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Plenary Lectures

PL1

Closed-Loop System: Dream or Reality?

M Phillip

Jesse Z. and Sara Lea Shafer Institute for Endocrinology and Diabetes, Schneider Children's Medical Center of Israel, National Center for Childhood Diabetes, Tel Aviv, Israel.

Despite the fact that patients with diabetes and medical staff are doing their best to achieve tight glycemic control, most patients all over the world do not achieve the goal. Good glycemic control is crucial to prevent diabetes related complications as well as hypoglycemic episodes, seizure, coma and death. The Diabetes wiREless Artificial Pancreas ConsortiuM (DREAM) was established by three diabetes centers in Slovenia, Germany and Israel, with a goal to reduce the risk of hypoglycemia while improving blood glucose control and reducing patients' burden of diabetes management by using the MD-Logic system, which is a wireless fully automated closed-loop system based on a fuzz-logic theory algorithm, with a learning capability, a personalized system settings and safety alert module.

Since October 2010, *in silico* studies using the FDA approved UVA simulator ($n=300$ virtual patients) and clinical studies were conducted by the three centers with more than 200 children, adolescents and adults with T1D. After the successful conclusion of first feasibility in-hospital studies, a set of prospective randomized controlled, multicenter, multinational, cross-over studies were conducted in hospitals, at diabetes camps and at patients' homes. We first targeted at the night time, with the GlucoSitter as a solution for need of nocturnal blood glucose control and recently a full 24 h closed-loop system was tested successfully at patients' homes.

Studies' results demonstrated the safety and efficacy of the MD-Logic system for overnight glucose control and during the day. In all studies, the MD-Logic system achieved significantly less hypoglycemia, tighter overnight glucose control compared to sensor augmented pump therapy.

The MD-Logic system may safely integrate into lives of people with diabetes, providing a potent tool to lower the rate of nocturnal hypoglycemia and improve overall glucose control. The DREAM consortium is now evaluating the MD-Logic system in a longer study period at patients' homes.

PL2

Learning from Histopathology to Design Novel Immune-Therapies for Type 1 and 2 Diabetes

M von Herrath

Center for T1D Research, LJI, La Jolla, California, USA

Study of the histopathology of human type 1 and 2 diabetes through the national pancreatic organ donor (nPOD) consortium has yielded interesting new insights that should also aid us in developing improved therapeutic approaches.

1. When insulinitis is observed, it usually shows a predominance of CD8 T cells, some of which are autoantigen specific (see also Coppieters *et al. JEM* 2012). It will be therapeutically challenging to remove/prevent CD8 memory effector cells from attacking islets, especially in more advanced disease. Autoreactive CD8 cells are also present in the blood of type 1 patients.

2. Islets exhibit a characteristic overexpression of MHC class I in T1D, the cause of which is unknown and could be viral (entero or herpes virus for example). It is thus possible that islets in type 1 diabetes are selectively sensitized towards CD8 attacks. In contrast, autoreactive CD4 cells can be isolated and detected in blood from both, type 1 and 2 diabetes patients, possible caused by presentation of islet antigens through MHC class II following β -cell stress.

3. The exocrine pancreas might play a hence under-appreciated role in the pathogenesis of both, type 1 and 2 diabetes. We observe increased infiltration by CD8 lymphocytes, in type 1 diabetes also in autoantibody positive individuals.

4. Destruction of β -cells in type 1 diabetes occurs in a lobular fashion, indicating that there might be events that render whole pancreatic lobes susceptible to attack and loss of β -cells. Localized bacterial and viral infections are potential candidates.

An optimal immunotherapeutic strategy would in our opinion involve a combination of a systemic induction phase, which should ideally eliminate some of the autoreactive CD8 cells without causing excessive immunosuppression followed by a maintenance phase that re-instates islet specific immune regulation and metabolic control. Biomarkers will be required to identify those individuals most likely to respond.

PL3

Sex, Stem Cells and Decision of Cell Fate

R Lovell-Badge

London, UK

Abstract unavailable.

PL4

Gene Therapy

P Aubourg

University Paris-Sud and INSERM, Le Kremlin-Bicêtre, Paris, France

Background: X-linked adrenoleukodystrophy (X-ALD) presents with two phenotypes: i) an adult form (adrenomyeloneuropathy, AMN), that involves axonal tracts without demyelination within the spinal cord and affects adult males and more than 80% of X-ALD heterozygote women in adulthood resulting in severe paraplegia. This far the most frequent form of X-ALD. Addison's disease is very rare in X-ALD women but frequent in adult AMN males, very often with onset years or decades before neurologic symptoms appear. Importantly, 35% of AMN males develop cerebral demyelination which has the same poor prognosis as in X-ALD boys; ii) a childhood cerebral demyelinating form that affects boys between 4 and 12 years and leads to vegetative stage or death within few years. As in adult males with X-ALD, Addison's disease precedes often the cerebral disease in boys. Whereas there is yet no treatment for AMN, allogeneic transplantation of normal hematopoietic stem cells (HCT) can arrest the progression of cerebral disease in boys and adult X-ALD males with good quality of life in long term, provided the procedure is performed at an early stage of cerebral disease. This emphasizes the crucial need to screen systematically all boys or adult males with Addison's disease for X-ALD (measurement of VLCFA in plasma) and perform on a regular basis brain MRI in all X-ALD males with isolated Addison's disease to detect early signs of cerebral demyelination. **Objective and hypotheses:** Allogeneic HCT is not always possible due to lack of HLA-matched donor and remains associated with important mortality risks. It is the reason why autologous transplantation of hematopoietic stem cells (HSC) genetically corrected *ex vivo* with a lentiviral vector has been attempted in four boys with cerebral X-ALD. **Method:** HSC gene therapy has been performed in four boys with cerebral X-ALD. **Results:** Results with a follow-up of 4–7 years indicate similar efficacy than with allogeneic HCT with no complication due to the use of integrative viral vector and a phase III trial has recently been launched.

PL5

Obesity: Novel Treatments and the Imperative for Prevention

Donal O'Shea

Dublin, Ireland

Obesity has doubled in the developed world in the last 10 years. In the last year both the EU and WHO have launched high level commissions to address childhood obesity. The increase in young

onset type 2 diabetes is already with us and we are increasing our understanding of how childhood obesity increases the likelihood of developing cancer and more severe infection. Meanwhile the food and drinks industries continue to ignore their own voluntary codes of practice as well as legislation and are promoting high fat high sugar high salt food and drinks to the youngest possible audience. Aggressive prevention strategies are essential and must be driven by the medical profession.

Novel treatments will emerge from a better understanding of how weight is controlled. Experience with bariatric surgery is growing in the adolescent population. Temporary devices that mimic aspects of the gastric surgeries are being developed in adults with a view to being studied in children. Over the last few years, a number of effects of obesity on the immune system have been identified. These are likely to contribute to the increase seen in the incidence of a range of diseases in obesity along with their worse outcomes. The surprising observation was that the immune system defects were themselves contributing to weight gain and thus perpetuating a cycle further weight gain. In turn the immune system is being regulated by gut hormones including GLP1 and insulin. Furthering our understanding of this immune system-weight regulation axis is already leading to candidate novel weight loss treatments.

PL6

Making a Diagnosis in Severe Complex Obesity

Sadaf Farooqi

Metabolic Research Laboratories, Wellcome Trust Senior Clinical Fellow, Wellcome Trust-MRC Institute of Metabolic Science, University of Cambridge, Cambridge, UK

With the rising prevalence of childhood obesity, there has been an increase in the number of children presenting with severe obesity. Whilst only a relatively small proportion of severely obese children will have the classical features associated with the well-established genetic obesity syndromes such as Prader-Willi syndrome, there is increasing recognition that highly penetrant genetic disorders can frequently present as severe obesity alone without developmental delay, dysmorphology or other distinct clinical signs. It is, therefore, important for Physicians to have a systematic approach to the assessment of these patients. The diagnosis of a genetic obesity syndrome can provide information that has diagnostic value for the family and may help children and their families deal with the social stigma that comes with severe obesity in childhood. The finding of a genetic cause for a patient's severe obesity can in some cases lead to specific therapeutic interventions and in others, can inform Physicians as to the utility of other interventions such as bariatric surgery. The use of techniques such as whole exome sequencing has accelerated the discovery of new genes and mechanisms that are likely to explain a variety of previously unrecognized childhood obesity syndromes.

Symposia

S1.1

Pseudohypoparathyroidism

Murat Bastepe

Harvard Medical School and Massachusetts General Hospital,
Boston, Massachusetts, USA

Pseudohypoparathyroidism (PHP) is a disorder of hormone resistance characterized by end-organ resistance to the actions of parathyroid hormone (PTH). The resistance primarily occurs in the renal proximal tubule, thus leading to hypocalcemia, hyperphosphatemia, and elevated serum PTH. Indicating the resistance in this tissue, patients with PHP show blunted phosphate excretion in response to exogenously administered PTH. In PHP type I, the patients additionally demonstrate blunted PTH-induced urinary cAMP excretion. Patients with PHP-Ia demonstrate resistance to additional hormones, including TSH and gonadotropins. Moreover, these patients present with Albright's hereditary osteodystrophy (AHO). PHP-Ia is caused by heterozygous inactivating mutations in *GNAS*, the gene encoding the alpha-subunit of the stimulatory G protein ($G_{s\alpha}$). These mutations, which are located in $G_{s\alpha}$ -coding *GNAS* exons, cause PHP-Ia after maternal inheritance but lead to pseudo-pseudohypoparathyroidism (PPHP) after paternal inheritance. PPHP is a disorder characterized by AHO in the absence of hormone resistance. Reflecting the inactivating nature of the $G_{s\alpha}$ mutations, biochemical assays using easily accessible cells of PHP-Ia and PPHP patients show ~50% reduction in $G_{s\alpha}$ bioactivity. Another form of PHP type I is PHP-Ib, which is typically characterized by the presence of PTH and mild TSH resistance in the absence of AHO. Hormone resistance in PHP-Ib is also inherited from female obligate carriers only. Others and we have found that PHP-Ib is caused by maternally inherited microdeletions that disrupt the imprinting of the *GNAS* complex locus. Various deletions within the *GNAS* locus itself or the neighboring *STX16* gene have been identified, with the most frequent mutation being a 3-kb deletion removing *STX16* exons 4–6. PHP-Ic is a PHP variant clinically similar to PHP-Ia, but erythrocyte $G_{s\alpha}$ activity appears normal in these patients, particularly when direct $G_{s\alpha}$ stimulators are used in the assay. Several PHP-Ic cases are caused by coding $G_{s\alpha}$ mutations that disrupt receptor coupling but not basal activation. In addition to $G_{s\alpha}$, *GNAS* gives rise to several gene products that show exclusive monoallelic expression. $G_{s\alpha}$, however, is expressed biallelically in most tissues; however, its expression is monoallelic in certain hormone responsive tissues, including renal proximal tubules and thyroid. The paternal $G_{s\alpha}$ allele is silenced in those tissues, allowing a heterozygous maternal mutation to result in a dramatic reduction in $G_{s\alpha}$ level/activity. The tissue-specific monoallelic $G_{s\alpha}$ expression explains the imprinted mode of inheritance for the hormone resistance in PHP type I. Data from reported patients with PHP-Ia or PHP-Ib indicate that the clinical outcome of PTH resistance does not occur at birth but instead develops after infancy or even later in childhood. Our investigations using a mouse model of PHP-Ia/PPHP confirmed that proximal tubular PTH resistance

develops gradually after birth. We furthermore showed that the maternal and paternal alleles contribute equally to $G_{s\alpha}$ expression at birth but the paternal allele is silenced gradually after the early postnatal period in the renal proximal tubule. In contrast, the paternal $G_{s\alpha}$ silencing is already established in neonatal mouse brown fat. The delay of the allelic $G_{s\alpha}$ silencing in the renal proximal tubule could explain the latency of PTH resistance in PHP-Ia, although other possible mechanisms exist.

S1.2

McCune–Albright Syndrome

M Collins

Bethesda, USA

The McCune–Albright syndrome can be a disease of striking complexity, the management of which can be challenging. However, an understanding of the physiologic consequences of the underlying molecular and developmental biology makes the evaluation and treatment of this disease relatively straightforward. MAS arises from activating mutations in the ubiquitously expressed cAMP-signaling protein, $G_{s\alpha}$. The mutations occur very early in development, prior to gastrulation. The timing and location of the mutational event dictate the 'map' of affected tissues. As such, a thorough phenotyping at presentation allows for the identification of all affected and, equally important, unaffected tissues that will track over a patient's lifetime. Identifying affected and unaffected tissues, and understanding the effects of cAMP signaling in a given tissue, explains the clinical presentation, infers treatment, and allows for accurate prognostication. Each patient is different, and the array of tissues affected range from few to many. In complex cases, care often involves the coordinated efforts of multiple subspecialists. Patients suffer and parents are often frustrated with the fragmentation of care that can occur. A fairly comprehensive, evidenced-based literature exists to guide physicians in the diagnosis and treatment of MAS. In this symposium a concise distillation of this literature and an algorithm to guide the diagnosis and treatment will be reviewed that will equip the pediatric endocrinologist with the tools to understand the disease, and coordinate and direct care of this often challenging and complex disease.

S1.3

New Therapies in Metabolic Bone Disease: PTH

Agnès Linglart^{a,b}

^aAPHP, Le Kremlin-Bicêtre, France; ^bParis 11 university,
Le Kremlin-Bicêtre, France

Hypoparathyroidism is a rare disease manifesting as hypocalcemic seizures, developmental delay, sluggishness, paresthesias and/or dyskinesia. Symptoms reveal hypocalcaemia associate with increased serum phosphorus and undetectable, low or unadapted

PTH levels. Known causes of hypoparathyroidism are cervical surgeries causing irreversible damage to the parathyroid tissue, toxic attack of the parathyroid cells by antibodies, and genetic defects affecting parathyroid development, PTH secretion, or excessive signalization of the calcium-sensing receptor. Except for the transient inhibition of PTH secretion by proton pump inhibitors or alcohol, once diagnosed, hypoparathyroidism is definitive and unrepairable. The majority of hypoparathyroidism cases are well controlled under conventional treatment with calcium and vitamin D analogs. As such therapy increases filtered load of calcium in absence of PTH-driven calcium reabsorption, physicians advise their patients to avoid normalization of serum calcium because it can cause hypercalciuria and heterotopic calcification. As a consequence, patients -including infants and children- spend most of their life in hypocalcaemia. In spite of this precaution, the rate of complications appears substantial. During the past 10 years, several groups have reported the efficacy of recombinant PTH1-84 or teriparatide PTH1-34 in children and/or adults in restoring near normal levels of serum calcium. Although not approved by regulatory agencies, recPTH may be an alternative to current therapy in patients with refractory hypoparathyroidism who experience life-threatening complications of their disease. Normalization of serum calcium to ensure proper cognitive development, and restoration of normal urinary calcium excretion to prevent renal failure should be the objectives of recPTH.

S2.1

PTEN: A Gene Involved in Overgrowth and Cancer

P Dennis

Baltimore, Maryland, USA

Abstract unavailable.

S2.2

MEN1 in Children and Adolescents

Maria Luisa Brandi

Department of Surgery and Translational Medicine, University of Florence, Florence, Italy

Background: MEN1 is an autosomal dominant disorder that is due to mutations in the tumor suppressor gene MEN1, which encodes a 610-amino acid protein, menin. MEN1 is characterized by the occurrence of parathyroid, pancreatic islet, and anterior pituitary tumors. The prognosis for MEN1 patients might be improved by presymptomatic tumor detection and undertaking treatment specific for MEN1 tumors. **Objective and Hypotheses:** Genetics is increasingly becoming integrated into the practice of modern clinical endocrinology. This has resulted in early diagnosis of MEN1 and better understanding of its physiology and penetrance. **Method:** Tumorigenesis in MEN1 occurs relatively late in life, with parathyroid adenomas, islet cell

tumors, and pituitary adenomas being detected between ~20 and ~80 years of age. However, this may also be due to a relatively late stage of analysis, and current screening programs advocate evaluation to begin at ~10 years of age. **Results:** Epidemiological and clinical information on the penetrance of MEN1 is derived mainly from clinical case reports of children presenting with manifestations of this disorder and from screening data within dedicated centers. **Conclusion:** The presentation will be focused on the present knowledge of MEN1 tumor expression in children and adolescents. Also biochemical and radiological diagnostic guidance in the young population carrying the MEN1 gene mutation is going to be offered.

S2.3

DICER1 Syndrome: A Review of the Syndrome with a Focus on Endocrine Aspects

William Foulkes

McGill University, Montreal, Quebec, Canada

Background: DICER1, a ribonuclease, cleaves non-coding small RNA precursors to generate mature microRNAs (miRNAs), of ~21 nucleotides in length. MiRNAs alter gene expression post-transcriptionally by directly binding to mRNA transcripts and subsequently down-regulating gene expression. It is estimated that expression of ~30-70% of all mammalian protein-coding genes are regulated in this manner. **Method:** Sequencing of DICER1 in various tumors, accompanied by studies in RNA and protein. **Results:** We have identified germ-line and/or somatic *DICER1* mutations in those affected by pleuropulmonary blastoma, cystic nephroma, Sertoli-Leydig cell tumors, cervical rhabdomyosarcoma, Wilms tumor, anaplastic sarcoma of the kidney, pituitary blastoma, pineoblastoma, nasal chondromesenchymal hamartoma, gonadal germ cell tumors, multinodular goitre and differentiated thyroid cancer. While the germ-line mutations are generally truncating and are widely scattered across the gene, remarkably, nearly all the somatic mutations affect key metal-binding amino acids within the RNase IIIb domain and likely alter miRNA production. **Conclusion:** DICER1 syndrome is a recently discovered syndrome with a mainly pediatric, adolescent and young adult presentation. I will review the syndrome, with a focus on pediatric and endocrinological manifestations.

S3.1

Differential Diagnosis of Monogenic Diabetes

K Owen

Oxford, UK

Abstract unavailable.

S3.2

Neonatal Diabetes: New Genes, New Mechanism, New Phenotypes

S Ellard

Institute of Biomedical and Clinical Science, University of Exeter Medical School, Exeter, UK

Recent years have seen significant progress towards defining the genetic aetiology of neonatal diabetes with >20 subtypes identified. It is likely that all cases of neonatal diabetes result from a single gene disorder since markers of autoimmunity associated with type 1 diabetes are rare in patients diagnosed before 6 months.

Heterozygous activating mutations in the *KCNJ11* and *ABCC8* genes encoding the Kir6.2 and SUR1 subunits of the K_{ATP} channel are the most common cause of neonatal diabetes. Most of these patients can achieve improved glycaemic control on sulphonylurea tablets. Around 20% also have developmental delay which may be improved through high dose sulphonylurea therapy. Mutations in the *INS* gene are reported as the second most common cause. Most are dominant missense mutations that cause misfolding of the insulin molecule leading to β cell apoptosis but recessive loss-of-function mutations preventing insulin synthesis are more common in consanguineous families. Transcription factor mutations identified through candidate gene studies or homozygosity mapping strategies account for the majority of other known cases.

The advent of next generation studies allows a hypothesis free approach for finding new genetic aetiologies. Exome sequencing has shown that *de novo* *GATA6* mutations are the most common cause of pancreatic agenesis. A genetic approach to gene discovery was necessary since mouse models failed to recapitulate the phenotype. The human phenotype associated with heterozygous *GATA6* mutations is very variable, ranging from complete absence of the pancreas, gall bladder and cardiac malformations, to patients with isolated diabetes diagnosed in adulthood. Most recently, a combination of genetic linkage, genome sequencing and epigenomic annotation revealed a novel enhancer 25 kb downstream from *PTF1A* in which mutations cause pancreatic agenesis with no cerebellar phenotype in contrast to the *PTF1A* coding mutations that result in cerebellar agenesis.

S3.3

Epidemiology of Monogenic Diabetes

W Mlynarski

Lodz, Poland

Abstract unavailable.

S4.1

Management of Central Hypothyroidism

P van Trotsenburg

Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands

Central hypothyroidism (CeH) can be defined as a lower than desirable secretion of thyroid hormone by a normal thyroid gland resulting from (quantitative or qualitative) insufficient TSH secretion. Causes are congenital and acquired functional or anatomic defects of the hypothalamus, pituitary gland or both. CeH can be difficult to diagnose, especially in children without a history of brain defects or brain damaging treatment (e.g. irradiation), and when plasma FT4 concentration lie around the lower border of the age specific reference interval. Congenital CeH can be detected by (total or free)T4+TSH-based neonatal screening programs. Analysis of the Dutch screening program showed the incidence of permanent congenital CeH to be approximately 1 in 18 000. Approximately 75 to 80% of detected neonates have additional anterior pituitary hormone deficiencies, like ACTH or GH deficiency, stressing the importance of early detection. Therefore, neonates with CeH need assessment of the integrity of their hypothalamo-pituitary adrenal and GH/IGF-1 axes. Mutations of the TRH receptor and TSH beta subunit genes are well known causes of isolated permanent congenital CeH. Recently, mutations in the *IGSF1* gene were found to be a third genetic cause. Like primary (or thyroidal) hypothyroidism, CeH is an indication for thyroxine treatment. Thyroxine dose adjustments should be guided by measurement of the plasma or serum FT4 concentration. Unanswered questions with regard to treatment concern the 'best' plasma FT4 concentration to aim at, and thyroid hormone target tissue parameters that might be helpful herein.

S4.2

Novel Role(s) for Immunoglobulin Superfamily, Member 1 (IGSF1) in the Hypothalamic-Pituitary-Thyroid Axis

Daniel Bernard

McGill University, Montreal, Quebec, Canada

Background: Immunoglobulin superfamily, member 1 (IGSF1) was originally proposed to function as an inhibin co-receptor in pituitary gonadotroph cells. More recently, however, loss of function mutations in the human *IGSF1* gene were linked to a novel syndrome of central hypothyroidism, testicular enlargement, and variable prolactin-deficiency. *Igsf1*-deficient mice are also centrally hypothyroid, with reduced pituitary thyrotropin-releasing hormone receptor (*Thrhrl*) expression. Although these observations provide some insight into the potential causes of central hypothyroidism in *IGSF1*-deficient patients, *IGSF1*'s normal function in pituitary and

hypothalamus remains unresolved. **Objective and Hypotheses:** The objectives of our ongoing studies are to understand: i) how pathogenic mutations in *IGSF1* impair protein expression, and ii) physiological roles of IGSF1 in the HPT axis. **Method:** To address these research objectives, we are using a combination of *in vitro* biochemical and cell biological approaches in heterologous and homologous cell lines, and *in vivo* analyses of *Igsf1*-deficient mice. **Results:** Preliminary data indicate the missense mutations in *IGSF1* not only impair membrane trafficking of the IGSF1 protein (as previously reported), but also decrease the protein's stability. Recent *in vitro* and *in vivo* results may finally uncover IGSF1 function(s) in the brain and/or pituitary gland. **Conclusion:** Genetic analyses in humans and mice have established a previously unappreciated role for IGSF1 in the hypothalamic-pituitary control of thyroid function. Novel data promise not only to define IGSF1's normal functions in cells but to provide mechanistic insight into how the loss of these functions result in a novel endocrinopathy.

S4.3

Novel Insights into Thyroid Hormone Resistance

V K K Chatterjee

University of Cambridge Institute of Metabolic Science,
Addenbrooke's Hospital, Cambridge, UK

Resistance to thyroid hormone mediated by defective TR β (RTH β) or TR α (RTH α).

Separate genes (*THRA*, *THRB*) undergo alternate splicing, generating nuclear receptors (TR α 1, TR β 1, TR β 2) with distinct tissue distributions, which mediate thyroid hormone action; the function of a non-hormone binding protein (α 2), derived from the *THRA* locus, is unknown.

RTH β a dominantly-inherited disorder associated with \sim 150 different heterozygous *THRB* mutations, is characterised by elevated thyroid hormones, with non-suppressed TSH levels. Features in childhood can include failure to thrive and attention deficit hyperactivity disorder. The adult RTH β phenotype is characterised by features of both hyperthyroidism (e.g. tachycardia, raised metabolic rate, low bone mineral density) and hypothyroidism (elevated cholesterol), reflecting either resistance or retention of hormone sensitivity in TR β versus TR α -expressing peripheral tissues.

Recently, the first patients with *THRA* defects have been identified. Features in childhood include growth (lower segment) retardation, skeletal dysplasia (macrocephaly, epiphyseal dysgenesis), constipation, motor dyspraxia and variable cognitive impairment. Whilst these features suggest hypothyroidism in specific tissues, patient's thyroid function tests (low/low-normal T₄, high/high-normal T₃, normal TSH) are near-normal; however, low T₄/T₃ ratio, subnormal reverse T₃ and raised muscle CK levels with mild anaemia in these cases, provide a biochemical signature for the

disorder. Four patients harbour highly deleterious heterozygous mutations in TR α 1, abolishing its function; three further cases have a milder, missense mutation involving both TR α 1 and α 2 proteins, with no readily-discernible added phenotype attributable to mutant α 2. Thyroxine therapy may be beneficial in this disorder, suggesting that early identification of cases will be important.

The contrasting phenotypes of RTH β and RTH α exemplify the differing importance of receptor subtypes in tissues, providing a rational basis for development of receptor-specific hormone analogues.

S5.1

Aetiology of Congenital Hypoadrenalism

John Achermann

UCL Institute of Child Health, London, UK

Congenital adrenal insufficiency is a potentially life-threatening condition that can present soon after birth in many different ways. The classic presentation is a salt-losing crisis due to mineralocorticoid insufficiency, often between a week and two of life, but babies with predominant glucocorticoid insufficiency can present with other features such as prolonged jaundice, hypoglycaemia and hyperpigmentation. Most children with congenital adrenal insufficiency present to emergency paediatric services and might initially be diagnosed with sepsis, renal or metabolic disease. Often specific investigations are not performed at the time, or are difficult to interpret once the child is established on steroid replacement treatment, so reaching a precise diagnosis in some children has been challenging. The International Classification of Paediatric Endocrine Diagnoses provides a useful overview of paediatric adrenal disorders many of which can present in early life. These include: i) various forms of congenital adrenal hyperplasia (*StAR*, *CYP11A1*, *HSD3B2*, *CYP21A1*, *CYP17A1*, *CYP11B1*, *POR*); ii) secondary forms of adrenal hypoplasia (e.g. isolated ACTH deficiency or multiple pituitary hormone deficiencies); iii) ACTH-resistance-like conditions (e.g. FGD (*MC2R*, *MRAP*), Triple A syndrome, and defects in *NNT* and *MCM4*); iv) primary adrenal hypoplasia (e.g. *DAX-1/NROB1*, IMAGE syndrome); v) metabolic dysfunction (e.g. Smith-Lemli-Opitz); and vi) disorders predominantly associated with salt loss (e.g. mineralocorticoid resistance, mineralocorticoid deficiency (*CYP11B2*)). Many of these conditions have overlapping clinical and biochemical features and genetic approaches to diagnosis are proving invaluable in many cases. Establishing a specific diagnosis can be important for identifying associated features, tailoring treatment to an individual, establishing long-term prognosis, and identifying other family members at risk of developing adrenal insufficiency or of having affected children in the future. Several clinical examples will be presented to highlight how combining careful clinical assessment with endocrine tests and genetic analysis has altered our approach to management.

S5.2

Adrenarche: Coming of Age in the Era of Genomics and Metabolomics

William Rainey

Departments of Molecular and Integrative Physiology and Internal Medicine, University of Michigan Medical School, Ann Arbor, Michigan 48109-5622, USA

The human adrenal cortex produces a wide range of steroids that includes aldosterone, cortisol and a variety of 19 carbon (C₁₉) steroids; the most studied being DHEA. In humans, adrenarche is the endocrine developmental process manifested by an increased adrenal output of DHEA. This phenomenon corresponds with the expansion of the zona reticularis of the adrenal gland. However, the physiological mechanisms that trigger adrenarche remain elusive. Our research focuses on better defining the C₁₉ steroids that are produced during adrenarche as well as the mechanisms regulating C₁₉ steroid production. Recently, we employed genomic and metabolomic analyses to better define the adrenal changes associated and the steroids produced during adrenarche. Transcriptome analysis was accomplished using laser captured fasciculata and reticularis, and metabolomic analysis of C₁₉ steroids was done using liquid chromatography quadrupole mass spectrometry (LC-MS/MS). Microarray comparison of fasciculata and reticularis defined a unique steroidogenic phenotype for both zones. The expression pattern of key steroidogenic enzymes tracked with reticularis development during adrenarche and the pattern explains the onset of DHEA production. Analysis of C₁₉ steroids in serum from children progressing through adrenarche and adult adrenal vein samples, demonstrated the production of a spectrum of C₁₉ steroids that includes, DHEA, 11β-hydroxyandrostenedione and androstenedione. My presentation will provide an update of our findings related to the intra-adrenal changes seen and the steroids produced during adrenarche.

S5.3

CAH: Health Status in Adults (CaHASE)

W Arlt

Birmingham, UK

Abstract unavailable.

