APS, almost exclusively type II). We describe a case of autoimmune hypoparathyroidism coexisting with celiac malabsorption. **Objective and hypotheses:** Valentina was a 7 year old female child when she was admitted in hospital because she had generalized seizures at home. She had normal weight and height, no dysmorphism; she had laryngospasm and Trousseau's sign. No familiar history for tetania; no personal history of recurrent infections or mucocutaneous candidiasis. First blood exams: hypocalcemia (4.4 mg/dl) and low ionised calcium; hyperphosphatemia (9.1 mg/dl); Magnesium 1.6 mg/dl (n.v. 1.7–2.4). ECG: prolonged QTc. PTH not dosable, hypocalciuria, normal phosphaturia, normal alcaline phosphatase, 25OHD3 22 ng/ml (n.v. 30–100). She had hypocalcemia secondary to hypoPTH. **Method:** We administered her intravenous calcium gluconate and oral 25OHD3: the clinical signs regressed within some hours, but, when we tried to give the child oral calcium, calcemia went down again. In the next days we had a possible explanation to this problem: antibodies for celiac disease were positive! The duodenal biopsie was made: she had a celiac disease (HLA DQ 2 and DQ 8 were positive) and a duodenitis caused by helicobacter pylorii. CATCH22 and AIRE mutations were absent, cariotype was 46,XX, the anti-Calcium Sensing Receptor (CaSR) Antibody was positive. **Results:** At 12 months from the diagnosis, the CD antibodies were negative, but PTH was still undoseable. We could exclude the role of CD antibodies in the hypoparathyrodism origin. Her actual therapy is oral calcium and D vitamin. **Conclusion:** autoimmune hypoparathyroidism **i**s an unusual association with celiac disease outside of an APS, We think that our child needs an adequate follow up to discover precociously other immune mediate disorders.

P2-P715

Management of Endocrine Complications of Thalassemia

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Background: β-thalassemia is the most common single gene disorder worldwide, in which hemoglobin β-chain production is decreased. Today, the life expectancy of thalassemic patients is increased because of a variety of treatment methods. However, osteoporosis and cardiac dysfunction remain frequent complications. **Objective and hypotheses:** The aim of the study, was to analyze the diagnostic and prognostic role of ferritin for endocrinopathies and metabolic disorders in βT patients. **Method:** This is a prospective study of previously chelated patients, and new patients followed at the pediatric hospital day since March 2010. Seventy-six βT patients were treated with different regimen of cheation. Sixty-three are under Deferasirox chelation. Data recorded included age, gender, haemoglobin and ferritin levels, biochemical and endocrine tests, liver, transfusion regimen, iron chelation, splenectomy, and bone mineralization by dual X-ray absorptiometry. The package of measures was made in a standard confidence interval of 95% and standard error consented risk is 5%. **Results:** Thirty-seven (46.1%) males and 33 (53.9%) females were studied, with mean age of 106,57 months, mean haemoglobin 9.2 ± 1.5 g/dL, median ferritin 895.40 ± 494.8; forty nine patients 49 had been transfused, occasionally (27/76, 35.5%); 19/76 patients had been splenectomized (25%); 63(83%) were on chelation therapy. Endocrinopathies were found in 10 patients: 08 hypogonadism, and one diabetes. Bone disease was observed in (14%) patients, osteoporosis in 3 /76 (7.9%), and osteopenia in 1/76 (1.5%). One fracture, six bone deformities and a hotbed of extra medullary hématopoeise, were objectived. **Conclusion:** Iron chelation therapy in adequate dosage, early diagnosis and treatment of endocrine insufficiency and regular blood transfusions can help to achieve an optimal endocrine function.

P2-P716

Endocrine Disorders in Children with Thalassemia Major – A Hospital Based Retrospective Study

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Background: The estimated prevalence of beta thalassemia is 3–8% in India, Pakistan, Bangladesh and China. The combination of regular blood transfusions and chelation therapy has dramatically increased the life expectancy of thalassemics, but it has led to iron overload and chelation toxicity, with many complications including – growth failure, gonadal dysfunction, hypothyroidism, hypoparathyroidism, DM, etc. **Objective and hypotheses:** To study the incidence and prevalence of endocrine disturbances in thalassemia major children, receiving regular blood transfusions. Also to study the correlation between-Age of starting transfusion/Average Sr. Ferritin levels/Age of starting chelation AND incidence of Endocrine problems in these children. **Method:** Basic information for each child was determined – age of presentation, onset of transfusion and chelation/Anthropometric data/Pubertal status(tanner staging). Blood investigations-Sr. Ferritin and average ferritin levels, Hb level, Sr. Calcium/Phosphorus/Alkaline Phosphatase, PTH, Thyroid profile, OGTT, LH/FSH, Sr. Estradiol (girls), Sr. Testosterone (boys). **Results:** See Table 1 below. **Conclusion:** In our study endocrine complications increased with Age – maximum seen in age group > 15 years.

- No association was found between age of onset of transfusion and chelation with incidence of endocrinal problems.
- Increased incidence of Hypogonadism, Hypothyroidism, Hypoparathyroidism was found with high average ferritin levels- at levels > 2500 ng/ml.

P2-P717

15-Year Old Girl with APS Type IIIc, with Post-Thymectomy Remission – Case Report

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Background: Autoimmune polyglandular syndromes (APS) is a group of heterogeneous conditions characterized by the association of at least two organ-specific disorders, concerning both endocrine and non-endocrine organs. On the basis of the clinical features, they are divided into four main types. Type III is defined as the combination of autoimmune thyroid disease and other autoimmune condition – divided into subtypes A, B and C. **Objective and hypotheses:** We describe a 16-year old female patient – with the family history of thyroid diseases in her mother (hyperthyroidism) and aunt (hypothyroidism), and Addison's disease in her grandmother – who has simultaneously developed the symptoms of autoimmune thyroid disease with the clinical picture of hyperthyroidism (emotional lability, irritability, decreased concentration, weight loss, hand tremor) and myasthenia gravis (decreased physical activity tolerance, ptosis, swallowing difficulties, voice change) at the age of 15. **Results:** The autoimmune thyroid disease (Graves' disease as indicated in the further laboratory investigation) was recognized about 2 months before myasthenia. Co-existence of those diseases allow us to diagnose APS type IIIc. After a few months we have discovered positive GAD-Ab (whilst blood sugar levels remain normal and without DM symptoms). No evidence of other autoimmune condition was observed. In this patient the standard GB and MG treatment was administered. When the CT scan revealed thymus enlargement, thymectomy was performed. After the surgery we observe not only MG remission, but a significant decrease of TRAb as well. **Conclusion:** Our patient's case confirms that, even in already diagnosed APS, the organ-specific Ab screening can help identify other latent and subclinical autoimmune diseases before patient's develop clinical symptoms. The case also indicates the possibility to achieve post-thymectomy remission of not only MG but other APS components.

P2-P718

Endocrine and Metabolic Evaluation of Children with Neurodevelopmental Disability

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Table 1. (for abstract P2-P716)

Endocrine complications (% in both sexes)	Country					
	Cyprus (435)	Greece (262)	Italy (1861)	Tehran (220)	N. Am (262)	Our study (225)
Hypothyroidism	5.9	4	6.2	7.7	4	4.9
Hypoparathyroidism	1.2	4	3.6	7.6	4	4.4
DM/IGT	9.4	5/27	4.9	8.7	5	8/4.9
Hypogonadism Delayed Pub/Arrested Pub	32.5	42	49	17.5/35.1	42	13.8/4.9/5.8

Introduction: Neurodevelopmental disability (NDD) is a common problem in children health, occurring in 5–10% of the pediatric population. **Aim:** To evaluate the endocrine and metabolic complications described in patients with NDD. **Material and method:** Children with NDD, aged below 9 years old, admitted to 1st Pediatric Clinic of Children Emergency Hospital, Timişoara, România, between January 2014-March 2016 were included in this study. Their evaluation was complex and included a detailed medical history, clinical and anthropometric evaluation, Tanner stages, multiple serum analyses and sophisticated imagistic investigations. **Results:** A total of 15 children (53.33% boys) diagnosed with NDD, with a mean age of 6.5 ± 1.9 years were eligible for this study. The main complaints of patients were in 93.33% developmental delay and in 6.67% developmental regression. Cerebral palsy was the most common clinical syndrome (60%), being caused mostly by perinatal hypoxic-ischemic encephalopathy (55.56%) and prematurity with intraventricular haemorrhage (33.33%). Metabolic disorders were diagnosed in 13.33% of patients (one with phenylketonuria and one with renal tubular acidosis), while one had clinical manifestations of neurodegenerative disorders (X-linked adrenoleukodystrophy). Severe malnutrition was encountered in 66.67% of them and short stature in 60%. Hypocalcemia with vitamin D deficiency (60%), hypophosphatemic rickets (6.67%), osteopenia (20%) and osteogenesis imperfecta (6.67%) were responsible for atraumatic fractures in almost one third of cases, especially in patients with seizures treated with an association of two (50%) or more anticonvulsivants (33.33%) and difficulty feeding problems (66.67%). Four children with subclinical hypothyroidism and one with adrenal insufficiency were identified in this group. Premature sexual development consisted in the presence of premature adrenarche (46.67%), premature thelarche (33.33%) and central precocious puberty in two girls (13.33%). **Conclusion:** Evaluation of endocrine and metabolic complications in patients with NDD is essential and helps for appropriate rehabilitation, family counseling and management of these associated medical conditions.

Keywords: neurodevelopmental disability, children, central precocious puberty, hypocalcemia

P2-P719

Endocrine Complication in Survivors of Childhood Cancers

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Background: Approximately 20–50% of children rescued from malignancy will develop at least one endocrine disorder into adulthood. With regard to the role of endocrine disorders on the quality of life in children rescued from malignancy, the aim of this study was to evaluate the prevalence of endocrine complications in survivors of childhood cancer. **Method:** A cross sectional study was done on 72 survivors of childhood cancer patients 2–18 years-old, all recruities were under follow up in pediatric oncology clinic of Tabriz children's hospital during last ten years. Age, sex, type and site of malignancy and medications were recorded. After clinical examination, Blood samples were sent to the reference laboratory for the study of endocrine function. Brain MRI, bone age, ultrasound of the gonads, bone mineral density, GH stimulation test and glucose tolerance test were done on a case by case basis. **Results:** The mean age of patients, at the time of the study and diagnosis of malignancy were 11.43 ± 3.39 and 3.2 ± 1.34 years, respectively. 77.8% male and 22.2% were female. The most common malignancy was ALL (55.6%). 88.9% of patients received vincristine. 7/27 percent of the cancer survivors had at least one endocrine disorders; 8.3% had hypothyroidism, 2.7% had hypogonadotropic hypogonadism and 16.7% had impaired fasting glucose tolerance. **Conclusion:** Children rescued from cancer are at high risk for endocrine disorders, especially thyroid and gonadal dysfunction and impaired glucose metabolism. With early diagnosis and treatment can reduce mortality rate in vulnerable individuals.

P2-P720

Familial Williams Syndrome

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Background: Williams Syndrome (WS) is a multisystemic genetic syndrome, which includes characteristic appearance of "elfian face", growth retardation, mild mental retardation, hypersociality, infantile hypercalcemia, and other endocrine, cardiovascular, and urinary abnormalities. WS is caused by the microdeletion of chromosome 7q11.23; it is usually sporadic but rare autosomal dominant familial cases have been reported in the literature. We present a boy and his mother with WS. **Case report:** 12-month-old boy was admitted to the pediatric clinic with complaints of fever, vomiting, constipation, and fatigue for one week. He was referred to our pediatric endocrinology clinic after laboratory results revealed hypercalcemia (calcium (Ca): 15.8 mg/dL). His weight was 7.5 kg (<3p), his height was 70 cm (75p), and his head circumference was 45 cm (10p). Physical examination revealed prominent forehead, sunken nasal bridge, long philtrum, prominent lips, and periorbital puffiness. There was 3/6 systolic murmur, which is best heard in the pulmonic valve area. After patient was admitted to the pediatric ward, hydration and intravenous furosemide treatment were initiated. On the second day of admission, serum Ca was measured 20 mg/dL and intravenous pamindronate was added to treatment. Because of infantile hypercalcemia and typical facial appearance, WS was suspected. Echocardiography revealed peripheral pulmonary stenosis. Abdominal ultrasound examination was normal. His mother's facial appearance was similar to her son's with prominent features of elfian face. Genetic analysis of both patient and mother revealed microdeletion of chromosome 7q11.23 which confirmed the diagnosis of Familial WS. **Conclusion:** In conclusion, WS is a multi-system disorder that primarily affects the cardiovascular system. General anesthesia and sedation are risky for pediatric WS patients because of craniofacial deformities that make it

challenging to open airway and increased risk of myocardial ischemia, which can frequently lead to death. Although the syndrome is rarely vertically transmitted, suspected family members should be examined for chromosomal microdeletion.

the first pediatric case of MEN1 with two synchronous pancreatic adenomas.The genetic confirmation of diagnosis of MEN1 is mandatory to assess other family members for the presence of the mutation, to monitor regularly for potential endocrine problems and to avoid unnecessary work-up due to "phenocopy".

P2-P721

Stanazolol Abuse: Diagnostic Dilemma in an Adolescent with Persistent Hypoglycemia

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Background: Multiple endocrine neoplasia (MEN)1 is a rare autosomal dominant disorder with primary hyperparathyroidism, enteropancreatic neuroendocrine tumors and anterior pituitary adenomas. **Patient:** A16-yr-old male was referred to our center due to recurrent seizures. Family history was significant for maternal death due to metastatic adenocarcinoma of the lung,paternal history of low-grade liposarcomas and nephrolitiasis. Physical examination was normal, with a well-built, muscular adolescent. Biochemical tests revealed venous glucose: 24 mg/dl, cortisol: 18 μg/dl, growthhormone: 13 ng/ml, insulin: 8 μU/ml, Cpeptide: 1.34 ng/ml; consistent with hyperinsulinism.Anti-insulin antibodies were negative.Serum liver enzymes and creatine kinase levels were high. Extensive work-up for inborn errors of metabolism was normal. Thin-slice pancreas CT and MRI were normal. On further questioning, the patient admitted receiving stanazolol to strengthen his muscles. Liver enzymes andCK levels subsided back to normal ranges within 2 weeks after cessation of stanozolol. Hypoglycemia did not recur on 200 mg diazoxide/day. Biochemical evaluation also revealed primary hyperparathyroidism. Parathyroid scintigraphy revealed an adenoma in the inferior right parathyroid gland. Upper gastrointestinal endoscopic ultrasound revealed two lesions in the corpus and tail of the pancreas. Serum prolactin levels and pituitary MRI were normal. DNA sequence analysis of menin gene revealed a novel "pW183S" heterozygous deletion. The same mutation was found in his father and his14-year-old brother, who had asymptomatic primary hyperparathyroidism. Distal pancreatectomy revealed two adenomatous masses (1.1 cm and 1.4 cm):an insulinoma and a non-secretory adenoma. **Conclusions:** Our case emphasizes the need to question drug abuse in adolescents presenting to clinics. This is

P1-P722

Role of the Metabotropic mGlu5 Glutamate Receptor in the Initiation of Puberty and Reproduction in Female Mice

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Background: The neuroendocrine mechanisms of the initiation of puberty are still incompletely deciphered. Accumulating data indicate a main role of the glutamate system in regulating hypothalamic GnRH. However, the underlying neurobiological mechanisms are yet poorly investigated. Mice lacking metabotropic mGlu5 receptors (mGluR5) show sever unexplained infertility. **Objective and hypotheses:** We aimed in the present study to analyze the specific role of mGluR5 in the initiation of puberty and reproduction in mice. **Method:** Sexual maturation of mGluR5 knockout (KO) and wildtype littermates was investigated by recording in vivo vaginal opening (VO) and estrous cycles (using vaginal smears) and uterine weight after sacrifice. Further we investigated the reproductive performance (total number of pups born per female) and serum gonadotropin hormone (assessed by magnetic bead immunoassay) in mGluR5 KO and wildtype females. All experiments were approved by the German Committee on Animal Care. **Results:** mGluR5 KO mice showed markedly delayed puberty, as determined by time of VO (32.54 $\pm$ 0.57 days in mGluR5 $-/-$ mice, $n=13$; 29.76 $\pm$ 0.55 days in wildtype mice, $n=29$, $P<0.05$), first estrus (52.4 $\pm$ 1.47 days in mGluR5 $-/-$ mice, $n=5$; 34.5 $\pm$ 2.23 days in wildtype, $n=6$, $P<0.001$) and uterus weight (7.63 $\pm$ 0.58 mg in mGluR5 $-/-$ mice, $n=8$; 14.13 $\pm$ 1.45 g in wildtype mice, $n=7$, $P<0.001$). Additionally, significant decrease in serum levels of follicle-stimulating hormone (FSH, 232.09 $\pm$ 26.37 pg/ml, $n=9$ in wildtype female, 134.91 $\pm$ 11.08 in mGluR5 $-/-$ female, $n=8$, $P<0.01$) and reduced reproductive performance (0.11 $\pm$ 0.11 pups/female mGluR5 $-/-$ mice, $n=9$; 7.79 $\pm$ 0.38 in wildtype mice, $n=19$, $P<0.001$) were recorded. **Conclusion:** These results suggest an important role of mGluR5 in the modulation of puberty onset and fertility. Our data support future research on the role of this glutamate receptor in the GnRH-mediated gonadotropin secretion and its impact on puberty and fertility.

P1-P723

Effect of Dietary Control on Pubertal Onset and Immunoreactivity of Kisspeptin and Neurokinin B in Female Offspring Rats Fed High Fat Diet During Perinatal Period

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Background: Nutrition is an important factor to regulate reproductive function. Some studies showed that high fat diet (HFD) may influence to puberty onset and irregular estrous cycles in the female rats. However, underlying regulation mechanism of nutrition on pubertal maturation and reproductive function is not well-known. Kisspeptin and neurokinin B (NKB) are an essential factor for regulation of pubertal development. **Objective and hypotheses:** In this study, we examined pubertal development and the immunoreactivity (IR) of Kisspeptin and NKB in female offspring rats fed HFD during perinatal period. Furthermore we evaluated the IR of Kisspeptin and NKB after change to normal diet (ND) in female offspring fed a HFD. **Method:** After mating, rats were randomized to control dams fed a ND or dams fed a HFD from conception until the end of lactation. Post-weaning (P15), offspring were fed a control or HFD until postnatal (P) 45 days. The offspring, which exposed to HFD, were fed ND from P45 to P85. Puberty onset was assessed by vaginal opening from P25. Immunohistochemistry of offspring brain was performed with Kisspeptin and NKB antibody at P45 and P85. **Results:** HFD during perinatal period significantly increased body weight (BW) and accelerated puberty onset of female offspring. At P45, the density of Kisspeptin and NKB-IR cells in arcuate nucleus of HFD rats was different from those of control rats ($P<005$). Interestingly, at P85, the mean BW of rats which stopped HFD were similar with those of control diet rats and there was no difference between control and HFD-stopped rats in the density of Kisspeptin and NKB-IR cells in arcuate nucleus. **Conclusion:** These data suggest that HFD during perinatal period has altered pubertal onset and IR of Kisspeptin and NKB in female offspring rats. These effects may be reversible by dietary control.

P1-P724

Estimating the Psychosocial Impact of Idiopathic Central Precocious Puberty (ICPP) in Girls Aged 6 to 8 Years: A Qualitative Study

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Background: Emotional and behavioural problems are often used in support of GnRH agonists therapy in girls with early pubertal timing. However, there is little evidence to show that CPP leads to psychological distress and whether treatment is associated with improved psychological outcome. **Objective and hypotheses:** The objective of this qualitative study was to explore the psychosocial impact of ICPP in recently diagnosed girls. **Method:** 27 girls and their parents were included until data saturation was reached. Data were collected from individual interviews and thematically analysed by an anthropologist, a psychologist and an endocrinologist. Three main themes emerged from the analysis, describing body changes, relationship with family members and peers, understanding of the condition and its treatment. **Results:** Girls' interviewees described the emotions they felt (pride or embarrassment due to breast development), the emotional situations they faced (rare bullying, embarrassment due to pubic or axillary hair, "social" benefit from pubertal changes and tall stature). They perceived CPP either as a normal condition but coming too early or as a disease requiring medical care and worried about painful injections. Mothers' interviewees revealed anxiety and fear of body changes and early menses. Mothers felt disturbed by the femininity of their daughters' body, raising the issue of early sexual behaviour and even pregnancy. They reported emotional instability and sometimes conflicting relationship with their daughters. Both parents worried about the perception of pubertal signs in the social environment of their daughters. Mothers were more prone to ask for therapy to stop pubertal progression than fathers. **Conclusion:** Emotions varied widely among CPP girls and their parents. Thus, considering emotions to justify treatment is hazardous. These data will allow the creation of a tool to assess the psychosocial functioning of patients and families. Such an instrument is needed to improve decision making on treatment in this context.

P1-P725

Metabolic and Pubertal Alterations in Children with Narcolepsy-Cataplexy

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Objective: To study the effect of orexin deficiency on metabolic and pubertal characteristics in narcoleptic children, we compared the metabolic and pubertal alterations between 15 children with narcolepsy with cataplexy (NC) and 15 control children matched for age, body mass index (BMI) z score. **Method:** Narcoleptic data were collected from the Reference

Center for Narcolepsy and control common obese data from the department of pediatric endocrinology in Mother-Children's Hospital in Lyon, France. Narcoleptic patients underwent clinical interview, polysomnographic recordings, and human leukocyte antigen typing. Height, weight, BMI, waist circumference, arterial blood pressure and Tanner pubertal stage were evaluated in both children groups. Plasma lipid and glucose profiles were analyzed. When an altered pubertal development was clinically suspected, plasma concentrations of hypothalamic-pituitary-gonadal axis hormones were determined. **Results:** In this study, all the narcoleptic children had cataplexy, HLA DQB10602 and were obese. Both narcoleptic and obese control children were 12.5 years (5–17), 50% male, had a median BMI 27.6 kg/m^2 (21–41) and BMI z score 3.6 SD (2.5–5). 73% of narcoleptic children had metabolic syndrome compared to 11% in control obese ($P=0.004$). Seven narcoleptic children had insulin resistance with an increased HOMA-IR index and 8 showed hepatitis steatosis. None of the common obese children had elevated HOMA-IR ($P=0.04$) and only one boy showed hepatitis steatosis ($P=0.008$). In the narcoleptic group: two girls and one boy had advanced puberty and three girls and two boys had precocious puberty. In the common obese children group: only one girl and one boy had advanced puberty (NS), none had precocious puberty ($P=0.02$). **Conclusion:** BMI-independent metabolic and pubertal alterations in NC children suggest that orexin-A influences the etiology of this phenotype. A careful pubertal and metabolic follow-up of these patients is mandatory as well as tailored therapeutic management.

P1-P726

Time Course of Central Precocious Puberty Development Caused by an MKRN3 Gene Mutation: A Prismatic Case

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Background: Loss-of-function mutations in the imprinted gene MKRN3 represent the most common known genetic defects associated with central precocious puberty (CPP). The penetrance of these mutations remains to be established. To date, all reported individuals with MKRN3 mutations were already in puberty or postpubertal and were identified retrospectively. **Objective and hypotheses:** To report the first case of a prepubertal child with an *MKRN3* mutation who was followed prospectively and developed CPP. **Method:** We describe the complete clinical and laboratory features of a female patient carrying an *MKRN3* mutation, detected in childhood, followed until the development of pubertal signs. **Results:** The patient was screened at the age of 4 years because of positive family history – her sister developed CPP at the age of 6 years and was found to harbor the *MKRN3* p.Pro161Argfs*16 mutation, inherited from their asymptomatic father. During close follow-up, this young girl initially developed increased growth velocity at age 6 years (9 cm/year), followed by a slightly increased basal LH level (0.4 mIU/ml) and, ultimately, clinical thelarche, with rapid progression (Tanner stage 1 to 3) between the ages of 6.3 and 6.7 years, when the LH level became clearly pubertal (0.9 mIU/ml). In the context of a loss-of-function *MKRN3* mutation and a positive family history, these features established the diagnosis of CPP and supported the initiation of treatment with GnRH analog, with complete regression of the thelarche after 6 months of therapy. The absence of significant bone age advancement, of pubic or axillary hair, or of behavioral or social problems at the diagnosis could be ascribed to the early diagnosis. **Conclusion:** The identification of carriers of *MKRN3* mutations may contribute to early diagnosis of CPP, facilitating treatment decisions and guiding genetic counseling and prompt intervention in familial cases. This case deepens the available information on the penetrance and clinical characteristics of *MKRN3* mutations, and illustrates how genetic testing can be useful in the clinical setting.

P1-P727

Changes of Serum AMH and Inhibin B Levels in Girls with Central Precocious Puberty before and During Treatment with GnRH Agonists

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Background: In girls with central precious puberty (CPP), the hypothalamic-pituitary-gonadal axis is prematurely activated. If the girl is treated with GnRH agonist (GnRH-a), gonadotropins levels become suppressed. **Objective and hypotheses:** We aimed to evaluate whether serum antimu llerian hormone (AMH) and inhibin B levels are affected in girls with CPP and whether pituitary suppression by GnRH-a affects serum AMH and inhibin B levels. **Method:** Thirty-six girls who were diagnosed with CPP by GnRH stimulation test followed during GnRH-a treatment. We analyzed serum AMH and inhibin B levels before, 6 and 12 months after initiation of treatment. To investigate whether AMH and inhibin B levels were affected in girls with CPP, baseline levels were compared with levels in age-matched healthy girls ($n=35$). **Results:** Before treatment, serum AMH levels (mean$\pm$S.D.) in girls with CPP showed no significant difference compared with levels in controls (7.5 ± 6.8 vs 7.1 ± 2.4 ng/mL, $P=0.742$). However, serum inhibin B levels in girls with CPP were significantly higher than that in controls (66.7 ± 51.4 vs 16.4 ± 7.9 pg/ml, $P<0.001$). After 6 months of treatment, AMH declined to 5.3 ± 3.7 ng/ml ($P=0.016$) and inhibin B also decreased to 37.8 ± 29.4 pg/ml ($P<0.001$). The AMH and inhibin B levels were more suppressed after 12 months of treatment (AMH: 4.4 ± 3.2 ng/ml, $P<0.001$, inhibin B: 22.5 ± 19.8 pg/ml, $P<0.001$). At baseline, serum AMH levels were not correlated with basal LH, basal FSH, peak LH, peak FSH, Estradiol and inhibin B levels. **Conclusion:** Our results suggest that the partial suppression of AMH by GnRH-a treatment is mediated by direct ovarian

suppression, not by pituitary suppression. Further studies including the result after discontinuation of treatment are needed to prove these findings.

P1-P728

FGFR1 Loss-of-Function Mutations of in Three Japanese Patients with Isolated Hypogonadotropic Hypogonadism and Split Hand/Foot Malformation

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Background: Heterozygous loss-of-function mutations of FGFR1 are known to cause Kallmann syndrome (KS) and isolated hypogonadotropic hypogonadism (IHH). Furthermore, recent studies have also indicated that heterozygous loss-of-function mutations lead to IHH and split hand/foot malformation (SHFM). **Objective and hypotheses:** The objective of this study was to examine *FGFR1* in three Japanese patients with IHH and SHFM. **Method:** This study consisted three Japanese patients (cases 1–3) with IHH and SHFM. Case 1 was a 3-month-old boy with micropenis, low serum LH (<0.1 mIU/ml) and testosterone (<0.03 ng/ml) at mini-puberty, and right split hand. Case 2 was a 17-year-old boy with no pubertal development, low serum LH (<0.1 mIU/ml) and testosterone (<0.03 ng/ml), and bilateral split hands and feet. Case 3 was a 34-year-old female with primary amenorrhea, low serum LH (0.4 mIU/ml) and E2 (<10 pg/ml), and left split hand. We performed direct sequencing for *FGFR1* coding regions and their flanking splice sites, luciferase analysis for missense mutations, and RT-PCR based sequence analysis and *in silico* analysis for a splice donor site mutation. **Results:** Direct sequencing identified two heterozygous missense mutations (a previously reported p.G97S in case 1 and a novel p.R744T in case 2) and a novel heterozygous splice donor site mutation (IVS12+1G>T in case 3). The two missense mutations had drastically reduced luciferase activities, without a dominant negative effect. The splice donor site mutation was found to have yielded a small amount of mRNA skipping exon 12 (p.Ser518_Gly555delinsCys), and was predicted to have produced two aberrant mRNAs that satisfy the condition for nonsense-mediated mRNA decay, by using an alternative splice donor site (p.G555fsX630) and by escaping splicing at the IVS12 exon-intron junction (p.G555fsX571). **Conclusion:** The results provide further support for the notion that heterozygous loss-of-function mutations of *FGFR1* cause IHH with SHFM.

P1-P729

Clinical and Mutational Spectrum in Slovenian Patients with Hypogonadotropic Hypogonadism

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Background: Congenital hypogonadotropic hypogonadism (HH) is a rare but clinically and genetically heterogeneous disease characterized by an absent or incomplete puberty and infertility. The association of HH with hyposmia or anosmia is defined as Kallmann syndrome. Molecular genetic testing of HH is valuable, as it can prompt the treatment in adolescence. **Objective and hypotheses:** To identify causative variants in genes associated with HH in a cohort of 13 Slovenian patients. **Population and Method:** 13 subjects (12 males, 1 female) with congenital HH were included. Targeted next generation sequencing (NGS) of 24 genes known to be associated with HH was used to identify causative genetic variants that were subsequently confirmed by Sanger sequencing. **Results:** Three males had normosmic HH, all other patients had Kallmann syndrome, two of those in association with characteristics of CHARGE syndrome. Of the subjects with normal *CHD7* gene, four subjects had other associated disorders including colour blindness, schizophrenia, sensorineural hearing loss and hypocalciuric hypercalcemia caused by a *CASR* gene mutation. Nine mutations in six genes (*PROK2, GNRHR, PROKR2, FGFR1, CHD7* and *FGF8*) were identified in 9 out of 14 patients (64%), each of them carrying a single heterozygous mutation in a single gene. Among them, three variants namely *PROK2* c.171_172delTT (p.Ile57MetfsTer17), *FGFR1* c.196T>C (p.Typ66Arg) and *CHD7* c. 5050+1G>T have not yet been described. Of the remaining five patients two were part of the pedigrees with multiple affected members, which suggests an unidentified genetic cause. **Conclusion:** NGS enables fast and reliable identification of causal mutations in several genes related to HH simultaneously. Presented subject group with HH was genetically very diverse and the results expand the spectrum of mutations implicated in HH. By examining known genes oligogenicity was not identified and variable penetrance demonstrated in some pedigrees remained unexplained.

P1-P730

MKRN3 Mutations and Central Precocious Puberty

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Background: Central precocious puberty (CPP) results from premature activation of the hypothalamic-pituitary-gonadal axis and increasing evidence suggests a genetic origin. Premature activation of the GnRH secretion in CPP may arise either from gain-of-function mutations of the *KISS1* and *KISS1R* genes or loss-of-function manner mutations of the *MKRN3* gene leading to MKRN3 deficiency. **Objective and hypotheses:** To identify loss-of-function mutations in the makorin RING-finger protein 3 (*MKRN3*) gene or gain-of-function mutations in the *KISS1* and *KISS1R* genes that lead to CPP. **Method:** We investigated potential sequence variations in the intronless *MKRN3* gene and the *KISS1 and KISS1R* genes by Sanger sequencing in a cohort of 24 index girls with CPP. Four of these 24 index cases reported familial history of CPP. A phenotype-genotype correlation was evaluated between the *MKRN3* mutated and non mutated patients. **Results:** Mutational analysis of the *KISS1 and KISS1R* genes did not identify any genetic defect. *MKRN3* mutations however were identified in one sporadic and two familial cases of CPP. The novel missense g.Gly312Asp (p.G312D) and the novel p.Glu298Term (p.E298*) nonsense mutation were respectively identified in 2 nonrelated familial index cases with CPP. Additionally, in a sporadic case with CPP the known frameshift p.Met268ValfsTer23 (p.M268Vfs*23) was found. The imprinted novel *MKRN3* mutations identified in this study were also identified as expected in the unaffected fathers following an imprinted mode of inheritance. The pathogenicity of the alterations at the protein level was verified via i*n silico* structural modeling. Age at the onset of puberty was similar among patients with *MKRN3* mutations and was earlier compared to those without *MKRN3* mutations. **Conclusion:** The identification of mutations in the *MKRN3* gene in children with a family history of CPP further supports the role of MKRN3 in the onset of pubertal development and supports the fundamental role of this gene in the suppression of the hypothalamic GnRH neurons. Therefore, *MKRN3* gene analysis should be considered as an additional critical tool for the diagnosis of familial CPP.

P1-P731

Precocious Puberty in Patients with Primary Adrenal Insufficiency due to Melanocortın Receptor 2 Mutation

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Background: Precocious puberty has a complex and polygenic etiology. To describe genetic factors affecting onset and regulation of puberty and pathophysiology of precocious puberty, further studies are needed. Although, it is reported that ACTH receptor *MC4R* has impact on premature adrenarche, *MC2R* is expressed in the adrenal cortex and has a major role on the control of hypothalamo-pituitary-adrenal cortex. Melanocortin signaling system is reported to have leptin mediated affect on the regulation of GnRH neuron activity and has an important role in the onset of puberty and fertility. **Objective and hypotheses:** To evaluate the early onset puberty of patients with primary adrenal insufficiency due to Melanocortin receptor 2 (*MC2R*) gene mutation. **Methods and patients:** Four patients (3M,1F) with primary adrenal insufficiency, two of whom are siblings were included in the study. Age of diagnosis was between 6 days-11 months and follow up period was 7.6–20.4 years. The female patient had also congenital hypothyroidism due to dyshormonogenesis and thyroid hormone levels were in normal ranges with L-thyroxine replacement. All the patients were from consanguinous families and there was no family history of precocious puberty. All the patients were term and appropriate for gestational age. Patients had severe *MC2R* mutation(c..560delT,p.V187Afs*29) causing adrenal insufficiency In two brothers and the third male patient central precocious puberty started at 8.5, 7.4 and 9.5 years, respectively. Female patient's central precocious puberty was detected at the age of 8.5 years. LH, T (male)/Estradiol (female) levels of the patients were in pubertal ranges. Puberty had rapid progression in one of the brothers and GnRH analogue was started when he was 11 years old. Precocious puberty was newly detected in his brother and progression is still at follow-up. The third male patient had also completed pubertal progression and his final height was −2.6 SDS (Target height SDS: −1.0). Female patient's age of menarche was 11 years old and she had completed puberty. **Conclusion:** We report that ACTH receptor-*MC2R* gene mutation and onset and regulation of puberty may be related. We also recommend that these patients must be closely followed for precocious pubertal development.

P1-P732

Association between Estrogen Receptor Gene Polymorphisms and Premature Thelarche

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Background: Premature thelarche (PT) is a benign, non-progressive condition defined as isolated breast development without the activation of the hypothalamic-pituitary axis. While the pathophysiology of PT remains unclear, increased sensitivity to estrogen may cause PT. **Objective and hypotheses:** The aim of this study was to investigate the association between

polymorphisms in the estrogen receptor alpha (ERα) gene and PT in girls. **Method:** In this case-control study, we examined 96 girls referred for early breast development (before the age of 8 years). The control group included healthy Korean females with normal pubertal progression. Anthropometric and hormonal parameters were measured and PvuII and XbaI ERα gene polymorphisms were evaluated by PCR. Out of the 96 girls, all coding exon and exon-intron boundaries of ERα were sequenced from the DNA of 46 girls. **Results:** There was no significant difference in the distribution of PvuII and XbaI polymorphisms between patients and controls. However, the carriers of XbaI polymorphisms had more advanced Tanner stage than did the non-carriers. Also, four ERα gene polymorphisms were previously identified, but these polymorphisms had no clinical significance. **Conclusion:** No association was found between the ERα gene polymorphisms and PT in girls. However, XbaI polymorphisms may contribute to early breast budding. Further studies are needed to validate the role of ERα gene polymorphisms in PT.

P1-P733

The Influences of Circulating Leptin, Kisspeptin, and Neurokinin B Levels to Precocious Puberty in Obese Girls

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Background: Leptin has a major role in the metabolic gating of pubertal maturation. Kisspeptin is an essential gatekeeper of puberty. Neurokinin B (NK B) is not widely known in the precocious puberty (PP) but it is coexpressed with kisspeptin in the arcuate nucleus and synchronizes the pulsatile secretion of kisspeptin. **Objective and hypotheses:** Leptin, kisspeptin, and NK B are influenced by energy balance and metabolic status has a clear impact on the timing of puberty. Therefore, we aimed to investigate the relationships of circulating leptin, kisspeptin, and NK B levels with PP in overweight/obese girls and to evaluate the usefulness of these serum markers in the initiation of puberty. **Method:** One hundred forty PP girls aged 6–9 years and 38 age-matched normal control (NC) girls were enrolled. PP girls were classified according to their body mass index (BMI) as follows: normal weight (NW), 5 percentile ≦ BMI z-score < 85 percentile; overweight/obese (OW/OB), 85 percentile ≦ BMI z-score. All NC girls were normal weight. Chart reviews were done for anthropometric data and biochemical results. Serum leptin, kisspeptin, and NK B levels were measured by ELISA or EIA kits. **Results:** Median serum leptin levels were 2.2 ng/ml in NC girls, 3.8 ng/ml in NW PP girls, and 4.8 ng/ml in OW/OB PP girls and those differences were significant ($P<0.001$). Serum leptin levels had positive correlation with BMI z-score regardless of pubertal status ($r=0.383$, $P<0.001$). Serum kisspeptin levels of NW PP girls (0.57 ng/ml) were lower than OW/OB PP girls (0.64 ng/ml, $P=0.039$) but those were not differ from NC girls (0.57 ng/ml). Serum NK B levels were not different among three groups. Serum leptin, kisspeptin, and neurokinin B levels were not related to basal LH/FSH/estradiol and peak LH/FSH levels. Considering as a diagnostic marker, serum leptin levels had no priority than serum IGF-1 level (AUC of leptin = 0.725; AUC of IGF-1 = 0.928; $P=0.001$). **Conclusion:** Serum leptin levels showed significant correlation with PP and obesity as they are known so far, but it is hard to use commercially compared to conventional indices. Meaningless results of serum kisspeptin and NK B levels may be because their serum levels do not reflect their tissue concentations proportionately.

P1-P734

Pseudopuberty in a Young Girl with Adrenocortical Carcinoma During Mitotane Therapy

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Background: The Adrenocortical Neoplasm (ACN) is a rare condition in childhood (0,3 cases/1000000). In paediatric age, ACN at stage 1 is treated by complete adrenalectomy, while at stages 2 and 3 surgery is followed by adjuvant treatment with Mitotane (M). Chemotherapy is required in metastatic cases (stage 4). **Objective and hypotheses:** M is an adrenal cytotoxic agent which has both adrenolytic action on ACN cells and inhibition on steroid hormone synthesis apparently without cellular destruction. Furthermore M it seems to modify the peripheral metabolism of steroid. It was been hypothesized that the M may also have a partial suppressive effect on pituitary ACTH-secreting cells. Gynecomastia (G) was described as side effect of M in men and in one little boy. It was associated with increased binding capacity of SHBG in the plasma compartment modulating hormonal disposal for target cells. **Method:** In the 2008–2016 period we observed 8 patients affected by ACN (3 males and 5 females, aged 0–32 months at diagnosis). Histologic results: malignant lesion in 5 cases, neoplasm with uncertain behaviour in 2 cases, and adenoma in 1 patient. All children affected by malignant or uncertain lesions underwent surgery, followed by M adjuvant treatment. One child was also treated with chemotherapy due to advanced disease (stage 4). **Results:** We report a young girl, affected by ACN with uncertain behaviour (stage 2), who, at the age of 2.5 years, underwent M therapy developing adrenal insufficiency, treated with hydrocortisone, and progressive telarche. The full hormonal testing (LH-RH Test, basal 17-Beta-estradiol, progesterone, adrenocortical hormones and their precursors) showed a normal pre-pubertal panel. The telarche completely reverted after the stop of M therapy (2 gr/m^2 per daily for 1 year). **Conclusion:** To our knowledge this is the first reported case of abnormal breast development in a young female child treated with Mitotane for adrenocortical neoplasm.

P1-P735

Prolactinomas in Children and Young Adults: 10 Year Experience in a Tertiary Regional Paediatric - Young Adult - NeuroEndocrine Surgical Centre

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Background: Prolactinomas are rare in the prepubertal and adolescent age group. Therapeutic approaches are guided by experience from treating adults. Few series have been reported. **Objective:** Retrospective analysis of presenting features, treatment and outcomes in young patients presenting to a Tertiary Endocrine Service (total referral population ~3.5 million) managed jointly between Paediatric and Adult Endocrine and Neurosurgical services. **Patients and Methods:** Patients presenting to the Paediatric/Adolescent Endocrine & Neurosurgical services under 20 year age with Prolactinoma from 2005–2015. Clinical records reviewed and outcome to latest follow-up (2–10 years) is reported. **Results:** 9 patients (5 Female) presented age 13–19 years. Symptoms were: Menstrual disturbance (4), Galactorrhoea (3 F), Headache 4 (3 macro-/1 micro-adenoma), Visual field loss (2), Gynaecomastia (1), Weight loss (1), Hirsutism/PCOS (1), Pubertal growth delay (1). MRI defined microadenoma (<10 mm intrasellar lesion) in 4 patients (basal Prolactin levels 2800 – 5200 mIU/l) and macroadenoma (3 haemorrhagic) in 5 patients (basal Prolactin levels 3800, 4850, 7600, 45000 & 130,000 mIU/l). 3 macroadenoma patients had co-existing pituitary hormone deficiencies (ACTH/TSH/GH) and one had GH hypersecretion. No patients had family history of Multiple Endocrine Neoplasia. All patients received initial dopaminergic agent treatment with Cabergoline under shared Paediatric/Adult Endocrine Services, with reduction in Prolactin, variable tumour shrinkage and no side effects. Microadeomas have come under stable control (1 patient off treatment). 4 patients with macroadenoma underwent trans-sphenoidal surgery, 3 for tumour debulking and 1 for persistent, severe headache despite tumour shrinkage to within the sella. One of the two patients with giant macrodenoma (both male) proceeded to chemotherapy (Temozolomide) and radiotherapy with successful outcome to date. **Conclusion:** Paediatric and Young Adult patients with Prolactinomas benefit from being managed in shared/Transitional care with the Adult Endocrine and Neurosurgical Teams.

P1-P736

Cut-Off Values for Nocturnal Salivary Testosterone to Enable Detection of Early Puberty

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Background: In boys with suspected delayed puberty, serum testosterone is used for the evaluation of gonadal function. It is known that early in puberty testosterone levels show a sleep wake rhythm, with nocturnal levels increasing ahead of daytime levels. To evaluate the onset of puberty, the use of salivary testosterone would be an appealing alternative to serum analysis as it is non-invasive and allows multiple nocturnal sampling. Moreover, it is thought that salivary testosterone reflects the free fraction of plasma testosterone. To the best of our knowledge, to date there are no publications regarding cut of values for nocturnal salivary testosterone using Liquid Chromatography Tandem Mass Spectometry (LC-MS/MS). **Objective and hypotheses:** Our study aimed to establish cut-off values of salivary testosterone in preadolescent boys and adult men at 03.00 a.m. and 08.00 a.m. **Method:** Salivary testosterone levels were determined in twenty healthy preadolescent boys, in the age of six until nine years, and nineteen adult men in the age group eighteen until forty years, at 03.00 a.m. and 08.00 a.m., using LC-MS/MS. **Results:** Salivary testosterone levels in preadolescent boys were median 47 pmol/L, with a reference interval of 14 – 127 pmol/L (p2.5 – p97.5) at 03.00 a.m. and at 08.00 a.m. median 49 pmol/L, with a reference interval of 10 – 155 pmol/L (p2.5 – p97.5). In adult men levels of salivary testosterone were median 260 pmol/L, with a reference interval of 84 – 540 pmol/L (p2.5 – p97.5) at 03.00 a.m. and at 08.00 a.m. median 300 pmol/L, with a reference interval of 90 – 1480 pmol/L (p2.5 – p97.5). As these reference values overlap, cut-off values were defined, being 70 and 170 pmol/L. Based on these cut-off values 81% of samples can be correctly classified as being pre- or post pubertal. **Conclusion:** We established cut-off values for nocturnal salivary testosterone to evaluate pubertal status.

P1-P737

Screening of PROP-1, LHX2 and POU1F1 Mutations in Patients with Ectopic Posterior Pituitary Gland

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Background: Ectopic posterior pituitary gland (EPP) is characterized by an abnormal pituitary stalk and hypoplasia of the anterior hypophysis. The genetic mechanisms involved in the development of EPP remain uncertain. **Objective and hypotheses:** The aim of this study is to determine whether mutations in the three genes, PROP-1, LHX2, and POU1F1, are associated with the risk for and the characteristics of EPP. **Method:** In the Endocrinology Outpatient Clinic of Dr. Behcet Uz Children's Hospital, 27 patients with EPP were submitted to sequencing analyses of the PROP-1, LHX2, and POU1F1 genes. **Results:** Growth hormone, thyrotropin, corticotropin, gonadotropin, and vasopressin deficiency were observed in 22 (81.5%), 23 (85.2%), 17 (63%), 14 (51.9%), and two (7.4%) patients. Thirteen

patients (48.1%) presented with hyperprolactinemia. Fourteen patients (51%) had a history of birth dystocia, and 12 cases (42.1%) had a history of breech presentation. Central nervous system abnormalities in EPP patients included five cases with corpus callosum agenesis, one case with schizencephaly, and one case with Chiari type 1 malformation. We identified a homozygous p.S109* mutation in exon 2 in one male patient with EPP and two different PROP1 gene polymorphisms (A142T or c.109+3 G>A polymorphism) in thirteen patients. **Conclusion:** Our results suggest that PROP1 gene abnormalities might explain the genetic mechanisms involved in the development of EPP.

Keywords: PROP 1 mutation, ectopic posterior pituitary gland, ectopic neurohypophysis, multiple pituitary hormone deficiency

P1-P738

Oxytocin Deficiency is Associated with Hyperphagia and Weight Gain in Hypothalamic and Common Obesity: A First-in-Humans Proof-of-Concept Study

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Background: Hypothalamic obesity (HyOb) is a rare form of treatment-resistant morbid obesity associated with congenital or acquired hypothalamic damage. Its pathophysiology has been attributed to hyperphagia and hyperinsulinaemia. The wider roles of oxytocin (OXT) in regulating appetite and weight have recently emerged in animal and human studies, but there is no human evidence that hypo-oxytocinaemia contributes to weight gain. **Hypothesis:** Hypo-oxytocinaemia is associated with an increase in appetite and weight in HyOb. **Method:** Fasting and oral glucose-stimulated OXT concentrations in HyOb and lean (HyLean) children with hypothalamic damage were determined by internally validated ELISA comparing them to age-matched common obesity (Ob) and lean controls. Hyperphagia was quantified using the Dykens' Hyperphagia Questionnaire Score (DHQS). **Results:** Patients (42 HyOb, 15 HyLean, 22 Ob, 14 Lean; 52.7% male) were of median age 11.8 (8.6–14.4) years with a BMI SDS of +2.8 (+2.5 – +3.1) and +1.0 (−0.1 – +1.7) in the obese and lean groups respectively. HyOb patients had a higher DHQS compared to lean controls (25 (15–34) vs 16 (11–21), $P=0.009$), but not HyLean (22 (14–30), $P=$NS) or Ob (23 (17–28), $P=$NS) patients. Although not statistically significant, fasting OXT concentrations were lower in both HyOb (98.5 (78.9–123.1) pg/ml) and Ob (101.8 (82.3–125.8) pg/ml) patients compared to HyLean (145.2 (80.1–169.3) pg/ml) and lean (133.1 (71.6–157.9) pg/ml) controls ($P=$NS for all comparisons). OXT concentrations were negatively correlated with DHQS ($\rho=-0.3$, $P=0.02$) and not stimulated by an oral glucose load. **Conclusion:** This study supports the role of OXT as an anorexigen, suggesting that hypo-oxytocinaemia is common to all human obesity. Hyperphagia is not unique to HyOb, is associated with hypo-oxytocinaemia and is present in all forms of obesity. Further recruitment to power this study ($n=120$) and paediatric trials of OXT supplementation will help confirm this theory and determine its efficacy in treating childhood obesity.

P1-P739

Evaluation of Puberty in Children with Sickle Cell Anemia: A Case Control Study in Yaounde, Cameroon

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Background: Puberty is reported to be impaired in children with Sickle cell Anemia (SCA). Studies about this topic are rare in Sub-Saharan region **Objective and hypotheses:** Assessment of pubertal development of children with SCA compared to healthy children in Mother and Child Center, CHANTAL BIYA Foundation. **Method:** We matched a group of 64 children with SCA (26 males, 38 females) with 94 healthy controls aged of 8–17 years old. Clinical features as height, weight, body mass index, body composition and sexual maturation were assessed. Hormonal measurements were performed for Follicle Stimulating Hormone, Luteinizing Hormone and sexual steroids (estrogens/testosterone) at Robert Debré application Hospital in Paris with radio-immunologic assays. A logistic regression analysis was performed to determine relationship between severity of disease and sexual maturation. **Results:** Delayed puberty was reported in 11.54% of boys and 10.6% of girls with SCA. Median age of menarche was delayed to 3 years compared to controls. SCA patients had stunting, low body mass index, free fat mass and lean body mass compared to controls. Abnormal levels of gonadotropins and sexual steroids were reported in cases. Delayed sexual maturation was associated with frequency of painful crisis and number of blood transfusion. **Conclusion:** Delayed puberty was frequent in children with sickle cell Anemia. Sexual maturation was affected by severity of the disease.

P1-P740

Standard Triptorelin Therapy May Not Fully Suppress Pubertal Progress in Adolescents with Gender Dysphoria

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Background: Adolescents presenting with persistent gender dysphoria (GD) may undergo pubertal suspension via the use of

GnRH analogues such as triptorelin (Gonapeptyl Depot) to allow further consideration of the dysphoria. Locally, a standard monthly dose of this drug is administered for an initial target duration of 12 months prior to re-assessment. **Objective and hypotheses:** The need to obtain full gonadotrophin and sex hormone suppression to ensure accurate decision making is unknown. Should the standard dose be individualised? **Method:** Serum LH, FSH, testosterone and oestradiol were measured in 74 adolescents with GD (15–18y) before and after 6 months triptorelin 3.75 mg 4 weekly. Results are presented as medians and undetectable measurements were analysed using the assay's limit of quantitation. **Results:** 25 natal males & 49 natal females were treated initially for a mean of 7 months (range 3–13). Endogenous gonadotrophins were significantly ($P<0.0001$) reduced in both males (LH by 88%, FSH 64%) and females (LH 94%, FSH 42%). LH was completely suppressed in six females but both LH and FSH were measurable in all other instances. Post-treatment serum testosterone in males was reduced overall by an average of 94% and was undetectable in five patients. In females, testosterone was measurable in 33 of 42 individuals. Serum oestradiol was undetectable in 77% of patients post-treatment but was measureable in one male and 14 females ($\leq$101 pmol/L). There was no correlation between age, duration of treatment, or body surface area with the response to triptorelin. **Conclusion:** LH, FSH, testosterone, and oestradiol were all significantly reduced following initial triptorelin treatment. However, LH and/or FSH remained detectable in nearly all adolescents suggesting continued gonadal stimulation. This is supported by measurable testosterone, but not oestradiol, in most subjects. The effect of measurable sex hormones on long term decision making is unclear. The lack of direct correlation with auxologic measurements means greater attention to individual treatment responsiveness is required.

P1-P741

Serum Anti-Mullerian Hormone Levels in Precocious Puberty Girls According to the Timing of GnRH Agonist Treatment

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Background: Few studies have investigated the long-term effects of gonadotropin releasing hormone (GnRH) agonist treatment on reproductive function. **Objective and hypotheses:** We assessed ovarian function by analyzing serum anti-mullerian hormone (AMH) levels in central precocious puberty (CPP) girls according to GnRH agonist-treatment timing. **Method:** Our study included 505 CPP girls subdivided into five groups based on the timing of GnRH agonist treatment: before treatment ($n=98$), 3 months after initiation ($n=103$), 12 months after initiation ($n=101$), 24 months after initiation ($n=101$), and 6 months after discontinuation ($n=102$). We compared serum AMH levels with 100 bone age-matched controls (before treatment; $n=55$, after discontinuation; $n=45$). **Results:** At baseline, mean AMH level in CPP girls was 5.9 ± 3.6 ng/ml. AMH levels decreased to 4.7 ± 3.2 ng/ml after 3 months of GnRH agonist treatment, and recovered after 12 months of treatment. Six months after discontinuation, AMH levels were similar to pre-treatment levels. Before and after GnRH agonist treatment, AMH levels were similar to those of bone age-matched controls. **Conclusion:** In precocious puberty girls, AMH levels according to the timing of GnRH agonist were all within the normal reference range. Our study suggested that there are no adverse effects of GnRH agonist treatment on reproductive function.

P1-P742

Precocious Puberty in Septo-Optic Dysplasia Syndrome – Presentation of 2 Cases

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Background: Septo-optic dysplasia (SOD) is a rare, congenital condition that mostly occurs sporadically, but can also be caused by mutations in HESX1, OTX2, SOX2, SOX3 genes. Symptoms of SOD include: optic nerve hypoplasia, hypopituitarism and midline brain abnormalities such as absence of septum pellucidum and/or corpus callosum. Hypopituitarism in SOD usually manifests as growth hormone deficiency followed by central hypothyroidism as well as deficiency of gonadotropines. Precocious puberty is a rare finding among patients with SOD. **Materials:** We present evaluation of SOD in two girls, at the moment aged 10.5 and 13, suffering from blindness caused by bilateral optic nerve hypoplasia and developmental delay. In both cases MRI revealed lack of septum pellucidum. Younger girl was prenatally diagnosed with midbrain arachnoid cyst requiring surgery at the age of 2 years. Both patients had hiperbilirubinemia and hypernatremia in neonatal period and infancy. Symptoms subsided once treatment of central hypothyroidism and diabetes inspidus was introduced. Endocrine evaluation excluded ACTH insufficiency. Since the first year of their life obesity, tall stature and accelerated bone age were observed despite of growth hormone deficiency. At the age of 5 years both patients presented with thelarche, at 5.5 and 8 years respectively premature menarche appeared. Central precocious puberty was diagnosed in both girls. The diagnosis was based on laboratory evidence of pubertal levels of gonadotropins in LHRH test, high levels of estradiol and accelerated bone age. Regarding rapid progression of puberty that occurred in younger patient long acting GnRH analog therapy was applied. The above treatment was withdrawn within less than 6 months because of recurrent urticaria. **Conclusion:** In most cases SOD is associated with multiple pituitary hormone deficiency, including gonadotropins. This report implicates the necessity for long-term monitoring as pituitary insufficiency may evolve over time and does not rule out precocious puberty.

P1-P743

Proton Therapy as a Promising Therapeutic Option for Children with Aggressive and Uncontrolled Pituitary Macro Adenoma: A Case Report

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Background: Non functioning pituitary macro adenoma is rare during childhood. Therapeutic options are reduced to surgery and radiotherapy. Proton therapy is a particle therapy that uses a beam of protons to irradiate the tissue with the chief advantage that as a charged particle the dose is deposited over a narrow range and there is minimal exit dose. **Objective and hypotheses:** Proton therapy is largely used in France for paediatric craniopharyngiomas irradiation and more recently for some adult pituitary adenomas. Proton therapy could be a good therapeutic option for benign tumor as pituitary adenoma in a young child to reduce side effects observed usually with conventional radiotherapy. **Method:** We report a 10 years old boy with invasive and aggressive non-functioning pituitary adenoma treated by surgery and proton therapy with more 24 months follow up. **Clinical case:** No significant familial or personal history. He was referred for a sudden lost of visual acuity and bilateral hemianopsia, but normal clinical examination (P1G1). Brain MRI showed a voluminous (3.5 cm) intra and supra sellar tumor with right cavernous sinus invasion and chiasma compression. GH and TSH deficiency were documented by endocrine testing while blood prolactin, FSH, αsubunit levels were normal. The search for gene mutations were negative for AIP, NEM1 and GNAS genes. Neurosurgeon performed partial resection twice, first and 9 months later for progression and visual defect recurrence. Histopathology studies confirmed aggressive pituitary adenoma with focal immunolabelling for FSH and αsubunit (40%), PRL $<$ 3%; P53: 3% and MIB1: 6%. Radiotherapy was then decided with proton therapy 54 Gy proposed because of the young age. From the end of treatment, as long as 24 months, we didn't observe progression on tumor size on MRI with complete visual rescue and no additional endocrine deficit. GH treatment was initiated after 1 year following with excellent catch-up growth. **Conclusion:** Non-functioning pituitary adenoma is a rare paediatric disease. Proton therapy seems a good option in replacement to conventional radiotherapy to treat it. However long-term outcome is necessary.

P1-P744

A Prospective Evaluation of Urinary Gonadotrophins for Assessment and Management of Pubertal Disorders

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Background: An increasing need for non-invasive, outpatient based investigations has necessitated a re-evaluation of urinary gonadotrophins (uGn) for assessing puberty. **Objective:** Prospective evaluation of the relationship between first morning uGn measured by immunoassay and corrected for creatinine (uLH:uCr; uFSH:uCr), and basal serum gonadotropins (sLH, sFSH) and in response to LHRH stimulation test. Prospective evaluation of uGn trend in patients receiving GnRH analogue (GnRH-a) (Decapeptyl SR, 11.25 mg, every 10–12 weeks). **Methods:** (15M) patients were evaluated for delayed puberty, 15 (1M) for suspected precocious puberty and 18 (3M) who were starting on GnRH-a. Three first-morning urine samples were collected before the stimulation test or before the GnRH-a injection. In the latter, three samples at midpoint between the injections were also collected. Data were expressed as median (range), and analyzed by SPSSv10.0 ($P < 0.05$). **Results:** The median coefficient of variation (CoV) for uLH:uCr and uFSH:uCr was 29% (0,140) and 24% (5,100), respectively. A strong correlation was detected between sLH and uLH:uCr ($r = 0.7$; $P < 0.001$) and between sFSH and uFSH:uCr ($r = 0.7$; $P < 0.001$). The median uLH:uCr for cases with a sLH peak of > 5 IU/L and < 5 IU/L was 0.12 (0.01, 0.57) and 0.02 (0.01, 0.11), respectively ($P < 0.001$). Based on receiver operator characteristics analysis, a uLH:uCr value of 0.03 IU/mmol as a cut-off would detect a sLH peak > 5 IU/L with a sensitivity of 89% and a specificity of 82%. In those on GnRHa therapy, the median uLH:uCr at 0.01 IU/mmol (0.0.14) was lower than those for cases with a peak stimulated sLH < 5 IU/L ($P = 0.03$). Median uLH:UCr and uFSH:UCr before injections was 0.01 IU/mmol (0.005, 0.043) and 0.34 IU/mmol (0.001, 0.6), respectively and at treatment midpoint was 0.01 IU/mmol (0.005, 0.042) and 0.09 IU/mmol (0, 0.42) ($P < 0.01$). **Conclusion:** UGn is a valuable, non-invasive instrument for diagnosis of early puberty. Its clinical utility in personalising GnRH-a therapy needs further exploration.

P1-P745

Constitutional Delay of Puberty or Hypogonadotropic Hypogonadism: Diagnostic Value of Inhibin B and AMH Measurements

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Background: Boys with delayed puberty represent one of the main cause for pediatric endocrine referrals. Although the majority of them have constitutional delay of growth and puberty (CDGP), it is important to identify isolated hypogonadotropic hypogonadism (IHH) for optimal management. **Objective and hypotheses:** The aim of the study was to evaluate the usefulness of inhibin B and AMH as biological markers for distinguishing between CDGP and IHH. **Method:** Observational, retrospective and monocentric study. Inclusion criteria included age older than 14 years and Tanner stage I or II. **Results:** Forty-five patients with delayed puberty were included, 30 patients with CDGP and 15 with IHH. Compared with CDGP patients those with IHH had lower inhibin B levels (76 ± 75 pg/ml vs 127 ± 63 pg/ml, $P = 0.016$), especially those with Tanner stage I (40 ± 45 pg/ml vs 100 ± 39 pg/ml, $P = 0.005$). In CDGP and IHH patients, sensitivity was 53%, specificity 90% and positive predictive value (PPV) 73% for inhibin concentration of 60 pg/ml or less. In patients with Tanner stage I, sensitivity was 70%, specificity 100% and PPV 100% for inhibin concentration of 41 pg/ml or less. Basal LH concentrations and LH response to LH-RH were significantly lower in IHH vs CDGP (0.64 ± 0.70 UI/L vs 1.20 ± 1 UI/L, $P = 0.028$ and 8.2 ± 8.8 UI/l vs 13.9 ± 6.9 UI/L, $P = 0.026$ respectively). There were no significant differences for AMH, testosterone or FSH levels. **Conclusion:** Inhibin B marker is confirmed as the best diagnostic tool to discriminate IHH from CDP in early adolescence. This new study updates the cut-off to 60 pg/ml when using new specific inhibin B reagents (from Anshlabs).

P1-P746

Prognostic Significance of the Proliferative Index Ki67 for Patients with Craniopharyngiomas

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Background: Craniopharyngioma is a benign, slow-growing epithelial tumor, in children it contributes to 5–10% of all brain tumors. Its incidence is 0.5-2 per 1,000,000 person-years. 30–50% of these tumors are recognized in childhood, most often in ages 5–14, no sex predilection is observed. It is located mainly in the sellar/parasellar region, in children adamantinomatous variant, with tendency to recur, is the most common type. Views on the usefulness of immunohistochemical examinations Ki67 in predicting recurrences are inconclusive. The examination was conducted on small group containing both children and adults, so it concerned both adamantinomatous and papillary variants. **Objective and hypotheses:** The aim of the study was to evaluate the prognostic value of Ki67 in recurrence of craniopharyngioma in children. The research was conducted on 84 patients with craniopharyngiomas (male 42, female 42). Median age at tumor diagnosis was 10,22 (2–18) years. Patients were surgically treated, 73 patients underwent total resection and the other 11 received partial resection. All cases were adamantinomatous variant. Tumor recurrence and regrowth occurred in 20 of 84 patients (23.8%), 12 after total resection and 8 after partial resection, over a period from 0.5 to 6.5 years (mean 2.28) since treatment. **Method:** All specimens were routinely stained with hematoxylin and eosin (H&E) and index of proliferation Ki67 was performed by immunohistochemistry (IHC). Mitotic rate was counted on 5 random fields in area of the greatest number of mitotic figures. **Results:** Nuclear index Ki67 varied from 0% to 20% (mean 4.1%) in patients, in which recurrences were not observed and from 0% to 20% (mean 4.2%) in patients with observed recurrence. No statistical difference between both groups has been shown. Ki67 of primary tumors was 4.8% and of recurrent tumors 5.3% (examinations were conducted on 9 tumors). **Conclusion:** Ki67 labeling indices of primary tumors did not have prognostic value for predicting tumor recurrence. Proliferative index Ki67 of recurrent tumors was insignificantly higher than that of primary tumors.

P1-P747

Etiology, Differential Diagnosis and Clinical Course of Delayed Puberty: A Single Center Experience

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Background: Delayed puberty (DP) is generally considered a benign condition. We investigated the diagnoses underlying DP and its outcome predictors. **Objective:** A retrospective chart review which included clinical and biochemical data of 174 boys and 70 girls evaluated for DP in a single tertiary care center between 2004 and 2014. **Results:** Thirty etiologies that underlie DP were identified. No markers of clinical value could be identified in the girls, whereas a history of cryptorchidism in the boys was associated with an 8-fold increase in the risk of permanent hypogonadism (positive predictive value 57%, 95% CI; 20–88). The conditions that cause functional hypogonadotropic

hypogonadism were more frequent in the boys with the growth velocity below 3 cm/yr than in those growing faster (19% *vs* 4%, $P<0.05$). The best marker to discriminate the prepubertal boys with constitutional delay of growth and puberty (CDGP) from those with congenital hypogonadotropic hypogonadism (CHH) was testicular volume (cut-off 1.1 mL with a sensitivity of 100% and a specificity of 91%), followed by GnRH-induced maximal LH (cut-off 4.3 IU/L; 100%, 75%) and basal inhibin B level (cut-off 61 ng/l; 90%, 83%). **Conclusions:** A history of cryptorchidism and slow growth velocity are two important clinical cues that help to predict the clinical course of DP in boys. In prepubertal boys, testicular size is a simple diagnostic parameter for differentiating CHH from CDGP.

P1-P748

GH Therapy Assessment in GH Deficient Patients During the Transition Period

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Background: GH treatment in severe GH deficiency during the transition period is a key matter. **Objective and hypotheses:** To assess the outcome of 30 severe GH deficient (GHD) patients after a structured transition program, in a French Universitary Hospital between 1988 and 2014. **Method:** 30 patients treated with GH until final height for congenital deficiency: 16/30 (12 ectopic posterior pituitary), brain tumors: 11/30 (5 Rathke's cleft cyst) and radiotherapy-induced GHD for leukemia: 3/30, persistent and severe GHD after pituitary reassessment (10 isolated and 20 multiple pituitary hormone deficiencies). Mean age at transfer was 17.4 ($\pm$1.9)y. Data in the last pediatric visit and 1, 2, 3 and 5 years later: GH doses, IGF1, and metabolic and bone status. **Results:** Median follow-up was 3 years. 17/25 (68%) were still treated at one year, 14/19 (73.6%) at 2 years, 14/16 (87.5%) at 3 years and 8/11 (72.7%) at 5 years. Only 5/30(16.6%) dropped out of the follow-up after one year, and 2/25 (23.3%) after 2 years. IGF1 levels in the target (0.5$\pm$2DS) only for 5/25 (31.2%) at 1 year, decreasing to 2/19 (14.2%) at 2 years and 1/14(l7.1%) at 3 years, with average GH doses of 1.2, 0.9 and 0.8 mg/d. Decrease of BMI for men (24.8 kg/m^2 vs 23.6 kg/m^2), increase for women (26 kg/m^2 vs 29.2 kg/m^2). Bone status, glycaemia and lipids levels were stable after 5 years. **Conclusion:** Most of GHD patients are still treated 5 years after transition, underlying an active collaboration between pediatric and adult teams. However, the insufficient initial IGF1 levels and its quick decrease afterwards suggest the need to emphasize patient education, through a motivational approach.

P1-P749

Age of Onset of Puberty in Yaounde, Which Normative Reference Data?