S6.1

Roles of Hypothalamic microRNAs in the Regulation of Puberty

Manuel Tena-Sempere^{a,b,c}

^aDepartment of Cell Biology, Physiology and Immunology, University of Córdoba, Córdoba, Spain; ^bCIBER Fisiopatología de la Obesidad y Nutrición, Córdoba, Spain; ^cInstituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC), 14004 Córdoba, Spain

Puberty, as the developmental continuum between infancy and adulthood, is a complex maturational transition, affecting different body systems, which is under the control of sophisticated regulatory networks. Concerning the pubertal awakening of the reproductive axis, much has been learnt in the last decades on the central mechanisms whereby puberty onset is driven. However, most of the information so far available is limited to the roles of specific neurotransmitters and their receptors, as well as the transcriptional mechanisms responsible for their regulation. The sophisticated nature of puberty, though, makes it reasonable to predict that its precise regulation involves not only the *classical* control of gene transcription, but also the participation of additional regulatory events, such as epigenetics, defined as the mechanisms for genetic control other than the information encoded by the mere DNA sequence. Such epigenetic mechanisms include not only DNA methylation and histone modifications, but also the regulatory actions of small, non-coding (nc) RNAs, mainly microRNAs. MiRNAs are small (~22 nt), nc RNAs that operate as post-transcriptional regulators by virtue of their ability to bind seed sequences at the 3'-UTR of different target RNAs, thus resulting (in most cases) in gene silencing. While the role of other epigenetic phenomena (e.g. methylation of specific repressors) in the central control of puberty has been recently documented, the involvement of putative miRNA pathways in the modulation of central (or peripheral) elements of the reproductive axis remains scarcely evaluated. Yet, human and functional genomic data have recently suggested the participation of the RNA-binding protein, Lin28B, in the control of puberty; the major known role of Lin28B being to inhibit the maturation of the members of the miRNA family, let-7. Departing from these observations, in this presentation we will review our, as yet limited, knowledge on the roles of miRNAs in the central control of reproduction and gonadal function. Special attention will be paid to summarize data from expression analyses and recent functional genomic studies addressing the pubertal impact of conditional elimination of miRNA synthesis in key neuronal populations of the reproductive brain. In doing so, we intend to provide an updated (and broader) view of the actual mechanisms whereby maturation of the reproductive axis is finely controlled (and eventually deregulated) during puberty onset.

S6.2

New Syndromes Resulting in Secretory Pathway and Gonadotropic Axis Regulation Defects

N de Roux

Paris Diderot University, Paris, France

Puberty is defined by the appearance of secondary sexual characteristics and the maturation of reproductive function. It is driven by an increase in sexual steroid hormone synthesis under the control of the gonadotropic axis. The key event in puberty initiation is an increase in the pulsatile release of the GnRH by hypothalamic neurons, triggering the release of LH and FSH. This pubertal increase in GnRH secretion is associated with increases in glutamatergic inputs and decreases in GABAergic inputs to GnRH neurons. It is also facilitated by hypothalamic glial cells, which interact directly or indirectly with GnRH neurons. Kisspeptins are currently thought to be the principal hypothalamic neuropeptides controlling GnRH secretion, not only at puberty, but also during adulthood. The activation of the kisspeptins signaling pathway in the hypothalamus is seen as the major hallmark of puberty onset, and its control is partly epigenetic. Characterization of the genetic defects underlying the isolated form of congenital hypogonadotropic hypogonadism (CHH) has proved crucial, not only for elucidating the fundamental role of kisspeptins in the central regulation of the gonadotropic axis and puberty, but also for determining the role played by Neurokinin B. CHH may be associated with anosmia, due to olfactory bulb agenesis, in Kallmann syndrome. CHH has also been associated with complex neurodevelopmental disorders caused by loss-of-function mutations in genes encoding proteins involved in diverse cellular pathways. This association indicates that the same etiopathogenic mechanism may be responsible for a specific neuroendocrine deficiency and common neurological dysfunctions. Here, I will review genetic causes of these syndromic CHH without anosmia and presented our recent data on a new syndrome which associates GnRH deficiency with complex neurological and endocrine phenotypes.

S6.3

Genetic Dissection of Puberty in Mice

U Boehm

Hamburg, Germany

Abstract unavailable.

S7.1

Evolution of Feminising Genitoplasty

J L Pippi-Salle

Sidra Medical and Research Center, Doha, Qatar

Great controversy exists in regard to the timing and technical alternatives to perform feminizing genitoplasty in children. Opponents to an early approach argue that the reconstruction can be risky in terms of clitoral/vaginal function therefore surgery should be postponed until the patient herself can sign an informed consent and be aware of potential risks as well as confirms the desire to undergo the procedures. Such negative feelings in regard

to early reconstruction are based on published long-term follow-up in patients who underwent outdated surgical procedures, mostly done in centers with various surgeons performing different procedures. The surgical approach for feminizing genitoplasty has evolved significantly over the years. Modern techniques aim to spare the nerves involved in the clitoral sensitivity. In addition there were significant learning in how to improve the approach to these structures in order to minimize injuries to the vagina. In this lecture we present the historical evolution of surgical techniques for feminizing genitoplasty, emphasizing the main points that will likely improve future outcomes. It will be also emphasized that, regardless of conservative or surgical approach, it is essential to have these patients closely followed and monitored by a multidisciplinary team that should include individuals with adequate psych-social training to deal with this population.

S7.2

Pros and Cons of Early or Late Feminising Genitoplasty

G Conway

London, UK

Abstract unavailable.

S7.3

Masculinising Genitoplasty

A El-Ghoneimi

Paris, France

Abstract unavailable.

S8.1

Novel Therapies Used in the Management of Congenital Hyperinsulinism

Khalid Hussain

Institute of Child Health, London, UK

Congenital hyperinsulinism (CHI) is characterised by the dysregulation of insulin secretion leading to severe hyperinsulinaemic hypoglycaemia. Recent advances in molecular genetics have provided unique insights into understanding how insulin secretion becomes unregulated in CHI. Abnormalities in the genes *ABCC8/KCNJ11* (encoding the two components *SUR1/KIR6.2* of the pancreatic β -cell KATP channel respectively) is the most common genetic causes of CHI. Histologically there are two major subgroups of CHI, namely diffuse and focal. The accurate pre-

operative localisation of focal disease with ^{18}F -DOPA-PET scanning has greatly improved the management of patients with focal disease who can now be cured once the focal lesion is resected. The real challenge in CHI is the management of patients with severe diffuse disease. Until recently a near total pancreatectomy was the standard surgical management of these patients. However several new treatment modalities are being developed which in the long term will change our approach to patients with diffuse CHI. During the talk I will review the recent advances in managing patients with diffuse disease.

S8.2

Treatment of Hypophosphatasia

C Greenburg

Manitoba, Canada

Hypophosphatasia (HPP), an inborn-error-of-metabolism, has broad-ranging severity caused by inactivating mutation(s) in the gene for tissue non-specific alkaline phosphatase (TNSALP). HPP in children features premature loss of deciduous teeth often with impaired skeletal mineralization, poor growth, static myopathy, and compromised physical function. To date there are no approved treatments for HPP. Perinatal and infantile forms have very high morbidity and mortality and the juvenile and adult forms also often cause very debilitating disease. Asfotase alfa (bone-targeted recombinant human TNSALP) is in clinical development for treatment of HPP. In a series of clinical trials in progress since 2007, infants and children with HPP treated with asfotase alfa have shown significant improvement in radiologic signs of HPP, respiratory function, survival, gross motor function, and stamina in follow-up now through 3 years of treatment, with no serious adverse events reported by Investigators as definitively related to the drug. Results of trials to date will be presented highlighting the promise that ERT will change the natural history of this bone disorder.

S8.3

Congenital Adrenal Hyperplasia

Evangelia Charmandari^{a,b}

^aDivision of Endocrinology, Metabolism and Diabetes, First Department of Pediatrics, University of Athens Medical School, 'Aghia Sophia' Children's Hospital, Athens, Attiki, Greece; ^bDivision of Endocrinology and Metabolism, Clinical Research Center, Biomedical Research Foundation of the Academy of Athens, Athens, Attiki, Greece

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders resulting from deficiency of one of the enzymes required for synthesis of cortisol in the adrenal cortex. The most

common form of the disease is classic 21-hydroxylase deficiency, which is characterized by decreased synthesis of glucocorticoids and often mineralocorticoids, adrenal hyperandrogenism and impaired development and function of the adrenal medulla. The clinical management of classic 21-hydroxylase deficiency is often suboptimal, and patients are at risk of developing in tandem iatrogenic hypercortisolism and/or hyperandrogenism. Limitations of current medical therapy include inability to control hyperandrogenism without employing supraphysiologic doses of glucocorticoid, hyperresponsiveness of the hypertrophied adrenal glands to ACTH and difficulty in suppressing ACTH secretion from the anterior pituitary. Current therapy with immediate-release hydrocortisone is most commonly used for glucocorticoid replacement in patients with classic 21-hydroxylase deficiency. However, conventional hydrocortisone treatment cannot simulate the physiologic rhythm of cortisol secretion. Optimization of current treatment has been attempted with thrice-daily dosing, which still fails to simulate the normal diurnal rhythm of cortisol secretion and results in temporary over- or under-replacement. Proof-of-concept studies using hydrocortisone infusions predict improvement in biochemical control and quality of life. Delayed and sustained release oral formulations of hydrocortisone are being developed, and these represent a novel treatment approach that offers the prospect of physiologic cortisol replacement. Other therapeutic alternatives that might be used in conjunction with substitution therapy include GnRH analogs, anti-androgens and aromatase inhibitors, however, many of these agents still require further evaluation in patients with the classic form of the disease.

S9.1

Visualizing Cell-Cell Communication *Within* and *Between* Pituitary Cell Networks

Patrice Mollard

Department of Endocrinology, Institute of Functional Genomics-CNRS UMR5203-INSERM U661-University of Montpellier, Montpellier, France

In the early 2000's, our lab began its efforts to characterize the large-scale functional organization of endocrine cell types within the mammalian pituitary gland. These studies were driven by a long-standing paradox of pituitary function: endocrine cell populations are capable of mounting massive hormone pulses *in vivo* (e.g. a 1,000-fold increase in GH levels in young mature males), while the same cells isolated from their tissue context respond weakly to secretagogue (two- and five-fold increase in GH levels in response to hypothalamic GHRH). Thus, we hypothesized that cell organization *in situ* might be a pivotal component in the build-up of hormone pulses. To address this paradox, we applied large-scale cellular microscopy to animal and more recently human pituitaries to examine the positioning and signaling activities of the embedded endocrine cell populations. In combination with other techniques (e.g. Ca^{2+} -imaging, RNAseq

and qPCR analyses...), we have been able to: 1) Show that mouse pituitary endocrine cells are organized as 3D networks, allowing the gland to integrate and memorize numerous external cues to appropriately adapt downstream tissue output to the prevailing environmental conditions; 2) Provide evidence that highly-organized networks of endocrine cells (at least somatotrophs and corticotrophs) also exist with the human pituitary parenchyma; 3) Identify a mode of cell-cell communication within homotypic cell networks which may provide a useful diagnostic marker for staging aggressiveness in common human adenomas (GH and PRL); 4) Show that pituitary development involves inter-network communication; and 5) Identify how energy expenditure during the build-up of hormone pulses depends on paracrine interplay between endocrine cell networks and pituitary pericytes. As such, the large-scale organization of endocrine cells into networks boosts pituitary hormone release by supporting complex cell-cell information exchanges, and components of this may be targeted by pathological insults to perturb normal gland architecture and function.

S9.2

Sox2+ve cells in the adult murine pituitary are stem cells with tumour-inducing potential

Juan Pedro Martinez-Barbera^a, Cynthia Andoniadou^b

^aInstitute of Child Health, London, UK; ^bKing's College London, London, UK

Background: Several lines of evidence suggest that the adult pituitary contains a population of tissue-specific stem cells capable of differentiating into hormone-producing cells. Previously, we have shown that Sox2+ve cells are able to self-renew and differentiate in vitro, suggesting that this population of undifferentiated cells may contain stem cells in vivo. When targeted with oncogenic mutations adult stem cells can become cancer stem cells, able to self-renew and give rise to cell progeny that colonise the tumour. Our research has revealed that pituitary embryonic precursors and adult stem cells may be involved in pituitary tumorigenesis. However, important questions remain unknown. **Objective and hypotheses:** 1) Are Sox2+ve cells tissue-specific adult stem cells in the murine pituitary? 2) Can Sox2+ve cells generate cancer stem cells? **Method:** We have performed genetic tracing of Sox2+ve cells in vivo using a Sox2CreERT2 mouse line to investigate the role of Sox2+ve cells in adult pituitary cell turnover and in tumorigenesis. **Results:** First, we demonstrate that Sox2+ve cells are able to self-renew and differentiate into all hormone-producing cells in vivo. In addition, we show that the expression of oncogenic beta-catenin specifically in Sox2+ve cells results in pituitary tumours resembling childhood craniopharyngioma. Finally, we reveal that tumours form in a non-cell autonomous manner whereby oncogenic Sox2+ve cells signal to surrounding cells leading to transformation and tumour growth. This novel paracrine model of tumorigenesis implies that the cell sustaining the oncogenic mutation and the cell of origin of the

tumour are different. **Conclusion:** 1) Sox2+ve cells are tissue-specific stem cells in the adult murine pituitary. 2) Sox2+ve cells can induce tumours in a paracrine manner, which is different to the cancer stem cell paradigm.

S9.3

Pax7 Dictates Alternate Pituitary Cell Fates During Development

Jacques Drouin

Institut de recherches cliniques de Montréal, Montréal, QC, Canada

Background: Pituitary gland development is a well conserved process that starts with formation of Rathke's pouch and specification of the primitive intermediate and anterior pituitary tissues. This early developmental sequence is conserved in humans compared to other mammals despite the fact that the human intermediate pituitary regresses during early gestation. **Objective and hypotheses:** We have identified the transcription factor Pax7 as key regulator for specification of intermediate lobe identity in different species and we showed that Pax7 dictates the alternate cell fates of the two POMC-expressing lineages, the corticotropes and melanotropes, through its pioneer transcription factor activity (Budry *et al.* The selector gene Pax7 dictates alternate pituitary cell fates through its pioneer action on chromatin remodeling. *Genes and Dev.* 2012, 26:2299–2310). **Results:** Pioneer transcription factors have the unique ability to remodel chromatin and change genome accessibility. For pituitary POMC-expressing cells, remodeling of chromatin by Pax7 changes the outcome of Tpit-driven differentiation to dictate the melanotrope instead of corticotrope fate. This presentation will emphasize recent findings on developmental mechanisms and their implications for pituitary pathogenesis.

S10.1

The Metabolically Healthy Obese Child

Dénes Molnár

Department of Pediatrics, University of Pécs, Pécs, Hungary

Background: Recent interest has focused on a unique subgroup of overweight and obese individuals who have normal metabolic features (MHO) despite increased BMI. According to the WHO obesity is considered a disease itself. In the light of the WHO statement it is most strange to speak about healthy and unhealthy obesity. Nevertheless, we all know that a certain portion of obese persons are free from some (most frequently investigated) obesity-related metabolic consequences. **Objective and hypotheses:** The purpose of the present lecture is to find answers

to the following questions: 1) Do we have enough scientific proof to use the term 'healthy obesity'? 2) Do we have a standard set of criteria to define metabolic health? 3) Is the development of metabolic complications only question of time? 4) Can we distinguish metabolically healthy and unhealthy obese individuals by using different obesity indices or on the basis of dietary and lifestyle factors? 5) Does the metabolic phenotype modify the mortality and morbidity associated with higher BMI? **Method:** Literature review and analysis of the Healthy Lifestyle in Europe by Nutrition in Adolescents (HELENA) project investigating adolescents (age range: 12.5–17.5 years). **Results:** Due to the diverse criteria used in reviewed studies the prevalence of MHO has varied considerably with proportions ranging from 6 to 40% in both adults and children. The duration of exposure to the metabolic-BMI phenotypes was not investigated in the reviewed studies therefore MHO can be only a transient phenomenon. HELENA results: no significant difference between the two phenotypes could be demonstrated regarding body composition, blood pressure, heart rate, leptin concentration, etc. **Conclusion:** No characteristic marker of the MHO phenotype could be identified. There are studies suggesting that there is no healthy pattern of obesity. Several definitions are currently used to describe MHO resulting in widely varying prevalence estimates.

S10.2

Childhood and Adolescent Obesity: Can Treatment Response be Predicted?

R Weiss

Jerusalem, Israel

Abstract unavailable.

S10.3

Natural Course of Impaired Glucose Tolerance in Obese Children

T Reinehr

Datteln, Germany

Abstract unavailable.

NP1.1

Non Coding RNA's: Introduction to Non-Coding RNAs and the Role of MicroRNAs in GnRH Neurons

V Prévot

Inserm, Development and plasticity of the postnatal brain, U837,
University of Lille 2, Lille, France

Fertility and puberty onset are controlled within the brain by a neural network that drives the secretion of gonadotropin-releasing hormone (GnRH) from hypothalamic neuroendocrine neurons. During postnatal development, various permissive signals must be integrated for the initiation of sexual maturation but the molecular events that orchestrate the timely activation of the GnRH neurons remain a major unsolved biological mystery. Increasing evidences point out Micro-RNAs (miRNAs) as a key regulatory layer that controls gene expression at the post-transcriptional level supporting crucial neurobiological events from the embryonic development to the adulthood but nothing is known about their putative role in the neuroendocrine control of reproduction.

Here, we investigate the role of miRNAs in the development and function of the GnRH system using conditional knockout mice with a targeted deletion of Dicer (GnRH^{DicerKO}), an essential protein for miRNAs biogenesis, in GnRH neurons.

The analysis of GnRH^{DicerKO} mice showed that a lack of miRNAs in GnRH neurons causes defective sexual development resulting in hypogonadotropic-hypogonadism and infertility in both males and females. The characterization of the embryonic development of GnRH system has shown no overt deficit in GnRH neuron migration or projections to the median eminence. Strikingly, immunofluorescent analyses combined with genetic labeling of GnRH neurons revealed a progressive loss of GnRH expression in the hypothalamus during the late infantile period in postnatal life probably due to an alteration of the genetic network controlling the GnRH promoter.

Indeed, miRNA and gene expression profiling on FACS isolated GnRH neurons show that GnRH neurons express a specific set of GnRH transcription modulators as well a discrete population of miRNAs at specific postnatal ages. Moreover bioinformatic analyses revealed that a subset of these miRNAs, organized in few conserved clusters, targets known activators and/or repressors of the GnRH promoter. Finally, gene expression analysis on GnRH neurons from GnRH^{DicerKO} mice confirm that the lack of miRNAs cause a profound alteration of the expression profile of known GnRH transcription modulators and leads to a dramatic decrease of GnRH expression.

Altogether, these results shed light on a new role of miRNAs in neuroendocrine processes and point out a specific set of miRNAs as key component of the genetic network that controls GnRH promoter activity. This supports the modulation of GnRH expression levels according to the developmental clock and to

specific environmental/physiological changes to contribute to the postnatal activation of GnRH neurons.

NP1.2

The Role of MicroRNAs in Diabetes

Romano Regazzi

University of Lausanne, Lausanne, Switzerland

Background: MicroRNAs are small non-coding RNAs that regulate gene expression and play major roles in many physiological and pathological processes. **Objective and hypotheses:** Determine whether changes in microRNA expression contribute to β -cell dysfunction and/or loss and favor the development of diabetes. **Method:** Analysis of the changes in microRNA expression occurring in pancreatic islets of diabetes animal models and assessment of their functional impact in β -cells. **Results:** The manifestation of diabetes is associated with alterations in the level of several microRNAs. Detailed analysis of the role of differentially expressed microRNAs revealed that some of them promote glucose-induced insulin secretion, enhance β -cell proliferation and/or improve β -cell survival, suggesting that they contribute to adaptive changes in the functional β -cell mass in response to insulin resistance. In contrast, the alterations in the level of other microRNAs result in β -cell dysfunction and death, favoring the development of diabetes. Besides their well-established regulatory function exerted inside the cells, microRNAs can be released in the extracellular space and are detected in a variety of body fluids. We provide evidence that circulating microRNAs released by activated lymphocytes can be delivered to β -cells and can affect their survival, potentially contributing to β -cell loss during the initial phases of type 1 diabetes. **Conclusion:** The balance between changes in the level of microRNAs with opposing functional effects may determine whether individuals maintain blood glucose homeostasis or progress toward glucose intolerance and diabetes. We discovered that microRNAs produced by lymphocytes can be taken up by β -cells and can influence their activity, potentially contributing to the development of diabetes. Measurement of circulating microRNAs in blood or urine may provide a new class of biomarkers to predict the appearance of diabetes and its long-term complications.

NP2.1

Regenerative Medicine for β Cell Replacement

R Scharfmann

Paris, France

Pancreatic β cells develop from endodermal pancreatic progenitors that first proliferate and next differentiate into functional insulin-producing cells. This developmental process is complex, each step being controlled by yet unknown signals. Theoretically, the development of a functional β cell mass can be

enhanced by: i) activating the proliferation of pancreatic progenitors; ii) activating their differentiation into β cells; iii) activating the proliferation of β cells themselves.

During the past years, we first developed bioassays based on rodent models to search for signals that control specific steps of β cell development. With such bioassays, we screened and characterized a number of signals that regulate pancreatic progenitor cell proliferation and differentiation. We also developed models of human pancreatic development, to transfer to human, data generated in rodent models. Such models were instrumental for the development of functional human β cell of lines first and second generations. Such an approach, that aims at better dissecting signals regulating functional β cell mass in rodent and human will be presented.

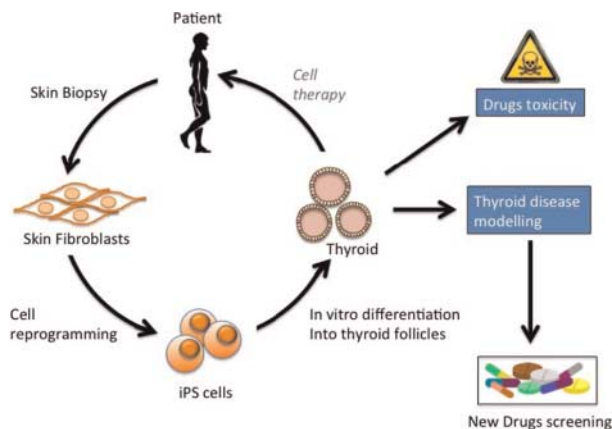


Figure 1

NP2.2

Formation of a Thyroid Gland from Embryonic Stem Cells

S Costaglio

IRIBHM Universite Libre de Bruxelles, Brussels, Belgium

Induced overexpression of defined transcription factors has been shown to have a directing effect on the differentiation of embryonic stem cells (ESCs) into specific cell types. Nevertheless, protocols promoting coordinated self-assembly of differentiated cells into distinct morphological units with functional properties reminiscent of organs and tissues *in vivo* are still very sparse. Our group recently reported efficient rescue of hypothyroidism in athyroid mice transplanted with functional thyroid follicles generated from mouse ESCs *in vitro*. In this work, we show that an overexpression of the transcription factors NKX2.1 and PAX8 is sufficient to direct ESCs differentiation into thyroid follicular cells (TFC) and promotes *in vitro* self-assembly of TFC into three-dimensional follicular structures, when associated to a subsequent TSH treatment. Cells differentiated by this protocol show

significant iodide organification activity, a hallmark of thyroid tissue function. Importantly, athyroid mice grafted with ESCs-derived thyroid follicles show normalization of plasma T4 levels with concomitant decrease of plasma TSH. In addition, a full normalization of body temperature at 4 weeks after transplantation was observed. Together, these data clearly demonstrate that grafting of our ESCs-derived thyroid cells rescues the hypothyroid state and triggers symptomatic recovery along with the normalization of plasma hormone concentrations. By using human pluripotent stem cells, our system would provide an unprecedented opportunity to improve our understanding of the molecular mechanisms underlying congenital hypothyroidism or to study papillary thyroid carcinoma risk allele under controlled *in vitro* conditions. Those thyroid diseases could be modelled, opening new therapeutic perspectives. One example could be the generation of functional thyroid tissue from induced pluripotent stem cells (iPSC) derived from patients skin fibroblasts with the ultimate aim being the transplantation of iPSC-derived thyroid tissue to replace absent, ablated or damaged thyroid and restore an euthyroid state lifelong without a substitution therapy.

Prize Winners

HA1

Deciphering the Functional Mechanisms by which MKRN3 Regulates Puberty Initiation

Ana Paula Abreu^{a,b}, Victor Navarro^a, Martha Bosch^c, Joy Liang^a, Delanie Macedo^b, Serap Simavli^a, Sekoni Noel^a, Iain Thompson^a, Oline Ronnekleiv^c, Rona Carroll^a, Ana Claudia Latronico^b, Ursula Kaiser^a

^aHarvard Medical School, Brigham and Women's Hospital, Boston, Massachusetts, USA; ^bDisciplina de Endocrinologia e Metabologia, Laboratório de Hormônios e Genética Molecular/LIM42, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Sao Paulo, SP, Brazil; ^cOregon Reg Primate Rsrch Ctr, Portland, Oregon, USA

Background: We recently identified loss-of-function mutations in makorin ring finger 3 (*MKRN3*) as a cause of familial central precocious puberty (CPP). Analysis of *Mkfn3* expression in the arcuate nucleus of mice showed high expression levels in juvenile mice, with a marked reduction prior to puberty onset, suggesting that MKRN3 inhibits puberty initiation. The function of MKRN3 is not known but based on its amino acid sequence, it is predicted to act as an ubiquitin ligase. **Objective and Hypotheses:** To elucidate the mechanism by which MKRN3 regulates GnRH secretion. **Method:** As a first step to analyze if MKRN3 acts as an ubiquitin ligase, we performed affinity purification of HEK293T cells co-transfected with MKRN3 and His-tagged ubiquitin (Ub-His). Secondly, we performed *in situ* hybridization (ISH) assays to analyze *Mkfn3* expression and map the distribution of *Mkfn3* in the hypothalamus of mice. Finally, to detect *Mkfn3* expression in two neuronal populations critical for reproduction -GnRH and Kiss1 neurons- we performed single cell RT-PCR in cells derived from Kiss1-GFP and GnRH-GFP female mice. **Results:** MKRN3 was detected in immunoprecipitated Ub-His protein complexes suggesting that MKRN3 acts as a ubiquitin ligase. ISH detected high diffuse *Mkfn3* expression in the hypothalamus at postnatal day (PND) 1, with more localized expression in the arcuate and ventromedial nuclei at PND10, which decreased to very low levels by PND15. Our single cell RT-PCR studies showed that *Mkfn3* was expressed in ~35 and

20% of arcuate Kiss1 neurons at age PND13 and in adult mice, respectively; and in ~30% of GnRH neurons at PND13 but not in adults. **Conclusion:** Our *in vitro* studies show that MKRN3 likely acts through ubiquitination. The temporal and spatial pattern of *Mkfn3* expression and co-localization in Kiss1 and GnRH neurons suggests that MKRN3 acts as a 'brake' for GnRH secretion and corroborates our genetic findings in humans.

HA2

Pubertal Onset in Girls is Strongly Influenced by Genetic Variation in Promoters Affecting FSH Action

Casper P Hagen, Kaspar Sørensen, Lise Aksglaede, Annette Mouritsen, Mikkel G Mieritz, Jeanette Tinggaard, Christine Wohlfart-Veje, Jørgen H Petersen, Katharina M Main, Ewa Rajpert-De Meyts, Kristian Almstrup, Anders Juul

Department of Growth and Reproduction, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

Background: FSH stimulates ovarian follicle maturation and estradiol synthesis which is responsible for breast development. Age at pubertal onset varies substantially among healthy girls. Although more than half of the variation is heritable, only a small part has been attributed to specific genetic polymorphisms identified so far. **Objective and Hypotheses:** We assessed the effect on pubertal onset of three genetic polymorphisms affecting FSH action. **Method:** Combined cross-sectional and longitudinal cohort study of 964 healthy girls, age 8–13 years. Puberty was defined as Tanner breast stage ≥ 2 by palpation. DNA was isolated from blood and *FSHB* -211 G>T, *FSHR* -29 G>A, and *FSHR* 2039 A>G were genotyped by competitive allele-specific PCR. **Results:** Girls homozygous for *FSHR* -29 AA (reduced FSH receptor expression) entered puberty 7.4 (2.5–12.4) months later than carriers of the common variants *FSHR* -29 GG+GA, $P=0.003$. In a combined model, puberty occurred on average 8.0 months later in carriers of either *FSHR* -29 AA or *FSHB* -211 TT (reduced FSH production) compared with girls with at least one WT allele (10.63 vs 9.96 years, $P=0.001$). The number of minor alleles (*FSHR* -29 A and *FSHB* -211 T) was positively associated with age at pubertal onset (β 1.9 months, $P=0.025$). **Conclusion:** For the first time we demonstrate that age at breast development is highly influenced by genetic variation in promoters affecting FSH action. To our knowledge, this is the strongest genetic effect on age at pubertal onset in girls published to date.

Working Groups

WG1.1

Unravelling GH Actions on the Growth Plate and its Promotion of Linear Growth

Colin Farquharson

University of Edinburgh, Edinburgh, UK

The functional activities of growth plate chondrocytes are tightly controlled to regulate the pace of linear growth. Simplistically, growth rate is determined by the number of cells within the proliferative zone which is regulated by their rate of proliferation and also their rate of differentiation into the hypertrophic phenotype. In turn, a strong positive correlation exists between the final hypertrophic cell volume and the rate of growth. Interruption and/or deregulation of this highly ordered sequence of events results in impaired bone growth and short stature which, in a significant number of children, is not rectified by catch-up growth. Inhibitors of growth can act both exogenously (e.g. physical trauma and pharmacological agents) or endogenously (e.g. altered autocrine/paracrine and systemic control). Examples of the latter include alterations to the GH/IGF1 axis which is recognised to be a key pathway in the regulation of bone growth. Whilst the growth promoting role of GH on linear bone growth is well accepted the relative contributions to post-natal growth of the direct or indirect effects of GH remain unclear. The GH indirect effects are via endocrine and/or local (growth plate cartilage) IGF-1 production. Various spontaneous mouse mutations in GH/IGF1 signalling have been informative. Also, the mouse genetic revolution with the creation of various transgenic and knock-out (inducible and tissue specific) strains of mice e.g. SOCS2 null mice, have helped us understand more fully the role of GH and IGF1 initiated pathways together with their negative feed-back loops and associated kinases and phosphatases in the linear bone growth process. Notwithstanding the direct effects of GH on growth plate chondrocytes it is likely that these two systems function in a highly coordinated manner to regulate growth plate function and linear bone growth. This presentation will summarise the current state of understanding and introduce emerging insights.

WG1.2

The Effect of Stimulatory G Proteins on Differentiation within the Growth Plate

Murat Bastepe

Harvard Medical School and Massachusetts General Hospital, Boston, Massachusetts, USA

Endochondral bone formation regulates bone growth both during embryonic development and after birth. Several different autocrine/paracrine or hormonal mechanisms govern the regulation of endochondral bone formation. Among those is the pathway involving stimulatory G protein, which primarily mediates the actions of parathyroid hormone-related peptide (PTHrP) in the growth plate. PTHrP is synthesized in the perichondrial cells and chondrocytes at the end of bones. In the growing bone, chondrocytes proliferate, differentiate, and undergo apoptosis in a coordinated fashion, leading to the formation of bone and its lengthening. PTHrP acts to sustain the proliferative capacity of chondrocytes and inhibit their differentiation through various different mechanisms. The actions of PTHrP are mediated by the G protein coupled PTH/PTHrP receptor. Activation of this receptor causes a GDP-GTP exchange on the alpha-subunit of Gs (Gs α) and, thereby, leads to the dissociation of Gs α from G $\beta\gamma$ subunit. The free, GTP bound Gs α then stimulates the generation of cyclic AMP (cAMP), a ubiquitous second messenger molecule. cAMP molecules bind to the regulatory subunit of protein kinase A (PKA), thus releasing the catalytic subunit. Activated PKA phosphorylates multiple different targets, which collectively mediate the effects of PTHrP in the growth plate. The Gs α -cAMP-PKA signaling pathway is regulated by the activation of cAMP phosphodiesterases, which convert cAMP into AMP. Genetic defects directly affecting the different components of this signaling pathway result in impaired bone growth and are the cause of various skeletal dysplasias in humans, including Blomstrand's chondro-osteodystrophy, Jansen's metaphyseal chondrodysplasia, Albright's hereditary osteodystrophy, acro-dysostosis, brachydactyly-mental retardation syndrome, and brachydactyly type E2.

WG1.3

New Therapies in Metabolic Bone Disease: Denosumab

M Collins

Bethesda, USA

Osteoclasts are bone-resorbing cells important in normal growth plate development and bone remodeling. The development of osteoclasts is potently driven by mononuclear RANK and osteogenic cell RANKL interaction. Denosumab is a monoclonal antibody drug that targets RANKL and inhibits osteoclastogenesis. It is a potent and effective treatment for pathologic processes that involve bone resorption, such as osteoporosis and bone metastases, conditions for which it is approved. Denosumab is also approved for the treatment of giant cell tumors, benign neoplasms composed primarily of fibroblast-like cells of osteogenic origin with abundant osteoclast-like multinucleated giant cells the highly express RANK. Denosumab has been successfully used off-label, including in children, in other bone diseases that involve osteoclast-driven bone resorption and giant cell-rich diseases such as hypercalcemia of malignancy and fibrous dysplasia of bone. However, its use and discontinuation, especially in diseases with high bone turnover, can be associated with significant adverse side effects. In addition,

the use of this potent drug in children raises concerns of untoward effects at the growth plate. This concern is similar to that raised when bisphosphonates were first used in children. While the stigmata of bisphosphonate use in growing children are evident for years after discontinuation in the sclerotic bands seen on radiographs, over 10 years of experience has assured us that at appropriate doses normal linear growth can be maintained. This point, and our case report demonstrating resumption of normal growth plate histopathology 17 months after discontinuation of denosumab in a child with fibrous dysplasia, offers reassurance that denosumab use in children may be safe once appropriate regimens have been determined. Before this promising drug can be used in children, work remains to identify and manage patients at high risk for side effects, and determination of a regimen that allows normal growth to proceed.

WG1.4

Abstract unavailable.

WG2.1

Technological Horizon for the Treatment of Diabetes

Moshe Phillip

Institute for Endocrinology and Diabetes, Schneider Children's Medical Center of Israel, Petah Tikva, Israel

The daily treatment of pediatric patients with diabetes is challenging for patients, parents and medical teams. This is probably the reason why most patients all over the world do not meet the targets of glucose control defined by world organizations like ISPAD, EASD and the ADA as the safe zone for preventing complications, extending life expectancy and improving quality of life. New emerging technologies are in the pipeline of both academic centers and industry that promise to change the way diabetes is treated.

Advisors, coaches, calculators, new medications, automatic systems, cellular manipulation, genetic engineering, telemedicine and automatic insulin delivery systems are all in the horizon for patients with diabetes to cure or at least alleviate the burden of the patients' shoulders, parents and care givers in their constant attempts to navigate the glucose control towards the safe range of diabetes control.

WG2.2

Non-Insulin Glucoregulatory Therapy for Type 1 Diabetes

Peter Bang

Abstract unavailable.

WG2.3

Debate: Should all Newly Diagnosed Patients with Diabetes Need to be Hospitalised?

Nadia Tabiana-Rufi

Abstract unavailable.

WG2.4

Debate: Sensor/Pump Therapy from the Onset of Diabetes?

Tadej Battelino, Liat de Vries

Abstract unavailable.

WG2.5

Debate: do we Need Long Acting Insulin Analogs?

Carine de Beaufort, Ragnar Hanas

Abstract unavailable.

WG2.6

Early Implementation of Insulin Pump Therapy after Diabetes Onset: is There Added Benefit?

Liat de Vries

The Jesse Z and Lea Shafer Institute of Endocrinology and Diabetes, National Center for Childhood Diabetes, Schneider Children's Medical Center of Israel, Petah Tikva, Israel

Patients with type 1 diabetes (T1D) and their caregivers continue to face the challenge of maintaining blood glucose levels in the near-normal range, preventing sustained hyperglycemia associated with long-term microvascular and macrovascular complications, and avoiding recurrent episodes of hypoglycemia, especially at young ages when they can adversely affect cognitive function. In a follow-up to the Diabetes Control and Complications Trial, the Epidemiology of Diabetes Interventions and Complications study showed that achieving optimal metabolic control as early as possible in the course of the disease delays the onset of diabetes-related complications.

Over the past decade, continuous s.c. insulin infusion (CSII) has become a standard treatment option for patients with T1D. CSII mimics physiologic insulin release better than multiple daily injection (MDI) therapy and allows for greater flexibility in food intake and physical activity. These evident benefits raise the question 'Does early initiation of CSII treatment in patients with T1D shortly after diabetes onset yield added benefit?'

The evidence regarding the impact of early CSII treatment initiation on glycemic control and β cell preservation will be discussed.

WG2.7**Long Acting Insulin: Friend or Foe?***Carine de Beaufort*

DECCP, Pediatric Clinic /CH de Luxembourg, GD de Luxembourg, Luxembourg

Current treatment in type 1 diabetes focuses on the development of physiological insulin replacement. Although this has led to the increased progress in the development of semi closed loop systems and different algorithms allowing this, the majority of youth still has to cope with insulin injections. Improving metabolic outcome with injection therapy has become more demanding, imposing an increased number of injections and improved knowledge of food composition. For those able to calculate the appropriate meal dose and without injection phobia these intensified multiple dose strategies have led to improved outcome, and more flexibility in life style. To cover for the overnight period, an insulin without peak and of at least 12 h effect should be used. The development of these products have led to a reduction in nocturnal hypoglycemia and improved outcome.

Over time it has clearly been shown that this option does not fit all. Numeracy may be one problem as well as non acceptance of diabetes or need phobia.

In the adolescent group this problem can be observed regularly and potentially one injection may be given. Current development includes longer acting insulins which may cover at least 18–24 h. Although meal adjustment is still requested the basal need could be covered by such products. Not only adolescents with type 1 diabetes, but as well the increasing number of youths with type 2 diabetes form a potentially relevant group as the early use of metformin and insulin becomes more frequent.

Further studies are needed to identify the best use for these products in the different age groups, improving metabolic control without increased weight gain or acute complications. This will allow the clinician to tailor the treatment to the individual patient ensuring optimal long term outcome.

WG2.8

Abstract unavailable.

WG3.1**Genetic Variation in Human SF-1 (NR5A1): Clinical Consequences for Individuals, Families and Populations***John Achermann*

UCL Institute of Child Health, London, UK

Steroidogenic factor-1 (SF-1, *NR5A1*) is a key regulator of adrenal and gonad development, and controls transcription of

many genes in these endocrine axes. A role for SF-1/*NR5A1* in human endocrine conditions was first established 15 years ago when rare individuals with adrenal hypoplasia and 46,XY DSD (testicular dysgenesis, Müllerian structures) were reported. Although it was felt that adrenal failure would be a key feature of SF-1 disruption, in the past decade it has emerged that variations in SF-1/*NR5A1* are relatively frequently associated with a range of 46,XY DSD phenotypes in individuals who have normal adrenal function. These phenotypes range from 46,XY complete testicular dysgenesis, through varying degrees of hypospadias/undescended testes, to male factor infertility and potential progressive endocrine dysfunction. Changes in SF-1/*NR5A1* are also associated with primary ovarian insufficiency in DSD families or in sporadic cases. Evidence suggesting a causative (or at least strongly-associative) role for SF-1/*NR5A1* in DSD comes from the strong co-segregation of phenotype with genotype within families, the high rate of *de novo* dominant or sex-limited dominant inheritance, and ‘burden testing’ showing a much higher prevalence of SF-1/*NR5A1* variation in DSD populations compared to controls. However, variable penetrance of phenotype is seen and an unexpected number of (non-validated) SF-1/*NR5A1* changes are being described in so-called control population databases of exome sequencing (e.g. EVS, 1000 genomes). Are these artefacts, non-penetrant phenotypes or could these changes represent a pool of population infertility? How do we counsel families about progressive changes in endocrine function or the risk of POI? Will individuals with SF-1/*NR5A1* changes be at risk of adrenal insufficiency, or features such as obesity, anxiety or hyposplenism reported in mice? Is the p.G146A polymorphism important in humans? How do we get better information about the complexities of SF-1-associated conditions to health professionals and families? These issues will be discussed.

WG3.2**The Potential Role of the Alternative ‘Backdoor’ Pathway for Androgen Synthesis and Virilisation in CAH***Clemens Kamrath*

Justus-Liebig University, Giessen, Germany

Data from urinary steroid metabolomics approach gave evidence that the ‘backdoor’ pathway might act as a source of androgen synthesis in CAH. Although the prenatal role of this pathway in CAH is unknown, the backdoor pathway could be involved in fetal androgen metabolism and could contribute to genital virilisation. The traditional concept of androgen synthesis in CAH postulates that androstenedione acts as a precursor of testosterone and dihydrotestosterone, and that androstenedione is normally produced by metabolism of DHEA. Additionally, the Δ^5 pathway via DHEA strongly predominates in the human testis and adrenal because the catalytic efficiency for the 17,20-lyase reaction of CYP17A1 is nearly 100-fold greater for Δ^5 17 α -hydroxypregnenolone than for Δ^4 17 α -hydroxyprogesterone. However, the fetal adrenal normally produces abundant DHEA which is further

converted to estriol in the placenta, protecting the female fetus from virilisation. As backdoor pathway derived androgens are already 5 α -reduced, they cannot be aromatized to estrogens. Therefore, this new concept of androgen synthesis via the backdoor pathway in CAH might contribute to better understanding of virilisation in CAH.

WG3.3

Long-term Outcome of Prenatal CAH Therapy

Svetlana Lajic

Karolinska Institutet, Stockholm, Sweden

Prenatal treatment of CAH has been employed since the mid 1980's, but long-term evaluation of this experimental treatment is scarce. *In utero* replacement with dexamethasone suppresses the fetal adrenal and reduces the androgens that virilise the female CAH fetus. The CAH girls are thus born with normal external genitalia and avoid early genital surgery. There is however an ethical dilemma, since the treatment with DEX has to be initiated early in gestation before genetic testing is possible and seven out of eight fetuses are thus treated during early gestation without any benefit of the treatment *per se*. Accumulating evidence tells us that the hormonal and nutritional milieu *in utero* predisposes the child to a range of diseases later in adult life. Whether prenatal DEX therapy as used in the treatment of CAH has any adverse effects on the treated fetus has been the subject of debate during the last decade. Excess levels of glucocorticoids given to experimental animals during fetal life have shown both short- and long-term consequences. In Sweden, prenatal treatment of CAH has been administered within the frameworks of a clinical study since 1999. The aim of the study is to evaluate treatment efficacy and to identify potential side-effects in the pregnant woman, the fetus and the growing child until adult age. Longitudinal growth, metabolic status and neuropsychological outcome in conjunction with structural and functional effects on the developing brain are evaluated. Fetal programming effects at a molecular level are also addressed. The importance of continued long-term follow-up of treated cases is emphasized by previous studies from our group indicating a negative effect on working memory in children exposed to DEX during the first trimester. These first reports has led us to halt further prenatal treatment of CAH in Sweden (since 2011) until we know more about the long-term outcome of this experimental therapy.

WG3.4

Detailed Phenotyping of DSD: External Virilisation

Michelle Welsh

University of Glasgow, Glasgow, UK

Background: During fetal development, the reproductive tissues of a male and female are initially identical until around

7 weeks of gestation. At this point, chromosomal sex dictates the development of a testis or ovary which in turn drives phenotypic sex of the individual. This involves a pre-programmed series of events which results in the differentiation of the indifferent reproductive tissues into sex-specific organs. The brain must also undergo sex-specific development which may in turn influence gender identity. However, research suggests that this may rely on different signals and may be controlled at different times of development.

The sex-specific development of the external genitalia is immediately apparent at birth and is thus commonly used to identify and diagnose individuals with possible disorders of sex development (DSD). Atypical genitalia that may point towards a DSD occur in about 1:300 births. These may present with ambiguous genitalia or with genitalia which have not developed along the typical male or female pathway, presenting as hypospadias or cliteromegaly. There are many steps in typical sex development, of which any one can be impaired in DSDs, therefore correct diagnosis and clinical management of esthese individuals requires an understanding of typical sex development to ensure a high quality of life. **Objective and Hypotheses:** The process of typical sex development and how this can be altered in DSDs will be discussed in this presentation. Furthermore, recent research suggests that measuring anogenital distance (AGD) could provide a life-long readout of androgen action during masculinization and therefore provide new insights into androgen action during this previously 'hidden' period of development. The clinical implications of this will also be discussed.

WG3.5

Imaging of the Urogenital Tract

Lutz Wunsch

Lubeck, Germany

Disorders of sex development present with a wide spectrum of phenotypic variations. The gonads, sex ducts and genitalia as well as the urinary system are must be evaluated to make a diagnosis and a plan for treatment or observation. Ultrasound stands out as the most versatile imaging modality. Investigation of the urinary tract, the uterus and the examination of normally developed gonads are possible. Perineal ultrasound provides additional information on the pelvic floor, the bladder neck and urogenital sinus anomalies. Ultrasound is most useful at diagnosis and during follow-up. Magnetic resonance imaging allows complete imaging of the pelvis and abdomen, but motion artefacts and lack of resolution are limiting factors. MRI is a useful technique for adolescents and adults both at diagnosis and during follow-up. Genitoscopy, urethroscopy and laparoscopy require anaesthesia and are useful at the end of the diagnostic evaluation, if biopsies, hernia repairs or gonadectomies are planned. Examples of imaging results in typical clinical situations are discussed.

WG3.6

I-DSD and I-CAH Registry Update

Jillian Bryce

University of Glasgow, Glasgow, UK

Background: Effective clinical care and research in disorders of sex development (DSD), as well as assessment of long-term outcome of these rare conditions, requires multicentre collaboration across national boundaries and across multiple clinical and research disciplines. This registry is currently funded by the UK MRC as the International DSD Registry (www.i-dsd.org) which adheres to the highest standards of data governance and security. From this platform, the I-CAH Registry has also been developed to support research and improvement in clinical care of patients with congenital adrenal hyperplasia. **Results:** In February 2014, there were 1300 cases added by registered users from 31 centres in 19 countries across four continents. A further 65 centres from 26 countries covering all six habitable continents have registered as users. The median year of birth of cases entered is 1997 (range 1927–2013). Over 50% of cases are now over 16 years old and registered clinicians can contact other clinicians to discuss expert management of similar cases. The commonest disorder type is disorders of androgen action (377) followed by disorders of gonadal development (295). The Registry has been developed into an optional modular structure for adding clinical data. The Registry supports the development of new primary research through generation of new modules (such as the newly launched CAH module) and also supports secondary research on the existing dataset. Two such projects were recently completed: a review of associated congenital anomalies and a study of trends in sex assignment. There are currently seven active studies based in five countries, with a further six in development. **Conclusions:** The I-DSD and I-CAH Registries are open to new researchers and clinical contributors who can register at www.i-dsd.org (I-DSD) or www.i-cah.org (I-CAH). In addition to acting as a resource for performing studies, the I-DSD Registry is facilitating the development of a network of DSD centres and specialists and can form the backbone of initiatives such as DSDnet.

WG3.7

DSD-Life: Clinical European Study on the Outcome of DSD

Birgit Köhler

Charite, Paediatric Endocrinology, Berlin, Germany

dsd-LIFE is a comprehensive clinical outcome study investigating medical, surgical, psychosocial and ethical issues to improve treatment and care of patients with the different diagnoses included in the umbrella term disorders/differences of sex development (dsd). The multidisciplinary dsd-LIFE consortium consists of 15 experienced European scientists in the areas endocrinology, psychology, surgery, gynaecology, urology and ethics. The fields of investigation of dsd-LIFE are HRQOL

psychological well-being, psychosexual development, surgery, hormones, metabolism, patients' view, ethics and cultural context. In 2013 the study protocol and the online database have been developed in six languages. Patient support groups have contributed to the study protocol, Physicians, psychologists and nurses have received training on standard operating procedures (SOP) to perform the study in a standardized manner in all study centres. The study is conducted in Germany, United Kingdom, France, Sweden, the Netherlands and Poland.

The recruitment phase of participants has started in February 2014 (duration February 2014–July 2015). Patients with the various diagnoses included in dsd are invited to participate in the study: Turner syndrome, Klinefelter syndrome, congenital adrenal hyperplasia (CAH), impaired testosterone synthesis (e.g. 5- α -reductase-2 deficiency, 17- β -HSD-3 deficiency, LH-receptor defects), impaired androgen action (complete androgen insensitivity, CAIS; partial androgen insensitivity, PAIS), dysgenesis of the testes or ovaries, mixed gonadal dysgenesis, karyotype 46,XY/46,XX, 46,XX or 46,XY ovotestes, hypospadias. Participants should be 16 years or older.

Please inform your patients with dsd about the study. For further information how to participate in the study the local study centers are pleased to help. Please find detailed contact information of the local study centers on our website. Study flyers in the different languages are also available on the website. <http://www.dsd-life.eu/participant-information-about-the-study/>. **Funding:** European Union seventh Framework Programme (FP7/2007-2013) under grand agreement no 305373.

WG3.8

DSDnet: a COST Action on the Systematic Elucidation of Differences of Sex Development

Olaf Hiort

University of Lübeck, Lübeck, Germany

Background: The European Programme on Cooperation of Science and Technology (COST) funds the formation of networking activities. These are especially favorable for research around rare diseases, because experts and scientists maybe at different centres and an international collaboration is needed.

In November of 2013 the COST Action DSDnet was started. Currently 18 different European countries are participating and countries from all continents have voiced an interest for collaboration. The aims are to form a network of scientists for translational research, to bring forward a European Reference Network on DSD connecting national centres of expertise for better care, and to provide information to professionals, stake holders, and the public on the topic.

To reach these aims, DSDnet has build five working groups, which will provide consented information on (a) clinical approaches, (b) genetics and biology, (c) laboratory aspects, (d) perception of research, and (e) dissemination of information. Information will be made available through a public website. An agenda of future research necessities will be compiled and funding bodies approached.

WG4.1

Abstract unavailable.

WG4.2**Natural Course of Impaired Glucose Tolerance in Obese Children**

Thomas Reinehr

Department of Pediatric Endocrinology, Diabetes and Nutrition Medicine, Vestische Children's Hospital Datteln, University of Witten/Herdecke, Witten, Germany

Obesity in childhood is associated to several cardiovascular risk factors summarized in the definition of metabolic syndrome such as hypertension, dyslipidemia and impaired glucose tolerance. Besides others, the pathogenetic background is insulin resistance, which deteriorates in mid puberty and normalizes at end of puberty. Accordingly, blood pressure, lipids, fasting glucose and 2 h glucose in oGTT increased from prepubertal stage to pubertal stage and decreased from pubertal stage to postpubertal stage as demonstrated in a longitudinal study of 287 untreated obese children of our obesity cohort. Re-evaluating 128 obese children with impaired glucose tolerance (IGT) and without intervention demonstrated that even degree of overweight remained stable 5 years after baseline only 2% of the children suffered from type 2 diabetes (T2DM) at this timepoint, 16% of children remained in IGT state and 75% of children showed a normal glucose tolerance test, while 7% got lost to follow-up. In another 1-year follow-up study of 79 untreated obese children with IGT, 66% converted to normal glucose tolerance, while 32% remained IGT and one child was diagnosed with T2DM. Predictive factors for normalization of IGT were lower weight, HbA1c and 2 h glucose levels in oGTT, as well as late pubertal stage at baseline. However, the long-term outcome of obese pubertal children with IGT after 10–20 years is unknown and they may be prone to develop T2DM at this age. Due to the normalization of insulin resistance associated comorbidity in obese children moving from pubertal to postpubertal stage the necessity of a drug treatment such as metformin is questionable especially in obese pubertal children with only slightly elevated 2 h glucose levels in oGTT. Moreover, all studies dealing with drug treatment in this age group must have an untreated control group to account for the normalization of insulin resistance at the end of puberty.

WG4.3

Abstract unavailable.

WG5.1**New Markers of Ovarian Function in Girls**

Anders Juul

Department of Growth and Reproduction, Rigshospitalet, Copenhagen, Denmark

The hypothalamo-pituitary-gonadal axis (HPG) is activated in healthy girls during infancy; the so-called minipuberty occurring 2–3 months postnatally. Minipuberty is followed by a relative quiescent period during childhood, during which gonadotropins and gonadal steroids circulates at extremely low concentrations. At the onset of puberty the HPG axis is reactivated. Evaluation of ovarian function is clinically relevant in girls with pubertal disorders (early and late). However, it is also important to evaluate remaining or future ovarian function in girls with sex chromosome disorders (45X), or girls who are exposed to gonadotoxic stimuli (chemotherapy, galactosaemia, etc). Evaluation of ovarian function is determined by measuring of basal levels of gonadal steroids and peptides. Determination of estradiol has proven valuable for decades but requires use of an ultrasensitive RIA or by LC-MS/MS. Other ovarian markers include progesterone, inhibin A, inhibin B, AMH and Insl3 which can now be determined by commercially available immunoassays. Levels of these markers before, during and after normal puberty will be presented.

WG5.2**Amenorrhea and Hypothalamic–Pituitary Dysfunction**

N Pitteloud

Service d'endocrinologie, diabétologie et métabolisme, Lausanne, Switzerland

Female reproductive disorders due to a hypothalamic–pituitary defect include hypothalamic amenorrhea (HA), polycystic ovarian syndrome (PCOS) and hyperprolactinemia. This talk will review the clinical presentation of HA, PCOS and hyperprolactinemia in adolescents and young adults and will provide an overview of recent clinical advances in the field.

WG5.3

Abstract unavailable.

WG5.4

Abstract unavailable.

WG5.5**Contraception in Adolescence from a Public Health Perspective***Pierre-André Michard*

Multidisciplinary Unit for Adolescent Health, Lausanne, Switzerland

Recent data pertaining to the bio-psychosocial development of the adolescent, particularly from a neurobiological perspective, indicate that both at the level of individual care and of preventive strategies, the concepts, languages and strategies used should be adapted to the maturity of the adolescents. Moreover, since around thirty years under the era of AIDS, the medical scientific literature tackling the issue of adolescent sexuality and sexual behavior has sadly focused either on the prevention of pregnancy, or the issue of STIs, rarely both. This gap deteriorates the impact of health care delivery and prevention or health promotion.

We propose an integrated approach to the issue of oral contraception during adolescence taking into account the physiological and maturational vulnerability of minor adolescents, and addressing the three developmental stages of adolescence.

On the individual level the policies which govern adolescent care should incorporate issues such as confidentiality and the right to make decision. On the level of school and community health, the preventive strategies that are implemented should be evidence based and involve adolescents themselves. At a broader level, the legal framework and the policies developed should improve access to oral contraception, including the use of emergency contraception.

WG5.6**Contraception in Adolescence: Current Options***Catherine Gordon*

Hasbro Children's Hospital and Brown University, Providence, Rhode Island, USA

Adolescent girls may present to their pediatric or reproductive endocrinologist seeking advice regarding contraception. In 2014, there are many methods available, and the risks and benefits of each must be weighed in determining which method is most appropriate for a given patient. This lecture will provide an overview of contraceptive methods, with a focus on oral contraceptive pills, transdermal patches, and the vaginal ring. Methods will be reviewed with a focus on thrombotic risk and bone health as potential health risks. Recommendations for evidence based prescribing will be discussed, considering guidelines from the World Health Organization (WHO) and US Centers for Disease Control and Prevention (CDC). Cases will be used to illustrate points including the amenorrheic athlete, adolescent girl with polycystic ovary syndrome, and the receipt of other medications that may affect hormonal metabolism, and therefore, have implications for contraceptive efficacy.

WG5.7**Lessons Drawn from Rare Gynaecological Disorders in Relation with Ovarian Malfunction***Maud Bidet*

Center of Gynaecologic Rare Diseases, Paris, France

In 2004, in France a national plan for rare diseases was structured. The improvement in healthcare provision for rare diseases constitutes a major challenge for public health owing to the epidemiological data, the consequences of these pathologies for the quality of life of the patients and their families and the challenges for research in the domains of diagnosis and treatment. In 2007, with a significant experience about gynaecological care of children and adolescents with rare diseases, a National Center of Gynaecologic Rare Diseases has been created.

Pathologies of center are: rare benign breast disease, gynaecological consequences of inherited bleeding disorders, Mullerian malformations and gynaecological consequences of rare chronic disease.

Rare chronic disease can disrupt ovarian function or gonadotropic axis due to the disease itself or because of their consequences. For example, premature ovarian failure (POF) has been described in rare hereditary metabolic disorders like in patients with galactosemia or congenital disorders of glycosylation (CDG) syndrome. Classic galactosemia and CDG syndrome are rare hereditary disorder of galactose metabolism and glycoprotein synthesis respectively. Long-term diet-independent complications of galactosemia consist of premature ovarian failure and cognition sequela. CDG I type is the most frequent form of CDG is characterised by multisystem manifestations, in particular the nervous system.

We report clinical criteria, biological and sonographic characteristics to evaluate the gonadal function in these women, establish recommendations on the management of their puberty and fertility and assess the indications of ovarian preservation for women with galactosemia.

We report 101 filled questionnaires, from 45 males and 56 females with galactosemia. Sixty-nine percent of women had a spontaneous puberty with a first stage of breast development appearing at 12 years ($n=31$) and 25/31 women had spontaneous menarche at 14.6 years (14 women had induced menarche at 17 years old). This is significantly later than in 251 girls from a French cohort who had menses at 12.6 years ($P<0.01$). Fifty percent of women had secondary amenorrhea. Eleven girls under 16 had an FSH dosage, with an average of 8.1 IU/l for girls with spontaneous puberty and 103 IU/l, for girls without. Women over 16 years old had an average FSH level of 73 IU/l. All the pelvic ultrasounds ($n=15$) showed small ovaries $<0.3\text{ cm}^3$ without visible follicles. Four women out of five desiring a pregnancy succeeded, 3/4 with spontaneous puberty, 2/4 with regular menstrual cycles.