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Background: The age of onset of puberty varies from country to another and, within every country, from one socioeconomic group to another. In Sub-Saharan Africa, particularly in Cameroon, there is paucity of data on this topic. **Objective and hypotheses:** To determine clinically meaningful normative reference data that describe the timing of sexual maturity indicators among Cameroonian children and to determine factors that influence the onset of this maturity. **Method:** Cross-sectional analytical study consisting of 1382 Cameroonian boys and girls aged 8–15 years and living in urban area of Yaounde, selected from 11 schools. We performed two simple random samplings in two stages without replacement at each stage. Secondary sexual characteristics were recorded according to Tanner staging as well as self-reported date of menarche (if any). We also collected data concerning their sociodemographic status, food consumption and anthropometric parameters. **Results:** In girls, the median ages (95% CI) of Tanner stage 2 pubic hair growth (P2) and stage 2 breast development (B2) were 8.73 (8.31–9.04) years and 8.89 (8.53–9.17) years, respectively. The median age of menarche was 13, 03 (12, 47–13, 83) years. In boys, the median ages (95% CI) of Tanner stage 2 testicular development (G2) and stage 2 pubic hair growth (P2) were 9.63 (9.32–9.89) years and 10.05 (9.73–10.09) years respectively. This was lower than the age of the 1980s generation confirming a secular trend of puberty. **Conclusion:** Cameroonian boys and girls, living in urban areas start their puberty around 9 years precociously than 1980s generation in the same area.

P1-P750

Personalized Health Care: Home POCT Sodium Measurement in Diabetes Insipidus Centralis in a Patient with Impaired Thirst Perception

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Background: Central diabetes insipidus (CDI) is caused by deficiency of antidiuretic hormone (ADH). Patients with CDI are at risk for fluid balance disturbances, especially when there is impaired thirst perception or inability to access water freely. Serum sodium measurement gives a good reflection of the actual fluid balance but is generally not available in the home situation. For patients in which CDI is difficult to manage sodium measurement at home may be a good instrument for more

self-reliance and possibly less emergency room visits and/ or hospital admissions due to dysregulation of fluid balance. **Aim:** We describe a case of a boy with CDI and impaired thirst perception in whom the use of serum sodium, measured by the use of an i-STAT analyzer, has successfully led to more self-reliance and quality of life for him and his family. **Case description:** We describe a 5-year old boy with an optical pathway glioma with a complicated course of disease. As a consequence of his treatment he has psychomotor retardation, is blind and developed anterior hypopituitarism and CDI. He has an impaired thirst perception and is behaviorally focused on drinking. He was frequently admitted to the hospital because of dysregulation of his CDI as it was not possible to adequately adapt DDAVP dosage to his drinking behavior in the home situation. We found thei-STAT POCT analyzer (Abbott) to be a reliable system for sodium measurement at home. Expenses were covered by the health insurance company for a trial period (respectively 2 and 3 months). During the trial period there was no need for ER visits or clinical admission due to dysregulation of fluid balance. His parents are more in control, it saves them time and stress due to ER visits/ hospital admissions. It leads to less disturbances in every day family live. **Conclusion:** i-STAT sodium home measurement is an excellent example of personalized health care leading to more self-reliance and improvement of quality of life.

P1-P751

Transcriptional Basis of Idiopathic Central Hypogonadism in Isolated Congenital Cryptorchidism with Defective Mini-Puberty

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Objective and hypotheses: The objective was to use whole-genome RNA profiling of testicular biopsies by DNA strand-specific RNA-sequencing to explore the causative role of isolated congenital cryptorchidism in azoospermia and/or infertility. **Method:** Fifteen cryptorchid patients, aged 7 months to 5 years, were enrolled in this study and underwent orchidopexy. During surgery, testicular tissue biopsies were collected and split in half for histological examination and RNA-seq. **Results:** Our RNA profiling data strongly supports the theory that idiopathic central hypogonadism induces impaired mini-puberty, resulting in azoospermia and/or infertility. The identification of multiple differences in gene expression between high and low-infertility risk groups further underscores the importance of an intact hypothalamic-pituitary-gonadal axis for fertility development. GnRH receptor expression is likewise regulated by Msx1, Dlx2, and Dlx3 in mice. Further mediators of GnRH receptor gene expression have been reported and include Sf1, Nr4a1/Nur77, Lhx3, Six3, and Six6. In our expression study, the *MSX1*, *DLX2*, *DLX3*, *NR4A1,* and *LHX3* genes were decreased in the high infertility risk group. **Conclusion:** Our finding of insufficiently expressed genes directly involved in the modulation of αGSU and LHβ expression implies a direct effect on LH production and provides a plausible explanation for the reduced LH levels measured in HIR patients. Furthermore, our molecular data supports the hypothesis of insufficient *PROK2* gene expression participating in induction of luteinizing hormone deficiency, with *EGR4/PITX1* as gene controller.

P1-P752

A Novel MKRN3 Frameshift Mutation in a Bulgarian Girl with Central Precocious Puberty

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Background: Precocious puberty is defined as the onset of pubertal signs in girls younger than 8 years of age and in boys younger than 9 years of age. Central precocious puberty is due to an early activation of the hypothalamic-pituitary-gonadal axis. Different candidate genes were involved in the etiology of the disease. To date, mutations in the maternally imprinted gene MKRN3 are most frequently found in families with CPP. **Objective and hypotheses:** The aim of our study was to search for mutations in *MKRN3* in cases of sporadic CPP. **Method:** We screened 10 Bulgarian girls diagnosed with idiopathic CPP for mutations in *MKRN3*. **Results:** Heterozygous mutations in the *MKRN3* gene were detected in two girls – one novel frameshift mutation (p.Arg351Serfs*44) and a previously reported one (p.Pro161Argfs*10). Genetic testing of the members of the two families revealed the paternal origin of the detected mutations. Two of the males with paternally inherited *MKRN3* mutations did not have early activation of hypothalamic-pituitary-gonadal axis. **Conclusion:** We report a novel mutation in gene *MKRN3* (p.Arg351Serfs*44) with a very probable deleterious effect in a girls with CPP. Although paternally inherited *MKRN3* mutations are responsible for CPP in females, it seems that they do not necessarily lead to precocious pubertal development in males. We assume that this is due to any of the epigenetic mechanisms involved in gene expression control, particularly in this 15q11-q13.3 critical region.

P1-P753

The Intra- and Inter-User Reliability of Testicular Volume Estimation – A Simulation Study

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Background: Measuring testicular volume (TV) by orchidometer is a standard method of pubertal staging in boys. A paucity of evidence exists as to its inter and intra-user reliability and the impact of clinicians' gender, training and experience on the accuracy of measurements. **Objective and hypotheses:** We engineered prosthetic models of different size testes to investigate the reliability of TV estimation. **Method:** The study was conducted over the three-day British Society Paediatric Endocrinology and Diabetes (BSPED) meeting, November 2015. Three child-sized mannequins displayed latex scrotum containing prosthetic testicles of 3, 4, 5, 10 and 20 ml. Demographic data, paediatric endocrinology experience, TV examination training, information on examination technique and TV estimations were collected anonymously. Delegates were asked to repeat their measurements later during the meeting. Scrotum order was changed daily to minimise recall bias. **Results:** 208 delegates participated (158F, 50M): 50% consultants, 30% trainees, 9% clinical nurse specialists, 11% other. Ninety delegates performed repeat measurements. 25.5% had received formal training in TV estimation. There was variability in examination technique, the majority preferring the patient recumbent and using both look and feel for estimation. Delegates measured TV accurately on 30% of occasions. Overestimations were made on 30% of measurements and underestimation on 40%. Males and females were similarly inaccurate, males estimating correctly on 31.4% of occasions and females on 29.7%. Experience improved accuracy with consultants scoring accurately 31.7%, paediatric trainees 28.4%, nurse specialists 27.2% and newly qualified doctors 11.1% of the time. Inaccuracies were highest at the smallest volumes: 57% overestimating 3 ml testis, compared with 17% for the 20 ml testis. This is clinically pertinent considering the different management decisions made at smaller volumes. **Conclusion:** Overall TV estimation accuracy was poor. There was considerable variation between subjects and at lower volumes. Seniority improves measurement estimation. Delegate feedback supported more training and developing these models for teaching simulation.

P1-P754

The Metabolic Negative Effect of Gonadotropin-Releasing Hormone Agonist Therapy in Childhood: Is it Short-Term and Reversible?

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Background: Data on metabolic effects of gonadotropin-releasing hormone agonist (GnRHa) therapy are still controversial. **Objective and hypotheses:** To longitudinally evaluate the effect of GnRHa therapy on BMI, glycaemic metabolism and lipid profile in children affected by idiopathic central precocious puberty (CPP). **Method:** This longitudinal retrospective study included data from 42 children (7.70 ± 0.80 years, 2 males) affected by CPP and treated with GnRHa followed from January 1996 to December 2007 in a tertiary center of paediatric endocrinology. Medical history together with anthropometric (BMI-SDS) and biochemical data (fasting glycaemia (mg/dl) and insulin (uIU/ml), Homeostatic model assessment (HOMA) index, total cholesterol (TC), LDL-cholesterol (LDL-C), HDL-cholesterol (HDL-C), triglycerides (TG) (mg/dl), LDL-C/HDL-C and TC/HDL-C ratios) were collected before starting GnRHa therapy (T0), during the treatment (T1) and after GnRHa discontinuation (T2). **Results:** At T0, 23 and 16.7% of patients were found overweight and obese, respectively. On GnRHa, BMI-SDS further increased (0.76 ± 0.85 vs 0.98 ± 0.92, P 0.03). At T2 (7.54 ± 1.59 years after T0), even if the 29 and 14% of population was still overweight and obese, respectively, BMI-SDS (0.73 ± 1.21) decreased from T1 (P 0.01). Similarly, insulin-sensibility and lipid profile got worse during GnRHa treatment (T0 vs T1: HOMA index 1.02 ± 0.74 vs 1.87 ± 1.17, P 0.03; LDL-C/HDL-C ratio 1.44 ± 0.38 vs 1.68 ± 0.50, P 0.04) although the same deterioration did not persist at T2 (T2: HOMA index 1.41 ± 0.82, LDL-C/HDL-C ratio 1.41 ± 0.41). **Conclusion:** It is known that early sexual maturation contributes to an adverse metabolic programming. Our results support a direct and negative effect of GnRHa *per se* on BMI, glycaemic metabolism and lipid profile in children affected by CPP. Nevertheless, these consequences appear to be short-term and reversible.

P1-P755

Gonadotropin-Releasing Hormone Stimulation Test in Girls Younger than 3 Years Old: Does the Stimulated LH Greater Than 5 IU/l Always Mark Central Puberty Precoccious?

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Background: Premature thelarche is the isolated breast development in girls <8 years of age unaccompanied by other signs of puberty including advanced bone age or growth spurt. The GnRH stimulation test is used to distinguish between premature thelarche and central precocious puberty. **Objective and hypotheses:** We studied accuracy of the gonadotropin responses to GnRH stimulation in predicting pubertal progression in children diagnosed with premature thelarche under the age of three. **Method:** Data from thirty female patients under the age of 3 (20 ± 7 months) diagnosed with premature thelarche was

presented. At the time of diagnosis, the patients were evaluated based on the bone age, pelvic USG, and GnRH stimulation tests and those without pubertal progression during a minimum of 1 year follow up were included in the study. **Results:** Among the patients, 26.6% of the patients ($n=8$) had Tanner stage 2 breast development while 73.3% had ($n=22$) Tanner stage 3. The bone age was within mean $\pm$2S.D. for chronological age in all patients. Pelvic ultrasonography revealed no abnormality. In the GnRH stimulation test, the baseline median LH value was 0.29 (0.10–0.74) IU/l, baseline median FSH value was 4.96 (3.18–7.05) mIU/ml, the stimulated median LH value was 5.75 (3.31–8.58) IU/L, the stimulated mean FSH value was 40.38 $\pm$ 20.37 mIU/ml and the stimulated mean LH/FSH ratio was 0.17 $\pm$ 0.09. Among the patients, 33.3% ($n=10$) had baseline LH values $>$0.3 IU/l, 67% ($n=20$) had stimulated LH values $>$5 IU/l, 16.6% had ($n=5$) stimulated LH values $>$10 IU/l and the stimulated LH/FSH ratio in all the patients was below 0.66. **Conclusion:** Although consensus statements define baseline LH values $>$0.3 IU/l, stimulated LH values $>$5 IU/l, and LH/FSH ratios $>$0.66 as diagnostic cut-offs for central precocious puberty, since the baseline and stimulated LH values in children under 3 years of age may be higher due to mini-puberty, these values do not help to distinguish between premature thelarche and central precocious puberty. Our results have demonstrated that the dominant FSH response to the GnRH stimulation and a LH/FSH ratio $>$0.66 are more valuable than the peak LH response in the differential diagnosis in these patient group.

P1-P756
β-hCG from an Occult Source Causing Peripheral Precocious Puberty: Identification of the Tumour 6 Years After Presentation

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Background: β-hCG secreting germ-cell tumors (β-hCG-ST) are rare causes of Peripheral precocious puberty (PPP) in boys and usually located in intracranial region. Liver, retroperitoneum, testis and mediastinal cavity are the other localizations reflecting embryonic germ cell sites. **Objective and hypotheses:** We present a patient with PPP due to elevated β-hCG levels, but extensive efforts to find the source of elevated β-hCG was unrevealing for 6 years. We want to emphasize the difficulties at diagnosis of β-hCG-ST. **Case:** 10.7 years-old male presented with pubic and body hair for 2.5 years. On physical examination; height was 172 cm (+5 SDS), weight was 60.5 kg (+2.28 SDS), testes were 10 cc bilaterally with genital/pubic hair of Tanner stage 5. Bone age was 16 years. FSH and LH was supressed with extremely elevated total testosterone (17 ng/ml). An elevated β-hCG level of 104 mIU/ml (Normal: 0–5) prompted a search for the source. Cranial MRI showed 7 mm contrast enhanced hypophyseal lesion which was taken out by trans-sphenoidal surgery. However, β-hCG remained elevated and the pathology came-back as normal pituitary tissue. Subsequently, an inferior petrosal sinus sampling was performed which also did not show any gradient or lateralization. Follow-up cranial/thoracal/abdominal/pelvic MRIs were normal. A testis ultrasound showed generalized microlithiasis but a biopsy to rule out tumour revealed only mild hyperplasia of Leydig cells. Testicular arterial and venous catheterization also did not show any β-hCG gradient. PET/CT revealed a small uptake in mediastinum and excisional biopsy of the lesion was done which showed thymus hyperplasia. Annual MRIs did not show any tumors for the next 6 years in which time β-hCG levels ranged 100–154 mIU/ml. At 6th years, his β-hCG abruptly increased to 2039 mIU/ml at which time MRI showed a 5.5 cm mediastinal mass. Tumor is excised completely and pathology was consistent with mixed germ cell tumor (70% mature teratom, 30% seminoma). Karyotype of tumor was 47,XXY (15)/48,XXY, +MAR (12). Peripheral karyotype was 46,XY. **Conclusion:** β-hCG ST can not be evident at presentation and close follow up is mandatory in patients with PPP and elevated β-hCG.

P1-P757
Silent Corticotroph Adenoma with Adrenocortical Choristoma in an 11-Years Old Boy

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Background: Silent corticotroph adenomas are adenomas composed of corticotrophs but are different from corticotroph adenomas. Despite being silent, they show more aggressive behavior than other clinically nonfunctional adenomas. Adrenocortical choristomas in silent corticotroph adenomas (i.e. the presence of adrenocortical cells in the heterotopic location of the sella) were reported in three patients 16 years or older until now. **Objective:** Here we report, to our knowledge, the fourth and the youngest case of silent corticotroph adenoma with adrenocortical choristoma. **Case report:** The patient had been receiving L-thyroxine treatment and was on follow-up for compensated hypothyroidism (exaggerated TSH response to TRH) since four months of age. At 11 years, despite L-thyroxine treatment, findings compatible with secondary hypothyroidism (low free T4 and low TSH) was found. Cortisol was also low (4.82 ug/dl) and ACTH was not elevated (11.78 pg/ml). Physical examination was unremarkable except the presence of double urethral meatus. On MRI, a 11$\times$11$\times$10 mm lesion in the pituitary region which contrasted later than the pituitary gland was found to be primarily suggestive of an adenoma. Before the patient underwent adenomectomy, ACTH deficiency was confirmed with a peak cortisol of 15.27 ug/dl to low-dose ACTH and cortisol replacement was added to L-thyroxine replacement. Pathological evaluation revealed the presence of two types of cells in the excision

material:Small cells which express ACTH and larger cells rich in mitochondria which are similar to adrenocortical cells and which do not secrete any of the pituitary hormones. Pathological diagnosis was ACTH expressing pituitary adenoma and adrenocortical choristoma. **Conclusion:** The lack of biochemical and clinical evidence of Cushing syndrome despite ACTH expressing cells in the adenoma indicated the presence of a silent adenoma. The presence of a second group of cells similar to adrenocortical cells in this heterotopic location is compatible with choristoma. The younger age of our patient than those of previously reported cases and clinical significance of silent corticotroph adenoma in general make this case of rare entity more remarkable.

P2-P758

Clinical Symptoms, Endocrine Dysfunction and Radiologic Findings in Children with Rathke's Cleft Cyst

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Background: Rathke's cleft cyst (RCC) is a benign, sellar or suprasellar lesion arising from the remnants of Rathke's pouch that have failed to disappear in the normal development of the embryo. Patients with RCCs are mostly asymptomatic but can also exhibit various symptoms related to pituitary insufficiency. With increasing interest on endocrinology disorders of children or adolescents, the prevalence of RCCs is also on the rise. However, the studies on children or adolescents with RCCs were insufficient so far. **Objective and hypotheses:** We investigated clinical manifestations, endocrinology dysfunction, radiological features of patients confirmed RCC and underwent linkage analysis in multiple aspects with sufficient number of enrolled children and adolescents with RCCs. **Method:** According to the retrospective review of medical records in the present study, we obtained patients' clinical information. We also examined endocrinology function of enrolled cases by basal hormones test or combined pituitary function test or a gonadotropin releasing hormone stimulation test. MRI findings of RCCs were classified with the size, the location and the signal intensities at T1 weighted and T2 weighted settings. Then we tried to investigate association among clinical symptoms, endocrine disorders and radiologic characteristics. **Results:** Chief complaints of patients varied depending on the age group. About 80% of patients who performed endocrine function test revealed to have pituitary insufficiencies, most common of which was central precocious puberty. There was no significant difference between the endocrine disorder group and normal group regarding the MRI findings. Seven of ninety-three patients received surgery for various reasons – to alleviate symptoms, to check malignancy, or due to continuously increasing size of RCC. It was found that the RCC size of patients who needed operation was significantly larger than those who had no need of the operation. In addition, among those who received the operation, the number of RCCs that were restricted to the suprasella or extended to that area was significantly greater. However, the endocrine disorders in three of seven patients were aggravated after the surgery. Lastly, we discovered that among 66 patients who performed 2-year follow up MRI, about 20% of patients experienced the increase of RCCs. **Conclusion:** We can conclude that it is necessary to perform routine following ups of endocrine function test and image study in patients with RCCs.

P2-P759

A Case of Central Precocious Puberty in a Patient with Prader-Willi Syndrome

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Background: Hypogonadism is one of the major diagnostic criteria of Prader-Willi syndrome (PWS). A hypogonadotropic hypogonadism is often present as a result of hypothalamic dysfunction (together with other hormonal disorders, such as growth hormone deficiency and hypothyroidism). **Presentation:** A 8.5-year-old boy with genetically-confirmed PWS (maternal uniparental disomy) presented in our Endocrinology Unit for routinely follow-up. Therapy with rhGH was started at 1.5 years without provocative diagnostic testing, with good response on growth and motor performance. Therapy with L-thyroxine was started at 2 years because of central hypothyroidism. At 3 years, congenital cryptorchidism was surgically corrected with bilateral orchidopexia, which resulted in asymmetric testis (hypotrophy of the left one). A physical examination revealed precocious pubertal development: volume of the right testis 5 ml, Tanner stage II for pubic hair and genitalia. BMI was in normal range. Growth rate was accelerated (9.4 cm/year, +4.83 SDS) with advanced bone age (10 years according to the Greulich and Pyle method). A GnRH test revealed premature activation of the hypothalamic-pituitary-gonadal axis (peak value LH 11.6 mUI/ml, FSH 10.8 mUI/ml) with pubertal testosterone levels (1.15 ng/ml). Serum IGF-1 level and thyroid function test were normal. A brain MRI showed mild hydrocephalus (as a result of neonatal intraventricular haemorrhage) and a normal pituitary gland. Gonadal ultrasound demonstrated testicular microlithiasis. Tumour markers (hCG, aFP) were negative. With a final diagnosis of central precocious puberty (CPP), LHRH analogue therapy was started, obtaining good clinical and hormonal response. **Conclusion:** Fourteen cases of CPP in PWS have been reported so far. The aetiology remains largely unknown (except for few cases with pituitary anomalies or brain ischemic damage). Our patient presented CPP with only one functioning microlithiasic testis. We hypothesize that perinatal brain damage could have contributed to premature activation of the axis.

P2-P760

Is Amh Level Diagnostic for Premature Telarche, Premature Adrenarche and Central Precocious Puberty?

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Background: Antimüllerian hormone (AMH) is produced by granulosa cells surrounding follicles. There are limited studies about the change of AMH levels at the pubertal onset. **Objective and hypotheses:** The aim of this study was to identify whether AMH levels could be diagnostic for central precocious puberty (CPP), premature thelarche and premature adrenarche (PA) and to investigate the factors influencing AMH regulation. **Method:** Girls with CPP ($N=21$), PT ($N=24$), PA ($N=42$), control prepubertal ($N=22$), control pubertal ($N=39$) are included in the study. **Results:** Chronological age in PT, PA, CPP groups was more advanced than the control prepubertal group but behind the control pubertal group. HSDS, WSDS and BMISDS were similar between the groups. AMH levels were not different between the groups. AMH levels showed a significant positive correlation with 17OHP levels in all five groups. AMH levels showed a significant negative correlation with LH, f-testosterone and DHEA-SO4 levels in the PT group. AMH levels were negatively correlated with BMI SDS values and positively correlated with SHBG levels in the CPP group. These levels were positively correlated with SHBG levels in the control prepubertal group. **Conclusion:** Serum AMH level is not affected from the activation of the pubertal and adrenal axis in female children and follow a stable course in the prepubertal and pubertal years. LH, 17OHP, f-testosterone, DHEA-SO4 and SHBG are the factors that are effective in AMH regulation.

P2-P761

Paediatric Cushing Disease: One Patient's Path to Cure

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Background: Paediatric Cushing disease (CD) is rare but can be severe. Diagnosis and proper management are often delayed and the course of disease is unpredictable. Support from experts in the field is essential. **Objective and hypotheses:** We present a male patient, diagnosed with Cushing syndrome elsewhere more than two years after his initial signs and symptoms. For 6 months he underwent numerous investigations, which were inconclusive and was left untreated. Subsequently, he underwent transsphenoidal surgery (TSS) which was unsuccessful. The patient had no further treatment and his health further deteriorated until he presented to our centre 2 months later. **Method:** The patient's 24 h urine Cortisol was 1012 μkg/24 h (r.r. 55.5–286). Serum cortisol and plasma ACTH at 0:00h were 601.94 nmol and l/117 pg/ml, respectively. We performed additional investigations, including overnight high-dose dexamethasone suppression test (8 mg Dexamethasone) which resulted in $>85\%$ Cortisol/ACTH suppression. IPSS localised the corticotroph adenoma to the left of the pituitary. The boy was commenced on oral Ketoconazole and planned for a second TSS. After 3 weeks on Ketoconazole he experienced liver toxicity and deterioration, related to the hypercortisolemia. Due to his rapid health decline a decision for bilateral adrenalectomy (BA) was made. **Results:** Preoperatively he was treated with i.v. Etomidate (first use as adrenolytic in the country) and underwent BA successfully. Postoperatively he was managed with Hydrocortisone, Fludrocortisone and antihypertensives. During the first weeks the patient had elevated blood pressure, leg swelling and anxiety attacks. After 3 months he is recovering well, with no signs of Nelson's syndrome and is gradually overcoming his depression. Pituitary hormone deficiency testing is planned. **Conclusion:** Treatment of paediatric CD and its related complications is complex. Many factors can change the therapeutic course. Multidisciplinary approach and collaboration with experts in the field are crucial for a successful outcome.

P2-P762

Recovery of Hypothalamic Pituitary Function After Stalk Transection and Panhypopituitarism in an Adolescent

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A 12 year old boy sustained a severe head injury by a passing car whilst crossing the road. Injuries were confined to massive basal skull fracture, right sided blindness, acute onset diabetes insipidus, extradural and subdural bleeding requiring surgical decompression. Pre-operative physical examination revealed a healthy looking boy, height 60th centile for age, Tanner stage III puberty, 10 ml testes bilaterally. MR head demonstrated apparent pituitary stalk transection and right optic nerve transection, confirmed during surgical exploration. Pituitary function testing 1, 6, 16 days post-surgery. Hydrocortisone, thyroxine and DDAVP replacement were commenced immediately post-operative. Over 12 months, linear growth failure and pubertal arrest occurred. Glucagon stimulation confirmed GH deficiency. rGH was commenced, with improved growth parameters. As bone age was advanced (14 years at 12), consistent with pubertal status at admission, testosterone replacement was delayed to age 14, then commenced, achieving final height of 165 cm, appropriate for MPH. GH was ceased at end of linear growth. Over 7 years, to age 21, he received thyroxine, hydrocortisone, testosterone and vasopressin. At age 21 he stopped taking thyroxine. Thyroid

hormone levels remained normal. Attempted reduction in hydrocortisone resulted in severe tiredness. Testosterone supplementation was ceased at age 23. Testosterone remained normal at 22 nmol/l. Hydrocortisone was gradually withdrawn between ages 23–25, cortisols 200–252 nmol/l. Due to excessive lethargy, formal GH testing with ITT was performed – max GH 5 μ/l, cortisols 200–250 nmol/l but no stress response to hypoglycaemia. GH replacement at 2.5 mg/m^2 per week was given, with restoration of good health. Diabetes insipidus is persistent and advice given for steroid cover for stress. Due to excessive lethargy, formal GH testing with ITT was performed – max GH 5 mu/l, cortisols 200–250 nmol/l but no stress response to hypoglycaemia. GH replacement at 2.5 mg/m^2 per week was given, with restoration of good health. Diabetes insipidus is persistent and advice given for steroid cover for stress.

P2-P763

A Novel CHD7 Mutation in an Adolescent Presenting with Pubertal and Growth Delay

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Background: Mutations in the gene encoding the Chromodomain Helicase DNA-binding protein 7 (*CHD7*) are found in 60% of patients with CHARGE Syndrome (Coloboma, Heart Defects, Choanal Atresia, Retarded growth and development, Genital hypoplasia, Ear abnormalities and/or hearing problems) and in 6% of patients with Kallmann syndrome. **Objectives and hypotheses:** To describe a novel *CHD7* mutation and its clinical presentation. **Methods:** Case report with clinical evaluation, endocrine investigations, neuroimaging and genetic analysis were performed. **Results:** 13.5 year-old male was addressed for investigation of pubertal and growth delay. Family history was marked by delayed puberty in both parents. The patient was born full term; eutrophic after an uneventful pregnancy. He was operated at 5 days of life for bilateral choanal atresia. Development was normal. Height and weight were −2.04 SDS and −1.74 SDS respectively. He exhibited a Tanner A1P2G1 stage with micropenis (4×1 cm). Gonadotrophines were low (LH:0.2U/L, FSH:0.9U/L); At age 14, LHRH test suggested hypogonadotrophic hypogonadism. Sniffing test revealed complete anosmia. MRI demonstrated semi-circular canal and olfactory bulb hypoplasia, vestibular, cochlear and right VII cranial nerve malformation, and a decreased hypophyseal volume (160 mm^3). According to the Verloes' 2005 Criteria, the patient was diagnosed with partial CHARGE syndrome. We identified a *de novo* heterozygous *CHD7* mutation (c.4234T>G, pTyr1412Asp) located in the Helicase C domain. This is a private variant, absent in ExAC database and predicted to be deleterious by 10/10 prediction algorithms. **Discussion and conclusion:** CHARGE syndrome remained undiagnosed in this patient until adolescence despite the presence of suggestive features. Genetic testing promotes the broadening of phenotypic and genotypic spectrum of CHARGE syndrome and may give insight to the mild end of phenotypic spectrum, ensuring optimal follow up and appropriate genetic counselling.

P2-P764

Kallmann Syndrome Due to a Homozygous Missense c.217C>T (p.R73C) Mutation Detected in the Exon-2 of the PROK2 Gene

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Background: Kallmann syndrome (KS), the prototype of anosmic idiopathic hypogonadotropic hypogonadism (IHH), is charecterized with HH acompanied by anosmia, absence or hypoplasia of olfactory bulbus due to defective morphogenesis. Mutations in 10 genes have been reported to cause KS while can clarify the underlying molecular defect in about 30–50% of IHH/KS cases. Beside, *PROK2* gene mutations are extremely rare cause of KS. Herein, we present KS due to a homozygous missense c.217C>T(p.R73C) mutation detected in exon-2 of the *PROK2* gene in a consanguineous Turkish family. **Case report:** The index case was a 13 year-old male presented with delayed puberty and

Table 1. (for abstract P2-P762)

	fT4 pmol/l (10–24)	TSH mU/l (0.5–4)	IGF1 nmol/l (25–95)	Cortisol nmol/l (240–400)	FSH U/l (0.7–6)	LH U/l (0.9–6)	Testosterone nmol/l (3–10+ pubertal)
Day I	23.4	1.04		67			
Day 6	11	<0.01		Treated			1.0 nmol/l
Day 16	9.6	<0.01	<1 nmol/l		0.4	<0.1	<0.3

small penis. His past medical history was unremarkable. Parents were first cousin. In the physical examination his height was 143.1 cm (25th pc.), weight was 37.4 kg (25th pc.). His genitourinary system examination revealed a penis size of 4 cm, a left testis of 2 ml in the scrotum with a non-palpable right testis. He had anosmia. Hormonal work/up revealed prepubertal gonadotropin levels with undetectable testosterone (FSH:0.546 mIU/ml, LH:0.13 mIU/ml, total testosterone: < 20 ng/dl). Ultrasonographic examination showed a 10 × 5 × 5 mm testis on right inguinal canal and left testis in the scrotum. A dagnosis of KS was considered and right orchiopexy had been performed. Molecular genetic analysis detected a previously reported homozygous missense c.217C > T (p.R73C) mutation in the exon-2 of *PROK2* gene. A prepubertal male sibling was also homozygous for the mutation. His clinical and laboratory investigations are still in process. Unaffected parents, three males and one female siblings were heterozygous for the mutation. **Conclusion:** Since KS due to *PROK2* gene mutations is extremely rare, present family with case(s) having clinical characteristics of KS and homozygous missense c.217C > T(p.R73C) mutation in *PROK2* gene and those who were unaffected and heterozygous for the mutation would help to further understand the underlying molecular genetics etiology of KS.

P2-P765

Symptomatic Rathke Cleft Cyst in Pediatric Patients – Clinical Presentations, Surgical Treatment and Postoperative Outcomes – An Analysis of 38 Cases

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Background: Rathke cleft cysts are benign, epithelium-lined intrasellar and/or suprasellar cysts believed to originate from remnants of the Rathke pouch. Although its prevalence in adults is rather high, Rathke cleft cysts are rare in children. Often they are asymptomatic findings, however depending on their size and localization they can present with a wide spectrum of symptoms. **Objective and hypotheses:** The aim of the study was to analyse the symptoms and surgical outcome of patients with the diagnosis of Ratke cleft cyst based on histopathological examination of postoperative material. **Method:** The study is a retrospective analysis of 38 cases of children who underwent a neurosurgical treatment due to Rathke cleft cyst in Children's Memorial Health Institute in Warsaw, Poland between 1994–2015. **Results:** Sex ratio was 1:0,9 (20 girls and 18 boys), two female patients were twins. At diagnosis patients were between 6 years 11 months and 17 years 10 months old with mean age of 13 years and 8 months. Average diameter of the cyst was 16,7 mm. In six cases calcifications in the lesions were observed either in brain imagining or intraoperatively. Most common symptoms were: headaches (50%), hypothyroidism (50%), short stature and/or decreased growth velocity (47%), delayed puberty and menstrual abnormalities (37%), diabetes insipidus or polydipsia and polyuria (26%), adrenal dysfunction (26%), sleepiness and general weakness (13%), visual disturbances (11%). 29 patients underwent a transsphenoidal operation and in 9 a craniotomy was performed. All but one were successful (one patient died due to postoperative neurosurgical complications). The most common postoperative complications were: diabetes insipidus, adenohypophysis, overweight and obesity. **Conclusion:** Although Rathke clefts cysts are considered to be benign, non-neoplastic lesions they can present with serious symptoms that deteriorate significantly patients' quality of life. In spite of successful neurosurgical treatment in most of the analysed cases patients required a long-term pharmacological treatment due to endocrinological complications.

P2-P766

Congenital Craniopharyngioma: Report of Two Cases

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Introduction: Craniopharyngiomas are slow growing epithelial tumors located in the sellar or suprasellar region of the brain. Adamantinomatous subtype affects mainly children and accounts for 5–10% of all intracranial paediatric tumors. Diagnosed antenatal and neonatal craniopharyngiomas are very seldom, about 40 such cases have been detected to date. They are characterised by large size, progressive hydrocephalus and a poor prognosis. **Aim:** The aim of the study was to analyse the clinical symptoms and treatment efficacy in children with diagnosis of congenital craniopharyngioma (adamantinomatous subtype). **Materials and Methods:** A retrospective analysis included two children with craniopharyngioma diagnosed in prenatal period (28 hbd) and in the second month of life. **Results:** *Case 1*. The first patient was diagnosed at 28 Hbd of pregnancy using an MRI scan. A 36-week-gestation boy was delivered by cesarian section. The newborn weighed 3410 g and scored nine points on APGAR scale. Postnatal MRI of the brain showed solid-cystic tumour with the solid part measuring 49 × 40 × 58 mm and the cystic part:29 × 24 × 31 mm in the suprasellar region. Four weeks later, due to an increasing hydrocephalus, the baby underwent radical resection. It was diagnosed with an adenohypophysis, diabetes insipidus and blindness. Aged 7 now, the boy suffers from epilepsy, hypotonia and is disabled. *Case 2*. A 39-week-gestation girl was from uneventful pregnancy and normal vaginal delivery. At birth, she weighed 3680 g and scored nine points on APGAR scale. At 2 months of age, due to vomiting, respiratory distress and bradycardia up to 40/min, the girl was hospitalized. The MRI of the brain revealed the presence of a mass measuring 22 × 26 × 24 mm in the supra and intrasellar region. At the 5 months of age, the baby underwent radical resection. After the surgery, an adenohypophysis and temporary diabetes insipidus (1 year duration) was diagnosed. From 1st to 18th year of age, growth hormone therapy was used. Now, the18-year-old girl measures 167,6 cm of height, weights 67.0 kg and is a capable student. **Conclusions:** Congenital craniopharyngiomas are rare tumours which can present a wide spectrum of symptoms depending on size and localisation. The outcomes can vary.

P2-P767

Congenital Hypopituitarism in a Patient with 18p- Syndrome

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Background: 18p- syndrome is very rare (1:50000 live-born infants). Hypopituitarism as part of the syndrome is found in 13% of cases. Here we present a case of congenital hypopituitarism in a girl with 18p- syndrome. **Objective and hypotheses:** Description of a rare clinical case of congenital hypopituitarism as a feature of 18p- syndrome. **Method:** Hormonal and biochemical blood tests, MRI, karyotyping, echocardiogram, specialists' examination. **Results:** A girl to non-consanguineous healthy parents was born at term with normal height and weight. From the first week of life the child had marked muscular hypotonia, dysphagia, recurrent hypoglycaemia and signs of cholestasis (hepatomegaly, acholic stool, increase in total and direct bilirubin, GGT, cholesterol and AST, ALT). Later, she was diagnosed with congenital cataracts and a heart disease (atrial septal defect). The child was held karyotyping, which detected the 18p- syndrome ((46 XX, del (18)(p 11.1; p 11.32)). At the age of 3 months she was diagnosed hypopituitarism: secondary hypothyroidism, secondary adrenal insufficiency (ACTH −6.05 pg/ml, cortisol −11.1 nmol/l, TSH – 1.6 mIU/l, fT4 – 7.37 pmol/l). Empty sella syndrome was diagnosed on MRI. Therapy with levothyroxine (6.25 mkg/kg/day) and hydrocortisone (10 mg/m^2) has been started. Over the next month cholestasis and hypoglycaemia were occupied. At 2 years, the girl was diagnosed with growth hormone deficiency. Growth hormone therapy has been started, with good effect. A girl has a strong psychomotor retardation. **Conclusion:** Diagnosis of congenital hypopituitarism is extremely difficult in the neonatal period. We present a case of congenital hypopituitarism which has manifested after birth with signs of severe cholestasis, hypoglycemia. In addition, the girl was found to have congenital cataracts and a heart disease. In our cases the patient had typical features of the 18p- syndrome in places without centromeric region. Further research and monitoring of patients are needed to determine the prognosis of the disease.

P2-P768

10 Years Review of Endocrine Diseases in Spanish Patients Diagnosed with Primary Brain Tumors in a Tertiary Hospital

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Background: Pediatric Central Nervous System (CNS) neoplasms are the most frequent solid tumors in children. Since the increase in survival, the patients are in high risk of developing long term sequelae. Endocrinological sequelae may be due to the oncological disease itself but usually derived from the treatment received, and they affect 20–50% of patients long-term. We aimed to review our experience from 2005 to 2015. **Objective and hypotheses:** Describe the actual situation/outcomes in our tertiary unit. **Method:** An observational retrospective study of clinical diagnosis of oncological disease and subsequent monitoring endocrinological data; collected both at diagnosis and follow-up, including anthropometric variables, oncological treatment received and endocrinological pathology diagnosed. Statistical analysis SPSS22. **Results:** We studied 103 patients (48% female) diagnosed at the age of 6.8 ± 4.2 years. The most frequent anatomical location was posterior (48%) followed by midline fossa (35%). The most prevalent histological types were astrocytomas (29%), medulloblastoma/PNET (17%) and Craniopharyngiomas (7%). Global mortality was 42%. Subgroup of survivors ($n=59$): The age at diagnosis was 7.6 ± 4.5 (vs. 5.8 ± 3.6; $P=0.036$), the complete surgical resection was 67% (vs. 29%; $P=0.03$), and the posterior fossa involvement was 40% (vs. 60%; $P=0.03$). Survival was higher in astrocytomas and craniopharyngiomas. Chemotherapy and radiotherapy were given in 39% and 29%, respectively. 23% of survivors developed transient postoperative neurohypophyseal deficiency (SIADH, diabetes insipidus or both). Permanent sequelae subgroup ($n=17/59$): The most frequent endocrine sequel was Panhypopituitarism (64%). The axes involved in descending order were: thyroid, GH, ACTH, ADH and FSH/LH. **Conclusion:** In our review, permanent endocrinological deficits were mostly influenced by location and surgery in craniopharyngiomas. Almost one-third develop short-term endocrine pathology. Panhypopituitarism incidence is high. Increased risk tumors are craneofaringiomas and meduloblastomas.

P2-P769

Novel Uses of Psychiatric Drugs to Treat Hypothalamic Obesity

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Background: Hypothalamic obesity (HyOb) is a disease characterized by weight gain resistant to lifestyle changes and dietary restriction. The main clinical findings are hyperfagia and decline of satiety, high levels of insulin and an increase of adipogenesis. The major problem for these patients is that conventional treatments, either medical or surgical are not succesful and have variable results. **Objective and hypotheses:** We aim to describe the natural history of the disease in patients who have attended our centre from early in their childhood until adolescence and to find new uses for psychiatric drugs that might shed new light in the treatment of this disease. **Method:** We

recollected data from 10 patients (seven women and three men) diagnosed of HyOb by a multidisciplinary team. The data included anthropometrics, clinical data and treatment received to stop gain weight and comorbiditiesd in periods of 6 months. We used the Tanofsky-Kraff et al (EAHQ) questionnaire to asses the alimentary behaviour of the subjects. **Results:** The main causes of excessive gain weight that we found were of tumoral origin: two pilocytic astrocytoma, one hypothalamic neurocytoma, one anaplastic astrocytoma and one craniopharyngioma. We recollected four patients with Prader-Willy syndrome and one late onset meningitis by group B streptococcal infection. We found that the psychiatric drugs we used (methylphenidate, dextroamphetamine, fluoxetine and topiramate) associated to eating habits modifications managed to lower the weight ($P < 0.05$) in our patients. **Conclusion:** Treatment of HyOb should be assesed early in the diagnosis. There is limited evidence about the effect of psychiatric drugs on HyOB. Some of these drugs might be useful and improved quality of life.

P2-P770

Postoperative Water and Electrolyte Disorders and Affecting Factors in Children with Intracranial Tumors

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Introduction: Water and electrolyte disorders due to anterior and posterior pituitary deficiencies are common in children which are referred with intracranial tumors, especially arising from suprasellar and pituitary regions. But the prevelance and affecting factors of these disorders are not clear. We aimed that to determine the prevelance of postoperative water and electrolyte disorders and affecting factors in pediatric patients with intracranial tumors. **Method:** We analized data from the medical records of patients with intracranial tumors diagnosed before the age of 18 years, and were consulted to pediatric endocrinology department postoperatively. Clinical data included serum sodium, pre- and postoperative pituitary hormones, cranial MRI results of patients, complications and treatment modalities. **Results:** This study included 29 patients (male: 15). 15 patients (51.7%) had craniopharingeoma. In postoperative first 4 days, diabetes insipitus (DI) developed in 17 patients. 6 of these patients had DI before the operation. Postoperative syndrome of inappropriate antidiuretic hormone secretion (SIADHS) occured in 9 (31%) patients. Only one pateint had SIADH syndrome without DI. SIADHS occured during 2–11 days postoperatively. Of the 29 patients, 14 (48.3%) had permanent DI. 69% ($n = 20$) of the patients had adrenal insufficiency, 75.9% ($n = 22$) had central hypothyroidism. All patients who had permanent DI also had central hypothyroidism. Triphasic response was seen only in six patients. These patients were younger than others, and had lower weight, BMI, height, free T4 value, and higher sodium value. **Discussion:** Water and electrolyte disorders are common in children and adolescence with intracranial tumors. Lower free T4 levels in patients who experienced triphasic phase and central hypothyroidism presence in all patients with permenant DI were interesting. Limitation of this study is the small sample size, this can explain why there is no relation between tumor size and location and the water- electrolyte disorders.

P2-P771

Compound Heterozygosity for Two Novel POU1F1 Mutations in Siblings with Isolated Childhood Onset Growth Hormone Deficiency (CO-GHD)

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Background: CO-GHD can be caused by a variety of aetiologies, including pituitary or brain structural abnormalities, and increasingly recognised genetic mutations of pituitary transcription factors. Idiopathic GHD is a diagnosis of exclusion. POU1FI is a late pituitary transcription factor. Mutations of POU1F1 have autosomal recessive (AR) inheritance, and phenotypically present with a normal or small anterior pituitary gland on magnetic resonance imaging (MRI), they are associated with GH, prolactin and variable TSH deficiency. **Objective and hypotheses:** To describe the clinical history of two siblings diagnosed with CO-GHD from their diagnosis until the completion of growth of the older sibling, and the results of genetic investigations. **Method:** A retrospective description of two siblings with CO-GHD. **Results:** The boy was diagnosed with GHD at the age of 5.4 years, presenting with severe short stature (Height SDS −4.1). Excellent response to recombinant GH (r GH) was seen with a final height (−0.19 SD) within genetic target. At age 17 years insulin tolerance test, confirmed persistent GHD. His younger sister presented with neonatal hypoglycaemia associated with a low GH level and low IGF-1 SDS. Growth failure was noted by the age of 2 months (length SDS was −3.35). She has responded to rGH with a current height SDS is −1.19 SD at age 3 years. Pituitary MRI and thyroid function in both siblings were normal. Given the similar phenotypes within the same family investigations were undertaken which identified two novel genetic mutations of POU1F1 in exon 3 and 4- p.K166E and P.E224K respectively. **Conclusion:** The phenotype of early presentation of severe GHD is consistent with previously reported cases of POU1F1 mutations. As CO-GHD is rare, reoccurrence within the same family should prompt genetic investigation to explain the underlying aetiology, to guide on surveillance for other hormonal deficiencies, and to help predict persistence of GHD into adulthood.

P2-P772

Brain MRI in Evaluation of Endocrine Diseases of Childhood: Causal and Incidental Lesions

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Background: Brain MRI is an essential tool in the diagnosis of neuroendocrine disorders and aims at detecting anatomical abnormalities and tumors. However, it may lead to the identification of unrelated or questionably related abnormalities in the hypothalamic-pituitary region and/or the rest of the brain parenchyma. **Objective and hypotheses:** To establish the prevalence of causal lesions on brain MRI of children evaluated for hypopituitarism, assess the frequency and nature of incidental. **Method:** Retrospective single-center study based on the analysis of brain MRI realized with focus on the pituitary region (radiological protocol) from January 1st 2007 to December 31st 2008 for suspected hypopituitarism. **Results:** Of the 219 MRI analyzed, 56% showed an anomaly and 34% involved the hypothalamic-pituitary region. Most of these abnormalities were minor and consisted of hypo- or hyper-plasia of the anterior pituitary and cysts. Seven causal lesions (ectopic posterior pituitary, no tumor) were identified (3.2%). Finally, 75 extra-hypothalamic-pituitary lesions were identified of which 61 (28%) were incidental. Twenty-one MRI were repeated after the initial evaluation (9.6%) of which 38% were to control an incidental finding. **Conclusion:** Brain MRI performed in the context of anterior pituitary hormone deficiency identified a causal lesion in 3.2% but detected incidental unrelated MRI abnormalities in a large proportion of patients, leading to a high number of repeat examinations. Further work should be done to further refine the indications for brain MRI in these patients and avoid unnecessary examinations and the risk of incidental findings.

P2-P773

Primary Thirst Defect is a Rare But Important Complication Following Surgery for Hypothalamic Hamartoma and Intractable Epilepsy

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Background: Diabetes insipidus (DI) is a well-recognized post neuro surgical complication arising after hypothalamic-pituitary surgery. DI occurring in the post-operative period can be transient happening within 24–48 hour of surgery, secondary to trauma to the connections between the magnocellular bodies and the nerve terminals in the posterior pituitary, or to axonal shock from disturbances in the vascular supply to the pituitary stalk and posterior pituitary. **Objective and hypotheses:** We report primary thirst defect, a previously unreported rare complication following surgery for hypothalamic hamartoma in an adolescent girl. **Method:** An eighteen-year-old girl with intractable epilepsy, secondary to hypothalamic hamartoma was admitted for the resection of her hypothalamic lesion. She developed hypernatremia with hyper-osmolality but without thirst or polyuria 24 hours after surgery. She had normal plasma cortisol reserve (plasma cortisol: 679 nmol/l), thyroid and renal function tests. **Results:** A hypertonic saline test was performed. The results are shown in Table 1. A targeted fluid intake of 2.6 litres/day after appropriate rehydration subsequently led to the improvement of plasma osmolality (298 mosmol/kg) and normalisation of plasma sodium(144 mmol/l). **Conclusion:** Primary thirst defect, is a rare and dangerous complication that can occur after epilepsy surgery for hypothalamic hamartoma. This can cause a confusing picture with DI and vigilance is required to identify and recognise the problem early to initiate the most appropriate management.

Table 1.

Time (hours)	15:57	16:11	16:29	17:30	18:00
Plasma Osmolality (mosm/kg)	306	305	307	311	312
Plasma sodium (mmol/l)	148	149	150	151	152
Urine Osmolality (mosm/kg)				614	643
Plasma AVP (pmol/l)	0.9	0.9	1.6	32.6	38.7
Thirst (visual analogue scale 1–10)	0	0	2	7	9

P2-P774

Insulin Sensitivity in Girls with Central Precocious Puberty at Diagnosis and at 6 Months of GnRH Analogue Treatment

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Background: Puberty is associated with a physiological decline in insulin sensitivity. Overweight and obesity are common among girls with Central Precocious Puberty (CPP). CPP and early menarche have been considered as risk factors for obesity and cardiovascular diseases during adulthood. Besides, concern has been raised by the potential impact of GnRH analogues (GnRH-a) treatment on body weight and metabolic profile. **Objective and hypotheses:** To evaluate BMI and metabolic parameters in CPP girls at diagnosis and during GnRHa treatment. **Method:** We performed a cross sectional and prospective longitudinal study of 15 CPP girls at diagnosis and at 6 months on GnRHa therapy with an oral glucose tolerance test (OGTT). Glucose and insulin levels were measured at 0, 30, 60, 90 and

120 minutes. Fasting lipid profile was also evaluated. Surrogates indices for fasting (SFI) insulin resistance (IR) [HOMA-IR, G/I, QUICKI] were calculated and evaluated according to own local cutoff. Matsuda Index was calculated from OGTT. **Results:** At baseline median chronological age was 7.8 years (5.7–8.5). All girls were on Tanner stage 3. Eight patients had normal weight, whereas 7 were overweight (OW) or obese (Ob). No significant change in BMI was observed between baseline and on treatment. Six patients had at least 2 impaired indices for insulin sensitivity (three of them had normal weight) and two patients only one. During OGTT five patients with OW or Ob showed hyperinsulinemia. Few patients had dyslipidemia. Matsuda index was low in three patients at diagnosis. There were not significant changes in SFI and during OGTT between diagnosis and on GnRHa treatment. **Conclusion:** Our cohort of CPP girls showed a high frequency of OW and Ob as well as high frequency of IR. BMI and metabolic profile did not show changes at six month of GnRHa treatment. Further studies will be necessary to determine long term metabolic risk in these patients.

P2-P775

Effect of Gonadotropin Releasing Hormone Analogues (GnRHa) on Final Height in Girls with Borderline Early Puberty or Normal Physiological Puberty Depend on Bone Age Advancement and Predicted Height

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Background: Borderline precocious and normal-onset puberty can show slow or fast course. The fast development of pubertal signs can be resulted in decrease in final height (FH) via accelerated growth and bone maturation. **Objective and hypotheses:** To study the effectiveness of GnRHa in improving FH in girls with advanced bone age (BA) and decreased predicted height (PH) in borderline early or normal physiological puberty. **Method:** 135 girls whose puberty started between 6.83 and 9.73 years (yr) were divided into two groups according to BA advancement and decreased PH after 7.28 ± 8.88 months of follow up after the onset of puberty: group I with low PH was treated with GnRHa for 2.22 ± 0.85 year, group II with normal PH was followed without treatment. **Results:** Values between the groups were compared at the onset of therapy in group I and at respective time in group II. The results are shown in the Table 1. GnRHa delayed sexual maturation as well as BA and cause increased PH in group I. 87.3% of patients in group I and % 86.5 of girls in group II achieved their FH within their target height (TH) range (TH-1 SDS). Stepwise linear multiple regression analysis for both groups showed that height gain was mainly affected by BA and PH at the start of treatment. Basal LH level also was a contributing factor. **Conclusion:** The patients with advanced BA and decreased PH should be evaluated in terms of treatment. Slowly progressing puberty cases do not need treatment.

Table 1.

	Group I ($n=63$)	Group II ($n=72$)	*P*
Cronological age (CA) (yr)	9.13 ± 0.89	9.58 ± 0.96	0.007
BA (yr)	11.12 ± 1.06	10.27 ± 1.76	0.003
Height SDS	0.86 ± 1.32	0.61 ± 1.09	0.240
BMI SDS	0.8 ± 1.07	0.76 ± 0.96	0.840
ΔBA/ΔCA	1.97 ± 1.29	1.07 ± 1.31	0.003
PH SDS	−1.1 ± 1.29	−0.38 ± 1.03	0.002
TH (cm)	156.9 ± 5.42	158.17 ± 4.75	0.147
PH SDS- TH SDS	−0.01 ± 1.1	0.46 ± 1.03	0.025
LH (mIU/mL)	2.31 ± 2.28	1.09 ± 1.5	0.038
FSH (mIU/mL)	4.1 ± 2.13	3.66 ± 2.71	0.496
Peak plasma LH to GnRH (mIU/mL)	14.9 ± 17.04	5.87 ± 7.28	0.037

P2-P776

Central Nervous System Abnormalities on Brain Magnetic Resonance Imaging Among 200 Korean Girls with Central Precocious Puberty

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Background: Central precocious puberty (CPP) may result from organic lesions, but it is most frequently of idiopathic origin in girls. **Objective and hypotheses:** The objective of the study was to identify central nervous system abnormalities in girls with CPP. **Method:** This retrospective study was performed in 3-tertiary care hospitals between 2005 and 2015. During this period, 200 girls with CPP performed brain magnetic resonance imaging (MRI). Of the 200 girls, 12 (6.0%) were younger than 6 years, 188 (94%) were between 6 and 7 years. We analyzed the radiologic findings and evaluated related clinical and biochemical factors. **Results:** Brain MRI showed no abnormalities in 183 (91.5%), abnormalities of the hypothalamic-pituitary area in 16 (8.0%), and tuber cinereum hamartoma in one girls (0.5%). Abnormalities of the hypothalamic-pituitary area included microadenoma ($n=6$), pituitary hypoplasia ($n=5$), Rathke's pouch cyst ($n=3$) and cyst of pituitary pars intermedia ($n=2$). Three (25.0%) of 12 girls aged <6 years had abnormal brain MRI findings, whereas 14 (7.4%) of 188 girls aged 6–7 years had abnormal brain MRI findings ($P=0.054$). There were no significant differences in clinical and biochemical parameters between girls with abnormal brain MRI findings and those with normal findings. **Conclusion:** A small, but not negligible proportions of girls with CPP have organic lesions, most of which are benign.

P2-P777

Impaired Growth Hormone Secretion Associated with Large Hypothalamic Hamartoma

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Background: Hypothalamic hamartomas (HH) are rare non-progressive brain tumor malformations that occur early during brain development. Most of the cases are sporadic and nonsyndromic. Variation in size and location of the hamartoma within the hypothalamic region is not always associated with the severity of the clinical presentation. A wide range of symptoms could occur - from nonsymptomatic to severely affected cases that include seizures (mostly gelastic), behavioral difficulties and endocrinological disturbances. Among all, precocious puberty is most common endocrinological dysfunction; others present less frequently. **Objective and hypotheses:** Evaluation of GH in a child with hypothalamic hamartoma. **Method:** A girl approached our clinic due to the short stature. The child was born on term BW3350gr/BL50 cm. During early infancy growth was within the normal curve. Growth velocity started to decline after the age of 4 years. At the age of 7 years the child was 4SDS below the mean for height and 3SDS for weight. Pubertal development started at 8.5 years of age. **Results:** GH deficiency was confirmed with stimulation tests (peak value of 4.3 ng/ml) and low IGF1. MRI of the pituitary showed large hypothalamic hamartoma without tendency for growth during the two following years, whereas the pituitary gland was normal. The girl showed behavioral problems - shyness, timidity and inability to accustom to school activities. Also she had frequent headaches and episodes of crying. Neurological examination as well as ortooptic testing was normal. Other pituitary hormones were normal as well. **Conclusion:** Clinical presentation of HH is mostly associated with a particular position of the hamartoma. Since the size of HH in our case is 30 mm, both possible mechanisms could be involved – impaired GHRH secretion from the lower parts of the hypothalamus (arcuate nucleus) and inadequate control of somatostatin levels produced from upper parts of the hypothalamus (rostral periventricular nucleus). However, short stature should be considered as a rare feature of HH.

P2-P778

Comparison of Triptorelin Versus Leuprolide in Treatment of Girls with Central Precocious Puberty

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Background: GnRH agonists, leuprolide acetate (LA) and triptorelin acetate (TA), have been widely used in the treatment of central precocious puberty (CPP). But, a comparative data on the effectiveness of these two drugs for CPP treatment is very scarce. **Objective:** To compare the efficacies of TA and LA treatments in girls with idiopathic CPP. **Patients and Methods:** Sixty girls with rapidly progressive CPP treated with LA ($n=30$) or TA ($n=30$) were studied in a retrospective analysis. Inclusion criteria for treatment were breast development before 8 years, pubertal LH level (basal >0.3 IU/l or peak >5 IU/l), accelerated bone age (BA $>+2$SD) and predicted adult height (PAH) <155 cm or progressive compromise of PAH (at least 3 cm in 6 months). Initial dose of both drugs was 3.75 mg/28 days. A pubertal LH response to GnRH agonist at the third month of treatment was indicative of non-suppression and a need for dose increment. One-year follow-up data of two groups were compared. **Results:** Baseline characteristics including age, pubertal stages, BA, PAH, basal and peak gonadotropin levels and drug doses per kg of body weight were similar in two groups. However, GnRHa-stimulated LH levels at the third month were significantly higher in LA group than in TA groups (3.1 ± 2.3 vs 1.4 ± 0.9 IU/l; $P<0.001$). While an increment in LA dose was required in seven patients (23%), no patient needed a TA dose increase ($P=0.011$). Nevertheless, at the end of one year, clinical progression (Tanner stages, growth velocity, skeletal maturity, etc.) of two groups were not different, with similar doses of LA and TA (126 ± 66 and 119 ± 25 μg/kg; $P=0.59$). **Conclusion:** Despite similar clinical efficacy with leuprolide, triptorelin provided better LH suppression without a need for dose increment. So it might be more preferred for treatment of girls with CPP because it.

P2-P779

Central Precocious Puberty in a Female with Gonadal Dysgenesis and Bilateral Gonadoblastoma

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Background: Gonadal dysgenesis may be rarely associated with precocious puberty (PP) and development of gonadoblastoma. In these patients cases of peripheral PP have been reported. On the contrary, a central PP has been very rarely described. **Objective and hypotheses:** To describe a female with central PP associated with a bilateral gonadoblastoma. **Results:** A 8 year and 5 month old phenotypically female child, presenting suspected PP was remitted to our attention. Clinical examination revealed a B3 AH2 PH3-4 Tanner stage associated with the development of a mild clitoris hypertrophy in the last months; bone age was advanced (18 months); no evidence of dismorphic features. The height was 129.3 cm (50 th centile), weight 39.400 Kg (90 th centile), BMI 23.27 (>97 th centile). Pelvic ecography showed pre-puberal gonads and uterus. Routine blood examimations revealed normal levels of CEA, hCG, αFetoprotein, ACTH, 17-OH-Progesterone,

Aldosterone, Renin, DHEA-S, Δ4-Androstenedione, and 17β-Estradiol. However, Testosterone was very high (233 ng/dl). GnRH test showed very high levels of LH and FSH. Finally, MRI showed apparently normal gonads and hypoplasic uterus. Karyoptype was 45,X/46,XY(50%/50%). An explorative videolaparoscopy disclosed a hypoplasic uterus, right monolateral fallopian tube and left epididymis. The histological evaluation of the gonads showed the presence of a bilateral gonadoblastoma. So, the patient carried out a bilateral salpigogonadectomy. **Conclusion:** Our case emphasizes the importance of taking into account among the different causes of PP the possibility of steroid hormone secreting tumors and, at the same time, to find the phenotypic characteristics that may make us assume a more complex etiology of the clinical picture.

P2-P780

Precocious Puberty: A Single Academic Center Experience

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Background: The frequency of makorin RING-finger protein 3 gene (MKRN3) mutations in Finnish patients with precocious puberty (PP) is not known. As a first step to investigate this, we describe the diagnoses underlying PP in a single academic center. **Objective and hypotheses:** To review the diagnoses in children who were presented with signs of PP (adrenarche excluded) at the Helsinki University Hospital, with a special emphasis on the identification of familial cases. **Methods:** In this retrospective chart review, we searched the hospital electronic patient records with ICD-10 codes for premature thelarche (PT), peripheral precocious puberty (PPP), organic central (OCPP), and idiopathic central precocious puberty (CPP) to identify children that had been evaluated for the clinical signs of puberty before the age of 8 years in girls and 9 years in boys. **Results:** This study cohort contained (4/2016) more girls ($n=69$) than boys ($n=4$, $P<0.05$). The most frequent diagnoses were CPP (66% of the cases), PT (19%), OCPP (8%), and PPP (5%). In girls, the most common diagnosis was CPP (70%), and, in boys, OCPP (75%). Interestingly, 34% of patients with PP reported a positive family history for early puberty. Patients with CPP or OCPP had significantly higher basal LH, FSH, and GnRH-induced LH levels than those with PT or PPP ($P<0.05$). A brain MRI scan was performed in 48% of the patients of whom 20% showed an abnormal result. **Conclusion:** In Finland, similarly as described in other European countries, idiopathic precocious puberty affects girls more often than boys, and a pathological cause in boys should always be suspected. We are currently gathering data on the familial cases for the MKRN3 substudy.

P2-P781

Does Pituitary Volume have the Diagnostic Value on Growth Hormone Deficiency and Prognostic value on the Response to Growth Hormone Therapy?

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Background: Pituitary gland imaging is conventionally done after the diagnosis of growth hormone (GH) deficiency was established, to ascertain the cause of GH deficiency. **Objective and hypotheses:** We aimed to determine the differantial diagnostic value of pituitary volume (PV) on GH deficiency, and effect of PV on responses to GH therapy. **Method:** This retrospective study was conducted on 102 growth hormone deficient (GHD) patients (52 females, 50 males), treated and/or being treated with GH in respect of the current guidelines and 43 non GHD short children (17 female, 26 male). The patients' data was collected from medical records. Other pituitary hormones had been evaluated. Patients with any other pituitary hormone deficiency, history/clinical evidence of any chronic diseases, or other endocrine abnormalities, genetic syndrome, prematurity/small for gestational age birth, head injury, craniospinal irradiation were excluded. Patients were also divided into two groups according to pubertal status. PV was calculated according to formula: (height × width × length) × 0.52. **Results:** There were no significant differences in age at the time of diagnosis, female/male ratio, puberty distribution, birth weight between two groups. None of the participants had any structural pituitary abnormalities. PV of non GHD short children was greater than GHD patients ($P=0.009$). PV was also greater in pubertal GHD and non GHD short children ($P=0.002$) than prepubertal patients. PV was significantly correlated with age, bone age, IGF1 SDS, peak GH values ($r=0.26$ $P=0.007$, $r=0.28$ $P=0.004$, $r=0.32$ $P=0.001$, $r=0.24$ $P=0.015$, respectively). However there was no correlation between PV and changes in the height SDS increase in GHD children under GH therapy ($P>0.05$). **Conclusion:** This study emphasizes the differential diagnostic value of PV on GHD, but no prognostic value of PV on response to GH therapy.

P2-P782

Early Puberty; Diagnosis, Treatment and Prognosis

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The aim of this study was to evaluate the diagnosis at the first examination and last visit, etiology, prognosis, clinical properties of girls referred to the pediatric outpatient clinic with a

presumptive diagnosis of early puberty for ten years and defining the effect of treatment on final height (FHt). In this single-center study, we included 1330 patients who were diagnosed during the years 2004–2014. History, anthropometric data, bone age (BA), hormones and pelvic ultrasonography were analyzed. Bone age was determined by left hand X-ray and predicted adult height was calculated. Of the 1330 girls referred for early onset breast development 336 (25.2%) had false alarms for puberty, 22 (1.6%) had peripheral early puberty (PEP), 16 (1.2%) had central early puberty (CEP) with an organic origin. The prediagnosis of the remaining 936 girls were, early puberty (EP) (31.6%), prematüre thelarche (PT) (43.6%) and early onset puberty (EOP) (24.7%). All of the girls predignosed with EP were determined idiopathic central early puberty (ICEP) for definitive diagnose. %37 of the girls prediagnosed with PT were determined ICEP for definitive diagnose and the remaining %63 weren't progressed rapidly. All of the 232 girls prediagnosed with EOP were determined EOP for the final diagnose. According to the first pubertal signs; FHt and FHt SDS of <7 years ($P=0.022$, $P=0.041$) and 7–8 years ($P=0.001$, $P=0.001$) girls was significantly higher in treated groups than untreated groups, however, there was no statistically significant difference between treated and untreated group in >8 years girls. The age of menarche was significantly higher in treated girls than untreated girls. In conclusion, if pubertal signs developed before 8 years, $GnRH_a$ treatment is effective in preserving height and delaying menarche in girls. When treatment is started after 10 years of chronological age in rapidly progressive puberty, there is no significant change in final height.

P2-P783

Basal Levels of FSH and LH can be Helpfull in Diagnosis of Puberty Precocious?

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Background: Luteinizing hormone stimulating hormone (LHRH) test is the gold standard test in the diagnosis of puberty precocıous (PP). The basal levels of FSH (follicular stimulating hormone) and LH (luteinizing hormone) cannot be always reliable. **Objective and hypotheses:** To investigate the relation between the LHRH test and basal levels of FSH and LH. **Method:** Girls with puberty started before the age 8 are investigated. Eighty nine girls diagnosed as central PP between January 2014-June 2015 were involved in the study. Laboratory examination (LH, FSH and estradiol), bone age and pelvic ultrasonography and LHRH test performed in all the patients with LH levels under 0.3 IU/l. Peak LH >5 IU/l accepted as positive for the test. The relation between basal hormone levels and LHRH test results are investigated. **Results:** The ages of the patients ranged from 3.08–9.75 years. LHRH test performed in 59 patient. 39 patients (66.1%) with basal LH <0.1 IU/l test results and 22 of them (56.4%) had peak LH >5 IU/l. There was no correlation between basal LH and peak LH. We detected significant relation between basal FSH and peak LH ($P<0.001$, r: 56), and there was no correlation between basal and peak LH when the effects of bone age excluded. **Conclusıon:** Basal LH levels below 0.1 IU/l is not reliable to exclude PP. In our study, 56.4% of the patients had unmeasurable basal LH levels but diagnosed as central PP with the LHRH test and clinical findings. In some studies, FSH secretion starts in prepubertal period and LH pulsations becomes dominant at the stage 2 puberty. Significant correlation of basal FSH and peak LH in this study, may suggest that basal levels of FSH can be predictive of PP diagnosis.

P2-P784

Body Mass Index and Body Fat Composition are Both Related to Central Precocious Puberty in Chinese Girls

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Background: Obesity in children and adolescents has become an increasing clinical and public health concern. It was reported that obesity is positively associated with sexual maturation in both boys and girls in China. However, the effect of obesity on pubertal development is incompletely elucidated. **Objective and hypotheses:** To evaluate the fat mass and body composition by dual-energy x-ray absorptiometry (DEXA) in Chinese precocious puberty girls, and to examine the association between body fat composition, body mass index (BMI) and pubertal mutation in girls. **Method:** Sexual maturation was evaluated by physical assessment. Skeletal age was determined by a left-hand roentgenogram and assessed by a radiologist according to the technique of Gruelich and Pyle. Ovarian volume was estimated by transabdominal ultrasound. Basal estradiol, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were measured. CPP girls were diagnosed according to their clinical characters and the results of LHRH stimulating test. Total body fat mass and percent body fat (%BF) was assessed with DEXA. **Results:** Altogether, 26 central precocious puberty (CPP) girls and 28 age-matched prepubertal girls (age, 7 to 9 years) were enrolled in this study. The %BF of the CPP girls was significantly higher than control group (30.53 VS 28.33, $P<0.05$); while the BMI of the two groups was 16.84 and 15.78, respectively ($P<0.05$). In the CPP girls, the peak LH level in the LHRH stimulating test was negative correlated with the %BF and BMI. **Conclusion:** Higher BMI and %BF are found in CPP girls and adiposity is associated with early pubertal development in Chinese girls. The use of DEXA has been shown to be a reliable and accurate measurement of fat mass while BMI is also an equivalent measure for assessed the degree of obesity in Chinese girls. Because of its low cost and rapid administration, BMI is still a useful measurement for screening obesity and puberty in large population samples.