Premature ovarian failure (POF) has been usually described in CDG women. We report ovarian function in 17 patients CDG Ia (15.7 years (1.9–35.9) and two patients with CDG1b. In the ten patients with CDG1a aged of more 13 years old, none had spontaneous puberty. FSH level ($n=17$) was high, except in two patients aged 8.8 and 9.3 years old and AMH ($n=13$) was undetectable or below the normal range. In pelvic ultrasound ($n=15$), normal ovary area was described in only one patient. In

contrast, in two patients with CDG 1b, one had spontaneous puberty and FSH and AMH levels were normal. Finally, 64% (9/14) had a risk of thrombosis (antithrombin III, and/or protein S and/or protein C defect) and 7/14 had bleeding disorders.

In conclusion, in galactosemia and CDG syndrome patients, POF consist a long-term complication. POF seems fluctuating in galactosemia and more severe and precocious in CDG I syndrome. In these two pathologies, mechanisms of ovarian injury remained to be fully elucidated and which help us to understand pathways in ovary or gonadotropic axis. POF is often overlooked in adolescents with chronic rare disease. With other rare disease centers (for example centers for metabolic disorders), a systematic follow up of the puberty for these patients can be organized. Moreover, the center is multidisciplinary. So, with adult colleagues and surgeon colleagues we can organize transition and preservation of fertility. We believe that such a center for rare gynaecological disorders is fully relevant to improve quality of care.

WG6.1

Liver Involvement in Turner Syndrome

Dominique Roulot-Marullo

Hopital Avicenne, Groupe Hospitalier Paris-Seine Saint-Denis, APHP, Université Paris 13, Sorbonne Paris Cité, Paris, France

Liver test abnormalities are frequent in adult patients with Turner syndrome, corresponding to various pathophysiological mechanisms. Steatosis, steatofibrosis and steatohepatitis are the most frequently reported lesions, caused by metabolic disorders, which are commonly related to overweight. Marked architectural changes, including nodular regenerative hyperplasia, multiple focal nodular hyperplasia and cirrhosis, found in some patients, are associated with a risk of severe liver-related complications. Architectural changes are often observed and are associated with vascular disorders caused by congenitally abnormal vessels. Finally, small bile duct alterations resembling sclerosing cholangitis occur in several patients. Oestrogen replacement therapy does not cause liver toxicity in patients with Turner syndrome and is not contraindicated in case of elevated liver enzymes. Moreover, in recent studies, oestrogen therapy was reported to improve liver function tests. Because of the wide spectrum of potential liver injuries that may occur in Turner syndrome patients, a regular screening of liver enzymes is recommended for early detection and treatment. Liver stiffness measurement by transient elastography might be a useful tool to identify patients necessitating more invasive diagnostic procedures (liver biopsy).

WG6.2

Abstract unavailable.

WG6.3

Abstract unavailable.

WG6.4

Motor Performance in Turner Syndrome

Janielle van Alfen

Radboud University Medical Centre, Nijmegen, The Netherlands

The aim of this presentation is to give an overview of motor disabilities in girls with Turner syndrome (TS), the impact on daily life and suggestions for treatment.

Girls with TS show substantially lower performance in gross and fine motor function tests and motor milestones are achieved relatively late. Moreover, girls with TS frequently encounter problems in specific motor functioning i.e. oral-motor and visual-motor coordination, motor learning and problems with accuracy and movement speed.

In our clinic, evaluation of motor function is part of the routine multidisciplinary evaluation in patients with TS. At the age of 5, 11, and 16 years, patients are screened for motor performance impairments by means of the movement assessment battery for children-2 (MABC-2). Visual coordination of visual perception in relation to finger-hand movements is tested by means of the developmental test of visual motor integration (VMI) and if appropriate a test for handwriting difficulties is used. In this presentation, we present the results of our motor screening.

Impaired motor ability can result in multiple practical problems that are age specific. Examples of these practical consequences include feeding difficulties (infant), problems with writing, participation in sports (school age), choice of study and employment (adolescents). We discuss practical suggestions for coaching and treatment.

In our opinion, adequate counseling by an experienced physical therapist and physician is important to optimize support for girls with TS at the level of activities and participation.

WG7.1

Quality of Life and Anxiety in Adolescents with Differentiated Thyroid Cancer

Melissa Anne Benoit

The Hospital for Sick Children, Toronto, Ontario, Canada

Background: Clinical observations of children and adolescents with differentiated thyroid cancer (DTC) patients led us to investigate quality of life and anxiety. Although adult DTC survivors have similar or slightly worse quality of life (QOL), this has not been evaluated in the pediatric population. **Objective and Hypotheses:** In this cross-sectional pilot study, our objective was

to compare QOL and anxiety in adolescents with DTC to patients with acquired autoimmune hypothyroidism. **Method:** In this cross-sectional pilot study, our objective was to compare QOL and anxiety in adolescents with DTC to patients with acquired autoimmune hypothyroidism. Three validated questionnaires were administered to 16 adolescents with DTC and 16 controls for assessment of QOL and anxiety levels. These included teen and parent PedsQL, multidimensional anxiety scale for children (MASC), and Coddington life events scales for adolescents. The contribution of age, time since diagnosis, and biochemical variables were compared with the outcome measures. **Results:** There were 16 DTC patients (seven males); 13 had papillary carcinoma, one had follicular carcinoma, and two had mixed type. At diagnosis, five DTC patients had lymph node involvement and two had lung metastases, although at time of assessment, only one DTC patient had lymph node involvement. DTC patients were older than control subjects ($P=0.004$) and had lower TSH levels than control subjects at time of assessment ($P=0.013$). QOL and anxiety levels did not differ between DTC patients compared with control subjects and with previously reported scores in a healthy cohort. QOL and anxiety level parameters were not influenced by age, time since diagnosis, or free T_4 levels measured at the time of assessment. **Conclusion:** We conclude that adolescents with DTC have similar QOL and anxiety levels compared with autoimmune hypothyroidism patients and with a healthy normative population. However, further areas of research are warranted.

WG7.2

Evolving GH Therapy Patient Training in a Digital World

Galit Asher

Institute for Endocrinology and Diabetes National Center for Childhood Diabetes Schneider Children's Medical Center of Israel, Petah Tivka, Israel

Introduction: In recent years there have been rapid advances in modern communication technologies that have reached almost every child in the western world. The ways children interact and consume new information have changed in the digital age. Yet, most of the GH patients' training is based on a face to face interaction using written materials. **Aims:** To increase patients' knowledge, enhance positive feelings and decrease significantly fears of the unknown as well as shorten the time devoted by the nurses for GH therapy (GHT) GHT education. **Methods:** We have developed an application for training, which is children-friendly, using known technologies such as touch screen tablets and interactive apps, which are usually associated with children's enjoyment and excitement when playing games and communicating one another. We are conducting a pilot prospective study, evaluating and comparing the 'conventional' and 'interactive' GHT patient training, by asking patients and their parents to fill questionnaires. Parameters that are being studied are: length of training, patients' knowledge levels as well as parents' and patients' satisfaction. **Results:** The results of the pilot study will be presented at the meeting. **Conclusions:** New digital methods

familiar to children of the current generation should be tested in GHT education to enhance efficiency and to improve patients' satisfaction and their knowledge.

WG7.3

Endocrine Nursing, Social Media, and Research: Results of an International Study

Kate Davies

Great Ormond Street Hospital, London, UK

Background: Social media usage is rapidly changing and advancing methods of communication, both personally and professionally. To bridge the theory practice gap, nurses need to be involved in research, both conducting, reading and disseminating. Currently, no journal exists for endocrine nurses. **Objective and Hypotheses:** To explore endocrine nurses' experiences in conducting, reading and disseminating research, and whether social media would be an appropriate channel, or if a new endocrine nursing journal or platform could be developed. **Method:** An International Internet Survey was distributed to UK Nurse members of the British Society of Paediatric Endocrinology (BSPED) and the Society of Endocrinology. Flyers with a link to the survey were distributed at The Society of Endocrinology Nurse Update (Stratford upon Avon, UK, 2013), European Society of Paediatric Endocrinology (ESPE) Nurses session (Milan, Italy, 2013), BSPED Nurses meeting (Brighton, UK, 2013), European Congress of Endocrinology Nurses Session (Wroclaw, Poland, 2014) and the joint International Congress of Endocrinology/American Endocrine Society (ICE/ENDO) Nurses Symposium (Chicago, 2014). Key representatives from endocrine nursing groups in Australia, the USA and Europe were also emailed. We actively encouraged respondents to distribute the survey link within their professional networks. **Results:** The majority of endocrine nurses use social networks on a professional basis, however a sizeable minority use them to keep up to date with current research and professional development. A considerable proportion of endocrine nurses expressed an interest in contributing to an endocrine nursing journal, with a strong preference being shown for nurse led research, case histories, guidelines, and literature reviews. **Conclusion:** In the light of the results, we conclude that endocrine nurses are well motivated to create and consume primary research in a networked environment, and that neither existing journals nor non-specialist social networks adequately meet their professional needs.

WG8.1

Global Pediatric Endocrinology and Diabetes: Opportunities and Call for Membership Involvement

Jean-Pierre Chanoine

University of British Columbia, Vancouver, British Columbia, Canada

Global Pediatric Endocrinology and Diabetes (GPED) aims at addressing needs that are common to all societies and is not intended to duplicate the specific societies' activities. GPED's website (www.globalpedendo.org) allows for registration of members as well as for a search function.

Specific existing and potential projects include:

- i) Preventing redundancy of resources: development of an environmental scan that aims at sharing resources for health professionals and families such as protocols, guidelines, medical condition information in various languages (ongoing).
- ii) e-learning: GPED members benefit from the modules developed by the ESPE through a direct link to the espe-elearning.org site (ongoing). GPED will support a version of the modules that is reflecting the specific needs of low income countries.
- iii) Promoting access to essential medicines: GPED will stress the importance of non-communicable diseases (NCDs) for the global health agenda and advocate for better access to essential medicines in low income countries.
- iv) Research funds: GPED will support GPED members to develop research projects that are relevant to their community and patients.
- v) Clinical case discussions: GPED is considering the development of a confidential forum for the discussion of clinical cases. GPED is presently looking for members who will want to devote time to actively work on existing and future projects in the field of training, mentoring, advocacy, grant writing and who will contribute to the development of GPED.

WG8.2

Management of Type 1 Diabetes Mellitus in Sudanese Children: Can We Implement International Guidelines?

Mohamed Abdullah

University of Khartoum, Khartoum, Sudan

Like many other parts of the world the incidence of type 1 diabetes is increasing in Sudan leading to the double load of communicable and noncommunicable diseases. Many international guidelines for management of these cases have been published to help managing these children. In developing countries proper implementation of these guidelines is faced with difficulties due to lack of trained personnel, health care structure, accessibility to medical services, lack of facilities in addition to low health care budget. This is compounded by poverty, ignorance and adapted to the high illiteracy rate. Most medications and monitoring facilities are costly and beyond the ability of most of the families. Therefore these guidelines might need to be on adapted to suit the local situation of each country taking into consideration the sociocultural factors.

In this communication we will share our experience sudanese on building up services for caring of children with diabetes and show the outcome of collaboration between the local NGOs (Sudanese Childhood Diabetes Association), the Government Nd International NGOs. Management guidelines have been adapted, services made accessible as well as medications and monitoring

facilities. The rate of acute complications and death at onset have been reduced. However still a lot have to be done to improve on HbA1c and chronic complications. Governments need to be more committed and more budget made available for health services this in addition to fighting against poverty and ignorance.

WG8.3

Global Inequalities: Limited OI Treatment Options in Indonesia

Aman Pulungan

Department of Child Health, University of Indonesia-RSCM, Jakarta, Indonesia

Background: It is estimated that 12 000 people in Indonesia experience OI, yet only 35 patients diagnosed with OI until September 2013. It portrayed many under-diagnosed and misdiagnosed OI cases. The limited number of diagnosed OI cases made the management not prioritized and aggravated the lack of awareness of OI. As a consequence, zolendronic acid (ZA), the drug of choice in treating OI in the world, had not yet registered on the list of national essential drugs. **Objective and Hypotheses:** To improve awareness and the number of diagnosed cases of OI; to have ZA as the drug of choice, covered by the national health care insurance, and included in the national guidelines. **Method:** Indonesian Paediatrics Society (IPS), working together with Caring and Living as Neighbours (CLAN, Australia), and Royal Children Hospital (RCH, Australia) generated educational courses for the patients and the family, paediatricians, and medias in November 2013. They also established a family community of OI, FOSTEO. **Results:** Within just 3 months, the registered OI patients raised up to 70. ZA has been used as the choice of treatment in the national hospital, Cipto Mangunkusumo Hospital (RSCM), with rigorous monitoring and scheduled treatment. ZA has also been included on the list of drugs covered by the national health insurance. 26 patients treated with ZA in RSCM since January 2014. **Conclusion:** Although there were a lot of improvements on the management and OI awareness, there are still disparities and inequalities on OI medication access in every region in Indonesia. Accurate understanding is needed in the health care system in order to maintain the compliance of the treatment. We decided to make a new protocol on OI treatment in the health care system. With the presence of FOSTEO, we imposed sharing system of the drug, that every patient will get treated equally.

WG8.4

Inequities of Treatment Options in Developing Countries: Congenital Adrenal Hyperplasia

Margaret Zacharin

Royal Children's Hospital, Parkville, Victoria, Australia

Adrenal insufficiency of any cause results in major morbidity and increased lifetime risk for adrenal crisis and potential mortality. A majority of those affected by disorders of either congenital or acquired origin have deficiencies of both glucocorticoid and mineralocorticoid. Preferred replacement treatment for infants, children and adolescents with growth potential is considered to be with hydrocortisone and fludrocortisone. Both medications are advocated for optimization of linear growth but neither are readily available or able to be procured in many countries including Africa, Eastern Europe, South America, and parts of south East Asia. Despite both being listed on WHO list of essential medicines for the past 6 years, little progress has been made to improve availability and distribution of either.

Where hydrocortisone is not available, appropriate titration of prednisolone can be a satisfactory management strategem for corticosteroid replacement but no alternative is available for fludrocortisone. While pressure is put on governments to provide hydrocortisone, less attention has been paid to mineralocorticoid, although lifetime safety and normalization of linear growth are also dependent upon prevention of hyponatraemia.

Early identification of CAH reduces infant mortality but renders the affected child permanently corticosteroid dependent, another dilemma for families living in resource constrained environments. Strategic plans directed towards improvement in equitable availability of these essential medicines will require a central model with in principle agreement with the WHO, to reduce morbidity and mortality of children with adrenal insufficiency worldwide.

WG8.5

Congenital Hypothyroidism Screening Program: the Costa Rican Experience

Roberto Bogarin

Costa Rica's National Children's Hospital, San Jose, Costa Rica

Background: The term congenital hypothyroidism was introduced more than 60 years ago when Radwin *et al.* first described children with hypothyroid-associated features of severe intellectual disability and growth retardation. It is the most common endocrine congenital disorder and preventable cause of mental retardation. Newborn screening programs are an efficient tool for the secondary prevention of mental retardation associated with untreated congenital hypothyroidism. In Costa Rica newborn screening was started on 1985 with three diseases: congenital hypothyroidism, maple syrup urine disease and phenylketonuria. Nowadays 25 diseases are screened through our program.

Objective and Hypotheses: To present the Costa Rican experience with the Congenital Hypothyroidism Screening Program. **Method:** Costa Rica is a small country the territory is 51100 km², population is 4 301 712 million people. The estimated Gross National Income (GNI) per capita is \$ 8820 USD. The life expectancy at birth is 79.7 years (82 for women and 77.5 for men); the infant mortality rate (per 1000) is 8.6%. The health expenditure per capita is \$950.8 USD.

The national newborn screening program started on 1985 with three diseases, currently 25 diseases are screened; during 2013 69 356 first samples were processed. With a cost of \$21.22 USD per test. Since 1990 until 2013, 454 cases have been detected, which gives us a prevalence of one in 3336 screened infants. The national coverage of the program since 2007 until 2012 is superior to 98%.

WG8.6

Neonatal Screening for Congenital Hypothyroidism in Ghana: Don't Take it for Granted!

Emmanuel Ameyaw

Komfo Anokye Teaching Hospital, Kumasi, Ghana

In Ghana, iodine deficiency, which represents the most common cause of preventable brain damage in the world, has been virtually eliminated. As a consequence, congenital hypothyroidism (CH) secondary to dysgenesis or enzymatic defects is now likely to be the most common cause of hypothyroidism in neonates. The prevalence of CH in Ghana is however unknown. Based on data in the African American population, it is thought to be less common than in Caucasians.

Ghana and many other resource-constrained countries do not offer systematic newborn screening programs for CH. However, Ghana is now piloting a regional neonatal screening program for the early diagnosis of sickle cell disease.

The signs of CH may be absent of very modest at birth, and diagnosis is therefore completely missed or delayed in affected neonates. Only 5%–10% of the cases have characteristic clinical findings at birth, preventing early treatment of CH in countries where neonatal screening is not routinely performed. However, when diagnosed and treated early, its most important complication, mental retardation, is preventable. At the present time, it is recommended that doctors and other health professionals who attend to neonates and children have high level of suspicion and screen babies for hypothyroidism based on clinical signs or refer them to centers where they can be investigated and managed. In conclusion, with the elimination of iodine deficiency, Ghana is well positioned to consider the development of a systematic screening for CH. This could conceivably be performed through point of care determination of TSH or by joining forces with the screening for sickle cell disease. TSH assay is readily available and treatment by l-thyroxine is present and affordable in Ghana.

WG8.7

Abstract unavailable.

Free Communications

FC1.1

Molecular mechanisms of nongenomic glucocorticoid actions: the role of human glucocorticoid receptor S-palmitoylation

Nicolas C Nicolaidesa, Michael L Roberts^a, Tomoshige Kinob, Eleni Katsantoni^c, Amalia Sertedaki^d, George P Chrousos^{a,d}, Evangelia Charmandari^{a,d}

^aDivision of Endocrinology and Metabolism, Biomedical Research Foundation of the Academy of Athens, Athens, Attiki, Greece; ^bUnit on Molecular Hormone Action, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland, USA; ^cDivision of Hematology, Biomedical Research Foundation of the Academy of Athens, Athens, Attiki, Greece, ^dDivision of Endocrinology, Metabolism and Diabetes, First Department of Pediatrics, University of Athens Medical School, 'Aghia Sophia' Children's Hospital, Athens, Attiki, Greece

Background: In humans, glucocorticoids (GCs) regulate a broad spectrum of physiologic functions, exerting both genomic and nongenomic actions through their ubiquitously expressed glucocorticoid receptor (hGR). The rapid nongenomic actions of GCs are likely to be mediated by membrane hGRs that transduce the glucocorticoid signal via activation of kinases. S-palmitoylation plays an important role in plasma membrane localization and occurs through a highly conserved nine amino acids motif in the ligand-binding domain (LBD) of steroid receptors. A highly homologous sequence (663YLCMKTLLL671) is present in the LBD of the hGR α protein, suggesting that the hGR might also undergo S-palmitoylation. **Objective and Hypotheses:** To determine the role of the motif 663YLCMKTLLL671 in mediating rapid non-genomic glucocorticoid signaling following translocation and binding to the plasma membrane. **Methods and Results:** Immunofluorescence experiments showed that both the hGR α WT and the mutant receptors hGR α Y663A, hGR α C665A, and hGR α LL670/671AA demonstrated similar distribution under the plasma membrane. These results were confirmed by subcellular fractionation experiments. Addition of a palmitoylation inhibitor, 2-bromopalmitate, did not prevent membrane localization of the receptor or colocalization with caveolin-1. In kinase signaling assays, neither the mutant receptors nor the addition of 2-bromopalmitate prevented the diphasic activation of MAPK signaling pathway in the early time points. Moreover, there was no essential difference in the activation of PI3K pathway, both in the absence or presence of the 2-bromopalmitate. Finally, palmitoylation assays surprisingly showed that the hGR α did not undergo palmitoylation. **Conclusions:** The motif 663YLCMKTLLL671 does not play a role in the membrane localization of hGR α and it is not involved in mediating rapid non-genomic glucocorticoid effects. Moreover, the hGR α is not a palmitoylated protein.

FC1.2

Clinical Phenotype of Patients with MCM4 Mutation Suggests Pubertal Delay in Males in Addition to Adrenal Failure, Absent Adrenarche, and Short Stature in Boys and Girls

Claire Hughes^{a,b}, Adrian Clark^b, Louise Metherell^b, Colm Costigan^a

^aOur Lady's Children's Hospital, Dublin, Ireland; ^bQueen Mary University, London, UK

Background: We previously reported the first human mutation in mini-chromosome maintenance homologue 4 (MCM4) in a cohort of patients with adrenal failure, immunodeficiency and chromosomal fragility. **Objective and Hypotheses:** To report the full endocrine phenotype of 14 patients with MCM4 mutations. **Method:** Patients case notes were examined and investigations performed to fully assess adrenal function, pubertal development, gonadal function, and growth. **Results:** 13 of 14 patients have developed isolated glucocorticoid deficiency with age of diagnosis ranging from 0.5 to 12 years. Five patients initially had normal adrenal function but subsequently developed glucocorticoid deficiency. All patients have undetectable DHEAS levels and low androstenedione levels. Clinically all children > 8 years have absent adrenarche. Renin and aldosterone levels were normal. Children had low birth weight (average, -2.3 SDS) and subsequent short stature (-2.6 SDS). Boys showed lack of a pubertal growth spurt and final height was significantly shorter than girls (males, -2.8 SDS and females, -1.8 SDS, $P=0.01$). The GH and IGF1 axis was normal. Four girls were of pubertal age; all entered and progressed through puberty normally and have normal menstrual cycles. In contrast all five boys of pubertal age had severe delay of growth and puberty and one required testosterone injections to induce puberty. Initially LHRH stimulation tests showed a pre-pubertal response. Subsequently two boys showed evidence of endogenous testosterone production with normal gonadotrophins and morning testosterone levels. **Conclusion:** Patients with MCM4 mutations have isolated glucocorticoid deficiency with no evidence of mineralocorticoid deficiency. Both clinically and biochemically children have no evidence of adrenal androgen production suggesting failure of development of the zona reticularis. In addition boys have evidence of a significant delay in pubertal development. This potentially indicates a role for adrenal androgen priming in male puberty or a novel function of MCM4 in pubertal development.

FC1.3

Genetic Engineering Using TALENs to Study the Redox Regulation of Steroidogenesis *in vivo*

Aliasha Griffin^a, Silvia Parajes^{a,b}, Angela Taylor^a, Ferenc Mueller^a, Nils Krone^a

^aUniversity of Birmingham, Birmingham, UK; ^bMax Planck Institute for Heart and Lung Research, Bad Nauheim, Germany

Background: Transcription activator-like effects nucleases (TALENs) have recently been developed as an efficient method for *in vivo* genome engineering. Zebrafish are becoming an increasingly popular model to study translational aspects in endocrinology. The redox cofactor ferredoxin (FDX1) is essential for mitochondrial cytochrome P450 (CYP) enzymes including those required for steroidogenesis. *In vitro*, FDX1 modifications influence the catalytic rate of steroidogenic CYP enzymes; however, to date mouse knockouts of Fdx1 have not been reported. **Objective and Hypotheses:** To use TALENs to generate a zebrafish knockout of the mitochondrial redox cofactor ferredoxin (fdx1b) for investigating redox regulation of steroidogenesis *in vivo*. **Method:** Genetic disruption was achieved by designing fdx1b specific TALENs using the golden gate assembly method. Genomic analysis for fdx1b knockouts was performed by high resolution melting curve analysis (HRM). RT-PCR of fdx1 and fdx1b was used to determine individual expression patterns. Transient knockdown studies were performed by microinjecting antisense morpholinos targeting fdx1b. Liquid chromatography tandem mass-spectrometry (LCMS/MS) was used to establish whole embryo steroid profiles. **Results:** We identified duplicated zebrafish ferredoxin genes; Fdx1 and Fdx1b. While Fdx1 was ubiquitously expressed, fdx1b was restricted to steroidogenic tissues; the interrenal gland (counterpart of the mammalian adrenal), gonads and brain. This suggests Fdx1b is the paralog required for steroidogenesis in zebrafish. Transient knockdown of fdx1b by antisense morpholino confirmed larvae fail to synthesize cortisol suggesting a key role in glucocorticoid production. Using TALENs we specifically targeted fdx1b to generate F1 knockout lines which was confirmed by HRM. **Conclusion:** Developments in genome engineering make zebrafish an advantageous model to explore development and disease. Through transient knockdown studies we show Fdx1b is essential for cortisol synthesis. Using TALENs we generated the first vertebrate model of a ferredoxin knockout. This knockout line will provide a valuable tool for determining the mechanisms of how redox cofactors modulate steroidogenesis.

FC1.4

A Novel Non-Invasive Short Synacthen Test

Charlotte Elder^{a,b}, Trevor Johnson^c, Martin Loxley^d, Brian Keevil^e, Jerry Wales^{a,b}, Neil Wright^b

^aUniversity of Sheffield, Sheffield, UK; ^bSheffield Children's Hospital, Sheffield, UK; ^cSimcyp Ltd, Sheffield, UK; ^dSheffield Teaching Hospitals NHS Trust, Sheffield, UK; ^eUniveristy Hospital South Manchester, Wythenshawe, UK

Background: The short synacthen test (SST) is a popular diagnostic investigation for adrenal insufficiency (AI). Cannulation and blood sampling are required making it invasive, time-consuming and resource-intensive. Salivary cortisol is a well-established alternative to serum sampling. **Objective and Hypotheses:** To develop a non-invasive alternative to the 1 µg SST, using a novel formulation of Synacthen (with a nasal drug enhancer, chitosan) given nasally and utilising saliva to measure

the cortisol response. **Method:** We undertook a pharmacokinetic dose escalation study with five doses of nasal Synacthen (tetracosactide): 25, 100, 100 µg with chitosan, 500 and 500 µg with chitosan, administered to 12 healthy adult males on different occasions and compared them to a 1 µg i.v. test. During each 3-h visit, 15-paired blood and saliva samples were taken and measurements of plasma Synacthen, serum cortisol and salivary cortisol and cortisone made. Volunteers were dexamethasone suppressed enabling measurement of Synacthen on an ACTH RIA. **Results:** The 25 and 100 µg doses showed minimal absorption. Addition of the chitosan improved bioavailability and cortisol response but dose escalation increased the absorption of nasal Synacthen more than the chitosan. The 100 µg with chitosan and 500 µg formulations showed a comparable cortisol response to the 1 µg i.v. dose. Nasal administration of the 500 µg Synacthen with chitosan formulation resulted in the highest bioavailability and was the only dose in which all volunteers attained a peak serum cortisol of more than 500 nmol/l. Salivary cortisol and cortisone samples had a close and reliable relationship with serum samples. Salivary cortisone was the more sensitive marker of adrenocortical response at lower values. **Conclusion:** Synacthen is absorbed nasally and appears safe and well tolerated. Nasally administered 500 µg Synacthen with chitosan and salivary cortisol or perhaps cortisone sampling at 60, 75, and 90 min may provide a useful alternative to the low-dose SST.

FC1.5

Antenatal Glucocorticoid Treatment and Polymorphisms in Glucocorticoid and Mineralocorticoid Receptor Genes are Associated with Long-Term Neurodevelopmental Outcomes in Preterm Survivors

Bibian van der Voorn^a, Sylvia van der Pal^b, Jan Wit^c, Ingrid Meulenbelt^c, Eline Slagboom^c, Joost Rotteveel^a, Martijn Finken^a

^aVU University Medical Center, Amsterdam, The Netherlands;

^bTNO Prevention and Health, Leiden, The Netherlands; ^cLeiden University Medical Center, Leiden, The Netherlands

Background: Preterm survivors are found to exhibit deficits in several neurodevelopmental domains. It is unknown whether this could be explained by antenatal glucocorticoid treatment. **Objective and Hypotheses:** We studied whether antenatal glucocorticoid treatment is associated with behaviour and IQ in young adults born preterm. In addition, we studied whether these associations could be modified by the R23K and N363S polymorphisms in the glucocorticoid receptor (GR) gene and by the -2G/C and I180V polymorphisms in the mineralocorticoid receptor (MR) gene. **Method:** 344 19-year-old with a gestational age of 30 ± 1.5 weeks and a birth weight of 1328 ± 336 g were drawn from the project on preterm and small-for-gestational-age birth cohort. Behaviour was assessed by the Young Adult Self-Report and the Young Adult Behaviour Checklist for parents, and IQ by the digital Multicultural Capacity Test-Intermediate Level. **Results:** Antenatal glucocorticoid treatment was associated with higher scores on both self-reported and parent-reported

internalizing behaviour and with a higher score on parent-reported externalizing behaviour. Independent of glucocorticoid treatment, carriage of the MR I180V variant was associated with a lower score on internalizing behaviour. Glucocorticoid treatment was not associated with IQ score. Independent of glucocorticoid treatment, carriage of the GR R23K variant was associated with a 9.3 (95% CI 3.4–15.1) points higher IQ score and carriage of the MR –2G/C ‘CC’ variant with a 6.2 (95% CI 1.9–10.5) points lower IQ score. Interaction between glucocorticoid treatment and GR N3633 carriage on IQ score was observed, with treated variant allele carriers showing a reduction in IQ score of 16.4 (95% CI 1.2–34.0) points. **Conclusion:** Antenatal glucocorticoid treatment and polymorphisms in GR and MR genes have long-lasting effects on behaviour and IQ in preterm survivors. Replication in independent samples is warranted.

FC1.6

Molecular Characterization of Testicular Adrenal Rest Tumours in Congenital Adrenal Hyperplasia; Lesions with both Adrenocortical and Leydig Cell Features

Evelien Smeets^{a,b}, Paul Spanc^c, Antonius van Herwaarden^b, Ron Wevers^b, Fred Sweep^b, Hedi Claahsen-van der Grinten^a

^aDepartment of Paediatrics, Radboud University Medical Center, Nijmegen, The Netherlands; ^bDepartment of Laboratory Medicine, Radboud University Medical Center, Nijmegen, The Netherlands; ^cDepartment of Radiation Oncology, Radboud University Medical Center, Nijmegen, The Netherlands

Background: Characterization of testicular adrenal rest tumours (TART) are one of the major long-term complications in congenital adrenal hyperplasia (CAH) patients. Although several adrenal-like properties have been assigned to these benign lesions, the exact etiology has not been established yet. **Objective and Hypotheses:** The aim of this study was to analyze several (steroidogenic) characteristics of TART tissue which may be classified as adrenal cortex or Leydig cell specific. **Method:** Gene expression analysis by qPCR was performed for 15 genes in TART tissue ($n=12$) and compared with the expression in healthy control fibroblasts (non-steroidogenic control). The genes were subdivided in a common group for both adrenal cortex and Leydig cells (*STAR*, *CYP11A1*, *CYP17A1*, *HSD3B2*, and *NR5A1*), an adrenal cortex specific group (*CYP21A2*, *CYP11B1*, *CYP11B2*, *AGTR2*, and *MC2R*), a group with Leydig cell specific genes (*LHCGR*, *INSL3*, and *HSD17B3*) and a group with genes that mainly function in peripheral tissues (*CYP19A1* and *SRD5A1*). In addition, a comparison was made with the expression levels in testes ($n=9$) and adrenal tissue ($n=13$). **Results:** Nearly all genes were highly expressed in TART tissue, including all genes that encode the main steroidogenic enzymes. TART expression levels are in the majority almost identical to those found in adrenal tissue. The expression of adrenal cortex specific genes (*CYP21A2*, *CYP11B1*, *CYP11B2*, and *MC2R*) in both TART and adrenal tissue

is ~1000–10 000 times higher than that in testes samples ($P<0.05$). In addition, expression of Leydig cell specific markers insulin-like 3, 17 β -HSD3, and LH/hCG receptor was found in testes as well as in TART tissue, with significantly higher levels than the adrenal for *INSL3* and *HSD17B3* ($P<0.01$). **Conclusion:** Our study shows for the first time that TART have multiple steroidogenic properties, which include not only the expression of specific adrenal cortex but also of Leydig cell markers. Therefore, the origin of these tumours might be a more totipotent embryonic cell type that may be stimulated by ACTH and LH.

FC2.1

Asfotase Alfa: Sustained Improved Growth and Function with Extended Treatment in Children with Hypophosphatasia

Katherine Madson^a, Cheryl Rockman-Greenberg^b, Agustin Melian^c, Scott Moseley^d, Tatjana Odrlijin^d, Amy Reeves^a, Michael Whyte^a

^aShriners Hospitals for Children, St Louis, Missouri, USA;

^bUniversity of Manitoba, Winnipeg, Manitoba, Canada; ^cAlexion Pharmaceuticals, Cheshire, Connecticut, USA; ^dAlexion Pharmaceuticals, Cambridge, Massachusetts, USA

Introduction: Hypophosphatasia (HPP) is the rare, inherited, metabolic disease with broad-ranging severity caused by inactivating mutation(s) in the tissue-nonspecific alkaline phosphatase (TNSALP) gene. In the childhood form of HPP, there are mineralization defects of the bones and teeth, often with impaired physical function, muscle weakness, and decreased growth. We previously reported sustained radiographic improvement in rickets compared to historical controls in 5–12 year old patients (pts) receiving treatment with asfotase alfa, a bone-targeted recombinant human TNSALP, for up to 3 years.¹ Here we report improvement in physical function and growth in these children. **Methods:** In this randomized, multinational, open-label extension study of asfotase alfa, changes from baseline (BL) in physical function (6-min walk test, 6MWT), strength and agility (Bruininks-Oseretsky Test of Motor Proficiency, 2nd edition, BOT-2), muscle strength (dynamometry), and height (z -score) were assessed. **Results:** 12/13 patients (one withdrew: elective surgery) received ≥ 3 years of treatment. By parental report, all pts at BL had abnormal gaits and 8 (62%) had muscle weakness. Mean 6MWT improved from BL (345 m) 59% predicted to 76% at 3 months ($n=11$) and to 89% at 3 years ($n=7$), both: $P<0.0001$. The other four patients, evaluated at 3.5 years, had 6MWT of 71, 75, 96, and 99% predicted. Mean strength and agility standard score (healthy normal=50) improved from 27 (BL) to 35 at 3 months ($P=0.0035$) and to 48 at 3 years ($P<0.0002$, $n=7$). The other four patients, evaluated at 3.5 years, had BOT-2 scores of 36, 38, 52, and 58. Right hip abductor muscle strength best effort 13 lbs, 43% predicted, ($n=12$) at BL increased to 54% at 3 months ($n=11$) and to 80% at 3 years ($P=0.0124$, $n=6$). The other four patients improved to 57, 64, 92, and 93% predicted. Median height z -score was -1.26 at BL and -0.74 ($P=0.0538$) at 3 years.

Conclusion: Children with HPP and difficulty walking, muscle weakness, and significant rickets at baseline¹, then treated with asfotase alfa, showed gains in height with rapid and sustained improvement in strength, agility, and function.

FC2.2

Hypophosphatasia: Gross Motor Function and Height Improvement in Infants and Young Children Treated with Asfotase Alfa for up to 3 Years

Nicholas Bishop^a, Jill Simmons^b, Richard Lutz^c, Tatjana Odrljina^d, Scott Moseley^d, Agustin Melian^e, Dawn Phillips^f, Michael Whyte^g

^aSheffield Children's Hospital, Sheffield, UK; ^bVanderbilt Children's Hospital, Nashville, Tennessee, USA; ^cNebraska Medical Center, Omaha, Nebraska, USA; ^dAlexion Pharmaceuticals, Cambridge, Massachusetts, USA; ^eAlexion Pharmaceuticals, Cheshire, Connecticut, USA; ^fUniversity of North Carolina, Chapel Hill, North Carolina, USA; ^gShriners Hospitals for Children, St Louis, Missouri, USA

Introduction: Hypophosphatasia (HPP) is caused by inactivating mutation(s) within the gene for tissue nonspecific alkaline phosphatase (TNSALP). Patients with the perinatal and infantile forms of HPP suffer rickets, poor growth, and delayed gross motor function. In 2012, we detailed significant improvement in skeletal mineralization and respiratory function in such patients treated for 1 year with asfotase alfa, a bone-targeted recombinant human TNSALP,¹ and recently for up to 3 years.² We now report functional and height measures from these patients up to 3 years. **Methods:** Multinational, phase II, open-label trial of asfotase alfa (1–3 mg/kg, 3×/week, s.c.). Height/length at each time point was the mean of three repeat measures and Z-scores were calculated according to population-appropriate growth standards. Motor development was assessed using the Gross Motor Subscale of the Bayley Scales of Infant Development III (BSID-III) for patients aged 0–42 months and the Locomotion Subscale of the Peabody Developmental Motor Scales 2nd edition (PDMS-2) for patients ≥43 months. BSID-III scores are presented as scaled scores (SS) relative to healthy peers. The mean (s.d.) BSID-III SS for healthy, same-age peers is 10 (3), thus increases in SS would indicate accelerated acquisition of skills. **Results:** Eleven patients enrolled with a median age (min, max) of 6.8 months (2.9 weeks, 3 years)¹. One patient died (sepsis unrelated to study drug) and 1 withdrew, thus nine patients were studied long-term. At baseline (BL), median (min, max) Z-score for height was –3.7 (–9.2, –0.7; n=11) and increased by a median change from BL (min, max) of +1.2 (–1.0, +1.9; n=9), +1.5 (–1.5, +3.8; n=9), and +2.3 (–1.4, +4.1; n=8) at 48, 96, and 144 weeks, respectively. Median BSID-III Gross Motor SS (min, max) increased from 1 (1, 8; n=11) at first assessment to 2 (1, 5; n=7 patients with data available), 5 (1, 7; n=6), and 6 (6, 7; n=3) at 48, 96, and 144 weeks, respectively. Two patients transitioned to the PDMS-2 at week 72 and continued to demonstrate gross motor improvements at week 144. **Conclusion:** Profound delays in growth and gross

motor function in pediatric patients with severe HPP improved substantially during treatment with asfotase alfa for up to 3 years, consistent with accompanying skeletal improvement.^{1,2}

FC2.3

Calcium Homeostasis in Adolescents with β-Thalassemia Major: Effect of i.m. Injection of a Megadose of Cholecalciferol

Mohamed Elkholy, Mohsen Elalfy, Rasha Hamza, Nermine Mahmoud, Mohamed Saleh, Heba Elsedfy

Ain Shams University, Cairo, Egypt

Background: The etiology of bone disease in thalassemic patients is multifactorial. Factors such as hormonal deficiency (especially gonadal failure), bone marrow expansion, increased iron stores, desferrioxamine toxicity, calcium, and vitamin D deficiency seem to have a serious impact on impaired bone metabolism in this disease. **Objectives:** To estimate the frequency of calcium homeostasis abnormalities in adolescent thalassemic patients, and to investigate the effect of a megadose of vitamin D3 on these parameters. **Methods:** Thirty fully pubertal adolescent thalassemic patients aged 15–35 years completed an experimental trial for 1 year where they received an i.m. dose (600 000 IU) of cholecalciferol at the beginning of the study. Parameters of calcium homeostasis (serum calcium, phosphorus, alkaline phosphatase (ALP), parathyroid hormone (PTH), and 25 hydroxyvitamin D (25OHD)) were measured at 0, 6, and 12 months. Vitamin D insufficiency was defined when 25OHD ranged from 20 to 30 ng/ml and deficiency when 25OHD level was <20 ng/ml. **Results:** At baseline, ten patients (33.3%) were hypocalcemic, 23 (76.6%) were hyperphosphatemic, 12 (40%) had high serum ALP, 4 (13.3%) had 25OHD deficiency and 13 (43.3%) had 25OHD insufficiency. At 6 months, one patient (3.3%) was vitamin D deficient and three patients (10%) were insufficient. At 12 months, two patients (6.6%) were deficient and five patients (16.6%) were insufficient. There was a significant effect of vitamin D injection on serum calcium level at 12 months ($P=0.036$), serum ALP level both at 6 ($P=0.009$) and 12 months ($P=0.006$), and on serum 25OHD level both at 6 and 12 months ($P=0.000$) with no significant effect on PTH level. **Conclusion:** A once yearly i.m. cholecalciferol injection (600 000 IU) is a suitable therapeutic option for treating vitamin D deficiency in most patients with β-thalassemia major.

FC2.4

Fractures in Children with Chronic Inflammatory and/or Disabling Conditions: the SNAP Study

Nicola Crabtree, Wolfgang Hogler, Nicholas Shaw

Birmingham Children's Hospital, Birmingham, UK

Background: The SNAP study is a prospective fracture study of children with chronic inflammatory and/or disabling

conditions. **Objective and Hypotheses:** The overall aim of the study is to establish if there is a causal link between measured body-size related bone density and low trauma fracture. **Method:** 280 children, aged 5–18 years, from seven disease groups namely; acute lymphoblastic leukaemia (ALL), rheumatological disease, inflammatory bowel disease, cystic fibrosis, coeliac disease, Duchenne muscular dystrophy (DMD), and cerebral palsy, were recruited. At baseline, bone density by DXA (lumbar spine and total body less head (TBLH)) and pQCT (radius), spinal radiographs, muscle strength, fracture, and medical history were assessed. **Results:** Fifty-one children (18%) had a history of long bone fracture of either the upper ($n=32$) or lower limb ($n=19$). Spinal radiographs identified 52 children with vertebral height loss, of which the incidence was highest for children with ALL (12/30) and DMD (14/40) ($P<0.001$). Steroid exposure was reported in 65% of the children and back pain was reported in 37%. Although the highest levels of steroid exposure and the greatest incidence of back pain were reported for ALL and DMD, no significant statistical differences were reported between the groups. Bone density z -scores were significantly lower than 0 for L2L4BMD, TBLH BMD, trabecular BMD, and strength strain index (SSI), but failed to discriminate between children with and without long bone fractures. Similarly, L2L4BMD and SSI z -scores were not significantly different for children with vertebral or without vertebral fractures. However, trabecular bone density at the radius was significantly reduced, $z = -1.2$ (1.1) and -0.5 (1.3) ($P<0.001$) for those with and without vertebral fractures respectively. **Conclusion:** In conclusion, disease and steroid exposure have significant impact on the identification of individuals at risk of vertebral fracture. However, the greatest odds ratio for vertebral fracture was low bone density as measured by pQCT. Evidence of the predictive power of these measurements will only be confirmed with future follow-up of this group.

FC2.5

Pharmacokinetics and Pharmacodynamics of a Human Monoclonal Anti-Fibroblast Growth Factor 23 Antibody (KRN23) Following 4 Month Intra-Dose Escalation in Adults with X-Linked Hypophosphatemia

Xiaoping Zhang^a, Erik Imel^b, Mary Ruppe^c, Thomas Weber^d, Mark Klausner^e, Takahiro Ito^a, Maria Vergeire^a, Jeffrey Humphrey^a, Francis Glorieux^e, Anthony Portale^f, Karl Insogna^g, Munro Peacock^b, Thomas Carpenter^g

^aKyowa Hakko Kirin Pharma, Inc., Princeton, New Jersey, USA; ^bIndiana University School of Medicine, Indianapolis, Indiana, USA; ^cThe Methodist Hospital, Houston, Texas, USA; ^dDuke Clinical Bone Laboratories, Duke University Medical Center, Durham, North Carolina, USA; ^eShriners Hospital for Children, Montreal, Quebec, Canada; ^fUniversity of California, San Francisco, California, USA; ^gYale Center for X-Linked Hypophosphatemia, Yale University School of Medicine, New Haven, Connecticut, USA

Background: In X-linked hypophosphatemia (XLH), abnormally elevated serum fibroblast growth factor 23 (FGF23) results

in low renal maximum threshold for phosphate reabsorption (TmP/GFR), low serum phosphorus (Pi), inappropriately normal 1,25-dihydroxyvitamin D (1,25(OH)₂D) and development of rachitic deformities. **Methods:** Up to four s.c. KRN23 doses were given every 28 days to 28 adults with XLH according to a dose-escalation algorithm (0.05–0.1–0.3–0.6 mg/kg). Blood and urine samples were collected pre-dose and on days 3, 7, 12, 18, and 26 after each dose. **Results:** Mean KRN23 dose increased from 0.05 to 0.48 mg/kg. Mean times to maximum serum KRN23 level were similar across four dosing intervals (7.0–8.5 days). The mean KRN23 maximum, minimum, and area under the concentration–time curve (AUC_n) for the nth dosing interval increased proportionally with increases in mean dose. Mean KRN23 half-life was 16.4 ± 5.8 days. Serum Pi and TmP/GFR increased from baseline at all subsequent samplings except the first-dose trough ($P<0.05$). Serum 1,25(OH)₂D increased from baseline except for first and second-dose troughs ($P<0.05$). Bone markers increased significantly for BALP and CTx after three doses, osteocalcin after two doses, and P1NP after one dose ($P<0.05$). Serum KRN23 and Pi concentrations changed in parallel throughout the dosing interval, supporting a direct pharmacokinetics (PK)–pharmacodynamics (PD) relationship. The AUC_n for change from baseline in TmP/GFR, serum Pi, and 1,25(OH)₂D at each dosing interval increased linearly with increase in KRN23 AUC_n. No meaningful PK–PD correlations were observed for serum calcium, parathyroid hormone, 25-hydroxyvitamin D, 2-h urine calcium/creatinine ratio, or 24-h urine calcium. **Conclusion:** The effects of KRN23 on serum Pi, TmP/GFR, and serum 1,25(OH)₂D levels were sustained after each dose. PK dose proportionality and the linear PK–PD relationship between serum KRN23 concentrations and serum Pi concentrations support adjusting the dose based on serum Pi levels.

FC2.6

Efficacy and Safety Following 4 Monthly s.c. Doses of a Human Anti-Fibroblast Growth Factor 23 Antibody (KRN23) in Adults with X-linked Hypophosphatemia

Munro Peacock^a, Erik Imel^b, Xiaoping Zhang^b, Mary Ruppe^c, Thomas Weber^d, Mark Klausner^b, Takahiro Ito^b, Maria Vergeire^b, Jeffrey Humphrey^b, Francis Glorieux^e, Anthony Portale^f, Karl Insogna^g, Thomas Carpenter^g

^aIndiana University School of Medicine, Indianapolis, Indiana, USA; ^bKyowa Hakko Kirin Pharma, Inc., Princeton, New Jersey, USA; ^cThe Methodist Hospital, Houston, Texas, USA; ^dDuke Clinical Bone Laboratories, Duke University Medical Center, Durham, North Carolina, USA; ^eShriners Hospital for Children, Montreal, Quebec, Canada; ^fUniversity of California, San Francisco, California, USA; ^gYale Center for X-Linked Hypophosphatemia, Yale University School of Medicine, New Haven, Connecticut, USA

Background: In X-linked Hypophosphatemia (XLH), abnormally elevated serum Fibroblast Growth Factor 23 (FGF23) results in low renal maximum threshold for phosphate reabsorption (TmP/GFR), low serum phosphorus (Pi), inappropriately normal 1,25-dihydroxyvitamin D (1,25(OH)₂D) and development of

rachitic deformities. **Methods:** Up to four SC KRN23 doses were given every 28 days to 28 adults with XLH (26 completed) according to a dose-escalation algorithm (0.05–0.1–0.3 to 0.6 mg/kg). The primary outcome was Pi response. **Results:** At baseline, 96.3% of subjects had serum Pi <2.5 mg/dl. Mean KRN23 dose increased from 0.05 to 0.48 mg/kg. Serum Pi, TmP/GFR, and serum 1,25(OH)2D increased from baseline after all doses, more with each subsequent dose. Mean serum Pi and TmP/GFR peaked at day 7 (1,25(OH)2D at days 3–7) and all declined before the next dose. Peak serum Pi increased from 2.21 ± 0.33 mg/dl after dose 1–3.03 ± 0.42 mg/dl after dose 4. Pre-dose serum Pi increased from 1.89 ± 0.33 at baseline to 2.54 ± 0.37 mg/dl after dose 4. Peak serum Pi increased to 2.5–≤3.5 mg/dl on day 7 in 14.8, 37.0, 74.1, and 70.4% of subjects after dose 1, 2, 3 and 4 respectively. Serum Pi reached 3.5–≤4.5 mg/dl only after dose 4 in 14.8% of subjects and never exceeded 4.5 mg/dl. There were no clinically significant changes in PTH or serum or urinary calcium. The most common adverse events were nasopharyngitis and arthralgia. There were no serious adverse events, deaths, anti-KRN23 antibodies, or significant changes in electrocardiograms (including development of LVH) or renal ultrasound. One subject with a baseline coronary artery calcification score of 0 had a minor increase post-treatment. **Conclusions:** Monthly injections of KRN23 blocked the pharmacodynamic effects of excessive FGF23 in adults with XLH. KRN23 has potential as a novel treatment for adult and paediatric XLH.

FC3.1

High Mobility Group Box-1 Serum Concentrations Increase at Onset of Diabetes in Cystic Fibrosis Patients

Luisa Montanini^a, Arianna Smerieri^a, Giovanna Pisi^a, Ida Giardino^b, Maria Angela Ziveri^a, Maria d'Apolito^b, Silvia Cesari^a, Cinzia Spaggiari^a, Silvia Merli^a, Sergio Bernasconi^a, Maria E Street^a

^aUniversity Hospital of Parma, Parma, Italy; ^bUniversity of Foggia, Foggia, Italy

Background: The DNA-binding High Mobility Group Box-1 (HMGB1) is an intracellular gene regulator that can be secreted also in response to inflammatory mediators, including interleukins, binding subsequently to both RAGE and Toll-like receptors forming a self-reinforcing inflammatory circle. Cystic fibrosis (CF) is a condition characterized by chronic inflammation. Elevated serum HMGB1 concentrations were described in serum of obese children and to be associated with the metabolic syndrome that originates from a state of insulin-insensitivity. This latter is a feature of cystic fibrosis related diabetes also (CFRD). **Objective and Hypotheses:** We aimed to assess HMGB1 serum concentrations in CF patients and verify whether there were any relationships with the state of glucose tolerance. **Method:** Forty-three CF patients in stable clinical conditions and

21 controls of comparable age, sex, and pubertal stage (18.73 ± 1.74 years, 6M, 15F) were enrolled. Glucose tolerance was established in patients based on a five point oral glucose tolerance test, according to actual American Diabetes Association criteria for CF. Three groups were considered: normal tolerant subjects (14.54 ± 1.21 years, 8M, 12F), glucose intolerant (15.56 ± 2.74 years, 7M, 8F), with CFRD at diagnosis (21.47 ± 2.17 years, 2M, 6F). HMGB1 was assayed using a specific ELISA Kit (IBL-America). **Results:** HMGB1 concentrations were similar in control subjects and in glucose tolerant patients (2.7 ± 0.3 ng/ml vs 2.8 ± 0.3 ng/ml respectively), and increased progressively in glucose intolerant subjects (3.96 ± 0.96 ng/ml) and in CF subjects at onset of diabetes (7.66 ± 1.7 ng/ml, *P* < 0.05). In all subjects analysed HMGB1 concentrations were positively correlated with the fasting glucose/insulin ratio (*R*: 0.34; *P*: 0.042). **Conclusion:** HMGB1 concentrations increased with worsening of glucose tolerance. The high concentrations at onset of diabetes could be related with the well described decline in clinical conditions from thereafter. The relationship with the fasting glucose to insulin ratio suggested it might be involved in the regulation of insulin sensitivity, as in obesity.

Further studies are warranted to verify whether HMGB-1 could become a marker of onset of CFRD and/or of severe worsening of clinical conditions and lung disease in CF.

FC3.2

HbA1c Level as a Predictive Marker of Progression to Clinical Diabetes

Lenka Petruzalkova, Jana Vcelakova, Jana Labikova, Jan Lebl, Stanislava Kolouskova

Department of Paediatrics, 2nd Faculty of Medicine, Charles University in Prague and University Hospital Motol, Prague, Czech Republic

Background: It has been shown that a proportion of relatives with multiple islet auto antibodies do not develop diabetes for many years, indicating that a more accurate marker of advanced insulinitis is needed. **Objective and Hypotheses:** We evaluated whether the level of HbA1c can discriminate children at risk of T1D onset in a cohort of auto antibody positive relatives. **Method:** A total of 74 subjects < 18 years of age who were participating in the Czech Prediction Programme for T1D, a longitudinal study which prospectively monitors siblings and offspring of diabetic patients for T1D development, were recruited. The median of their follow-up was 3 years (range 1–12 years). They have risk HLA-DQ genotype. All of them developed persistent islet auto antibodies and six of them progressed to diabetes during follow-up. HbA1c was measured at least once (one to ten times, two measurements on average) during follow up until T1D onset. The Markov chain model addressed the predictive strength of HbA1c levels on T1D development. **Results:** HbA1c level was effective in discriminating children at risk of T1D development, fitted log-linear effect 0.052

with 95% CI (0.0137, 0.09). The estimated hazard ratio was 1.05 (95% CI (1.014, 1.094) and tells us that a 1 mmol/mol HbA1c increase is associated with 5% higher risk of T1D development. An estimate of the optimal threshold from this data is 37.7 mmol/mol with associated hazard ratio 1.95 (95% CI (1.23, 3.08), which means that a 1 mmol/mol increase over the threshold is associated with a twofold risk increase. **Conclusion:** HbA1c monitoring increases the effectiveness of T1D prediction. Children with persistent islet auto antibody and HbA1c over 37.7 mmol/mol may be at greater risk of T1D onset.

FC3.3

Improved Hepatic Insulin Sensitivity in Children Randomized to CSII Treatment from Onset of Type 1 Diabetes

Klas Ekström^a, Lars Skogsberg^b, Hans Fors^c, Christine Carlsson-Skwirut^a, Peter Bang^d

^aPediatric Endocrinology Unit, Department of Women's and Children's Health, Karolinska Institute and University Hospital, Stockholm, Sweden; ^bDepartment of Pediatrics, Gävle Hospital, Gävle, Sweden; ^cDepartment of Pediatrics, Northern Älvsborgs Hospital, Trollhättan, Sweden; ^dDivision of Pediatrics, Department of Clinical and Experimental Medicine, Linköping University, Linköping, Sweden

Background: Our first report of this randomized controlled trial (RCT) demonstrated improved treatment satisfaction but no difference in HbA1c between the CSII and MDI treated groups, and added to the controversy as to whether CSII improves HbA1c or not. Therefore, we thought it would be valuable to assess if CSII had other potential advantages and if our finding of lower insulin dose requirements could be explained. **Objective and Hypotheses:** To study how different insulin regimens affect IGF1 and IGF-binding protein-1 (IGFBP1) in relation to fasting C-peptide and insulin doses in children with type 1 diabetes mellitus (T1DM). **Method:** In an open, parallel, multicenter study, children (7–17 years of age) with newly diagnosed T1DM were randomized to receive multiple daily insulin (MDI) injections ($n=38$) or continuous s.c. insulin infusion (CSII) ($n=34$). At inclusion and after 6, 12, and 24 months IGF1, IGFBP1 and C-peptide concentrations were determined. **Results:** The CSII group had significantly lower IGFBP1 levels at 12 and 24 months ($P=0.007$ and $P<0.001$ respectively). The mealtime and basal insulin doses in the CSII group were significantly lower at these time points. IGF1 or C-peptide did not differ between the treatment groups. The $\ln(\text{C-peptide})$ correlated significantly with IGF1 and IGFBP1 at 6 and 12 months in both groups, and at 6 months the decrease in IGF1 and the increase in IGFBP1 for a given decrease in C-peptide were more marked in the MDI group. **Conclusion:** Lower IGFBP1 in the CSII group is a marker of improved hepatic insulin sensitivity and, in accord therewith insulin dose requirements were lower. CSII treatment failed to

normalize IGF1 deficiency and did not improve endogenous insulin secretion. One potential effect of the improved hepatic insulin sensitivity on CSII is that both generation of IGF1 and the inhibition of IGFBP1 are less dependent on endogenous insulin secretion.

FC3.4

Genetics of Paediatric Type 2 Diabetes: ABCC8 Mutation in Obesity-Associated Insulin Secretion Defects

Susanna Wiegand^a, Deimante Simaite^b, Almut Dannemann^c, Peter Kühnena^a, Heiko Krude^a, Maolian Gong^b, Klemens Raile^b

^aInstitute of Experimental Paediatric Endocrinology, Charité, Berlin, Germany; ^bExperimental and Clinical Research Center, Charité, Berlin, Germany; ^cInterdisciplinary Social Paediatric Center, Charité, Berlin, Germany

Background: Type 2 diabetes in children and adolescents is a rare disease with an estimated incidence (age 0–20 years) of below 5/100 000 in Germany. **Objective and Hypotheses:** We hypothesize that monogenic alterations might contribute to early-onset insulin secretion defects, if islet function was challenged by obesity-associated insulin resistance. **Method:** We follow more than 1500 children and adolescents with obesity. Patients are initially screened for impaired fasting glucose, insulin, or HOMA > 95th percentile. Overall 264 children with abnormal lab-tests (glucose or HOMA-index) or extreme obesity ($\text{BMI} > +2.5$ SDS) are currently followed by annual oGTTs. Patients that display impaired glucose tolerance or diabetes (IGT/DM) and have an overall maximum insulin level below 130 mU/ml (during 0–120 min oGTT) are categorized as being at risk for defective insulin secretion. All cases were auto antibody-negative. In total, 32 patients with lowest insulin secretion were selected for genetic testing in this project. All coding exons and exon-intron boundaries of ATP-dependent potassium channel (K_{ATP}) genes *KCNJ11* and *ABCC8* were screened by Sanger sequencing. **Results:** We identified two unrelated individuals with the same heterozygous mutation $\text{c.1616A} > \text{G/p.Tyr539Cys}$ in exon 10 of *ABCC8*. The tyrosine at position 539 is highly conserved among vertebrates and this functionally uncharacterized variant is reported in dbSNP (rs193922397) as observed in one child with neonatal diabetes. Patient one (girl, 11.5 years) was obese ($\text{BMI} 27.7 \text{ kg/m}^2$) and had polyurea, hyperglycemia and increased HbA1c (8.9%). Her diabetes was initially treated with insulin but recovered completely under weight reduction. Patient two (boy, 12.8 years, $\text{BMI} 26.8 \text{ kg/m}^2$) had abnormal fasting glucose and impaired glucose tolerance but his glucose levels normalized as he reduced weight. **Conclusion:** Pathogenic variants of genes involved in insulin secretion, like *ABCC8* might contribute to early-onset type 2 diabetes in a monogenic or oligogenic fashion, especially if insulin secretion was challenged by obesity-associated insulin resistance.