P2-P785

Hyperleptinemia in Obese and Non-Obese Children with Early Puberty

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Background: Leptin is mainly produced by adipocytes. In animal and human, it is a potnet anorectic and increases in obesity. Some reported that precocious puberty is prevelent in children with obesity. **Objective and hypotheses:** This study was done to see the changes of blood leptin levels in both obese and non-obese children with early puberty or precocious puberty. **Method:** Study patients consist of 325 children with early puberty or precocious puberty showing abnormally high blood leptin levels (>7.8 ng/ml) who visited our institute for GnRH stimulation tests between Jan 2014 and Feb 2015. Their medical records were reviewed retrospectively. And their clinical and laboratory data was analyzed. **Results:** They are 273 girls and 52 boys. Their mean ages are 9.2 ± 1.7 years. 254 out of 325 (78%) were non-obese, and 71 (22%) were obese. Hyperleptinemia was more frequent in non-obese group than obese group. Blood leptin levels (ng/mL) was significantly higher in obese group compared to non-obese group, 17.0 ± 7.8 vs 12.6 ± 4.9, respectively ($P<0.001$). In obese group, boy's blood leptin levels (ng/mL) are significantly higher than girl's, 23.2 ± 11.2 vs 16.1 ± 6.8, respectively ($P<0.05$). Blood leptin levels does not show any significant difference between GnRH (+) (peak LH >5 mIU/ml) and GnRH (−) groups. In GnRH (+) group, their age was significantly older compared to the age of GnRH (−) group in both girls and boys ($P<0.05$). Interestingly, obese GnRH (+) girl's age was younger than non-obese GnRH (+) girls ($P<0.05$), this would be said that obesity may associates with earlier pubertal onset in GnRH (+) girls with hyperleptinemia. **Conclusion:** hyperleptinemia was more frequently found in non-obese sexually precocious children than expected. Further study regarding the mechanism of hyperleptinemia and its clinical significance in non-obese children with early puberty or precocious puberty is necessary.

P2-P786

Association between Congenital Hypopituitarism and Agenesis of the Internal Carotid Artery: A Case Report

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Background: The abnormalities of the Internal Carotid Artery (ICA) are very rare phenomenona and the agenesis, in particular, has an estimated incidence of 0,01% among the general population. It could also be associated with another rare condition: the congenital hypopituitarism. **Objective and hypotheses:** To describe a very rare case characterized by the association between congenital hypopituitarism and abnormalities of the internal carotid artery. **Method:** Here we describe the case of a 5 months old female that presented respiratory distress after the birth and 1 month later, because of prolonged jaundice, was found to have low FT3, FT4, and TSH (FT3 was <2.3 pmol\l FT4 was <3.5 pmol\l, TSH which was <0.1 microUI\l). She also had an undetectable Cortisol (<9 nmol\l) and IGF1 ($<3{,}3$ mmol\ l). **Results:** MRI imaging demonstrated an ectopic posterior pituitary gland and the anterior pituitary gland appeared very small/hypoplastic. It also showed absence of the right ICA with an anastomotic vessel arising from the cavernous segment of the left ICA, crossing the midline, reconstituting the terminal right ICA and forming the right Middle Carotid Artery further on. **Conclusion:** The case report we described is about a 5 months old patient with congenital hypopituitarism secondary to a hypoplasia of the pituitary gland, an ectopic posterior pituitary gland and the agenesis of the right internal carotid artery. Up to now this is the 14 th case with the association of congenital hypopituitarism and abnormalities of the ICA and the 4 th one under the first year of age. Considering that a reduction of the blood supply is very unlikely to be the cause of the hypopituitarism, the hypothesis of a new, unknown, genetic mutation that could have caused both the pituitary hypoplasia and the agenesis of the ICA seems to be more likely.

P2-P787

Giant Macroprolactinoma in a Female Adolescent – Case Report

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A female patient was firstly evaluated at the age of 12 years, complaining of headaches and visual loss. Physical examination demonstrated adequate height and weight, Tanner stage P1B1. Papillary edema was confirmed by fundus examination. MRI showed a pituitary macroadenoma, $6.6 \times 7.3 \times 6.1$ cm with compression of the optic chiasm and bilateral cavernous sinus invasion. The first prolactin value obtained was 169.164 uUI/ml (normal <210) with the other pituitary axis within normal ranges for gender and age. Due to a sudden bitemporal hemianopsia and threat of vision loss, surgical debulking via classic approach was performed, and tumor volume was reduced. The histopathological examination revealed a prolactinoma with a high proliferative activity (Ki Index $=17\%$). Subsequently, she was treated with cabergoline, with doses ranging from 1 mg to 2.5 mg/week. However, the lowest prolactin level achieved was 538,9 ng/ml

(normal 30–144). Tumor size decreased by only a further of 35% after two years of medical treatment. At the age of 14 year-old, she was addressed to our department for a close monitoring. After 6 months of cabergoline at a dose of 3.5 mg/week, the prolactin nadir was 150 ng/ml, with persistent gonadotropin and thyrotropin insufficiency. Her height was 154 cm (−1,4 DS) associated with an inadequate weight (+3,2 DS) and insulin resistance signs. No spontaneous signs of puberty were observed. The latest MRI revealed a persistent sellar and suprasellar mass (48/30/33 mm) with discreet extension to the cavernous sinus, but with no general mass effect. Partial optic atrophy at the ophthalmological follow-up was highlight. **Case particularities:** Being this fairly rare tumor, there is a lack of treatment guidelines. The postoperative management of this case proves to be provoking, both in the control of the secretion of this large sellar mass, but as well in the ensuring of growth and puberty installation.

P2-P788

Adenomas Pituitary in Children

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Background: Pituitary adenomas are rare in children. Most of them are found in adolescents. Macroadenomas and secreting adenomas are the most common. They can be sporadic, familial, belong to tumor syndromes and be associated with distinct genetic defects. **Objective and hypotheses:** Report phenotypic and genotypic characteristics of pituitary adenomas in children. **Method:** Eight children with pituitary adenoma were identified in 20 years. All underwent clinical examination, paraclinical Assessment (hypophysiogramme, MRI ± CT, Ophthalmic bilan) and a genetic study (Menine, AIP, FIPA). **Results:** Average age was 7±0.4 (6–11) years. Sex ratio F/G: 1.5. Tumor syndrome is constant with ophthalmological disorders in 70% and gigantism in one case. The causes are: prolactin adenoma: 6; Somatotropic adenoma: 2. The tumor lesion is large in all cases: mean tumor height: 26 mm±0.8 (18–45) Endocrine evaluation revealed dissociated anterior pituitary insufficiency n: 100% (GH: 7, TSH: 8, ACTH: 5). The genetic investigation revealed NEM 1 n: 4. The search for the AIP gene and FIPA was negative for the others cases. **Conclusion:** Pituitary adenomas are exceptional in pre pubertal period. They are in large majority, characterized by clinical and genetic diversity. Prolactin adenoma is the most frequently. They must be diagnosed and treated precociously because of their locoregional agressivity.

P2-P789

A Patient with Multiple Endocrine Neoplasia Type 1 Presented with Precocious Puberty

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Background: Multiple Endocrine Neoplasia Type 1 (MEN1) is an autosomally transmitted hyperplastic or neoplastic disorders of some endocrine and non-endocrine organs. Pituiatry tumors develop in 30–70% of patients with MEN1. Mean age at onset of MEN1 associated pituitary tumors is the 4th decade and its occurence before and during puberty is very rare. Although there are two case reports about MEN1 and delay puberty, early and rapidly progressive puberty with MEN1 has no reported yet. **Case:** Eight years and 5 months girl whose father has MEN1, applied with pubic and axillary hair that were detected first 10 months ago. At that time, her tanner stage was 2. The patient was diagnosed as central precocious puberty as a result of LHRH test. Bone age was advanced (2.5 years more than chronological age). The predicted adult height was calculated considerably shorter than the target height and GNRH anologue treatment was started to patient. In pituitary MR, hypointense region which was stabil in size during the follow up, was seen in intermediate lob but it was not interpreted in favor of the adenoma. In biochemical tests at admission, serum calcium level was high whereas serum phosphorus, PTH and 25-OH vit D levels were normal. In follow up, PTH increased, hyperparathyroidism was detected and patient was diagnosed as MEN1 same as her father. Furthermore, growth velocity decreased and patient needed also growth hormone therapy. **Conclusion:** This case emphasize relevance of early screening of endocrine disorders for members of families with MEN1 because of diversity of endocrine disorders and also it should be kept in mind that rare endocrine presentations as precocious puberty can also be detected in the follow up of patients with MEN1.

P2-P790

Precocious Puberty in a Girl With Prader Willi Syndrome

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Background: Prader Willi Syndrome (PWS) is a rare genetic disorder with a wide range of symptoms manifestation. Main characteristics are hypotonia, growth retardation, feeding difficulties in neonatal period, increased appetite and obesity in childhood, delayed puberty or hypogonadism in adolescence. It is also associated with behavioral disturbances and impaired cognitive function. The genetic defect is located on the 15q11-13 chromosome. **Objective and hypotheses:** A 7 years old girl with PWS, admitted to our unit for the regular follow up due to growth hormone treatment. She was diagnosed at the age of 2 months. Her

genetic test showed deletion of paternal 15q11-13 and presence of one maternal allele on the D15S10, Gabrb3 and D15S113. **Method:** Physical examination revealed bilateral thelarche and pubarche (Tanner stage: B2A1P2M0). Her height was 118.7 cm (−0.47SDS), her weight was 27 kg (1.7 SDS) and her BMI was 19.16 kg/m^2 (1.68 SDS). GnRH test result was indicative for puberty (peak LH:17.4 mIU/ml, peak FSH:13.4 mIU/ml). **Results:** The patient didn't follow puberty suppression treatment as the thelarche was spontaneously regressed. In the next 6 months thelarche relapsed, increased growth rate was noted and the laboratory tests revealed augmented LH, FSH and Estradiol levels. On the physical examination, height was 127.6 cm (0.06 SDS), weight was 36 kg (3.4 SDS) and BMI was 22.32 kg/m^2 (2.25 SDS). She was put on GnRH analogue treatment. **Conclusion:** The most common pubertal disorders of the PWS are delayed or incomplete puberty. In our case the patient presented with incomplete precocious puberty but later progressed to complete precocious puberty. There is a very limited amount of information in the literature concerning association of precocious puberty with PWS (<4%), probably due to deletion of specific genes on the affected part of the chromosome. Recently MKRN3 gene mutation, which is located on the affected part of the causative chromosome, has been correlated with precocious puberty in patients with PWS.

P2-P791

Menstrualcharacteristics and Problems in 9–18 Years Old Turkish School Girls

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Background: The aim of this study is to determine menstruating girls' sectional characteristics and the frequency of the menstrual problems. **Method:** The study was done in randomly selected primary, junior and high schools at Kayseri Province between December 2014–March 2015. After obtaining the permits adolescent girls in 9–18 age groups were included in the study. Following preliminary information, informed consent forms and questionnaires were distributed. Participants were asked about epidemiological characteristics of menstruation and accompanying problems. The questionnaires were then evaluated. **Results:** This study consists of equal number of participants ($n=2000$) from all age groups. 63.7% of girls ($n=1274$) had started menstruating. It was found that the mean age at menarche was 12.74 ± 1.03 years, the mean menstrual cycle length was 28.1 ± 5.7 days, duration of menstrual flow was 5.9 ± 1.4 days and number of pad used per day during period was 3.4 ± 1.3. With a prevalence of 84.8% ($n=1080$), dysmenorrhea was the most prevalent menstrual disorder and the average pain score of dysmenorrhea was 5.87 ± 2.45. Of menstruating girls, 34% ($n=439$) were found to use painkillers, the common one was paracetamol;during this period the prevalence of non-medical methods to relieve pain was 35.2%; the rate of seeking medical help for dysmenorrhea was 9.3% ($n=119$). Of participants 90.8% were discussing their menstrual problems with their mothers. In menstruating girls, the rate of school absenteeism was 15.9% as general and 18% in the group with dysmenorrhea. Of participants 5.2% ($n=104$) reported having hypertrichosis and 40.9% ($n=818$) of them have acne problems. **Conclusion:** Problems related to menstruation are common in adolescents and affects their social life. In adolescent girls the most common menstrual problem is dysmenorrhea and it affects school performance and attendance and those with menstrual problems showed a low rate of seeking medical help.

P2-P792

Haplo-insufficiency for *LHX4* Alone does not Result in Hypopituitarism

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Background: Two LIM homeodomain transcription factors, Lhx3 and Lhx4, are critical in the development of the nervous system and pituitary gland in mice. *Lhx4* null mice die shortly after birth and have abnormal pituitary gland development. Recently, the first human homozygous *LHX4* mutation was described, resulting in congenital hypopituitarism and neonatal death. Heterozygous *LHX4* variants have been described and are linked to hypopituitarism but have variable penetrance. **Hypothesis:** Haplo-insufficiency for *LHX4* per se does not cause hypopituitarism; either *LHX4* variants act in a dominant negative fashion or a second genetic/environmental abnormality is required to affect pituitary function. **Clinical case:** The index case was born at term weighing 3.1 kg. She had neonatal pneumonia, and feeding problems and continued to have delayed milestones and learning difficulties. She also had day and night enuresis without evidence of diabetes insipidus. A CGH array showed a 2.2 Mb deletion of chromosome 1q25.2–1q25.3 which includes *LHX4*; the deletion was not present in the mother. Investigation showed normal pituitary function and a normal pituitary and brain on MRI. She grew along the 9–25 th centile with a midparental height on the 2 nd–9 th centile. She entered puberty at a normal age (9–10 years) although she had menarche at the age of 10.5 years. There was a family history of learning difficulties, deafness, renal abnormalities and anencephaly in three paternal cousins. The father is healthy. His genetic analysis is still pending. **Conclusion:** Haplo-insufficiency of *LHX4* in itself does not result in pituitary pathology. Redundancy or rescue by other transcription factors may be responsible for the absence of a pituitary phenotype in *LHX4* dosage reduction. Heterozygous *LHX4* mutations described in hypopituitarism may be part of a digenic or oligogenic cause of disease or act in a dominant negative fashion.

P2-P793

A Nursing Perspective: Best Practices for Pubertal Suppression for Individuals with Central Precocious Puberty and Transgender

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Background: Through nursing collaboration within the Canadian Pediatric Endocrine Nurses (CPEN) network it has become evident that there are differences in practices across the country in the suppression of puberty**. Objective and hypotheses:** Exploration of these differences for pubertal suppression in Central Precocious Puberty (CPP) and Transgender (TG) youth coupled with a thorough search of current literature can inform future best practice. Aside from effective suppression of puberty, goals of treatment should include 1) minimizing clinical side effects of treatment, 2) lowering pain and anxiety of anticipated treatments for child and parent, 3) providing least cost alternatives for the family related to the prescribed product and time expended for injections around parking costs and missed time at work and school, and 4) considering least cost options for the healthcare system related to nursing time for teaching and administering the treatment. **Method:** Pediatric endocrine nurses from 15 centres across Canada were invited to participate in an online survey that explored their clinical practice in providing treatment for pubertal suppression. **Results:** Presented data includes such elements as products, dosing schedules, techniques used to lessen pain and anxiety, aspects of funding and cost coverage and options for who administers the medication. **Conclusion:** Through collecting and exploring these results, we provide information that will be used to identify and disseminate best practices related to suppression of puberty in CPP and TG individuals.

P2-P794

An Unusual Association between Empty Sella and Central Precocious Puberty

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Background: Empty sella refers to the radiographic appearance of an enlarged or deformed sella turcica and it is considered a rare occurrence in childhood. Many reports have suggested that it is associated with hypothalamic-pituitary dysfunction, with a high prevalence of growth hormone deficiency, as well as multiple pituitary hormone deficiency, idiopathic delayed puberty and isolated diabetes insipidus. **Objective and hypotheses:** We describe the case of a girl in whom central precocious puberty was diagnosed in association with a partially empty sella and who had no other hypothalamic-pituitary dysfunction. **Methods:** The girl was evaluated at the age of 6 years and 6 months for an early pubertal development. Family history could not be assessed because the child has been adopted in Nepal. Breast development corresponded to Tanner stage II. We noticed an increase in growth velocity that was of 6 cm in six month. She performed blood count, urinalysis, hepatic profile, thyroid function, tumour markers, a GnRH stimulation test, bone age, pelvic ultrasound and a brain MRI. **Results:** All tests performed were normal. The GNRH test revealed a pubertal response with a FSH peak concentration of 19.9 mUI/ml and LH peak of 38.1 mUI/ml, both at 30 minutes. Her bone age (Greulich and Pyle method) was 8 years. Pelvic ultrasound showed higher uterine volumes and fundus/cervix ratio and increased ovarian volume with multiple follicles. The MRI of the hypothalamic-pituitary region revealed a partially empty sella. She performed: basal growth hormone, cortisol, IGF-1, prolactin and serum electrolyte that were all normal. **Conclusion:** The association of central precocious puberty with primary empty sella has been documented infrequently, and it may be due to the stretching of the pituitary stalk causing an increase of the LHRH transport mechanism by the hypothalamus to the pituitary gland.

P2-P795

Congenital Anomalies of the Kidney and Urinary Tract (CAKUT) in Children Born Small for Gestational Age (SGA) - Our Experiences

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Background: Congenital anomalies of the kidney and urinary tract (CAKUT) represent several types of malformations with occurrence of 1 in about 500 live births. **Objective and hypotheses:** Small for gestation age (SGA) may influence prevalence of CAKUT and progression of chronic kidney disease (CKD) in children. The aim of this study was to elaborate prevalence, clinical features and outcome of SGA born children with associated CAKUT. **Method:** Our cohort consisted of 100 SGA born children investigated for associated congenital anomalies of urinary tract. We analysed anthropometric and clinical birth data in these children with diagnosed CAKUT and estimated a stage and time of onset of chronic kidney disease by biochemical and imaging technics. **Results:** We revealed that 7 (7.0%) SGA born children had associated CAKUT. Their mean birth weight was very low (1855 gr/−3.93 SDS) and birth length (45.57 cm/−2.17 SDS), as well. A significant growth failure with

reduced weight and BMI were noticed at the time of diagnosis. A diagnosis of CAKUT in 4/7 of them was established in the first few months of life, but in others 3 later in early childhood. Two of three children diagnosed with unilateral kidney agenesis had normal glomerular filtration rate (GFR). Two children with hypodysplastic kidneys and 1 child with vesicoureteral reflux grade 2 had Stage 2 CKD (GFR 60–90 ml/min/1.73m^2). Another patient with vesicoureteral reflux grade 3 was staged 3 CKD at GFR 47.2 ml/min/1.73 m^2. One child with stage 5 CKD needed kidney transplantation. **Conclusion:** Herein we presented 7 SGA born children with CAKUT from Macedonia. Early recognition, assessment and treatment of these anomalies might improve the quality of life of these children.

P2-P796

Severe Juvenile Hypertrophy of the Breast with Hypercalcaemia; Mastectomy v's Reduction Surgery

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Background: A 10 year old girl with a background history of severe autism and developmental delay presented with significant and rapidly progressive asymmetrical breast enlargement accompanying her relatively rapid progress through puberty. There was associated tissue breakdown exacerbating her discomfort and leading to increasing problems with anxiety and behaviour. **Objective and hypotheses:** To explore the aetiology of the huge breast development and the mechanism of hypercalcaemia and consider the options for treatment and the ethical dilemma that this presented regarding mastectomy v's reduction surgery. **Method:** Case presentation. **Results:** Endocrine investigations including LH, FSH, IGF, IGFBP-3 and prolactin were all within normal range. An Ultrasound scan revealed hyperstimulated breast tissue with no abscess or malignant features. The case highlights a rare and interesting condition; cases of severe juvenile hypertrophy of the breast have been previously reported but there remains a paucity of evidence. Options for treatment were to continue with medical management or consider surgical intervention. A literature review suggested the most appropriate surgical intervention was total simple mastectomy. **Conclusion:** Total, simple mastectomy was undertaken following initial management with Gonapeptyl and Tamoxifen. Samples were sent for PTH-rP and 1,25 OH vit D to further evaluate the cause of hypercalcaemia. Histology of the breast tissue revealed features consistent with massive juvenile hypertrophy.

P2-P797

Report Two Cases of Dopa-Responsive Dystonia

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Background: Dopa-responsive dystonia is a genetic disease that rarely reported in domestic and foreign. Its clinical characteristics is so complex and diverse that it is easy to lead to misdiagnosis and delayed treatment. However, early diagnosis and timely and appropriate treatment can completely improve symptoms. Fortunately, now we can take advantage of gene sequencing to diagnose this rare disease. **Objective and hypotheses:** Understand the research progress of dopa-responsive dystonia by reporting two cases of this rare disease. **Method:** Analysed the clinical characteristics and gene mutation of two cases of dopa-responsive dystonia patient and reviewed the related literatures. **Results:** Gene Diagnosis of two cases of dopa-responsive dystonia and a dramatic and sustained response to treatment of levodopa. **Conclusion:** Dopa-responsive dystonia is a rare genetic disease. Its characteristics include: (1) Symptoms show marked diurnal fluctuation in childhood; (2) Small dose of levodopa treatment show complete and sustained effects; (3) Regulating role of dopamine D2 receptors result in the high level of prolactin. Besides, full exon sequencing contributes to the diagnosis of dopa-responsive dystonia, therefore, the children who highly suspected the disease should be taken genetic test for early diagnosis and promptly exactitude therapy, which can manifestly reduce complications.

P1-P798

Abstract withdrawn.

P1-P799

NPR2 Gene Mutations Associated with Acromesomelic Dysplasia Maroteaux Type are Mostly Unique to Families

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Background: Acromesomelic dysplasia Maroteaux type (AMDM) (OMIM 602875) is a rare autosomal recessive skeletal disorder with an approximate prevalence of 1/1,000,000) and characterized by severe dwarfism accompanied by shortness of distal and middle segments of extremities. Mutations in the *NPR2* gene which encodes for the natriuretic peptide receptor B (NPR-B) is the underlying genetic cause of this disorder. **Objective and hypotheses:** Genetic confirmation of AMDM and the identification of the causal mutations in *NPR2* gene. **Method:** A total of 8 Individuals, belonging to 7 families, diagnosed of AMDM plus relatives were referred from UK, France, India and Spain for genetic analysis. The patients fulfilled clinical and radiological criteria of AMDM and the informed consent was obtained. Molecular genetic study: DNA was extracted from peripheral blood leukocytes by standard techniques. All the coding exons as well as intro-exon boundaries of NPR2 gene were amplified and directly sequenced by Sanger method. **Results:** The clinical diagnosis was genetically confirmed in all the patients. Ten novel mutations were identified and each mutation was unique for each patient (P) or family (F) Table 1. **Conclusion:** 1) We have identified ten novel mutations in *NPR2* as the cause of AMDM, which broadens the spectrum of inactivating mutations in this gene. 2) These *NPR2* mutations are 'private': unique to individuals and/or families. 3) The identification of the causal mutation in AMDM is important not only to confirm the clinical and radiological diagnosis but to enable a proper genetic counseling and an eventual prenatal diagnosis.

Table 1.

P	F	Mutation at cDNA level (RefSec NM_003995.3)	Mutation at protein level
1	1	c.[494del];[494del]	p.[Arg165Leu*fs**80]; [Arg165Leu*fs**80];
2	1	c.[494del];[494del]	p.[Arg165Leu*fs**80]; [Arg165Leu*fs**80];
3	2	c.[1330del];[1330del]	p.[Asp444Thr*fs**33]; [Asp444Thr*fs**33]
4	3	c.[245T>C];[2118C>A]	p.[Leu82Pro]; [Asp706Glu]
5	4	c.[2548_2551del]; [.2548_2551del]	p.[Glu850Leu*fs**32]; [Glu850Leu*fs**32]
6	5	c.[1124G>A];[1124G>A]	p.[Gly375Asp]; [Gly375Asp]
7	6	c.[1084_1089del]; [2137A>T]	p.[Leu362_Arg363del]; [Ile713Phe]
8	7	c.[1351+7G>A]; [2107C>T]	p.[?]; [Gln703*]

P1-P800

Rare Cases of Ornithine Transcarbamylase Deficiency and Variant Turner Syndrome

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Background: Turner syndrome, a condition that affects only girls and women, result when the X chromosome is missing or partially missing. Ornithine transcarbamylase (OTC) deficiency, the most common inherited urea cycle disorder, is transmitted as a partially dominant X-linked trait. The OTC gene maps to Xp21.1 and spans approximately 73 kb, containing 10 exons and 9 introns. OTC deficiency is diagnosed using a combination of clinical findings and biochemical testing, while confirmation is often done using molecular genetics techniques. Here, we report two girls diagnosed with OTC deficiency and Partial Xp deletion. **Case 1:** A 15-years-girl was diagnosed with OTC deficiency on the basis of clinical and biochemical findings including hyperammonemia, high level of glutamine and low citrulline in plasma and increased orotic acid in urine at 13 months of age. No mutation of OTC gene was identified by Sanger sequencing. Although ammonia was well-controlled with low protein diet and ammonia scavenging agents, the patient showed intellectual disability and autistic-like behavior. Subsequently, karyotyping was performed in the patient because she demonstrated profound short stature (height <3th percentile) and primary amenorrhea. High resolution chromosome study revealed a large deletion within chromosome X, bands p 21.1 to p 11.4. **Case 2:** A 3 year-old girl was presented with lethargy and vomiting. At that time, plasma ammonia increased to 308 μmol/l (normal range <50 μmol/l) and the additional results of plasma amino acid analysis and urinary orotic acid were compatible with OTC deficiency. Targeted sequencing of OTC gene was normal, then multiplex ligand probe analysis revealed all nine exons deleted. As short stature and pigmented retinopathy were observed in the subject, the CGH microarray was performed additionally. We confirmed a deletion within chromosome X, bands p 21.1 to p 11.4, about 5 Mb. **Conclusion:** We described two girls with rare inborn error disorder, OTC deficiency due to Xp deletion. Further evaluations will be needed to elucidate the role of X-linked genes in Turner syndrome.

P1-P801

Prepubertal Ultra-low-dose Estrogen Therapy is Associated with Better Lipid Profile than Conventional Estrogen Replacement for Pubertal Induction in Adolescent Girls with Turner Syndrome – Preliminary results

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Background: Estrogen replacement is a treatment of choice for pubertal induction in adolescent girls with ovarian failure due to Turner syndrome (TS). Recently published data show, that prepubertal low dose estrogen replacement is more physiologic, and can optimize response to growth hormone treatment, pubertal timing, and improve cognition. The metabolic effects of such treatment regimen have not been fully investigated to date. **Objective and hypotheses:** The study aimed to compare the impact of prepubertal low-dose estrogen therapy (LE) vs. conventional estrogen replacement (CE) on glucose and lipids metabolism in adolescents with TS. **Method:** The study included 28 TS patients treated with human recombinant growth hormone. In LE group ($n=14$, mean age 13.8, SD 1.55) low dose of oral 17β-estradiol (62.5 μg daily) was introduced before age 12 (mean 10.5, SD 0.95) and followed by a pubertal induction regimen after age 12, in CE ($n=14$, mean age 16.4, SD 1.64) pubertal induction was started after age 12 (mean 14, SD 1.96). In all participants before, and 3 years after starting 17β-estradiol, total cholesterol (TC), LDL cholesterol (LDLc), HDL cholesterol (HDLc) and triglycerides (TG) were measured. Standard oral glucose tolerance test was performed with the assessment of fasting (G0) and after 120' post-load of glucose (G120), and insulin levels (I0, I120). Insulin resistance index (HOMA-IR) was calculated. **Results:** There was no significant differences between LE and CE in any parameters before introduction of 17β-estradiol (TC 4.1 vs 4.3 LDLc 2.2 vs 2.4 HDLc 1.6 vs 1.4 TG 0.9 vs 1.0 G0 4.2 vs 4.4 G120 4.8 vs 5.5 mmol/l; I0 6.8 vs 8.0 I120 21.3 vs 67.0 μIU/ml; HOMA-IR 1.3 vs 1.6). Three years after 17β-estradiol: TC and LDLc levels were significantly lower in LE group (3.8 vs 4.4 mmol/l, $P=0.004$; 1.9 vs 2.4 mmol/l, $P=0.03$). The other parameters did not differ significantly (HDLc 1.5 vs 1.6 TG 1.2 vs 1.3 G0 4.6 vs 4.8 G120 5.2 vs 6.0 mmol/l; I0 12.3 vs 15.6 I120 62.7 vs 83.7 μIU/ml; HOMA-IR 2.5 vs 3.6). **Conclusion:** Prepubertal LE is associated with better lipid profile than CE in girls with TS. LE should be considered for girls with TS not only due to positive effects on growth and puberty course, but also because its positive metabolic effects.

P1-P802

Cognitive Evaluation in Silver Russell Children

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Background: Silver-Russell syndrome (SRS) is a heterogeneous syndrome characterized by severe intrauterine and postnatal growth retardation and typical dysmorphic features. The major abnormality is the hypomethylation of paternal allele of 11p15 imprinting centre region 1. In 10% of cases a maternal uniparental disomy of chromosome 7 (UPD7) can be detected. Speech delay and learning difficulties have been reported in these patients. **Objective and hypotheses:** The primary end point was to evaluate neurological and cognitive state in SRS children. The secondary end point was the comparison of the two groups UDP7 and 11p15. **Method:** Neuropsychological assessments, including evaluation of intellectual efficiency, cognitive functions, and learning abilities, were performed in 30 patients (17 males, 13 females), aged 6 to 11 years (mean age 7, 5 years) followed at Trousseau Pediatric Hospital (France) from 2008 to 2016. **Results:** Mean overall IQ score in the total SRS sample was 93.36 with a range between 52–118 (the mean IQ in 11p15 group was 97; the mean IQ in UDP7 group was 90.6). 57% of all children needed speech therapy especially in UDP7 group (90% of UDP7 children). A correlation between low birth weight and low IQ has been found, as well as a correlation between birth head circumference and Processing Speed Index (PSI). We have found a link between severe hypoglycemia and low Perceptual Reasoning Index (PRI) and a correlation between enteral nutrition and IQ and lower PRI. Verbal comprehension Index (VCI) is lower in UDP7 children than in 11p15. 2 children with UDP7 had myoclonus. **Conclusion:** We conclude that a cognitive assessment is necessary in SRS patients and UDP7 children should be monitored for the development of movement disorders. We underline the importance to educate parents to prevent hypoglycemia and to recognize the early signs of hypoglycemia.

P1-P803

Body Surface Area Estimation in Girls with Turner Syndrome: Implications for Interpretation of Aortic Sized Index

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Background: Aortic sized index (ASI) defined as aortic root size/body surface area (BSA) is used to provide information on dissection risk in Turner Syndrome (TS). There are multiple equations for estimation of BSA. The impact of using a different BSA equation for calculation of ASI is unknown. **Method:** We calculated BSA of 114 TS girls from 2273 outpatient visits using

Dubois, Mostellar, Haycock, Gehan, Boyd and Furqan formulae. BSA estimation with Dubois [original equation] was used as gold standard. We compared ASI using the different BSA equations in 130 other girls, median age 16.9 years (1.1, 58.2), with aortic root measurements on echocardiogram. **Results:** All BSA formulae were highly agreeable, with Mosteller (mean error −0.007, −0.021 to 0.007), and Haycock (mean error 0.001, −0.014 to 0.016) having all estimations accurate to within 5%. However, ASI calculated using all BSA equations underestimate ASI compared to when BSA was estimated with Dubois, with mean error ranging from −0.033 [Mostellar] to −0.091 [Furqan]. Up to 2% of girls in the high risk ASI [using Dubois BSA] will be reclassified as moderate risk [using Boyd and Gehan BSA]. Up to 8% of girls in the moderate risk ASI [using Dubois BSA] will be reclassified as low risk [using Boyd and Furqan BSA]. In multiple linear regression of factors affecting ASI error, height and weight were significant independent factors ($P < 0.0001$). **Conclusion:** Whilst the limits of agreement between the five equations for estimation of BSA compared with Dubois is high, our study demonstrated for the first time that aortic dissection risk using ASI may be underestimated in some TS girls simply by using the other BSA equations. Given the significant clinical implications, we believe that more accurate and robust methods of evaluating dissection risk in TS are needed.

Table 1.

		TS	NS(F)	NS(M)
Start	Age (yrs)	9.6±3.0	9.7±3.1	11.0±3.1
	Height SDS*	−3.3±1.0	−3.8±1.0#	−3.2±0.9##
	Height SDS**	0.1±1.0	−1.1±0.9#	−1.0±0.9
NAH	Age (yrs)	16.9±1.6	16.7±1.8	18.4±1.6##
	Height SDS*	−2.3±1.1	−2.5±1.2	−2.1±1.2
	Height SDS**	1.6±1.1	0.1±1.1#	0.5±1.2
	Delta Ht SDS*	1.0±0.8	1.3±0.7#	1.1±0.9
	Mean GH (mg/kg/wk)	0.29±0.1	0.30±0.1	0.27±0.1

*Prader reference; **DSR; # = $P < 0.01$, NS (F) vs TS; ## = $P < 0.01$; NS (F) vs NS (M).

doses than those approved. RhGH treatment was started during late childhood. At rhGH start TS girls had an average height on the TS curve but the NS patients had an average height in the lowest quartile. TS girls gained about 1 SD whereas NS (F) gained 1.3 SD and NS (M) 1.2 SD in height (Prader reference curve). As in TS, the height gain in NS is mostly explained by: height at start first year growth and GH dose (positive) and age (negative) Table 1. **Conclusions:** TS patients responded as expected (1.0 SD gain) taking into account the late onset of treatment and the suboptimal GH dose. NS patients responded slightly better which may be explained by their larger growth deficit at the start of treatment.

P1-P804

Near-Adult Height in a Large Cohort of Patients with Turner Syndrome and Noonan Syndrome Treated with rhGH: Results from Pfizer International Growth Database

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Background: Pfizer International Growth Database (KIGS) contains data of Turner syndrome (TS; $N = 7378$) or Noonan syndrome (NS; $N = 613$, female = 224; male = 389) patients who were treated with rhGH. **Objective:** To compare the effect of rhGH on near adult height (NAH) in TS and NS patients. We hypothesized a similar outcome in both diagnoses. Determinants of the treatment outcome in NS patients were also assessed. **Patients and Methods:** Patients with TS ($n = 2766$) or NS (F = 66; M = 74) who reached NAH were analyzed. For demographic data Prader and disease specific references (DSR) were used (1–3). **Results:** Clinical characteristics of the cohorts at GH start and at NAH are tabulated. All groups received lower GH

P1-P805

Percutaneous Epiphysiodesis Around the Knee Effectively Reduced Predicted Excessive Final Height. Preliminary Results on Final Height, Complications and Satisfaction in a Large Cohort of Dutch Boys and Girls

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Background: Percutaneous epiphysiodesis (PE) around the knee is the treatment of choice in the Netherlands to reduce predicted excessive final height. Studies until now are limited, had small numbers of patients and short follow-up periods. **Objective and hypotheses:** This nationwide Dutch long-term retrospective follow-up study aimed to assess final height (FH), complications and satisfaction after PE. Primary hypothesis was: 'The PE around the knee is an effective and safe treatment to reduce final height in constitutionally tall boys and girls.' **Method:** All constitutionally tall boys and girls who were surgically treated with PE in the Netherlands between 2006 and 2015 were included and their outcomes were compared with those of controls who did not

receive any treatment. Anthropometric data were collected including height, weight, and measurements to evaluate body proportions as well as complication records of surgery. All participants were asked to complete a questionnaire regarding satisfaction, late consequences and current function of the knee. **Results:** In total, approximately 400 constitutionally tall boys and girls were surgically treated in the Netherlands between 2006 and 2015. Preliminary results showed that FH in the intervention group ($n=16$) was 194 cm (r:180–217), with a prediction of 202 cm (r:185–224). In controls ($n=8$), FH was 195,5 (r:180–204) with a prediction of 196 cm (r:180–207) In this sample, final height reduction via PE was 8 cm (r:2–17). Reported surgical complications were limited angle of squatting, long caput fibulae and pain after prolonged exercise. Patients were highly satisfied with the outcome of the operation and all would recommend PE as treatment of choice for relatives and friends with tall stature. **Conclusion:** Results in this first sample of the cohort of 400 patients showed a remarkable reduction of final height. Satisfaction was high, despite minor reported complications. The sample size will be extended to the whole cohort of 400 young adults.

P1-P806

Metabolic Health and Safety of GH-Treatment in Silver-Russell Syndrome

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Background: Silver-Russell syndrome (SRS) is characterized by small for gestational age (SGA) birth, severe short stature and variable dysmorphic features. Children born SGA are at increased risk to develop adult-onset disease at a relatively young age. Growth hormone (GH)-treatment is a registered growth-promoting therapy for short children born SGA, including SRS. Data on metabolic health and long-term safety of GH-treatment in SRS are limited. **Objective and hypotheses:** To compare metabolic health and long-term safety of GH-treatment between GH-treated SRS and non-SRS subjects born SGA. **Method:** We measured Fat Mass percentage (FM%) and Lean Body Mass (LBM) by DEXA-scan, blood pressure, serum lipid levels and insulin sensitivity (Si) by frequent sampled intravenous glucose tolerance (FSIGT)-test in 30 SRS ($n=15$ hypomethylation 11p15, $n=6$ mUPD7, $n=9$ clinical SRS) and 151 non-SRS subjects, at start of GH-treatment, at attainment of adult height (AH), and 2 years thereafter. **Results:** At start of GH-treatment, mean (SD) age was 5.3 (3.0) years in SRS and 6.9 (2.3) in non-SRS ($P=0.01$). SRS subjects had a lower weight for height SDS ($P<0.001$) and there was a trend towards lower FM% (7.0 (4.3) in SRS vs. 10.4 (5.0) in non-SRS ($P=0.20$)) and LBM SDS (-2.30 (2.9) in SRS vs. -0.83 (2.2) in non-SRS ($P=0.13$)). At AH, after a mean treatment duration of 10.4 years, FM% and LBM SDS had increased in both groups, but LBM was still lower in SRS ($P=0.005$). Blood pressure, serum lipid levels and Si were similar in SRS and non-SRS during and after cessation of GH-treatment. In both groups, no adverse events considered to be drug-related were observed. **Conclusion:** Besides a lower LBM and FM%, GH-treated SRS subjects have a similar metabolic health profile as non-SRS subjects born SGA, and show no adverse events during long-term GH-treatment.

P1-P807

Auxological Features in Patients with Juvenile Idiopathic Arthritis Treated with Biologic Therapy Preliminary Study Data

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Background: Juvenile idiopathic arthritis (JIA) is a heterogeneous group of diseases associated with an increase of inflammatory cytokines that may to influence child growth. However this is already known, to date auxological data published of JIA patients during biologic treatment are incomplete and very heterogeneous. **Objective and hypotheses:** To evaluate the auxological features in a selected cohort of patients with JIA treated with biologic drugs. **Method:** This single-center retrospective study have evaluated 43 children (22 with polyarticular and 21 with oligoarticular JIA onset) long-term treated with biologics and compared with 86 age and sex-matched healthy controls. Patients with endocrinological or other chronic comorbid conditions or long-term steroid treatments were excluded at the beginning. **Results:** All patients received antiTNFalpha treatment; nine patients received CTLA-4Ig; one patient received anti-IL6. Fifteen patients received >1 biologics. The median height SDS at JIA diagnosis was -0.57 ± 0.80 *vs* 0.09 ± 0.84 SDS of controls ($P<0.0001$) (-0.45 ± 0.85 SDS for oligoarticular ($P<0.05$) and -0.73 ± 0.72 SDS for polyarticular ($P<0.0001$)). The target height SDS was not statistically different (0.02 ± 0.66 *vs* 0.05 ± 0.79 SDS). After disease modifying antirheumatic drugs (DMARDs) and at biologic therapy onset the height was -0.4 ± 0.98 SDS *vs* 0.14 ± 0.86 of controls ($P<0.005$) (-0.37 ± 0.95 SDS ($P<0.05$) for oligoarticular and -0.43 ± 1.03 SDS ($P<0.05$) for polyarticular). After a follow-up of 7.61 ± 2.43 years height SDS was -0.28 ± 1.02 *vs* 0.08 ± 0.81 SDS ($P<0.05$) (-0.19 ± 0.96 SDS (p=NS) for oligoarticular and -0.37 ± 1.09 SDS ($P<0.05$) for polyarticular). The Δheight during biologics treatment was statistically significant considering the all JIA group and oligoarticular ($P<0.0001$) but not polyarticular onset *vs.* controls and between oligoarticular and polyarticular onset ($P<0.0001$). **Conclusions:** Long-term biologic treatments may cause a significant increase of height SDS in JIA patients. However, polyarticular onset JIA may not ameliorate their height SDS despite the obvious clinical improvement of the disease.

P1-P808

Identification of 11p14.1-p15.3 Deletion Probably Associated with Short Stature, Macrocephaly and Delayed Closure of the Fontanelles

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Background: Interstitial deletions of the short arm of chromosome 11 are rare chromosomal anomalies, and are considered to be associated with several clinical conditions including WAGR syndrome. **Objective:** To report the clinical and molecular findings in the first case of a heterozygous 11p14.1-p15.3 deletion. **Patient:** A Japanese female patient was born at 39 weeks of gestation after an uncomplicated pregnancy and delivery. At birth, her length was 42.0 cm (–3.3 SD), weight 3.15 kg (+0.9 SD), and ***occipital-frontal circumference*** (OFC) 36 cm (+2.2 SD). She was found to have large cranial fontanelles and sutures. The closure of the cranial fontanelles was delayed. At 3 years of age, the patient was referred to us because of a short stature. Her height was 83.8 cm (–3.5 SD), weight 11.2 kg (–1.8 SD), and OFC 51 cm (+1.8 SD). She had relative macrocephaly and frontal bossing. She did not show either any motor or mental development delay, and had no other dysmorphic features. Endocrinological studies indicated normal growth hormone secretion and thyroid functions. **Genetic analyses:** A G-banded chromosome and SNP array analyses showed a 9.2-Mb heterozygous deletion at 11p14.1-p15.3 in the patient. 25 genes, including *NELL1,* have been associated with this deletion. The clinically normal parents were found to not have the deletion. **Conclusions:** The loss of the Nell1 function leads to skeletal defects in the cranial vault and vertebral column, and overexpression of *Nell1* causes craniosynostosis in mice. These results imply that short stature and an abnormality of membranous ossification could be explained by haploinsufficiency of *NELL1* on 11p14.1-p15.3.

P1-P809

Early Treatment with rhGH in Patients with Prader-Willi Syndrome Results in Improved Height with No Respiratory Adverse Effects

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Background: Prader-Willi syndrome (PWS) is a complex genetic disorder caused by lack of expression of paternally inherited imprinted genes on Chr15q11-q13. rhGH has beneficial effects on growth, body composition and development. Starting age, dose titration and monitoring remain controversial. **Objective:** To study retrospectively children who presented in our multidisciplinary PWS clinic and assess response to rhGH treatment, auxology, IGF1 concentration and potential complications. **Method & Patients:** In total of 47 patients (male 27, female 20) were followed up; 5/47 were lost to follow-up and 2/47 refused rhGH treatment. 40 patients were treated with rhGH, all had detailed sleep studies before, and six weeks after starting treatment. **Results:** Treatment started at a mean age of 2.1 ± 2.6 years (range 0.58–12.8), 45% of patients ($n=18$) started rhGH before the age of one (0.58–0.97 years). 15% ($n=6$) had evidence of sleep apnoea, requiring non invasive ventilation before starting rhGH. Mean starting rhGH dose was 0.025 mg/kg per day (0.5 mg/m^2 per day) increased to 1 mg/m^2 per day following the second sleep study. At one year, mean dose was 0.7 ± 0.2 mg/m^2 per day. Pre-treatment mean height was -1.65 ± 1.1 SDS (-4.47 to 0.37 SDS), with a weight of -1.43 ± 1.8 SDS (-5.5 to 3.3) and BMI of -0.46 ± 1.6 SDS (-3 to 4). After one year there was an increase of 1.37SDS in Ht (mean -0.28 ± 0.94, range -2.4 to $+2.3$), with a mean weight of -0.24 ± 1.8 SDS (range -4.0 to 3.7) and BMI of 0.08 ± 2 SDS (-3.0 to 4.6). No patient had worsening respiratory status and 2/6 patients discontinued ventilatory support. IGF1 was $> +2.0$ SDS in 60% and the dose of rhGH remained unchanged with repeat yearly IGF1 measurement. One patient stopped treatment (pause in treatment during spinal surgery). **Conclusion:** Early treatment with GH results in improved height in the first year with no adverse effect on respiratory function. We recommend dose titration using auxology and IGF1 concentration.

P1-P810

Phenotypic Variability in a Family with a New SHOX Gene Mutation

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Background: The phenotype of SHOX aploinsufficiency is highly variable also in affected members of the same family with broad differences in severity of short stature, disproportion, presence of Madelung deformity. **Case presentation:** We present a family with a new mutation of SHOX gene. A 2.3 years old girl, born at term from unrelated parents, came to our observation for short stature. Her height was -2.02 SDS, arm span was normal, sitting heigh/height was $+1.3$ SDS, she had cubitus valgus. Target

height was −1.7 SDS; in particular her mother's height was −3.1SDS, sitting height/height +3.7SDS; cubitus valgus, Madelung deformity and mesomelia were present. SHOX gene analysis, performed on the basis of mother's phenotype, revealed an heterozygous nonsense mutation (c.382C>T p. Gln 128Ter) both in the proband and in her mother. The same mutation was found in other four related adults and three children: the grandmother's height was −3.9 SDS with normal proportions; an uncle had Madelung deformity, mesomelia, height −3.1 SDS, sitting height/height +2.97 SDS; a cousin of the mother of our proband had stature −2.5 SDS, sitting height/height +3.7SDS; another cousin of the mother of our proband had a stature −1.58 SDS, normal proportions, bilateral bowing of tibia. As to children, mutation was identified in: a 4 years old boy with height −1.46SDS, sitting height/height +3.5SDS; a 8 years old girl with height −2.04 SDS, sitting height/height +3.5SDS; a 14 years old girl with Madelung deformity, stature −2.08 SDS, sitting height/height +2.7 SDS. **Conclusion:** In preschool age SHOX defect related phenotype can be silent and a careful clinical evaluation of parents is useful for diagnosis. In our family clinical expression of SHOX aploinsufficiency is highly variable but almost all affected patients show increased sitting height/height. This confirms the usefulness of sitting height/height ratio, expressed in SDS for age and sex, as an index of suspicion of SHOX aploinsufficiency.

P1-P811

Correlations between Prepubertal and Pubertal Estrogen Levels and Final Height Out-Come in Growth Hormone (GH) Treated Boys with Silver Russell syndrome

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Background: Children with Silver Russell syndrome (SRS) suffer from severe intrauterine growth retardation. During infancy, short stature and delayed bone maturation are common features. A majority of these children initially have a good growth response to GH treatment. A catch-up period of skeletal maturation is often seen in early puberty. Later in puberty poor height acceleration may be seen. **Objective and hypothesis:** The objective of this study was to evaluate the association between prepubertal and pubertal estrogen levels and final height (FH) out-come in GH treated boys with SRS. The hypothesis was that altered adrenal activity with increased dehydroepiandrosterone (DHEA) secretion stimulates skeletal maturation through the conversion to estrogens. **Method:** Serum concentrations of estrone (E1) and estradiol (E2) were determined by gas chromatography-tandem mass spectrometry at different ages and compared to auxological measures including FH in 11 boys with SRS. Subjects with FH ≤ −1 SDS from target height (TH) were considered responders and subjects with FH > −1 SDS from TH were considered non-responders. **Results:** At the age of 10 all subjects were prepubertal. The majority had entered puberty at the age of 12. Non-responders had significantly higher levels of E2 (median 2 versus 1 pmol/l, $P<0.05$ and 23.1 versus 1.6 pmol/l, $P<0.01$) at the age 10 and 12, and lower E1/E2 ratio (3.2 versus 26.1, $P<0.01$) at the age of 12 compared to responders. **Conclusion:** There is an association between high levels of E2 at the age of 10-12 and low E1/E2 ratio at the age of 12 leading to impaired final height out-come. An increase in E2 secretion before puberty is most likely derived from the adrenal gland. The E2 levels may be sufficient to accelerate skeletal maturation but far lower than what is normally seen during puberty which explains why there is no enhanced growth prepubertally in the non-responder group.

P1-P812

Skeletal Disproportion in Girls with Turner Syndrome

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Background: Turner Syndrome (TS) is associated with short stature and skeletal disproportion. The impact of treatment with recombinant human growth hormone (rhGH) and oestrogen therapy on body proportions is unclear. **Objectives:** To evaluate sitting height (SH) and leg length (LL) in TS before growth promoting therapies and at adult height. **Method:** Retrospective study of height (Ht), SH and LL standard deviation score (SDS) in TS. Body proportion was also evaluated using SH SDS-LL SDS and SH:Ht ratio SDS. Eligible girls were d at least 4 years at baseline, had not yet started rhGH and had no other chronic disease. Thirty girls had serial measurements until adult height. **Results:** In 59 prepubertal girls prior to rhGH (6.6±0.3 years), Ht SDS was −2.6±0.1 with disproportionately shorter legs, LL SDS −3.4±0.2 compared to spine, SH SDS −1.2±0.1 [$P<0.001$]. SH SDS-LL SDS was 2.2±0.1 (>2 SD in 34/59 [58%]) and SH:Ht ratio SDS was 2.3±0.1 (> +2.0 SD in 37/59 [63%]). Disproportion did not differ between girls with 45,X, ($n=19$) and those with other karyotypes (n=38). Therapy with rhGH and oestrogen led to stabilisation of SH SDS but continued improvement in LL SDS. LL SDS pre-rhGH, pre-oestrogen and at adult height were −3.6±0.2, −3.0±0.2 ($P<0.0001$ vs pre-rhGH) and −2.1±0.2 ($P<0.0001$ vs pre-rhGH and pre-oestrogen), respectively. SH:Ht ratio SDS did not change with rhGH therapy prior to pubertal induction: 2.5±0.2 to 2.3±0.2 ($P=0.21$ vs baseline) but was 1.8±0.1 at adult height ($P<0.0001$ vs baseline), suggesting a lesser degree of

disproportion. **Conclusion:** Prepubertal girls with TS have significantly shorter legs compared to their spine. Our study is the first to evaluate the impact of rhGH and oestrogen on body proportions in TS. At adult height, disproportion was still present but less pronounced.

P1-P813

Reconsideration of Mid-Parental Height Calculation

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Background: Estimation of the child's genetic height potential (target height) is an important tool in evaluating growth disorders. Midparental height (MPH) calculated as (Mothers height + Fathers height)/2 ± 6.5 cm), used for this purpose, represents the child's expected height based on parental heights. **Objective and hypotheses:** To evaluate the classical MPH calculations for our population and to explore the optimal MPH model using different mathematical models. **Method:** Height measurements of 988 young adults and their both parents were taken. **Results:** The average heights were 164.46 ± 6.2 cm in girls and 177.1 ± 6.8 cm in boys. On average, girls were 3.1 cm, taller than their mothers and boys were 3.4 cm taller than their fathers. Compared to their calculated MPH, offspring's actual heights were taller (3.8 ± 5.7 cm in males and 2.7 ± 6.4 in females). Correlation of actual height with MPH was slightly stronger in females than males (r: 0.537 vs 0.487, $P < 0.01$). Furthermore, actual heights of females showed stronger correlation with their mother than their father (r: 0.486 vs r: 0.373), whereas in males, these were almost equal (r: 0.400 vs r: 0.404). Subgroup analyses demonstrated that in short (HtSDS < −1) subjects, height was significantly correlated only with maternal height in both genders. In tall (HtSDS > 1) subjects, males' heights correlated better with paternal height while in females this was similar for both parents. When there was a big difference (> 2SDS) between parental heights, offspring's height correlated better with maternal height than paternal height in both genders (r: 0437 vs r: 0.196 in females, r: 0.479 vs 0.064 in males). Based on our data, multilineer regression models were tested to find the best model to estimate the height of the offspring using the parents' heights yielded the formula below as the best model to make the closest estimations. Height SDS: A × Mothers height SDS + B x Fathers height SDS + C. A: Mother's coefficient (0.364), B: Father's coefficient (0.247) C: Intercept (0.421). **Conclusion:** Classical MPH calculation explains only 25% variance in the offsprings height and this becomes less when the offspring is short, tall or when parental height difference is large. Modifications of MPH calculation using multilinear regression model improves accuracy to some extent (Table 1).

P1-P814

Changes to Thyroid Function (TF) Following Treatment with Growth Hormone (GH) Therapy in Children with Prader-Willi Syndrome (PWS)

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Background: Normal TF is necessary for optimal growth. Changes in the hypothalamic-pituitary-thyroid (HPT) axis following GH therapy are reported. GH therapy has been suggested to centrally inhibit TSH production as well as peripherally increasing T4 to T3 conversion which increases negative feedback on TSH production. Hypothalamic dysfunction is a feature of PWS, therefore these patients may be at risk of developing central hypothyroidism associated with GH therapy. **Objective/Hypotheses:** We evaluated the impact of GH therapy

Table 1. (for abstract P1-P813)

	All Females	All Males	Short females	Short males	Tall females	Tall males	Parents discrepant for height	
							Height of Female offspring	Height of Male offspring
MPH	0.537	0.487	0.279	0.175	0.322	0.249	0.470	0.417
Maternal height	0.486	0.373	0.315	0.395	0.256	0.117	0.437	0.479
Paternal height	0.400	0.404	0.089	0.114	0.245	0.276	0.196	0.064

on thyroid status in children with PWS and we hypothesised that they may be at increased risk of central hypothyroidism during GH therapy. **Method:** A retrospective review of children with PWS with growth data recorded on OZGROW (Australian GH database) was performed. FT4 (Free Thyroxine) and TSH (Thyroid Stimulating Hormone) was assessed before and after GH therapy. Between 2003 and 2014, 87 patients had at least one recorded FT4 and TSH test. FT4 and TSH results were standardized by expressing them as a % of the reference range (RR). x% = 100 × ((x-L)/(U-L)), where x is the test result and U and L are the upper and lower values of the RR. Mean test % were compared to an expected mean of 50% for tests taken one year pre-GH and post-GT. We also assessed change in test % for those who had tests before and after GH commencement (Δ%) using a paired t test. **Results:** In the year prior to GH, most FT4 and TSH were in the low normal range while 4 patients had FT4 below the RR (Table 1). Following GH therapy, FT4 and TSH decreased further. This effect was sustained for 3 years (Table 2). **Conclusion:** FT4 was significantly lower than expected in patients with PWS. This further decreased during GH therapy. Whether these changes have adverse clinical effects on growth is unclear. GH therapy has been suggested to decrease TSH by both a direct central and an indirect peripheral mechanism. Analysis of T3 levels is required to distinguish between these hypotheses and elucidate whether Thyroxine supplementation would be of benefit.

Table 1. Mean Test %.

	Baseline	1st Year of GH
N	87	73
Mean FT4 (sd)	33.1 (19.2) %[a]	21.7 (17.5)%[a]
Mean TSH (sd)	38.2 (22.7) %[a]	25.4 (22.6)%[a]

[a]$p < 0.001$, [b]$p < 0.01$, [c]$p < 0.05$.

Table 2. Mean Δ%.

	1 year post GH	2 years post GH	3 years post GH
N	54	34	21
FT4 Δ% (sd)	−11.5 (23.0)%[a]	−8.9 (19.3)%[c]	−8.1 (15.5)%[c]
TSH Δ% (sd)	−12.9 (26.5)%[a]	−15.0(18.6)%[a]	−11.4(18.4)%[b]

P1-P815

6-Year-Old Girl with Mutation in *DNMT3A* – A New Overgrowth Syndrome

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Background: Overgrowth disorders are a heterogeneous group of conditions characterized by increased growth and other clinical features. Overgrowth may be apparent at birth and can be static or progressive. Some syndromes are associated with increased tumor risk. **Objective and hypotheses:** A 6-year-old girl with accelerated growth rate was referred. She was born at term and was 55 cm long at birth (+2.4 SD). At 6 years, she was 134.4 cm tall (+3.7 SD) with a high growth rate at 8.9 cm/year. The weight was 30.2 kg (+2.3 SD). Her growth was above the range for her family. There were no signs of precocious puberty except an advanced bone age of more than 3 years. She had cognitive impairment and slightly retarded motor development. The only dysmorphic sign was heavy horizontal eyebrows. Because of the phenotype a mutation in the DNM3TA was considered. **Method:** Standard DNA sequencing of all coding exons and flanking UTR regions of *DNMT3A* was performed. **Results:** A *de novo* mutation (*DNMT3A* c.1232dup) was detected. In 2014, Katrina Tatton-Brown et al described a study where they found 13 different *DNMT3A* mutations in 152 individuals with overgrowth phenotype. A consistent phenotype was evident amongst the 13 individuals with *DNMT3A* mutations: distinctive facial appearance, tall stature and intellectual disability. *DNMT3A* is a frequently mutated gene in acute myeloid leukemia and have also been reported in other hematological malignancies. **Conclusion:** When assessing a child with tall stature and intellectual disability mutations in *DNMT3A* is important to have in mind. In general, follow-up of children with overgrowth syndrome should be conducted due to the potential increased tumor risk. However, the *DNMT3A* related tumor risk may be linked to a different mechanism and may not be present in patients with truncating mutations.

P1-P816

A Case of Patient with Rubinstein-Taybi Syndrome Type 2 with Complete Deletion of EP300 Gene and Complex Phenotype

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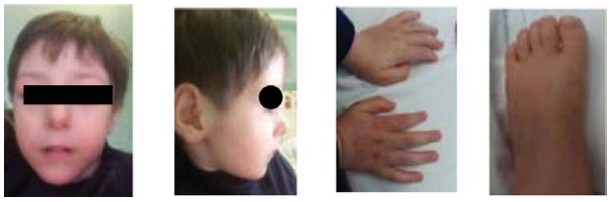
Background: Rubinstein-Taybi syndrome (RSTS) is a rare genetic syndrome characterized by postnatal growth retardation, intellectual disability, microcephaly, peculiar facial features, broad thumbs and big toes and other organs malformations. There are two forms: RSTS type 1 characterized by CREBBP gene mutations (16p13.3); RSTS type 2 dues to mutations/ deletions in EP300 gene (22q13.2). The type 2 is associated with mild phenotype with possible absence of the typical diagnostic signs as broad thumbs and big toes. **Clinical case:** V.B.G has come to our attention at the age of 4 years for diagnostic study. He was born at 36 weeks of gestational age by caesarean section for IUGR. At birth he presented congenital heart disease, hypospadias, post-axial appendix of left hand, choroidal cysts, dysmorphia of corpus callosum, rostrum hypoplasia, agenesis of right olfactory bulb,



enlargement of cerebral ventricles and CSF spaces. The array-CGH showed 22q13.2 deletion of 1.69 Mb with diagnosis of RSTS type 2. At the age of 3 years he presented psychomotor regression with onset of focal seizures. At our observation the child had growth retardation, dysphagia for liquids, constipation, characteristic face, broad toes, limbs dystonia, absent language. **Conclusion:** In literature there are known 34 cases of RSTS associated with EP300 alteration. Of these, only one has complete gene deletion (del22q13.2) of 376 Kb. This patient has a complex phenotype in contrast with "mild" phenotype of the other patients. Because of the larger size of our child's deletion his clinical complexity could also be related to the involvement of adjacent genes. In addition it would be useful scanning EP300 gene also on other tissues to identify a possible mosaicism. Our case represents the second known patient suffering from type 2 RSTS with complete EP300 deletion and clinical features in contrast with a "mild" phenotype. A genotype-phenotype correlation for EP300 disruptive mutations is needed.

P1-P817

Silver-Russell Syndrome with 11p15 Epimutation: Clinical Analysis of Adrenarche, Central Puberty and Body Mass Index in a Cohort of French Children

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Background: Silver-Russell syndrome (SRS) is characterized by intrauterine and postnatal growth retardation, a typical phenotype and feeding difficulties. It is related to 11p15 ICR1 hypomethylation in up to 50% of the cases. Some patients may exhibit signs of early puberty or premature adrenarche, including premature pubarche and/or an exaggerated adrenarche (high dehidroepyandrosterone sulfate (DHEAS) levels for chronological age). Despite early feeding difficulties, some children develop a rapid weight catch-up, probably when overfed, resulting in a marked BMI gain. **Objective:** To analyse the clinical features of a group of 11p15 SRS children, regarding signs of adrenarche, signs of central puberty and anthropometric data. **Method:** We analysed 16 patients 10 years or older followed at the same paediatric endocrinology unit, collecting retrospectively the following data: anthropometric data, age of pubarche, age of thelarche or testicular enlargement, DHEAS levels and baseline insulin-like growth factor 1(IGF-1) levels (without growth hormone (GH)). **Results:** From the 16 patients analysed, 6 (37%; 5 boys and 1 girl) had premature pubarche, and 9 (56%; 6 boys and 3 girls) had exaggerated adrenarche. One girl presented with precocious puberty. Thirteen (81%) presented first with adrenarche signs. Baseline IGF-1 levels were $\geq$ 2.0 SD in 7 (44%), and between 0 and 2.0 SD in 6 (37%). All patients (100%) had a marked BMI increase 1 to 2 years before puberty and/or adrenarche onset (BMI increase of at least +1.0 SD). Final height was available for 6: 3 did not catch-up to a height $>$ −2.0 SD and 2 did not catch-up to their target heights, regardless of GH treatment. **Conclusion:** Premature and/or exaggerated adrenarche seems to be common among these patients, regardless of gender. A rapid increase in BMI may lead to premature adrenarche and early puberty, compromising thereby the final height despite GH treatment.

P1-P818

Haploinsufficiency of Short Stature Homeobox Containing Gene: Clinical Signs and Anthropometric Measurements in Children

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Background: Haploinsufficiency of short stature homeobox containing gene (SHOX) is one of the main monogenic causes of short stature. The phenotype of SHOX deficiency (SHOX-D) is often mild, making difficult to identify which short-statured children should be screened. **Objective and hypotheses:** To estimate the prevalence of SHOX-D in Italian short-statured children and to analyse their phenotype and the sensitivity of various scores and anthropometric measurements in identifying SHOX-D. **Method:** SHOX gene analyses was performed by MLPA (multiplex ligation-dependent probe amplification) in 281 subjects, aged 2–18 years (mean age 8.6±4.0 years, 50.7% females, 70.8% prepubertal, mean height SDS −2.0±0.5) referred for short stature to our Endocrinology Unit. SHOX-D patients were compared to 117 age-, gender- and pubertal status matched children without SHOX mutations (mean age 8.0±3.7 years, 55.3% females, 78.1% prepubertal, mean height SDS −2.0±0.6) for clinical features. **Results:** SHOX mutations were identified in 15 subjects (5.3%). SHOX-D patients showed significantly higher prevalence of micrognathia (66.7% vs. 26.5%, $P<0.01$), short forearm (26.7% vs. 3.4%, $P<0.01$), muscular hypertrophy (40.0% vs. 14.5%, $P<0.05$) and Madelung deformity (13.3% vs. 1.7%, $P<0.01$). No difference was found between SHOX-D and non SHOX-D patients for ear's anomalies, short neck, scoliosis, bowing of forearm and cubitus valgus prevalences. The arm span, the sitting height and the ratios of arm span to height and sitting height to height were similar in the two groups. Using a Rappold score $>$7 points and $>$4 points, as screening criterion to perform the genetic analyses of SHOX gene, out of 15 children with SHOX mutations, 11 and 9 subjects would be missed, respectively. **Conclusion:** The phenotype of children with SHOX-D is highly variable and a positive Rappold score as criterion to screen for SHOX mutations would miss most of SHOX-D subjects.

P1-P819

Clinical and Molecular Characterization of a Newly Recognized Overgrowth Syndrome: Interstitial 7q22.1-7q22.3 Microdeletion

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Background: Overgrowth syndromes comprise a group of disorders associated with excessive growth and other features such as facial dysmorphism, developmental delay, neurological problems and an increased risk of neoplasia. The genetic basis for many of these conditions is being increasingly elucidated. Here, we report on a 3-year-old boy who was referred for evaluation of generalized overgrowth. **Objective and hypotheses:** Our hypotheses is that unclassified overgrowth syndromes may be caused by subtle genomic imbalances. **Method:** Array-CGH was performed as the first line investigation, using DNA extracted from the blood and analyzed utilizing an Affymetrix cytoscan 750K array (Genome build: Hg19). **Results:** A 3-years-boy is the second child of unrelated healthy parents of normal stature. He was born at term with uneventful. Dysmorphic features included high and prominent forehead, hypertelorism, and small mouth. Other features were noted, including cryptorchidism, retractile testis, and developmental delay. Vigorous appetite was also shown in the patient at 1 year of age. He began to walk unaided at 23 months of age, and could sign one words at 3 years of age. To date, at 3 years, height was 106.1 cm ($>97^{th}$ percentile), weight 26.4 kg ($>97^{th}$ percentile) and head circumference 56 cm ($>97^{th}$ percentile). In order to determine putative chromosomal imbalances, microarray array was performed, resulting in a 2.2 Mb deletion in chromosome region 7q22.1-22.3 covering 2,244,033 bp region. The deletion was starting from 102,877,293 bp extending to 105,121,326 bp which contain involved 9 genes including PMPCB, DNAJC2, PSMC2, SLC26A5, RELN, ORC5, LHFPL3, KMT2E, and SPRK2. **Conclusion:** This is the first report on generalized overgrowth syndrome having 7q22.1-7q22.3 microdeletion. We should consider performing array-CGH for the diagnosis of unclassified overgrowth syndromes, because some still it may be caused by subtle genomic imbalances.