FC3.5

Pancreatic N-Methyl-D-Aspartate Receptors as Novel Drug Targets for The Treatment of Diabetes Mellitus

Alena Welters^{a,b}, Jan Marquard^{a,b}, Silke Otter^{b,c}, Alin Stirban^e, Jan Eglinger^{b,c}, Diran Herebian^a, Andraz Stozers^a, Stephan Whendt^h, Lorenzo Piemontiⁱ, Martin Köhlerⁱ, Freimut Schliess^e, Marjan Slak Rupnik^g, Tim Heise^e, Per-Olof Berggrenⁱ, Nikolaj Klöcker^f, Ertan Mayatepek^a, Daniel Eberhard^b, Martin Kragl^{b,d}, Eckhard Lammert^{b,c}, Thomas Meissner^a

^aDepartment of General Pediatrics, Neonatology and Pediatric Cardiology, University Children's Hospital, Düsseldorf, Germany; ^bInstitute of Metabolic Physiology, Heinrich-Heine University, Düsseldorf, Germany; ^cInstitute for Beta Cell Biology, German Diabetes Center (DDZ), Leibniz Center for Diabetes Research, Düsseldorf, Germany; ^dGerman Center for Diabetes Research (DZD e.V.), Helmholtz Zentrum München, Neuherberg, Germany; ^eProfil Institute for Clinical Research, Neuss, Germany; ^fInstitute of Neuro- and Sensory Physiology, University Hospital Düsseldorf, Düsseldorf, Germany; ^gInstitute of Physiology, Medical Faculty, Centre for Open Innovations and Research, University of Maribor, Maribor, Slovenia; ^hMLM Medical Labs GmbH, Mönchengladbach, Germany; ⁱDiabetes Research Institute (DRI), San Raffaele Scientific Institute, Milan, Italy; ^jThe Rolf Luft Research Center for Diabetes and Endocrinology, Karolinska Institutet, Stockholm, Sweden

Background: N-methyl-D-aspartate receptors (NMDARs) are ionotropic glutamate receptors that are widely expressed in the CNS where they play an important role in neurotransmission and cell viability and serve as drug targets for the treatment of neurodegenerative disorders. **Objective and hypotheses:** Much less is known about the role of pancreatic NMDARs. Since neurons and pancreatic islets have many features in common, we hypothesized that drugs acting on the CNS might also act on pancreatic β cells and may be useful for the treatment of insulin secretion disorders. **Method:** We used a genetic and pharmacologic approach to inhibit NMDA receptors in rat insulinoma cells, mouse and human pancreatic islets and pancreas of mice to elucidate the role of pancreatic NMDARs in insulin secretion, glucose tolerance and calcium oscillations. We further studied the effect of the NMDAR antagonist dextromethorphan (DXM) on glucose tolerance, islet insulin content and β cell mass in a type 2 diabetes mouse model. Finally, we conducted a phase IIa clinical trial in type 2 diabetic patients. **Results:** Here, we demonstrate for the first time that antagonizing pancreatic NMDARs, either genetically or pharmacologically with the over-the-counter drug DXM, selectively increases glucose-stimulated insulin secretion (GSIS) from rat insulinoma cells, mouse and human pancreatic islets and improves glucose tolerance in mice without affecting basal insulin release. We further show that long-term treatment with DXM delays the onset of overt type 2 diabetes and increases islet insulin content and β cell mass in a relevant type 2 diabetic mouse model (*db/db*). Finally, in a phase IIa clinical trial DXM selectively increased postprandial plasma insulin concentrations and improved glucose tolerance in type 2 diabetic patients. **Conclusion:** In summary, our data reveal a regulatory role of NMDARs in pancreatic islets and proposes NMDARs as novel drug targets for diabetes treatment.

FC3.6

Alpha-Lipoic Acid and Anti-Oxidant Diet Helps to Improve Endothelial Dysfunction in Children and Adolescents with Type 1 Diabetes

Andrea Scaramuzza, Saverio Ungheri, Francesca Redaelli, Alessandra Bosetti, Elisa Giani, Matteo Ferrari, Valentina Comaschi, Valentina Giudici, Gian Vincenzo Zuccotti

Department of Paediatrics, Luigi Sacco Hospital, University of Milano, Milano, Italy

Background: Endothelial dysfunction is a macrovascular complication of type 1 diabetes. Children and adolescents with type 1 diabetes may suffer of endothelial dysfunction, irrespective of chronological age and disease duration. **Objective and hypotheses:** After evaluating the prevalence of early endothelial dysfunction, as measured by mean of reactive hyperaemia in adolescents with type 1 diabetes, at baseline and after 1-year follow-up, we started a 6-month, double-blind, randomized trial to test the efficacy of an anti-oxidant diet ($\pm\alpha$ -lipoic acid supplementation) to improve endothelial dysfunction. **Method:** Sixty-one children and adolescents, ages 16 ± 3.5 years, with type 1 diabetes since 8.9 ± 4.3 years, using intensified insulin therapy, were randomized into three arms: i) anti-oxidant diet 10 000 ORAC + α -lipoic acid; ii) anti-oxidant diet 10 000ORAC + placebo; iii) controls. BMI, blood pressure, fasting lipid profile, HbA1c, insulin requirement, dietary habits, and body composition were determined in each child. **Results:** After 3 months BMI, blood pressure, lipid profiles, HbA1c, and body composition did not change, while insulin requirement significantly decreased only in patients in arm with anti-oxidant diet and α -lipoic acid (0.74 ± 0.18 vs 0.83 ± 0.26 U/kg/day, $P < 0.05$), as well as bolus insulin (22.0 ± 9.4 vs 26.3 ± 10.8 U/day, $P < 0.05$), but not basal insulin (25.9 ± 9.4 vs 25.5 ± 8.6 U/day, PNS). After 6 months same data were observed regarding insulin requirement with lower doses only in patients using supplementation. A significant improvement of endothelial function was observed in the two groups using the anti-oxidant diet, but not in controls. In group treated with α -lipoic acid a further slighter improvement was observed. **Conclusion:** Adolescent with type 1 diabetes displayed evidence of endothelial improvement after α -lipoic acid and anti-oxidant diet, but not in controls. Moreover, to our knowledge these data demonstrate for the first time an of α -lipoic acid in sparing insulin requirement in young patients with type 1 diabetes.

FC4.1

Heterozygous IGF1R Mutations Represent a Frequent Finding in Patients with Pre- and/or Postnatal Proportional Undergrowth and Low, Normal or Supranormal IGF1

Angel Campos-Barros^{a,b}, Ana Gómez-Núñez^{a,b}, Isabel González-Casado^c, Luis Salamanca-Fresno^c, Sixto García-Miñaur^{a,b}, Purificación Ros-Pérez^d, Victoria Borrás-Pérez^e, Laura Audí^{f,g}, Jordi Rosell-Andreo^h, Diego de Sotto-Estebani,

Beatriz García-Cuartero^j, Amparo González-Vergaz^j,
Jaime Cruz-Rojos^k, Lucía Garzón^k, Elena Gallego-Gómez^k

^aHospital Universitario La Paz, INGEMM, IdiPAZ, UAM, Madrid, Spain; ^bCIBERER (U753), ISCIII, Madrid, Spain;

^cHospital Universitario La Paz, Pediatric Endocrinology, Madrid, Spain; ^dHospital Universitario Puerta de Hierro-Majadahonda, Pediatric Endocrinology, Madrid, Spain; ^eHospital General de Granollers, Pediatric Endocrinology, Barcelona, Spain;

^fHospital Vall d'Hebrón, Pediatric Endocrinology, Barcelona, Spain;

^gVHIR, CIBERER (U712), ISCIII, Autonomous University, Barcelona, Spain; ^hDepartment of Genetics, Hospital Universitari Son Espases, Palma de Mallorca, Spain; ⁱHospital Universitari Son Espases, Pediatric Endocrinology, Palma de Mallorca, Spain;

^jHospital Universitario Severo Ochoa, Pediatric Endocrinology, Madrid, Spain; ^kHospital Universitario 12 de Octubre, Pediatric Endocrinology, Madrid, Spain

Background: IGF1 resistance syndrome (IGF1RS) is characterized by intrauterine and postnatal growth deficit with normal or supranormal IGF1 levels. Additional features may include intellectual deficit, microcephaly and dysmorphisms. IGF1RS may be caused by genomic or genetic defects affecting the *IGF1R* locus (15q26.3). **Objective and hypotheses:** To investigate the frequency of *IGF1R* mutations in a cohort of patients with pre- and/or postnatal proportional undergrowth. **Method:** *Subjects:* 46 children born small for gestational age (SGA) and/or presenting with postnatal proportional undergrowth without known molecular defects in *GHR*, *IGF1* and *IGFALS*. Molecular studies: Mutation screening of the coding sequences, intron/exon boundaries and regulatory regions of *IGF1R* by HRM and sequencing; deletions/duplications analysis of *IGF1R* coding regions by MLPA and chromosome 15q26.3 region by aCGH. **Results:** 8/46 patients (17.4%) presented a heterozygous mutation in IGF1R. Two were de novo deletions of the 15.q26.2–26.3 region encompassing IGF1R. The remaining six patients presented five different mutations, four novel, all classified as probably pathogenic by bioinformatic prediction tools. Four were missense mutations affecting highly conserved residues and the fifth a frameshift duplication predicted to elongate and alter the protein C-terminal sequence. **Conclusion:** Heterozygous *IGF1R* mutations represent a frequent finding (17.4%) in the patients born SGA and/or with postnatal proportional undergrowth examined. The clinical phenotypes of the individuals with *IGF1R* mutations are very variable. IUGR, microcephaly and psychomotor developmental delay, together with increased IGF1 levels, are the predominant findings, though not present in all patients. These results indicate that heterozygous *IGF1R* mutations cause a phenotypically variable IGF1 resistance syndrome associated with proportional undergrowth with a higher prevalence than initially predicted.

FC4.2

The Effect of *grB10*-Deficiency in Zebrafish: A Translational Animal Model to Study Human Growth

Chiara De Leonibus^a, Irene Barinaga-Rementeria Ramirez^b,
Adam Hurlstone^b, Peter Clayton^a, Adam Stevens^a

^aManchester Academic Health Sciences Centre, Royal Manchester Children's Hospital, Manchester, UK; ^bFaculty of Life Sciences, The Michael Smith Building, University of Manchester, Manchester, UK

Background: *GRB10* negatively regulates IGF1 signalling, influences growth and promoter polymorphisms are associated with GH response¹. *GRB10* knockout-mouse models display foetal overgrowth², however, the mouse model has only partial similarity to human growth³. There is evidence that the zebrafish is an appropriate model to study growth⁴ and has the advantage of being easily genetically manipulated. **Objective:** To use zebrafish as a vertebrate animal model to study the effects of *GRB10*-deficiency on growth and development. **Methods:** *GRB10* expression was analysed by developmental stages and tissue distribution using qPCR. Transgenic zebrafish were obtained by injecting a splice-blocking morpholino (MO) into WT embryos to generate *GRB10*-deficiency. Dose-dependent titration of MO injection was performed (0.1, 0.5, 0.7, and 1 mM) into one-cell stage embryos with mock-injected zebrafish (dye only) as a control. Growth measurements and embryo development were assessed by time-lapse microscopy from birth up to 72 h post-fertilization. **Results:** *GRB10* gene expression changes were identified during the growth phases, with a major peak in early embryogenesis followed by a gradual age-dependent decrease until the adult stage. *GRB10* was widely expressed in all adult tissues examined, with the highest expression in kidney, brain, ovaries, and bone. We observed a dose-dependent overgrowth in *GRB10*-deficient embryos compared to controls, with proportional increase in length, head size, and eye distance ($P < 0.05$), along with gradual increase in mortality compared to controls (22, 33, 43, and 46% at MO increasing dose vs 8%, $P = 0.013$). Time-lapse microscopy showed *GRB10*-deficient embryos progressing through the first 72 h of embryogenesis at the same rate as controls, with no significant change in pigmentation and organogenesis. **Conclusion:** Our results indicate a major role of *GRB10* in zebrafish development. These findings support zebrafish as a vertebrate model whereby genetic dysregulation of *GRB10* leads to proportionate overgrowth, implying important effects on growth suppression and whole-body size.

FC4.3

Oscillations in Gene Expression Profiles Across Childhood Highlight the Relation of Growth and Specific Metabolic Functions in Both Sexes

Adam Stevens^a, Christopher Knight^b, Chiara De Leonibus^a,
Andrew Dowsey^a, Neil Swainston^c, Philip Murray^a, Peter Clayton^a

^aManchester Academic Health Sciences Centre, Royal Manchester Children's Hospital, Manchester, UK; ^bFaculty of Life Sciences, The University of Manchester, Manchester, UK; ^cManchester Institute of Biotechnology, The University of Manchester, Manchester, UK

Background: The phases of human growth are associated with gene expression (GE) changes¹, raising the possibility that rhythmic patterns of GE occur throughout childhood. **Objective:**

In this study, we have assessed time-series patterns of GE profiles associated with age to characterise oscillations. **Methods:** GE analysis was conducted on cells of lymphoid origin from normal individuals through childhood ($n=87$, 43 males and 44 females, range 2 months–29 years)¹. Clustered patterns of GE time-series were identified by STEM (short time-series expression miner)² and confirmed using unsupervised multidimensional scaling (MDS) (Qlucore Omics Explorer 3.0). Statistically associated GE was assessed using ANOVA ($P<1\times 10^{-4}$). Associated causal networks associated with GE were identified algorithmically (Ingenuity Pathway Analysis). **Results:** Gender associated groups of gene probe (GP) set profiles were identified with oscillations of gene expression; 487 GP sets in males and 3302 in females with an overlap of 145. MDS and time-series analysis identified two underlying patterns of GE (i and ii), the first (i) with peaks at 5.0, 7.2 and 12.1 years (99 GP-sets) and the second (ii) with peaks at 5.6 and 10.2 years (388 GP-sets) in males; similar oscillations were seen in females with (i) peaks at 5.0, 7.0 and 11.3 years (1221 GP-sets) and (ii) 3.7 and 7.0 years (2081 GP-sets). Causal network analysis on these GE profiles in both sexes implicated metabolic processes ($P<1.3\times 10^{-3}$) with specific differences in the second pattern of oscillation (ii) in GE between males and females in lipid and amino acid metabolism (both $P<0.017$). The overlap in GE between the sexes was associated with growth ($P<1.3\times 10^{-5}$) causally linked to GH and IGF1 action. **Conclusion:** This study has identified gender specific variations in age-related GE oscillations associated with human growth and development that highlight gender-specific differences in metabolism and emphasise the role of the GH/IGF1 axis.

FC4.4

Short Stature, Accelerated Bone Maturation, and Early Growth Cessation due to Heterozygous Aggrecan Mutations

Ola Nilsson^{a,b}, Michael Guo^{c,f}, Nancy Dunbar^d, Jadranka Popovic^e, Daniel Flynn^e, Christina Jacobsen^c, Julian Lui^a, Joel Hirschhorn^{f,g}, Jeffrey Baron^a, Andrew Dauber^{c,g}

^aProgram in Developmental Endocrinology and Genetics, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland, USA; ^bPediatric Endocrinology Unit, Department of Women's and Children's Health, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden; ^cDivision of Endocrinology, Boston Children's Hospital, Boston, Massachusetts, USA; ^dConnecticut Children's Medical Center, Hartford, Connecticut, USA; ^eChildren's Hospital of Pittsburgh, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA; ^fDepartment of Genetics, Harvard Medical School, Boston, Massachusetts, USA; ^gProgram in Medical and Population Genetics, Broad Institute, Cambridge, Massachusetts, USA

Background: Most children with idiopathic short stature (ISS) have a delayed bone age (BA). ISS with advanced BA is far less common. We studied three families with autosomal dominant short

stature, unexplained BA acceleration, and premature growth cessation. **Objective and hypotheses:** To identify the genetic cause of this condition and describe its clinical spectrum. **Method:** Whole exome sequencing was performed in selected individuals from the three families. **Results:** Family 1 included two brothers with short stature (-3.5 , -1.9 SDS) and advanced BAs (3.5, 3.0 years over chronological age (CA)). Their mother was a normal height until her linear growth stopped at age 10 years (2 years prior to menarche) with an adult height of 145.9 cm (-2.7 SDS). Similarly, in families 2 and 3, all affected children had short stature (-2.1 to -2.9 SDS), advanced BA (1.5–4.0 years over CA). All affected adults reported early linear growth cessation (age 12–13 years) despite normal puberty, yielding decreased adult heights (-4.0 to -2.4 SDS). No endocrine explanation for short stature or advanced BA was detected in any affected individual. Less consistent features included macrocephaly, midface hypoplasia, brachydactyly, exaggerated lumbar lordosis, and early onset knee osteoarthritis. In each family, whole exome sequencing identified a novel, heterozygous variant in aggrecan (ACAN), a proteoglycan component of the extracellular matrix in growth plate and other cartilage structures. The mutations were present in all affected subjects, but in no unaffected family members. Two of the variants were predicted to be complete loss-of-function variants, one frameshift and one canonical splice site mutation, and the third variant was a missense variant leading to loss of a highly evolutionarily conserved residue in the C-type lectin domain of ACAN. **Conclusion:** Our findings indicate that aggrecan mutations can present as autosomal dominant short stature with advanced BA and early growth cessation. Our findings expand the spectrum of aggrecan defects and provide a molecular genetic etiology for the unusual child with short stature and accelerated skeletal maturation.

FC4.5

Fetal and Postnatal Growth in Turner Syndrome and their Associations with the Dosage Effects of the X-Linked Gene: a Cross-Sectional Data Base Analysis of the French National Rare Disease Network

Delphine Zenaty^{a,b}, Elodie Fiot^{a,b}, Sophie Dos Santos^{a,b}, Priscilla Boizeau^c, Jeremie Haignere^c, Juliane Leger^{a,b}, and the French Turner Syndrome Study Group^d

^aPaediatric Endocrinology Diabetology, Robert Debre Hospital, Assistance Publique Hopitaux de Paris, Université Paris Diderot, Paris, France; ^bReference Center for Rare Endocrine Growth Diseases, Paris, France; ^cClinical Epidemiology Department, Robert Debre Hospital, Assistance Publique Hopitaux de Paris, Université Paris Diderot, Paris, France; ^dFrench Endocrine Rare Diseases for Growth Network, Cemara, France

Background: Shox gene, located on the short arm (p) of the X chromosome, is expressed in the growth plate cartilage in pre and post natal life. Whereas the dose dependent association between the number of active copies of the SHOX gene and height is well established, studies addressing a more subtle variability between the quality of fetal growth, the severity of post natal height deficit and karyotype subgroups in Turner syndrome (TS) are still

Table 1. (for Abstract FC 4.5)

	XrX <i>n</i> = 101	Iso (Xq) <i>n</i> = 283	45X0 <i>n</i> = 568	45X/46XX <i>n</i> = 223	Presence of Y <i>n</i> = 73	Others <i>n</i> = 241
Birth weight SDS	-1.56 ± 1.33	-1.22 ± 1.20	-0.96 ± 1.13	-0.73 ± 1.31	-0.68 ± 1.21	-0.89 ± 1.21
≤ -2 SDS	32%	26%	16%	15%	12%	14%
Birth length SDS	-1.52 ± 1.12	-1.31 ± 1.18	-1.21 ± 1.06	-0.85 ± 1.23	-0.99 ± 1.04	-1.08 ± 1.11
≤ -2 SDS	33%	31%	24%	17%	18%	21%
Height -TH SDS	-2.7 ± 1.1	-2.8 ± 1.1	-2.4 ± 1.1	-2.1 ± 1.0	-2.2 ± 1.2	-1.9 ± 1.3
Chronological age (years)	8.0 ± 4.2	9.1 ± 4.1	8.1 ± 4.3	9.4 ± 3.9	8.7 ± 3.4	9.1 ± 3.8

limited. **Objective:** The aim of this large observational cohort study was to examine whether fetal and post natal growth in TS were associated with the karyotype subgroups. **Method:** Birth weight and length, expressed as SDS for gestational age, and height minus target height (TH) SDS before GH treatment, were analyzed according to karyotype in a national cohort of 1532 patients with TS. **Results:** Unless in patients with caryotype including ring X, BW were less affected than BL in all subgroups. The degree of fetal growth retardation and the post natal height deficit in untreated GH patients were associated with the karyotype subgroups, with patients with structural abnormalities of the X chromosome (isoXq which includes deletion of the short and duplication of the long arms, and ring X formation) or monosomy X more severely affected than patients with mosaicism or with the Y chromosome. **Conclusion:** In TS, the deficit of fetal and post natal growth is related to karyotype.

FC4.6

Longitudinal Growth of Finnish Children With Gestational Diabetes in Mothers

Tiina Hakanen, Nina Vuorela, Ludmila Lipiäinen, Matti K Salo, Tapio Nummi, Marja-Terttu Saha

University of Tampere, Tampere, Finland

Background: With the increase of overweight prevalence an increasing number of women develop gestational diabetes. **Objective and hypotheses:** We evaluated the growth of 6902 children of mothers with gestational diabetes. The secular trends in the prevalence of children with gestational diabetes in mothers was studied during 30 years.

The material consisted of children born 1974 (*n* = 1108), 1981 (*n* = 977), 1991 (*n* = 583), 1995 (*n* = 786), 2001 (*n* = 765), and 2003–2004 (*n* = 2683). **Method:** The measurement data was collected from health records. BMI was calculated. The BMI between children with gestational diabetes in mothers and with non-diabetic mothers were compared using the Mann–Whitney *U*-test. Pearson's χ^2 test was used for analysing association between overweight and gestational diabetes. **Results:** The prevalence of children with mothers presenting with gestational diabetes has increased from 0.1% in 1974 to 17.6% in 2004. The mean BMI was significantly higher in children with gestational diabetes in mothers at the age of 5, 7, and 12 years compared to children

with non-diabetic mothers (*P* values < 0.001). Furthermore, overweight was significantly more common (*P* value < 0.001) at the age of 5, 7, and 12 years (24, 30, and 42%) compared to children with non-diabetic mothers (16, 18, and 19%, respectively). **Conclusion:** Following the increasing prevalence of overweight, the number of children born to mothers with gestational diabetes is increasing. These children grow bigger already at the age of 5 years compared to their peers of non-diabetic mothers. The difference in growth proceeds towards adolescence.

FC5.1

Derivation of GnRH Neuron-Like Cells from Human Embryonic Stem Cell-Derived Neural Crest Progenitors

Parinya Noisa^{a,d}, Hataiwan Chochechwattanalert^a, Carina Lund^a, Timo Tuuri^b, Taneli Raivio^{a,c}

^aInstitute of Biomedicine/Physiology, University of Helsinki, Helsinki, Finland; ^bResearch Programs Unit, Molecular Neurology, Biomedicum Stem Cell Centre, University of Helsinki, Helsinki, Finland; ^cChildren's Hospital, Helsinki University Central Hospital, Helsinki, Finland; ^dSchool of Biotechnology, Institute of Agricultural Technology, Suranaree University of Technology, Nakhon Ratchasima, Thailand

Background: Neural crest (NC) cells emerge at the interface between neural and non-neural ectoderm, and migrate extensively to form a variety of NC derivatives such as peripheral neurons, glia, melanocytes, endocrine cells, and mesenchymal precursor cells. NC cells possess various unique properties and are capable of undergoing cell fate decisions across multiple tissues and germ layers. In zebrafish and mouse, GnRH neurons are reported to arise also from NC. **Objective and hypotheses:** Here we show that GnRH neuron-like cells can also be obtained from NC cells, which are derived from human pluripotent stem cells (hPSCs). **Method:** We first induced NC fate from hPSCs by our recently published protocol; these hPSC-derived NC cells expressed NC-specifier genes, including *MSX2*, *PAX3*, *SLUG*, *TWIST1*, and *SOX10*, and were confirmed to be multipotent. We next differentiated hPSC-derived NC cells toward neuronal lineage, which resulted in upregulation of a set of neuronal genes including *TUJ1*, *MASH1*, and *NGN2*. **Results:** Peripheral sensory neurons and sympathetic neurons were detected by immunocytochemistry. Importantly, genes related to GnRH neuron development such

as *EBF2*, *DCC*, and *VAX1* were increased upon neuronal induction. *GnRH1* expression did not increase significantly, but GnRH1-immunopositive cells were detected among TUJ1-positive neurons. The resulting GnRH1-positive cells were co-localized with NC markers, such as *SOXE*, *p75(NGFR)* and *HNK1*. **Conclusion:** GnRH-expressing cells can be generated from hPSC-derived NC cells. We are currently investigating the implications of these findings with Kallmann syndrome patient-derived induced pluripotent stem cells.

FC5.2

Mutations in the Maternally Imprinted Gene *MKRN3* are a Frequent Cause of Familial Central Precocious Puberty

Nancy Mekhail^a, Ibrahima Ba^{b,g}, Dominique Simon^{a,b}, Anne Paulsen^{a,b}, Delphine Zenaty^{a,b}, Muriel Houang^c, Monique Jesuran-Perelroizan^d, Gianpaolo de Filippo^e, Maria Carolina Salerno^f, Jean-Claude Carel^{a,b}, Juliane Léger^{a,b}, Nicolas de Roux^{b,g}

^aService d'Endocrinologie et Diabétologie Pédiatrique, Hôpital Robert Debré, Paris, France; ^bINSERM U1141, Paris Diderot University, Paris, France; ^cService d'Endocrinologie Clinique, Hôpital Trousseau, Paris, France; ^dEndocrinologie Pédiatrique, Toulouse, France; ^eService d'Endocrinologie Pédiatrique, Hôpital Bicêtre, Kremlin-Bicêtre, France; ^fService d'Endocrinologie Pédiatrique, CHU Federico II, Naples, Italy; ^gLaboratoire de Biochimie-Hormonologie, Hôpital Robert Debré, Paris, France

Background: Recently, mutations in the maternally imprinted *MKRN3* gene have been associated to familial idiopathic central precocious puberty (iPPC). The clinical phenotype and the frequency of these mutations are poorly described. **Objective and hypotheses:** Delineate the frequency of *MKRN3* mutations in iPPC and perform a genotype-phenotype correlation in *MKRN3* mutated patients. **Method:** 59 index cases with iPPC have been included in the study. The criteria to include patients were: passage to Tanner stage 2 before 8 years in girls and 9 years in boys, with or without pubarche in both sexes, advanced bone age with an accelerated growth spurt, increased basal and peak LH after GnRH test and a normal brain MRI. *MKRN3* has been sequenced by the Sanger method from DNA extracted from blood lymphocytes. **Results:** 38 cases were familial and 21 cases were sporadic. four faux-sens mutations, one nucleotide insertion or two nucleotides deletion leading to a frame shift of the coding sequence were found in 11 familial cases. Faux-sens mutations were novel and they were considered as loss of function mutation by *in-silico* analysis. No mutation was found in sporadic cases or in cases with mother-daughter transmission. The familial analysis has confirmed the transmission of the mutated allele by the father. The analysis of the phenotype in mutated patients, revealed a pubertal onset between 3.5 and 7.5 years and an explosive LH and FSH response to GnRH stimulation. The evolution of the puberty and the response to GnRH treatment were similar in mutated and

non mutated patients. **Conclusion:** *MKRN3* must be sequenced in familial iPPC with a possible transmission of the mutated allele by the father. All *MKRN3* mutations are loss of function mutations. The phenotype indicates a possible pituitary defect in addition to the hypothalamic defect initially suspected.