P1-P820

International Cooperative Growth Study, NutropinAq® European Registry (iNCGS): Countries Specificities

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Table 1. (for abstract P1-P820)

	Idiopathic GHD		Organic GHD		TS		CRI		SGA		ISS	
	n*	Mean (SD)	n*	Mean (SD)	n*	Mean (SD)	n*	Mean (SD)	n*	Mean (SD)	n*	Mean (SD)
Age- at first Nutropin intake (years)												
GE	812	8.8 (3.5)	89	9.4 (4.0)	108	8.2 (3.5)	26	7.1 (5.0)	106	7.6 (2.9)	66	9.7 (3.8)
FR	573	10.4 (3.6)	85	9.1 (3.8)	41	7.4 (4.1)	3	12.0 (4.4)	124	8.6 (3.5)	24	11.0 (2.9)
IT	172	10.0 (3.1)	2	8.0 (5.7)	9	8.4 (4.6)	18	9.9 (4.7)	4	12.3 (2.2)	4	11.8 (2.1)
SP	261	9.0 (3.7)	11	7.4 (4.5)	15	9.3 (3.6)	10	7.7 (3.7)	47	6.9 (2.9)	23	10.5 (3.5)
RO	123	8.1 (3.3)	15	6.7 (3.3)	14	9.4 (2.8)	0	–	5	5.4 (2.4)	1	12.0
Height SDS art first Nutropin intake												
GE	809	−2.7 (0.9)	89	−2.8 (1.1)	107	−2.9 (0.8)	8	−2.6 (1.4)	105	−2.9 (1.2)	66	−3.0 (1.2)
FR	571	−2.0 (0.8)	85	−1.7 (1.2)	41	−2 0 (1.1)	2	−2.6 (0.3)	124	−2.3 (0.9)	24	−2.6 (0.9)
nr	170	−2.3 (0.9)	2	−3.2 (1.7)	9	−2.2 (0.8)	5	−3.8 (1.7)	4	−2.7 (0.5)	4	−2.5 (1.0)
SP	258	−2.1 (1.0)	11	−2.7 (2.0)	15	−2.3 (1.4)	10	−22 (0.9)	47	−24 (0.9)	22	−1.8 (1.4)
RO	122	−2.6 (1.0)	15	−3.1 (1.3)	14	−2.5 (1.0)	0	–	5	−3.1 (1.0)	1	−0.6
Initial dose of Nutropin (µg/kg/day)												
GE	811	28 (6)	89	27 (6)	109	42 (8)	8	37 (12)	105	33 (6)	66	28 (5)
FR	572	37 (7)	84	35 (7)	41	45 (9)	2	48 (3)	125	41 (10)	24	40 (8)
ITT	172	31 (6)	1	41	9	39 (7)	5	46 (2)	4	31 (06)	4	32 (1)
SP	259	31 (5)	11	30 (4)	15	43 (6)	10	45 (22)	47	35 (7)	23	37 (7)
RO	123	30 (6)	15	31 (5)	14	41 (9)	0	–	5	37 (7)	1	13

*n available data.

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Background: The European iNCGS registry aims to collect long-term safety and effectiveness information in paediatric patients receiving NutropinAq® for growth failure. **Objective and hypotheses:** To report patient baseline characteristics and exposure to NutropinAq® per country. **Method:** International, multicentre, open-label, non-interventional, post-marketing-surveillance study. **Results:** As of 31-Dec-2014, 3250 patients were enrolled in Germany (GE, $n=1552$), France (FR, $n=884$), Italy (IT, $n=222$), Spain (SP, $n=387$), Romania (RO, $n=168$), UK ($n=37$). Within countries, patients presented primarily with idiopathic growth hormone deficiency (IGHD), while other aetiologies were variably represented. In most countries, IGHD and Idiopathic Short Stature (ISS) were generally diagnosed at the most advanced age, Turner Syndrome (TS), Chronic Renal Insufficiency (CRI), Small for Gestational Age (SGA) at the youngest age. Height SDS at diagnosis and at commencement of NutropinAq® was lower (−3) in GE for all aetiologies (see Table 1). Except for TS, NutropinAq® was commenced at a slightly older age in FR and IT (mean (SD): 10.0 (3.6)), compared to other countries (mean (SD): 8.7 (3.6)). Time from diagnosis to treatment initiation ranged from several months (GHDs, ISS) to several years (TS, CRI, SGA). Globally, lowest initial doses were administered in GE and highest in FR (any aetiology). Dose adjustments over time were mostly carried out in GE, FR, IT. GHD patients has the same mean (SD) dose (μg/kg/day) of 30 (5) in GE/IT, and a slightly higher dose in FR: 38 (8). **Conclusion:** The study shows IGHD as the main indication for NutropinAq® treatment among participating countries. The doses used were consistent with labelling recommendations for each indication. Initial doses were lower in GE; highest doses were administered in FR. Although mean age at diagnosis was as expected, treatment initiation was driven by the aetiology, often reflecting delay between diagnosis and treatment initiation.

P1-P821

Case Report of 48,xxyy Syndrome Associated to Father's Radioactive Contamination During the Cesium Accident in Goiânia – Goiás, Brazil

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Background: In total of 48,XXYY Syndrome occurs in 1:20.000–1:50.000 male births. It used to be considered as a variant of Klinefelter syndrome, but now it is considered as a distinct clinical and genetic entity with increased risks for congenital malformations, additional medical problems and more complex psychological and neurodevelopmental involvement. 48,XXYY Syndrome results from the fertilization of a normal female oocyte (Xm), with an aneuploid sperm (XpYpYp) produced through nondisjunction events in both meiosis I and meiosis II of spermatogenesis. Literature shows that 100% of the triploid gamete is from paternal origin. **Objective and hypotheses:** We report a case of 48,XXYY Syndrome, whose father was contaminated by radioactive Cesium 3 years before the proband conception. Since radiation can induce abnormal chromosome segregation during mitotic division, we hypothesis that the father's Cesium contamination might be responsible for this rare occurrence. **Case Report:** SFAD, male, second child of a non-consanguineous young couple. At 12 years of age, he searched for genetic testing due to agenesis of hart palate and nasal septum. At 13 years of age, he was referred to the Pediatric Endocrinologist service, presenting with: tall stature, eunuchoid body habitus, ocular hypertelorism, epicanthal folds, prominent elbows, cubitus varus, single malformed kidney, bilateral inguinal hernia, pes planus, thoracic vertebrae fusion, bilateral femur-patellar arthrosis, hypergonadotrophic hypogonadism, mild intellectual disability, emotional immaturity, anxiety, impulsivity and obsessive-compulsive behaviors. He evolved with osteoporosis (14y), hypertension, insulin resistance, obesity, dyslipidemia (18y), prediabetes (23y), testicular volume was of 5 ml as an adult, infertility due to azoospermy. He died at age 24 due to pulmonary embolism. **Conclusion:** Recognition of medical, developmental and psychological problems that are associated to 48,XXYY Syndrome is important for early diagnosis and interventions, as a way to best outcomes.This is the first reported case of 48,XXYY associated to the Cesium Accident.

P1-P822

Neonatal Haematological Complication in Noonan Syndrome – Future Concerns about Growth Hormone Therapy

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Background: Noonan syndrome (NS) is an autosomal-dominant inherited condition defined clinically by a short stature, specific phenotype, congenital heart disease, bleeding and hematologic abnormalities (particularly leukaemia). There is also a genetic heterogeneity, with all mutations involved in the RAS/mitogen-activated protein (MAP) kinase pathway and with PTPN11 gene mutations counting for almost 50% of patients. **Objective and hypotheses:** To describe the case of a newborn

girl with antenatal diagnosis of NS and neonatal haematological complication (juvenile myelomonocytic leukemia (JMML)-like picture) raising questions about safety of growth hormone (GH) therapy in such particular situation. **Method:** During the intrauterine life, the foetus developed a bilateral pleural effusion. An amniocentesis was performed and the diagnosis of NS (p.G503R c.1507G>C mutation in exon 13 of the PTPN11 gene) was made. The baby was born at 30 weeks of gestation, with 1370 g and 38.5 cm. At the age of 10 days, the peripheral blood profile (leukocytosis – 45.000/mm^3 and thrombocytopenia – 70.000/mm^3) and the bone marrow smear morphology (myelodysplasia) fulfilled the international criteria for JMML. **Results:** The clonality of this myeloproliferation was negative and a spontaneous regression was noted. A regular follow-up was started with the child registered in a European long-term follow-up concerning the risk of malignancy in NS. At the age of 1 year 9 months, the toddler is well-appearing, with characteristic facial appearance and short stature (height is 69,5 cm, on −1 DS on Noonan growth chart). The retrospective diagnosis of NS was made in the mother and maternal grandmother. **Conclusion:** Antenatal NS diagnosis provided important clues for early multidisciplinary approach. A myeloproliferative disorder, even with spontaneous resolution, in a child with NS and PTPN11 germline mutation deserves a very close clinical follow-up. GH therapy to promote growth should be considered in relation to the genotype, the stature gain and the potentially amplified tumour risk.

P1-P823

Effects of a Stressful Environment (SE) on Height, BMI and Menarche

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Background: Children's exposure to stress predicts poor health. Poor growth and maturation are recognized indicators of poor health. **Objective and hypotheses:** SE correlates with height, BMI and menarche. We correlated seven indicators of SE with countries' average adult height, BMI and menarche age. **Method:** Data for 57 countries of average men and women's height, BMI and menarche age were collected from WHO report. They were correlated with the countries' score for SE, built on seven indicators (data World Databank and Transparency International): annual homicide rate, GDP per capita, income inequality (Gini coefficient), corruption perception, urban air pollution and life expectancy at birth. PCA clustered the indicators, and we assessed the effects of SE on height, BMI and menarche age by regression analyses. **Results:** The SE indicators clustered in two: QOL, including pollution, life expectancy, GDP and corruption, and the Social factor, including homicide and inequality perception. The QOL cluster correlated positively with male ($r=0.63$; $P<0.0001$) and female height ($r=0.55$; $P<0.0001$) and with male BMI ($r=0.41$, $P=<0.0001$), while the female BMI (quad $r=0.38$, $P=0.024$) and menarche age showed a U-shape regression (quad $R=0.57$, $P<0.0001$). The Social cluster correlated negatively with male ($r=0.46$, $P<0.0001$) and female height ($r=0.44$, $P<0.0001$) and female but not male BMI (-0.47, $P<0.0001$). **Conclusion:** 1. Adult height, as a measure of child's growth, is a strong and BMI a weak indicator of SE. 2. Women's BMI is low and menarche is strongly delayed in the lowest and less so in the highest QOL score countries. 3. The strongest indicator for poor growth is the QOL cluster: pollution, life expectancy, GDP and corruption, followed by the Social factor: homicide and economic inequality.

P1-P824

Growth Hormone Deficiency in Noonan Syndrome: Does it Influence Clinical Response to GH Therapy?

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Background: Short stature is a main feature of Noonan syndrome (NS). Although rhGH is commonly used in NS patients, it is not known whether a defect in the secretion of GH influences the response to rhGH therapy. **Objective and hypotheses:** The aim of this study was to evaluate the efficacy and safety of rhGH treatment in NS patients, according to the presence of GH deficiency at the baseline. **Method:** We retrospectively collected data of 34 patients with NS (18 males, mean age 9.1 ± 3.4 years, 28 of 34 prepubertal). Genetic test was positive in 27 cases (24 with PTPN11 mutation). Before starting treatment with rhGH, at an average dose of 0.031 ± 0.005 mg/kg per day, patients undertook GH secretion test after stimulation. With normal secretion test (peak >8 ng/ml), rhGH was administered off-label. Growth was evaluated as change in height Z-score (Delta-Height-SDS) at one, two and three years after the start of therapy. **Results:** At the baseline 13 patients had a deficiency of GH secretion (Def group: 7.9 ± 3.3 years; mean height -3.06 ± 1.00 SDS, mean GH peak 5.4 ± 1.3 ng/ml), while 21 showed no failure (NoDef group: $9.7\pm$

3.2 years; −2.95±0.81 SDS, 10±2 ng/ml). After 1 year, therapy with rhGH was effective in improving linear growth in both groups (Delta-Height-SDS Def 0.53±0.40, $P<0.001$; NoDef 0.32±0.31, $P<0.001$). Between the two groups we found no significant difference in growth at 1, 2 and 3 years from baseline, although a tendency was present at the second year (Delta-Height-SDS Def 0.90±0.53; NoDef 0.53±0.49, $P=0.06$). As side effects, insulin resistance (HOMA-IR>2.5) was reported in 5 subjects (Def: 3, 23.1%; NoDef: 2, 9.5%). **Conclusion:** Therapy with rhGH significantly increases growth in patients with Noonan syndrome, regardless of the initial presence of a GH deficiency and in the absence of significant side effects even in subjects with normal stimulation test.

P1-P825

Screening of Birth Length and Parental Height Detects Infants with Poor Catch-Up Growth at Age 2 Years

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Background: A programme of measuring birth length (BL) and parental heights (PH) for neonates classified as Small for Gestational Age (SGA, Birth Weight (BW) $<9^{th}$ centile, UK 1990 reference data) has been adopted in one Scottish hospital since 2008. Neonates with Short Stature (BL≤−2 standard deviation scores/SDS) are invited for re-measurement of weight and height at age 2 years, thus making medical services aware of individuals who have not had adequate catch-up growth relative to their family pattern. **Objective and hypotheses:** To determine whether: (1) catch-up growth has occurred in neonates of short stature by age 2 years; (2) there is a genetic influence on their stature. **Method:** BL and PH were measured for all SGA neonates born in Ayrshire Maternity Unit from October 2013-October 2014. Mid-parental height (MPH) and lower end of parental target range (LTR) were calculated (UK 1990 reference data). For those of short stature, height and weight at age 2 years was measured to determine catch-up growth. **Results:** Of 3482 live births, BW was $<9^{th}$ centile in 416 neonates (11.9%). Short stature was detected in 89 neonates (21.4%) of 28–42weeks gestational age (GA). To date, 34 children have been invited for follow-up, 24 (71%) of whom have attended. Of these, 3 (12.5%) remain ≤-2SDS for height comprising: a preterm infant (BW 1.15 kg, GA $30^{4/7}$) with Ht SDS −3.26 at 2 years, maternal Ht SDS −2.34; and two term babies with Ht SDS −2.86 and −1.95 at 2 years (LTR SDS −2.05 and −2.12 respectively). **Conclusion:** The smallest babies at birth were not the smallest at 2 years and those with the smallest parents had shown good catch-up growth. As expected ~10% of the short cohort remain short at 2 years, two of whom would not have been detected without the screening programme. The number of children requiring re-measurement at 2 years (89/3482) is relatively modest and consideration should be given to extending accurate BL measurement to infants with BW≤15th centile (462 in the current study) since it is known that a cut-off BW of ≤9th centile ($n=257$ for this study) will not detect all cases of short stature at birth[1].

[1]Sardar et al., Short Stature Screening By Accurate Length Measurement Of Infants With Birthweight $<9^{th}$ Centile. Hormone Research in Paediatrics, 2015.

P1-P826

Etiologic Distribution and Characteristics of Patients with Short Stature in a Pediatric Endocrinology Clinic

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Background: Short stature (SS) is one of the most frequent reasons for referral to pediatric endocrinology clinics. **Objective and hypotheses:** We aimed to analyse the etiological factors of SS, in patients of our clinic, who are referred from general paediatrics with high likelihood of endocrinological problems after primary screening. **Method:** 1519 patients (693F) with height <3% were included. Clinical, anthropometric, radiological and laboratory data were recruited from patient's charts. GHD was diagnosed when stimulated GH≤7 ng/ml in two tests, low IGF-I/IGFBP-3 with subnormal growth velocity. **Results:** Presenting age was 10.2±4.2 years (0.2–19.2). Initial height SDS was −3.1±1.0. Target height SDS was −1.4±0.9. Severe SS(<−3.0 SDS) and disproportionate SS were detected in 41.5% and 15.7% of the cases, respectively. SGA was more prevalent in mothers with severe SS (33.3% vs. 19.4%, *P*:0.003). Etiologic distribution of SS was as follows: 33.0% familial and/or constitutional, 18.4% syndromic, 12.7% endocrine disorders, 10.7% chronic diseases, 5.9% non-syndromic IUGR, 4.1% skeletal dysplasia, 4.7% idiopathic, 8.4%. undetermined. Turner Syndrome (TS) was detected in 3.9% of the population and 8.5% of the females. Cytogenetic analysis was performed in 47% of girls; 18% of them were consistent with TS. Isolated GHD, multiple pituitary hormone deficiency and hypothyroidism were detected in 6.8%, 3.5% and 1.6% respectively. Celiac disease was detected in %0.6, despite screening of Celiac antibodies in 46% of the population. In patients with severe SS, skeletal dysplasia and endocrine causes were more common, while, in non-severe SS (Height<−2 SDS, >−3 SDS), normal variant, idiopathic, chronic disease and IUGR were more common

($P<0.001$). **Conclusion:** The initial screen and referring of high likelihood of endocrine problems lead to lower ratio of normal variant SS. When shortness gets more severe, the possibilities of endocrine causes and skeletal dysplasia increase. Having a severely short mother increases the likelihood of being born SGA and subsequent SS.

P1-P827

OSBPL5 Methylation Abnormalities may be Pathogenic in Silver Russell Syndrome Through Genomic Methylation Analysis

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Background: SRS is a typical epigenetic disease. Approximately 40% of patients can not be detected genetic and epigenetic disturbances. **Objective and hypotheses:** To analysis whether there is unknown genes or imprinted genes associated with pathogenicity of SRS and to detect the fine mapping SRS hypomethylation position through the Illumina Methylation 450K chip to detect genome-wide methylation differences. **Method:** To detect genome-wide methylation sites through the Illumina 450K Infinium Methylation BeadChip chip in 7 cases of SRS diagnosed in Beijing Children's Hospital and 5 controls matched age. The two methods were validated by using the classical method of sequencing with focal phosphate and digital PCR. Methylation site probe screening standards meet the following 2 points: (1) adjust Pval $<$ 0.05, if adjust Pval$\geq$0.05, the Pval requires less than 0.05 before correction; (2) case vs control Beta-Difference should be not less than 0.2. That is |Beta-Difference| $=$0.2. **Results:** Screening out 116 differential methylation sites in 484821 probes. Through the GO Pathway enrichment analysis, found the cg25963939 site of OSBPL5 was the most significant methylation difference in case group and normal control group ($P=0.023$, $\beta=-0.243$). The classical method of sequencing with focal phosphate and digital PCR validated it. And the gene is located on 11p14 5'UTR region, it is quite possible pathogenic. **Conclusion:** Through whole genome methylation chip detection, we found the imprinted gene OSBPL5 detected a significant differential hypomethylation site. OSBPL5 may be related to the pathogenicity of SRS.

P1-P828

A Study of Bone Health Index (BHI) in Girls with Turners Syndrome

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Background: Turners Syndrome (TS) is associated with osteoporosis in later life. 'BoneXpert' has enabled the automated assessment of bone age (BA) and Bone Health Index (BHI). Strong correlations between BoneXpert BHI and dual-energy x-ray absorptiometry and peripheral quantitative computed CT measurements are reported. BoneXpert produces a standard deviation score for BHI (BHI-SD) relative to a healthy cohort of children according to BA. **Objective and hypotheses:** To investigate relationships between BHI SDS and hormone treatment in a cohort of girls with TS. **Method:** All patients in our database with TS were reviewed. BA and BHI data analysed against age and therapy received. If patients had multiple readings over time they were grouped according to therapy at time of BHI analysis. **Results:** females had data available and from these 57 x-rays were analysed. All results reported median (range). The BHI-SD of the 57 x-rays was -0.6 (-3.4 to 2.8). GH and oestrogen combined favours bone health with a significant difference in the BHI-SD of patients treated with GH and oestrogen versus those with no GH ($P=0.01$) and those with GH alone ($P=0.0004$). **Conclusion:** This is the first study to review BHI-SD in TS. BHI-SD seems to change over time. Treatment improved BHI-SD score and in particular oestrogen therapy in this study has the most significant impact. A larger cohort study is required to establish the exact nature of the relationship between BHI and treatment for TS.

Table 1. A comparison of age, TW2 BA and BHI-SD for various treatments (for abstract P1-P828).

	No treatment ($n=13$)	Growth Hormone (GH) ($n=21$)	GH and oestrogen ($n=22$)	Oestrogen (after GH) ($n=1$)
Age (yrs)	9.19 (6.31–15.9)	11.59 (6.25–17.3)	15.47 (11.22–18.77)	15.57
TW2 BA	9.17 (6.43–13.71)	11.08 (5.14–15.41)	13.09 (9.4–14.7)	15.71
BHI-SD	-1.8 (-3.4–0.1)	0.4 (-2.41–2.8)	-0.75 (-2.5–0.7)	-1.5

P1-P829

Premature Adrenarche in Silver-Russell Syndrome: A Longitudinal Study

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Background: Silver-Russell syndrome (SRS) is reported to be associated with early adrenarche, but substantial studies are lacking. **Objective and hypotheses:** We aimed to determine the median age at onset of adrenarche, the prevalence of premature adrenarche as well as its causes and consequences. **Method:** Currently we have collected longitudinal data from 40 children with SRS seen during the last 20 years in our centre. The patients fulfilled ≥ 4 of the following criteria: SGA, failure to thrive, short stature, relative macrocephaly, prominent forehead or skeletal asymmetry. Maternal uniparental disomy of chromosome 7 was present in 3 patients, 11p15 loss of methylation in 9 patients, structural chromosomal aberrations outside of 11p15 in 2 patients, 12 patients were negative and 14 patients were incompletely tested. Out of the 40 patients, 33 were treated with GH. Age at adrenarche was defined as the first time point when serum DHEAS was >500 ng/ml or pubarche (PH2) began. Start of adrenarche before 8/9 years of age (girls/boys) was defined to be premature. DHEAS was measured by the same chemiluminescence immunoassay during the full study period. **Results:** The median age at onset of adrenarche was 8.2 years in females (range, 6.1–10.1) ($n=8$) and 9.8 years in males (range, 6.1–12.2)($n=19$). Within the total group, 44% (12/27) had premature adrenarche. The predictor of premature adrenarche was birth weight ($P=0.011$), but not birth length, sex, BMI or height SDS at 2 years of age ($n=27$). Based on the current data a deleterious effect of early adrenarche on the outcome of GH therapy was not detectable. **Conclusions:** Premature adrenarche was frequent and predictable by birth weight, but not by birth length, sex, height or BMI at 2 years of age. The collection of longitudinal data of additional SRS patients is necessary to analyse consequences for metabolism and growth.

P1-P830

A Rare Case of Deletion in 2q24.1: Clinical Features and Response to Gh Hormone Treatment

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Background: Chromosomal imbalances are often due to sub microscopic deletions or duplications not evidenced by conventional cytogenetic methods. **Objective and hypotheses:** CGH array can help in the diagnosis of severe short stature, associated with mental retardation and dysmorphisms. **Method:** We describe the clinical case of a 13.1-year-old girl, born at 35 weeks, from a triplets pregnancy. She was 127.5 cm (<-5 SDS), 33 kg (<-3 SDS); SPAN: 122 cm; PH2B2, bone age: 11 years; mild psychomotor delay, facial dysmorphism (malformed years with a low-set, microcephaly) and feet malformations (flexion deformities, broad halluces). Born SGA, with a growth velocity <-3 SDS, a severe short stature she was a candidate to GH treatment. She started GH at the dosage of 0.035 mg/kg per day with a significant improvement of growth velocity. She had FSH, LH, TSH, fT4: in the normal range; low IGF-1 levels: 139 ng/ml (n.v. for age: 183–850). **Results:** CGH array evidenced a microdeletion of chromosome 2 (2q24.1), interesting genes UPP2, CCDC148, CCDC148-AS1, partially gene PKP4. MRI of CNS and pituitary revealed a small hypophysis with an intrasellar arachnoid cyst. After 11 months of GH treatment she was 134.8 cm (-3SDS), 37 kg; PH3B2. **Conclusion:** A few cases of deletion of 2q24 are reported in literature, and the association of low birth weight, growth delay, mental retardation, facial dysmorphism, cardiac malformations, feet and hands deformities is specific of this deletion. The mild phenotype of our patient could be explained by the small deletion (2q24.1). For this reason, it could be considered a continuous gene syndrome. At our knowledge this is the first case reported in the literature treated with GH and showing a satisfactory growth.

P1-P831

Serum Levels of IL-6, TNF-a, Omentin-1 are Increased in Girls with Turner Syndrome

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Objective: To assess the serum levels of IL-6, TNF-a and Omentin-1 in girls with Turner Syndrome (TS) and to analyze their association with FPG, FINS, TC, TG, HDL-c, LDL-c, and BMISDS. **Methods:** In total of 33 TS girls aged (12.8 ± 3.9) yr and 33 age-matched normal girls aged (12.6 ± 3.7) yr were recruited in the study. Height (Ht) and Weight (Wt) were measured; FPG, FINS, TC, TG, HDL-c, LDL-c, IGF-1 and E2 were also measured; BMI and BMISDS were calculated. Serum IL-6, TNF-a were tested by CBA method and serum omentin-1 were tested by ELISA method. **Results:** In TS group, BMI and BMISDS are greater than that in control group (all $P<0.05$), and the levels of TC, LDL-c, IL-6, TNF-a, omentin-1 are higher than that in control group (all $P<0.05$). IGF-1 and E2 levels are lower than those in control group (all $P<0.01$) (details in table 1).

Table 1. Comparison of the IL-6, TNF-a, Omentin-1 and associated parameters in TS group and control group ($\bar{x} \pm s$).

Parameters	TS group	Control group	*P* value
Age (yr)	12.8±3.8	12.7±3.7	>0.05
Body height (cm)	126.4±13.2	143.2±17.5	0.000
Body weight (Kg)	28.0±7.7	34.8±11.0	0.000
BMI (kg/m^2)	17.2±2.2	16.1±1.9	0.008
BMISDS	−0.5±1.0	−1.0±0.8	0.023
IGF-1 (ng/ml)	191.5±90.6	331.1±172.5	0.001
FINS (μu/ml)	6.5±1.4	6.6±1.4	>0.05
FPG (mmol/L)	4.7±0.4	4.6±0.3	>0.05
HOMA-IR	1.4±0.4	1.4±0.3	>0.05
TC (mmol/L)	4.5±0.7	4.1±0.4	0.007
TG (mmol/L)	1.0±0.5	0.9±0.3	>0.05
HDL-c (mmol/L)	1.4±0.3	1.4±0.2	>0.05
LDL-c (mmol/L)	2.8±0.6	2.5±0.2	0.014
E2 (pg/ml)	10.4±1.1	34.4±18.5	0.002
IL-6 (pg/ml)	2.7±2.1	1.2±0.9	0.000
TNF-a (pg/ml)	0.9±0.8	0.4±0.5	0.004
Omentin-1 (ng/ml)	1.6±1.2	0.9±1.7	0.008

There is no statistically different of FINS, FPG and HOMA-IR between the two groups. IL-6 is positively correlated with BMISDS and TNF-a ($r_s=0.292$, $P<0.05$; $r_s=0.565$, $P<0.001$); TNF-a is positively correlated with BMISDS ($r_s=0.420$, $P=0.001$); omentin-1 was positively correlated with BMISDS ($r_s=0.322$, $P<0.05$). **Conclusions:** Serum levels of IL-6, TNF-a, Omentin-1, TC, and LDL-c are increased in girls with TS. Further investigation is needed to illustrate the relationship among these factors and the metabolic disorders in TS patients.
Keywords: IL-6; TNF-a; Omenitn-1; Turner syndrome; Children and adolescents

P1-P832
Effect of Dietetic Management on Weight in Children with Bardet-Biedl Syndrome

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Introduction: Bardet-Biedl syndrome (BBS) is a monogenic disease characterized by retinitis pigmentosa (>90%), obesity (72–86%), insulin resistant diabetes, and hypogonadism. Weight management is challenging due to frequent association of learning and visual impairment. At our BBS MDT clinic, dietetic review is provided at each visit. Dietetic input focuses primarily on reduced fat and sugar content in diet and exercise is encouraged. Individualised written dietary plan is provided. **Aims:** To assess the effect of dietetic input on BMI-SDS in BBS children. **Methods:** All children attending our MDT BBS clinic between January 2007-December 2014 with at least 3 years follow-up data were included. Paired t-test using SPSS was performed to compare the mean difference in BMI-SDS at baseline and follow-up. **Results:** There were 48 children [median age 8.1 (range 0.9–15.1) years at baseline]. The mean (±SD) BMI-SDS at baseline and after 3 years follow up were similar 3.14 (±1.1) vs 3.18 (±0.9). Patients were grouped into Group A, < 5 years old at baseline ($n=10$) and Group B, >5 years old at baseline ($n=38$). In group A at baseline the median (range) age was 2.4 years (1–4.4) and mean (±SD) BMI-SDS at baseline, 2 and 3 years were 3.8 (±1.7), 4.4 (±1.2) and 4.5 (±0.88) respectively. In group B at baseline the median age was 9.7 years (range 5.01–15.1) and mean BMI-SDS at baseline, 2 and 3 years were 2.8 (±0.68), 2.7 (±0.7) and 2.6 (±0.6) respectively. The reduction in BMI-SDS at baseline and 3 years was not statistically significant ($P=0.19$). Six children (12.5%) developed type 2 diabetes and one had hyperlipidaemia. Prevalence of hypertension was high at 33% ($n=16$) due to the associated renal problems. **Conclusion:** Excess weight gain in early life may be attributed to delayed walking and difficulty in dietary restriction. Despite the increased risk of weight gain in later childhood associated with visual impairment, provision of individualised dietary plans are associated with a non-significant trend towards BMI-SDS reduction.

P1-P833
Analysis of Phenotype and HRAS Gene Mutation in a Chinses Girl with Costello Syndrome

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Background: Costello syndrome is a rare congenital disorder with characteristic findings involving multiple organ systems. The Costello Syndrome Family Network estimates that the birth prevalence in the United Kingdom is at least 1/500,000. So far, there has been only one affected individual reported in China. **Objective and hypotheses:** Diagnose the case of autosomal dominant Costello syndrome by direct squencing of HRAS gene. Analyze the correlation between phenotype and HRAS gene mutation of Costello syndrome. **Method:** Total genomic DNA was extracted from peripheral blood of the patient and her parents. The coding exons 2∼5 of the HRAS gene were amplified by polymerase chain react on (PCR) and sequenced

directly. **Results:** The 7 years old girl was born by vaginal delivery at 35^{+6} weeks of gestation. Birth weight was 3.55 kg, length unknown. Severe feeding difficulty and failure to gain weight were noted during the infant term. The development milestones, mental and language development were delayed. Seizures occurred three times. Her height was 100 cm (−3SD), weight 16 kg (−3SD) and head circumference 52 cm. Her distinctive facial features were characterized by epicanthus, ptosis, low-set ears, wide nasal bridge, full lip and large mouth. Physical findings present include striking deep creases in the palms and soles, coarse skin, worsening kyphoscoliosis, sparse and curly hair. A heterozygous de-novo point mutation in HRAS showed the nucleotide substitution c.34G>A, resulting in p.Gly12Ser amino acid change. **Conclusion:** The phenotype of Costello, Noonan, and CFC syndromes shows such significant overlap that a clear distinction cannot always be made on clinical criteria alone, but rather molecular testing is necessary. HRAS consists of six exons. The G12S mutation is the most common change found in Costello syndrome.

P2-P834

Auxological Features in Patients with Vernal Keratoconjunctivitis

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Background: Vernal keratoconjunctivitis (VKC) patients have an elevated incidence of growth hormone deficiency and thyroid diseases. Nevertheless, no auxological data are available in these subjects. **Objective and hypotheses:** The purpose of this study was to evaluate the auxological features in a cohort of patients with VKC. **Method:** This study included 179 Caucasian VKC patients (119 males, 60 females; mean age 9.63±2.98 years) who were evaluated using standard deviation scores (SDSs) for prepubertal height (PrH), pubertal height (PH), body mass index (BMI), final height (FH), target height (TH), FH minus PrH, and FH minus TH. The control group was 274 Italian children and adolescents (185 males, 89 females; mean age 9.41±3.58 years). **Results:** We found that VKC patients grew better than controls and had significantly higher height SDSs ($P<0.005$). However, their PrH SDSs were not significantly different than their PH SDSs or their TH SDSs. Nevertheless, they had significantly higher PrH and PH SDSs than healthy controls (PrH $P<0.005$; PH $P<0.05$), whereas FH SDSs and TH SDSs were not different. Finally, weight excess percentage was significantly lower in VKC patients compared to controls (10.6% vs 31.7%, $P<0.005$), and significantly lower body mass index SDS than controls ($P<0.001$). These differences were maintained when VKC patients were divided by sex (female $P<0.001$, male $P<0.001$), even if there was a higher frequency of overweight and obesity in prepubertal versus pubertal VKC patients, particularly in the females. **Conclusion:** Our study showed that VKC patients expressed particular auxological features differently than healthy controls, particularly higher height SDSs and lower body mass index SDSs. Further studies could clarify this issue and the underlying mechanisms in order to better understand the etiopathogenetic characteristics of this disease.

P2-P835

Turner Syndrome: Does GH Treatment Influence Glucose Homeostasis?

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Background: Growth hormone (GH) has been shown to reduce insulin sensitivity in Turner girls, however a compensatory increase of insulin secretion by pancreatic beta cells usually occurs, probably stimulated by GH itself. Oral disposition index (ODI) express the capacity of beta cells to adapt to insulin sensitivity. **Objective and hypotheses:** To study longitudinally the insulin sensitivity (HOMA-S), the insulin secretion (IGI) and the ODI in a group of girls affected by Turner syndrome (TS) treated with GH. **Method:** We studied 104 GH treated (0.33 mg/kg over 7 days) TS girls (first evaluation at 9.1±3.4 years) for a median period of 7.2 years (range 2.04–13). Puberty started spontaneously in 46/104 (44%) girls at a mean chronological age of 13.2±2.3 years, however, 41 girls required estrogen treatment to complete pubertal development. In the other 58/104 (56%) girls who did not spontaneously enter into puberty, estrogens were started at a median age of 15.7 years. Every year the children underwent an OGTT which was employed to calculate the HOMA-S (1/((insulin×glucose)/22.5)), the insulinogenic index, IGI ($\Delta I30/\Delta G30$) and the ODI (disposition index=HOMA−S×IGI). **Results:** GH treatment induced a significant increase in height SDS ($P<0.001$) between the first and the last visit, while BMI SDS did not significantly change (from 0.06±1.2 to 0.3±1.2 SDS; NS). No significant changes over the years were observed in term of HOMA-S, IGI, or ODI. IGF-I serum level, after 7 years

treatment, was 475 ± 203 ng/ml (range 343 to 580 ng/ml) in normal range for age. **Conclusion:** This study, while further confirming the safety of GH treatment in TS girls, suggests that it is unnecessary to check annually the glucose tolerance in those girls, reserving glucose homeostasis control in selected patients (i.e obese TS). This approach would lead to a significant reduction of the expenses without lowering the quality of care in our patients.

P2-P836

Renal Anomalies in Children with Turner Syndrome: Experience from a Single-Centre

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Background: Renal abnormalities are estimated to be present in 30–40% of Turner Syndrome (TS). Monosomic patients have a reported greater risk for renal anomalies. **Objective:** To assess the frequency of renal malformations in TS according to karyotype; and report related complications at most recent follow up. **Methods:** The medical records of 182 patients with TS born between 1970 and 2013 were retrospectively reviewed. **Results:** Twenty-one girls (11.5%) were identified with renal/urological anomalies: 15 (71%) horseshoe kidney (HSK), 1 (4.7%) malrotation, 2 (9.5%) single kidney, 1 (4.7%) duplex collecting system (DCS) associated with renal arteries abnormalities and vesicoureteral reflux (VUR), 1 (4.7%) pelvic kidney and 1 (4.7%) crossed fused ectopia associated with DCS. In addition 5 (33%) patients with HSK had associated urological anomalies: VUR (1), DCS and VUR (1), pelvic-ureteric junction obstruction (1), calyceal and pelvic dilatation (2). In 12 patients (57%) urological anomalies were identified incidentally, in 7 (33.3%) diagnosis followed recurrent urinary tract infections (UTI) while 2 (4.7%) were diagnosed antenatally. Karyotype was 45,X in 9 (43%) with mosaicism in the rest and no correlation between karyotype and specific renal abnormalities (p, 0.265 OR 1.49 (95% CI 0.598, 3.716). Each patient had a renal ultrasound and DMSA to confirm the diagnosis, while 3 underwent micturating cystogram. On long term follow 9 developed nephro-urological complaints: 3 were found to have renal parenchymal damage on DMSA scan, 2 recurrent UTI, 2 hypertension, 1 recurrent haematuria, 1 progressed to chronic kidney disease stage 1. Only one patient required surgical intervention (pyeloplasty). **Conclusion:** Renal anomalies were detected in about 12% of our large series of patients with TS. Most recent follow-up shows that 43% of our study population developed renal complaints, highlighting that once a urological anomaly is detected, close follow-up is warranted.

P2-P837

Abstract withdrawn

P2-P838

A Novel Fibrillin-1 Gene Mutation Leading to Marfan Syndrome in Korean Girl

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Background: Marfan syndrome is one of the most common over-growth conditions and the cardinal features occur in ocular, skeletal and cardiovascular systems. Clinical variation is common and signs are age-dependent. **Case:** A 9-year-old girl was referred to our pediatric endocrinology clinic for tall stature. Physical examination revealed a lens dislocation with strabismus, high palate, positive wrist and thumb signs, joint hypermobility, and pes plenus. Dilatation of aortic root was revealed on transthoracic echocardiography. She was diagnosed with Marfan syndrome based on well-defined clinical criteria (the revised Ghent diagnostic criteria). Molecular investigation identified heterozygous c.2810G > A mutation in the FBN1 gene leading to the amino acid substitution in affected patient, but was absent in her parents. **Conclusion:** To our knowledge, c.2810G > A mutation is novel and has not been reported. We hypothesize that this novel FBN1 mutation might be able to cause a disruption of FBN1 function and is probably involved in the development Marfan syndrome in this patient.

P2-P839

Evaluation of Referrals for Short Stature to a Regional Paediatric Centre

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Background: Referrals to pediatric endocrine clinics for short stature are common. Height velocity (HV) is an

essential component of the evaluation of short stature as growth deceleration often reflects an underlying pediatric endocrine diagnosis (PED). Access to previous measurements facilitates prompt calculation of HV. **Objective and hypotheses:** To determine availability of previous measurements at time of referral for short stature, to characterize PED and to determine predictors of a PED. **Method:** A retrospective chart review was performed on all referrals for short stature to a single pediatric endocrinologist between January 2008 and December 2014. Standard practice following receipt of a referral for short stature included repeated requests to the referring physician for previous measurements. Data were analyzed using t-tests, chi-squared tests, and logistic regression. **Results:** A total of 326 charts of patients, aged 11 months to 18 years, were reviewed and 286 (68% male) were eligible for inclusion. The mean age at referral was 9.5 years and the mean height *z*-score was −2.3. Previous measurements were available in 72.4%, and 44.8% were found to have a PED. Of those with a PED, 65% had growth hormone deficiency (GHD). There was a significant relation between HV $<25^{th}$ percentile and a PED ($P<0.0001$) and between height deficit (HD) (mid parental height *z*-score minus height *z*-score) and a PED ($P<0.0001$). Logistic regression analysis showed that a HV $<$25th percentile and a HD >2 standard deviations, increased the odds of a PED by a factor of 5.12 ($P<0.001$) and 1.39 ($P<0.005$), respectively. **Conclusion:** HV is a significant predictor of a PED and we found GHD to be the most common PED. Our higher rate of previous measurement availability is likely due to our effective referral screening protocol. The availability of these measurements, which are essential for HV calculation, reduces delay in diagnosis and management.

P2-P840

Testosterone Therapy Improves the First Year Height Velocity in Adolescent Boys with Constitutional Delay of Growth and Puberty

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Background: Constitutional Delay of Growth and Puberty (CDGP) is a transient state of hypogonadotropic hypogonadism associated with prolongation of childhood phase of growth, delayed bone age and pubertal delay. CDGP can cause significant psychological stress and anxiety in adolescent boys. Although testosterone usage in this group has not been shown to affect the final adult height, the effect on the first year height velocity is not widely reported. **Objective and hypotheses:** The aim of this study is to determine whether testosterone treatment improves the first year height velocity in boys with CDGP when compared with height velocity in boys with CDGP who go through puberty spontaneously. **Method:** Retrospective growth data from 23 adolescent boys with CDGP was analysed. CDGP was diagnosed based on medical and family history, examination, and auxology and exclusion of pathology by appropriate investigations. Ten out of 23 boys received monthly testosterone injections for 3–6 months in total. One-way ANOVA was used to compare the height velocity between boys who received testosterone and those who proceeded through puberty spontaneously. **Results:** The mean (±SD) chronological age was 13.8 year (±1.6) with a bone age of 11.6 year (±1.7) and mean baseline height SDS of −2.0 (±0.75). The mean baseline testicular volume in the treated and untreated groups was 4.5 ml (±1.2) and 4.7 ml (±1.1) respectively. The mean (& 95% CI) height velocity one year after treatment was 8.4 cm/year (7.2, 9.7) when compared to 6.1 cm/year (4.8, 7.4) in the patients who did not receive treatment [$P=0.01$]. There was no significant difference in the final predicted height between the 2 groups. **Conclusion:** Testosterone therapy can significantly improve the first year height velocity in boys with CDGP, without influencing the final predicted height, leading to a potential reduction in anxiety and psychological distress that affects this group of children.

P2-P841

Safety and Efficacy of Growth Hormone (GH) in Combination with the Gonadotrophin Releasing Hormone Agonist Leuprorelin in Pubertal Children with Idiopathic Short Stature

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Background: Due to delays in diagnosis of Idiopathic Short Stature (ISS), puberty has often started when Growth Hormone (GH) is initiated. **Objective and hypotheses:** To compare GH+leuprorelin (GH+L) with GH alone in patients with ISS and at Tanner puberty stage 2 or 3. We hypothesised that co-administration of GH+L for 2–3 years would delay puberty, prolong GH efficacy and increase adult height. **Method:** A phase 3, randomised, open-label study to examine

safety and efficacy of GH to be administered until adult height reached, with or without leuprorelin, in pubertal children with ISS. However, following disclosure of the SAGhE study results, the French Drug Agency requested that GH be stopped early; consequently leuprorelin was also stopped. Patients from France entered a long-term follow-up until near adult height (NAH). **Results:** Of 89 randomised patients, 45 received GH + L and 43 received GH. Mean (standard deviation; SD) GH treatment duration was 28.9 (10.9; range, 1.7–49.2) months with GH + L and 29.9 (10.7; range, 3.1–51.3) months with GH. Mean (SD) exposure to leuprorelin was 20.9 (6.4; range 3.0–33.1) months. Mean (SD) height velocity standard deviation score (SDS) was −0.3 (0.6) with GH + L and 0.3 (0.5) with GH at 2 years when leuprorelin was stopped; at 4 years respective values were 0.7 (0.5) and −0.0 (0.6). Mean height SDS gain from baseline was 1.0 (0.6) and 0.9 (0.4) at 4 years. Mean NAH SDS was −1.8 (0.5) in the GH + L group ($n = 19$) and −1.8 (0.8) in the GH group ($N = 17$). Seven versus 3 patients had bone fractures during GH + L versus GH. No deaths occurred. No unexpected adverse events occurred during or after treatment. **Conclusion:** Treatments were stopped early and no conclusion can be made for comparative efficacy of GH + L versus GH alone. Long-term safety follow-up revealed no new safety concerns regarding GH treatment.

P2-P842

Linear Growth in Infants and Children with Atopic Dermatitis

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Introduction: Skin barrier defects play central role in the pathogenesis of atopic dermatitis (AD) affecting local immunity and skin hydration. Severe AD may deleteriously affect growth and nutrition in these children. **Objectives:** To 1) measure the effect of AD on linear growth in infants and children 2) to study the effect of hypoalbuminemia and hypo-proteinemia on the growth of these children. **Methods:** We studied linear growth and BMI all children with severe AD (<14 years) ($n = 162$) seen at Ped Allergy-Immunology clinics of Hamad General Hospital during June 2014–2015 with severe AD. SCORAD and anthropometric data were collected Serum total protein, albumin, 25OHD, and IgE concentrations were measured. **Results:** Children with severe AD had height SDS (HtSDS) = −0.75 ± 0.8. 22/162 (13.60%) of children had HtSDS < −2, 57/162 (35%) had HtSDS < −1. BMI of the patients = 15 ± 6.4. BMISDS was < −2 in 14% of patients. 16% of patients had hypoalbuminemia. AD severity scores (SCORAD) was 61.3 ± 22.3. Twenty six patients with hypoalbuminemia had low BMI 11.2 ± 2% compared to 26 normo-albuminemic patients who had BMI 19.1 ± 38.1%. SCORAD was higher in hypo-albuminemic-low-BMI patients compared to normo-albuminemic-normal-BMI patients (67.9 ± 22.1 vs 58.3 ± 22.5). Vitamin D deficiency was found in 58% of the patients. HtSDS and BMI did not correlate significantly with the severity of the disease (SCORAD). **Conclusions:** Children with severe AD had high prevalence of hypoalbuminemia due to loss of albumin through the diseased skin. Albumin loss may lead to malnutrition and low BMI in these patients. HtSDS of 35% of children was < −1. It is important to closely monitor growth, nutrition and biochemical makers in the management of severe AD.

P2-P843

The Specific Pubertal Height Gain is Higher in Boys as Well as in Children with Lower BMI_{SDS}

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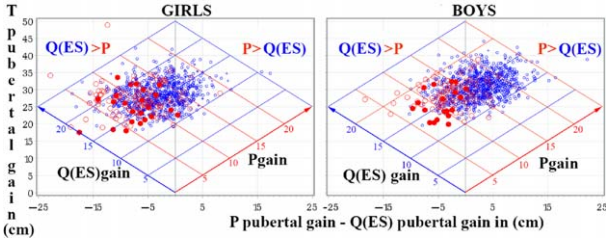
Background: Growth in height during puberty can be described by the QEPS-model as a combination of continuous basal growth, *QES*, and a specific pubertal growth function, *P*. **Objective and hypotheses:** To study the relationship between childhood BMI_{SDS} and the prepubertal gain and pubertal gain related to growth functions from the QEPS-model. **Method:** The longitudinally followed GrowUpGothenburg 1990 birth cohort, was analyzed, by the QEPS-model. Individual maximal BMI_{SDS} values, from 3.5–8.0 years of age ($n = 1901$) were calculated for



linear and subgroup analyses, underweight (blue cross), normal (blue open circles), overweight (red open circles), obese (red circles). **Results:** For girls (Figure left), total pubertal gain (*Tpubgain*) depended more on *QESgain* during puberty. For boys, total pubertal gain depended more on specific *Pgain* (Figure right). With higher BMI_{SDS} this balance was shifted towards less *Pgain* for both girls and boys. Before puberty, children with higher BMI_{SDS} were taller, expressed as higher *QESgain*, with a linear correlation over the whole BMI–range ($P < 0.001$for both girls/ boys). **Conclusion:** During puberty, girls grew more due to the *QES* than the *P* functions, with opposite findings in boys. For both boys and girls, there were less *Pgain* and more *QES- gain* with higher childhood BMI_{SDS}. Before puberty, children with higher BMI_{SDS} were taller.

P2-P844

Growth Screening in Children Aged Three to Five Years Seen in Community Paediatrics in Dreux District, France: Preliminary Results

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Background: Over 90% children grow normally, and attain final height within their genetic target. Up to 10% of all children do not spontaneously catch-up by the age 3 years, besides some cases of TS are diagnosed late, and others with SGA go undiagnosed and unattended. **Objectives & Hypothesis:** Early screening of growth patterns in children attending Child Protection Visits (PMI, France) in Dreux district. Our objective was the evaluation of prevalence of growth retardation in preschool aged children. **Method:** Standard measures of weight, height and BMI were collected for all children aged 3–5 years during systematic PMI visits. Birth variables, family history of short stature, maternal smoking, ethnic origin, etc. were also recorded. Each child was measured twice (wall stadiometer), and mean height recorded. Parents of those with height < -2.0 SDS received information and written proposal to attend hospital growth visit. Pubertal stage was recorded according to Tanner staging. **Results:** 590 children were screened from 2013 to 2015 (301 boys, 289 girls), mean age 4.33 ± 0.76 SD years, 48% were Caucasians, 13.7% North Africans, 2.5% black Africans, 0.8% Asians. 526/575 (91.5%) children were term-born, 8.5% (49/575) were preterm. 89.6% (484/540) children were AGA and 10.4% (56/540) were SGA (Usher & McLean curves). Mean BL was 49.03 ± 0.71 cm, mean BW 3258.7 ± 205.1 g and mean HC 34.49 ± 0.71 cm. 11% infants of north African descent were macrosomic. Catch-up growth was complete in 98% children, whereas 2% (11/540) were short at age 5 years. 8/11 (73%) children attended our growth clinics (7 short stature and 1 obesity with micropenis), 2 are GH treated. **Conclusion:** These preliminary results show that growth screening in community is important as it enables both early diagnosis and follow-up in children with growth problems. Our results probably underestimate the true prevalence of short stature as results are partial at this point.

P2-P845

The 3M Syndrome: A Cause of Pre- and Post-Natal Severe Growth Retardation

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Background: 3-M syndrome is an autosomal recessive growth disorder characterised by severe pre- and post-natal growth retardation caused by mutations in CUL7, OBSL1 or CCDC8. Clinical characteristics include dysmorphic facial features and fleshy prominent heels with a variable degree of radiological abnormalities. **Objective and hypotheses:** Evaluation of four new patients from two different families. Cases: **Family-1/Patients-1,2:** Two brothers (16.6 (patient-1) and 8.5 (patient-2) years-old) were referred for marked short stature. Their anthropometric measurements at birth was not known but they were born small. Their parents were first degree cousin. Physical examination revealed a severe short stature (HeightSDS:–6.1/–5.8) and dysmorphic features. Pubertal stages were Tanner-2 and Tanner-1. Their motor and mental developments were normal. Endocrine work-up was normal. Genetic testing confirmed a mutation in the CUL7 gene. They had a normal response to GH stimulation test. Adequate rise was noted in insulin-like growth factor-I(IGF-I) and IGF binding protein-3(IGFBP-3) levels with IGF-1 generation test. GH Metin veya web sitesi adresi yazın ya da bir dokümanı çevirin. treatment was started at 11 years-old (Patient-2). Pubertal stage of patient-2 is Tanner I at thirteen years of age. **Family-2/Patients-3,4:** Two sisters [Elder one (patient-3) at 0.75 years-old, younger one (patient-4) at 2.5 years old] were referred for marked short stature. They had intrauterine growth retardation. Their parents were third degree-cousin. Physical examination revealed a severe short stature (HeightSDS:-6.0/-5.3) and dysmorphic features. Their motor and mental development were normal. Endocrine work-up was normal. Genetic testing confirmed a mutation in the OBSL1 gene. They had a normal response to GH stimulation and IGF generation test. GH

treatment was started at 4.8 years-old (Patient-3) **Conclusion:** syndrome should always be considered in the differential diagnosis of short patients with intrauterine growth retardation. Children are often treated by GH but there is no obvious demonstration of its efficiency. 3M syndrome might cause delayed puberty in boys.

P2-P846
Should We Construct Specific Growth Charts for Ethnic Subgroups?

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Background: Romania has a 3.3% Rromanes population according to the latest census, but no specific growth charts for this ethnic minority. Current national protocol recommends using the Swiss growth charts developed in 1989. Specific growth charts exist for ethnic subgroups like Turks in Germany and the Netherlands. **Objective and hypotheses:** A comparison between a Rromanes and a Romanian group of children regarding weight and height disturbances' prevalence according to the Swiss, WHO and IOTF charts. **Method:** Case-control study including 75 children of Rromanes ethnicity and 103 age and sex matched children of Romanian ethnicity evaluated in November 2013 in two schools from Mures County, Romania. Variables: age, sex, ethnicity, height SDS, BMI SDS. Short stature was defined as height below −2SDS, and overweight was defined as BMI above 1SDS. Statistical analysis used M.O. Excel and MedCalc v. 12.0 with a level of significance $\alpha = 0.05$. **Results:** Mean age (8.5 years for the Rromanes group, respectively, 8.6 years, $P = 0.45$) and sex ratio of the two groups were similar (M: F Rromanes 1.1:1, respectively 1.4:1, $P = 0.54$). The Rromanes children are significantly shorter and thinner ($P < 0.001$). Short stature in the Rromanes group had a prevalence of 29.33% according to Swiss charts and 18.67% according to WHO, whereas in the control group it had 2.91% (Swiss) and 1.94% (WHO). For overweight, the prevalence was higher when using WHO and IOTF criteria for both groups, 32.03% in the Romanian group (WHO) and 13.33% in the Rromanes group. **Conclusion:** There are significant differences for weight and height disturbances between the Rromanes and the native population in Romania, regardless of the growth standards used, with the recommendation to construct specific growth charts as existent in other countries.

P2-P847
Late Presenting Girls with Turner Syndrome can Achieve a Normal Final Height

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Background: The diagnosis of turner syndrome (TS) must be included in the differential diagnosis of all girls with short stature. Despite overall earlier diagnosis and treatment there still remain patients with TS who present late with delayed puberty. Although growth hormone (GH) is known to increase final height (FH) in girls with TS, little evidence exists on treatment in late-presenting girls. **Objective and hypotheses:** To assess the effect of late GH treatment along with delayed pubertal induction on FH of girls with TS. **Method:** Thirteen girls with TS presenting after 12 years of age were studied. Standard GH treatment was initiated immediately after diagnosis and 8/13 were also treated with the anabolic steroid oxandrolone. Oestrogen treatment was started at a mean of 1.75years (SD:0.77) after initiation of GH (minimum age 13 years). FH was calculated when the height velocity was ≤ 2 cm/year. **Results:** Mean(SD) age was 14.37(1.7) years at GH start and 15.22(1.3) years at oestrogen replacement initiation. The mean(SD) FH-SDS using normal girls growth charts [−0.89(0.70)], as well as TS-specific charts [1.12(0.63)] was statistically significantly higher compared to presentation height SDS (normal female growth charts [−2.62(0.56)] and TS charts [2.28(0.77)]) both $P < 0.0001$. The FH range was 151.2–165 cm ie. within the normal range for girls without TS. There was no statistically significant difference in FH-SDS between those patients who received oxandrolone and those who did not. **Conclusion:** We have shown that despite late GH treatment in girls with TS presenting with delayed puberty, a normal FH can be achieved. Previous studies have shown that late pubertal induction improves FH, as well as oxandrolone treatment, factors that seem to have had a positive effect in our patients.

P2-P848

Growth of Children Born Preterm During the First 8 Years of Life

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Background: Approximately 15 million children are born preterm worldwide yearly. **Objective and hypotheses:** To evaluate spontaneous growth during the first 8 years of life. **Hypotheses:** Preterm born children have spontaneous recovery of weight and height in the first 8 years of life. **Method:** Measurements at birth, 6, 12 and 24 months of corrected age and at recall [6.4 ± 0.5 years (5.2–8.0)]. Weight, length/height and BMI SDS were calculated (reference of Fenton & Kim until 50 weeks; WHO 2006–2007 after this age). Data are presented as mean ± SD (range), otherwise stated. **Results:** In total of 170 children (97 boys), gestational age (GA) 32.5 ± 2.9 weeks (24.0–36.7), median birth weight 1772.5 g (range, 580–3135), length 41.3 ± 4.6 cm (30–49). Fifteen children were extremely preterm (GA < 28 weeks), 20 were small for GA (SGA). 32.7% of preterm children born AGA presented extrauterine growth restriction, defined as a difference ≥ 2SD between birthweight and/or birthlength to 40 weeks post-conception. Median weight SDS at 6, 12 and 24 months of corrected age and at recall were −0.6, −0.2, −0.5 and −0.3 SDS, respectively. Correspondent values for lenght/height SDS were −0.4, −0.3, −0.3 and −0.3 SDS. Children born with less than 32 weeks and children born preterm SGA were leaner and shorter compared with those born after 32 weeks of GA ($P < 0.01$) and those born AGA ($P < 0.05$). Median BMI SDS at recall was 0.0 (−2.7–5.0). Twelve children (7.1%) were underweight, 6 (3.5%) presented short stature, 27 (15.9%) were overweight and 14 (8.2%) were obese. Longer duration of breastfeeding was associated with less weight gain during the first 2 years of life ($r = -0.27$; $P = 0.001$), whereas weight gain during the first 2 years of life was associated with BMI at recall ($r = 0.54$; $P < 0.0001$). **Conclusion:** Most preterm children recovered weight and length until 6 months of life; rapid weight gain during the first 2 years was a risk factor for overweight/obesity during childhood.

P2-P849

Genetic Variability in Patients with Noonan Syndrome in the Republic of Macedonia

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Background: Noonan syndrome is autosomal dominantly inherited disease with an incidence of 1:1000 to 1:2500 newborns. It is caused by different gene mutations involved in the RAS/MAP kinase signaling pathway in the cells. Phenotype including expression of dysmorphic features and visceral organ affection is variable. Different gene mutations are found in approximately 60–70% of tested patients. **Objective and hypotheses:** To report mutational analysis in 10 patients with clinical phenotype concordant with the Noonan syndrome. **Method:** Clinical diagnosis was based upon the presence of majority of minor and/or major abnormalities characteristic for Noonan syndrome. All recommended analyses such as biochemical blood tests, ultrasound of heart and kidney, and evaluation of the growth were performed. Molecular analysis was performed by the NGS method including genes: NRAS, ROT1, SCHOC2, HRAS, CBL, KRAS, PTPN11, SPRED1, MAP2K1, NF1 and MAP2K2. **Results:** Six patients (60%) had a relevant mutation: four patients had PTPN11 mutation (40%o), one had RAF1 and one had KRAS mutation. No mutation was detected in four patients(40%) two of whom had most of the characteristics of Noonan syndrome. Search for mutations of some other or regulatory gene mutation in this family is warranted. Patient with the RAF1 mutation had severe myocardiopathy as previously described, however similar finding appeared in a child with PTPN11. Three children had pulmonary stenosis that was treated surgically in three children. Short stature was detected in 4 (40%) children, three carrying heterozygous mutation in PTPN11 gene and treated with growth hormone with a modest response. One short child had a rare KRAS mutation accompanied with a significant developmental delay. **Conclusion::** This is the first report of the genetics of Noonan syndrome in a country from Balkan region. Clinical recognition of the syndrome was successful. Two rare mutations detected in a small number of patients require further genetic analysis in this region.

P2-P850

An Unusual Cause of Short Stature in a Phenotypic Male with Type I Diabetes Mellitus due to an Unexpected Deletion of the Y Chromosome

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Background: Short stature homeobox (SHOX) gene, located on the pseudoautosomal region of the sex chromosome plays an important role in the development of skeleton and its mutations/deletions can cause skeletal dysplasias. **Objective and hypotheses:** We report a male, with Type I Diabetes (T1DM) with Y chromosome deletion and short stature due to the concurrent loss of SHOX. **Method:** A 15-year-old boy with T1DM for 6 years was referred for short stature (148.1 cm, −2.62SDS) assessment. His height velocity continued to be poor despite optimisation of his diabetes control. Further investigations to look for other chronic illnesses were normal. A mild body disproportion with an upper and lower segment ratio of 1.3 was noted. He was pubertal with testicular volumes of 8–10 ml. The IGF1 was normal and the bone age was advanced at 17.5 years. **Results:** The skeletal survey showed subtle madelung deformity with mild relative shortening of the ulnar bones and epiphyseal ossification.

Microarray analysis showed loss of most of the Y chromosome. Fluorescent in Situ Hybridisation studies using specific centromere probes for X and Y chromosome showed no Y chromosome in 73% of the cell lines and presence of isodicentric Y chromosome, i(Y) with SRY gene in 23% of the cell lines, giving rise to the karyotype 45X/46X, i(Y) The clear male phenotype and short stature in our patient is probably due to degree of mosaicism with higher distribution of i(Y), in the gonads and 45X in the growth plates. **Conclusion:** Loss of Y chromosome and resultant deletion of a copy of SHOX in a patient with TIDM has not been previously reported. Infertility can be an associated problem. The skeletal deformities can be subtle in the radiographs with typical bone age advancement. Microarray is helpful as an initial test to detect SHOX deletion.

P2-P851

An Unusual Case of Growth Hormone Replacement Therapy in a Child with Hereditary Multiple Exostoses and Growth Hormone Deficiency

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Background: Hereditary multiple exostoses (HME) is an autosomal dominant heritable disorder characterized by exostoses located mainly in the long bones of extremities. HME is caused by mutations in two genes: EXT1, EXT2. **Objective and hypotheses:** Growth hormone (GH) deficiency is very rare in children with HME and GH replacement therapy has not been well described. **Method:** A 12.5 years old girl was referred to our Department because of short stature (132 cm, −2.8 SDS). Her weight was 24 kgr (BMI 13.77, −2.53 SDS), she had reduced growth rate (2.3 cm/year) and was on pre-pubertal maturation stage. Physical examination was normal. Her father had multiple exostoses on scapulae and long bones and was under orthopedic follow up. Hypothyroidism, chronic diseases, malabsorption and skeletal dwarfism were excluded. GH deficiency was diagnosed by two stimulation tests: insulin (GH peak: 5.36 ng/ml) and L-dopa administration (GH peak: 7.35 ng/ml) and confirmed by low IGF-I values (214 ng/ml). Bone age was delayed (10.5 years) with exostoses on third metacarpal, distal radius bone and middle phalanx of third finger. X-rays showed exostoses on scapulae, knees and distal femurs. She was referred to orthopedics who confirmed the diagnosis of HME. **Results:** GH replacement therapy (0.025 mg/Kg per day) showed good response on linear growth: 6.1 cm (1.4 SDS) during the first year and 4.2 cm (3.0 SDS) the second year of therapy. Her mother was negative for exostoses while her sister (10 years old) showed short stature (141.8 cm, −2,5 SDS), reduced growth rate 2.8 cm/year and exostoses (right scapulae and knees) at x-ray examination. GH deficiency was diagnosed by insulin (GH peak 2.11 ng/ml), L-dopa stimulation tests (GH peak 2.35 ng/ml) and low IGF-1 (207 ng/ml).GH replacement treatment (0.025 mg/kg per d) showed moderate response: 5.5 cm/year (−0.8 SDS) the first year and 3.8 cm/year (−0.8 SDS) the second. **Conclusion:** GH deficiency has rarely been found in HME patients. GH replacement treatment seems to improve their stature, however close follow up of exostoses is mandatory.

P2-P852

Assessment of the Medical and Psychological Status of Women with Turner-Syndrome in Young Adulthood

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Background: Difficulties in transition of adolescent Turner Syndrome (TS) patients to adult health care has been reported in many studies. **Objective and hypotheses:** We conducted a medical and psychological follow-up of adult patients with Turner Syndrome which had been treated at our tertiary pediatric endocrine centre. **Method:** We screened for expected comorbidities and provided a questionnaire asking for current medical care. Furthermore, we assessed quality of life with the SF36v2 forms, and general mood with the Beck-Depression Inventar. **Results:** In total of 9 out of 64 patients, aged 21 to 43, agreed to participate in the study. Almost 20% had not been treated with growth hormone during pediatric care. About 40% of the participants did not consult a general practitioner after transition and only 15% were seen by an endocrinologist or a cardiologist regularly. About 23% are not in gynaecological follow-up. Only 80% take oestrogen substitution, with only 43% of these in an adequate dosage. The QoL Scores were surprisingly good for both mental and physical health when compared to the reference population. We did not observe any correlation between these scores and final height, age or comorbidities. Three patients were diagnosed with depression. Hypertension, diabetes mellitus type II, aortal dilatation or coeliac disease were newly diagnosed in nine participants. **Conclusion:** The surprising results might indicate a tendency to minimalize the symptoms and underestimate the importance of regular follow-up in adult Turner Syndrome patients. This, together with a suboptimal setting of the adult care leads to a large rate of lost to follow-up, increasing the risk for untreated comorbidities and additional costs for the health care system. On the basis of the suggestions of our adult patients, we propose a tight collaboration with a specialized endocrine gynaecologist from late adolescence

complemented by an adult endocrinologist. Information about health issues and development of health care autonomy is central.

P2-P853

A 3-year-old Boy with Growth Hormone Deficiency and Clinical Features of Ritscher–Schinzel Syndrome

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Ritscher-Schinzel (cranio-cerebello-cardiac, 3C) syndrome is a very rare recently delineated disorder with Dandy-Walker malformation, congenital heart defects and dysmorphic craniofacial features; however, the full spectrum of this disorder has not been determined. **Objective and hypotheses:** To present a patient with short stature and growth hormone (GH) deficiency as a part of the clinical manifestations of Ritscher-Schinzel syndrome. **Method:** A boy was born from third complicated pregnancy to a 29-year-old mother with sarcoidosis, at 37 weeks of gestation by Cesarean section due to severe intrauterine growth retardation and oligohydramnion. His birthweight was 1750 g (SDS −2.98), length 38 cm (SDS −5.89) and head circumference 32 cm (SDS −1.50). He had retarded cardiopulmonary adaptation with perinatal asphyxia, RDS and cardiac murmur diagnosed as PDA and ASD II, umbilical hernia and dilated lateral ventricles. The baby was ventilated and given anti-failure treatment, no surgical cardiac intervention was performed. At the age of 3 months bilateral ocular coloboma was noted. He showed hypotonia and developmental delay, with frequent episodes of rectal bleeding due to constipation and anal fissures. At the age of 3 years he was admitted because of symmetrical short statute – height 88.3 cm (SDS −2.84), weight 9.9 kg (SDS −4.13) and head circumference 47.9 cm (SDS −1.52). **Results:** On physical examination abnormal features were noted – low-set ears, retromicrognathia, down-slanting palpebral fissures, broad forehead, clinodactyly, muscular waste. Laboratory investigations showed fasting hypoglycemia, dyslipidemia, low IGF-1; GH deficiency was confirmed with peak GH levels <5 ng/ml on two stimulation tests. Bone age was slightly delayed with hypoplasia of the 5th distal phalanges. Brain imaging showed Dandy-Walker variant with cerebellar vermis hypoplasia, slightly dilated 4th ventricle and moderate communicating hydrocephalus. Treatment with rhGH was initiated. **Conclusion:** GH deficiency should be considered as a possible cause of short stature seen in this condition.

P2-P854

Growth Pattern, Response to GH Treatment and the Effects of Pubertal Spurt on Final Height in Patients Affected by RASopathies

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Background: Reduced growth is a common feature in RASopathies. Poor data are available about pubertal spurt and the effect on final height (FH) in patients with these disorders. **Objective and hypotheses:** To study growth, body proportions, pubertal pattern, and FH including subject treated with GH-therapy for proven GH deficiency. **Method:** We analized growth trend and body proportions in 88 patients affected by RASopathies with molecularly confirmed diagnosis, pubertal pattern in 44 of them and FH reached in 33 subjects, including 16 treated with GH therapy for proven GH deficiency. **Results:** Thirty-three patients showed GH deficiency after pharmacological tests, and were GH-treated for an average period of 6.8 ± 4.8 years. Before starting therapy, HV was -2.6 ± 1.3 SDS, and mean basal IGF1 levels were -2.0 ± 1.1 SDS. Long-term GH therapy, starting early during childhood, resulted in a positive height response compared to untreated patients (1.3 SDS in terms of height-gain), normalizing FH for Ranke standards but not for the general population (GP) and the Target Height. First pubertal clinical signs were observed at age of 11.8 ± 1.9 yrs in female and 12.1 ± 1.3 yrs in males. Pubertal growth showed a lowered peak (6.2 ± 1.5 cm/yrs in female and 6.8 cm/yrs in males), and a delay in onset by about 6 months, compared to the GP. Pubertal spurt length resulted 5.3 ± 1.1 yrs in female and 4.7 ± 0.6 yrs in males. The delayed pubertal development and the inadequate pubertal catch-up growth could explain the impaired FH. **Conclusion:** Our patients on GH-therapy benefitted from the therapy if started in prepuberty and given for a long time. Probably, the prepubertal start of GH-treatment could compensate the lack of a satisfying pubertal growth spurt.

P2-P855

The Usefulness of Magnetic Resonance Imaging of the Heart and Aorta in the Diagnostic Work-up in Girls with Turner Syndrome

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Background: Congenital heart defects are found in 50% of girls with Turner syndrome (TS). The evaluation of cardiovascular system is an important element in the diagnostic work-up of TS and is of particular significance of cardiologic monitoring, safety aspects of rGH treatment and any pregnancy planning. **Objective and hypotheses:** Assess the cardiovascular system in TS girls with magnetic resonance imaging of the heart and aorta (CMR and angioMR). **Method:** CMR and angioMR was performed in 30 children with TS. For the analysis of selected 26 girls. The mean age was 14.65 years. CMR was performed using 1,5T Magnetom Avanto machine. AngioMRI was performed with a gadoline contrast agent and type TWIST sequence. With a volumetric method using a CINE sequence the morphology and function of left and right ventricle were obtained. "Phase contrast" type sequences served for the assessment of a flow through the aorta and pulmonary truncus. **Results:** Aortic diameters were measured at nine levels with maximum-intensity projection images. Regression analysis of diameters in relation to BSA demonstrated linear relationship between the cross-sectional aortic diameters and the square root of BSA ($BSA^{0.5}$). Diameters were described regression function ($-3.48+25.42*BSA^{0.5}$) mm for aortic sinus, ($-1.52+20.39*BSA^{0.5}$) mm for sinotubular junction, ($1.07+18.94*BSA^{0.5}$) mm for ascending aorta, ($3.67+15.35*BSA^{0.5}$) mm for at the origin of brachiocephalic, ($-4.62+21.26*BSA^{0.5}$) mm for first transverse segment, ($-4.43+19.3*BSA^{0.5}$) mm for second transverse segment, ($2.16+13.24*BSA^{0.5}$) mm for isthmic region, ($6.21+9.08*BSA^{0.5}$) mm for descending aorta, ($6.61+7.33*BSA^{0.5}$) mm for diaphragm. The results were compared to ranges developed by Kaiser et al. Comparison of the correlation coefficient of the regression of the study group and the regression function Kaiser revealed in the 7 to 9 aortic levels statistically significant difference. Aortic stenosis index >2.5 cm/m^2 was in 1 patient. **Conclusion:** CMR, particularly angioMRI, allows to detect vascular abnormalities of the aorta. The aorta dimensions are higher compared to the values in healthy population. AngioMRI is important tool for prognosis and planning further medical care.

P2-P856

A Rare Cause of Short Stature: Patient with 3M Syndrome Revealed a New Mutation in *Osbl1* Gene

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The 3M syndrome is a rare autosomal disorder that can lead to short stature, dysmorphic features and skeletal abnormalities with normal intelligence. A-one year and four month-female patient had been reffered to our clinic for growth and developmental delay. Case history revealed a birth weight of 1740 grams on 39th week of gestation, with 42 cm body height and no prior hereditary conditions of clinical significance in her family. On physical examination, her height was 67 cm (-4 SD score), body weight was 7.2 kg (-3.5 SD score) with a head circumference of 42 cm. She also had numerous characteristic physical features like a triangular face, fleshy nose tip, a long philtrum, prominent mouth and lips, pointed chin, significant lumbar lordosis and prominent heels. As her growth and developmental delay had a prenatal onset and the physical examination results were suggestive of a characteristic profile, the diagnosis of 3M syndrome was considered. Genetic assessment of the patient revealed a novel homozygous p.T45Nfs*40 mutation in the *OSBL1* gene. It is recommended that physicians pay further attention to this condition during the differential diagnosis of children with severe short stature conditions as well as mild skeletal deformities.

P2-P857

A Case of Familial Silver-Russell Syndrome

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Background: Silver-Russell syndrome (SRS) is a heterogeneous condition characterized by intrauterine growth restriction, relative macrocephaly at birth, postnatal growth retardation, body asymmetry, feeding difficulties/ low body mass index and dysmorphic craniofacial features. SRS is caused by DNA hypomethylation at the H19/IGF2-imprinting control region (ICR1) on chromosome 11p15 or maternal uniparental disomy of chromosome 7 (mUPD7) in approximately 50% and 10%, respectively. Most cases are sporadic. **Objective:** To present a family with clinical SRS, suggestive of a dominant mode of inheritance. **Case presentation:** Patient 1 was born spontaneously after an uneventful pregnancy as a child of non-consanguineous parents (maternal height: 153 cm, paternal height: 169 cm) in the 39th week of gestation with a weight of 1.96 kg, length of 45 cm and relative macrocephaly. At the age of 2.5 years, he was referred because of poor postnatal growth and severe short stature (height: -4.28 SDS). Clinical examination showed a triangular face with a prominent forehead and low-set ears. IGF-1 and IGFBP-3 levels were normal. Patient 2 is the maternal half-brother of patient 1 (paternal height: 183 cm). At birth, he was

small for gestational age. At time of referral at 5.4 years, he had short stature, mild dysmorphic craniofacial features and clinodactyly V. The mother of patient 1 and patient 2, born as a child of tall parents (maternal height: 178 cm, paternal height: 193 cm), reached a final height of 153 cm. She has clinodactyly V and subtle SRS-like features. Interestingly, array CGH as well as studies for ICR1 hypomethylation and mUPD7 were normal in patient 1. Additional genetic analyses are currently being carried out to identify the underlying etiology of the familial SRS. **Conclusion:** We present a multigenerational family with three members affected by clinical SRS suggestive of a dominant mode of inheritance of still unknown genetic etiology.

P2-P858

Central Precocious Puberty in a Case of SOTOS Syndrome

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Background: Statural overgrowth in SOTOS syndrome is well recognised. However excessive growth away from the usual growth trajectory should prompt assessment for other causes of growth acceleration. **Case:** TE was referred for a growth assessment at 6.8 years as he appeared to have grown more in the previous year. He was 142.9 cm (Ht SDS +4.32), weight 44.4kg (BMI SDS +2.85). He had no formal genetic diagnosis except that he was clearly dysmorphic with global developmental delay and had an 'overgrowth syndrome'. He was delivered at 36 weeks gestation and presented with sepsis at day 23. He suffered from sleep apnoea in the neonatal period which resolved by age 3 years, then obstructive apnoea until his adenoidectomy at age 4 years. Due to his large size and global delay, a genetics opinion was sought at 4 years following investigations which included a normal brain MRI and array CGH. No unifying diagnosis was made apart from an overgrowth dysmorphic syndrome. Further genetic tests were organised. When he was examined at 6.8 years, it was noted that he had large hands and feet, large ears, slightly long palpebral fissures and a pointed chin. He was also hypertrichotic and in puberty Tanner A1P1G2 with bilateral 8ml testes. He had selective eating habits. **Investigations:** Bone age, pituitary MRI, tumour markers, LHRH stimulation test. **Results:** Central precocious puberty was confirmed with LH peak of 9 IU/L, FSH 4.2 IU/L. Bone age was 11 years 6 months at a chronological age of 7 years 3 months. Pituitary and brain MRI was normal. Tumour markers were negative. Further genetic testing revealed a de novo loss of function mutation in the NSD1 gene. These results were only available after the diagnosis of precocious puberty. **Management:** TE was started on regular treatment with GNRH analogue. **Conclusion:** Growth and puberty data reported in SOTOS have not included an increased incidence of central precocious puberty although advanced bone age and early menarche have not resulted in excessive tall final heights in women. Most adult SOTOS men have final heights within the normal range. Excessive growth should always prompt investigation regardless of the underlying diagnosis.

P2-P859

Hypoglycaemia in Isolated GH Deficiency beyond Infancy

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GH deficiency (GHD) associated hypoglycaemia in infancy is an indication for GH treatment, although it is described in GHD1in older children. At that time, GH is prescribed in GHD for short stature. Here, two children are described in whom hypoglycaemia is the main reason to treat with GH. Patient one had hypoglycaemic seizures due to GHD in infancy. GH treatment was stopped with 5.5 y for reassessment. Growth rate diminished and hypoglycaemias occurred. Treatment of GH was restarted and continuous glucose was monitored during GH. Patient two with partial monosomy 18q had hypoglycaemias up from 6 y. Pre-treatment continuous glucose was determined and GH started. Assessment for metabolic or endocrine disorder was performed in both patients. Both patients had only GHD. Patient one, borderline cortisol induced a substitution between 2 and 5.5 y. Then, normal cortisol (peak in diurnal profile 21 mg/dl) was encountered. Peak GH concentrations after stimulation were 8.8 ng/dl for patient one and 4.75 ng/dl for patient 2. Patient 1 had no GH above 6 ng/ml in spontaneous GH secretion – assessed due to continuing hypoglycaemias. Nadir glucose was 45 mg/dl in patient 1 and 48 mg/dl in patient two. Both had day and night time hypoglycaemias. During assessment, we noticed that patient one ate large amount of sucrose to counter regulate hypoglycaemia. Since GH reduced but did not stop this, we re-monitored glucose profile. Hypoglycaemias occurred in the morning and around 6 pm. We divided the GH dose into 1/5 am and 4/5 pm. Then, low blood glucose occurred only around 6 pm, which was managed by diet. In patient two, we therefore started with divided GH doses with no further hypoglycaemias. Hypoglycaemia may be the predominant feature of GHD beyond infancy. The management of day time hypoglycaemias must be considered in GHD.

P2-P860

Referral Pattern of Children with Short Stature to a Pediatric Endocrine Clinic in Kuwait

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Background: Short stature is a prominent complaint for which children are referred to pediatric endocrinologists. Data on

short stature is lacking in the Arab states in the gulf region despite the fact that treatment is easily accessible. The study aimed to describe the referral pattern, baseline characteristics, and etiological profile of children referred with short stature to a pediatric endocrine clinic in Kuwait. **Method:** This is a cross-sectional retrospective review of children referred to the Endocrine Clinic at the Department of Pediatrics in a major hospital in Kuwait with the complaint of short stature between 2008 and 2015. Short stature was defined as height or length below the 3rd centile or less than −2 Standard Deviation Score (SDS) as per the WHO growth standards. **Results:** A total of 221 children were referred during the study with no significant gender difference ($P=0.346$). Almost one fifth of these children had normal statural growth. At time referral, children with short stature were 7.7 (4.7, 10.3) years of age, mostly pre-pubertal (88.6%), and had a mean height SDS of −2.67 (0.68). There was no significant differences between males and females in relation to age, puberty status, height, BMI, and target height at the time of referral. The most common diagnoses were normal variants of growth, Growth hormone deficiency, and short stature secondary to chronic diseases. **Conclusion:** Our study highlights the need to improve the referral process in order to avoid unnecessary investigations and alleviate parental anxiety. There is no gender bias in referral of children with short stature in Kuwait. Our data highlight the need for further investigation of children with short stature in the country and the region

P2-P861

The Effect of Iron Intervention on the Anthropometric Parameters: Pilot Study among Egyptian Preschool Children with Iron Deficiency Anemia

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Background: Iron deficiency anemia (IDA) causes detrimental effects on physical growth which is attributed to poor appetite, altered endocrinologic profile and neurotransmitter metabolism consequent to iron deficiency. **Objective and hypotheses:** To investigate the iron status of preschool children with IDA and its association with the degree of growth retardation at presentation, and to detect the effect of iron supplementation on growth velocity (GV) over a period of one year. **Method:** a prospective pilot study conducted in Diabetes Endocrine Metabolism Pediatric Unit in collaboration with the Pediatric Haematology clinic at Children's Hospital, Cairo University included baseline and follow up anthropometric and hematological parameters of 40 IDA patients compared to 40 healthy clinically non-anemic, age and sex-matched controls. A daily total dose of 6 mg/kg/day of ferrous sulfate (20% elemental iron by weight) in 2–3 divided doses were given between meals to patients with IDA. **Results:** At presentation, patients with IDA had low hemoglobin, hematocrits, serum iron, serum ferritin, height standard deviation score (SDS), weight SDS, and BMI SDS which improved significantly after treatment. The GV of IDA patients correlated significantly with serum ferritin concentration and also their BMI SDS correlated significantly with the serum ferritin concentration. **Conclusion:** The GV and other anthropometric parameters of preschool children with IDA had markedly improved by oral iron therapy and correction of anemia.

P2-P862

Dopamine Beta-Hydroxylase Deficiency Leading to Growth Hormone Deficiency

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Background: Dopamine beta-hydroxylase (DBH) deficiency is characterized by lack of sympathetic noradrenergic function. Affected individuals exhibit profound deficits in autonomic regulation of cardiovascular function. DBH deficiency is a congenital disorder; however, the diagnosis is not generally recognized until late childhood. In this report, we present a case with DBH deficiency leading to growth hormone deficiency. **Case:** A ten year old girl who has been taking growth hormone therapy was referred with a history of sudden onset malaise and somnolence. Her body weight and height were 19 kg (−2.4 S.D) and 115 cm (−2.3 S.D.), respectively. Physical examination findings were unremarkable except for irregular heartbeat and blood pressure, somnolence, and weak deep tendon reflexes. Ophthalmoscopic eye and cardiovascular examinations were normal. Laboratory studies revealed abnormal levels of serum catecholamins and their urine metabolites. Serum epinephrine was measured as 11.1 pg/ml (*N*: 4–83), norepinephrine as 78.1 pg/ml (*N*: 80–498), dopamine as 52.9 pg/ml (<30), urine metanephrine as 47 μg/day (*N*: 26–230), and normetanephrine as 40.8 μg/day (*N*: 44–540). Other laboratory and radiological studies were unremarkable. Oral administration of 50 mg Droxidopa, twice daily, increased blood pressure and reversed all symptoms. **Conclusion:** This patient with growth hormone deficiency is the first case associated with DBH deficiency. Norepinephrine is a major regulator of the release of growth hormone. Low norepinephrine synthesis inhibits growth hormone secretion. DBH deficiency should keep in mind in case of irregular heartbeat and blood pressure together with growth hormone deficiency.

P2-P863

Quality of Life in Growth Hormone Treated Children and Adolescents with Growth Hormone Deficiency and Smallness for Gestational Age

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Background: The potential benefit of growth hormone (GH) therapy on health-related QOL (HQoL) of children with short stature related to GH deficiency (GHD) or smallness for gestational age (SGA) has not been well documented. **Objective and hypotheses:** Our objective was to assess potential disease and treatment related predictors for a poor HQoL in GH treated children. Children with male gender, SGA disorder, greater height deficit at start of GH and poor height gain were expected to be at risk. **Methodology:** The QoLISSY questionnaire - a cross-culturally developed height specific instrument - was sent to 157 children with idiopathic GHD and 219 non-syndromic SGA children, between 8 and 18 years old, being treated for at least one year with GH for short stature (height SDS < -2.5) at a Belgian GH treatment center. The questionnaires were filled out by the child. **Results:** Median total QoLISSY scores (tQS) of 22 (14 male) GHD and 55 (32 male) SGA children with complete data (20% response rate) were similar (76%), but significantly ($P < 0.001$) higher than reported in untreated short children (65%). Whereas no gender difference in tQS was present in GHD patients, SGA females had a lower median score (71.4 vs 80.9%). Despite a similar median age and height SDS at start and a similar median height gain at evaluation, height SDS at evaluation, GH exposure time as well as total height gain SDS correlated positively with tQS only in the GHD group. Using linear regression, gender and height gain were the best predictors of the tQS in the whole group. **Conclusion:** In a written survey with a low response rate, GH treated SGA girls were found to have the lowest HQoL. Females and children with the lowest height gain GH appear most at risk for presenting the lowest HQoL under GH therapy.

P2-P864

Secretion of Somatostatin and Growth Hormone (GH) in Various Forms of Hereditary Pathology

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Background: Patients with HP have stunting of various degree of expression but the most pronounced stunting is found in patients with Russell-Silver syndrome, Sekkel syndrome and Cornelius de Lange syndrome which is associated with disorders in the hypothalamus – hypophyseal system (somatostatin - GH). **Objective and hypotheses:** To study secretion of somatostatin and insulin-like growth factor (IGF-1, IGFBP-3) in various forms of hereditary pathologies (HP). **Method:** We studied 87 patients with HP (Russell Silver syndrome – 9 patients, Noonan syndrome – 13, Sekkel syndrome – 14, Prader-Willi syndrome – 11, Cornelius de Lange syndrome – 8, Turner syndrome (TS) – 32 patients aged 8 to 17 years old. A level of somatostatin and GH in blood serum and anthopometrical data (SDS) were studied **Results:** Stunting of various degree of expression was noted in all patients with HP but the most pronounced stunting was observed in patients with Russell-Silver syndrome (-5.16 ± 1.18 SDS), with Sekkel syndrome (-4.18 ± 1.12 SDS) and Cornelius de Lange syndrome (-6.10 ± 1.14 SDS). A reliably high level of somatostatin was in patients with Cornelius de Lange (98.30 ± 4.38 pg/ml, $P < 0.05$), Russell-Silver syndrome (85.36 ± 3.44 pg/ml, $P < 0.05$), Sekkel syndrome (69.27 ± 3.27 pg/ml, $P < 0.05$) on the background of a low level of GH in these patients. Patients with Noonan syndrome, TS and Prader-Willi syndrome the level of somatostatin and GH was within the lower border of normal ranges. **Conclusion:** Patients with HP have stunting of various degree of expression but the most pronounced stunting is found in patients with Russell-Silver syndrome, Sekkel syndrome and Cornelius de Lange syndrome which is associated with disorders in the hypothalamus – hypophyseal system (somatostatin – GH).

P2-P865

Postnatal Growth and Factors Modifying it in Very Low Birth Weight Preterms (PT) with Bronchopulmonary Dysplasia (BPD)

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Background: Different severities of bronchopulmonary dysplasia (BPD) may adversely affect postnatal growth of small preterm infants (PT). **Objective:** To measure postnatal growth data for 69 (39 F, 30 M) preterms with BPD. **Method:** We studied growth parameters of 69 PT with BPD for 16 ± 3 months postnatally. 40 had mild, 20 had moderate and 9 had severe BPD. **Results:** 96% of infants were appropriate for gestational age (AGA). Only 4% preterms had birth weight SDS < -2 for GA, and 4% had length SDS (LSDS) < -2. 84% of PT-BPD had normal or accelerated GV during the 16 ± 3 months period.

At 8±2 months of uncorrected age 45% had LSDS < −2 and at 16±3 months of age 25% had LSDS < −2. At 8±2 months 13% had body mass index SDS (BMISDS) < −2 and at 16±3 months 5.8% had BMISDS < −2. At 8±2 months 52% had HCSDS2 < −2. At 16±3 months 27.5% had head circumference SDS (HCSDS) < −2. 72.5% of PT-BPD had normal HCSDS compared to FT infants at 16±3 months. The co-existence of BPD with sepsis, NEC, PDA, twinning significantly affected their growth parameters postnatally. **Conclusion:** At 16±3 months postnatally, BPD-PT with severe BPD were shorter and had smaller HCSDS versus those with moderate severity.

P2-P866

Endocrine and Metabolic Parameters before Onset of rGH Treatment: Potential Predictive Factors of GH Response in Children Born SGA? Results from Cohort of Nancy

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Background: In spite of many studies demonstrating efficiency of recombinant growth hormone (rGH) on adult height in children born small for gestational age (SGA), great variability of response exists between treated patients. Predictive factors have been already studied such as age at start of treatment, rGH dose,…, but few data are available regarding the predictive values of pretherapeutic data on growth response. **Objective and hypotheses:** The main objective of this study is to identified predictive factors of rGH response in children born SGA with specific focus on clinical and biological data, especially regarding weight evolution, during the first years of life before the onset of treatment. **Method:** This is retrospective and monocentric study in hospital of Nancy. rGH response is defined by variation of height DS measured at 1, 2 years of treatment, at the end of treatment and at final adult height. Clinical and biological data before and during GH treatment were collected in files of treated children. Bivariate and multivariate analysis were performed. **Results:** In total of 108 children born SGA received GH treatment in Nancy, 91 patients were included. Amplitude of rGH response at final adult height is significantly positively correlated with pretherapeutic cholesterol ($r=1.64$; $P=0.0341$), not significantly with HDL cholesterol ($r=3.13$; $P=0.0705$), significantly negatively correlated with pretherapeutic cortisol ($r=-0.02$; $P=0.0217$), and negatively correlated with T_4 (-0.31; $P=0.0417$) in bivariate analysis. At 2 years of treatment, rGH response is significantly positively correlated with TSH before onset of treatment ($r=1.1$; $P=0.0204$) in multivariate analysis. No statistical correlation was found with weight evolution first years of life. **Conclusion:** This study highlights potential implication of thyroid, adrenal function and lipid profil on rGH response in children born SGA. Absence of association with weight evolution may be due at lack of statistical power, further studies with larger size are needed.

P2-P867

Growth Hormone Treatment in a Child with Trisomy 21 and Turner Mosaicism

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Background: Short stature occurs in Trisomy 21 but it is relatively slight during childhood. Turner syndrome would contribute significantly to short stature but the combined occurrence of both syndromes, even Turner mosaicism is unusual and could result in significant short stature. **Case:** SP was referred for a growth assessment at 2.5 years. Her parents were counselled about short stature occurring in both syndromes but were worried that her height was significantly short even for either syndromes. Her height was 75.5 cm (HtSDS −3.6 non Turner, HtSDS −1.8 Turner, $<5^{th}$ centile Downs), weight 9.26 kg (10^{th} centile Downs). Facial features were consistent with Downs syndrome. The only Turner features were hyper convex nails. Her height velocity was noted to fall to 3.5 cm/year by 2.8 years, with height now at 76.8 cm (HtSDS −4 non Turner, HtSDS −2.1 Turner), further away from the lowest centile of the Downs syndrome growth chart. The decision was made for a trial of growth hormone treatment and Turner doses with close monitoring of her IGF1 levels. She has now been on treatment for over 5 years. Auxology, IGF1 levels, GH dose are in the Table. **Investigations:** Pre-treatment IGF1 171 ng/ml (51–303), TSH 1.79 mU/l (0.4–4) fT_4 9.8 pmol/l (6.3–14). Coeliac screen, Thyroid peroxidase antibodies negative. Renal ultrasound is normal. No cardiac lesions on echocardiogram. IGf1 11 months into treatment was 327 ng/ml (49–289), her GH dose was reduced when levels increased further. **Conclusion:** Growth data over 5 years is presented, dose titration during pubertal induction would be most challenging.

Table 1. (for abstract P2-P866)

	7.4.10	3.12.10	21.3.11	31.10.11	11.11.13	13.8.14	16/2/15	6/11/15
HtSDS (Turner)	−2.01	−2.08	−1.95	−1.29	−0.57	−0.54	−0.64	−0.39
HtSDS (nonTurner)	−3.97	−3.95	−3.84	−3.21	−2.59	−2.6	−2.7	−2.58
IGF1					49.7 (3.3–31.7)	46.2 (3.3–31.7)	48.2 (5.1–48.2)	50.2 (5.1–48.2)
GH (mg/m^2/wk)		4.2	7	8.4	9.5	5.8	4.9	5.6

P2-P868

Pubertal Development and Final Height in Some Rare Genetic Diseases

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Background: Pubertal growth, age of puberty onset and pubertal spurt duration are correlated to final height (FH). Few data are available in subjects with rare genetic syndromes. **Objective and hypotheses:** To evaluate pubertal pattern and its influence on FH in subjects with different genetic syndromes including the effect of GH-therapy for GH deficiency (GHD) and GnRH analogs for precocious puberty (PP). **Method:** We studied for growth and pubertal development 30 patients affected by genetic conditions with molecularly confirmed diagnosis: Kabuki Syndrome (KS) (3 pts), Silver-Russel Syndrome (SRS) (9 pts), Williams Syndrome (WS) (11 pts), 22qdel (7 pts), followed-up until the FH in comparison with the General Population (GP). **Results:** Sixteen patients were treated with GH-therapy for an average period of 7.2 years (range 2.7–14.5). In the females long-term GH-therapy resulted in a positive height response compared with untreated patients. While GH-treated males reached a mean FH significantly lower than non-treated ones ($P=0.03$) (SDS −2.8 vs −1.3 SDS). PP was observed in 8 females, who were treated with GnRH analogue for 3.3 years (range 1–4.6), no significant differences were observed in the FH between treated and untreated pts. In del22q11 subjects the pubertal pattern was similar to that of the GP. SRS and WS subjects showed a shorter and lowered pubertal growth spurt and the peak height velocity was anticipated of 1 or 2 years than in the GP. This pubertal pattern leaded to a pubertal height gain of 10 cm lesser than in the GP of the same age and sex. Pubertal height gain slightly correlated with the FH ($P=0.05$). **Conclusion:** In SRS, WS and KS subjects early pubertal development and the inadequate pubertal growth contribute to an impaired FH. In GHD subjects, GH-therapy seems to improve FH, while the effects of GnRH analogue therapy were not so satisfying.

P2-P869

Growth Hormone Deficiency in a Patient with Ring Chromosome 18

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Background: Ring chromosome 18 [r (18)] syndrome belongs to a rare group of chromosomal abnormalities (only about 70 cases reported). The association of r(18) and growth hormone deficiency (GHD) is extremely rare (3 descriptions with different responds to GH treatment). Patients with r(18) syndrome are characterized by short stature, obesity, microcephaly, mental retardation, hypertelorism, epicanthic folds, micrognatia and small hands with short tapering fingers. Also atypical manifestations have been observed, with facial anomalies only. **Case report:** A 12 years old girl was referred to our clinic because of short stature. She was born at 36 weeks of gestation, her birth weight was 2200 g, length 51 cm, head circumference 32 cm. There was no family history of genetic or congenital disorders. The clinical examination revealed a girl with proportional short stature. Her height was 136 cm (−2,7 SDS), weight 40.6 kg, BMI 22.5 (1,1SDS), Tanner stage: 2 breast, 1 pubic hair development, discreet epicanthic folds, strabismus, lower-set ears and slightly smaller jaw. Her mental development was in lower normal range. Bone age was 10 years. GH stimulation tests showed a GHD (GH peak response to clonidine: 2.69 ng/ml, to insulin: 3.61 ng/ml). Baseline LH, FSH, TSH, prolactin and ACTH concentrations were in normal ranges for age. Magnetic resonance imaging of hypothalamic-pituitary region revealed a small hypophysis (2 mm). Chromosome analysis showed: 46, XX.ish r (18)(wcp18×1)[11]. No ultrasound abnormalities in abdomen and thyroid were shown. Echocardiogram showed minimal mitral regurgitation- clinically not relevant. GH replacement therapy was indicated with the dose of 0.33 mg/kg per day. After the first year of treatment she reached a height 146.8 cm (−1,8 SDS) with the height increase Δ 0,9 SDS. After the second year her height was 152.8 cm (−1,46 SDS), after the third:156.5 cm (−1,1SDS). Menarche occurred at the age 13 years 6 months. **Conclusion:** Our patient's growth response to GH treatment was similar to that observed in children with isolated GHD without r(18) syndrome. In children with r(18) exclusion of GHD should be taken under consideration.

P2-P870

Children with Down's Syndrome Show Quantitative, Phenotypical and Functional Differences of Effector T-Cells Compared to Immunocompetent Controls

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Background: Trisomy 21 is associated with an increased susceptibility to respiratory infections. **Objective and hypotheses:** For a more detailed characterization of the adaptive immune response, we analyzed the cellular and humoral immunity to specific pathogens in blood samples of 40 children with Down's syndrome in comparison to 51 age-matched controls. **Method:** We quantitatively analyzed lymphocyte subpopulations using flow cytometry. In addition, the T-cell effector function was characterized by functional and phenotypical analysis after polyclonal stimulation with staphylococcal enterotoxin (SEB) and antigen-specific stimulation with antigens of Varicella zoster virus (VZV), Cytomegalovirus (CMV) and *M.tuberculosis* (tuberculin). Results

were correlated with humoral immune responses. **Results:** The proportion of NK-cells within the lymphocytes of children with Down's syndrome was strikingly increased whereas the B-cell percentage was decreased. While the total amount of T-cells showed no differences, children with Down's syndrome revealed less CD4+ and more CD4+CD8+T-cells. Within the CD4+T-cell population, we detected a higher percentage of regulatory and Th17-cells and a higher Th1/Th2 ratio as well as a higher expression of the anergy markers PD-1 and CTLA-4. Percentages of polyclonally activated cells were significantly higher in children with Down's syndrome and showed an altered expression profile of the cytokines INFγ, TNFα and IL-2. Analysis of pathogen-specific immune responses showed an age-appropriate level of endemic infection with CMV, VZV and mycobacteria in both groups. CMV-specific cellular and humoral immunity correlated in all children. Among VZV IgG positive children, a higher percentage of VZV-specific T-cell-positive individuals were seen in the Down's syndrome group. **Conclusion:** No pronounced differences were detectable in pathogen-specific immune responses of children with Down's syndrome and controls. Besides a general proportional shift of leukocyte and lymphocyte subpopulations, effector T-cells seem to be functionally impaired which may promote a higher susceptibility to infections. The simultaneously higher fraction of reactive effector T-cells could represent a compensatory effect of functional anergy and/or be a consequence of a more pronounced history of infection.

P2-P871

Cardiovascular Anomalies in Turner Syndrome

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Background: Turner syndrome (TS) has several defects affecting different organs. Heart defects are the most common. They can be symptomatic (Heart murmur, high blood pressure) or diagnosed systematically. The chromosomal profile affects the nature of the anomalies encountered. **Objective and hypotheses:** Report cardiac abnormalities in the ST. **Method:** This is a retrospective study of 60 TS patients identified in 20 years. Mean age was 16±0.4 (3 months-17) They were given a complete physical examination, a cardiovascular evaluation (ECG, Doppler ultrasound and cardiac MRI) and a karyotype at diagnosis. Annual Cardiovascular revaluations (ECG, Doppler ultrasound) and at the slightest sign were made **Results:** Heart abnormalities are found in 45% of cases. The most frequent abnormalities are bicuspid aortic valve (30%) and coarctation of the aorta (10%). Interatrial communications, pulmonary valve or blood abnormalities ((stenosis and/or mitral disease (prolapse) were noted in 5% of cas. Cardiac abnormalities were present at diagnosis. Revaluations have noted the appearance of a hypertension in 10% associated with e hypercholesterolemia (6%) and diabetes mellitus in 4%. There was a genotype-phenotype correlation. Heart abnormalities are present in 70% of subjects with monosomies 45 X0; they are less common (15%) in case of chromosomal formulas mosaic. Aortic coarctation xas more common in formulas 45 X0, pulmonary stenosis in mosaics X0 45 - 46 XX **Conclusion:** The frequency of cardiovascular abnormalities in T S justifies systematic cardiological assessment. Many of these defects are curable surgically. prolonged cardiac monitoring of these patients is necessary for screening scalability.

P2-P872

Metamemory in Turner Syndrome: A Study Comparing Episodic and Semantic Memory

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Background: Tuner syndrome (TS) is associated with a distinctive cognitive profile including memory impairments. The current study focuses on metamemory defined as our knowledge about our memory functioning and yet never been explored in TS. **Objective and hypotheses:** The aim of this preliminary study is thus to determine what patients with TS know about their memory functioning and when their memory is impaired whether or not they are aware of those deficits. To assess metamemory, this study focused on the Feeling-of-knowing paradigm. This paradigm consists in asking participants to predict whether or not they will be able to recognize later an information that they currently cannot recall. Many studies have shown than people are accurate using such paradigms and therefore know what they will be able to retrieve later. **Method:** The aim of this preliminary study is thus to determine what patients with TS know about their memory functioning and when their memory is impaired whether or not they are aware of those deficits. To assess metamemory, this study focused on the Feeling-of-knowing paradigm. This paradigm consists in asking participants to predict whether or not they will be able to recognize later an information that they currently cannot recall. Many studies have shown than people are accurate using such paradigms and therefore know what they will be able to retrieve later. **Results:** Results show that participants with TS recall fewer face-name associations but similar number of famous faces, thus showing a dissociation between episodic and semantic memory. Furthermore, participants with TS gave accurate Feeling-of-knowing judgments, showing that these patients have a good knowledge of their memory performance (and deficits).

P2-P873

A XO/XX Girl with Lack of Morphological UTS-Features, Short Stature and Precocious Puberty

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Background: Ullrich-Turner-Syndrome is usually characterized by typical morphological features. Short status, delayed bone age in childhood and gonadal dysgenesis with delayed or lacking pubertal development, amenorrhoea and infertility. Other symptoms like thyroid dysfunction, heart defects, diabetes, behavioural or learning problems vary. The genotype/phenotype correlation may be poor. Especially in UTS mosaicism, spontaneous puberty may occur. **Objective and hypotheses:** We report a girl with UTS mosaicism with lack of morphological features and precious puberty. **Patient and Methods:** She is the first of 2 children born after normal pregnancy at term with low birth weight of 2820 g. Her uncle suffered from Klinefelter syndrome. At the age of 8 she developed pubertal hair and thelarche. Bone age was 12.5y and she measured 139 cm with a target height of 169 cm. LH was 2.5 U/l (<12), FSH 6.3 U/l ((0.4–6.6), oestradiol 25 ng/l (6–27) with normal levels of beta-HCG, alpha-1-foetoprotein, testosterone, prolactin, IGF1 and IGFBP3. She then showed behavioural problems and learning difficulties. Menarche was at the age of 9 8/12y. She also developed an insulin insensitivity with a peak insulin level of 302.3 μU/ml after 60 min and had a thyroid dysfunction. An ACTH-Test showed normal levels. We treated the patient with growth hormone, gonadotropin-releasing hormone analogues and thyroid hormones. A chromosomal analysis war added. **Results:** The chromosomal result was 46/45 XX/X0 female. During the treatment the girl showed moderate growing (growth rate 7.2 cm), while we managed to stop puberty development and bone age acceleration. **Conclusion:** Our patient showed a rare condition of UTS which is not recognized by appearance. Apart from hypothyroidism, for therapeutic considerations, short stature and precocious puberty with mental development are relevant. Chromosomal analysis should be mandatory in short stature or reduced prospective height even if there are no morphological features.

P2-P874

Transverse Myelitis in Turner Syndrome

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Background: Transverse Myelitis (TM) is an auto-immune syndrome with neural injury to the spinal cord. The TM may be first clinical manifestation of Multiple Sclerosis (MS). It is known that Turner's Syndrome (TS) is associated to the presence of autoimmune diseases. **Case Report:** A 15-year old female, began with manifestations of loss of strength on the lower limbs evolving rapidly with sensorial loss, tetraparesis and hemodynamic instability, requiring intubation. Two days later she was transferred to the intensive care unit (ICU). The patient had hypothyroidism diagnosed at the age of 2 and TS at age of 11, and had been in use of vitamin D and calcium carbonate, conjugated estrogen, progestogen, levothyroxine, oxandrolone and growth hormone. On examination, she had BMI 29.5, Glasgow 15, flaccid tetraplegia and areflexia. MRI showed extensive hypointense signs on T1 and T2 on the central region of the cervical spine. She was diagnosed with TM and received 7 cycles of plasmapheresis, pulse therapy with methylprednisolone for 5 days followed by Rituximab with partial improvement of the strength and weaning of vasoactive drugs and mechanical ventilation. She was discharged from the ICU 2 months after admission, tracheostomized and bedridden. One month later she was discharged with prednisolone and azathioprine. **Conclusion:** TS is associated to the presence of autoimmune diseases (AID), though its association with TM or MS has been rarely reported. Despite the strong association between TS and AID is well known, the underlying immunopathogenic mechanism remains unexplained. Recent studies have displayed that TS patients do not show an excess of immunogenic risk markers. This is evocative for a higher responsibility of X-chromosome abnormalities in the development of AID. Early diagnosis and regular screening for potential associated autoimmune conditions are essential in the medical follow-up of TS patients.

P2-P875

Tricho-Rhino-Phalangeal Syndrome Type I in a Girl with Growth Hormone Deficiency

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Tricho-rhino-phalangeal syndrome Type I (TRPS I) is a rare autosomal dominant genetic disorder clinically characterized by craniofacial and skeletal abnormalities, associated with cone-shaped epiphyses, brachydactyly and short stature. Although patients with TRPS I present various degrees of short stature, there are only four reports of growth hormone deficiency in patients with TRPS I. We present the case of TRPS I and partial GH deficiency. A 15-year-old female was referred to our clinic for short stature. Her height was: 141 cm (−3.7 S.D.), and weight: 46 kg (−1.1 S.D.). Physical examination showed sparse hair, protruding ears, bulbose nose with long filtrum, significant shortening of bilateral metacarpal and metatarsal bones. Neuromotor development was normal. She had menarche when she was 11 years old. Biochemial and metabolic test results were normal. Thyroid functions were normal as well. Bone age was 15 y according to Greulich and Pyle method. X Rays revealed brachydactyly, cone-shaped epiphyses, Perthes-like changes of the femoral head, coxa plana and coxa magna. DEXA scan corrected for height age showed Lomber spine *Z* score of −2,9. Growth hormone (GH) stimulation tests showed low response after clonidine (GH peak of 6.2 ng/ml) and levo-dopamine (GH peak of 4.1 ng/ml) administration. Sellar MRI showed a normal size and location of the pituitary gland and stalk. TRPS I is a rare genetic disorder characterised by typical craniofacial and skeletal abnormalities. Short stature is a common characteristic of TRPS patients. This is the fifth report of a patient with TRPS I showing partial GH deficiency.

P2-P876

Project Epi Peg-Premeb. Clinical Situation of a Person Born SGA Followed from Birth Cohort. GLOBAL Causes and Clinical Situation of Partial Birth Cohort and 12 Months

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Up to 50% of children born SGA to 2 years have not made a proper catch up (by excess or defect), with repercussions in size, metabolic and cardiovascular disorders, DM, etc. epiPEG-PreMeb project to study during their first two years of life. **Goals::** Establish a SGAcohort for monitoring, evaluation catch-up, and analysis of medium-environmental and social factors. To study the influence of these variables on clinical, laboratory and metabolic profiles. Somatometry draw graphs and tables of biochemistry normal. Create a serum bank for future biochemical and genetic studies. **Material and methods:** They studied live births of singletons in our hospital during 2012–2014, and are classified according to EG and weight/height (Spanish Tables 2008). Estimated N: 110 visits are made at 0, 3, 6, 9, 12, 15, 18 and 24 months, measurements, weight, height and perimeters. blood samples analyzed and store are obtained. Results at the end of the initial selection: SGA103 recruited in 24 months (♂56, 55%). Epidemiological data: Average age 32.2 years mother brothers 18/103 previous PEG (17%); smoking mothers during pregnancy 40/103 (38%), 4 (3–15) cigarettes/day; worker during pregnancy 67/103 (65%), of which 85% relate with > 3 hours walking/day; drugs during pregnancy 29/103 (28%), 70% for asthma, 20% l-thyroxine and 10% other. Pathologies associated with gestation: 54/103 (52%) (gestosis, preeclampsia, DM, thyroiditis, psychogenic stress). Childbirth: a term 67/103 (65%), eutocic 88/103 (85%). Facts children at birth: Middleweight DS −2.7 [−3.5 to 2.0], medium size DS −2.4 [−3.2 to 2.1], for sex, and EG. EBF: 77/103 (74%) during the 1st month of life. RN income or pathology in the 1st month of life 24/103 (23%). SGAcases that have reached 12 months of follow up 62 cases. Income over 12 months 5/62 (8%) (bronchitis). With 12 months of life have 10/62 cases (16%) no suitable catch up with P and/or T <P10, 32/62 cases (48%) catch up very fast with P and/or T> P90. **Conclusions:** The age of pregnant women, their current lifestyle (snuff, stress and work) and taking regular medication (asthma), is causing a higher rate of SGA. In our study it notes that about women Euskadi rate of pregnant women with SGA smokers is higher and younger age. These children PEG require greater use of artificial feeding, a higher rate of hospital admissions of children with birth SGA, but later is not a disease risk population, or bronchiolitis. However it detected since 70% of RN PEG have an inadequate development somatosensory metric per year of life, which may have future repercussions.

P2-P877

Pituitary Gigantism and Central Precocious Puberty Presenting with Prognathism in a Pediatric Patient

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Case Report: A 13-year old male presented to a dental office for evaluation of prognathism. After evaluation, his dentist referred him to pediatric endocrinology. He had no significant past medical history. He denied any signs or symptoms associated with any hormonal deficit or excess, as well as headaches or visual disturbances. Denied excessive growth of hands or feet. Parents reported that he had been having pubic and axillary hair, mild acne, and significant growth for the last few years. On exam, he was found to be above the 95th centile for height (mid-parental height around the 20th centile) and at the 90th centile for weight. Genitalia and pubic hair were both were Tanner stage IV. Previous growth records revealed a growth acceleration, starting at around age 8 years old, and that he had crossed height percentiles from the 75th to above the 95th from age 8 to age 11 years old. Bone age was read at 17 years, at a chronological age of 13 years (>3SD above the mean). Hormonal evaluation revealed growth hormone (GH) levels of 7.3 ng/ml (0–5.0) and IGF1 levels of 725 ng/ml (upper limit of normal for his Tanner stage). Thyroid function tests, morning cortisol and prolactin were normal. FSH, LH and testosterone were late pubertal. GH suppression test was abnormal, and confirmed the suspected diagnosis of GH excess. MRI with contrast revealed a pituitary macroadenoma. The patient had a transsphenoidal resection of the macroadenoma. On follow up he reported, no further mandible growth, his growth was normal as were all his pituitary hormones. He did not need any hormonal replacement. Post-surgical MRI showed no evidence of residual mass. He was referred for jaw reconstruction. **Discussion:** Pituitary gigantism results from persistent increased secretion of GH and it occurs before fusion of the epiphyseal growth plates, hence it will have an effect on stature. Clinical manifestations include above normal growth velocity with concurrent rapid weight gain, and occasionally growth of hands and feet, frontal bossing and prognathism. It seems our patient had a component of central early puberty as well (early pubertal development, elevated puberty hormones and advanced bone age), related to his macroadenoma, which resulted in premature epiphyseal closure.

P2-P878

The Monitoring of Endocrine Functions in Children with Rare Genetic Syndromes

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Background: Children with rare genetic disorders may have different endocrine problems **Objective and hypotheses:** To present 4 paediatric patients (3 M, 1 F) aged 4.3 – 16.9 y.o. (mean age 11 ± 5.5 years) with different genetic syndromes: Pallister-Hall, Holt-Oram, Ellis–van Creveld and Marshall. **Method:** Retrospective study. **Results:** Mean age of diagnosis was 5.3 ± 2.7 y.o. All children had growth hormone (GH) deficiency confirmed by stimulation tests. Mean age of GH treatment start was 6.5 ± 2.2 y.o. and treatment duration varied between 1.0 to 9.9 years (4.6 ± 4.3 years). In all cases, good effect of GH was observed, even if child with Holt-Oram and Marshall's syndromes had multiple pituitary hormone deficiency. Apart of GH deficiency, the patient with Holt-Oram syndrome developed consecutively with age central hypothyroidism, hypocorticism and hypogonadism and was treated with multiple hormone replacements. The patient with Marshall's syndrome also had central hypothyroidism and severe hypoglycemia before GH treatment. However, under GH hypoglycemia disappeared; hypocorticism has not been detected. The child with Pallister-Hall syndrome which includes hypothalamic hamartoma had normal puberty. In him, weight excess and impaired insulin sensitivity developed during the monitoring required metformin administration. All patients described had hypothalamo-pituitary anomalies on MRI. Several non endocrine manifestations have been diagnosed. **Conclusion:** Children with rare genetic syndromes may have severe endocrine problems and need careful monitoring by a multispecialist team.

P2-P879

SHORT Syndrome and rhGH Treatment – Is It Useful?

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Background: SHORT syndrome is an autosomal dominant genetic multisystem disorder determined by PIK3R1 gene mutations, which normally plays a role in cell signalling. SHORT is an acronym for short stature, hyperextensibility of joints and/or hernia, ocular depression, Rieger anomaly and teething delay. It is a rare condition; its prevalence is unknown with only few affected individuals and families reported worldwide. **Case report:** We report a case of 4 years 2 months old girl, evaluated at the Endocrinology Department, for short stature (height = 87 cm, −4.4 S.D., weight = 11 kg, normal family history) associating low birth weight (2080 g, 39 w, < −2DS), ocular anomalies (deformed pupil, tractioned to the superolateral nasal region), dental defects (multiple caries, tooth fracture) and particular facies (triangular face, prominent forehead, deep-set eyes, thin nasal alae, down-turned corners of the mouth). The evaluation of the somatotropic axis revealed GH of 0.269 ng/ml, low IGF-1 = 27.1 ng/ml (N = 49–289) with normal thyroid function. Hand-wrist X-ray showed delayed bone age (3 years). Due to eye defects, ophthalmology evaluation was performed and diagnosed iris atrophy suggestive for Rieger anomaly, which together with the other phenotypic particularities pleaded for SHORT syndrome. Unfortunately genetic testing could not be performed due to lacking resources. Low birth weight (born SGA), persistent severe growth retardation, delayed bone age and low IGF1, made rhGH treatment to be taken into consideration. Further evaluation of glucose metabolism revealed no anomaly and brain MRI showed normal hypothalamic-pituitary morphology. Thus the rhGH treatment was started at a dose of 0.039 mg/kg per day, with good growth rate 0.83 cm/month after 1 year. **Conclusion:** SHORT syndrome is a rare disease and given the few cases, there is not a definite attitude toward short stature management. To our knowledge this would be the first case treated with rhGH. The growth response was good with no metabolic side effects.

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Late Diagnosis of Mixed Gonadal Dysgenesis – Clinical and Psychological Implications

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Background: Mixed gonadal dysgenesis (MGD) is a disorder of sex development associated with a numerical sex chromosome abnormality. Reported genital phenotypes range from female external genitalia or mild clitoromegaly through all stages of ambiguous genitalia to hypospadias or a normal penis, depending on the proportion of monosomic cells. **Case presentation:** 18 years old girl, with a history of hypertension, ventricular septal defect and obesity presented with primary amenorrhoea and lack of secondary sexual characters. Physical examination revealed: obesity, normal stature, B1P4 pubertate development (Tanner), normal female type external genitalia, Turner syndrome stigmata (epicanthic folds, short 4th/5th metacarpals, hyperconvex nails, broad chest), acanthosis nigricans and her bone age was delayed (16 years). The genital examination identified an 8 cm vagina. Laboratory data reveals: high FSH (49.5 mIU/ml), high LH (17.7 mIU/ml) and low Estradiol (< 5 pg/ml), normal Testosterone (0.15 ng/ml) and dyslipidemia. Abdominal and pelvic ultrasound detected hepatic steatosis, a small uterus (41/11/9 mm), two small hypoechogeny formations (possible ovarian residue) and the chromosomal analysis revealed 45,X/46,XY. Psychological consultation identified generalized anxiety disorder and female gender identity. After discussion with the patient and her parents, the *decision* was *made to proceed* with a *diagnostic laparoscopy* and bilateral gonadectomy owing to her increased risk of malignancy and continuation of secondary sexual maturation with hormone replacement. **Discussions:** Early diagnosis of MGD is very important because a timely hormonal therapy can avoid complications induced by hormonal imbalance: lack of secundary sexual characters and because the increased risk of developing malignancy gonadal tumors. Delayed diagnosis favoured several complications like: obesity, hypertension, dyslipidemia, hepatic steatosis, insulin resistance and last but not least, generalized anxiety disorder.

P2-P881

The Structure of Genetically Determined Types of Short Stature in Uzbekistan According to Retrospective Analysis

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Background: Stunting in children is a heterogeneous state. Many endocrine, somatic, genetic and chromosomal diseases are accompanied by stunting. It can adversely affect indicators of the final height of the child; therefore timely diagnostics and treatment stunting is very important. **Objective and hypotheses:** To carry out a retrospective analysis of case histories of children and adolescents with genetically determined types of short stature who admitted a paediatric department of a clinic of Research Institute of Endocrinologyduring 2003–2013. **Method:** An analysis of case histories of children and adolescents with short stature 3–17 years who undertook inpatient treatment in paediatric department of RIE clinic during 2003–2013 is carried out. **Results:** During 2003–2013, 642 children and adolescents with stunting and disorders of sexual development (236 boys or 36.8% and 406 girls or 63.2%) were hospitalised and examined; of them there were 197 children at the age of 3–11 years (30%) and 455 adolescents aged 12–17 years (70%). Mean age of patients at diagnostics makes 12.7 ± 3.9 years. The following structure of genetically determined types of short stature is found: TS -57.1% (average age 13.8 ± 3.5 years); with multiple deficiency of adenohypophysis hormones (MDAH) – 23%; the ratio between boys and girls made 1.5:1; primordial dwarfism in 5.2%; hypochondroplasia in 4.6%; Noonan syndrome in 3.2%; Sekkel syndrome in 2.4%, Rassel-Silver syndrome in 2.1%; PraderWilli syndrome in 1.5%; Laron syndrome in 0.9%. **Conclusion:** Results of the retrospective analysis show: In Uzbekistan the greatest percent of children and adolescents with genetically determined types of short stature is made by patients about TS and MDAH, in comparison with other genetic variants of short stature - Late diagnostics and a low level of detectability of children with genetically determined types of short stature in the Republic.

P2-P882

Evaluation of Growth Pattern in Prader-Willi Syndrome

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Background: The main reason of decrement of growth in children with Prader-Willi Syndrome (PWS) is dysfunction of hypothalamo-hypophseal axis (HHA) and a decrease in the capacity of secretion of growth hormone (GH). In fact, in some cases, GH levels are normal, so there may be other factors in the etiology. **Objective and hypotheses:** In this study, 19 months old PWS case with growth failure is represented. **Method:** 13 months old male patients admitted to pediatric endocrinology. He was born to unrelated healthy parents. When he was 8 months old, he was diagnosed PWS His anthropometric measurements were shown in table 1. Thyroid function tests, IGF1, IGFBP3 levels were normal. When he was 19 months old, a decrease in height percentile was observed. Height percentile was greater than 3 percentile. GH secretion abnormalities were evaluated by a 4-hour sleep profile. **Results:** GH peak levels (<15 ng/dl) and numbers (<3 times 5 ng/dl) were low; mean density was low (<3.5 ng/dl). **Conclusion:** 90% of etiology of pathological short stature in PWS cases is due to GH deficiency. Cases with NSD, as in our case in younger ages, are very rare. ***NSD may be a prodromal stage before evident GH deficiency develops in PWS cases***. There isn't any consensus about treatment in this stage. In fact, there are a few opinions such as early GH treatment may normalize body fat composition and may help reaching target height. This case is represented to discuss the early GH treatment in PWS cases diagnosed with NSD in younger ages.

Table 1.

Anthropometrics	13 months	19 months
Weight (kg)	11.5 (75–90p)	12 (25–50p)
Height (cm)	77.7 (50p)	81.5 (25–50p)
Height SDS	1.01	0.1
Body mass index (kg/m^2)	19.16	18.07
Bone Age (months)	15	18
IGF-1 (ng/ml)	74.4 (0,1 SDS)	255 (2.3, 3 SDS)
IGFBP3 (ng/ml)	4933 (>3 SDS)	2963 (1.28, 2 SDS)

P2-P883

Prader-Willi Syndrome – Different Patients, Different Attitude

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Introduction: Prader-Willi Syndrome (PWS) is a multisystemic genetic disorder caused by lack of expression of genes on the paternally inherited chromosome 15q11.2–q13, characterized by dysmorphic features, hypotonia, mental retardation, behavioral abnormalities, hyperphagia with progressive obesity and endocrine dysfunctions as hypogonadism and GH deficiency (GHD). **Cases report:** We present 3 cases: 2 females and 1 male with specific clinical features of PWS and genetic confirmation. After the age of 1, they presented hyperfagia with rapid weight gain. The boy had the first endocrinological examination at the age

of 17 years and presented epiphyseal closure, with a final height of 159 cm (−2.7 S.D.) and moderate overweight. In spite of confirmed GHD, no treatment was initiated because of parents' option. At the age of 10, first girl had important obesity (+10 S.D.) and a surprising height at +2 S.D. despite of partial GHD. With strict diet, her weight did not excessively increase. She had low hormones of gonadal axis and her actual height remains higher than expected (−0.5 S.D.). Although basal GH remains low and IGF1 at the inferior limit, the association of confirmed sleep apnea temporized the GH treatment. At the first endocrinological examination at the age of 6, MF presented moderate obesity (+3 S.D.), high normal height (+2 S.D.). The confirmed GHD, with the possible aggravation of obesity, in the absence of sleep apnea, justified the rhGH therapy. With rigorous alimentation and constant psychological and parental support, their weight did not excessively increase. **Conclusion:** GH therapy in PWS represents a unique therapeutic challenge with varied therapeutic goals that are not focused exclusively on increased height. GH treatment is recommended and should be individualized for patients with PWS in conjunction with dietary, environmental and lifestyle interventions, the major concern being aggravation of sleep apnea.

P1-P884

Clinicopathological Characteristics of Papillary Thyroid Cancer in Children With Emphasis on the Pubertal Status and Association With BRAFV600E Mutation

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Background: Papillary thyroid cancer (PTC) constitutes more than 90% of the thyroid cancer in children. PTC behaves differently in prepubertal children than in pubertal children and between children and adults. BRAF gene activating mutations lead to PTC by creating aberrant activation. The most common mutation is $BRAF^{V600E}$. **Objective and hypotheses:** To evaluate clinicopathological characteristics of PTC patients with emphasis on the pubertal status and investigate association of BRAFV600E mutation with disease characteristics. **Method:** Medical records of 75 patients with PTC were reviewed retrospectively. $BRAF^{V600E}$ mutation status was found in medical records of 56 patients. **Results:** Mean age at diagnosis was 12.4 ± 3.8 years. There was no difference in sex, symptoms and tumor histopathology between prepubertal and pubertal children. $BRAF^{V600E}$ mutation was similar. Although prepubertal children had greater tumor size, there was no difference in pathological evidence of tumor aggressiveness. Lymph node and lung metastasis were more prevalent in prepubertal children. Prepubertal children needed at a greater frequency lateral neck dissection ($P=0.043$) and more frequently treated with second or more dose of radioactive iodine ($P=0.048$). Persistent disease or recurrence were more frequent in prepubertal children ($P=0.02$). $BRAF^{V600E}$ mutation was found in 14(25%) patients and was high in classic variant PTC ($P=0.024$). It was similar in girls and boys ($P=0.7$), and in tumors larger than 1 cm or smaller than 1 cm ($P=0.7$). Multicentrisite was high in $BRAF^{V600E}$ mutation ($P=0.01$) but lymphovascular invasion, perineural invasion, thyroid capsular invasion, extrathyroidal invasion of the tumor were similar. There was no relation between $BRAF^{V600E}$ mutation and lymph node and pulmonary metastasis at diagnosis. **Conclusion:** PTC is more aggressive in prepubertal children. $BRAF^{V600E}$ mutation is not correlated with a more extensive or aggressive disease. Presence of the $BRAF^{V600E}$ mutation is not the cause of the differences in the biological behaviour PTC in prepubertal and pubertal children.

P1-P885

Elevation of Serum Fibroblast Growth Factor 21 in Congenital Hypothyroidism

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Background: Fibroblast growth factor 21 (FGF21) is one of the FGF superfamily, which regulates energy expenditure, glucose metabolism and lipid metabolism. FGF21 elevates of glucose uptake in peripheral tissues, and regulates body temperature in brown adipose tissue. **Objective and hypotheses:** This study is to reveal which endocrine diseases in children has elevation of FGF21. **Method:** We collected blood from 253 endocrine diseases in children, under 20-year-old, from April to December 2012 at Kurume University Hospital. Diseases were following: idiopathic short stature (90), GHD (20), short stature children born SGA (13), pan-hypopituitarism (5), Graves' disease (7), Hashimoto disease (4), transient hyper-TSH (22), congenital hypothyroidism (CH; 50), T1DM (22), T2DM (3), 21OHD (4), central precocious puberty (9), hypochondroplasia (2), achondroplasia (2), and healthy control (59). FGF21 was measured by ELISA (BioVendor, Czech). Kruskal-Wallis test was used for statistical analysis. **Results:** Only CH had significantly elevated FGF21 compared to control. Elevation of thyroid hormone increases FGF21 via THβ receptor and/or PPARα. This result implicated that administration of levothyroxine may be overdosed in CH. This study replicated previous literatures, in that T1DM had decreased FGF21, T2DM had increased FGF21, and growth was not related to FGF21. **Conclusion:** CH had elevated FGF21, indicating that levothyroxine may be overdosed in CH. FGF21 may be a new biomarker for optimal levothyroxine dose in CH.

P1-P886

Evaluation of Epicardial AdiposeTissue Thickness in Children Detected Subclinical Hypothyroidism

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Background: Childhood overt hypothyroidism is a chronic disease that affect many system adversely and requires treatment.

Table 1.

	SH	Control Group	P value
Age	8.28 ± 4.75	8.69 ± 3.9	$P > 0.05$
Sex. Puberty (Prepubertal/ pubertal)	F:11 M:14 16/9	F:10 M:15 17/8	$P > 0.05$
Weight	25–50 *percentile*	50 *percentile*	$P > 0.05$
Height	25–50 *percentile*	25–50 *percentile*	$P > 0.05$
BMI	25–50 *percentile*	50 *percentile*	$P > 0.05$
TSH	5.7 ± 1.59	3.7 ± 0.5	$P < 0.05$
sT4	1.27 ± 0.18	1.4 ± 0.21	$P > 0.05$
sT3	4.4 ± 0.62	4.1 ± 0.49	$P > 0.05$
EFT	4.16 ± 0.8	2.04 ± 1.1	$P < 0.05$

However, subclinical hypothyroidism (SH),defined obvious cases, impacts on other systems are unknown and there is no common approach to be treated. Moreover, SH may continue for many years, before they become overt hypothyroidism. Cardiovascular system (CVS) is one of the host system, which hypothyroidism adversely affects. Epicardial adipose tissue thickness (EAT) is known to be an important marker in terms of the cardiovascular risks. We aimed to determine the effects on CVS of subclinical hypothyroidism. **Method:** The study included were 25 patients with SH and 25 healthy children. SH was determined according to slightly higher TSH than the upper limit (4.2 M/l),normal free T4 and T3 levels. EAT was determined by transthoracic echocardiographic measurements in millimeters, in pediatric cardiology clinic. **Results:** Anthropometric measurements of all cases, thyroid function tests and EAT values are shown table 1. Epicardial fat thickness was significantly higher in SH children, than the children without thyroid dysfunction. **Conclusion:** This study suggests that subclinical hypothyroidism effects adversly the cardiovascular system in children before hypothyroidism become overt. In future this data may be marker at the begining of LT4 treatment in SH with children.

P1-P887

EEG Alterations are Common in Hashimoto's Thyroiditis

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Background: Steroid responsive encephalopathy with autoimmune thyroiditis (SREAT) is a clinically and electrographically heterogeneous steroid-responsive encephalopathy associated with thyroid autoantibodies. **Objective and hypotheses:** To investigate, whether children and adolescents with Hashimoto's Thyroiditis (HT) lacking acute clinical manifestation of SREAT show electroencephalogram (EEG) alterations, and to compare EEGs of HT patients with those of healthy subjects. **Method:** EEGs were performed in 31 patients with HT recruited via our paediatric-endocrine clinics and in 28 healthy controls matched for age and gender. Antibodies against thyroperoxidase and thyroglobulin were determined in all subjects. TSH and fT4 in HT were analysed in patients only. **Results:** Mean age of HT patients was 14.9 years (range 8.0–18.0 years), mean age of controls 14.3 years (range 10.0–18.0 years), without significant difference. The patients' fT4 values were all within the age-appropriate normal range. 19 patients had normal TSH values, while 7 had values marginally above, and 5 slightly below the normal range. No thyroid antibodies could be detected in control subjects. 8 out of 31 EEGs in the HT patient and 1 out of 28 EEGs in the control group were found to be abnormal ($P < 0.05$, Fisher's exact test). While EEG abnormalities such as photoparoxysmal response, focal sharp waves, and bilateral synchronous spike-waves, differed not between the two groups, HT patients showed significantly more often a mild to moderate background slowing than controls ($P < 0.05$, Fisher's exact test). **Conclusion:** Children/adolescents with HT without clinical signs of SREAT present more often with EEG abnormalities compared healthy controls. This could indicate a cerebral concurring in Hashimoto's thyroiditis. We speculate that those alterations might lead to SREAT as the maximal manifestation. Consequently, we suggest regular EEG checks in patients with HT.

P1-P888

"Semi-Hot" Thyroid Nodules Associated with GNAS Mutations in Three Adolescents

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Background: Hot thyroid nodules are uncommon in children and adolescents. Hyperfunctioning adenoma do not always produce hyperthyroidism, but can precede the apparition of a truly toxic adenoma. Autonomous adenoma can be associated with mutations of TSH-R and some mutations of GNAS. **Patients:** Patient 1 presented mild clinical hyperthyroidism. Patients 2 and 3 were asymptomatic and had clinical euthyroidism. Examination revealed a unique isolated thyroid nodule in the 3 patients (30.5, 30, 31 cm diameter). Café-au-lait spots were present in Patient 1. TSH was undetectable. FT3 was 7. 10. 13 pmol/l ($N < 6.5$). FT4 was 18, 18.3, 18.5 pmol/l (N 12–16). Ultrasonography showed encapsulated nodules with increased vascularity in all 3 patients. Radionuclide scintigraphy showed hyperfunctioning nodules with absent uptake in the surrounding tissues in 2/3 and decreased uptake in 1/3. Partial thyroidectomy was performed in 3/3 patients. Molecular examination revealed GNAS mutations in the 3 patients. Postoperative period was uneventful. **Conclusion:** Mild hyperthyroidism or thyroid palpation in asymptomatic patients can reveal hyperfunctioning nodules as the seemingly unique manifestation of GNAS mutations.

P1-P889

Evaluation of Body Composition via Bioelectrical Impedance Analysis in Children with Subclinical Hypothyroidism and Effect of LT4 Treatment; Follow-up Results

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Background: It's well known that overt hypothyroidism leads to weight and body fat content increase but there is limited data in the literature about the effect of subclinical hypothyroidism (SH) on body composition parameters. **Objective and hypotheses:** In our previous study body composition parameters were evaluated in patients with SH and it was concluded that trunk fat mass was increased in SH patients before any alterations in basal metabolism rate occur. In this study we aimed to assess the body composition via bioelectrical impedance analysis (BIA) in SH patients and determine the effect of LT4 treatment on body composition parameters. **Method:** Twenty patients diagnosed with subclinical hypothyroidism in-between 5–13 years were involved in the study. All the patients were evaluated with BIA (Tanita MC-780MA) before LT4 treatment and on the 6th month of LT4 treatment. The evaluated body composition parameters were as follows: weight, height, body mass index (BMI), body fat (%), trunk fat mass (TFM) (kg, %), fat-free mass (FFM) (kg, %), trunk fat-free mass (TFFM) (kg), trunk muscle mass (TMM) (kg), and total body fluid (TBF) (kg,%). **Results:** Mean age of the patients was 8.17 ± 2.73 years. TFFM (before treatment 13.13 kg $\pm$ 4.23 kg, after treatment 14.09 kg $\pm$ 4.66 kg; $P = 0.000$) and TMM (before treatment 12.30 kg $\pm$ 4.05 kg, after treatment 13.20 kg $\pm$ 4.5 kg; $P = 0.000$) were increased after LT4 treatment and found statistically significant. **Conclusion:** According data shows that after LT4 treatment, TFFM and TMM of the patients were increased, which shows the positive metabolic effect of correction of subclinical hypothyroidism. Identification of metabolic alterations in early stages of thyroid disease and correct intervention is important for prevention of obesity in these cases.

P1-P890

The Molecular Causes of Congenital Hypothyroidism: The Scottish experience

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Background: Inherited forms of congenital hypothyroidism (CH) account for approximately one quarter of all causes of CH. These include biosynthetic defects and developmental and morphological abnormalities. **Objective:** Describe the Scottish experience of genetic testing in CH. **Method:** Retrospective study over 37 years up to March 2016. Patients were selected on the basis of imaging findings or strong family history of CH. **Results:** From 970 infants referred by Scottish neonatal screening, 649 cases of permanent CH were identified. DNA was analysed in 66 cases of suspected dyshormonogenesis. Mutations or variants were found in 28 patients (43.8%; M:F 12:16) 4/28 cases (14.3%) had congenital cardiac abnormalities, two associated with Down's syndrome; one PAX8, one TSH receptor gene (TSHR). 18/28 (64.3%) had first degree relative with thyroid disease with an incidence of 54% compared with only 27% in patients with no detected mutation. Among patients with mutations there are five kindreds accounting for 11/26 individual patients. There were two additional cases of familial dysgenesis (one aplasia and one ectopia), 0.3% of all permanent CH. Mutations were identified in Thyroglobulin gene (Tg) $n = 10$ (36%), thyroperoxidase gene (TPO) $n = 8$ (29%), 4 in TSHR (14%) and in PAX8 (2;7%), and THOX2 (2;7%) genes. Two patients (7%) had TPO sequence variants, one with heterozygous Tg gene mutation. No significant difference was found between biochemical results at assessment for infants with TPO and Tg gene mutations; the median (range) TSH and fT4 values were 100 (21.9–385) vs 150 (7.17–401) mU/L and 5.45 (1.8–15.8) vs 7.45 (3.8–11.6) pmol/L and quantitative Tg 160($<$2.0–2993) vs 5 ($<$2.0–3977) μg/L respectively. On ultrasound, where available, patients with TPO mutation had normal or small glands whereas 80% of Tg gene mutations had remarkably large glands. All but two had permanent hypothyroidism one had TSHR and the other had TPO. **Conclusion:** Thyroid test results don't appear to be helpful for selecting patients for genetic analysis nor for targeting mutation analysis. However thyroid imaging could be useful for targeting mutation analysis as patients with Tg mutation had markedly large glands.

P1-P891

Newborn Screening Program for Congenital Hypothyroidism: Eighteen Years of Experience in Buenos Aires Province, Argentina

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Background: Newborn (NB) screening programs show a wide variation in congenital hypothyroidism (CH) incidence along the years. **Objective and hypotheses:** To describe CH incidence, etiology, associated malformations and Down Syndrome (DS) in children detected by our NB Screening Program. To search differences between permanent CH (PCH) and transient forms (TCH). **Method:** We analyzed NB with positive screening results referred between April 1995 and December 2013. Two periods were analyzed: 1995–2004 (P1) and 2005–2013 (P2).CH was confirmed with TSH $\geq$ 25 uUI/ml and T4 $<$ 10 μg/dl. Incidence, etiology, associated malformations and DS were described. At three

years of age, children were reevaluated to distinguish between PCH and TCH. Sex; delivery; birth weight; age, TSH, T4, levotiroxine dose (LTd) at start; and LTd at reevaluation were compared between PCH and TCH patients with eutopic thyroid gland. Student's and Mann Whitney tests were used for continuous variables and Kruskal Wallis test for comparison between groups. **Results:** Of 2.889.819 NB, 1331 were confirmed (F:M, 2:1) and treated with a mean LTd of 12.43 ± 2.12 μg/kg/day. Median age at diagnosis was 18 (14–26) days. Incidence was 1:2.171 (P1 = 1:2.425, P2 = 1:1.969). Twenty-three children had DS. Fifty-six children (3.45%) showed associated malformations. Of the total group, 675 children were reevaluated. Thirty-one (4.6%) had TCH and 644 (95.4%) had PCH. Etiologies of PCH forms were: athyreosis 161 (25.0%), ectopic disgenetic gland 368 (57.1%), eutopic disgenetic gland 14 (2.2%), and eutopic thyroid gland 101(15.7%). Patients with eutopic thyroid gland ($n = 132$) showed TCH forms in 31 (23.5%) cases. LTd was the only variable that showed significant differences between PCH and TCH patients with eutopic thyroid gland ($P < 0.0001$). **Conclusion:** Last years'CH incidence has increased in this program. Associated malformations were found in 3.45% of these CH patients. Transient forms showed a low frequency. Patients who required lower LTd at reevaluation were likely to have TCH forms.