FC5.3

Loss of Function Mutations in *pnpla6* Cause Hypogonadotropic Hypogonadism due to Impaired LH Release from Pituitary Gonadotropes

Ali Kemal Topaloglu^{a,d}, Alejandro Lomniczi^b, Doris Kretzschmar^c, Gregory A Dissen^b, Leman Damla Kotan^d, Craig A McArdle^e, A. Filiz Koc^f, Ben C Hamel^g, Metin Guclu^h, Esra D Papatyaⁱ, Erdal Erenⁱ, Eda Mengen^a, Fatih Gurbuz^a, Mandy Cook^c, Juan M Castellanoⁱ, M. Burcu Kekil^d, Neslihan O Mungan^a, Bilgin Yuksele^a, Sergio R Ojeda^a

^aDepartment of Pediatric Endocrinology, Faculty of Medicine, Cukurova University, Adana, Turkey; ^bDivision of Neuroscience, Oregon National Primate Research Centre, Oregon, USA; ^cCentre for Research on Occupational and Environmental Toxicology, Oregon Health and Science University, Oregon, USA; ^dDepartment of Biotechnology, Institute of Sciences, Cukurova University, Adana, Turkey; ^eLaboratories for Integrative Neuroscience and Endocrinology, University of Bristol, Bristol, UK; ^fDepartment of Neurology, Faculty of Medicine, Cukurova University, Adana, Turkey; ^gDepartment of Human Genetics, Nijmegen Medical Centre, Radboud University, Nijmegen, The Netherlands; ^hDepartment of Endocrinology and Metabolism, School of Medicine, Uludag University, Bursa, Turkey; ⁱDepartment of Pediatric Endocrinology and Metabolism, School of Medicine, Uludag University, Bursa, Turkey; ^jDepartment of Cell Biology, Physiology and Immunology, University of Cordoba, Cordoba, Spain

Background: Gordon Holmes syndrome (GHS) is characterized by cerebellar ataxia/atrophy and normosmic hypogonadotropic hypogonadism (nHH). The underlying pathophysiology of this combined neurodegeneration and nHH remains unknown. **Patients and methods:** We studied a cohort of multiplex families with GHS through autozygosity mapping and whole exome sequencing. **Results:** We identified patients from three independent families carrying loss-of-function mutations in *PNPLA6*, which encodes neuropathy target esterase (NTE), a lysophospholipase that maintains intracellular phospholipid homeostasis by converting lysophosphatidylcholine (LPC) to glycerophosphocholine. WT *PNPLA6*, but not *PNPLA6* bearing these mutations, rescued a well established *Drosophila* neurodegenerative phenotype caused by the absence of sws, the fly ortholog of mammalian *PNPLA6*. Inhibition of NTE activity in the L β T2 gonadotrope cell line diminished LH response to GnRH by reducing GnRH-stimulated LH exocytosis, without affecting GnRH receptor signaling or LH β synthesis. **Conclusion:** Thus NTE-dependent alteration of lipid homeostasis in GHS causes both neurodegeneration and nHH, the latter is due to impaired LH release from pituitary gonadotropes.

FC5.4

Reference Values for Urinary Gonadotropins in Preterm and Full-Term Infants in 'Minipuberty'

Tanja Kuiri-Hänninen^a, Esa Hämäläinen^b, Sanna Silvennoinen^a, Leo Dunkel^c, Ulla Sankilamp^a

^aDepartment of Pediatrics, University of Eastern Finland and Kuopio University Hospital, Kuopio, Finland; ^bHUSLAB, Helsinki University Central Hospital, Helsinki, Finland; ^cWilliam Harvey Research Institute, Barts and the London, Queen Mary University of London, London, UK.

Background: Hypothalamic–pituitary–gonadal (HPG) axis activates soon after birth, and this 'minipuberty' provides a transient phase for evaluation of the function of the HPG axis in early infancy. Substantial differences in postnatal gonadotropin secretion have been reported between preterm (PT) and full-term (FT) boys and girls. Therefore, when evaluating gonadotropin levels in infants, time from birth (calendar age), maturity (postmenstrual, PM age) and sex should be considered. **Objective and Hypotheses:** We constructed sex-specific reference intervals for urinary gonadotropin levels in FT and PT infants according to calendar and postmenstrual age. **Method:** LH and FSH levels were measured in spot urinary samples with time-resolved immuno-fluorometric assay (AutoDELFIA, Perkin Elmer, Wallac, Turku, Finland) and corrected for urinary creatinine. Altogether 989 urinary samples of 193 infants (101 boys) born at 23.4–42.1 gestation weeks were analyzed. Samples were collected from 1.0 week–6.5 months of age. **Results:** Infants were divided in three groups according to gestational age at birth: < 32, 32–36, and ≥ 37 weeks. Reference intervals for LH and FSH levels in urine were constructed for 1 week to 2 months of age, 2–4 months of age and > 4 months of age. PM age was strongly associated with both LH and FSH levels in PT infants, and from approximately 40 weeks of PM age, the levels of PT infants were in the same range as in FT infants. **Conclusion:** These data provide reference intervals for urinary gonadotropins during the first 6 months of life in infants born as early as at 24th gestational week. These normative values help to better understand the notable changes in gonadotropin levels during the first months of life in PT and FT infants.

FC5.5

Characterization of IGF1 Receptor Expression and Localization in Paediatric Gliomas Upon Diagnosis According to WHO 2007 Grading

Florencia Clément^a, Marcela Venara^a, Silvana Maglio^b, Ayelen Martín^a, Cecilia Matho^a, César Petre^c, Mercedes García Lombardi^d, Ignacio Bergadá^a, Patricia Pennisi^a

^aCentro de Investigaciones Endocrinológicas 'Dr César Bergadá' (CEDIE) CONICET – FEI – División de Endocrinología, Hospital de Niños Ricardo Gutiérrez., Buenos Aires, Argentina; ^bDivisión de Anatomía Patológica, Hospital de Niños Dr Ricardo Gutiérrez., Buenos Aires, Argentina; ^cDivisión de Neurocirugía, Hospital de

Niños Dr Ricardo Gutiérrez., Buenos Aires, Argentina; ^dServicio de Oncología, Hospital de Niños Dr Ricardo Gutiérrez., Buenos Aires, Argentina

Background: Gliomas are the most common subgroup of CNS tumours in children. Histologic grading is a means of predicting the biological behavior of these tumours and survival is strongly correlated with tumour gradation. The IGF system of ligands and receptors are known to play an important role in both normal and neoplastic growth. Recently, nuclear translocation of the type 1 IGF1R has been demonstrated in tumour tissues. Although the IGF1R expression has been described in CNS paediatric tumours, information about the intracellular localization and correlation with tumour grade is lacking. **Objective and Hypotheses:** To characterize the expression and intracellular localization of the IGF1 receptor in glial tumours from paediatric patients according to WHO 2007 grading. **Method:** Twenty-two patients (12 males/ten females), median aged 7.7 years, (range 0.9–18.2), with gliomas without previous medical treatment were included. Formalin-fixed 5 µm tumour tissue sections were immunostained for IGF1Rβ. IGF1R expression and intracellular localization were scored as positive or negative, nuclear or cytoplasmic respectively. Contingency tables were analyzed using Pearson's χ^2 test to assess relationships between IGF1R and tumour grade (low grades I–II and high grades III–IV). **Results:** IGF1R staining was positive in 11/17 (65%) low grade tumours and in 4/5 (80%) high grade tumours. Low grade tumours showed cytoplasmic localization of IGF1R in 8/11 cases, while in high grade tumours IGF1R localization was mainly nuclear (3/4) (χ^2 test: $P < 0.05$). **Conclusion:** Our results would indicate that both expression and intracellular localization of the IGF1R are different in low vs high grade glial paediatric tumours, suggesting a potential role for the IGF system in the biological behavior of these tumours. Further studies are necessary to confirm our results.

FC5.6

The Diencephalic Syndrome of Emaciation in Infantile Hypothalamochiasmatic Low-Grade Gliomas : a Retrospective Case–Control Study of Diagnostic Parameters and Long-Term Outcomes Over 30 Years of Follow-Up

Hoong-Wei Gan^{a,b}, Lisethe Meijer^{d,e}, Georgina Gullick^c, Margaret Senbanjo^c, David Walker^{d,e}, Helen Spoudeas^{a,b}

^aInstitute of Child Health, University College London, London, UK; ^bGreat Ormond Street Hospital for Children NHS Foundation Trust, London, UK; ^cUniversity College London Medical School, London, UK; ^dChildren's Brain Tumour Research Centre, The University of Nottingham, Nottingham, UK; ^eNottingham Children's Hospital, Nottingham University Hospitals NHS Trust, Nottingham, UK

Background: Diencephalic syndrome (DS) is a rare disorder of severe emaciation classically associated with infantile Hypothalamochiasmatic low-grade gliomas (HCLGGs) and GH excess. However, diagnostic criteria remain undefined and published

literature includes non-specific tumour-related cachexia. In a large optic pathway LGG cohort ($n=166$), we have previously demonstrated that DS independently predicts multiple tumour progressions and severe endocrine morbidity. **Objective and Hypotheses:** To improve diagnostic criteria for DS by determining the sensitivity and specificity of clinical and biochemical parameters and to compare long-term endocrinopathy with contemporaneous age- and tumour location-matched patients. **Method:** Retrospective subcohort analysis of patients presenting <2 years with HCLGGs to our centre between 1980 and 2010. **Results:** 28/166 infants with HCLGG were diagnosed at a median (range) of 0.9 (0.2–1.9) years and were followed up for 9.0 (2.4–28.1) years. 14/28 had DS and were more likely to have hypothalamic involvement ($P=0.0006$) and metastases ($P=0.04$) than non-DS patients. Weight ($P=0.00001$), BMI ($P=0.0005$) and weight-for-length (WFL) ($P=0.0001$) SDS were significantly lower in DS patients but height SDS were similar ($P=0.3$). 6/7 patients in whom fasting GH concentrations were measured had concentrations of >20 ng/ml (median, 32.7 ng/ml). GH excess was more sensitive (86%) and specific (100%, AUC=0.93) than BMI SDS <2 (AUC=0.90), hypothalamic involvement (AUC=0.82) or WFL SDS <2 (AUC=0.79) for the diagnosis of DS. DS patients tended to experience more tumour progressions ($P=0.01$), require multiple surgeries ($P=0.02$) and have multiple endocrinopathies, particularly ACTH deficiency ($P=0.03$). **Conclusion:** This is the first attempt to auxologically and biochemically differentiate DS in infantile HCLGG from non-specific tumour-related cachexia. We demonstrate that over 30 years' of follow-up there are differences between the endocrinopathies and tumour progressions experienced by DS and non-DS patients. The next pan-European SIOP LGG chemotherapeutic trial is in design with a specific focus on DS, providing a unique opportunity to prospectively study the pathophysiology of this extremely rare disorder.

FC6.1

Search for Genetic Defects in the Transcription Factor Genes *FOXL2*, *FOXE1*, *BMP15*, *NOBOX*, and *GDF9* in Children, Adolescents and Young Adults With Premature Ovarian Insufficiency POI

Nikolaos Settas^a, Margarita Anapliotou^a, Euthimios Deligeoroglou^b, Emmanuel Kanavakis^c, Eleni Fryssira^c, Christina Kanka-Gantenbein^a, Lina Michala^d, Catherine Dacou-Voutetakis^a, George Creatsas^b, George P Chrousos^a, Antonis Voutetakis^a

^aFirst Department of Pediatrics, School of Medicine, Athens University, Athens, Greece; ^bSecond Department of Obstetrics and Gynecology, School of Medicine, Athens University, Athens, Greece; ^cDepartment of Medical Genetics, School of Medicine, Athens University, Athens, Greece; ^dFirst Department of Obstetrics and Gynecology, School of Medicine, Athens University, Athens, Greece

Background: Molecular defects are rarely detected in Premature ovarian insufficiency (POI) patients. **Objective and Hypotheses:** We hypothesized that the frequency of causative

molecular defects could be higher in cases with early onset of POI. Moreover, the analysis of multiple genes in the same POI group could disclose co-existence of more than one molecular aberration. **Method:** In 25 subjects, aged 17.1 ± 7 years at POI onset, bidirectional sequencing of the coding region of *FOXL2*, *FOXE1*, *BMP15*, *NOBOX*, and *GDF9* genes was performed. **Results:** In the *FOXL2* gene, a novel, *de novo* heterozygous deletion (p.K150Rfs*121) was detected in one subject. In the *FOXE1* gene, a novel aberrant alanine tract was detected (8/16 alanine residues vs the normal 14/14) in one subject, while the 16/16 type was present in 12%. In the *BMP15* gene, the mutation p.Q115H/WT was detected in one subject (zero in the European population, 1000 genome project). *In silico* analysis of p.Q115H predicted to be damaging in 5/7 softwares. In the *BMP15* gene the mutation p.A180T/WT was detected in 4% (0.5% in the European population). *In silico* analysis of p.A180T predicted to be damaging in 2/7 softwares. The haplotype G-G-C (c.-9C/G, and c.308A>G, c.852C>T) of the *BMP15* gene was detected in 12% (Dixit *et al.*: 2.6% and zero in controls). 16% of our subjects were carriers of the p.D452N of the *NOBOX* gene (1.6% in the European population). No missense variants were detected in the *GDF9* gene. In two patients co-existing aberrations in two genes were identified. **Conclusion:** Genetic aberrations in POI-related genes were frequently detected in our POI group (48%). The co-existence of aberrations in two genes found in two of our subjects possibly indicates digenic inheritance.

FC6.2

Next Generation Sequencing of the Androgen Receptor Gene in Patients With Androgen Insensitivity Syndrome and Controls

Nadine Hornig^{a,b}, Hans-Udo Schweikert^c, Martin Ukat^a, Alexandra Kulle^a, Maik Welzel^a, Gaby Wehner^c, Ralf Werner^f, Olaf Hiort^f, Stenvert Drop^d, Martine Cools^e, Carine de Beaufort^g, Reiner Siebert^b, Ole Ammerpohl^b, Paul-Martin Holterhus^a

^aDepartment of Pediatrics, Christian-Albrechts-University Kiel and University Hospital Schleswig-Holstein, Campus Kiel, Kiel, Germany; ^bInstitute of Human Genetics, Christian-Albrechts-University Kiel and University Hospital Schleswig-Holstein, Campus Kiel, Kiel, Germany; ^cUniversity Hospital Bonn, Dermatologie, Bonn, Germany; ^dDivision of Pediatric Endocrinology, Department of Pediatrics, Rotterdam, The Netherlands; ^eDepartment of Pediatrics, University Hospital Gent, Gent, Belgium; ^fDepartment of Pediatrics, University of Lübeck and University Hospital Schleswig-Holstein, Campus Lübeck, Lübeck, Germany; ^gDCCP–Clinique Pédiatrique de Luxembourg, Luxembourg, Luxembourg

Background: In a large fraction of patients with clinically presumed Androgen Insensitivity Syndrome, no mutation of the *Androgen Receptor* gene can be detected. However, established Sanger sequencing techniques of the AR gene are often limited to the coding region. **Objective and Hypotheses:** To set up a next

generation sequencing (NGS) approach of the entire AR locus (including UTRs, exons, introns, up- and downstream regions) for a comprehensive AR gene mutation analysis in patients with AIS. **Method:** DNA was extracted from cultured genital skin fibroblasts (GSF=scrotum, foreskin, and labia) of 70 patients with known and presumed AIS, two patients with 17 β HSDIII deficiency, four patients with 5 α -reductase deficiency and ten control males. Patients were suspected to have AIS based on clinical findings, pathological androgen binding, reduced AR expression in GSF, a pathological APOD-assay (assay for AR function) or a combination of these. The AR-sequencing library was produced using a capture-based method (Haloplex; Agilent). The target sequence included the coding region, the UTRs, 90% of the intron sequences as well as a 9 kb upstream and 5 kb downstream sequence. Sequencing was performed on a Miseq benchtop sequencer (Illumina). Alignment to the hg19 reference genome and single nucleotide polymorphism (SNP) calling was performed by the MiSeq-Reporter Software (Illumina). **Results:** Targeted NGS confirmed AR mutations in all patients with mutations previously identified by Sanger sequencing. Additional mutations were detected by NGS, which affected, e.g. the UTR, and could be validated by Sanger sequencing. Normal male controls and patients having a different DSD diagnosis, e.g. 17 β HSDIII deficiency, showed no mutations in the AR locus. **Conclusion:** Targeted NGS is a valid method for AR-sequencing in presumed AIS and extends the diagnostic perspective beyond the coding regions.

FC6.3

LRH1 Rescues SF1 Deficiency for Steroidogenesis *in vitro* but Cannot Explain the Broad Phenotype of SF1 Deficiency in men

Núria Camats^a, Mónica Fernández-Cancio^b, Laura Audí^b, Pilar Andaluz^b, Primus E Mullis^a, Antonio Carrascosa^b, Christa E Flück^a

^aPediatric Endocrinology of Department of Pediatrics and Department of Clinical Research, University Children's Hospital Bern, Bern, Switzerland; ^bPediatric Endocrinology, Hospital Vall d'Hebron, CIBERER, Autonomous University, Barcelona, Spain

Introduction: Steroidogenic factor1 (SF1/NR5A1) regulates adrenal and sex development and function. SF1 mutations manifest with a broad phenotype; generally in 46,XY individuals with disorders of sex development (DSD) and in women with ovarian insufficiency. So far, no genotype-phenotype correlation has been found. We hypothesized that the broad phenotype of SF1 mutations may be due to a second hit in a gene with similar function. Liver receptor homolog-1 (LRH1/NR5A2), from the same family, was thought a good candidate. Thus, we studied the role of LRH1 in SF1 deficiency *in vitro* and *in vivo*. **Methods and patients:** *In vitro*, we assessed the interplay between DAX1, SF1 and LRH1 in non-steroidogenic HEK293 cells. V20L SF1 (present in a severely-affected 46,XY DSD subject and his healthy father) was chosen for comparative studies. We investigated the effect of

WT SF1 and V20L SF1 combined with LRH1 isoforms on SF1 regulated promoter-luciferase-reporter-constructs (*CYP17A1* and *HSD3B2*) in transfection experiments. We also assessed the expression of these factors (including LRH1 isoforms) in human steroidogenic tissues. *In vivo*, we searched for *NR5A2* mutations in 21 subjects harboring heterozygous *NR5A1* mutations. **Results:** *In vitro* assays showed that all LRH1 isoforms were able to transactivate the *CYP17A1* and the *HSD3B2* promoters. When SF1 activity was lost, all LRH1 isoforms transactivated the *HSD3B2* promoter. DAX1 inhibited SF1 and LRH1 mediated transactivation. Gene profiles revealed that LRH1 isoforms are all expressed in both human adult and fetal adrenals and testis. However, we found no mutations in *NR5A2* in our cohort of SF1 patients. **Conclusions:** *In vitro*, LRH1 can regulate transcription of steroidogenic genes similarly to SF1. LRH1 can (partially) replace SF1 in case of deficiency. However, there were no mutations in *NR5A2* in heterozygote *NR5A1* patients with a severe phenotype of SF1 deficiency. Thus the variability in phenotype with SF1 genotype remains elusive.

FC6.4

Familial 46,XY Complete Female External Sex Development and Primary Amenorrhea Along with Hidden Gonad Tumors, Secondary to a Novel p.met64val SRY Gene Mutation

Elisa Vaiani^a, Carmen Malosetti^b, Roxana Marino^a, Pablo Ramirez^a, Natalia Perez Garrido^a, Esperanza Berensztain^a, Florencia Da Col^b, Marcela Bailez^a, Josefina Sala^a, Laura Galluzzo^a, Mercedes Maceiras^a, Juan Manuel Lazzati^a, Marco Rivarola^a, Alicia Belgorosky^a

^aHospital de Pediatría Garrahan, Buenos Aires, Argentina; ^bHospital de Niños de San Justo, Buenos Aires, Argentina

Background: The SRY protein is a transcription factor that contains a high mobility group (HMG) homeobox domain which possesses sequence-specific DNA binding activity and regulates other genes involved in male sex determination pathway. The majority of the identified mutations occurred within the HMG-box motif. There are few reports of pedigrees with familial transmission. **Objective and Hypotheses:** To describe a paternally transmitted novel SRY mutation within the HMG-box (p.Met64Val) in two 46,XY sisters aged 16 (P1) and 14 (P2) years old, referred because of primary amenorrhea without sexual ambiguity. **Method:** Direct DNA sequencing and *in silico* tools were used to identify SRY gene mutations and to predict the pathogenicity. Hormonal, pelvic ultrasound (PU), and Histo-pathological studies were also carried out. **Results:** *In silico* prediction models indicated that the substitution p.Met64Val probably affects protein function. Breast development was Tanner II and IV, PU revealed Mullerian structures and two gonads resembling ovaries in P1 and P2 respectively. In P2, a complex 3.7 cm long cyst was found in left ovary. In P1 and P2 endocrine studies revealed high levels of LH (22.6; 24.7 mUI/ml) and

FSH (61.7; 73.8 mUI/ml), normal AMH (30.7; 21.6 pmol/l), low E₂ (<9; 33.6 pg/ml), and undetectable testosterone, AFP and βhCG respectively. Histopathological examination of gonads revealed: P1: left dysgenetic gonad without evidence of tumor, and right gonadoblastoma. In P2: left gonadal dysgerminoma, and gonadoblastoma in both. **Conclusion:** Complete penetrance and/or somatic mosaicism are two hypotheses that may explain a normal phenotype in a father carrying this novel SRY mutation transmitted to 46, XY daughters. 46 XY dysgenetic gonads have a high risk of developing germ cells tumors. Acyclic sexual development can occur due to estrogen synthesis by gonad tumor or dysgenetic cells. Mutations in human SRY associated with somatic sex reversal provide a model for a genetic switch in organogenesis.

FC6.5

Serum Levels of AMH Reflect Ovarian Morphology by MRI in 109 Healthy Peripubertal Girls

Casper P Hagen^a, Annette Mouritsen^a, Mikkel G Mieritz^a, Jeanette Tinggaard^a, Christine Wohlfart-Veje^a, Eva Fallentin^b, Richard A Anderson^c, Katharina M Main^a, Anders Juul^a

^aDepartment of Growth and Reproduction, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; ^bDepartment of Radiology, Rigshospitalet, Copenhagen, Denmark; ^cMedical Research Council, Centre for Reproductive Health, University of Edinburgh, Edinburgh, UK

Background: In adult women, serum levels of AMH reflect both the number of small growing follicles and remaining primordial follicles. AMH levels range 15 fold between healthy girls. Interpretation of AMH is contentious due to minor intra-individual changes around time of pubertal onset despite continuous loss of primordial follicles. **Objective and Hypotheses:** To describe ovarian morphology (volume, follicles) in healthy girls and adolescents in relation to serum AMH levels. **Method:** Nested cohort of 109 healthy peripubertal girls from The Copenhagen Mother-Child Cohort. Pubertal development by Tanner's breast stage (B1 – 5). Ovarian morphology from a total of 87 scans with acceptable picture quality of both ovaries (B1, n = 10; B2, n = 20; B3, n = 24; B4, n = 30, B5, n = 1; NA, n = 2): volume (length × height × width × 0.523); Follicle counts and measurements. Serum levels of AMH by ELISA (Beckman Coulter, generation I). **Results:** Ovarian volume increased with age and pubertal progression (linear regression, beta 0.461, $P < 0.001$ and 0.643, $P < 0.001$, respectively), however, the initial increase in total number of follicles (median 14 follicles (B1) vs 23 (B3), $P = 0.001$) levelled off (23 (B3) vs 20 (B4), $P = 0.247$). Overall, the number of small follicles (2–4 mm) was positively associated with larger follicles (≥ 5 mm) (0.477, $P < 0.001$), however, the ratio (small/larger follicles) declined through puberty (1.7 (B1) vs 0.8 (B4), $P = 0.038$). Serum AMH reflects both ovarian volume and follicle numbers (0.261, $P = 0.015$ and 0.525, $P < 0.001$ respectively). Follicles of 2–3 mm and 4–5 mm were the main contributors to serum levels of AMH (multiple

regression: β 0.344, $P = 0.002$ and 0.235, $P = 0.041$ respectively). **Conclusion:** As in adult women, AMH is a quantitative marker of small growing follicles (follicles producing AMH). Equilibrium of follicle numbers in different stages suggests that inter-individual variation of AMH reflects variation in the number of primordial follicles even in girls and adolescents. Minor intra-individual changes of AMH levels in peripubertal girls can be explained by changes in the number of AMH producing follicles.

FC6.6

Effects of Exposure to the Endocrine disruptor di(n-butyl) Phthalate on Testicular Dysgenesis Fetal Germ Cell Development in the Rat and in Human Fetal Testis

Rod Mitchell^{a,b}, Sander van den Driesche^a, Lenka Hrabalkova^a, Richard Anderson^a, Chris McKinnell^a, Sheila MacPherson^a, Ana Calarrao^a, Richard Sharpe^a

^aCentre for Reproductive Health, Edinburgh University, Edinburgh, UK; ^bRoyal Hospital for Sick Children, Edinburgh, UK

Background: Phthalate exposure results in endocrine disruption by inhibiting steroidogenesis, inducing focal dysgenesis and disrupting germ cell development in the rat fetal testis. Whilst phthalate exposure does not reduce testosterone production by the human fetal testis, its effects on germ cells and induction of dysgenetic areas in the developing human testis are less well described. **Objective and Hypotheses:** To determine the effects of phthalate exposure on human fetal germ cells and seminiferous cords using an established dynamic xenograft model. We hypothesized that the rat is an appropriate model for investigating such germ cell effects. **Method:** Immunohistochemistry, immunofluorescence, and quantitative real-time PCR for Sertoli cell adhesion proteins (Espn, vimentin, and N-cadherin), germ cell markers (OCT4-undifferentiated; VASA differentiated) on DBP-exposed rat testis and human fetal testis xenografts and proliferation markers (Ki67). **Results:** DBP-induced germ cell loss in human (and rat) fetal testes is confined to undifferentiated (OCT4⁺) germ cells (16 vs 12%; $P = 0.019$) with no effect on germ cell proliferation (59 vs 61%, $P > 0.05$). DBP also induces aggregation of differentiated germ cells, albeit sporadically in the human; however no focal dysgenetic areas were seen. The underlying mechanism for germ cell aggregation is loss of Sertoli-germ cell membrane adhesion, probably due to microfilament redistribution within Sertoli cells. **Conclusion:** Our findings demonstrate the endocrine disrupting effects of DBP *in vivo* on germ cell differentiation and aggregation in the human and rat. In the human, loss of undifferentiated germ cells is the main effect of DBP exposure, which may have potential health implications for the next generation. These results also demonstrate that the rat may represent a human-relevant model in which to explore the underlying mechanisms for the germ cell effects of DBP.

FC7.1

Genetic Markers of Insulin Resistance are Associated with GH Response in Short SGA Children: the North European SGA Study

Rikke Beck Jensen^{a,b}, Ajay Thankamony^a, Felix Day^c, Jeremy Kirk^d, Malcolm Donaldson^e, Sten-A Ivarsson^f, Olle Söders, Edna Roche^h, Hilary Hoey^h, Anders Juul^b, Ken Ong^c, David Dunger^a

^aDepartment of Pediatrics, Institute of Metabolic Science, University of Cambridge, Cambridge, UK; ^bDepartment of Growth and Reproduction, Rigshospitalet, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark; ^cMRC Epidemiology Unit, Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge, UK; ^dDepartment of Endocrinology, Birmingham Children's Hospital, Birmingham, UK; ^eDepartment of Endocrinology, Royal Hospital for Sick Children, Glasgow, UK; ^fDepartment of Clinical Sciences, Endocrine and Diabetes Unit, University of Lund, Lund, Sweden; ^gPediatric Endocrinology Unit, Department of Women's and Children's Health, Karolinska Institutet and University Hospital, Stockholm, Sweden; ^hDepartment of Pediatrics, The National Children's Hospital, University of Dublin, Trinity College, Dublin, Ireland

Background: There is wide heterogeneity in responses to GH treatment in children born small for gestational age (SGA). **Objective and Hypotheses:** The aim was to explore the impact of genetic markers on glucose metabolism and growth during first year high-dose GH treatment in SGA children. **Method:** In North European Small for Gestational Age Study (NESGAS) patients received high-dose GH (67 µg/kg per day) the first year. 97 patients were genotyped using the 'MetaboChip' a custom Illumina iSelect genotyping array enriched for single nucleotide polymorphisms (SNPs) associated with growth and metabolic traits. Combined multi-allele gene scores were generated comprising ten SNPs for insulin resistance (GS-IR) and 18 SNPs for insulin secretion (GS-IS). **Results:** Higher GS-IR was associated with shorter height ($B: -0.08$ SDS/allele, 95% CI: -0.15 to 0 , $P=0.048$) and lower weight ($B: -0.10$, 95% CI: -0.20 to -0.003 , $P=0.04$) after 1 year of treatment (corrected for age, sex and mid-parental height). GS-IR was inversely associated with first year change in IGF1 ($B: -0.16$ SDS/allele, 95% CI: -0.29 to -0.02 , $P<0.03$). GS-IR added significantly to the Ranke SGA growth prediction model, adding 8% to the variance explained in growth response (independent effect of GS-IR: $B: -0.20$, 95% CI: -0.38 to -0.02 , $P=0.03$).

GS-IS was associated with increased insulin secretion (IVGTT) (corrected for age, sex, and BMI) at baseline ($B: 0.03$, 95% CI: $0.004-0.05$, $P=0.02$) and 1 year ($B: 0.03$, 95% CI: $0.005-0.05$, $P=0.02$). There was no association to HOMA-S, but GS-IS was positively associated with Disposition Index at baseline ($B: 0.03$, 95% CI: $0.004-0.05$, $P=0.02$) and 1 year ($B: 0.03$, 95% CI: $0.01-0.05$, $P=0.002$). **Conclusion:** Increased genetic susceptibility to insulin resistance was associated with lower height and IGF1 responses to GH treatment in SGA children. Higher scores of insulin secretion alleles corresponded to increased insulin secretion and increased disposition index. These novel results highlight the potential role of genetic factors in defining the response of treatment in SGA patients.