P1-P892

Transient TSH Elevation in Infants Referred on Newborn Screening – Features, Prevalence and Trends

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Background: Up to 20% of infants referred on newborn congenital hypothyroidism (CH) screening are subsequently shown to have transient TSH elevation rather than permanent CH. Correct identification of such cases is important to avoid prolonged treatment with thyroxine and unnecessary clinic attendance. **Objective:** To determine the prevalence, trends and profile of infants with transient TSH elevation referred between August 1979 and December 2015 by the Scottish Newborn Programme. **Method:** Analysis of infants referred during the study period with initial/repeat capillary TSH ≥50/≥25 mU/l (1979–82); ≥40/≥15 (1982–89); ≥40/≥10 (1989–2002); ≥25/≥8 (2002–15) in whom venous thyroid function tests became normal off thyroxine. Details of gestation, birthweight (BW), "sickness" and extra-thyroidal congenital malformations (CM) were recorded. **Results:** Of 2,202,191 newborns screened, 936 were referred by the screening laboratory including 630 (68.9%) with definite CH; and 208 (22.8%) with transient TSH elevation. The transient group differed from the true CH group in terms of mean BW (2.68 vs 3.34 kg), BW <2500 g (30.3 vs 9.2%) gestation (36.5 vs 39.6 weeks), gestation <30 weeks (12.9 vs 0.5%), "sickness" (35.6 vs 7.1%), and presence of CM (20.7 vs 5.7%). Median capillary TSH (37.0 vs 167.5 mU/l), need for 2nd capillary sample (50 vs 12%), mean initial venous fT4 (15.15 vs 6.6 pmol/l) and TSH (12.5 vs 102 mU/l) were all significantly different ($P = < 0.001$). Specific aetiology in the 208 transient infants was found in a minority only and included blocking maternal antibodies (3), maternal carbimazole (1), Pendrin (1) and TSH receptor heterozygosity (1) and Down syndrome (12 cf 6 with true CH). The incidence of transient TSH elevation was 6.6 and 5.1/year between 1982–2004 and 2005–15. Of 43 transient cases with CM, 19 involved the digestive system/abdominal wall of which 15 were born ≤ 2004 when iodine antisepsis was largely discontinued in Scottish newborn units. **Conclusion:** Infants with low BW, extreme prematurity, sickness, additional malformations, Down syndrome and modest capillary/venous TSH elevation are particularly likely to have transient thyroid dysfunction and merit careful re-evaluation at ≥ 3 years of age. Trends in transient TSH elevation will be influenced by decreases in capillary TSH cut-off, reduced iodine antisepsis usage, and the currently unknown dietary iodine status in mothers.

P1-P893

Resolution of Hepatic Hemangiomas and Consumptive Hypothyroidism in an Infant Treated with Propranolol and Levothyroxine

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Infantile hepatic hemangiomas (IHH) particularly the diffuse subtype, can in severe cases be associated with hepatic and cardiac failure, compartment syndrome, and consumptive hypothyroidism. Early recognition and treatment of these pathologies is paramount in order to minimise the risk of longterm sequelae. Thyroid hormones are crucial for growth and neurodevelopment, with three to five IQ points lost for each month hypothyroidism remains untreated in the first year of life. This developmentally sensitive period parallels the proliferative phase of hemangiomas, and highlights a window of opportunity to screen for, and aggressively treat hypothyroidism in the context of diffuse IHH. We report a female twin conceived through in-vitro fertilization who presented aged eight weeks with systemic compromise and hepatomegaly in the absence of large or obvious cutaneous infantile hemangiomas (IH). Abdominal ultrasound showed innumerable hypoechoic nodules and increased vascularity within the liver, confirmed on CT and MRI. AFP was markedly elevated with associated derangement of her LFTs and coagulation profile. Findings were consistent with a diagnosis of diffuse infantile hepatic hemangiomatosis. Subsequent to this, assessment of her thyroid function confirmed consumptive hypothyroidism. She was promptly treated with oral propranolol at an initial dose of 1 mg/kg once daily in two divided doses, escalated to 2 mg/kg after five days. Treatment was well tolerated, with no adverse effects. At the same time, levothyroxine 9.6 micrograms/kg/day was commenced, with rapid

improvement in her clinical parameters. This case reiterates the importance of investigating for consumptive hypothyroidism in an infant diagnosed with IHH, particularly when there is systemic compromise. Consultation with endocrinology for specialist management is imperative if growth and intellectual retardation are to be prevented. In accordance with a growing body of evidence, we advocate propranolol as a single first line treatment for IHH, supported by thyroid replacement when appropriate.

P1-P894

Comprehensive Analysis of Seven *Toll-Like Receptor* Genes Including 15 Single-Nucleotide Polymorphisms with Autoimmune Thyroid Disease in Korean Children

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Background: The *Toll-like receptors (TLRs)* are germline-encoded receptors that play an essential role in initiating the immune response against pathogens. **Objective and hypotheses:** In this study, we assess the association of *TLR* polymorphism with autoimmune thyroid disease (AITD) in Korean children. **Method:** Seven *Toll-like receptor* genes (TLR-1, -2, -3, -4, -5, -6, -9) including 15 single-nucleotide polymorphisms were analyzed on 104 Korean children with AITD [Hashimoto′s disease (HD) = 40, Graves′ disease (GD) = 60 (thyroid-associated ophthalmopathy (TAO) = 29, non-TAO = 31)] and 192 healthy individuals. **Results:** In total AITD, the frequencies of these alleles had no statistical difference with controls. In HD, the frequencies of the TLR3 rs3775296 AA genotype (OR = 3.45, $P < 0.022$) was higher, whereas the TLR3 rs3775296 C allele (OR = 0.29, $cP < 0.044$) showed lower frequencies than in the healthy controls. In GD, the frequencies of the *TLR4 rs1927911* CC genotype (OR = 2.18, $cP < 0.027$) was higher, whereas the *TLR4 rs1927911* CT genotype (OR = 0.48, $P < 0.018$) and *TLR4 rs1927911* T allele (OR = 0.46, $cP < 0.018$) showed lower frequencies than in the healthy controls. Between HD and GD, the frequencies of the TLR4 *rs1927911* CC genotype in HD (OR = 0.37, $cP < 0.048$) was lower, whereas *TLR4 rs1927911* CT genotype in HD (OR = 2.63, $P < 0.017$) and *TLR4 rs1927911* T allele in HD (OR = 2.72, $cP < 0.032$) showed higher frequencies than GD. In TAO, the frequencies of the TLR4 *rs1927911* CC genotype (OR = 2.31, $P < 0.029$) was higher, whereas TLR4 *rs1927911* T allele (OR = 0.43, $P < 0.029$) showed lower frequencies than in the healthy controls. Between TAO and non-TAO, the frequencies of the TLR9 *rs 187084* CC genotype in non-TAO (OR = 5.52, $P < 0.028$) was higher, whereas TLR9 *rs 187084* T allele in non-TAO (OR = 0.18, $P < 0.028$) was lower than TAO. **Conclusion:** Our results suggest that *TLR-3,-4 and -9* gene polymorphisms may contribute to the pathogenesis of AITD and TAO.

P1-P895

Thyroid Cancer is the Most Frequent Secondary Solid Tumour Following Allogeneic Stem Cell Transplantation in Childhood – A Single Centre Experience

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Backgroud: Allogeneic haematopoietic stem cell transplantation (HSCT) is a potentially curative therapy for a variety of malignant and non-malignant disorders. With improved outcomes, increasing attention has been drawn to late complications in long-term survivors. Secondary cancer belongs to the most serious complications. **Objective:** Occurrence of secondary solid tumours at HSCT Unit, University Hospital Prague- Motol was analysed. **Methods:** We evaluated data on clinical and laboratory follow-up (including fT4, TSH, thyroid antibodies, thyroid function and ultrasound imaging) in 499 patients (315 M, 184 F) who underwent allogeneic HSCT during childhood between 1989 to 2014. **Results:** Secondary solid tumours were diagnosed in 16 patients (3.2%) at median time 11.4 (range 5.4–17.8) years after HSCT (thyroid carcinoma n = 8, carcinoma of oral cavity $n = 3$, malignant schwannoma $n = 2$, melanoma $n = 1$, peritoneal mesothelioma $n = 1$, breast cancer $n = 1$). 15 out of 16 patients (93.8%) had total body irradiation (TBI) 12–14.4 Gy as a part of conditioning regimen. All patients underwent surgery and/or chemo-radiotherapy and are alive. Papillary carcinoma (in all cases micronodular, T1 or T2 stage) was found in all 8 patients (5F, 3M) (50% of all with secondary solid tumour) at median time 10.8 years (range 5.4–17.0) after HSCT. Three of them were previously treated with thyroxine for autoimmune thyroid disease, one for hypothyroidism and another one for nodular goitre. All but one had HSCT for malignant disease, and 7/8 had TBI. **Conclusions:** The incidence and number of complications following allogeneic HSCT in childhood are increasing within time and thyroid cancer was the most frequent secondary solid tumour detected. The early diagnosis is one of the key tasks of long–life multidisciplinary post-transplant care including regular ultrasound evaluation of thyroid gland and neck especially more than 5 years after HSCT and namely after TBI. *Supported by MHCZ for conceptual development 00064203 University Hospital Motol.*

P1-P896

Iodide Transport Defect: Identification of a Novel Mutation in the Carboxy-terminus of the Sodium/iodide Symporter in a Pediatric Patient with Congenital Hypothyroidism

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Iodide (I^-) transport defect (ITD) is an autosomal recessive disorder caused by the inability of the thyroid follicular cell to actively accumulate iodide. Active I^- accumulation is mediated by the Na^+/I^- symporter (NIS), an integral plasma membrane glycoprotein located on the basolateral surface of thyrocytes. The diagnostic criteria for ITD include a variable degree of hypothyroidism and goiter, low to absent thyroid radioiodide uptake, and low I^- saliva-to-serum ratio. Here, we aimed to evaluate mutations in the gene encoding NIS in pediatric patient suspected of ITD on the basis of severely reduced $^{99m}TcO_4^-$ accumulation in a eutopic thyroid gland. The index patient showed abnormally high TSH level during neonatal screening (64 μIU/ml). Diagnostic confirmation of congenital hypothyroidism was achieved by measuring serum TSH 203 μIU/ml, FT_4 1.6 ng/dl, T_4 8.7 μg/dl, and T_3 121 ng/dl. Ultrasound showed a normal-sized gland. The analysis of the gene encoding NIS revealed a previously unidentified homozygous G > A transition at nucleotide + 1682 in exon 14 (c.1682G > A) resulting in a glutamic acid instead of a glycine at position 561 located in the intracellular carboxy terminus of the protein. Surprisingly, functional analysis revealed that Cos-7 cells—that do not express endogenous NIS—transfected with G561E NIS displayed $^{125}I^-$ uptake levels similar to those of cells expressing WT NIS. Flow cytometry analysis showed that the levels of G561E NIS at the plasma membrane were similar to those of WT NIS. Although the mechanism by which G561E mutation impairs NIS activity is currently unknown, we hypothesized that the negative charge of the Glu residue may interfere the recognition of the dileucine-like sorting motif ($L^{562}L^{563}$) located in NIS carboxy-terminus by adaptor proteins thus affecting NIS plasma membrane sorting in polarized epithelial cells. Further evaluation of G561E NIS in polarized cells is likely to provide novel evidence regarding NIS targeting to the plasma membrane.

P1-P897

Congenital Hypothyroidism: The Use of a TSH Cut-off Limit of 6mU/L and the ESPE Criteria for LT4 Treatment Leads to the Diagnosis of Mild but mostly Permanent Forms of Hypothyroidism

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Background: Since the initiation of neonatal screening programs for Congenital Hypothyroidism (CH) in the 1970's, a gradual decrease of TSH cut-off limits has been observed worldwide. Nevertheless, lack of universal consensus has led to wide variation of cut-off limits and LT4 therapy criteria among screening programs, even within the same country. The Greek neonatal CH screening program is carried out by a single laboratory that uses one of the lowest cut-off limits worldwide. **Objective and hypotheses:** To assess the effect of using a TSH cut-off limit of 6 mU/L in Guthrie cards. **Method:** The data of CH neonates born in 2009 were reviewed. At study initiation, all children were at least 6 years old and, therefore, characterization of CH as permanent or transient could be considered reliable. **Results:** From a total of 120.852 newborns screened for CH in 2009, LT4 treatment was initiated in 324 (~1 in 10 recalled). Data from 224 patients were available for analysis. Patients were divided in three groups according to the Guthrie card's TSH value: < 10, 10–30 and > 30 mIU/L (67%, 19% and 14% of total). CH proved transient in 41.5% (girls 35.6% and boys 45.5%), 35.7% (girls 42% and boys 28%) and 9.7% (girls 5% and boys 18%), respectively. We emphasize that 92% of patients in the < 10 mU/L group, started LT4 treatment according to the latest ESPE criteria. **Conclusion:** Use of a TSH cut-off limit of 6 mU/L in the CH screening program identifies milder but mostly permanent CH cases. If the screening program does not identify neonates with TSH levels between 6–10 mU/L in Guthrie cards, a substantial number of patients who fulfill the ESPE criteria for LT4-initiation will not be uncovered. Hence, the use of such low cut-off limits proves valuable with respect to the diagnosis and treatment of CH.

P1-P898

Do Different Initial Doses of L-T4 within the Range of 10-15 mcg/kg/day Influence Neurodevelopment during the First Two Years of Life in Children with Congenital Hypothyroidism?

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Background: The initial L-T4 dose currently recommended in the treatment of congenital hypothyroidism (CH) is 10–15 mcg/kg per day. **Objective and hypotheses:** We designed a multicenter randomized trial to evaluate the effects of different starting doses of L-T4 within the range 10–15 mcg/kg per day on neurocognitive

Table 1. Neurodevelopmental and growth outcomes in CH children at 24 months

	Group A	Group B	*P*
Global Developmental Quotient	112.6±22.0	112.1±22.6	Ns
Locomotor Subscale	111.8±22.1	98.7±23.1	Ns
Personal-social Subscale	99.7±21.9	91.7±20.4	Ns
Language Subscale	91.2±20.7	87.7±21.7	Ns
Eye-hand coordination Subscale	105.6±12.7	104.5±14.6	Ns
Performance Subscale	107.5±10.5	104.8±13.0	Ns
Length SDS	0.18±0.94	0.54±0.98	Ns
Weight SDS	0.11±1.28	0.28±1.08	Ns

development 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-T4 dose of 10–12.5 mcg/kg per day (group A) or 12.6–15 mcg/kg per day (group B). All patients underwent clinical examination and FT4 and TSH measurement periodically during the first two years of life. At the age of 12 and 24 months they underwent Griffiths Mental Development Scales to evaluate cognitive development. **Results:** Growth during the first two years of life was comparable in the two groups of patients. Neurodevelopmental evaluation showed no significant differences in Global and Subscales Quotients between the two groups both at 12 and at 24 months of age Table 1. **Conclusion:** Different initial doses of L-T4 within the range of 10–15 mcg/kg per day are not associated with differences in neurodevelopment and growth during the first two years of life in CH patients.

P1-P899

Clinical and Histopathologic Features and Follow-up of Paediatric Patients with Papillary Thyroid Cancer: A 10 Years Experience

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Background: The incidence of paediatric papillary thyroid cancer (PTC) is increasing. **Objective and hypotheses:** To describe the clinical and histopathologic features at diagnosis, and follow-up of paediatric patients with PTC at Children's Hospital of Mexico in a 10 years period. **Method:** Comparative longitudinal study. We included 22 paediatric patients with histopathologic diagnosis of PTC between 2004–2014, divided into risk groups according to AJCC TNM classification system. Descriptive statistics were performed, Student's *t* test or Mann-Whitney U test for independent samples, Fisher's exact test to compare frequencies and Kaplan Meier estimator for disease free survival. **Results:** The 72.7% ($n=16$) were feminine; the average age at diagnosis was 11.68±3.09 years. The median time from onset of symptoms was 4 (0–60) months, TSH 2.45 (0.6–15.2) mUI/mL, FT4 1.15 (0.9–2.0) ng/dL. At diagnosis, the 100% ($n=22$) had increased volume in neck, 18.2% ($n=4$) symptoms of dysthyroidism, positive antibodies in 31.8% ($n=7$) for anti-TPO, 36.3% ($n=8$) for anti-Tg. The 50% ($n=11$) had a positive FNAB for malignancy. The 63.4% ($n=14$) were high risk and 13.6% ($n=3$) had pulmonary metastases at diagnosis. The main postsurgical complication was hypoparathyroidism in 36.3% ($n=8$). Persistent disease was observed in the 50% (8/16) at 1 year, 25% (2/8) at 3 years; 10% (1/10) had recurrence at 2 years. No differences were found among groups in the persistence ($P=0.21$) or recurrence ($P=0.60$). Disease-free survival was observed in 50% of the patients at 16 months, 13% at 30 months and no differences were found by risk group ($P=0.77$), gender ($P=0.19$) or presence of lymph node metastasis ($P=0.77$). **Conclusion:** In our series of patients, clinical features at diagnosis were similar to those described in the literature. In our study, the high-risk group had a higher frequency of persistence of disease at 3 years, different to reported in other series of patients.

P1-P900

Meta-analysis of Children with Multiple Endocrine Neoplasia (MEN) Type 2A from 1995-2014: Impact of *RET* Mutation Screening on Age at Thyroidectomy and Frequency of Metastatic Disease

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Background: Medullary thyroid cancer (MTC) in MEN 2A is caused by mutations in *RET*. Guidelines (2001/2009/2015) recommend prophylactic total thyroidectomy (TT) based on mutation specific risk levels (ATA 2015: high/moderate). **Objective:** The aim of this study was to analyse changes of age at TT, frequency of metastatic MTC (MMTC), and frequency of TT according to guidelines since introduction of *RET* testing in 1995. **Methods:** Patients in publications from 1995–2014 aged 0–20 years with individual information on age at TT, histology, and *RET*-mutation, if available, were included. Patients were grouped according to publication year: groups A=1995–1999, B=2000–2004, C=2005–2009, and D=2010–2014. Median age at TT, rate of MMTC, and rate of TT according guidelines were compared in the four groups. **Results:** In 110 publications 601 patients were identified (A=128, B=149, C=220, D=107). Overall, median age at TT was not different in the four groups (11, 11, 10, 8 years), while frequency of MMTC decreased significantly (A=17% vs D=5%, $P<0.001$). In ATA 2015 high risk mutation carriers (c634, c883; $n=296$) median age at TT decreased significantly in the four groups from 13, 11, 9 to 7 years ($P<0.01$) in parallel with a significant decrease of MMTC in group A vs. D (27% vs 8%, $P<0.01$). However, in this high-risk group, the rate of children thyroidectomised at latest with 5 years according to guidelines remained low (15%, 22%, 20%, 30%) despite genetic testing. In ATA 2015 moderate risk mutation carriers (all 11 other MEN2A causing mutations; $n=263$) median age at TT did not differ between groups (9, 11, 12, 10 years) in accordance with risk level specific age recommendations for TT. **Conclusion:** Age at TT and MMTC rate decreased overall and in high risk mutations carriers. However, still 70% of high-risk mutation carriers are thyroidectomised beyond recommended age of 5 years.

P1-P901

Screening of Congenital Hypothyroidism in Low Birth Weight and Very Low Birth Weight Neonates: A Systematic Review

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Background: Congenital hypothyroidism (CH) is the most common cause of preventable mental retardation in children, thus screening programs of CH have been established for better management of the disorder and preventing its related neurodevelopmental consequences. Evidences from different screening programs indicated that the rate of CH is higher in pre-term and low birth weight newborns than normal ones due to the incomplete development of hypothalamic–pituitary axis in this group of neonates. Hence, there is a great need for a practicable systematic screening method for proper diagnosis of CH in this group of neonates. **Methods:** In this review, we systematically reviewed papers with the following key words([Congenital Hypothroidisn AND Screening AND Thyroxine AND Thyroid Stimulating Hormone AND low birth weight AND Premature]) in international electronic databases including PubMed, Scopus, and Google Scholar. After quality assessment of selected documents, data of finally included papers were extracted. **Results:** In this review, 1452 papers (PubMed: 617; Scopus: 714; Google scholar: 121) were identified through electronic database search.194 articles assessed for eligibility,from which 36 qualified articles were selected for final evaluation. From reviewed articles 38.9%, 11.11% and 8.3% recommended rescreening in this group of neonates, lowering screening cutoff of TSH and using cutoffs according to the gestational age, respectively. Some of them (13.9%) recommended for using both TSH and T$ for screening of preterm infants. According to the reviewed papers, TSH level >10 mU/L in 2nd week of birth is diagnostically meaningful and TSH level of 10–15 mU/L suggests "hypothyroidism with delayed TSH rise". **Conclusion:** After reviewing available data,we recommend repeating the screening test in pre-term, low birth weight and very low birth weight infants in age of two, six and ten weeks by measuring TSH and FT4 levels simultaneously and considering TSH = 10 mU/L as the cutoff level for positive and suspicious cases.

P1-P902

Identification of Zinc Transporter ZnT8 in Thyroid Tissues from Children and Adolescents with Thyroid Nodular Hyperplasia

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Background: Recent studies have revealed the presence of zinc and the expression of zinc transporter (ZnT) family members in most endocrine cell types. It has been demonstrated that the ZnT family plays an important role in the synthesis and secretion of different hormones. Furthermore, ZnT8Ab (zinc transporter-8 autoantibodies) together with GADAb (glutamic acid decarboxylase antibodies), IAA (insulin autoantibodies) and IA-2Ab (islet antigen-2 antibodies) are markers of autoimmunity in patients with type 1 diabetes mellitus (T1DM). **Objective and hypotheses:** We studied the expression of ZnT8 transporter in thyroid tissues from patients with thyroid nodular goiter (TNG). The study was performed in the group consisting of 17 patients with thyroid nodular hyperplasia (mean age, 17.8 years ± 4 years) and patients with pancreatic tumor as a positive controls. Patients were recruited from Polish endocrine centers. **Method:** The ZnT8 expression protein was evaluated using immunohistochemistry. The specimens were paraffin embedded tissues, derived from the pediatric patients, who had thyroid nodular hyperplasia. The antibody against ZnT8 was goat polyclonal antibody (Santa Cruz Biotechnology USA; sc-98243). The antigen was retrieval was done using high pH (PTLink DAKO) and antibody was incubated in 4 °C overnight in 1:50 dilution. **Results:** In all of the examined cases we observed the ZnT8 expression in the thyroid follicular cells. He staining was strong and diffuse and observed in almost all thyroid follicular cells. The staining was observed in the cytoplasm. However in 2 out of 17 cases we observed C cells hyperplasia and ZnT8 expression was identified in those cells, also in the cytoplasm and the perinuclear area of the hyperplastic C cells. **Conclusion:** According to our knowledge this is the first investigation which identified ZnT8 transporter in pediatric thyroid tissues. Further studies in thyrocytes covered by an autoimmune process are scheduled to confirm ZnT8 as a new thyroid autoantigen.

P1-P903

HABP2 as Genetic Susceptibility Factor for Familial Differentiated Thyroid Carcinoma

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Background: HABP2 is an extra-cellular matrix protein involved in cell proliferation. Recently, *HABP2* was proposed as

responsible for the familial clustering of Differentiated Thyroid Carcinoma (FDTC). However, its involvement was questioned by subsequent studies revealing high prevalence *HAPB2* polymorphisms (SNPs) in the general population, leaving its pathogenic role uncertain. **Objective and hypotheses:** To identify genetic *HABP2* variants/mutations and investigate their involvement in FDTC. **Patients and methods:** *HABP2* was sequenced in four index patients with FDTC. Variants identified were investigated in the rest of family members, and segregation analyses performed in affected and healthy individuals. Germline mutations were screened in lymphocyte DNA using PCR amplification and Sanger sequencing. *HABP2* SNP prevalence in Spanish population was determined from 178 control alleles. Public SNP databases served to estimate variant prevalence in Caucasian populations. *BRAF* "hotspot" mutations were studied in the paraffin-embedded tissue from index patient by PCR and Sanger Sequencing. **Results:** Two germline heterozygous *HABP2* variants (p.Glu393Gln and p.Gly534Glu) in exons 10 and 13, were respectively identified in individuals from 1 family with 2 affected (index patient, mother) and 5 additional healthy members of the kindred. Both variants are present in SNP databases (rs11575688, rs7080536) with Minor Alleles Frequencies (MAF) between 0.82-2.79% and 0.32-1.34%, respectively. In Spanish control alleles, p.Gly534Glu prevalence is 5.1%. However, pathogenicity programs predict they are possibly damaging. 3/7 individuals in the pedigree harboured both variants but their presence does not co-segregate with the phenotype. The index patient presented the most prevalent somatic mutation of *BRAF (*V600E) in PTC. **Conclusion:** *HABP2* G534E and E393Q variants are prevalent in the normal Spanish population and they do not co-segregate with the FDTC phenotype. Our findings do not support a relevant role of HAPB2 in the pathogenesis of FDTC. Other germline defects different from *HAPB2* must be investigated to explain the familial susceptibility in DTC.

P1-P904

Cardiac Size and Function in Children with Subclinical Hypothyroidism

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Background: The management of subclinical hypothyroidism (SH) is still challenging in particular for mild forms with TSH levels ranging between 4.5 and 10 mU/L. **Objective and hypotheses:** to compare left ventricular (LV) geometry and function of SH subjects and matched euthyroid controls, and to evaluate the effect of L-thyroxine (L-T4) therapy on cardiac parameters. **Method:** Thirty-six (36) children (19 females and 17 males), aged 8.6±3.7 years, with persistent SH (at least 2 years) and 36 euthyroid matched controls were enrolled in the study. At study entry height, BMI, heart rate, systolic and diastolic bloody pressure were assessed and Doppler echocardiography was performed in all subjects. Twenty-two SH children, who accepted to start L-T4 therapy, were reevaluated after 2 years of treatment and 22 matched controls were observed throughout the same period. **Results:** LV size and systolic function were comparable between SH subjects and controls at baseline and increased similarly over time, whereas SH children showed a significant prolongation of isovolumic relaxation time (IVRT) (87.2± 2.5 msec) compared to controls (78.8±2.5 msec, $P=0.02$), eventhough still within normal values for age. In the 22 SH children who underwent L-T4 therapy the IVRT significantly decreased (74.6±3.4 msec) vs baseline value (85.5±3.1 msec, $P=0.04$) and became similar to controls (74.9±1.3 msec). **Conclusion:** Long lasting mild SH in children seems to be associated with mild subclinical diastolic dysfunction, which improved with L-T4 therapy. Whether this subtle alteration may lead to clinical consequences should be further investigated.

P1-P905

Association of CTLA4, PADI4 and FTO Polymorphisms with Autoimmune Thyroid Diseases in Male Children

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Background: The etiology of Autoimmune thyroid diseases (AITDs), including Graves' disease (GD) and Hashimoto's thyroiditis (HT) is multifactorial and involves genetic and environmental factors. Family and population studies confirmed the strong genetic influence and inheritability in the development of AITD. Possible sex-related differences in overexpression of the cytotoxic T-lymphocyte antigen 4 (CTLA4) gene, peptidyl arginine deiminase 4(PADI4) gene, the fat mass and obesity-associated (FTO) gene polymorphisms on AITDs in children remain unclear. **Objective and hypotheses:** To identify the association between polymorphisms of CTLA4, PADI4 and FTO genes and Graves' disease (GD) and Hashimoto's thyroiditis (HT) prognosis in male children. **Method:** The study was performed in 145 patients with GD, 57 with HT and 160 healthy volunteers. The three single nucleotide polymorphisms (SNPs): rs231775 – CTLA4, rs1748033 – PADI4 and rs6499640 – FTO were genotyped by TaqMan SNP genotyping assay using the real-time PCR. **Results:** Rs231775 G alleles were more frequent in HT male patients in comparison to healthy males ($P=0.008$ with OR=3). Rs1748033 C alleles were more frequent in HT male patients in comparison to healthy males ($P=0.032$ with OR=3,4). Rs6499640 A alleles were more frequent in GD male patients in comparison to healthy males ($P=0.044$, OR=2). **Conclusion:** Rs231775 G/A, Rs1748033 C/T and Rs6499640 A/G polymorphisms could contribute to development of AITDs in male children. The main risk factor for rs231775 is G

allele and for rs1748033 is C allele. In case of rs6499640 the main risk factor is allele A.

P1-P906

Thyroid Cancers in Korean Pediatric Populations with Thyroid Nodules

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Background: South Korea is one of the adequate or excessive iodine nutritional state countries and high-iodine intake is related to papillary thyroid cancer. The prevalence of thyroid cancer of South Korea has increased and the proportion of thyroid papillary cancer has increased as 97.9–98.3% in 2010. Childhood thyroid cancer is rare, and the prevalence of thyroid cancer in pediatric population was reported as 20–26% of thyroid nodules worldwide. However, there have been few reports about thyroid nodule and cancer in pediatric population in Korea. **Objective and hypotheses:** In the present study, we firstly investigated to know the prevalence and clinical findings of thyroid nodule and cancer in Korean pediatric populations. **Method:** We investigated medical records of 311 patients had goiter, thyroid nodule, thyroid mass and thyroid cancer lower than 18 years of age. Twenty three patients were excluded of incomplete medical records and 186 were also excluded of diffuse goiter without nodule. Of the rest, fine needle aspiration biopsy (FNAB) was not done in 38 patients, therefore 64 patients were included in the present analysis. **Results:** Female and male patients were 55 (86%) and 8 (14%), respectively, and mean age of the patients was 16.0 ± 2.3 (8–18) years. Nodules on right thyroid lobe were in 37 (58%) patients, Left 23 (36%), both lobes 3 (5%), and was not described in one patient. Thyroidectomy was done to 15 patients and total thyroidectomy was done to 5 of the cancer patients. Of the 64 patients, 8 (12.5%) were finally diagnosed as thyroid cancer, and 6 (75%) were papillary cancer and 2 (25%) were follicular cancer. They were 1 male and 7 female patients and mean age was 15.6 years. No one was exposed to irradiation and 4 had positive thyroid autoantibodies. FNAB revealed malignant in 7 of them, and 1 s reported as benign on FNAB at first, however finally diagnosed as follicular cancer after 8 years of the initial visit. Otherwise, one patient was suspected to malignant on FNAB, the final pathologic diagnosis was nodular hyperplasia. Although the patient numbers were far different in the cancer patients and benign patients, we tried to compare clinical parameters in the two groups (cancer vs benign group). T3 levels were significantly higher in the cancer group than in the benign group (1.50 ± 0.97 vs 1.06 ± 0.19, $P = 0.004$). Cancer group has more right lobe dominant than the benign group (78% vs 55%, $P = 0.009$). Size or number of the nodules were comparable in the two groups. Cystic nature of the nodules was related to benign nodules. Although FNAB findings were discordant to the final diagnosis, 97% of FNA findings were concordant to the final diagnosis. **Conclusion:** Thyroid cancer prevalence was slightly lower in Korean pediatric populations than that of worldwide report and it is dominant on right thyroid lobe. Papillary thyroid cancers are dominant in Korean pediatric populations but lesser prevalent than in Korean adults. As be known well, FNAB was highly diagnostic to predict the nodules to be malignant.

P1-P907

Dysregulation of the Immune System in Children with Graves Disease – the Role of NK and NKT-Like Cells

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Background: Almost all cases of hyperthyroidism in children result from Graves' disease (GD). Recent studies have confirmed a significant role of T cells in the development of autoimmune diseases. However, the interactions between NKT-like cells and NK cells in GD are still poorly understood. **Objective and hypotheses:** The aim of the study was to assess the frequencies of peripheral blood T, NK and NKT-like cells in children with GD. **Method:** We studied 50 GD and 20 age- and sex-matched healthy children. Percentages of NK and NKT-like cells were evaluated with flow cytometry using monoclonal antibodies: anti-CD3/FITC, CD16CD56/PE, CD45/PerCP (BD Biosciences), which allowed for simultaneous assessment of $CD3^+$T lymphocytes and NK ($CD16^+CD56^+$) cells. During analysis, the $CD3^+CD16^+CD56^+$ population was also determined. Immunofluorescence studies on T cell subsets were performed using a combination of the following mAbs: CD3/FITC, CD19/PE, CD8/FITC, CD4/PE, purchased from R&D Systems. Statistical analysis of the results was conducted using Statistica 9.0. A value p less than 0.05 was considered statistically significant. **Results:** The mean frequency of CD3 + CD56 + CD16 + NKT-like cells in the peripheral blood of children with GD was 10.93% ± 11.02% and this value was significantly lower in comparison to the control group (21.15% ± 9.08%, $P = 0.0005$). The mean percentage of CD56 + CD16 + NK cells in the group of patients was 14.67% ± 6.89%, and was significantly higher compared to the healthy controls (4.71% ± 2.99%, $P = 0.000002$). The mean percentage of CD3 + T lymphocytes in the peripheral blood of children with GD was 67.91% ± 16.56% and was significantly higher in comparison to the control group (51.7% ± 24.12%, $P = 0.02$). The mean percentage of CD8 + T lymphocytes in the study group was 28.89% ± 11.68% and was significantly higher in comparison to the healthy controls (18.72% ± 6.86%, $P = 0.001$). **Conclusion:** Our findings of the abnormalities in immune cells distribution in peripheral blood of GD children suggest that GD development and progression is related to the dysregulation of the immune system.

P1-P908

Thyroid Function Anomalies in Children with Down Syndrome: Early TSH Alteration can Predict Future Hypothyroidism Development?

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Background: Subclinical hypothyroidism is a common finding in Down syndrome (DS) patients and transition towards overt hypothyroidism can occur, but there are no predictor factors to identify patients that will need replacement therapy later in life. **Objective and hypotheses:** This is a retrospective cohort study on a population of DS paediatric patients. This study was designed to evaluate possible early predictive features of hypothyroidism development. **Methods:** We retrospectively evaluated 49 paediatric DS patients (31 males and 18 females). Median (IQR) age at first evaluation was 3.47 (0.5 – 15.7) years and follow-up 4.3 years (1–9). Thyroid function was described as normal (TSH 0.31–5.00 μUI/ml), subclinical hypothyroidism (TSH 5.10–10.00 μUI/ml, normal fT_4 and fT_3) or overt hypothyroidism (TSH $>$ 10.00 μUI/ml). Autoimmune etiology was investigated through auto-antibodies positivity (AbTPO, AbTG; TRAb). Statistical analysis was performed using logistic regression and ROC curves, Mann-Whitney test, chisquare test and Odd ratio. The statistical significance was set at $P<0.05$. **Results:** In our study 38.8% of patients (19/49) showed subclinical hypothyroidism during follow-up. Therapy with L-thyroxine was initiated in 8 patients (16.3%), who were diagnosed with overt hypothyroidism (4/8 have autoimmune thyroiditis). We found that a TSH cut-off value of 5.07 μUI/ml at first evaluation was significantly predictive of overt hypothyroidism development during follow-up (sensibility 100%, specificity 43.9%). Moreover, patients who started replacement therapy during follow-up, had significantly increased thyrotropin values at first evaluation ($P<.01$). Also anti-thyroid antibodies positivity resulted to be predictive of thyroid disease ($P<.002$). Finally, we observed that TSH $>$ 5.07 associated with anti-thyroid antibodies positivity increased the risk of hypothyroidism of 12.6 time. **Conclusion:** Our study showed that an early increase of TSH value, using as cut-off 5.07 μUI/ml, associated with auto-antibodies positivity can identify DS patients who need a more careful follow-up, since the risk of hypothyroidism seems to be higher.

P1-P909

Identification of a "Cryptic" De Novo Deletion in *NKX2.1* in the Brain-Lung-Thyroid Syndrome using Genomic SNP Arrays

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Background: Genetic defects in *NKX2.1* (chromosome 14q13) are associated with hypothyroidism, choreo-athetotic movements and respiratory distress, known as the "Brain-Lung-Thyroid syndrome". **Objective and hypotheses:** To identify the genetic basis of a disorder compatible with the "*NKX2.1* syndrome" and extra features outside the typical triad. **Patients and methods:** 10-year old girl with congenital hypothyroidism on levo-thyroxine replacement, generalized hypotonia, mild respiratory distress at birth and following subsequent episodes of bronchiolitis. At follow-up delay on achievement of motor milestones, including late-onset walking, clumsiness, frequent falls and language delay. In early infancy she presented subtle choreic movements in extremities. Also, delayed teeth eruption (17 months) and partial absence of permanent teeth at age 10 in orthopantomography. Finally, marked joint hyper-extensibility of the upper arms was evidenced. Brain MRI, electromyogram and thyroid ultrasound were normal. Her parents and brother were healthy. PCR-Sanger sequencing, multiplex ligation-dependent probe amplification (MLPA) and SNP array were performed. **Results:** With suspicion of *NKX2.1* syndrome, the whole coding region of *NKX2.1* was PCR-amplified and directly sequenced, rendering normal results. Considering the strong consistency of diagnosis, MLPA was performed showing heterozygous loss of gen dosage in 3 probes corresponding to the gene. The defect was *de novo* and absent in the parental study. To identify the precise deletion size of this copy number variation (CNV) a Genomic SNP Array was performed showing a deletion of 3.44 Mb (14q13.2-q21.1) including *NKX2.1* and 30 additional genes. **Conclusion:** A novel *de novo* deletion was identified as cause of the *NKX2.1* syndrome. When clinical suspicion is fully consistent, monoallelic deletions of 14q should be searched for in these patients through genomic techniques that detect gene-dosage variations. Haploinsufficiency of *PAX9* is responsible for hypodontia, and we propose the presence of a still unidentified candidate gene for joint hyper-extensibility within the deleted genetic interval.

P1-P910

Partial Thyroxine Binding Globulin Deficiency in Test Tube Babies: Cases Report and Literatures Review

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Background: Partial thyroxine-binding globulin deficiency (TBG-PD) is an endocrine defect with a prevalence of 1:4 000 in newborns. Due to the presence of a single TBG gene on the X chromosome. **Objective and hypotheses:** To investigate the clinical characteristics of twins with thyroxine binding globulin deficiency and to find SERPINA7 gene mutations. **Method:** Data

related to clinical characteristics, serum biochemistry, gene mutations and pedigree of two children with TBG deficiency were collected, the related literatures searched form China National Knowledge Infrastructure, Wanfang Data Knowledge Service Platform, National Center for Biotechnology Information and PubMed (up to December 2015) by using search terms "Thyroxine binding globulin deficiency, gene, mutation". **Results:** Both patients were diagnosed as central hypothyroidism at beginning and treated with L-thyroxine. Both of the identical twins of the triplet were observed mutation in exon3, c.631G>A(p.A211T), a new mutation had not been reported, but their parents and another non-identical triplet brother were normal. Literatures reviewed showed that 23 foreign cases with SERPINA7 gene mutation had been reported. Among reported that SERPINA7 gene mutations located in exon, intron, promoter and enhancer. Up to now, there were 49 variants had been identified, 41 of them located to the mutated genes. Including this two cases, patients with thyroxine binding globulin deficiency is characterized by reduced serum TH levels, but normal free TH and TSH and absent clinical manifestations. **Conclusion:** The new mutation of SERPINA7 gene c.631G>A(p.A211T) is not transmit with the known X chromosome linked heredity, and as the cases were test tube triplet babies, we speculated it was a de novo mutation. The serum thyroid function test of TBG deficiency manifested as the decreased TT4, TT3 and normal TSH. And often misdiagnose as central hypothyroidism.No medicine should be taken to patient with TBG deficient and the only thing we should do is observation and follow-up.

P1-P911

Hyperthyroidism after Bone Marrow Transplantation: A Report of Two Cases

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Background: The thyroid dysfunction is one of the frequently seen complications after bone marrow transplantation (BMT). Although hypothyroidism is the most common thyroid disease after BMT, hyperthyroidism is a rare condition. Herein, we report a series of 2 patients who were euthyroid before BMT but developed hyperthyroidism after transplantation. **Objective:** Case reports and the frequency of hyperthyroidism after BMT in our institute. **Case 1:** A 10-year-old boy was diagnosed with adrenoleukodystrophy and underwent transplantation twice from his HLA-unmatched sister when 10 years of age. Conditioning regimens consisted of thoracoabdominal irradiation + Busulfan (Bu) + Cyclophosphamide (CY) + Antithymocyte globulin (ATG) for the first BMT and Bu + CY + ATG for the second BMT due to a rejection of the first BMT. At the time of both BMTs, his thyroid function tests were normal, respectively, and his donor had no history of thyroid disease. Prophylaxis against graft-versus-host disease (GVHD) was used short-term methotrexate (sMTX) and cyclosporine (CyA). He had acute GVHD presenting with nodular rash and prednisolone was initiated. Although subclinical compensated hypothyroidism was demonstrated after the first BMT, hyperthyroidism occurred 3 years after the first BMT. He was treated with methimazole. **Case 2:** A 15-year-old boy was diagnosed with severe aplastic anemia and underwent transplantation from his HLA-matched sister when 15 years of age. Conditioning regimens consisted of CY + ATG. Prophylaxis against GVHD was used sMTX and CyA. He had no acute and chronic GVHD. Hyperthyroidism occurred 3 years after BMT. After he was followed without treatment for 9 months, we started to treat with methimazole. **Results:** Systematic evaluation of thyroid function tests in 156 who underwent BMT and are follow-up at our institute gave a rate of hyperthyroidism at 1.3% in this study. **Conclusion:** The clinician should be alert to hyperthyroidism as a possible complication after BMT.

P1-P912

A Case of a Young Girl with High Risk RET Mutation Successfully Diagnosed as Medullary Thyroid Carcinoma in Very Early Stage

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Background: Multiple Endocrine Neoplasia type 2A (MEN2A) is an autosomal dominant disorder characterized by medullary thyroid carcinoma (MTC), pheochromocytoma and parathyroid hyperplasia. MTC shows near complete penetration and its presentation and prognosis highly depend on *RET* proto-oncogene mutation. To ensure the favorable prognosis in patients with MEN2A, planning surgical intervention for MTC at appropriate timing is important. We herein report a Japanese girl with high risk *RET* mutation, who was successfully diagnosed as early stage MTC by calcium infusion test. **Case presentation:** A 5 month-old Japanese girl presented to our hospital because her mother had been diagnosed as MEN2A. The *RET* gene analysis was performed and a mutation p. Cys634Gly in exon 11 was detected. Since then, she had been performed annual neck ultrasonography and calcium stimulation test. When she was 8 years old, the test result became positive (baseline calcitonin level of 11.3 pg/ml to the peak level of 333 pg/ml), while ultrasonography finding was negative. She underwent total thyroidectomy at 9 years of age and early stage MTC was confirmed pathologically. There was neither intrathyroidal infiltration nor regional lymph node metastasis. **Conclusion:** In American Thyroid Association guidelines, prophylactic thyroidectomy is recommended for the patients of MEN2A with high risk *RET* mutations. However, phenotype of the disease varies even among family members with the same genetic defects. Considering the complication risk and following hormone replacement, later surgery should be more favorable. Additionally, in most countries including Japan, prophylactic treatment could not get health

insurance coverage. So detecting very early stage MTC could be another major follow-up method in patients with MEN2A. We recommend that annual calcium infusion test should be performed for MEN2A patients with high risk *RET* mutations.

P1-P913

Nerve Conduction Studies in Children with Subclinical Hypothyroidism

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Background: Although contradictory results regarding neuromuscular functions have been reported in adults with subclinical hypothyroidism (SH), there is no study evaluating neuromuscular functions in children with SH. **Objective and hypotheses:** To assess neuromuscular functions using nerve conduction studies in children with SH. **Method:** Twenty-six children (5–18 years) with SH were enrolled in the study. Neuromuscular functions were examined by electroneuromyography (ENMG). Sensory and motor nerve conduction studies were performed in the left upper and lower limbs. Of the motor nerves, the median, ulnar, peroneal, and tibial nerves and of the sensory nerves, the median, ulnar, and sural nerves were examined. Combined muscle action potential in the motor nerves, amplitudes in the sensory nerves and distal latency and nerve transmission rates in the motor and sensory nerves were assessed. Results were compared with normal values according to age. **Results:** In six patients, the etiology was autoimmune thyroid disease. In ENMG, motor axonal involvement was observed in 10 patients (peroneal involvement in five patients (19.2%), tibial involvement in two patients (7.6%), ulnar involvement in two patients (7.6%), and median involvement in one patient), while no sensory axonal involvement was observed in any of the patients. While two patients with motor axonal involvement were symptomatic, other cases were asymptomatic. In one of the symptomatic patients, motor axonal involvement in three regions (ulnar, peroneal, and tibial) was observed. Nerve conduction values were normal in all patients. **Conclusion:** Our study findings suggest that subclinical or clinical axonal involvement may be present in children with SH. We believe that these findings may offer an insight in the treatment of SH, which still remains controversial, in this patient population.

P1-P914

Van Wyk Grumbach Syndrome with Kocher Smeglaine Debre Syndrome: Case Report of a Rare Association

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Background: Van Wyk Grumbach Syndrome (VWGS) is a rare presentation of juvenile hypothyroidism which manifests in females as chronic autoimmune hypothyroidism, isosexual pseudo-precocious puberty and multicystic ovaries. It uniquely presents with short stature and delayed bone age unlike other causes of precocious puberty. Kocher-Debre-Smeglaine Syndrome (KDSS) is a rare presentation of juvenile hypothyroidism manifesting as calf muscle pseudo-hypertrophy, delayed contraction and relaxation of reflexes, along with percussion myxedema. **Objective and hypotheses:** To diagnose the rare association of Van Wyk Grumbach Syndrome (VWGS) and Kocher-Debre-Smeglaine Syndrome (KDSS) and follow up of the patient on replacement therapy. **Method:** We present a case of 9 year female child who presented in endocrine department with complains of intermittent vaginal bleeding, short stature and difficulty in walking. On evaluation she was found to be having autoimmune hypothyroidism, FSH dominated isosexual pseudo-precocious puberty, delayed bone age, secondary pituitary macro-adenoma, delayed relaxation of deep tendon reflexes and pseudo-hypertrophy of calf muscles. The diagnosis of Van Wyk Grumbach Syndrome (VWGS) associated with Kocher-Debre-Smeglaine Syndrome (KDSS) was made. The Patient was put on initially on 25 mcg thyroxine replacement which was titrated accordingly and was followed after 6 months and one year. **Results:** All the features of syndrome improved after 12 months of adequate thyroxine replacement.

P1-P915

Macro TSH- a Rare Cause of High Levels of TSH

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Background: Macro TSH is a high molecule weighed complex with low bioactivity that is comprised of TSH and anti-TSH antibodies. Potentiality of macro TSH should be kept in mind in clinically euthyroid and asymptomatic patients with normal free T_4 and T_3 levels and relatively high TSH levels. Diagnosis of macro TSH is suspected if polyethylene glycol (PEG) precipitable TSH exceeds %75 and confirmed if high molecule weighed TSH is shown with gel filtration chromotography (GFC). Here we represent a case with macro TSH who had initially been treated with levothyroxine for subclinical hypothyroidism. **Case Presentation:** A 7 year old girl was admitted to hospital with high level of TSH detected in routine control. She did not have any complaints and her physical examination was normal. Serum levels of TSH was 19.6 μU/ml, free T_4 (fT_4) was 1.53 ng/dl and thyroid

antibodies were negative. 1 mcg/kg per day of levothyroxine was initiated. In the follow up TSH levels could not be suppressed although levothyroxine dosage was raised to 1.5 mcg/kg per day and the dosage could not be raised more because she had feeling of discomfort when she took the drug. There was %86 TSH precipitation with PEG (meanwhile TSH: 39 μU/ml, fT_4: 0.95 ng/dl). So the presence of macro TSH was suspected and levothyroxin treatment was stopped. At the end of seven months without treatment fT_4 level was 0.73 ng/dl, TSH level was 17.3 μIU/ml and PEG precitable TSH was %99. Immuno globulin G bound TSH was %57.7 and more than %90 of TSH was eluted at 150 kDa in GFC which confirmed macro TSH diagnosis. **Conclusion:** In subclinical hypothyroidism cases with TSH levels that are unexpectedly high and unresponsive to levothyroxine treatment, presence of macro TSH should be investigated to prevent unnecessary treatments.

P1-P916

Papillary Thyroid Carcinoma in a Mother and Child Evolving after the Manifestation of Grave's Disease

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Background: Familial PTC manifesting in childhood has been described only in single cases, mainly in the context of rare syndromes (APC-associated-syndrome, PTEN-hamartoma syndromes etc). PTC in Grave's disease (GD) has been described in adults, but not in familial cases including young children. **Objective and hypotheses:** We investigated the association of large metastatic papillary carcinoma (PTC) in a 10 years old female and her mother evolving rapidly in both after the manifestation of Grave's disease (GD). Our aim was to investigate the genetic basis for the occurrence of non-syndromic familial GD and PTC in an ethnic background with a reported high prevalence of thyroid carcinoma in adults Grave's disease. **Methods:** Genetic analysis of the tumor was performed by targeted array analysis to investigate known mutations to be involved in familial and syndromic PTC. Sequencing of the TSH-receptor gene was performed in DNA obtained from PBC of all living family members (index case, mother, four older siblings without thyroid disorders). **Results:** GD was confirmed biochemically in the clinically symptomatic patient. TSH-R Ab were elevated. A 2.1 x 1.3 cm nodule in the right lobe developed 3 months after manifestation of GD and turned out to be a PTC (FNAB and ablative thyroidectomy). GD and subsequent development of a metastatic PTC had been diagnosed in the mother a year preceding the diagnosis in her daughter. Panel sequencing of tumour tissue excluded somatic variants for RAF/11, DDR2 15-18, EGFR 18-21, ERBB2 5,6,15,20,23,29, FGFR1 3,7,13,17,FGFR3, HRAS 2-4,KIT 9-11,13,17,18, KRAS 2-4, MET 3,8,11,14,19, NRAS 2-, PDGFR 12,14,18, PIK3CA 3,5,10,16,21, RET 10,11,13-16, TP53 4-9, APC 1-16, DICER1 1-28, PRKARIA 1-11 and PTEN 1-9 and revealed the PTC-typical BRAF-Mutation (V600E) and 2 described TSH-R variants (c.154C>A?p.Pro52Thr and c.170+63G>C). Segregation of the phenotype with the TSH-R variants in the family could not be demonstrated by Sanger sequencing. **Conclusion:** A far undescribed association of familial GD and PTC was not associated with germline variants in the TSH-R gene. NGS (whole exome sequencing of the tumor and PBC derived DNA) will be used to detect the underlying genetic mechanism.

P1-P917

Hypercholesterolemia in Two Siblings with THRB Mutation

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Background: Resistance to thyroid hormones (RTH) is a rare disease, characterized by reduced sensitivity of target tissues to thyroid hormones. Pathognomonically, thyroid hormones are moderately elevated, whereas TSH levels are inappropriately normal or elevated. Over 100 thyroid hormone receptor beta (*THRB*) mutations have been reported, which are found in around 85% of RTH cases. Hypercholesterolemia was not previously reported in RTH patients. **Objective and method:** To assess the lipid levels in a Slovenian family (mother, two daughters and a son) with a previously reported causative *THRB* mutation p.Arg243Trp (c.727C>T). **Results:** Index case was referred to our outpatient clinic due to suspicion of thyroid malfunction at the age of 13.5 years. She had a history of weight loss (3–4 kg over previous month). She had borderline tachycardia and slightly enlarged thyroid gland. Her TSH levels were normal, whereas her free T_4 and free T_3 levels were moderately elevated; thyroid antibodies were negative. Her total cholesterol levels were slightly elevated (5.5 mmol/l), but her LDL-C levels remained in upper-normal range. Genetic analysis revealed the *THRB* mutation, which was later confirmed in her mother, younger sister and brother. All of them also had moderately elevated free T_4 and free T_3, whereas the younger sister was also the only one in the family with elevation of TSH (over 10 mE/l). Hypercholesterolemia with elevated total cholesterol (6.6 mmol/l) and LDL-C (4.2 mmol/l) levels was also detected in her younger sister, but not in her brother (parents were not tested). Genetic causes of familial hypercholesterolemia were excluded in younger sister. **Conclusion:** Mild hypercholesterolemia was present in 2 out of 3 tested family members with confirmed *THRB* mutation. Since the severity of hormonal resistance varies among different tissues, hypercholesterolemia in patients with *THRB* mutation might indicate the relatively hypothyroid state in the liver.

P1-P918

Thyroid Autoimmunity and Vitamin D Status in Euthyroid Girls with Hashimoto's Thyroiditis

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Background: Hashimoto thyroiditis (HT) is the most common autoimmune disorder. There are few studies that analysed the relationship between HT and serum vitamin D. **Objective and hypotheses:** It has been suggested that vitamin D acts as an immunomodulator in autoimmune diseases such as HT Therefore we planned to investigate vitamin D status in euthyroid girls with HT. **Method:** The study group consisted of 66 euthyroid pubertal girls recently diagnosed with HT and 41 subjects as the control group. Parameters of calcium metabolism, thyroid function tests, thyroid antibodies, and 25-hydroxyvitamin D [25(OH)D] levels were measured. Those with 25(OH) D levels of 21–29 ng/ml were characterized as vitamin D insufficiency while those with equal or less than 20 ng/ml were called vitamin D deficiency. **Results:** There was no difference between the patients and the control group in thyroid hormone levels. Vitamin D deficiency rate was not higher in the HT group compared with the control subjects (50.8% vs 61%, $P > 0.05$). Vitamin D insufficiency rate was also not higher in the patient group than in controls (38.5% vs 35.6, $P > 0.05$). In the HT group, mean 25(OH)D levels were not significantly different compared with the control group (19.9 ng/ml vs 18.7 ng/ml $P > 0.05$), but was inversely correlated with the antithyroglobulin (anti-Tg) levels ($r = -0.30$, $P = 0.007$). We also found marked higher PTH and lower Ca levels in our patients than in the controls. The inverse correlation among the patient group's 25(OH)D and PTH levels was worth noting even though it was not statistically significant ($r = -0.22$; $P = 0.084$; $P > 0.05$). The positive correlation between the patient group's 25(OH)D and Ca levels was found statistically significant ($r = 0.30$; $P = 0.016$; $P < 0.05$). **Conclusion:** In conclusion, We found similarly high rates of vit D insufficiency and deficiency among otherwise healthy controls and girls with HT. In Turkey, clothing habits, lack of vitamin D fortification programs markedly reduce the amount of the vitamin D, which may explain these low levels of vit D. The inverse correlation between vitamin D and anti-Tg suggests that vitamin D deficiency may have a role in the autoimmune process in HT in children.

P1-P919

Etiology and Severity of Congenital Hypothyroid Children Detected through Neonatal Screening: A Cut-off based Analysis

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Background: TSH cut-off (CO) levels has been lowered progressively in many screening programs. Nevertheless, population detected with lower CO levels differs in severity and etiology. **Objective and hypotheses:** To describe the etiological characteristics and severity of children detected by neonatal screening related to CO TSH levels. **Method:** We analysed the data of congenital hypothyroidism (CH) neonatal screening performed between June 2013 and January 2016 in 4 maternities. TSH (IFMA-DELFIA) was measured in DBS obtained by heel puncture at maternity discharge (CO:8 mUI/l blood). Patients were recalled and hypothyroidism was confirmed by serum TSH,T4,FT4 and TG. Tc^{99} thyroid scan was performed when available. Patients were characterized as athyreotic, ectopic or eutopic, or goiter as well as with mild or severe hypothyroidism (based on FT4 levels $>$ or $<$1 ng/dl). Findings were related to TSH levels intervals of detection: $>$20 mUI/l, 10–20 mUI/l, and 8–9.9 mUI/l. Diagnostic efficiency (DE) was calculated for the whole program and for each TSH interval. **Results:** A total of 20,441 newborn were screened, 81 recalled (Recall Rate:0.4%) and 28 confirmed diagnosis of CH (DE:34.5%). 18 patients were recalled with TSH $>$ 20 mU/L. All of them confirmed CH(DE:100%). 8 had ectopic thyroids, 3 were athyreotic, 2 had goiter, and 1 was eutopic. Etiology could not be stablished in 4. 72.2% of newborn in this group had severe hypothyroidism. 8/24 newborn recalled with TSH between 10–20 uU/ml confirmed CH (DE:30%). 2 were ectopic and 4 eutopic. In 2 images were not obtained. All patients presented mild HC. Finally, 2/39 recalled babies with TSH levels between 8–9.9 mUI/ml (DE: 5.1%) and started follow up. Both had eutopic thyroids with hyperthyrotropinemia. **Conclusion:** While higher TSH levels allowed detection of patients with dysgenesis and severe disorders with better efficiency, lower CO identified mainly mild thyroid disorders. Further evaluation will allow the better characterization of the hypothyroid spectrum and to delineate adapted guides on detection and follow up.

P1-P920

Lowering of the TSH cut-off Limit Substantially Alters Universally Accepted Key Features of Congenital Hypothyroidism. Reconsideration of the Use of FT4 levels for Diagnosis and Treatment

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Background: The term Congenital Hypothyroidism (CH) describes children with subnormal thyroid hormone levels present at birth. According to literature, CH has an incidence of ~1:1500–1:3000 births with a clear predominance of females (female:male ratio 2:1) and is mainly caused by thyroid dysgenesis (80%). Low FT4 levels have been used as important criteria for CH diagnosis and treatment initiation. The Greek neonatal CH screening program has followed the TSH cut-off lowering-trend, observed worldwide, from the initial 35 to 6 mU/L. **Objective and hypotheses:** To assess the impact of the TSH cut-off limit decrease on key CH features. **Method:** Medical records of CH patients of the Greek screening program were reviewed. **Results:** From 1980–2014 >3.6 million children were screened, 3209 were diagnosed with CH and in 2159 medical records were available. An increase in CH incidence from 1:3500 to 1:435 births was observed with the use of the cut-off limit of 35 and 6 mIU/L, respectively. Using the TSH cut-off limit of 35 mU/L, females comprised 78% of CH patients whereas, using cut-off limits <10 mU/L (i.e., last 15 years) marginal male preponderance was observed. In a total of 1839 patients in whom ultrasonographic data were available, thyroid dysgenesis was observed in only 16%. In patients with severe CH, thyroid dysgenesis, initial TSH >80 mU/L or patients who received a relatively high LT4 dose (>3 μg/kg per day) at the age of three years, ~32%, 13% and 67%, respectively, had normal FT4 levels (>8.5 pg/ml) at diagnosis. **Conclusion:** Lowering of the TSH cut-off limit substantially alters the universally accepted key CH features: incidence is higher, male predominance is observed and thyroid dysgenesis is not the main etiology of CH. Lastly, the use of low FT4 values for CH diagnosis or LT4 initiation therapy should be reconsidered.

P1-P921

Differentiated Thyroid Cancer: Onset and Outcome in a Pediatric Population with and without Risk Factors

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Background: Thyroid nodules (TN) are rare in children but often show more aggressive features than in adults. Irradiated childhood cancer survivors (CCS) are at risk for malignant thyroid nodules. **Objective and hypotheses:** To retrospectively compare the incidence of differentiated thyroid cancer (DTC), the clinical onset and the medium-term follow-up in a pediatric population (EC <18 years), with and without risk factors examined for TN, among 1990 and 2014 in our center. **Method:** We compared data of 52 patients (pts) (group 1) without DTC risk factors (genetic and/or iatrogenic) with 167 consecutive CCS (group 2) previously head/neck irradiated. All pts underwent clinical, laboratory and thyroid ultrasound evaluations. Fine needle ago-biopsy (FNAB) was performed in pts with suspicious ultrasonography. Pts with positive FNAB underwent total thyroidectomy and one or more cycles of Radioiodine Therapy (RT). **Results:** Group 1: 15/52 pts (29%) showed DTC (12 papillary carcinoma, 3 follicular variants). Follow-up data are available for 12/15 pts. 50% of pts showed lymphadenopathy and/or an already palpable TN at diagnosis occurred during routinary pediatric visits. Metastases were found in locoregional lymph nodes (7/12 pts) and in lungs in 4/12 pts. 7/12 pts needed more than a course of RT and only 8/12 pts were free of disease at the last control (range 10.5 – 23 yrs). Group 2: in 89/167 pts (53%) TN were found at 8.4±4 yrs from irradiation. 15/89 pts (17%) showed DTC (9 papillary carcinoma, 6 follicular variants). Metastases were found only in locoregional lymph nodes in 9/15 cases (60%). At last control (range 17 – 28 yrs), all pts were free of disease. **Conclusion:** Our data confirm the aggressive nature of the DTC in children. The good prognosis is ensured by an early diagnosis and the clinical evaluation of the cervical region should be recommended as part of the routine pediatric visit.

P1-P922

Evaluation of the Usefulness of Serum Cytokines IL-1β and sFasL Measurements in the Diagnosis of Autoimmune Hypothyroidism and Hyperthyroidism in Children

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Background: Autoimmune thyroid diseases (AITD) are one of the most common organ-specific autoimmune disorders, of which Hashimoto's thyroiditis (HT) and Graves' disease (GD) are 2 of the most common clinical expressions. HT is characterized by

hypothyroidism (hypoT) that results from the destruction of the thyroid by specific T cell-mediated cytotoxicity. In contrast, GD is characterized by hyperthyroidism (hyperT) induced by thyrotropin receptor-specific stimulatory autoantibodies. **Objective and hypotheses:** The aim of the study was to determine the relationship between concentration of cytokines IL-1β and sFasL with anthropometric, hormonal and immune thyroid factors in serum of children with autoimmune thyroid disease. **Method:** The group comprised 45 newly diagnosed children with Hashimoto thyroiditis, Graves' disease vs euthyroid control group: 11 hypoT (10 girls, 1 boy), 19 hyperT (15 girls, four boys) and 15 healthy subjects (seven girls, eight boys). Thyroid function, autoimmune and anthropometric parameters were evaluated. **Results:** In our study IL-1β concentration was significantly higher in hypoT children ([median] 2.16 pg/ml) vs control (1.88 pg/ml) ($P<0.05$) and vs hyperT (1.39 pg/ml) ($P<0.01$). IL-1β positively correlated with ATPO in hyperT children ($r=0.47$; $P<0.05$), as well as sFasL with BMISDS ($r=0.48$; $P<0.5$) Significantly higher sFasL level (0.26 ng/ml) was identified in children with hypothyroidism (0.06 ng/ml, $P<0.001$) and hyperthyroidism (0.14 ng/ml, $P<0.05$) compared to the controls. ROC analysis indicates that both cytokines IL-1β and sFasL effectively discriminated hypothyroid and healthy children (IL-1β: AUC=0.77; $P=0.003$ and sFasL AUC=0.897; $P<0.001$). sFasL with high sensitivity 100% and specificity 73.3% but IL-1β with low sensitivity 59.1% and high specificity 95%. Moreover IL-1β and sFasL effectively discriminated both clinically opposing states, hyperthyroidism and hypothyroidism among themselves: sFasL (AUC=0.833; $P=0.003$; sensitivity: 94.7%,specificity: 72.7%. and IL-1β (AUC=0.773; $P=0.002$; sensitivity: 72.7%; specificity: 86.4%). **Conclusions:** Both cytokines IL-1β and TNF-a may be useful markers in the assessment of thyroid dysfunction of autoimmune hypothyroid and hyperthyroid children.

Background: Infants referred with elevation of capillary TSH on newborn screening are classified as having transient TSH elevation when subsequently found to have normal venous thyroid function tests off treatment with thyroxine. Causes of transient TSH elevation include neonatal sickness, prematurity and maternal thyroid antibodies. There is little information on thyroid size in such infants. **Objective:** To determine thyroid volume by ultrasound in infants with transient TSH elevation. **Hypothesis:** That most subjects would show normal volume glands compared with population-specific data. **Method:** Two observers rated thyroid size by subjective evaluation (Sx) as small, small-normal, normal, large-normal and large, and then reached consensus where possible. On two separate occasions the observers measured volume of each lobe by objective evaluation (Ox) according to the formula length x breadth x depth x $\pi/6$ and deriving total gland volume as the sum of both lobes. Given population-specific mean (SD) volume of 1.61 (0.4) ml, Ox volumes corresponding to Sx were set at <0.8, 0.8–1.0, $>1-<2.2$, 2.2–2.4, and >2.4 ml. **Results:** Images from 15 infants (M: F=9:6), median (range) birthweight 3.06 (2.37–3.8)kg and gestation 39 (33–42) weeks were available for study. Three infants were scored as having large glands on Sx, with Ox volume 2.42 ml in one (Pendrin heterozygote) but 1.8 and 0.85 ml in the other two. One infant who was sick at birth due to placental abruption and renal failure had a normal gland on both Sx and Ox (volume 1.17 ml). Sx and Ox assessment was not possible in a further infant with allo-immune thyroiditis causing peri-thyroidal oedema. Of the remaining 10 infants Ox volume was <0.8 (range 0.48–0.76) ml in 8; and 0.82, 0.83 ml in the other two, Sx evaluation normal in 6 and small-normal in 4. Uptake of radioisotope was decreased in 5 and absent in 2 of these infants. Transient TSH elevation was attributable to blocking antibodies (3), heterozygous TSH receptor mutation (1) and cause unknown (6). **Conclusion:** Thyroid volume in infants with transient TSH elevation was unexpectedly reduced on objective measurement in 10/15 patients in our series. This emphasises the importance of careful Ox evaluation, and raises the question as to whether follow up with repeat thyroid function testing and imaging later in childhood might be more appropriate than discharge from clinic in "transient" cases.

P1-P923

Small Thyroid Volume on Ultrasound in Infants with Transient TSH Elevation Following Referral by Newborn Screening

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P1-P924

In Children with Autoimmune Thyroid Diseases the Association with Down syndrome can Modify the Clustering of Extra-Thyroidal Autoimmune Disorders

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Background: Autoimmune diseases have a higher incidence and prevalence among the individuals with Down syndrome (DS) compared to chromosomally normal people (increased risk for thyroid, gut and islet autoimmunity, juvenile idiopathic arthritis) These findings provide insights into a very aggressive phenotypic expression of autoimmunity in DS children. **Objective and hypotheses:** To investigate for the 1st time whether the association with DS might per se modify the aggregation of extra-thyroidal autoimmune diseases (ETADs) in children with the same index autoimmune disorders, by conditioning a different clustering in the cases with associated DS versus those without DS. **Method:** In the present cross-sectional study covering 832 children with autoimmune thyroid diseases (AITDs), we investigated the clustering of ETADs in 2 groups of patients with or without DS (Groups A and B, respectively). All the included patients were screened for the most common pediatric ETADs by specific anamnesis, clinical examination and some selected autoantibody assays. **Results:** The rate of children with no associated ETADs was much higher in Group B, whilst the rates of children with at least one or more associated ETADs were significantly higher in Group A. Moreover, the epidemiological distribution of the associated ETADs was significantly different in the 2 patient groups with or without DS; in particular, alopecia areata ($P=0.00001$), vitiligo ($P=0.00001$) and celiac disease ($P=0.0004$) were more often found in group A, whilst the distribution of T1 diabetes mellitus was not different. **Conclusion:** In a study population of children and adolescents with AITDs the association with DS might be able to: a) condition an increased risk of developing ETADs; b) modify the clustering of ETADs, which is generally observed in the children with AITDs but without DS, by favouring the aggregation of alopecia areata, vitiligo and celiac disease.

P1-P925

L-selenomethionine Supplementation in Children and Adolescents with Autoimmune Thyroiditis: Preliminary Results of a Randomized Double-blinded Placebo-controlled Clinical Trial

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Background: It has already been documented that selenium treatment has beneficial effects in adult patients with autoimmune thyroiditis, especially in those with a higher titer of antibodies and increased inflammatory disease activity. **Objective and hypotheses:** To investigate whether daily supplementation of organic selenium at a high dose (200 μg in the form of L-selenomethionine) has any effect on the titer of thyroid autoantibodies. **Method:** One hundred children and adolescents with a diagnosis of autoimmune thyroiditis were randomized to receive daily either 200 μg of organic selenium (in the form of L-selenomethionine) or placebo for 6 months. In all participants, the levels of fT4, TSH, as well as the titer of TPO and Tg autoantibodies are determined at 3 times (0, 3, 6 months) and ultrasonography of the thyroid gland is performed at 2 times (0, 6 months). Here is presented the analysis of the data obtained from 42 patients that completed 3 months and 23 patients that completed 6 months of treatment. **Results:** After a 3-month period, a difference, though not statistically significant, in the change of anti-Tg levels was detected in both groups (decrease in the intervention group vs increase in the control group: $\Delta: -84.6 \pm 72.0$ vs $+24.3 \pm 24.9$ IU/ml, $P=0.225$); after 6 months, a greater decrease in the change of anti-Tg levels was also observed in the intervention group ($\Delta: -156.8 \pm 115.0$ vs -59.8 ± 40.8 IU/ml, $P=0.592$). In contrast, no difference was detected in the change of anti-TPO levels (increase in both groups) either after 3 ($P=0.379$) or 6 months of treatment ($P=0.556$). **Conclusion:** Based on these preliminary results, selenium supplementation is suggested to decrease the levels of the antibodies against thyroglobulin in children and adolescents with autoimmune thyroiditis. The completion of the study, after the inclusion of all patients and for the whole study period, is needed in order to draw safer conclusions.

P1-P926

Minimally Invasive Video-Assisted Thyroid Surgery in Children: A Single Center Ten-Years Experience

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Background: Improved tools for diagnosis, a higher malignancy risk in thyroid nodules and the referral to surgery in Grave's

disease when medication fails, have lead to increased thyroidectomies in children. **Objective and hypotheses:** The aim of our study was to evaluate thyroid surgery outcomes and the presence of transient or permanent complications, in a cohort of children who underwent surgery, with the same surgical team, in the last 10 years. **Method:** children (24 F/11 M) were selected for thyroid surgery and longitudinally followed-up for 24.3 ± 13.88 (mean ± sds) months. Clinical features and indications to surgery were evaluated, along with complications: transient or permanent hypoparathyroidism, transient or permanent RLN (Recurrent Laryngeal Nerve) injury and post-operative bleeding. **Results:** 20 (15 F/5M) children underwent thyroid surgery for benign conditions (mean age 13.88 ± 2.33 years), and 15 (9 F/6 M) for malignant ones (mean age 13.93 ± 3.59 years), with no significant age difference in the two groups (*P* value 0.96). Of the benign conditions, 6 were Grave's disease and 14 other conditions; of the malignant ones, 1 was a multiple endocrine neoplasia type 2, 13 were papillary and 1 was medullary carcinoma. 12 children with malignant conditions underwent total thyroidectomy (TT): 3 of which with central compartment lymphadenectomy and 4 with central and lateral-cervical lymphadenectomy; 3 had an initial hemi-thyroidectomy, followed by complete removal of thyroid gland. Of the benign conditions, 13 underwent thyroidectomy while 7 underwent hemi-thyroidectomies. 5 children (all malignant conditions) suffered from post-operative hypoparathyroidism (only 1 was transient). One presented transient RLN injury (TT from benign condition) and 1 post-operative bleeding (TT for malignant condition). **Conclusion:** Using a multidisciplinary team (endocrinologists, radiologists and surgeons), a Minimally Invasive Video-Assisted Thyroid Surgery (MIVAT) approach for thyroid surgery and a careful pre-surgical preparation (Grave's disease) allowed us to reduce permanent severe complications in children.

P1-P927

Prevalence of Congenital Hypothyroidism and Thyroid Function Follow-Up of Children with Tsh Cutoff between 5 and 10 mIU/l in Neonatal Screening

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Objective: To determine the prevalence of congenital hypothyroidism (CH) in children with dry bloodspot TSH ($_b$-TSH) between 5 and 10 mIU/l in neonatal screening and evaluate their thyroid function evolution. **Methods:** Retrospective study of thyroid function in children born from 2003 to 2010 with $_b$-TSH between 5 and 10 mIU/l who were put on treatment in the first two years of life due to serum TSH ≥ 10 mIU/l. The prevalence of CH was determined, as well as the permanent congenital hypothyroidism (PCH) frequency among those born at term and healthy, who had been followed for at least 6 months after treatment withdraw. PCH was considered when the treatment was reintroduced due to steadily TSH ≥ 10 mIU/l. Thyroid scintigraphy with technetium-99m (^{99m}Tc) was done for etiologic investigation. **Results:** From 380,741 neonates screened, 3,713 (1.0%) had $_b$-TSH between 5 and 10 mIU/l, of which 339 (9.1%) had CH. Children born preterm (32), with neonatal anoxia (2) or genetic syndromes (13) or hyperthyroid mother (1), as well as 35 individuals who were not followed for 6 six months after thyroxin withdraw were excluded in the late thyroid function evaluation. From the remaining group of 256 children (152 males), 70 (27.3%) had PCH among which 4 thyroid dysgenesis (2 hemiagenesis, 1 lobe hypoplasia and 1 thyroid hypoplasia) and 8 goitres. Serum FT4 levels in the initial neonatal evaluation were lower in the PCH group ($P = 0.002$). Other relevant findings were that 22.6% of children took more than 4 months to develop CH and 25.7% of those with PCH had the diagnosis of the permanent deficiency only after 4 months of treatment withdraw. **Conclusion:** The $_b$-TSH screening-test cutoff of 5 mIU/l, along with clinical and laboratory follow-up allowed the early detection of 339 CH and 70 permanent hypothyroid children that would have been missed if the current $_b$-TSH cutoff of 10 mIU/l was used.

P1-P928

Preliminary Results: Body Composition of Adolescent Patients with Congenital Hypothyroidism and Correlation with Laboratory Parameters

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Background: Thyroid dysfunction may predispose to imbalanced body composition. **Objective and hypotheses:** The aim of the study is to evaluate bone, muscle and fat mass in teenagers with congenital hypothyroidism and correlate their bone profile with laboratory parameters, in an effort to offer more effective lifestyle counselling. **Method:** Adolescents diagnosed with congenital hypothyroidism through neonatal screening underwent thorough

clinical examination, thyroid function tests (TFTs) and basic bone profile, as well as bone mineral density scan, using dual-energy X-ray absorptiometry (DXA). For statistical purposes, a group of 57 healthy age- and sex-matched controls was also studied. **Results:** To date, 18 teenagers have been assessed, aged 14–18 years (12 female subjects); 4 with thyroid gland agenesis, 10 with ectopic thyroid gland, 2 with hypoplastic thyroid gland and 2 with dysormonogenesis. Five patients report a total of five post-traumatic fractures of long bones. 55% receive adequate calcium through their diet and only 33% exercise regularly. Their laboratory results (lipid profile, TFTs, 25(OH)D, parathormone) were within reference range, with a tendency of high-normal TSH values amongst boys. Compared to controls, the patients were heavier, with marginally higher fat mass, whereas their bone and muscle mass were comparable. A positive correlation was found between body weight and fat mass, which in turn was negatively correlated to vitamin D levels ($r = -0.77$, $P < 0.01$). **Conclusion:** Overweight patients with congenital hypothyroidism tend to have more pronounced adipose tissue accumulation and lower vitamin D levels, therefore they should be targeted towards regular exercise and a balanced diet, with adequate calcium intake. In patients whose hypothyroidism is under control, bone and muscle mass are not particularly affected.

P1-P929

Neonatal Thyrotoxicosis and Craniosynostosis Associated with Maternal Graves' Disease and High Dose maternal Thyroxine Therapy for Papillary Carcinoma

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Background: Neonatal Graves' disease (NGD) occurs in 1–2% pregnancies with maternal Graves' disease. Thyroid auto-antibodies can persist in the maternal circulation even 10 years after thyroidectomy and can lead to NGD in the absence of maternal thyrotoxicosis. Both maternal stimulating autoantibodies and maternal thyroxine can cross the placenta, and have been implicated in neonatal craniosynostosis. **Objective and hypotheses:** We report a case of NGD associated with craniosynostosis in a baby of a 33 year old female with a history of Graves' disease. She underwent a total thyroidectomy prior to the pregnancy and was started on suppressive doses of thyroxine therapy for incidentally detected papillary carcinoma of the removed thyroid. **Method:** During the pregnancy, which was unplanned, mother had poor antenatal clinic attendance and continued to take 200 μg of thyroxine daily. Baby was delivered by emergency section at 32 weeks of gestation, due to fetal distress. Birth weight was 1.7 kg and there was no goitre. Baby had tachycardia from birth and developed proptosis, diarrhoea and high blood pressure on day 5. **Results:** On day 2, TSH was low [0.005 mIU/l (1–20)] but f T4 was normal [4.6 ng/dl (2–5)]. By day 5, fT4 increased to 5.4 ng/dl (0.9–2.2). The baby was treated with carbimazole 0.5 mg/kg/d and propranolol. He showed clinical improvement, and normalisation of ft4 within 5 days. Carbimazole was gradually discontinued over 3 months and child remained euthyroid. However, he had poor cranial growth post-natally, and at 9 months, his anterior fontanel had closed completely, and he had microcephaly and developmental delay. **Conclusion:** In this unusual case of NGD, both maternal stimulating autoantibodies and high dose thyroxine therapy could have potentially contributed to development of craniosynostosis and microcephaly. It is important be vigilant of past autoimmune thyroid disease during pregnancy, and monitor the fetus and new-born accordingly.

P1-P930

Seasonality of Month of Birth in Children and Adolescents with Hashimoto Thyroiditis

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Background: A number of studies have previously described seasonality of birth in children with type 1 diabetes, thus suggesting that the autoimmune process may begin during fetal development. However, there is a lack of data regarding autoimmune thyroid disease in childhood. **Objective and hypotheses:** The aim of this study was to analyse the seasonal birth month pattern in young patients with Hashimoto thyroiditis and compare it with that of youth healthy controls. **Method:** Medical records of a total of 298 children and adolescents with a diagnosis of Hashimoto thyroiditis before the age of 18 years, made from 2005 to 2015, were retrospectively reviewed. In addition, 298 consecutive subjects that were evaluated, between 2013 and 2015, in a tertiary unit for any reason, provided that they had no personal or family history of thyroid or any other autoimmune disease at least in first-degree relatives, served as controls. Statistical analysis was performed using a chi-square test. **Results:** Significant differences were found between children and adolescents with Hashimoto thyroiditis and healthy controls as far as the pattern of month of birth distribution is concerned ($\chi^2 = 21.397$, 11 degrees of freedom, $P = 0.029$). The highest and lowest predispositions to Hashimoto thyroiditis were inherent in those born in March to May and October to December, respectively.

When analysis was performed separately for males and females, similar birth patterns of patients with autoimmune thyroiditis were obtained only in the subgroup of females ($\chi^2 = 18.283$, 11 degrees of freedom, $P = 0.07$ for females, $\chi^2 = 10.013$, 11 degrees of freedom, $P = 0.529$ for males). **Conclusion:** This study suggests that the effect of certain seasonal factors during fetal development, reflected by the seasonal differences in birth pattern, in children and adolescents with Hashimoto thyroiditis could contribute to long-term programming of an autoimmune response against the thyroid gland.

P1-P931

Radioiodine Therapy for Graves' Disease – the Experience of a Portuguese Single Centre

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Background: Besides surgery, radioactive iodine therapy (RAI) is an effective and safe option to treat children with hyperthyroidism from Graves disease (GD) who cannot achieve euthyroidism with antithyroid drugs. **Objective and hypotheses:** To present the experience of a Portuguese paediatric unit with the use of RAI in children with GD. **Method:** The authors performed a review of 7 cases of Graves disease of age under 18 years treated with RAI between 2010 and 2015. A previous trial on methimazole ("block and replace") was attempted in all patients. Indications for RAI were uncontrolled hyperthyroidism with thyroid mass less than 80 g and absence of active eye disease. The goal of RAI was achieving a hypothyroid state, after which therapy with levothyroxine would be started. Methimazole was routinely stopped 1 week before RAI and therapeutic activity was calculated based on 24 h radioiodine uptake and thyroid mass. **Results:** Patients, who were all female, had a median time of onset of 10.1years (9.9–10.8). RAI was administered after a long period under methimazole (41months (33–52)) to achieve an euthyroid state, at median age of 13.9 years (13.5–15.1), with a median activity of 10 mCi (9–13). After RAI, hypothyroidism was achieved after a median of 6 months (5.25–11.5) in 5 patients. The remaining two needed a second RAI dose of 7.6 and 10.9 mCi and became hypothyroid 1 month later. Globally, the 1-session RAI group were offered a 11 mCi (10–13) activity, compared to 17 mCi (15.1–19.0) of the 2-session group. There is also a trend in progressively higher activities of RAI, with better results. No side effects were related by any patients. **Conclusion:** RAI has been safely used in our unit with good results. Hypothyroidism is achieved 6 months later after RAI and 1 month later, when a second treatment is needed. Higher activities of RAI also seem to be associated with better results (more rapid onset of hypothyroidism).

P2-P932

Multinodular Goiter and Differentiated Thyroid Cancer in Pediatrics

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Background: In a recent report we have identified multinodular goiter (MNG) as a condition with an increased risk for thyroid malignancy in children and adolescents. **Objective and hypotheses:** To report the prevalence and characterization of a prospectively and uniformly followed cohort of pediatric patients with MNG and to retrospectively analyze differences between benign and malignant MNG before surgery in order to identify malignancy predictors. **Method:** We studied 32/104 patients under 19 years of age referred to our center for thyroid nodules between 2008 and 2015, who presented MNG and reached a final diagnosis (benign vs. malignant) by surgery (*n*:24) or by at least 1 year (range:1.5–6.5) of clinical follow up (*n*:8). Initial evaluation included clinical data, thyroid function, Doppler-US and US-FNAB cytology categorized with the Bethesda System. **Results:** Upon admission mean age was 13.6 years, 75% were females, 69% pubertal. Papillary thyroid carcinoma (PTC) was found in 8 patients (25%). Risk factors, present in 5/32, were not associated with malignancy. All patients with familiar MNG (*n*:6) had a benign diagnosis. Younger age (10.4 vs 14.8 years), prepubertal status (5/8 vs 5/24,) and pathologic lymphadenopathies (4/8 vs 1/24) were significantly associated with malignancy ($P < 0.05$). All malignant nodules were solid (8/8 vs 12/24, $P < 0.05$). Conversely, the finding of mixed/cystic nodules on US was always associated with a benign diagnosis ($P < 0.05$). Although within the normal range, median TSH concentration was higher in patients with PTC (3.5 vs 1.4 mIU/l, $P < 0.05$) and the likelihood of

PTC increased with rising TSH levels. Malignancy risk in Bethesda categories I, II, III, V and VI was 0, 7.7, 0, 75 and 100% respectively. PPV and NPV for Bethesda V-VI FNAB results were 86 and 96% respectively. **Conclusion:** MNG represented 31% of our thyroid nodule population. PTC incidence was 25%, similar to that reported in pediatric thyroid nodules. Younger age, prepubertal status, higher TSH concentrations, solid nodules and pathologic lymphadenopathies were significantly associated with malignancy. These findings should be considered when facing the therapeutic approach for these patients.

P2-P933

Clinical Case of Acute Liver Injury in Pediatric Patient with Autoimmune Hyperthyroidism

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Background: Autoimmune hepatitis (AIH) and methimazole (MMI)-induced toxic hepatitis are both rare diseases in pediatric age. **Case presentation:** We present the case of a 15-year-old girl affected by idiopathic arthritis and autoimmune thyroiditis. The autoimmune thyroiditis was diagnosed at 13 years of age. At 15 years old she developed hyperthyroidism (TSH <0.01 mcU/ml, FT4 2.3 ng/dl, FT3 8.4 pg/ml, TRAb 18 IU/l) and was treated with MMI (0.28 mg/kg per day). 2 weeks after the start of treatment FT3 and FT4 were normalized, but there was a relevant elevation of her transaminases (AST 493 U/l, ALT 614 U/l). MMI-induced toxic hepatitis, AIH, and viral hepatitis were all considered as possible diagnoses and we immediately suspended the MMI. Her transaminases remained stable but elevated in the 10 days following MMI suspension. We excluded the most common causes of viral hepatitis. Autoimmune screening tests showed a positivity of anti-LKM antibody with 1:80 titre. Smooth muscle antibodies were negative. Due to the lack of improvement of transaminases' values with the suspension of MMI and the positivity of anti-LKM antibody, we performed an echo-guided liver biopsy. The histological examination was suggestive of an AIH in the active phase. We made the diagnosis of AIH using the revised scoring system for AIH diagnosis provided by the International Autoimmune Hepatitis Group. We re-started MMI and started therapy with prednisone and azathioprine. Transaminases were normalized after 2 weeks and thyroid function was normalized after 1 month. **Conclusion:** AIH is a rare disease in pediatric age, however it is important to keep in mind that patients affected by autoimmune thyroiditis are at an increased risk to develop other autoimmune diseases. Therefore it must be considered in these cases. MMI-induced hepatotoxicity should also be considered, even though MMI causes less serious liver damage when compared to propylthiouracil.

P2-P934

Thyroid Function in Children Affected By Congenital Hypothyroidism (CH) with Eutopic Thyroid After Discontinuation of Treatment with Levothyroxine

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Objective and hypotheses: We analysed the prevalence of transient hypothyroidism in a cohort of children affected by CH with eutopic thyroid after Levothyroxine discontinuation. **Method:** 77 newborns (36 females, 41 males) affected by CH with eutopic thyroid from 1999 to 2011 were enrolled. The confirmation diagnosis of CH after screening was made within the first 15 days of life by assessing TSH value (mean 74.4 ± 82.2 μU/ml n.v 0.5–4.2) and fT_4 value (mean 8.9 ± 3.6 pg/ml, n.v. 9–17). Thyroid ultrasound was performed in all newborn who were also treated with Levothyroxine at a starting daily dose of 5–10 mcg/kg per day (median dose 8.5 mcg/kg per day). All children were re-evaluated at a mean age of 3.5 ± 1.0 years after treatment discontinuation for 4 weeks. They were divided in two groups according to TSH value at neonatal screening: group (A) TSH 7–U/ml and group (B) TSH >10.1 μU/ml (TSH cut-off value 7 μU/ml). **Results:** Forty-seven children (61.0%) had transient hypothyroidism and 30 (39.0%) had permanent hypothyroidism; the latter had a mean TSH value at neonatal screening of 23.08 ± 25.8 μU/ml (37.3% were in group A and 66.7% in group B) compared to the mean TSH value at diagnosis of 76.7 ± 95.1 μU/ml. Children with transient hypothyroidism had a TSH value at neonatal screening of 16.6 ± 16.1 μU/ml (40.4% were in group A and 51.1% in group B) compared to the mean TSH value at diagnosis of 75.1 ± 87.7 μU/ml. No significant relationships were found between the two groups for their outcomes indicated as transient vs permanent hypothyroidism, mean TSH values at neonatal screening ($P=0.79$), at diagnosis ($P=0.70$), and dosage of Levothyroxine at diagnosis ($P=0.12$). Moreover, no correlation was found between mean TSH values at neonatal screening and after therapy discontinuation ($r_s=0.15$). Conversely, a significant relationship between the number of Levothyroxine therapy variations and the final outcome was found in children with permanent hypothyroidism (2.1 ± 2.0) vs children with transient hypothyroidism (0.9 ± 1.1; $P=0.0097$). **Conclusion:** 39.0% of children with CH and eutopic thyroid presented true hypothyroidism after treatment discontinuation. Number of Levothyroxine therapy variations was the only significant factor as determinant of permanent hypothyroidism.

P2-P935

Hyperthyroidism in an Infant of a Mother with Autoimmune Hypothyroidism with Positive TSH Receptor Antibodies

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Background: Neonatal hyperthyroidism is a rare condition seen in infants born to mothers with Graves disease, with transplacental transfer of TSH receptor antibodies (TRAb) to the baby. Some patients have been shown to swing from hypothyroidism to hyperthyroidism as TSH receptor blocking and stimulating antibodies may coexist. **Objective and hypotheses:** To describe a rare clinical event of a neonate with severe Graves hyperthyroidism, born to a mother with autoimmune hypothyroidism **Method:** A baby boy born preterm at 35 weeks gestation had significant irritability, tachycardia and a suspicion of proptosis 36 hours after birth. The mother was known to have autoimmune hypothyroidism, diagnosed at age ten and was taking levothyroxine replacement with normal thyroid function throughout this pregnancy. She had never been thyrotoxic. She also had pernicious anaemia and extensive vitiligo. Her sister and grandmother have Hashimoto's thyroiditis. Her mother has Graves disease. The mother therefore was tested for TRab. **Results:** The baby's thyroid function on day 3 demonstrated gross thyrotoxicosis, TSH <0.01 mU/l (NR day 3 <10 mU/l), FT_4 >77 pmol/l (20–35) and FT_3 15.4 pmol/l. TRab was elevated at 18.4 IU/l (<1.8). The mother's TRab was high at 24.7 IU/l. The baby was commenced on propranolol on day 7, with some symptomatic improvement, however thyroid hormones continued to rise. After endocrine consultation, on day 17 carbimazole (CBZ) was commenced, at 0.3 mg/kg per day. Thyroid function normalized within 10 days, CBZ was gradually tapered and medication was weaned by 7 weeks. He has remained euthyroid. His mother continues to require replacement thyroxine. **Conclusion:** Rare cases of de novo development of TSH stimulating antibodies are described in patients on levothyroxine and might provide an explanation for our case. However, almost all infants reported with neonatal thyrotoxicosis were either de novo or associated with maternal history of active or treated Graves disease.[1] Our findings have important implications for future follow up of this family and for management of future pregnancies.

P2-P936

Thyroid Cancer Presentation in Children is Different than in Young Adults

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Background: Differentiated thyroid cancer (DTC) in pediatric age might have peculiar course and prognosis. **Objective and hypotheses:** To compare clinical, biochemical and ultrasound (US) features at diagnosis, histological grading and outcome in two groups of children and young adults with DTC. **Method:** Clinical, biochemical and imaging characteristics of 63 patients with DTC, diagnosed between 1999 and 2014 in our hospital, were retrospectively evaluated. Patients were divided in 2 groups according to age at DTC diagnosis: group A including 18 patients aged ≤ 18 years (mean age 15.4 ± 2.8); group B including 45 patients aged between 19 and 30 years (mean age 25.9 ± 2.7). All patients underwent both surgery and radioactive iodine therapy. Follow-up period was 6.7 ± 3.3 years for group A patients and 5.2 ± 3.2 years for those in group B ($P > 0.05$). **Results:** 1. Tumor size ($P < 0.01$) and metastasis rates ($P < 0.03$) at diagnosis were higher in group A. 2. The severity of lymph node involvement, as assessed by clinical and US evaluations, was higher in group A ($P = 0.045$). 3. Association with Hashimoto's thyroiditis (HT) and thyroid dysfunction biochemical signs were more frequent in group A ($P = 0.045$ and $P = 0.02$ respectively). 4. Tumor recurrence rate and free survival rate were similar in the two groups. **Conclusion:** DTC in children presents with a clinical and biochemical picture which differs from the one observed at presentation in young adults, due to following features: a) More frequent association with HT; b) More severe lymph node involvement; c) More frequent thyroid function biochemical alterations.

P2-P937

Starting Treatment in Congenital Hypothyroidism with Normal FT4 Levels and Thyroid Gland *in situ* Detected at Neonatal Screening

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Background: Recently congenital hypothyroidism (CH) is increased,particularly mild forms. Current guidelines recommend initial levothyroxine (LT4) dose of 10–15 mcg/kg per day as soon as possible, if diagnosis is confirmed by serum test, even if FT4 concentration is normal and venous TSH concentration is >20 microUI/ml. **Objective and hypotheses:** The aim of our study was to evaluate the initial LT4 dose in newborn with congenital hypothyroidism, normal FT4 and thyroid gland in situ. **Method:** We conducted a retrospective charts review of all CH patients seen at Bambino Gesù Children's Hospital from 2013-present. We included all newborn in whom confirmatory

serum test demonstrated TSH > 20 microUI/ml and normal FT4 levels. Thyroid ultrasonography showed a normal gland *in situ*. Exclusion criteria: preterm birth, genetic syndrome, chronic diseases. **Results:** We identified 24 patients (10 female e 14 male), mean (SD) birth weight was 3.2 (0.4) Kg. Median TSH at diagnosis was 38.65 microUI/ml (IQ 31.1–56),mean (SD) FT4 1 ng/dl (0.72–1.4). Patients started LT4 treatment at a mean (SD) age of 29.2 (7.9) days with a mean (SD) initial dose 5.6 (1.7) mcg/kg/day. Median TSH after 15 days of treatment was 2.1 microUI/ml (IQ 0.8–5.5) and after 1 month was 2.4 microUI/ml (IQ 0.5–3.7). Mean (SD) FT4 after 15 days of treatment was 1.6 ng/dl (0.28) and after 1 month was 1.58 ng/dl (0.28). 11 patients had thyrotoxicosis (FT4 $\geq$1.7 ng/dl) after 15 days of treatment at mean (SD) starting LT4 dose 6.7 mcg/kg per day (1.5) vs 13 patients with normal FT4 at mean (SD) starting dose 4.6 mcg/kg per day (1.16) ($P=0.002$). **Conclusion:** We obtained euthyroidism at 15 days of treatment at mean dose of 4.6 mcg/kg per day, avoiding thyrotoxicosis. These results indicate that CH mild forms may require lower LT4 dose. Larger prospective studies are needed to validate our findings and to investigate the optimal LT4 dose required in CH mild forms.

P2-P938

Distal Monosomy 10q Presented as Congenital Hypothyroidism

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Background: Distal monosomy 10q is a rare chromosomal anomaly characterized by unusually slow growth before and after birth, mild to severe intellectual disability and distinctive craniofacial features (hypertelorism, strabismus, a prominent or broad nasal bridge, and posteriorly rotated low-set ears). Some other anomalies have been described in various systems. The behavioral profile was characterized by marked inattention, hyperactivity and impulsivity. In recent years, subtelomeric rearrangements have been identified by MLPA test since conventional cytogenetic analysis may not be sensitive enough to detect very small deletions. Most 10q deletions occur de novo. **Method and results:** We report two cases (mother and daughter). The mother has been diagnosed with congenital scoliosis, facial dysmorphism and congenital hypothyroidism with goiter; because the high doses of Euthyrox®, we assumed an enzyme deficiency. She was operated for goiter and thyroid hormone replacement was made successfully. The daugther has also facial dysmorphism and congenital hypothyroidism (Euthyrox replacement treatment). **Conclusion:** Due to the association between congenital hypothyroidism and facial dysmorphism we recommended MLPA test who detected the presence of a subterminal 10q deletion for both, mother and daughter. In our family the risk of recurrence is high (50%). Once the family chromosome change is known, we recommended prenatal test in any future pregnancy to find out the presence of a subterminal 10q deletion.

P2-P939

Five-Year Prospective Evaluation of Thyroid Function Test Evolution in Children with Hashimoto's Thyroiditis Presenting with Either Euthyroidism or Subclinical Hypothyroidism

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Background: It had never been investigated to now whether the course of thyroid function in Hashimoto's thyroiditis (HT) may differ in the children who had presented with either euthyroidism or subclinical hypothyroidism (SH). **Objective and hypotheses:** To establish, by means of a 5-year prospective evaluation of 234 children with HT and no prognostic risk factors, whether thyroid status evolution over time may be conditioned by the biochemical pattern at HT diagnosis. **Method:** From the time of recruitment all of them were followed-up as outpatients every 12 months for a pre-established period of 5 years and only those who completed the overall follow-up period were taken into consideration for this study. At each examination TSH, FT4, thyroid peroxidase and thyroglobulin (TPOAb and TGAb) serum levels were measured. **Results:** In the entire series TSH values significantly increased during follow-up, whilst FT4 values decreased and the proportion of children with a thyroid dysfunction increased from 27.3 to 47.4% ($P=0.0001$). Such a trend was more evident in the patients presenting with SH (group B) than in those presenting with euthyroidism (group A). At the end of follow-up the prevalence of children with overt hypothyroidism was 12.3% in group A vs 31.2% in group B ($P=0.0007$). TPOAb and TGAb serum levels at entry were not significantly different in the patients who deteriorated over time thyroid function than in those who did not. **Conclusion:** a) children with HT are per se incline to show, during the first 5 years of disease, a spontaneous deterioration of thyroid function picture; b) such a trend is more evident in the patients who had presented with a SH than in those who were initially euthyroid; c) this trend is not significantly affected by the serum levels of TPOAbs and TGAbs at HT diagnosis.

P2-P940

An Unusual Case of Impaired Renal Function and Thrombocytopenia

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Background: Autoimmune thyroid disease can be sometimes associated with autoimmune thrombocytopenia and decreased renal function**. Case report:** A 17-year-old female patient was referred to our endocrine department for evaluation of hypothyroidism (TSH = 150 mcIU/ml, FT3 = 0 pg/ml, FT4 < 0.1 ng/dl) presenting severe fatigability and myalgia. From her medical history we mention that she was diagnosed with thrombocytopenia 1 year ago (85.000/mm^3) and significant menometrorагy in Nov 2015 (Hb = 4.5 g/dl) for which she was treated with oral contraceptives. After the vaginal bleeding her creatinine doubled and the patient was referred to the nephrologist. All the causes for thrombocytopenia and elevated creatinine were excluded (domestic and drug toxicity, viral infection, autoimmune) and the platelet autoantibodies were negative. The endocrine evaluation revealed mixedema, H = 156.6 cm (−1.3 SD), W = 45.5 kg, hoarseness, slurring of speech, pale, dehydrated skin. The blood test showed moderate thrombocytopenia (70000/mm^3) elevated VEM, moderate dyslipidemia, elevated creatinine (1.4 mg/dl), normal blood urea (52 mg/dl), elevated CK (1309 UI/ml). The hormonal profile showed severe autoimmune hypothyroidism (TSH > 75 mcIU/ml, TT3 < 40 ng/dl, FT4 < 0.3 ng/dl, antithyroglobulin antibodies > 3000 UI/ml, antiperoxidase antibodies = 392 IU/ml). The thyroid ultrasound revealed a small thyroid gland with a heterogeneous echotexture, decreased flow at color Doppler, abdominal ultrasound showed completely normal kidneys, but the echocardiography showed poor left ventricular performance and decrease in the rate of ventricular diastolic relaxation. A diagnosis of severe autoimmune hypothyroidism with myopathy was made and the elevated creatinine was thought to be secondary to excessive production rather than impaired renal function as the blood urea was normal. The associated thrombocytopenia has probably an autoimmune etiology, though the platelet antibodies were negative. Substitutive treatment with levothyroxine was started. **Conclusion:** Elevation in serum creatinine levels can occur even in the absence of a decline in the glomerular filtration rate, and one should look hard for unusual causes, especially in a patient with normal blood urea.

P2-P941

Celiac Disease in Children and Adolescents with Hashimoto Thyroiditis

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Background: Hashimoto thyroiditis (HT) is part of the spectrum of autoimmune thyroid diseases and is characterized by the destruction of thyroid cells by various cell- and antibody-mediated immune processes. **Objective and hypotheses:** The aim of this study was to evaluate clinical and laboratory findings and determine the prevalence of celiac disease (CD) in children with HT. **Method:** A total of 80 patients with positive anti-thyroid antibodies who were between 6-17.9 years of age were retrospectively studied. Age, gender, symptoms at the time of presentation, family history of thyroid disorders, clinical and laboratory findings were recorded. The levels of thyrotropin, free thyroxin thyroid autoantibodies (thyroid peroxidase and thyroglobulin antibodies), immunoglobulin A (IgA) anti-tissue transglutaminase antibodies (IgA-tTG) and thyroid ultrasound were enrolled. **Results:** The study consisted of a population of 80 patients with 81.2% (65) girls and 18.8% (15) boys. Family history of thyroid disease was determined in 38 (47.5%) patients. The most common symptoms were goiter (30%) and weight gain (25%). Forty three (53.8%) patients presented with euthyroidism, while 23 (28.7%) and 14 (17.5%) patients with subclinical hypothyroidism and hypothyroidism, respectively. Thirty seven (46.2%) patients had goiter. *IgA*-tTG was positive in only one patient (1.25%) with HT. The symptoms of CD were present and small intestine *biopsy* revealed villous atrophy and crypt hyperplasia in this patient. **Conclusion:** In our study, the major symptoms were goiter, weakness and weight gain and only one patient (1.25%) was found to have CD. This study has shown that the prevalence of CD in children with HT is higher than in the general population.

P2-P942

Euthyroid Hashimoto Thyroiditis in Children: Evolution Over Time

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Background: The natural evolution of euthyroid Hashimoto thyroiditis (HT) varies among children and treatment in children with HT and normal/mild elevated serum TSH is controversial. **Objective and hypotheses:** The aim was to study the natural course of HT in children and evaluate predictive factors of thyroid function **Method:** We evaluated data from 87 children retrospectively (63 girls, 24 boys), mean age 10.6 ± 3.2yrs, with HT

[antibody titers (anti-Tg and anti-TPO) at least double the upper limit of normal]. All children had FT4 within normal ranges at diagnosis, 64 had also normal TSH < 5 U/L (group 1), whereas 23 of them had subclinical hypothyroidism 5 < TSH < 10 U/L (group 2). Serum levels of FT4 and TSH were recorded at 6, 12 and 24 months after their diagnosis and thyroid ultrasound was performed at 12 and 24 months. **Results:** During follow up, 45 (70.3%) patients of group 1 remained euthyroid (TSH < 5 U/L), 11 (17.2%) presented mild elevation of TSH < 10 U/L and in 8 (12.5%) TSH rose > 10 U/L, among whom 4 developed overt hypothyroidism. In group 2, 8 (34.8%) presented normalization of TSH, 5 (21.7%) remained stable with mild elevation of TSH < 10 U/L, while 10 (43.5%) developed significant rise of TSH > 10 U/L and/or overt hypothyroidism. Children with deterioration of thyroid function (33.3%) during follow up had higher anti-TPO (660.2 ± 680 vs 329.7 ± 392 U/ml, $P = 0.04$) and anti-Tg levels (1288.6 ± 1037 vs 608.3 ± 536 U/ml, $P = 0.04$) at baseline and significantly higher increase of anti-Tg levels during follow-up (115.2 ± 78 vs 28.2 ± 25 U/ml, $P = 0.05$), compared to children who remained or reversed to normal. **Conclusion:** A significant percentage of children (66.7%) with HT remained or became euthyroid during a 2 year follow-up period. Antibody titers at diagnosis and their progressive increase may constitute predictive factors of future deterioration of thyroid function in children with HT.

P2-P943

Thyrotoxic Periodic Paralysis, an Under-Recognized Condition

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Background: Thyrotoxic periodic paralysis (TPP) is a rare clinical manifestation of hyperthyroidism, commonly seen in Asian males. Patients often present with sudden onset muscle weakness associated with severe hypokalemia. **Case presentation:** A 16-year-old Filipino male presented with acute onset bilateral lower extremities weakness. He woke up at night but was unable to move his legs. He denied any recent viral infections, ingestion of canned food or history of paralysis. He complained of occasional palpitation and more frequent bowel movement. He had a 2.5 kg weight loss despite increased appetite. He otherwise denied tremors, diaphoresis, mood lability or neck enlargement. Family history was non-contributory. On physical examination, he was afebrile, mildly tachycardic (pulse 120/min) with BP 133/66 mmHg. He had mild exophthalmos and subtle tremors. Thyroid gland was enlarged with audible bruits. He had bilateral lower extremity muscle weakness, 1/5 motor strength in proximal muscles with normal sensation. Reflexes were normal. Laboratory findings were significant for hypokalemia 2 mEq/L (3.5 – 5.5), hypomagnesemia 1.6 mg/dL (1.8 – 2.4), elevated creatine kinase 795 IU/L (39 – 308) but normal calcium level. ECG showed narrow complex sinus tachycardia and ST-T changes. He was managed with IV potassium and magnesium; Potassium normalized to 4.6 mEql/L and paralysis resolved upon discharge. Later tests revealed TSH < 0.02 mcIU/ml (0.5 – 4.5), free T4 > 7 ng/ml (0.8 – 2), total T3 > 7.8 ng/mL (1 – 2.1). Anti-thyroid peroxidase and anti-thyroglobulin antibodies were positive and thyroid stimulating immunoglobulin index (TSI) was markedly elevated 6.6 (< 1.3). He was diagnosed with Graves' disease and started on Methimazole and Propranolol treatment. **Conclusion:** Patients with TPP can have subtle signs and symptoms of thyrotoxicosis on presentation and is easily under-recognized. High index of suspicion is crucial in patients who present with acute paralysis associated with hypokalemia. Early diagnosis and treatment of the hyperthyroid state prevent life-threatening complications of hypokalemia and recurrence of paralysis.

P2-P944

Age at Diagnosis and Mental Development in Children with Congenital Hypothyroidism in the Absence of Newborn Screening Programme

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Background: The outcome of congenital hypothyroidism (CH) has dramatically changed since the start of neonatal screening. However the benefit of this program is not felt in Algeria and other countries where the pathology is still causing irreparable brain damage. **Objective and hypotheses:** To evaluate age at diagnosis of CH and its impact on the mental development in the absence of new-born screening. **Method:** Case notes of all patients referred to our Endocrine Clinic for congenital hypothyroidism (CH) were reviewed. Patients with Down's syndrome were not included in the study. True congenital hypothyroidism was diagnosed when imaging showed thyroid dysgenesis or dyshormonogenesis; or when venous TSH was > 50 mU/L with subnormal fT4 (< pmol/L) in healthy term babies in whom imaging was not performed. Developmental delay was classified as severe, moderate and mild, and analysed according to age at starting treatment (< 1 month, 1–3 months, 3–6 months, > 6 months); and to initial venous fT4. **Results:** Of 75 patients referred with elevated TSH 56 (F36:M20) had true CH. Mean (range) age at referral was 17.6 (0.4–138) months at which time 21 (37.5%) patients were already on treatment. Mean (range) fT4 at diagnosis was 5.9 (0.01–20.5) pmol/L, TSH: 132.6(5.74–1075) mU/L. Aetiologies were thyroid dysgenesis (29) due to hypoplasia (13), athyreosis (12) and ectopia (4); dyshormonogenesis (10) and unknown causes (16). Mean age at starting treatment was 10.38 months (0.3–138). Breakdown of age (months) at starting treatment/initial fT4 (pmol/L) (n) was < 1/5.25 (12), 1–3/10.7 (20), 3–6/10–13(10) and > 6 m/13.5 (14). Mental delay was considered severe in 5(8.9%) patients, moderate in 16 (28.6%) and mild in 3(5.3%). Severe mental delay was highly correlated with initial ft4 levels: 3.83 pmol/l (0.99–10.7) and age at starting

treatment: 11 (0.5–40) months. **Conclusion:** Diagnosis of CH is still considerably delayed in countries where newborn screening is absent, leading to mental impairment in affected children. Algerian paediatrician are seriously concerned by this situation and are actively working to set-up a national screening program.

P2-P945

Vitamin D Levels in Children with Hashimoto's Thyroiditis: Before and after l-Thyroxine Therapy

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Background: There is high prevalence of Vitamin D deficiency (VDD) in Hashimoto's thyroiditis (HT) as reported in literature. However, it is uncertain whether VDD is a cause or effect of HT. The effect L-thyroxine replacement on vitamin D levels in children with HT has not been studied. **Objective and hypotheses:** To study vitamin D level of newly diagnosed children with HT and to observe the change in vitamin D level after L-thyroxine therapy. **Method:** A prospective observational study was conducted on 35 consecutive children (less than 12 years old) who were newly diagnosed with HT, and not yet started on L-thyroxine, over a one year study period. Children with concomitant chronic kidney/liver disease, Celiac disease, on anti-tubercular therapy/antiepileptics or glucocorticoids and who received vitamin D supplements in last 6 months were excluded. Serum 25 (OH) D levels was estimated before starting L-thyroxine and on follow-up. Vitamin D levels were compared with historical controls (from a study from same centre on healthy children of similar age and epidemiological profile). **Results:** The mean vitamin D level in cases at diagnosis was significantly low as compared to controls (33.34 ± 16.93 nmol/L vs 65.13 ± 30.57 nmol/L; P value < 0.0001). Out of 22 Vitamin D deficient children with HT, who received vitamin D therapy, 7 (31.8%) remained deficient even at follow-up. Thirteen patients (with sufficient/insufficient vitamin D levels) who were not supplemented with vitamin D had a fall in vitamin D levels in follow-up. However, degree of fall in Vitamin D was not statistically significant. **Conclusion:** Children with HT were observed to have low vitamin D levels at diagnosis and L-thyroxine therapy lead to further compromise in vitamin D levels.

P2-P946

The Aim of This Study was to Recognize Difference between Transient Congenital Hypothyroidism (TCH) from Permanent Congenital Hypothyroidism by Determining Clinical Characteristics, Laboratory Tests and Imaging Studies

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Methods: We performed retrospective study using database of the patients with congenital hypothyroidism treated with or without Levo-Thyroxine at Bundang Jesaeng General Hospital, from January 1998 to February 2016. Their ages, birth weights, gestational ages, symptoms, ages at diagnosis and treatment were recorded. We measured TSH, free thyroxine (FT4), triiodothyronine (TT3) levels at diagnosis and treatment, and those levels at one, two and three months after treatment. Thyroid scan (Tc^{99m} scintigraphy) and thyroid ultrasonography reports were described. **Results:** Among the 282 neonates included in this analysis, 51 were diagnosed with congenital hypothyroidism. The sex distribution was male 51% (26/51) vs. female 49% (25/51). Their initial postnatal ages of starting Levo-thyroxine treatment were 26.97 ± 15.4 days. 27 patients out of 51 were identified as TCH and 24 were revealed Permanent Congenital Hypothyroidism (PCH). In the TCH patients group, male patients were 66.7% (18/27) and female patients were 33.3% (9/27). Ages of initial treatment of TCH were 31.15 ± 13.78 days. The sex distribution of PCH was male 33.3% (8/24) vs. female 66.7% (16/24). Ages of initial treatment of PCH patients were 27.93 ± 31.07 days. The mean duration of treatment in TCH group were 28.94 ± 13.89 months. Serum TSH levels were measured at diagnosis of PCH group (mean 150.49, median 77.70, 25–75% 43.8–185 μIU/ml) were significantly higher than those of TCH group (mean 30.29, median 21.40, 25–75% 17.1–291 μIU/ml) ($P < 0.001$). FT4 levels (PCH; 0.73 ± 0.50 ng/dl vs TCH; 1.17 ± 0.53 ng/dl, $P < 0.02$) and TT3 levels (PCH; 1.36 ± 0.68 ng/ml, vs TCH; 1.90 ± 0.35 ng/ml, $P < 0.019$) measured at start of treatment also showed significant differences. FT4 level measured at two months later from start of treatment in PCH group were significantly higher than TCH group ($P < 0.034$). Required treatment doses were significantly different only that of 2-years of therapy. Thyroid USG were normal in 53.3% of patients with PCH. Comparably, those of all patients of TCH group were normal. We found another difference in Tc^{99m} scintigraphy reports of both group. The sizes of thyroids in patients of PCH group were bigger than TCH group ($P < 0.033$). **Conclusion:** According to these data, we might consider initial measurements of serum TSH, FT4, T3 and size of thyroid as predictive factors in categorizing TCH from PCH.

P2-P947

Delayed Diagnosis of a TSH-Adenoma due to Coexisting Autoimmune Thyroid Disease

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Background: TSH-secreting pituitary adenomas are rare, accounting for less than 2% of all pituitary adenomas. Their diagnosis may be difficult when a coexistence of other diseases masks the typical clinical and biochemical manifestations of TSH-

hypersecretion. **Objective:** To report a case of a TSH-adenoma without signs/symptoms of hyperthyroidism due to underlying autoimmune thyroid disease. **Results:** Patient is a 17 year old male who presented for evaluation of an elevated TSH level. Thyroid levels had been checked because of a strong family history of thyroid dysfunction. Patient had complaints of mildly decreased energy, feeling warm, and jittery, and thought his hair was turning grey. He denied constipation, skin changes, and changes in weight gain or appetite. He felt that his thyroid was enlarged but not tender and denied difficulty with breathing or swallowing. His exam was only remarkable for firm and mildly tender thyromegaly. His initial lab evaluation showed subclinical hypothyroidism (free T4 15.45 pmol/L (7.7–22.5), total T3 2.56 nmol/l (0.85–2.61), TSH 17.78 mU/l (0.40–5.50)) with positive TPO antibodies (> 1000 IU/ml). He was started on 75 mcg/day L-thyroxine supplementation for presumed autoimmune thyroiditis. Follow-up tests showed a persistently elevated TSH despite increased fT4 and T3 levels (free T4 21.9 pmol/l, total T3 2.86 nmol/l, TSH 16.09 mU/l). L-thyroxine was discontinued at this time. Evaluations for interfering antibodies were negative, and IGF-1, LH, FSH, and prolactin levels were normal. However, α-subunit was 4.4 mcg/l with the α-subunit/TSH molar ratio elevated at 2.28. A brain MRI was obtained that showed a 12 mm sellar mass with imaging characteristics most consistent with a pituitary macroadenoma. **Conclusion:** The coexistence of autoimmune hypothyroidism may delay the diagnosis of TSH-adenomas. Practitioners should consider the possibility of a TSH-secreting pituitary adenoma when TSH levels do not adequately suppress in response to L-T4 replacement therapy and elevated thyroid hormone levels.

P2-P948

Kocher-Debre-Semelaigne Syndrome: Hypothyroidism with Muscle Pseudohypertrophy

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Background: Kocher-Debre Semelaigne syndrome (KDSS) is a rare form of myopathy in patients with longstanding moderate-to-severe hypothyroidism. **Objective and hypotheses:** We present the case of 7-year-old boy who developed muscular pseudohypertrophy, associated with long-term untreated hypothyroidism. **Method:** A 7-year-old boy presented with growth failure, lassitude and lethargy. He was born small for gestational age at 28 weeks gestation from twin pregnancy. His developmental assessment showed normal gross motor milestones during the first year of life. The child was apparently asymptomatic till 3–4 years of age, when the parents started noticing progressive weakness and lethargy along with deteriorating academic performance and growth retardation. The patient gave a history of chronic constipation. On examination he was found to be normal statured (height SDS = −1.67; height velocity SDS = −5.5) with prominent muscular build. He showed muscle hypertrophy with enlargement of the ***calf muscles.*** He had hoarseness of voice, a dry texture of skin, a macroglossia and an odematous face. **Results:** ***Brain imaging*** findings ***showed pituitary enlargement.*** The boy was found to have hypothyroidism [TSH = 807 μIU/ml (0.5–4.8), free T4 = 5.15 pmol/l (11–18,6)]. Primary autoimmune etiology was confirmed by raised anti-TPO antibody titre > 1000 mU/ml and ultrasound features of ***autoimmune thyroiditis***. The serum creatinine phosphokinase [447 U/l (30–200], aspartate transaminase [113 U/l (5–34)], alanine aminotransferase [176 U/l (0–55)] and the lactate dehydrogenase [256 U/l (125–220)] levels were elevated. A diagnosis of KDSS was made on the basis of the above mentioned findings, and the child was started on levothyroxine supplementation 50 μg/day. On follow-up after 3 months the child was found to be euthyroid, he showed significant improvements in his symptoms and regression in volume of calf muscles was noted. **Conclusion:** This report is to increase awareness of the uncommon presentation of hypothyroidism in the form of Kocher-Debre-Semelaigne syndrome, which is a rare and a reversible condition.

P2-P949

Thyroid Function in Obese Children and Its Correlations with Chosen Atherogenic Risk Factors

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Background: Moderately elevated thyroid-stimulating hormone (TSH) with normal serum concentrations of free thyroxine (fT4), suggesting subclinical hypothyroidism, is the most common hormonal abnormality in obese children. Controversy remains whether thyroid dysfunction related to obesity has an influence on the cardiovascular risk factors. **Objective and hypotheses:** The aim of the study was to assess correlation between TSH and fT4 and chosen atherogenic risk factors in obese children and adolescent. **Method:** The study group consisted of 110 obese children, aged 5 −18 years (11.54 ± 2.9 years) and 38 healthy children (13.4 ± 2.63 years). Obesity was defined using IOTF criteria. In each patient anthropometric measurements, blood samples (TSH, fT4, lipids profile, adiponectin) and carotid intima – media thickness (IMT) were taken. The resulting data was used to calculate indicators of atherogenesis: TC/HDL-C, TG/HDL-C, LDL-C/HDL-C. **Results:** Obese children had higher mean serum TSH levels compared to their lean peers (2.1 ± 1.0 μIU/ml vs 1.5 ± 0.6 μIU/ml, $P = 0.000$) and an adverse atherogenic lipid profile. Serum fT4 concentrations were comparable between groups. Serum TSH values correlated with TC/ HDL-C ($r = 0.286$, $P = 0.000$), TG/ HDL-C ($r = 0.236$, $P = 0.004$), LDL-C/ HDL-C ($r = 0.281$, $P = 0.001$) and IMT ($r = 0.02$, $P = 0.003$), but not with adiponectin. In multivariate regression analysis TSH weakly

correlated only with IMT after adjustment for age, gender and BMI ($\beta = 0.249$, $P = 0.04$). This relationship weakened after considering lipid profile ($\beta = 0.242$, $P = 0.058$). No relationship was found for fT4. **Conclusion:** Elevated level of TSH in obese children did not seem to impact atherogenic lipid indicators and carotid IMT. Therefore, adverse lipid profile should still be considered the main risk factor for development of cardiovascular disease in obese children.

P2-P950

The Evolution of Thyroid Function after Hashimoto's Thyroiditis Presentation is Different in Initially Euthyroid Girls with or without Turner Syndrome

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Background: Hashimoto's thyroiditis (HT) is the commonest autoimmune disorder in Turner syndrome (TS). Although there are in the pediatric literature many studies on the relationships between TS and HT, only few of them have specifically investigated whether the association with TS might be able to significantly affect the evolution over time of thyroid function in children and adolescents with HT, by conditioning a different thyroid status prognosis. **Objective and hypotheses:** In the present multi-center study we have prospectively investigated, through a 5-yr follow-up, whether thyroid status prognosis of HT is different in euthyroid girls with TS than in euthyroid girls without TS. **Method:** In 66 TS girls (aged between 4.5 and 17.9 yrs) and in 132 non-TS girls (aged between 4.5 and 17.9 yrs) with euthyroid HT and similar thyroid tests at HT diagnosis we followed up the evolution over time of thyroid status. At each annual examination TSH, FT4, thyroid peroxidase and thyroglobulin autoantibodies serum levels were measured. **Results:** At the end of 5-yr follow-up TSH levels were higher and FT4 levels were lower in TS girls. Therefore, at the end of follow-up, TS girls exhibited lower prevalences of both euthyroidism and subclinical hypothyroidism, but higher prevalences of both overt hypothyroidism and hyperthyroidism, irrespective of karyotypes. **Conclusion:** a) the association with TS is able to impair the long-term thyroid status prognosis in girls with HT; b) such effect is irrespective of thyroid function tests at HT diagnosis and is not necessarily linked with a specific karyotype.

P2-P951

Hashimoto's Thyroiditis in Childhood: An 8 Year Experience

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Background: Hashimoto's thyroiditis (HT) is the most common thyroid disorder in the pediatric population. **Objective and Hypotheses:** The aim of the present study was to observe clinical manifestations, clinical course and long term outcomes of HT in children and adolescents. **Method:** A total of 110 children and adolescents who presented to our center from 2008–2015, were evaluated retrospectively. Age and gender of the patients, as well as their complaints at the time of presentation, family history of thyroid disease, concomitant autoimmune diseases, TSH and fT4 levels and ultrasonography findings were reported. **Results:** Of the 110 patients included in the study, 70.9% were female and 29.1% were male (ratio 2.4/1). The mean age of the patients at the time of diagnosis was 10.2 y$\pm$2.6 y. (range 3.3–14.6 y). The most common complaint at presentation was goiter (43.5%), followed by incidental finding (27%) more often due to positive family history, growth retardation (10%), fatigue (7%), gain weight (6%), irregular menstrual cycle (4%), increased appetite (1%) and anaemia (0.5%). Thyroid function impairment and/or goiter were present in the family of 40% of patients. Autoimmune diseases co-existed in 9% (6 subjects diabetes mellitus type 1, 2 celiac disease and 2 alopecia). The prevalence of goiter is statistically significant higher in females. At presentation, the laboratory findings of thyroid function are demonstrated at the table 1. During the follow-up 18% of the euthyroid patients presented subclinical hypothyroidism and were treated. The use of levothyroxine significally decreases the goiter in HT patients. **Conclusion:** HT is more common in female and the complaint strongest referred is goiter. A positive family history of - autoimmune thyroid disease consists a risk factor for hypo-thyroidism or subclinical hypothyroidism and is associated with higher prevalence of HT.

Table 1. Thyroid status of patients at presentation.

	n	%
Hypothyroidism	8	7.3
Subclinical hypothyroidism*	48	43.6
Euthyroidism	52	47.3
Hyperthyroidism	2	1.8
Total	110	100

*TSH > 5 μIU/ml

P2-P952

Congenital Malformations, Dysmorphic Syndromes and Neurodevelopmental Problems in Children with Congenital Hypothyroidism

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Background: A high frequency of extrathyroidal congenital anomalies has been reported in infants with congenital hypothyroidism (CH) detected by neonatal screening. Current ESPE guidelines suggest that congenital malformations, underlying dysmorphic syndromes and psychomotor and language development should be sought for and monitored in CH patients. The identification of co-existing nosologies and malformations is helpful not only for clinical purposes but also for uncovering the underlying genetic defects of CH. **Objective and hypotheses:** To record malformations, dysmorphic syndromes and neurodevelopmental problems in children with CH diagnosed through the Greek neonatal screening program. **Method:** The medical records of CH patients were retrospectively analyzed. Pertinent data (e.g, ultrasonographic data on heart or kidney) were not available in each patient. **Results:** Data of 435 patients were analyzed (54.7% boys and 45.3% girls). Of these patients, 11.5% were born after *in vitro fertilization* and 25% were premature (<37 weeks). Thyroid dysgenesis was present in 17% of patients. Umbilical hernia was present in 12.2%, prolonged jaundice in 43%, cryptorchidism or retractile testes in 17.2% of boys. 13.8% of patients demonstrated a delay in speech or/and in motor development and speech therapy was necessary in 9.5%. A total of 9 patients were diagnosed with mental retardation; of these 7 have Down syndrome. In addition, autism was diagnosed in 2 patients. Severe hearing problems were documented in 4 patients. Of patients with pertinent ultrasonographic data, 5% had unilateral renal agenesis ($n=5$) and 11.5% had severe heart defects ($n=9$). Dextrocardia with situs inversus was found in one patient with thyroid gland size in the low normal limits. Interestingly, his brother has thyroid dysgenesis. **Conclusion:** Our data confirm that thorough physical examination, follow up and a structured diagnostic workup is necessary in children with CH.

P2-P953

Clinical Value of Thyroid-Stimulating Immunoglobulin in Paediatric Autoimmune Thyroid Diseases

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Background: In Autoimmune Thyroid Disease (AITD) two types of TSH receptor antibodies (TSHR-Ab) may be distinguished: thyroid- stimulating immunoglobulin (TSI) that promotes the production of thyroid hormones and thyroid- blocking immunoglobulin (TBI) inhibiting the activity of TSH what leads contrarily to hypothyroidism. **Objective and hypotheses:** The aim of this study was to compare mean TSI and TBI levels in large paediatric cohort with AITD and control. **Method:** A total of 240 serum samples were obtained from 206 paediatric patients with autoimmune diseases: 33 with Graves' disease (GD, 28 female, mean age 13.18 years), 69 with Hashimoto's thyroiditis (HT, 58 female, 13.33 years), 66 with type 1 diabetes (Dt1, 32 female, 13.24 years), 5 with juvenile arthritis (JA, 2 female, 13.8years) and 33 healthy controls (C, 11 female, 11.85 years). A commercial bioassay was used to register TSI level. Results were presented as percentage of specimen-to reference ratio (SRR%, cutoff 140%). TBIs were reported as percentage of inhibition –cutoff 40%. **Results:** Of all GD samples, positive values of TSI were detected in 47/53 (88.7%) whereas TBI was negative in 100%. In HT samples TSI and TBI were noted only in 4/83 (4.8%) and in 1/83 (1.2%), respectively. 2/4 (50%) of positive TSI samples were collected from patients with thyroid-associated orbitopathy (TAO). In GD with TAO samples mean TSI levels (SRR% 416.7) were significantly higher in comparison to group without orbitopathy (SRR% 294.3). Difference between those two groups according to TBI levels was unremarkably. In 2/66 (3%) children with Dt1, TSIs were noted (SRR% 459 and 182). All children with JIA and control group were TSHR-Ab negative. **Conclusion:** These results indicate strong correlation between TSI and GD. Occurrence of orbitopathy associates with TSI's presence both in GD and HT. Higher TSI levels in group with vs. without TAO are observed. TBI's utility seems to be uncertain.

P2-P954

Hearing, Language and Communication Abilities in Children with Congenital Hypothyroidism

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Background: Thyroid hormones are essential in the regulation of foetal and post-natal neurodevelopment. Despite early diagnosis and treatment of congenital hypothyroidism (CH) difficulties with language, hearing, memory and motor function

persist for some children. However, comprehensive data about hearing, language and communication function in children with CH are not widely available. **Objective and hypotheses:** To evaluate hearing, language and communication abilities in a cohort of children diagnosed with CH through newborn screening and treated early. **Method:** Thirty-four children age 6–16 years took part in the study. Sixteen had CH and 18 were typically developing controls (TDCs). Those with CH were identified through newborn screening and had TSH >375 mU/l and $T_4 <$ 3.9 pmol/l at diagnosis. All began thyroxine treatment within the first month of life and remained on treatment at the time of testing. Participants' hearing was evaluated using pure-tone audiometry and speech-in-noise testing. The Clinical Evaluation of Language Fundamentals (CELF-4) was carried out to examine language function. The Children's Communication Checklist (CCC-2) was completed by parents to assess communication. **Results:** Pure tone audiometry revealed hearing losses in three children (19%) in the CH group. One child had a unilateral mild to moderate sensorineural hearing loss and two had bilateral mild high-frequency hearing loss. Speech-frequency pure tone average was significantly better for TDCs as were speech-in-noise results. CELF-4 core language score was poorer for the group with CH and 20% showed evidence of a language disorder. CCC-2 results indicated lower General Communication Composite and higher Social Interaction Deviance Composite scores for the CH group with 38% of children rated has having communication impairment. **Conclusion:** Children with CH scored significantly more poorly on assessments of hearing, language and communication than TDCs. It is important to recognize that children with CH may continue to experience difficulties in several areas of development despite early treatment.

P2-P955

Lack of Catch Up Growth in Severe Hashimoto Thyroiditis (HT) in Young Children

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Background: Profound hypothyroidism due to Hashimoto thyroiditis (HT) is a cause of severe growth arrest in children. Although it is commonly thought that thyroxine replacement fully restores height deficit, no data on catch up growth are available. **Objective and hypotheses:** Assess the growth pattern and final height in a series of 10 patients with severe HT afec L-thyroxine therapy was initiated. **Method:** Monocentric retrospective observational study of 10 children referred for growth failure and diagnosed with severe hypothyroidism between 1999 and 2015. Values are presented as medians (min–max). Individual growth charts will be shown. **Results:** In total of eight girls and two boys aged 8 to 13.5 years at diagnosis of HT were included. HT was diagnosed based on TSH, T4L and anti-thyroperoxydase of 624 [100–1844] mUI/L (*N*:0.5–4), 0.645 [undetectable – 5.4] pmol/L (*N*:10–18) and 18 850 [310 – 25 310) (*N*<34) UI/ml, respectively. Children presented with severe growth failure as shown by the decrease in height SDS before diagnosis from -0.25 [-1; 2] SDS, to -2.9 [-4.7; 1] SDS (<0.0001). L-thyroxine replacement partially improved height SDS up to -2 [-3.8; 0] SDS ($n=9$) then -1 [-2.7; 1] SDS ($n=5$), at 1 and 3 years, respectively. In four children, final height was attained with a median of -1.1 [-2.7; 1.5] SDS. **Conclusion:** Despite the correction of hypothyroidism and improved growth velocity upon treatment, catch up growth is incomplete.

P2-P956

Perinatal Factors Associated with Neonatal Thyroid Stimulating Hormone in Normal Newborns

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Background: Neonatal thyroid stimulating hormone (TSH) is influenced by several factors. But the effects are not consistent but different depending on subjects and kind of blood sample. **Objective and hypotheses:** This study was to evaluate the effect of neonatal, maternal, and delivery factors on neonatal TSH of healthy newborns. **Method:** Medical records of 713 healthy infants born through normal vaginal delivery were reviewed. TSH level obtained by neonatal screening test was analyzed according to the difference of neonatal, delivery, and maternal factors. The relationships between neonatal TSH and free T4 and 17 α-hydroxyprogesterone (17 OHP) were also evaluated. **Results:** Sex, birth weight, and gestational age were not associated with neonatal TSH. Twin babies and neonates born through vacuum extraction had higher TSH levels than controls. There was a significant negative association between TSH level and time interval between birth and newborn screening test. First babies had higher TSH levels than babies of higher birth order. Duration of membrane rupture, Apgar scores and induction times did not influence TSH level. There was no difference in TSH level according to maternal disease such as diabetes, pregnancy induced hypertension, and thyroid disease, nor maternal medication such as insulin, steroid, and thyroid hormone. Neonatal TSH level was not associated with free T4 level but had a positive relationship with 17OHP level. Multiple linear regression analysis also showed that time interval from birth to test, twin baby, birth order, and vacuum assisted delivery influence on neonatal TSH level. **Conclusion:** Neonatal TSH level of healthy normal newborns is related with multiple factors. Acute stress during delivery rather than feedback mechanism of thyroxine may influence the neonatal TSH level in early neonatal period.

P2-P957

TBG Excess as a Cause of Hyperthyroxinemia and High T3 Detected Incidentally or Through Neonatal Screening Test

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Inherited thyroxine binding globulin (TBG) disorder can be identified incidentally or through neonatal screening test. TBG excess is characterized by high levels of thyroxine (T4) but normal level of free T4 (fT4), while TBG deficiency presents with low T4 levels and normal fT4 levels. TBG excess is caused by *TBG* gene duplication or triplication. A 27 day old newborn was brought to the hospital because of hyperthyroxinemia that was identified through neonatal screening test. His mother had no history of any thyroid disease. His fT4 and thyroid stimulating hormone (TSH) levels were 1.99 ng/dL (0.90–2.30) and 4.54 mIU/L (0.50–6.50), respectively. His serum total triiodothyronine (T3) level was 322.50 ng/dL (105.00–345.00). His TBG level was 68.27 mg/L (16.00–36.00), and his thyroid autoantibodies were all negative. At 6 months of age, his serum T3 and T4 levels were 322.10 ng/dL (105.00–245.00) and 16.70 ng/dL (5.90–16.00), respectively. His TSH and fT4 levels were 2.68 mIU/L (0.50–6.50) and 1.71 ng/dL (0.80–2.10), respectively, and his TBG level was 48.77 mg/L (16.00–36.00). At 12 months of age, his serum T3 and T4 levels were 333.30 ng/dL (105.00–269.00) and 21.30 ng/dL (7.30–15.00), respectively. His TSH, free T3 (fT3) and fT4 levels were 2.69 mIU/L (0.60–8.00), 6.48 ng/dL (2.80–5.20) and 1.82 ng/dL (0.80–2.00), respectively. His T3 uptake value was 19.1% (27–37), and TBG level was 50.20 mg/L (14.00–28.00). Hormonal studies showed consistently elevated T3 and T4 levels but normal fT4 and TSH levels. Concentrations of TBG were two to three times higher than normal values. His growth and development were normal. TBG excess is considered a clinically euthyroid condition that requires no treatment. TBG excess should be considered as a potential differential diagnosis for hyperthyroxinemia and especially high T3 levels.

P2-P958

Beta Thallassemia: The Relation between Ferritin and Hypothyroisdism and the Suppressing Effect of Ferritin on Autoimmune Disorders (a Hypothesis)

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Background: Thallassemia is a genetic disease with recessive autosomal pattern of inheritance which occurs as a result of disorders in hemoglobin structure clinicians assess endocrine function in patients with thallassemia in various intervals and distinguishing appropriate time for assessment can decrease the mentioned complications and promote their health. **Objective and hypotheses:** We aimed to investigate the prevalence of hypothyroidism and the relation between thyroid hormones and ferritin in patients with thallassemia major referred to 17 shahrivar hospital. **Method:** This is an analytic cross-sectional study which was conducted on records of patients with thallassemia major aged less than 20 years. All records of patients referred to blood and oncology clinic of 17 shahrivar hospital during January 2012–December 2013 were assessed. Data were gathered by a form including age, sex, weight, height, body mass index, the initiation time of blood transfusion, thyroid test results, and three consecutive hemoglobin and ferritin levels. Mean ferritin and hemoglobin levels were assessed. **Results:** Results showed significant linear correlation between first and mean ferritin with TSH ($P<0.05$) but no significant correlation was noted between levels of ferritin with T4 levels. **Conclusion:** It seems that further investigations may be necessary in patients especially with thallassemia and compare it with normal population.

P2-P959

Thyroid Hormones and Risk Factors in Obese and Overweight Children

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Background: Thyroid stimulating hormone (TSH) and free thyroxine (fT4) levels in children with obesity vary from normal to elevated. Thyroid hormones influence body weight, heart rate, serum lipids as well as carbonhydrates metabolism**. Objective and hypotheses:** The aim of current study is to determine the relation between thyroid function in obese and overweight children and clinical-laboratory parameters which have been associated with increased risk of cardiovascular diseases. **Method:** Thyroid hormone levels (TSH and FT4) of 380 overweight and obese children, aged 3 to 15.5 years old, were measured and correlated with several parameters such as BMI, blood pressure, waist circumference, fasting blood glucose, insulin levels and lipid profile. **Results:** Ten percent of obese and overweight children had elevated TSH levels (>5 μIU/ml). Very weak positive correlation was found between TSH and total cholesterol. Very weak negative correlation was reported between FT4 and BMI, HDL and LDL and moderate negative correlation between FT4 and waist circumference. No significant differences were observed between the other parameters and thyroid hormones. LDL levels were found significantly higher in children who had elevated TSH levels compared to those with low TSH levels. **Conclusion:** High TSH levels are associated with dyslipidemia. In clinical practice, elevated TSH levels can be used as cardio-metabolic risk factor in obese and overweight children. Further studies with greater power are needed to detect the cause and effect relationship between obesity severity and thyroid function in obese children and adolescents.

P2-P960

FNA: A Gold Standard in the Diagnosis of Thyroid Nodules in Children after Chemotherapy

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Background: Non Hodgkin lymphoma (NHL) is the fourth most common malignancy in childhood. Chemotherapy constitutes the first line treatment and may cause several endocrine side effects (growth retardation, hypergonadotrophic hypogonadism, bone mass loss and rarely secondary malignancy). In total of 1–2% of children may harbour thyroid nodules. The most common risk factors are: irradiation, female sex, iodine deficiency, puberty and past medical history of thyroid disease. In children with nodules, thyroid's malignancy incidence is higher than in adults (26.4% against 10% respectively). **Objective and hypotheses:** Report the case of an 11-year-old girl with thyroid malignancy after chemotherapy for NHL. **Patients and Method:** A 7-year-old girl was diagnosed with NHL and underwent chemotherapy until the age of 9years (BFM95 protocol: intensive phase of 6 months with vincristine, cyclophosphamide, aracytin, asparaginase and maintenance phase of 18 months with mercaptopurine and methotrexate). Her 6 months endocrine laboratory and imaging follow-up was normal. At 11 years thyroid ultrasound revealed a sonic mass sizing $1.23 \times 1.0 \times 0.68$ cm with blurred limits and heterogeneous consistency, presenting calcifications and moderate vascularity. A fine needle aspiration biopsy (FNA) revealed a papillary neoplasm. Total thyroidectomy followed and histopathology confirmed the diagnosis of a multi focused, diffused papillary carcinoma. **Conclusion:** While irradiation is a known risk factor of thyroid malignancy, increased thyroid's neoplasm incidence has not been described after chemotherapy. It is known that developing a second malignancy is more frequent in children first diagnosed at a younger age. Younger patients may have a genetic predisposition. Additionally, environmental and epigenetic interactions may contribute to the appearance of both primary and secondary malignancy. Our case emerges the necessity of systematic follow up of the thyroid gland (detailed medical history, physical examination and laboratory exams) for children that underwent chemotherapy. FNA represents the gold standard for diagnosing a thyroid nodule identified through palpation or ultrasound.

P2-P961

Profound Growth Failure in Peripubertal Adolescents Presenting with Severe Acquired Autoimmune Hypothyroidism: A Case Series

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Background: Children with severe hypothyroidism are known to present with significant growth restriction. Institution of treatment with thyroxine (T_4) results in catch-up growth. However, treatment commenced in pubertal period may result in loss of adult height in cases with longstanding severe hypothyroidism. **Objective and hypotheses:** The objective of our study is to evaluate the presentation, investigations and catch-up growth after initiation of treatment with T_4. **Method:** We describe a retrospective case series of three peripubertal girls who presented with severe growth restriction as a result of primary autoimmune hypothyroidism between September 2014 and April 2015. **Results: Case 1**: A 15-year-old girl presented with 1-year history of constipation and short stature, but no history of dry skin, cold intolerance, hair loss or lethargy. Her pubertal staging was B3P3A2M1. Her height SDS was −4.99 and weight SDS was −3.22. Her TPO antibodies were positive. Her bone age was delayed by 5 years. 6 months after starting treatment with T_4, her height SDS improved to −3.83. **Case 2**: A 13-year-old girl presented with 1-year history of cold intolerance, poor growth, low mood and constipation. Her pubertal staging was B3P3A2M1. Her height SDS was −3.23 and weight SDS was −0.61. Her bone age was delayed by 2 years. 6 months after commencing treatment with T_4, her height SDS had improved to −2.69. **Case 3**: A 14-year-old girl presented with dizziness and collapse at school. She also had two-year history of cold intolerance, dry skin and dry hair. Her pubertal staging was B2P2A1M0. Her height SDS was −4.35 and weight SDS was −1.93. Her bone age was delayed by 3.8 years. 6 months after starting treatment with T_4, her height SDS improved to −3.43. TSH was >100 mU/l, Free T4 was undetectable and thyroid ultrasound scan was suggestive of thyroiditis with no nodules in all three girls at presentation. Normal GH reserve was demonstrated in all girls by arginine stimulation test. **Conclusion:** Prompt recognition of hypothyroidism in early childhood is essential to initiate treatment early, so that adult height is not compromised.

P2-P962

Two Patients with Resistance to Thyroid Hormones

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Background: Resistance to thyroid hormone (RTH) is an inherited syndrome characterized by reduced sensitivity of target tissues to thyroid hormone. **Objective and hypotheses:** We describe the clinical, biochemical data and mutation analysis of two patients and their families with (RTH). **Method:** We conducted clinical studies and genetic analysis of these two patients and their families. **Results:** First patient referred to

pediatric endocrinology department for hyperthroidism associated with supraventricular tachycardia and thyroid hormone levels consistent with RTH. We found heterozygous c.962A>G mutation in THRB gene. The mother and siblings of this patient had no mutation in this gene. We could not evaluate this patient's father. Second patient admitted for hyperactivity and referred for the abnormalities in thyroid function tests. We found heterozygous c.1378G>A mutation in THRB gene in this patient and his father and brother. **Conclusion:** Goiter, hyperactivity and tachycardia are the most common clinical features in the patients with RTH syndrome. Diagnosis of RTH depends on the characteristic elevations in thyroid hormone and the exclusion of other causes of hyperthyroxinemia.

P2-P963

The Influence of Etiology and Treatment Factors on Intellectual Outcome in Congenital Hypothyroidism

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Background: Congenital hypothyroidism (CH) is the one of the most common preventable cause of mental retardation. Earlier and proper treatment is associated with better intellectual outcomes. **Objective and hypotheses:** The aim of the present study was to evaluate intellectual outcome of children with diagnosed congenital hypothyroidism (CH) and early onset treatment. **Method:** We retrospectively reviewed the medical record of 43 children of diagnosed CH. Children aged between 5 and 7 years were examined with the Korean Wechsler Intelligence Scale for Children or the Korean Wechsler Preschool and Primary Scale of Intelligence. **Results:** Of the 43 children included in this study, 22 (51.2%) were female and 21 (48.8%) were male with a female:male ratio of 1.047:1. Treatment with levothyroxine was started after mean of 27 days (range 13–60 days). K-WISC-III for intellectual outcome was performed at mean age of 5.9 years (range 5–7.6). Our patients achieved a mean IQ score of 103.13; mean verbal IQ was 99.02 and mean performance IQ was 104.81. None of them had intellectual disability (defined as an IQ <70). IQ scores of children with CH were not significantly associated with clinical variables, including gestational age, birth weight, pretreatment free T_4, TSH, age, and initial dose for levothyroxine. **Conclusion:** Our study demonstrates that children with CH received proper treatment did not affect their IQ scores.

P2-P964

An Unusual Complication of Graves' Disease

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Background: Atrioventricular (AV) conduction defects are rare but significant complications of hyperthyroidism. Beta-blockers and co-existent infection further increase the risk of such conduction abnormalities. **Objective and hypotheses:** We report the case of a 10-year old girl treated for tachycardia and hypertension associated with hyperthyroidism who developed symptomatic 2:1 heart block. **Method:** Our patient presented with a history of nausea, sore throat, pyrexia and chest pain 2 days after starting daily atenolol 32 mg (1 mg/kg per day) and carbimazole 40 mg. On examination, she appeared thyrotoxic, with inflamed tonsils and mild abdominal discomfort. A baseline bradycardia with sudden symptomatic episodes of self-limiting bradycardia to 28–45 beats per minute and hypotension to 57/43 mmHg was noted. The 12-lead electrocardiogram (ECG) identified 2:1 atrioventricular block with prolongation of the P-R interval (317 ms). Biochemistry confirmed hyperthyroidism (free T_4: 42.4 pmol/l, free T_3: 8.9 pmol/l, TSH <0.01 mlU/l) with white cell count: 13.7, neutrophils: 8.2 and C-Reactive Protein: 43. Echocardiogram showed no evidence of structural heart disease. She was admitted for cardiac monitoring; atenolol was discontinued, carbimazole was reduced to 10 mg twice daily and a 10-day course of oral phenoxymethylpenicillin for suspected tonsillitis was started. She was discharged after 48 h. **Results:** Repeat ECG before discharge revealed resolution of 2:1 atrioventricular block with persistent P-R prolongation (240 ms). Four months after presentation, and following an increase in carbimazole dose to 40 mg daily, there is improvement in thyroid function (free T_4: 14.3 pmol/l, free T_3: 9 pmol/l, TSH <0.01) and Graves' disease has been confirmed. Repeat electrocardiogram showed a normal heart rate and a P–R interval of 185 ms. Hypertension is still present and she remains under endocrine follow up. **Conclusion:** In view of this well-described association, we would recommend that a baseline 12-lead electrocardiogram is performed to look for evidence of AV conduction abnormalities before initiating beta-blocker therapy in children with hyperthyroidism.

P2-P965

An Unusual form of Precocious Puberty: Van Wyk and Grumbach Syndrome

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Introduction: The association of precocious puberty and/or polycystic ovaries, delayed bone age and hypothyroidism is known as the Van Wyk and Grumbach syndrome (VWGS). Clinically this syndrome is a diagnostic challenge because hypothyroidism usually leads to pubertal and growth delay, whereas in case of VWGS hypothyroidism it leads to growth delay and precocious puberty. We report a boy with long-standing, untreated hypothyroidism who presented with precocious puberty. **Case Report:** A boy aged 7 years and 4 months who had been followed

for congenital hypothyroidism in another hospital presented to our clinic for follow up. His medical history revealed congenital hypothyroidism diagnosis and irregular levothyroxine treatment since his birth. There was no compliance to levothyroxine treatment and the patient did not take his medication for last 7 months. He was born of nonconsanguineous marriage at full-term, normal vaginal delivery. His birth weight was 3.75 kg and he had normal gross motor development. There was no history of headache, vomiting, visual symptoms, and gelastic seizures. Physical examination revealed obesity with height 113 cm (−1.9 SDS, target height of 159 cm) and weight 30.5 kg (1.4 SDS), body mass index 23.8 (>95 p). His pulse rate was 78/min and blood pressure 98/60 mmHg. He had dry scaly skin. There was no goiter. There was no axillary hair and pubic hair was Tanner stage 1. Stretched penile length was 5 cm and testicular volume were 6 ml bilaterally. Levels of TSH were elevated (443 mIU/l, normal range 0.35–4.94 mIU/l) and levels of free thyroxin (fT_4) were decreased (fT_4 0.43 ng/dl, normal range 0.7–1.48 ng/dl). Basal gonadotropin levels were pre-pubertal as FSH: 0.35 mIU/ml (N, 1.37–13.5), LH: 0.09 mIU/ml (1.14–8.75) and total testosteron: <0.45 nmol/l. Serum prolactin level was 18.8 ng/ml (N, 2.58–18.12) and bone age was 4 year according to Greulich and Pyle's atlas. Peak LH and FSH response to intravenous LHRH was prepubertal as 4.1 and 1 mIU/ml, respectively. Visual acuity and fields and hypophysis magnetic resonance imaging were normal. The Van Wyk and Grumbach syndrome was diagnosed based on the co-occurrence of hypothyroidism, precocious puberty and delayed bone age. After levothyroxine therapy serum thyroid hormone levels normalized in 2 months. In conclusion, we report a boy with severe hypothyroidism presented with early puberty. VWGS should be kept in mind in patients with hypothyroidism, early puberty and delayed bone age.

P2-P966

Clinical Features of Newborn with Congenital Hypothyroidism Diagnosed by Neonatal Screening: Single Center Experience

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Background: Congenital hypothyroidism (CH) is the most important cause of preventable mental retardation. Therefore, screening programme has been using for early detection of hypothyroidism in our country since 2007. **Objective:** To compare clinical features of newborns with and without CH who were detected in screening programme between 2009 and 2014. **Method:** This study enrolled 710 (344 Girls) newborn referred from CH-screening programme to our clinic. All newborns were examined. Serum TSH and fT_4 levels were obtained from all newborns. L-Thyroxin was prescribed and thyroid ultrasonography was performed in newborns with hypothyroidism. According to admission time to clinic, they were classified into three groups: ≤30 days, 31–90 days, ≥91 days. **Results:** Group 1 consisted of 489 newborns, group 2 consisted of 181 newborns and group 3 consisted 40 newborns. Median age was 23 (18) days in study-population. CH was diagnosed in 17.4% of study-population. Neonatal TSH was 36.7±31 IU/l in newborn with (NBw) CH. There was a significant delay (2.27±1.4 month) in the normalization of serum TSH in NBwCH. There was no difference between birth weight of NBwCH and without CH. Of the 79.3% NBwCH was diagnosed in first month. Serum TSH was 17 (34.45) and fT_4 was 0.82 (0.54). LT_4 was prescribed mean 32±22 days. Ultrasonography showed that athyreosis 7%, hypoplasia 66%, 24% eutopic. Mean L-thyroxin dose was 9.3±2.3 μg/kg in athyreotic newborns, 7.6±3.1 μg/kg in hypoplasia group, and 7.0±2.0 μg/kg in eutopic group respectively. Birth weight was correlated with fT_4 (r: −0.230) in NBwCH. LT_4 dose was significantly correlated with serum TSH (r:0.505) and fT_4 (r: −0.230). **Conclusion:** Our study shows that all NBwCH are not diagnosed before than first months. Deterioration of cognitive function can be seen in untreated children with CH. Presence of high neonatal TSH in screening, serum TSH should be obtained and treatment should be initiated as soon as possible.

P2-P967

Postoperative Complications of Thyroidectomy in Children with Nodular Goiter

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Background: Objective and hypotheses: Rate the frequency and structure of post-operative complications of thyroidectomy in children with nodular goiter. **Method:** Twenty-seven children, 20 girls (14.5±3.64 years) and seven boys (14.68±4.09 years), which were performed thyroidectomy about multinodular goiter (n=23) and single-node goiter (n=4) from 2003 to 2015. Were evaluated complaints of patients, physical examination, biochemical blood test, electrocardiography data, fibrolaryngoscopy. As a biochemical marker of postoperative hypocalcaemia considered values of Ca^{2+} in blood serum: 1.03–0.9 mmol/l-mild; 0.8–0.9 mmol/l-moderate, <0.8 mmol/l-severe hypocalcaemia. **Results:** The frequency of postoperative complications was 26% (7/27): five girls and two boys (14.63±3.4 years). Complications have presented hypocalcaemia, and vocal cord dysfunctions. Vocal cord dysfunctions were diagnosed in 4% (1/27) – girl 11.69 years old, healed after 3 months. Diagnosed with hypocalcaemia 22% (6/27) of patients (67% (4/6) girls, 16.11±1.23 years, and 33% (2/6) boys (13.12±6.53 years) were occurred in the first days after thyroidectomy, and demanded treatment. The asymptomatic hypocalcaemia has observed in 17% (1/6)-girl. The symptomatic hypocalcaemia – in 83% (5/6) patients, in this group of children 80% (4/5) of them had the QT interval prolongation in their electrocardiogram (Me0.02[0.01;0.035] s). In case of 67% (4/6) patients Ca^{2+} 0.96±0.04 mmol/l. In case of 33% (2/6) patients Ca^{2+} 0.84±0.03 mmol/l. In case of 17% (1/6) patients hypocalcaemia are persistent (more than 6 months), and in case of 83% (5/6) patient–transient character–duration of

hypocalcaemia was observed from 7 to 30 days (Me 10[10; 18] days). Differences in volume of thyroid in patients with postoperative hypocalcaemia (Me16.99[9.84;24.63] cm^3) and normocalcaemia (Me19.6 [16.58;24.14] cm^3) weren't found ($p > 0,05$). In addition, there wasn't difference by rating of compression syndrome in the same treatment groups. So among the children with postoperative hypocalcaemia compression syndrome in 4/6 children, and among the children with normocalcaemia – in 10/21 children ($P > 0.05$). **Conclusion:** After thyroidectomy conducted over nodular goiter, vocal cord dysfunctions rare complication, hypocalcaemia occurs in every fifth child and is transient. In relation, it is necessary to search for predictors of postoperative hypocalcaemia in the preoperative stage during thyroidectomy, and find out the control of calcium and parathyroid hormone levels in blood serum in postoperative phase, starting from the first day.

P2-P968

Peculiarities of Course and Therapy of Basedow–Graves' Disease in Children in Different Age Groups

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Suitably treatment of Basedow–Graves' disease (BGD) provide the minimization of time to develop the medicamental remission. Research: determine clinical, laboratory particularities, evaluate efficiency of pharmaceutical treatment of BGD in children in different age groups. Materials and methods: 35 children with BGD were examined (4 boys, 31 girls): 1st group (Tanner 1) $n = 4$, 7.5 ± 0.65 years; 2nd – (Tanner 2–4) $n = 22$, 12.32 ± 0.31 years; 3rd – (Tanner 5) $n = 9$, 15.56 ± 0.24 years. Data of laboratory research (free thyroxine (FT_4); TSH; thyroid peroxidase antibodyies (TPOAb); TSH receptor antibodies (TRAb)), thyroid gland's ultrasound were analysed. Methods of variation statistics were used in statistical processing of results. **Results:** Increase of thyroid gland was marked in children with BGD in manifestation: 1st – $172.75 \pm 19.52\%$, 2nd – $169.59 \pm 13.2\%$, 3rd – $117.74 \pm 6.89\%$, $P < 0.05$. Elevation of FT_4 levels (pmol/l) (1st – 95.51 ± 27.61, 2nd – 57.9 ± 5.97, 3rd – 71.94 ± 22.57; n 10.0–23.2; $P < 0.05$), TPOAb (ME/ml) (1st – 168.75 ± 78.89, 2nd – 477.79 ± 105.25, 3rd – 827.57 ± 178.3; $n < 30$; $P < 0.05$), TRAb (ME/ml) (1st – 15.65 ± 2.5, 2nd – 18.47 ± 1.28, 3rd – 12.53 ± 0.61; $n < 4$; $P < 0.05$), decrease TSH values (uME/ml) (1st – 0.03 ± 0.01, 2nd – 0.04 ± 0.01, 3rd – 0.03 ± 0.01; n 0.25–5.0; $P < 0.05$) were revealed in manifestation. Block-regimen treatment was used. Initial dose of antithyroid drug (Thiamazole) (mg/kg per day): 1st – 0.86 ± 0.06, 2nd – 0.55 ± 0.05, 3rd – 0.43 ± 0.04, $P < 0.05$. Maintenance dose of Thiamazole (mg/kg per day): 1st – 0.22 ± 0.04, 2nd – 0.19 ± 0.02, 3rd – 0.12 ± 0.02, $P < 0.05$. Duration of treatment (years): 1st – 3.25 ± 0.85, 2nd – 2.89 ± 0.32, 3rd – 1.33 ± 0.24, $P < 0.05$. Control values of FT_4 in remission (pmol/l) (1st – 13.33 ± 1.68, 2nd – 15.32 ± 3.34, 3rd – 15.58 ± 1.25, $P < 0.05$), TSH (uME/ml) (1st – 3.75 ± 0.98, 2nd – 3.32 ± 0.64, 3rd – 2.6 ± 0.68, $P < 0.05$), TPOAb (ME/ml) (1st – 1.4 ± 0.21, 2nd – 2.26 ± 0.16, 3rd – 2.36 ± 0.4, $P < 0.05$). Negative correlation between patient's age and Thiamazole dose was found ($r = -0.39$, $P < 0.05$). Conclusions: more higher doses of antithyroid drug were used in the period of manifestation and medication remission of disease in prepubertal children compared to patients with Tanner 2–5; longer term of pharmaceutical treatment need to prepubertal children's recovery comparison to pubertal aged patients.

P2-P969

An Unusual Presentation of Hashimoto Thyroiditis (HT) and Precocious Puberty: The Van Wyk-Grumbach Syndrome

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Background: The association of primary hypothyroidism and isosexual precocious pseudopuberty in females was first described in 1960 by Van Wyk and Grumbach. The unique elements that lead to the diagnosis are FSH-dominated sexual precocity with non advanced bone age in the presence of hypothyroidism. **Objective and methods:** Describe an 8.5 years old girl with hypothyroidism due to HT and clinical and hormonal features of Van-Wyk and Grumbach syndrome. **Case report:** An 8.5 years girl was referred to the endocrinology department with a suspicion of precocious puberty. She had no history of visual disturbance or headaches but was overweight for her height. On examination her height was 130.6 cm (50th centile), mid-parental height target was 159.5 (25th centile) her weight was 30 kg (75th centile) and she had breast development Tanner's stage 2–3 with no pubic or axillary hair development. Hormonal investigations revealed high TSH levels at 32.46 μIU/ml (0.4–5) with low FT_4 levels at 0.98 ng/dl (0.9–1.9) and positive thyroid peroxidase and thyroglobulin Abs (379.2 IU/ml (< 16) and 543.6 IU/ml (< 100) respectively), which confirmed HT. LHRH testing showed an FSH-dominated, prepubertal response with a 0–60 min FSH rise from 2.17 to 6.01 mIU/ml and an LH rise from 0.38 to 2.54 mIU/ml. Oestradiol levels were at 40.7 pg/ml (< 27). Additional hormonal tests showed PRL levels at normal high range at 21.8 ng/ml (4.8–23.3) and normal testosterone: 2 ng/dl (2–20), DHEA-S: 69 μg/dl (2.8–85.2), 17-OHPRG: 0.57 ng/ml (0.2–0.5), β-HCG: < 1 U/lt (< 5) and α-FP levels: < 2 ng/ml (< 15 ng/ml). A pelvic ultrasound revealed a pubertal uterus ($37 \times 10 \times 20$ mm) and multicystic ovaries (RO: 5.4cc, LO:4.5cc) with multiple dominant follicles. In contrast to the pubertal Tanner stage 2–3 and the ultrasound appearance, the bone age was found to be equal to her chronological age. Thyroxine treatment was started at low dose of 25 μg/day and increased gradually to 50 μg/day. Clinical, hormonal and ultrasound findings returned to normal without additional therapy. **Conclusion:** Autoimmune thyroiditis, although usually predisposes to delayed puberty it may also lead to isosexual precocious pseudopuberty. Recognition of this syndrome is important because thyroid hormone substitution completely resolves symptoms and hormonal abnormalities.

P2-P970

Rare Case of Severe Hyperthyroidism due to Grave's Disease in a Female Toddler

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Background: Hyperthyroidism due to Grave's disease (GD) in children has a peak incidence between 10 and 15 years of age. It is a rare but serious disorder that if uncontrolled can have serious adverse outcomes on growth and development as well as health. The incidence of GD is believed to be between 0.1 and 3 per 100 000 children in the general population with a prevalence of 1/10 000 children in the US. GD is rare under the age of 5 years. **Objective and hypotheses:** To determine the etiology of a 2 year old female presenting to the ER with 1 day history of fever and lip swelling, as well as diarrhea, emesis, throat pain, and tachycardia. Hyperactivity, difficulty sleeping and tremors had been noted more recently. Parent noted a 'lump' the size of a golf ball appeared suddenly. Goiter appreciated on exam measuring 8 cm across and 5 cm vertically. I believed this to be acute, subacute, or autoimmune hyperthyroidism – Hashitoxicosis vs Grave's disease. **Method:** To obtain thyroid function tests, thyroid antibodies, ESR and thyroid ultrasound and follow serial tft's longitudinally. **Results:** TSH = 0.005 μU/ml, FT_4 = > 7.77 ng/dl (nl < 1.6), TT3 = 651 ng/dl (High), TT4 = 27.2 μg/dl (4.5–12.0), TGAB < 20 IU/ml, TPO AB = < 6 IU/ml, TSI = 252 (nl < 140), ESR = 6 (0–32). Thyroid ultrasound revealed enlarged thyroid gland bilaterally. Patient started on atenolol for symptom control and methimazole initially at 2.5 mg qd with peak dosing of 7.5 mg qd, with improving thyroid hormone values, however still remaining hyperthyroid until after 7 months of treatment, when she became euthyroid. **Conclusion:** Given severe protracted hyperthyroidism and highly positive TSI antibodies, patient diagnosed with autoimmune Grave's hyperthyroidism. To my knowledge, this is the youngest documented case of a female toddler with such severe autoimmune hyperthyroidism.

P2-P971

Youngest Known Case of Autoimmune Thyroiditis Causing Hyperthyroidism in a Down's Syndrome Toddler

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Background: The frequency of thyroid disease is elevated in patients with Down's syndrome starting in the newborn period where it is 0.7% (28× more frequent than in the general population). Most commonly, thyroid dysfunction in Downs Syndrome includes primary hypothyroidism, pituitary–hypothalamic hypothyroidism, TBG deficiency and chronic lymphocytic thyroiditis. The incidence of Grave's disease is believed to be between 0.1 and 3 per 100 000 children in the general population. Autoimmune thyroid disease is uncommon in young children with Down's syndrome less than 8 years of age with hyperthyroidism being quite rare. **Objective and hypotheses:** To determine if yearly screening labs done on a 15 month old female with Down's syndrome who has a strong family history of autoimmune thyroid disease with initial lab values of TSH = 5.77 and FT4 = 1.77 is due to Hashimoto's thyrotoxicosis, Grave's hyperthyroidism or transient. My hypothesis was that this was due to autoimmune thyroiditis given the elevated FT4 and strong family history. **Method:** To obtain thyroid stimulating immunoglobulins, thyroglobulin antibodies and thyroid peroxidase antibodies and to observe TSH and FT4 over time for progression. **Results:** Lost to follow up until age 21 months when labs obtained: TSH = < 0.001 μU/ml, FT4 = 2.25 ng/dl (nl < 1.6), TT3 = 215 ng/dl (High), TT4 = 16.4 μg/dl (4.5–12.0), TGAB < 20 IU/ml, TPO AB = 167 IU/ml (nl < 9), TSI = 284 (nl < 140). Patient started on methimazole 2.5 mg qd with labs 2 weeks later showing a TSH < 0.001 and FT4 of 2.52. Methimazole increased to 5 mg qd. **Conclusion:** Given progression of hyperthyroidism over a 6.5 month time course even after starting on methimazole, in a patient with highly positive TSI antibodies, this is very likely to be autoimmune hyperthyroidism caused by Grave's disease. To my knowledge, this is the youngest known patient with DS to have autoimmune hyperthyroidism to date. Family history of autoimmune disease may make DS patients even more susceptible to development of autoimmune thyroiditis at an earlier age.

P2-P972

Thyroid Hormones in Obese Children

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Background: Nowadays, childhood obesity is one of the biggest health emergencies in the developed countries. Obesity leads to multiple metabolic disorders. Thyroid function has been often described as altered in obese children. However, it is not clear whether the thyroid dysfunction is the cause or the consequence of the fat excess. **Objective and hypotheses:** The aim of the current study was to examine the thyroid function and to assess the frequency of thyroid dysfunction in obese children and adolescents. **Method:** TSH, T4, anti-TPO, anti-TG levels were determined in 119 obese pediatric patients as well as in a control group of 120 normal weight children (same age group). **Results:** Median values of TSH and T4 levels in obese children were normal, but significantly higher compared to those of normal weight. In addition, statistically significant correlation has been noticed between thyroid hormones concentrations and BMI *z*-scores of obese children. Elevated TSH (> 5 μIU/ml) with normal thyroxin level and negative antithyroid antibodies were detected in 5.5% of obese children but only in 0.7% of the control group, while subclinical hypothyroidism with positive antithyroid antibodies was reported in 7.2% of obese children contrary to 3.5% of control sample. Moreover, decrease of T4 levels was observed in 47.6% of obese children that had a significant weight loss ($P < 0.01$, Wilcoxon test). **Conclusion:** Thyroid hormones are increased in obese children and weight reduction seems to result in a decrease of their levels. A high prevalence of autoimmune thyroiditis is observed among the population of obese children.

P2-P973

A Case of Neonatal Graves in a Premature Infant with Negative Thyroid Stimulating Immunoglobulins (TSI)

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Background: Neonatal hyperthyroidism is almost always transient and related to the passage of maternal thyroid stimulating immunoglobulins (TSI). Positive TSI levels in a neonate is often diagnostic of neonatal Graves disease. The manifestation of symptoms has not been well characterized in premature infants. **Clinical Case:** A female infant was delivered at 27×4/7 weeks gestational age, with a birth weight of 827 g. Her mother was diagnosed with Graves disease 2 weeks prior to delivery, but was not started on any medications. Thyroid function tests obtained on the infant on DOL 2, showed a low TSH of 0.003 μIU/ml and normal FT4 of 1.4 ng/dl. TSI levels were negative. By DOL 7, the infant developed tachycardia. Repeat labs revealed a TSH of 0.005 μIU/ml and FT4 of 4.3 ng/dl. Methimazole was started at 0.4 mg/kg per day, as well as propranolol at 0.5 mg/kg per day divided into three doses. Four days after methimazole was started, TSH remained low, but FT4 normalized to 1.3 ng/dl and tachycardia resolved. By DOL 14, elevated liver enzymes led to discontinuation of methimazole. On DOL 18, tachycardia reoccurred, and FT4 had again increased to 4.7 ng/dl. TSI was again negative and liver enzymes had normalized. Methimazole and propranolol were restarted at lower doses (0.25 mg/kg per day and 0.4 mg/kg per day respectively). Within 3 days of therapy, FT4 normalized to 1.3 ng/dl. Other studies revealed a high thyroglobulin level of 131.9 ng/ml (2.8–40.9), negative thyroglobulin antibodies, high anti-TPO antibodies of 37.4 IU/ml and high thyrotropin receptor antibodies at 40% (normal<17%). Methimazole was continued for 7 weeks. FT4 remained normal, and TSH continued to be suppressed. By DOL 45, methimazole was stopped. Repeat labs done 1 week later showed a TSH of 0.013 μIU/ml and FT4 1.3 ng/dl. Thyrotropin receptor antibody was 20% at that time. Methimazole was restarted at 0.15 mg 3 times/week. One week later, she had a TSH of 0.022 μIU/ml and FT4 of 1.0 ng/dl. Methimazole was discontinued. **Conclusion:** This patient had TSI-negative neonatal Graves that was very sensitive to methimazole. The suspected cause for this infant's neonatal hyperthyroidism was the thyrotropin receptor antibodies, stimulating the TSH receptor. Patient's FT4 normalized almost immediately after starting methimazole. It was not until her thyroid receptor autoantibody levels declined that methimazole could be discontinued. In TSI negative patients with suspected Graves disease, another lab study to be considered would be thyrotropin receptor antibody.

P2-P974

Severe Growth Retardation and Hypothyroidism due to Hashimoto's Thyroidits

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Background: Hashimoto's thyroiditis is a common autoimmune disease in pubertal and adolescent girls. In the past years the incidence of this autoimmune disease of the thyroid gland has increased. **Objective and hypotheses:** We present a 12.5 year old girl who had her first visit at our Pediatric Endocrinology Department at the age of 10 years due to short stature and clinical signs of hypothyroidism. Her height was – 3SD SDS and her BMI was 12.7. The initial clinical examination showed an enlarged and firm thyroid gland. The ultrasound of the thyroid gland was consistent with Hashimoto's thyroiditis. **Method:** Levels of thyroid hormones and anti-TPO antibodies were measured. Her thyrotropin levels were >75.0 μIU/ml (0.400–4.5 μIU/ml). Her thyroid peroxidase antibodies were >1000 IU/ml (10–50 IU/ml) and total T4 levels were 87.1 μmol/l (71.2–141 umol/l). Her bone age was appropriate for an 8 year old, she also had a normochromic anemia and hyperlipidemia. **Results:** Treatment was started with L-thyroxine 100 $\mu g/m^2$ and 6 months after the commencing of the treatment the thyroid hormone levels normalized, even though the level of the anti-TPO antibodies remained elevated. She started to grow and her height reached μ1.5 S.D. After 2 years of treatment her height is within normal range (+1.0 S.D.) **Conclusion:** The regular follow-up continues for possible further complications.

P2-P975

Beta Thallassemia: the Relation between Ferritin and Hypothyroisdism and the Suppressing Effect of Ferritin on Autoimmune Disorders (a Hypothesis)

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Background: Thallassemia is a genetic disease with recessive autosomal pattern of inheritance which occurs as a result of disorders in hemoglobin structure clinicians assess endocrine function in patients with thallassemia in various intervals and distinguishing appropriate time for assessment can decrease the mentioned complications and promote their health, we aimed to investigate the prevalence of hypothyroidism and the relation between thyroid hormones and ferritin in patients with thallassemia major referred to 17 shahrivar hospital. **Method:** This is an analytic cross-sectional study which was conducted on records of patients with thallassemia major aged less than 20 years. All records of patients referred to blood and oncology clinic of 17 shahrivar hospital during Jan 2012–Dec2013 were assessed. Data were gathered by a form including age, sex, weight, height, body mass index, the initiation time of blood transfusion, thyroid test results, and 3 consecutive hemoglobin and ferritin levels. Mean ferritin and hemoglobin levels were assessed. **Results:** Results showed significant linear correlation between first and mean ferritin with TSH ($P<0.05$) but no significant correlation was noted between levels of ferritin with T4 levels. **Conclusion:** It seems that further investigations may be necessary in patients especially with thallassemia and compare it with normal population.

P2-P976

Severe Hyponatremia and Repeated Intestinal Resections for Intestinal Dysmotility Mimicking Congenital Aganglionic Megacolon due to Delay in the Diagnosis of Congenital Hypothyroidism

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Background: Congenital hypothyroidism (CH), the most common preventable cause of mental retardation in children, may presents with non-specific signs and symptoms. Beside, majority of the infants can be asymptomatic. Underestimation and/or misdiagnosis may cause delay in diagnosis and results in severe complications. **Case report:** A 5 months-old female admitted to our clinic with the history of repeated surgical operations due to the diagnosis of congenital aganglionic megacolon. Investigations performed in our clinic revealed a diagnosis of congenital (primary) hypothyroidism due to thyroid agenesis. Histopathologic evaluation of previously resected colon sample showed a normal ganglionic cell included colon. During follow up she developed severe hyponatremia with a plasma sodium level of 106 mEq/l. Hyponatremia was first corrected using saline infusion, whereas, eunatremia can be maintained following achievement of euthyroid state. Hormonal and biochemical work up did not show any specific etiology for hyponatremia. Therefore, hyponatremia was suggested to be due to hypothyroidism. **Conclusion:** Since presenting symptoms are variable and non-specific, for prompt diagnosis and proper management, congenital hypotyhroidism should be kept in mind in the differential diagnosis of neonates with persistent abdominal distention mimicking aganglionic megacolon and severe hyponatremia of unknown origin.

P2-P977

Very Early Onset of Autoimmune Thyroiditis in a Toddler with Multi-organ Involvement

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Background: In infants under 3 years of age acquired primary hypothyroidism caused by autoimmune thyroiditis is very rare. Hypothyroidism can manifest with different signs and symptoms and has a wide range of presentations from subclinical hypothyroidism to overt form. **Objective and hypotheses:** We describe a child with an unusual hypothyroidism presentation characterized by multi-organ involvement and related to acquired autoimmune thyroiditis during a very early period of life. **Method:** A 22-month-old white male patient with normal neonatal screening presented with a 6-month history of asthenia and cutaneous pallor. At general clinical and biochemical exams he showed weight gain, statural growth deceleration, poor movements, sleepy expression, instability while walking, myxoedema, bradycardia, open anterior fontanelle, changes in the face habitus, macrocytic anaemia, ascites, and high CPK, creatinine and cholesterol levels. **Results:** TSH, free thyroxine (fT_4), free triiodothyronin (fT_3) were >200 μIU/ml, 1.39 and 0.5 pg/ml, respectively. The levels of thyroid peroxidase antibodies and thyroglobulin antibodies were high (2017 and 1743 IU/l, respectively); sonographic thyroidal evaluation demonstrated normal anatomy with non-homogeneous echotexture. Because the neonatal screening for congenital hypothyroidism was normal, a diagnosis of hypothyroidism related to autoimmune thyroiditis was determined. The thyroxin replacement therapy normalized all the clinical and biochemical abnormalities. **Conclusion:** Our case could give useful learning points: i) hypothyroidism can have a misleading and multi-face clinical presentation; ii) anemia, rhabdomyolysis and high creatinine levels should always include the hypothyroidism in the differential diagnosis; iii) thyroxine replacement therapy is able to revert all the clinical manifestations related to the hypothyroidism; iv) evaluating the patient's previous pictures could play an important role in resolving a diagnostic conundrum.

P2-P978

A Case of the Thyroid Gland Dystopia in the Root of the Tongue

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Background: Dystopia thyroid is an anomaly of development and is the result of a violation of embryogenesis and often remains unrecognized, the true frequency of the dystopia of the thyroid gland is not known, described 800 cases of ectopic thyroid gland in the region of blind holes of the tongue in adults and 80 cases in children, half of them diagnosed congenital hypothyroidism. **Objective and hypotheses:** To reveal some features in the diagnosis and treatment of the ectopic thyroid in children. **Methods:** A female child of 9 years with the nodal goiter in the family history was under observation. Physical development, ultrasound investigation data (UID) and standard laboratory tests – thyrotropic hormone (TTH), free thyroxin (T_4), thyroid peroxidase antibodies (a/b to TPO), were measured in the dynamics of observation. **Results:** A dense reddish formation on a broad foot ($3.0\times4.5\times3.0$ in size), well vascularized, located anterior from vallecula, without fur has been found in the base of the tongue. Complaints: difficulty in swallowing solid food, pallor and dry skin, deep voice, bradycardia, tendency to constipation. Ultrasound investigation has established some changes in the thyroid ehostructure, its small size – 2.3 cm^3 (normal size 4.5–6.8 cm^3). Measurements: TTH – 16.77 mIU/l (normal findings

0.5–3.5 mIU/l), free T_4 – 11.3 pmol/l (11–21 pmol/l norm), and antibodies to TPO 19.64 IU/ml (30 IU/l norm). Hypothyroidism has been diagnosed in the patient. Replacement therapy with thyroid hormones in a dose of 75 mg per day has been prescibed. After 6 months noted positive dynamics of goiter size – the formation of the tongue has decreased to 1.5×2×1.5 cm, the complaint disappeared. The girl grows and develops according to age, the dose of T_4 in the 3 years of observation is increased to 100 mg per day, TSH level of 1.5 mIU/ml. **Conclusion:** Dystopic thyroid gland diagnosed in prepubertal girls, which was accompanied by an increase in the size of goiter and hypothyroidism. The treatment with thyroxine size of the crop of the tongue decreased.

P2-P979

Conversion of Hypothyroidism to Hyperthyroidism in A Child with Down's Syndrome

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Background: Patients with Down's syndrome have an increased prevalence of autoimmune disorders affecting both endocrine and non endocrine organs. The commonest autoimmune disease is related to the thyroid gland. **Objective and hypotheses:** To describe a child with down's syndrome who has been treated of hypothyroidism But converted to hyperthyroidism few years later. **Method:** A 5-year old boy with Down's syndrome presented with constipation, easy fatigability and cold intolerance. A clinical suspicion of hypothyroidism was considered, confirmed by a high serum (TSH) level (25.63 mU/l), and a low Free thyroxine (FT_4) of 8.2 pmol/l. Levothyroxine was prescribed. Requirement for levothyroxine gradually decreased, TSH levels became below 0.01 mU/l, and FT_4 was increasing (44.69 pmol/l). Child also developed symptoms and signs of hyperthyroidism, so levothyroxine was finally stopped. But the child kept irritable and restless. His TSH was less than 0.01 mU/l, FT_4 level still high(45.31 pmol/l). TSH-receptor antibodies (86.9 IU/l) and thyroid peroxidase antibody (386.46 IU/ml). Thyroid ultrasonography showed increased vascularity. thyroid scan showed a bit enlarged thyroid gland with no scintigraphic evidence of gross nodularity, with elevated thyroid uptake (6.1%). Therefore, the diagnosis of Grave's disease was settled and carbimazole started. The child's was followed-up every 3 months till present and he is stable clinically with normal TSH and FT4. **Results:** In this case report, we presented a boy with Down's syndrome who developed hyperthyroidism after few years of established hypothyroidism. The condition kept euthyroid on therapy for few years. However, when he developed hyperthyroidism, levothyroxine was gradually stopped. The child remained hyperthyroid after stopping levothyroxine. Therefore, anti-thyroid treatment was started. **Conclusion:** The presence of different antibodies specific to Hashimoto's and Graves' disease, puts the thyroid into a push–pull situation (hypo- or hyperthyroidism).

P2-P980

Transient Congenital Hypothyroidism: About Six Cases

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Background: Transient neonatal hypothyroidism (T N HT) is a rare entity important to recognize. It is due to placental transfer of antibodies antirécepteurs of pituitary TSH. It is distinguished from permanent congenital forms of hypothyroidism, because it requires only limited substitution treatment in time. **Objective and hypotheses:** Report the observations of 6 children who presented T N HT. **Method:** This is a retrospective study of six children(with two brothers) hospitalized for suspiscion of hypothyroidism. All children underwent a complete clinical examination with questioning of the parents, hormonal exploration (FT4, TSH, AC Anti-TPO), and cervical ultrasound. Once the diagnosis established, treatment with levothyroxine is undertaken. Regular reassessments were performed. **Results:** The average age at diagnosis is 3 months (20 days-5 months). Sex ratio F/G is 4/2. Hypothyroidism was diagnosed in front of clinical signs in four cases, persisting neonatal jaundice in two cases. Biological assessment confirmed hypothyroidism: FT_4 average 6.5 pmol/l, mean TSH 35 μ/l. TPO antibodies (TPO) were found in all cases (mean 30 ng/ml). Questioning the parents revealed an autoimmune thyroiditis in mothers. Clinical and radiological examinations did not show any malformation. LT_4 replacement therapy undertaken was screeching halt after 4.85 months (3–6). Hormonal reassessments showed no abnormalities and anti TPO were négatives. Growth stature and psychomotor development were normal. **Conclusion:** T N HT is very rare. It must be recognized precociously, to avoid inadequate diagnostic and therapeutic measures.

Late Breaking Posters

LBP1

46,XY DSD due to Isolated AMH Deficiency Resulting in Persistent Müllerian Duct Syndrome (PMDS) as a Consequence of a Single-Base Deletion in a SF1-Response Element of the *AMH* promoter

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Background: Isolated persistence of Müllerian ducts in an otherwise normally virilised 46,XY newborn, a condition known as PMDS, is a disorder of sex development (DSD) due to a defect limited to AMH-dependent Müllerian duct regression. **Objective and hypothesis:** We report the case of a patient with PMDS and extremely low serum AMH in whom no mutations were detected in the *AMH* gene coding sequences. A single base deletion identified in the *AMH* promoter was hypothesized to underlie isolated AMH deficiency. **Method:** Case report: a completely virilised newborn presented with nonpalpable gonads. Testosterone was high (358 ng/dl), AMH low (1.1 ng/ml), a uterus and Fallopian tubes were evidenced by USA, but CAH was ruled out owing to normal adrenal steroids and a 46,XY karyotype. PMDS due to AMH deficiency was suspected. DNA sequencing detected no mutations in the *AMH* gene coding sequences, but a homozygous single-base deletion (c.-225delA) was identified at a putative SF1 response element of the *AMH* promoter. To assess the effect of the c.-225delA variant, *AMH* promoter activity was analysed in luciferase assays, and the ability of SF1 binding to the −228 binding site in the *AMH* promoter was studied by EMSA. **Results:** The single base deletion c.-225delA decreased AMH promoter activity by 58±14%, to a similar extent of what was observed when the −228 SF1 site was completely disrupted by *in vitro* directed mutagenesis (66±5%). In EMSA experiments, interaction between SF1 and its AMH −228 binding site was lost when the oligonucleotide carried c.-225delA or the fully disrupted SF1 site. **Conclusion:** The single base deletion c.-225delA within the −228 SF1 site of the *AMH* promoter impairs SF1 binding to and transactivation of the AMH promoter, resulting in extremely decreased AMH production. This is the first description of an *AMH* promoter mutation leading to PMDS.

LBP2

Sexual Outcomes in Brazilian Patients with 46,XY DSD

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Background: Outcomes related to sexual life are poorly explored in 46,XY DSD patients and most studies focus only in 46,XX DSD (CAH). In 46,XY DSD the observations of sexual outcomes are scares, but they overall indicate that the SexQoL is impaired, particularly regarding sexual function and sexual satisfaction. **Objective and hypotheses:** To evaluate sexual outcomes in a cohort of patients with 46,XY in adulthood and compare these observations with the results described in adulthood Brazilian population **Method:** We evaluated the sexual outcomes by applying a questionnaire with 137 questions on social, sexual and psychological aspects. We invited 155 patients with 46,XY DSD from different aetiologies to participate in this study. These outcomes were compared between male and female patients, patients who change with those who maintained their social sex and DSD patients with the normal Brazilian population data. **Results:** DSD patients due to different etiologies (testosterone synthesis defects ($n=33$), androgen insensitivity syndrome ($n=34$) gonadal dysgenesis ($n=33$), 5αRD2 deficiency ($n=30$) and unknown etiologies ($n=10$) accepted to answer the questionnaire. Among these patients 115 maintained their assigned sex and 25 Individuals changed their assigned sex. At adulthood, the social sex was female in 89 patients and male in 51 patients. Patients from both social sexes showed adequate sexual performance, but male social sex showed better results than female social sex in terms of satisfactory intercourse, masturbation and orgasm ($p<.05$). Patients who changed the social sex demonstrated similar rates of sexual outcomes compared to those who maintained the social sex, except for the frequency of intercourse and self sexual life satisfaction ($p<.05$). Comparing with Brazilian population data, DSD patients starts sexual life later, have more steady partners and the same rate of heterosexuality. **Conclusion:** DSD patients presented adequate sexual activities. Male social sex demonstrated better sexual outcomes than female social sex. In male social sex, sexual outcomes were similar between patients who changed their social sex and who maintained.

LBP3

The Growth Hormone – Insulin Like Growth Factor I (IGF-1) System in Early Non-Alcoholic Fatty Liver Disease: From an Animal Model to a Children's Cohort

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Background: Non-alcoholic fatty liver disease (NAFLD) represents one of the most common obesity complications and can progress to non-alcoholic stetohepatitis (NASH). NASH is associated with lower insulin like growth factor I (IGF-1) and IGFBP-3, however no data are available regarding the growth hormone (GH)-IGF-I axis in early stage of NAFLD, characterised by hepatic steatosis. **Objective and hypotheses:** We aimed to investigate the GH-IGF-1 pathway in a diet-induced animal model of liver steatosis and proved the data in a human cohort of obese and lean children. **Method:** C57BL/6 mice ($n=12$) were fed with a standard diet (ND) or a high fat diet (HFD) ($n=12$) for 11 weeks. The hepatic lipid content was measured by MAS spectroscopy. Immunoblot and qPCR analyses were used to study activation of the hepatic GH-IGF-1 system. In serum of obese ($n=77$) and normal-weight children ($n=88$), IGF-1 and IGFBP-3 were measured. To estimate the liver steatosis, transient elastography (FibroScan®, Echosens™) was performed to measure the controlled attenuated parameter (CAP). **Results:** HFD mice presented a higher body weight and hepatic lipid content compared to ND mice ($p<0.005$). In addition, a lower hepatic expression of phosphorylated-STAT-5B, janus kinase-2 (pJAK2) and IGF-1 (-1.56, -2.7 and -1.9-fold) was found in HFD compared to ND mice. In obese children, higher CAP values were found compared to normal weight children (211.8 ± 76.7 vs 187.82 ± 37.7 dB/m, $p=0.0002$), indicating a steatotic phenotype. In addition, obese subjects presented lower IGF-1 compared to controls ($p=0.007$). After categorizing subjects according to tertiles of CAP, the IGF-1-SDS decreased significantly across the tertiles ($p<0.04$). An inverse correlation was found between IGF-1-SDS and CAP ($p=0.014$, $r=-0.254$). **Conclusion:** The GH-IGF-1 axis is impaired already in early NAFLD. In particular, IGF-1 could be an early marker to define the hepatic steatotic phenotype.

LBP4

Sirolimus Precipitating Diabetes in a Patient with Congenital Hyperinsulinism due to Autosomal Dominant ABCC8 Mutation

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Background: Studies have suggested that sirolimus might be diabetogenic, mostly in kidney transplant recipients. Sirolimus has now been shown to be effective in the management of patients with congenital hyperinsulinism (CHI). However to date, there are no publications regarding the diabetogenic effect of Sirolimus in CHI patients. **Objective and hypotheses:** To report the first case of sirolimus precipitating diabetes in a CHI patient with known genetic mutation. **Method:** Prospective follow up of patient with CHI who has a dominant ABCC8 gene mutation **Results:** A patient with CHI due to autosomal dominant ABCC8 mutation on high dose (15 mg/kg per day) of diazoxide was switched to sirolimus (4.25 mg/m^2 per day) therapy at the age of 16.6 years, as she developed severe hypertrichosis. Four months later, whilst receiving concomitant treatment with clarithromycin for folliculitis, she was found to be hyperglycaemic. Her mother carried the same mutation and spontaneously developed diabetes during adulthood (30 years). Despite reduction in the dose of sirolimus (and eventually stopping), investigations revealed persistent hyperglycaemia on the 24 hour blood glucose profile, and increased HbA1c (70H mmol/mol). She was started on a sulphonylurea, with the plan to increase it to the maximum dose and if no response to introduce metformin and if still hyperglycaemic to consider introducing other insulin sensitising agents. In the long term it is possible that she may require subcutaneous insulin injections. **Conclusion:** Dominant ABCC8 mutations are prone to diabetes at a later stage in life, but the timing may be influenced by medications such as m-TOR inhibitors. The diabetogenic impact of Sirolimus treatment in CHI patients should be confirmed in prospective studies.

LBP5

Development of Skeletal Microarchitecture and Biomechanics Over 2 Years Following 6 Month Intragastric Balloon Insertion in Obese Adolescents

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Background: A reduction in bone mass in adults and adolescents has been observed following Roux-en-Y bypass surgery with an increase in fracture risk reported in adults. However, the intragastric balloon (IGB) is a less invasive bariatric procedure. **Objective and hypotheses:** Given obese adolescents are at greater risk of fracture we studied the impact of a 6 month IGB insertion on skeletal mass, geometry and strength over 2 years. **Method:** We recruited 12 adolescents aged 13.8 to 16.8 years, BMI >3.5 SD, Tanner stage 4/5 to undergo IGB placement. Subtotal body and lumbar spine (LS:L1–L4) were measured by DXA and radial/tibial cortical and trabecular bone parameters were evaluated by high resolution pQCT imaging at 0, 6 and 24 months. Skeletal biomechanical parameters were defined by miocrofinite element analysis. Results are expressed as (mean difference (95%CI), significance(p)). **Results:** At 6 months BMI SDS fell by -0.27 SD (-0.43, -0.10), $p=0.005$, due to a reduction in perecntage fat mass of -2.0 (-3.9, -0.03), $p=0.05$. Weight loss was not sustained at 2 years. At 6 months subtotal

body BMC (g) (60.7(5.5,115.9), $p=0.03$), LS BMC (g) (2.5(1.4,3.6), $p=0.001$) and LS BA (cm^2) (0.8(0.4,1.2), $p=0.002$) all demonstrated expected age appropriate increases. Over 2 years there were overall increases in total body BMD (g/cm^2) (0.04(0.01, 0.06), $p=0.01$), LS BMC (g) (5.3(1.0,9.5), $p=0.02$) and LS BA (cm^2) (2.0(0.9,3.0), $p=0.003$). At the tibia, consistent gains were seen from baseline to 2 years in cortical area (mm^2) (10.1(1.7,18.5), $p=0.02$) and cortical thickness (mm) (0.09(0.002,0.173), $p=0.04$). Gains were only seen in cortical (14.0(8.3,19.6), $p<0.001$) and trabecular (4.1(0.5,7.6), $p=0.03$) BMD (g/cm^3) BMD at the radius at 6 months. Over 2 years bone stiffness (S, kN/mm) and ultimate failure load (F.Ult, kN) at the radius (S=4.1(1.3,6.9), $p=0.01$), (F.Ult=0.2 (0.1,0.3), $p=0.004$) and tibia (S=7.5 (0.6,14.5), $p=0.04$), (F.Ult=0.5(0.1, 0.9), $p=0.02$) increased. **Conclusion:** In the short term, an IGB placement offers significant reduction in BMI SDS. Unlike other bariatric procedures, bone accrual during adolescence continued at a time when bone mass accrual is critical.

LBP6

Children with Brain Tumors have Enhanced Visceral Adiposity Compared to Non-Cancer Controls: A Preliminary Analysis from the Canadian Study of Determinants of Endometabolic Health in Children Study

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Background: Survivors of childhood brain tumors (SCBT) are an emerging group that have premature mortality and morbidities that can negatively impact their quality of life and lifespan. Cardiovascular disease, obesity and diabetes are important causes of premature mortality in survivors, yet one of the major determinants of cardiometabolic risk i.e. visceral adiposity has not been determined in this group. **Objective and hypotheses:** This study is comparing two measures of visceral adiposity, the waist-to-hip ratio versus waist-to-height ratio, in SCBT and non-cancer controls and their relation to clinical and lifestyle variables **Method:** This cross-sectional study recruited SCBT ($n=59$) and non-cancer controls ($n=108$). Data collected include diet, physical activity, sleep, brain tumor type, location and treatment details. Total adiposity was determined using bioelectrical impedance, and visceral adiposity was determined by waist-to-hip and waist-to-height ratios. Regression analysis was used to determine the factors associated with visceral adiposity measures. **Results:** SCBT had higher visceral adiposity compared to controls (waist-to-hip ratio 0.87 ± 0.08 vs 0.82 ± 0.09, $p<0.0001$; Waist-to-Height ratio 0.48 ± 0.08 vs 0.45 ± 0.08, $p=0.007$). Female sex, high fat diet, and physical inactivity were the determinants associated with these profiles. **Conclusion:** Determination of visceral adiposity in SCBT is critical to identify those at future risk of cardiometabolic disorders, and to design targeted interventions to prevent visceral adiposity in survivors.

LBP7

Loss of Functional Osteoprotegerin: More than a Skeletal Problem

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Background: Juvenile Pagets disease (JPD), an ultra-rare, debilitating bone disease stemming from unopposed RANKL action due to loss of functional osteoprotegerin (OPG) is caused by recessive mutations in TNFRSF11B. A genotype-phenotype correlation spanning from mild to very severe forms is described. **Objective and hypotheses:** To describe the complexity of the human phenotype of OPG deficiency in more detail and to investigate heterozygous mutation carriers for clinical signs of JPD. **Method:** About three children with JPD from families of Turkish, German and Pakistani descent and 18 family members (13 heterozygous) were investigated. **Results:** A new disease-causing 4 bp-duplication: c.[25–28dup];[25–28dup] in exon one was detected in the German patient and a homozygous microdeletion including TNFRFSF11B in the Pakistani patient. Skeletal abnormalities in the affected children include bowing deformities and fractures (three patients), contractures (3), short stature (3) and skull involvement (3). Complex malformation of the inner ear (3) and vestibular structures (2) resulted in early deafness. Patients were found to be growth hormone deficient (2) displayed elevated inflammatory markers (2), nephrocalcinosis (1) motoric (3) and mental (1) retardation. No retinal changes were observed in any of the patients. Heterozygous family members displayed low osteoprotegerin levels (12), elevated bone turnover markers (7) and osteopenia (6). Short stature (1), vision impairment (2) and hearing impairment (1) were also present. **Conclusion:** Diminished osteoprotegerin levels cause complex changes affecting multiple organ systems in children with JPD and may cause osteopenia in heterozygous family members. Diagnostic and therapeutic measures should aim to address the complex phenotype.

LBP8

Impact of Weight Loss after Bariatric Surgery on Gonadic Function in Severely Obese Female Adolescents

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Background and objectives: To study short-term effects of consequent weight loss on ovarian function and its correlation with morphometric and metabolic changes at 1 and 2 years after a laparoscopic adjustable gastric banding (LAGB) placement in severely obese adolescents. **Subjects and methods:** Our retrospective and observational study was conducted between July 2015 and January 2016 in a single center. Menstruations, anthropology and biological data were collected prospectively before LAGB (M0, $n=17$), one (M12, $n=15$) and two (M24, $n=9$) years after surgery. Data of seventeen female adolescents, operated between April 2011 and November 2015, were included in the study (M0). Description of morphometric changes was made with calculation of BMI, excess body weight (EBW) and excess weight loss (%EWL). Metabolic changes were described using homeostatic model assessment (HOMA) for insulin resistance; gonadic function parameters were age at menarche, cycle length and serum androgen levels (testosterone) in adolescents free from oral contraception. **Results:** Mean BMI of our population before surgery was 42.4 ± 6.7 kg/m^2. At M12, mean EWL was 19.7 ± 14.1%. Age at menarche was significantly younger in obese adolescents compared to mean age of menarche of their mothers (11.6 ± 1.5 vs 12.3 ± 1.8 years old, $P=0.05$). Mean of cycle length in our population moved from 60.7 ± 34.9 days before surgery to 26.0 ± 3.4 days after surgery ($P=0.014$). Cycle length without hormonal contraception correlated positively with BMI before surgery ($r=0.687$ $P=0.043$). Neither insulin sensitivity (HOMA), nor testosterone level changed significantly at both 1 and 2 years after bariatric surgery. **Conclusion:** Consequent weight loss seems to have effects on improvement of ovarian function by normalizing menstruation cycle length in severely obese female adolescents, despite modest metabolic and hormonal changes.

LBP9

Osteoprotegerin and Insulin Resistance in Childhood Obesity: A New Interplay?

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Background: A positive association between osteoprotegerin (OPG) levels and cardiovascular morbidity and mortality has been recently reported. Additionally, there is evidence that OPG in obese adults participates in the pathogenesis of atherosclerosis and cardiovascular diseases by promoting inflammation, which is known to be linked to insulin resistance (IR). There is few data regarding the relationship among obesity-IR-OPG, in youth. **Objective and hypotheses:** To assess serum OPG levels in obese children/adolescents and investigate possible association with IR. **Methods:** A total of 160 participants (85 obese/75 healthy controls) aged 10.7 years (ranged: 2.6–17.8) were enrolled. Obese participants underwent an oral glucose tolerance test (OGTT), whereas IR was evaluated according to the homeostasis model assessment-IR index (HOMA-IR). Anthropometric measurements and serum OPG levels were assessed. **Results:** Osteoprotegerin levels were increased in obese compared to controls, but this difference was not statistically significant ($P=0.133$). During correlation analysis, OPG levels were positively correlated to BMI-SD ($r=0.24$, $p=0.028$), fasting insulin levels ($r=0.293$, $p=0.007$), area under the curve for insulin during OGTT ($r=0.224$, $p=0.046$), HOMA-IR ($r=0.289$, $p=0.009$) and negatively associated to age ($r=-0.22$, $p=0.043$) among obese. Only obese-IR exhibited significantly higher serum OPG levels compared to controls and to obese-nonIR individuals, even after adjustment for BMI-SD and age ($P=0.001$). Serum OPG levels did not correlate to impaired glucose metabolism. **Conclusion:** Insulin resistance may influence OPG levels in childhood obesity indicating a new interplay between them.

LBP10

Molecular Analysis of AR, *SRD5A2*, *NR5A1* and *HSD17B3* Genes in a Brazilian 46,XY DSD Cohort

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Background: Disorders of Sex Development (DSD) comprise several phenotypes due to dysfunction in genes involved in human sexual determination and differentiation. The most frequent aetiologies among 46,XY DSD are androgen insensitivity syndrome and 5-alpha-reductase type 2 deficiency due mutations in *AR* and *SRD5A2* genes, respectively. **Objective and hypotheses:** The purpose of this study was to investigate mutations in *AR* and *SRD5A2* genes in 21 paediatric patients classified as 46,XY DSD. For cases without mutation in these genes, complementary analysis of *NR5A1* or *HSD17B3* genes was performed, according to clinical and hormonal characteristics. **Method:** Genomic DNA was obtained from blood samples. Molecular alterations were investigated by sequencing exons and exon-intron junctions. Each fragment was amplified by polymerase chain reaction and used for direct sequencing. The sequences obtained were analysed and compared with the

reference sequence for each gene. **Results:** Six alterations were identified: p.Ala475Val and p.Leu57Gln in *AR*; p.Gly183Ser in *SRD5A2*; p.Arg39Cys in *NR5A1*; and, p.Ala203Val and p.Gly262Val in *HSD17B3*. **Conclusion:** Individuals with 46,XY DSD show significant overlap of clinical and hormonal features, which make it difficult to reach diagnosis, to indicate treatment and to perform genetic counselling. In the casuistic here analysed, six patients revealed sequence variations in *AR, SRD5A2, NR5A1* and *HSD17B3*. However, 15 patients did not show any abnormality indicating that other genes may be involved in the aetiology. The p.Arg39Cys alteration identified in *NR5A1* and p.Gly262Val in *HSD17B3*, are firstly described here. Although these findings are relevant to diagnostic elucidation, investigation of *in vitro* functional effects of novel mutations is crucial.

LBP11

Long-Term Safety and Effectiveness of Growth Hormone Treatment in Pediatric Patients with Growth Hormone Deficiency: Interim Results of LG Growth Study

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Background: Over 4 years, 1,526 patients received Eutropin® and EutropinPlus® (recombinant human growth hormone (GH), LG Life Sciences, Ltd.) while enrolled in the LG Growth Study (LGS), designed to monitor the long-term effectiveness and safety of GH. We present LGS experience for GH treatment during 4 years in growth hormone deficiency (GHD) **Objective and hypotheses:** To evaluate the long-term safety and efficacy of Eutropin® and EutropinPlus® in Korean pediatric patients. **Method:** A multicenter, long-term, prospective and retrospective study. The interim analysis was conducted in all patients who were enrolled from Jan 2012 to Mar 2016. **Results:** Total 901 patients with GHD were analysed for safety during 4 years of GH treatment in GHD (Organic GHD: 85, Idiopathic GHD (IGHD): 813; Complete IGHD: 146, Partial IGHD: 401 patients). Chronological age was 8.15 years and Height SDS was −2.38 at baseline. Male and female were 530 and 317 patients, respectively. Adverse events (AEs) were reported in 18.0% in total and most of them were mild. The incidence of adverse drug reactions was 4.0%. Total 619 patients were analysed for effectiveness. Height Velocity (HV) was 8.90 cm/year at 12-month and ΔHeight SDS was 0.64 during the first year of treatment. Height SDS was improved from −2.46 (baseline) to – 1.15 over 4 years of GH treatment. In the sub group analysis of GHD, Organic vs. Idiopathic and Complete IGHD vs. Partial IGHD, for HV and ΔHeight SDS, respectively, there were no statistical differences between groups. **Conclusion:** The growth response to GH (Eutropin® and EutropinPlus®) in GHD children remained effectively without specific safety concerns during 4 years.

LBP12

An Analysis of Symptoms and Signs of Adrenal Insufficiency in Children with CAH Admitted to Hospital in Australia

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Background: An adrenal crisis (AC) is a life-threatening complication of congenital adrenal hyperplasia (CAH). Despite modern therapies, children with CAH still present with symptomatic adrenal insufficiency (AI) and AC. **Objective and hypotheses:** The aim of the study was to determine the spectrum of symptoms and signs of AI in children with diagnosed CAH who were admitted to hospital for an acute illness, as well as to evaluate the use of stress dosing and parenteral hydrocortisone (HC) in these children. **Method:** We audited the records of all patients with a diagnosis of CAH who were admitted to one of two specialist paediatric referral hospitals for an acute illness in Sydney, Australia, between 2000 and 2015. All patients in the study were receiving glucocorticoid replacement therapy. Information on symptoms and signs of acute AI including hypotension, abnormal electrolytes and hypoglycaemia was collected, together with information on all diagnoses (including AC) and the use of stress dosing and parenteral HC. **Results:** There were 113 admissions between 2000 and 2015. Of these, 49 (43.4%) were in males; 20 (17.7%) were aged under 1 year; 45 (39.8%) were aged 1–5 years, and 48 (42.5%) were over 6 years of age. hypotension was recorded in 9 (8%) children; hyperkalaemia was reported in 8 (7.1%); hyponatraemia in 14 (12.4%); hypoglycaemia in 13 (11.5%); reduced consciousness in 12 (10.6%); vomiting in 53 (46.9%); diarrhoea in 24 (21.2%); lethargy in 27 (23.9%); fever in 37 (32.7%). Oral stress dosing was used prior to admission in 53 (46.9%) cases. Intravenous HC was given in hospital to 56 (49.6%)

children. Five admissions (4.4%) were identified as an AC. **Conclusion:** In children with treated CAH, admission to hospital with symptoms consistent with gastroenteritis and acute AI were common. The diagnosis of AC was rare in this group.

LBP13

Hyperprolactinemia in Children and Adolescents: A Review of Patients Presenting to a Tertiary Center in Australia

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Background: Hyperprolactinemia can be physiological or due to a pharmacological/pathological cause. It is relatively rare in childhood and poorly described in the literature. **Objective and hypotheses:** The aim of this study was to retrospectively evaluate the etiology, clinical findings and management of hyperprolactinemia in children. **Method:** We reviewed the records of 91 children with hyperprolactinemia (Prolactin level >760 mU/L) presenting to the Children's Hospital at Westmead between 2009 and 2014. Data collected included; age, gender, anthropometric data, symptoms, pubertal status, pituitary hormone profile, prolactin level, MRI brain and management details. **Results:** The mean age of presentation was 11.7 ± 5.01 years with equal sex distribution. Hyperprolactinemia was secondary to pharmacological agents in 30, prolactin secreting pituitary adenoma in four, hypothalamic-pituitary dysfunction in 12, hypothyroidism in two, macroprolactin in two, physiological causes in 24 and idiopathic in 16 patients. Risperidone was the commonest drug responsible for the hyperprolactinemia ($n=19$). The majority of patients (84%) were asymptomatic. The mean prolactin level was 1700 ± 2471 mU/L (761 to 20,288 mU/L) for the whole group, 1452 ± 806 mU/L (761 to 3922 mU/L) for drug induced hyperprolactinemia and 7968 ± 3507 mU/L (1660 to 20,288 mU/L) in patients with pituitary adenoma. MRI brain reports were available for 46 patients out of which 30 patients had abnormal findings; 16 with abnormality responsible for hyperprolactinemia and 14 with abnormality thought to be unrelated to hyperprolactinemia. Of the four patients with a pituitary adenoma, two patients were treated with surgery and two with dopamine agonists. **Conclusion:** Hyperprolactinemia presents mainly in late childhood and patients are often asymptomatic. Drug induced hyperprolactinemia was the commonest cause of hyperprolactinemia in children presenting to our tertiary service. Children with hyperprolactinemia should be investigated further if they are symptomatic or prolactin levels >1500 mU/L.

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