FC7.2

The rs1024531 GRB10 Promoter Polymorphism is Associated with Response to GH Therapy in Patients with GH Deficiency: Validation by *in vitro* Functional Analysis

Chiara De Leonibus, Daniel Hanson, Philip Murray, Adam Stevens, Peter Clayton

Manchester Academic Health Sciences Centre, Royal Manchester Children's Hospital, Manchester, UK

Background: GH response is influenced by genetic polymorphisms, including the rs1024531 polymorphism (A/G) in the promoter region of *GRB10*, a negative regulator of signaling through the IGF1 receptor. Allele A is associated with borderline lower baseline IGF1 SDS and 1.5-fold higher response to GH compared to allele G in children with GHD ($P=0.0006$). **Objective:** To test functional impact of the rs1024531 polymorphism in an *in vitro* cell system. **Methods:** Each allele, in a 500-bp fragment of *GRB10* promoter sequence, was cloned into a secreted alkaline phosphatase (ALP) reporter gene plasmid (pSEAP). The transcriptional activity (TA) of each construct was evaluated by ALP induction [relative light units (RLU)]. Transfection experiments were performed at baseline using the human HEK293 cell line. GH-stimulation was performed in human MCF7 cells known to be GH responsive,² with maximal dose (200 ng/ml). A GH dose-dependent titration (24 h) was also performed (range: 0, 2, 20, and 200 ng/ml). **Results:** At baseline, allele A was associated with greater TA than allele G (0.4 vs 1.4 RLU, $P=0.003$). Conversely, when GH stimulation was performed, allele G was associated with a relative 4.8-fold ALP induction compared to a 3.1-fold increase for allele A ($P<0.001$). When the cells were exposed to various GH concentrations, allele G induced significantly higher TA of the reporter construct than allele A at all levels of stimulation ($P<0.05$). A GH-induced suppression was found for allele A at lower concentrations [2 and 20 ng/ml vs baseline (both $P<0.05$)], a range comparable to *in vivo* stimulation. **Conclusion:** These cell models provide a platform to test the functional mechanisms that underlie clinical observations for *GRB10*, a negative growth regulator. Allele A is associated with higher TA at baseline, consistent with lower IGF1 values, but suppressed TA after GH stimulation, consistent with better growth on GH in GHD children.

FC7.3

Gene Expression Networks Associated with Changes in Serum Markers of Metabolism and Growth in GH-Treated Children with GH Deficiency

Adam Stevens^a, Chiara De Leonibus^a, Pierre Chatelain^b, Peter Clayton^a

^aRoyal Manchester Children's Hospital, Manchester, UK; ^bDépartement de Pédiatrie, Université Claude Bernard, Lyon, France

Introduction: Growth promoting effects of GH occur in parallel with its impact on insulin sensitivity and lipid metabolism;

underlying biological networks that link these actions are not defined. Our objective was to identify gene expression (GE) networks linking growth with metabolic responses in GH-treated children with GHD. **Methods/design:** Pre-pubertal children with GH Deficiency GHD ($n = 125$) were enrolled from the PREDICT short-term (NCT00256126) and long-term follow-up prospective studies (NCT00699855). Whole blood GE was determined prior to treatment with GH. Associations were identified by partial correlation between height velocity after 1 year (HV1) and serum biomarker levels (change over 1 month of treatment in IGF1, insulin (Ins), HOMA-IR and triglycerides). GE was correlated with biomarkers using rank regression, and overlap in GE profiles between these markers was used to build network clusters from which a priority list of biological functions was generated (Moduland algorithm¹ and hypergeometric test). **Results:** Correlations between the following parameters (HV1 or 1-month change in biomarker levels) were observed: i) HV1 with IGF1; ii) IGF1 with Ins and HOMA-IR; iii) triglycerides with Ins and HOMA-IR (all $P < 0.05$). The GE profile related to each correlation was defined. The GE common to *HV1/IGF1 to IGF1/Ins/HOMA-IR* included seven genes: *C1orf21*, *SPTBN1*, *IQCH*, *LINC00667*, *SFSWAP*, *SLC39A8*, and *UGGT2* (all $P < 0.05$). *C1orf21*, *SPTBN1*, and *IQCH* have been associated with adult height, *IQCH* with age at menarche, and all except *LINC00667* with diabetes and obesity. Two (*C1orf21* (associated with cell proliferation) and *SPTBN1* (associated with organization of organelles)) were also represented in the GE overlap between triglycerides/Ins/HOMA-IR ($P < 0.05$). GE network clusters indicated that cell cycle and adipogenesis pathways were the closest correlated functions ($P < 0.001$). **Conclusions:** This study identified distinct biological pathways and potential genomic markers that link growth and metabolic responses to r-GH therapy in GHD children.

FC7.4

A Decade of Clinical Experience in a Swedish University Centre Using Prediction Models to Optimize GH Treatment in Prepubertal Children

Jovanna Dahlgren

Department of Pediatrics, Göteborg Pediatric Growth Research Centre, The University of Gothenburg, Gothenburg, Sweden

Background: The individual growth response on a certain GH dose is an indirect measurement of tissue responsiveness to GH. Several models of predicting the first year growth response on GH treatment are published and a clinical trial has been performed based on these algorithms. However, no clinical unit has evaluated the practical use of these prediction models on GH treatment. **Objective and Hypotheses:** To use prediction models in clinical practice to choose those short children that will benefit of GH treatment. Prediction models can be used as a complement to optimize GH treatment. **Method:** The prediction model used is based on height_{SDS} and weight_{SDS} at GH-start, early growth, mid-parental height SDS, 24-h GH profile, IGF1_{SDS}. 122 short

prepubertal children (60% boys) (height < -2 SDS) were investigated at Queen Silvia Children's Hospital 2004–2012 with a 12/24-h profile and IGF1 levels. Exclusion criteria were chronic disease, malignancy, small-for-gestational-age and syndrome ($n = 20$) or predicted height gain < 0.7 SDS ($n = 39$). Mean height SDS was -2.6 (range, -4.2 to -2 SDS). **Results:** Mean predicted height gain the first 12 months on treatment was 0.85 SDS (range, 0.7–1.6). The observed height gain during these 12 months was 0.66 SDS (range, 0.5–1.3). This was studied with Bland–Altman plot. A difference between observed and predicted response of 0.20 SDS was found. Interestingly, the majority of children were systematically over-predicted 0.20–0.28 SDS, but still the individual diagnosis of very good or good responders before treatment was confirmed on treatment. **Conclusion:** We found a good correlation between predicted and reported first year growth in short children treated with GH, although with a systematic overestimation of the individually predicted values. This is expected by previous validations ($2 \times \text{SDres}$ of 0.37). Despite this overestimation, the model can be used as an integrated tool in decision-making at start of GH treatment.

FC7.5

Impact of GH on Adult Bone Quality in Turner Syndrome: a High Resolution Peripheral Quantitative Computed Tomography Study

Munier A Nour^a, Rebecca J Perry^{b,c}, David K Stephure^{b,c}, David A Hanley^b, Steven K Boyd^b

^aDepartment of Pediatrics, University of Saskatchewan, Saskatoon, Saskatchewan, Canada; ^bFaculty of Medicine, University of Calgary, Calgary, Alberta, Canada; ^cDivision of Pediatric Endocrinology, Alberta Children's Hospital, Calgary, Alberta, Canada

Background: Women with Turner syndrome (TS) are known to be at risk of osteoporosis and fracture. While childhood GH treatment is common in TS, the impact of this therapy on bone health has been poorly understood. **Objective:** The purpose of this study was to determine the effect of childhood GH-treatment on adult bone quality in TS women using dual X-ray absorptiometry (DXA) and high resolution peripheral quantitative computed tomography (HR-pQCT). **Methods:** TS subjects aged 16–45 years were included. DXA of lumbar spine, hip, and radius and HR-pQCT scans of the radius and tibia were completed. HR-pQCT micro-architecture analysis included total volumetric BMD, cortical BMD, trabecular BMD, and total area. Finite element (FE) analysis and polar moment of inertia (pMOI) were used to estimate bone strength. Group means were compared using independent t -tests. **Results:** Twenty-eight TS subjects were recruited (GH-treated = 12 and non-GH-treated = 16). Both groups were similar in regards to age and bone health related lifestyle parameters. GH-treated subjects were 7.4 cm taller than non-GH-treated subjects (95% CI 2.5–12.3 cm, $P = 0.005$). DXA determined areal BMD of hip, spine, and radius was similar between treatment groups. At the radius and tibia total bone area

was greater among GH-treated subjects (+20.4 and +21.2% respectively, $P < 0.05$) while other micro-architectural results were not different between groups. FE determined bone strength trended higher in the GH-treated group (radius, +12.3%; $P = 0.28$ and tibia, +8.1%; $P = 0.25$), but results were not statistically significant. pMOI was significantly greater among GH treated subjects (radius, +35.0%; tibia, +34.0%; $P < 0.05$).

Conclusions: Childhood GH-treatment in TS was associated with an increased height, larger bones and greater pMOI, while no significant difference in DXA derived BMD, HR-pQCT micro-architectural parameters, or FE estimated bone strength were detected. This increase in bone size may confer benefit for fracture reduction in these GH-treated patients.

FC7.6

Topicon™ ThermoMatrix™-Mediated Passive Transdermal Delivery of Human GH (hGH) Across EpidermFT™ Full-Thickness Human Skin Equivalent (HSE): Towards an Extended-Wear hGH Patch

Stephen Hsu^{a,b}, Carl Mangleburg^{a,b}, Hua Yao^{a,b}

^aPrometheon Pharma, LLC, Alachua, Florida, USA; ^bSid Martin Biotechnology Institute (University of Florida), Alachua, Florida, USA

Background: There is a need for a convenient and affordable alternative to daily s.c. injections for a growing incidence and prevalence of childhood- and adult-onset human GH (hGH) deficiency. **Objective and Hypotheses:** We sought to develop a convenient, non-invasive and affordable transdermal patch formulation capable of achieving passive delivery of large molecule drugs such as hGH and insulin for multiple days. **Method:** Prescription lyophilized hGH was reconstituted in a Topicon™ ThermoMatrix™ formulation that transitions from solid at 25 °C (room temp) to gel at 30–32 °C (skin temp). Formulations containing hGH were applied as 50 µl to EpidermFT[®] tissue inserts, which are mitotically and metabolically active HSEs when cultured in maintenance medium at 32 °C. Equal volume of medium was sampled and replenished every 12 h. hGH concentrations were measured by Quantikine[®] ELISA Kit (R&D Systems). Steady-state hGH flux (J_{ss}) was calculated using Fick's first law. **Results:** Topicon™ ThermoMatrix™ formulations over the dose range of 0.2–100 µg/06 cm² hGH achieved and maintained a maximum J_{ss} of 1.0 µg/cm² per h for 7-days. We observed a dose–response with saturation at 50 µg/06 cm². Extrapolated to 5 l human blood volume, 50 µg hGH in a <3 cm² patch would achieve target serum C_{max} of 23 or 21 ng/ml within 24 h, as observed in healthy adult male or pediatric volunteers after a single 0.03 mg/kg s.c. injection of Genotropin™ at a concentration of 5.3 mg/ml. MTT assay showed that epidermal cell viability was unaffected. **Conclusion:** We report a novel platform technology, the Topicon™ ThermoMatrix™ True-Patch™, applied to the needleless delivery of hGH (22 kDa). These *in vitro* studies support the feasibility of developing safe and

effective extended-wear hGH Topicon™ ThermoMatrix™ patches to eliminate the need for daily injections, while providing constant and consistent drug delivery.

FC8.1

Activation of the ER Stress Response in Cultured Human Umbilical Vein Endothelial Cells by Plasma Obtained from Prepubertal Obese Children

Tommaso de Giorgis^{a,c}, Sara Di Silvestre^{b,c}, Angelika Mohn^{a,c}, Natalia Di Pietro^{b,c}, Maria Loredana Marcovecchio^{a,c}, Vincenzo Cordone^{b,c}, Domitilla Mandatori^{b,c}, Valentina Chiavaroli^{a,c}, Giuseppina Bologna^{b,c}, Assunta Pandolfi^{b,c}, Francesco Chiarelli^a

^aDepartment of Pediatrics, University of Chieti, Chieti, Italy;

^bDepartment of Experimental and Clinical Sciences, University of Chieti, Chieti, Italy; ^cClinical Research Center and Aging Research Center (Ce.S.I), University Foundation Chieti-Pescara, Chieti, Italy

Background: Childhood obesity is commonly associated with signs of endothelial dysfunction, characterized by impairment of insulin signaling and vascular NO availability. Recently both these features have been associated with endoplasmic reticulum (ER) stress, however the role of ER stress in the mechanism/s leading to vascular dysfunction in childhood obesity remains still to be established. **Objective and Hypotheses:** To evaluate ER stress and insulin-stimulated NO availability in Human Umbilical Vein Endothelial Cells HUVECs cultured with plasma obtained from severely obese (OB) and normal-weight (C) prepubertal children. **Method:** Plasma were obtained from OB- ($n = 15$, age: 9.3 ± 2.00 ; SDS BMI: 2.38 ± 0.27) and C-children ($n = 14$, age: 9.3 ± 1.7 ; SDS BMI: 0.16 ± 0.026). Fasting insulin and glycaemic levels were measured. HUVECs were cultured with 10% C- and OB-plasma for 24 h and their effects on Grp-78/Bip, eIF2 α /phospho-eIF2 α , IKB α /phospho-IKB α , NF-kB and CHOP, respectively ER stress and inflammatory markers, were quantified by flow cytometry analysis. Moreover, cells were cultivated for 72 h in the same experimental conditions and insulin (100 nM) was added during the last 24 h to determine: HUVECs viability (MTT analysis); eNOS activity (conversion of L-[3H]-arginine into L-[3H]-citrulline) and NO bioavailability (intracellular cGMP levels by EIA). **Results:** OB-children presented higher fasting insulin levels (19.7 ± 8.5 vs 6.25 ± 1.56 mU/ml, $P = 0.0004$) when compared to C-children. No difference was found between two groups in terms of fasting glycaemia (86.5 ± 5.85 vs 83.3 ± 5.85 mg/dl; $P = 0.829$). ER stress induction was assessed by increased expression of Grp78/Bip, NF-kB, CHOP ($P < 0.05$) and enhanced phosphorylation of eIF2 α and IKB α . Moreover, insulin significantly increased eNOS activity (0.38 ± 0.07 vs 0.19 ± 0.02 pmoles/NO per mg prot tot, $P < 0.05$) and cGMP levels (1.2 folds) in HUVECs treated with C-plasma, whereas it was ineffective in OB-plasma treated cells. **Conclusions:** Taken together our *in vitro* data demonstrate that plasma from obese children are able to increased endothelial ER stress. This is associated to increased inflammation and reduced insulin-stimulated NO bioavailability.

FC8.2

MicroRNA-152 Promotes Hepatic Steatosis by Suppressing the Wnt Signaling Pathway

Xiao-qin Xu^a, Guo-hua Li^a, Chen-bo Ji^b, Xi-rong Guo^b, Jun-fen Fu^a

^aChildren's Hospital of Zhejiang University School of Medicine, Hangzhou, China; ^bNanjing Maternity and Child Health Hospital of Nanjing Medical University, Nanjing, China

Background: Non-alcoholic fatty liver disease (NAFLD) is a common chronic liver disease in both children and adults; however, the exact pathogenesis of NAFLD remains obscure. Accumulating evidence supports the effects of miRNA in the lipid metabolism and the regulation of insulin resistance, providing a potential linkage between the miRNA and NAFLD. **Objective and Hypotheses:** The aims of this study were to explore microRNA (miRNA) expression profiles in NAFLD, and to explore the function of miR-152 on the development of NAFLD in HepG2 cells. **Method:** Sprague–Dawley rats feeding a high-fat diet (HFD) for 4 and 12 weeks were used to establish a rat model of NAFLD. The miRNA expression profile of liver tissue was determined at 12 weeks by deep sequencing, and computational algorithms were used for target prediction. Selected miRNAs were then validated by stem-loop RT-PCR at both 4- and 12-week timepoints; furthermore, the expression level of these miRNAs was also assessed in HepG2 cells. Real time RT-PCR, function study of miRNA, lentiviral transduction, western blot, 3'UTR luciferase reporter assays, and other techniques were employed for target verification. **Results:** Our miRNA deep sequencing analysis identified 16 known upregulated miRNAs (fold change > 1.5) and 12 downregulated miRNAs (fold change < 0.5). Among the abnormal expressed miRNAs, miR-200a, miR-200b, miR-200c, miR-146a, miR-146b, and miR-152 were upregulated in both models by RT-PCR, as the same as what had been found in deep sequencing. Further analysis confirmed that miR-152 bound directly to the 3'UTR of the Wnt10b and promoted hepatic steatosis through Wnt10b downregulation. The miR-152/Wnt10b axis mediated hepatic steatosis through increased peroxisome proliferator-activated receptor β (PPAR β). Mitochondrial dysfunction was induced by the overexpression of miR-152. **Conclusion:** miRNAs may play a critical role in the pathogenesis of NAFLD, and miR-152/Wnt10b pathway could be a potential target for NAFLD prevention and treatment.

FC8.3

Identification of Death Ligand TNF-Related Apoptosis-Inducing Ligand as a Potent Mitogen in Human Preadipocytes

Jan-Bernd Funcke, Verena Zoller, Muad Abd El Hay, Klaus-Michael Debatin, Martin Wabitsch, Pamela Fischer-Posovszky
University Medical Center Ulm, Ulm, Germany

Background: Adipose tissue is an important endocrine organ. Its secretion profile is robustly changed in the context of obesity fueling the development of comorbidities such as insulin

resistance, diabetes mellitus type 2, and atherosclerosis. We have recently shown that the adipose tissue expression of the death ligand TNF-Related Apoptosis-Inducing Ligand TRAIL and its receptors is upregulated in obesity. **Objective and Hypotheses:** In this project, we investigated the effect of TRAIL on the adipose tissue-resident pool of precursor cells, particularly on preadipocyte proliferation. **Method:** Simpson-Golabi-Behmel (SGBS) and human primary preadipocytes were used as model systems. Cell proliferation was analysed by microscopic cell counting and ³H-thymidine incorporation. Cell signalling was analysed by western blot. **Results:** Stimulation of SGBS preadipocytes with TRAIL resulted in a pronounced, time- and dose-dependent increase in cell proliferation. After 72 h of treatment with 30 ng/ml TRAIL cell proliferation was increased by up to 60%. In comparison, a dose of 300 ng/ml of the well-studied mitogen IGF1 was required to induce a proliferative response proportionate to that of 30 ng/ml TRAIL. The potent mitogenic effect of TRAIL was also present in human primary preadipocytes. Furthermore, the related death ligands FasL and TNF α also showed a considerable mitogenic effect. Albeit no induction of apoptosis was observed in response to TRAIL, a rapid cleavage of caspase-8 and caspase-3 was detected. However, neither chemical inhibition nor genetic ablation of caspases were able to block TRAIL-induced proliferation. Further investigation revealed a delayed and sustained activation of the ERK1/2 cascade. Chemical inhibition of this cascade completely blocked TRAIL-induced proliferation. **Conclusion:** We identify TRAIL as a potent mitogen in human preadipocytes. From our data, we conclude that TRAIL functions as a regulator of the adipose tissue-resident pool of precursor cells, possibly modulating adipose tissue development and growth.

FC8.4

CREB-Regulated Transcription Coactivator 3: a New Adipokine Related to Childhood Obesity

Anna Prats-Puig^{a,b}, Pilar Soriano-Rodríguez^c, Gloria Oliveras^d, Adriana Blancafort^d, Ferran Díaz-Roldán^{a,b}, Gemma Carreras-Badosa^{a,b}, Francis de Zeghere^e, Lourdes Ibáñez^{f,g}, Judit Bassols^{a,b}, Teresa Puig^d, Abel López-Bermejo^{a,b}

^aGirona Institute for Biomedical Research, Girona, Spain;

^bDr Josep Trueta Hospital, Girona, Spain; ^cSalut Empordà

Foundation, Figueres, Spain; ^dFaculty of Medicine, University of

Girona, Girona, Spain; ^eUniversity of Leuven, Leuven, Belgium;

^fSant Joan de Déu Children's Hospital, Barcelona, Spain;

^gCIBERDEM, Barcelona, Spain

Background: CREB-regulated transcription coactivator 3 (CRTC3) is found in adipocytes where it may promote obesity through disruption of catecholamine signaling. CRTC3 knockout mice are resistant to diet-induced obesity. **Objective and Hypotheses:** The goals of the present study were i) to assess whether CRTC3 is a soluble protein secreted by adipose tissue ii) to explore whether CRTC3 is detectable and quantifiable in the circulation, and iii) to ascertain whether CRTC3 concentrations may be related to metabolic markers in children. **Method:** Explants of visceral and subcutaneous adipose tissue from 12 prepubertal children were cultured to study the secretion of

CRTC3 by adipose tissue using immunoblot and ELISA. We also performed a cross-sectional and longitudinal study in asymptomatic prepubertal Caucasian children to assess the presence of CRTC3 in the circulation and to study the associations between serum CRTC3 and metabolic markers, namely BMI, waist circumference, systolic blood pressure (SBP) and HMW-adiponectin, cross-sectionally in 211 children at age 7 years (52% girls; 19% overweight subjects) and longitudinally in 115 children from the same sample at age ~10 years. **Results:** Measurable concentrations of CRTC3 were found in conditioned media of adipose tissue biopsies and in serum samples from the study subjects. In the cross-sectional study, higher CRTC3 concentrations were associated with higher BMI ($P=0.001$), waist ($P=0.003$), SBP ($P=0.007$), and lower HMW adiponectin ($P=0.003$). In the longitudinal study, serum concentrations of CRTC3 at age ~7 years were associated with changes in BMI-SDS ($\beta=0.327$; $P=0.001$; $R^2=0.114$) and in HMW adiponectin ($\beta=-0.271$; $P=0.014$; $R^2=0.101$) at age ~10 years. **Conclusions:** In prepubertal children, CRTC3 is present in the circulation, partly as a result of adipose tissue secretion. Higher serum CRTC3 concentrations are related and predict a poorer metabolic profile. We herein suggest that CRTC3 is a new adipokine related to childhood obesity.

FC8.5

Putative Gain-of-Function in Rats Carrying the Ghnr Q343X Mutation

Philippe Zizzari, Yacine Chebani, Khadidja Chettab, Marie Pastor, Marie Korostelev, Jacques Epelbaum, Virginie Tolle, Jacques Pantel
INSERM, Université Paris Descartes, UMR-S 894, Centre de Psychiatrie and Neurosciences, Paris, France

Background: The deciphering of the physiological importance of the GH secretagogue receptor (Ghrnr), a G protein-coupled receptor (GPCR) depicted as the sole receptor of the pleiotropic hormone ghrelin, was initially compromised by the modest phenotype observed in *Ghrnr*^{-/-} animals. This lack of a robust response to total loss of Ghrnr may result from developmental compensatory signals. Still, the description of rare mutations in the GHRNR partially affecting receptor function in patients with short stature or partial GH-deficiency allowed us to ascertain its role in somatic growth. **Objective and Hypotheses:** We hypothesized that a recently generated line of rats carrying a premature termination codon in the *Ghrnr* gene (Q343X) might be an ideal model to explore Ghrnr physiology. **Method:** The mechanism of action of this specific mutation was deciphered using HEK293 cells. **Results:** The Q343X mutation does not impair cell surface expression of Ghrnr. The functional analysis of this GPCR in calcium flux experiments revealed that, compared to the WT isoform, the mutant isoform has an increased potency as well as a major increase of the maximal response in the presence of increasing concentrations of ghrelin ($EC_{50}=2.1 \pm 0.4$ and 0.6 ± 0.1 nM; $E_{max}=26 \pm 1$ and $39 \pm 1\%$ respectively, mean \pm S.E.M., $n=3$). Similar patterns of response were also found in reporter gene assays depicting the serum-response elements (SRE) or cAMP-response elements (CRE) pathways. Of note, when subjected

to a maximal dose of ghrelin, internalization of the mutated receptor is blunted compared to the WT receptor. **Conclusion:** These *in vitro* observations are supportive of a gain-of-function associated to the Ghrnr Q343X mutant allele. Interestingly, our very first *in vivo* data are consistent with an increased body weight and chow intake in adult rats carrying the mutated allele. This model therefore deserves an extensive phenotypic evaluation.

FC8.6

A Novel Missense Variant in the Insulin Receptor Gene in Three Unrelated Irish Families with Severe Insulin Resistance Syndrome: Evidence for an Irish Founder Effect

M Mavinkurve^a, S O'Connell^b, D Cody^c, I Isaac^d, J Harris^d, R K Semple^d, C Mc Donnell^e

^aChildren's University Hospital, Temple Street, Dublin, Ireland; ^bDepartment of Paediatrics and Child Health, Cork University Hospital, Cork, Ireland; ^cOur Lady's Children's Hospital, Crumlin, Dublin, Ireland; ^dWellcome Trust MRC Institute of Metabolic Science, University of Cambridge, Cambridge, UK; ^eNational Children's Hospital, AMNCH, Tallaght, Dublin, Ireland

Background: Genetic defects in the insulin receptor (INSR) are rare. Precise prevalence is unknown and significant clinical heterogeneity exists. Over 120 allelic variants have been described to date, spread throughout the receptor, and few geographical founder effects have been described. In this case series we identify a novel missense mutation in the tyrosine kinase domain of the INSR in three independently ascertained Irish families. **Objective and Hypotheses:** We aimed to characterise the three affected pedigrees in terms of biochemistry, phenotype and genotype. **Method:** Clinical assessment, biochemical profiling and DNA haplotype analysis was performed on the three probands. A detailed family tree was constructed for each index case tracing back over three to four generations reviewing family structure, medical history, features consistent with insulin resistance and migration history. **Results:** Two unrelated female and one male proband were identified following referral from three clinical services. Median age at presentation was 11.4 years (range 10.5–12.3). All were term births with weights in the low normal range. At presentation, all three had acanthosis nigricans and BMIs >91st centile (range 23.7–32.5 kg/m²). Fasting blood glucose levels were normal but one child had impaired glucose tolerance. Fasting insulin levels were grossly elevated (range 338–5250 pmol/l) confirming biochemical insulin resistance. All three probands and a parent of each were heterozygous for the novel p.Met1153Lys mutation in the INSR, with a shared haplotype at that locus. While all three unrelated families appeared geographically distinct, we have traced their ancestry to a region in South Central Ireland. **Conclusion:** This previously unpublished missense mutation of the INSR gene appears unique to the Irish setting. The shared haplotype provides strong evidence of an Irish founder effect supported by the close geographical proximity of the ancestry of each family. Biochemical and genetic testing of extended family members is in progress.

FC9.1

Inappropriately High Rates of Cell Proliferation in Diffuse Congenital Hyperinsulinism are Linked to Nuclear Expression of CDK6

Rachel Salisburys^a, Bing Han^a, Zainaba Mohamed^{a,b}, Ronald De Krijger^c, Laurienne Gardner^a, Julia Gardner^a, Karen Cosgrove^a, Raja Padidela^b, Melanie Newbould^b, Indraneel Banerjee^{a,b}, Neil Hanley^{a,b}, Mark Dunne^a

^aUniversity of Manchester, Manchester, UK; ^bCentral Manchester University Hospitals NHS Foundation Trust, Manchester, UK; ^cUniversity Hospital Dijkzigt, Rotterdam, The Netherlands

Background: Congenital hyperinsulinism of infancy (CHI) mainly arises from loss-of-function mutations in the KATP channel genes. As a consequence, insulin release is uncontrolled and causes persistent or recurrent episodes of hypoglycaemia in neonates. In patients with diffuse-CHI (CHI-D) increased rates of cell proliferation has been reported, but the causes of proliferation are unknown. **Objective/Hypotheses:** To assess the extent of cell proliferation and the role of CDK6 in control of the cell cycle in the CHI-D pancreas. **Methods:** We used immunostaining in paraffin-embedded samples of CHI-D ($n=7$, 2–13 months), age-matched control pancreata ($n=6$, 6 weeks–13 months) and foetal pancreas (10 weeks post-conception) to examine the extent of proliferation in different cell types including α - (glucagon+), β - (insulin+), ductal (SOX9+), and exocrine (GATA4+) cells. Ki67 was used to document cell proliferation and to define the proliferative index of the pancreas through high-content analysis of digital images. The control of cell proliferation was investigated via immunostaining of the cell cycle regulator CDK6. **Results:** In controls we found Ki67 staining correlated inversely with age between 6 weeks and 1 year after birth ($rs = -0.929$, $P < 0.01$). In contrast, proliferation remained elevated in all cell types in CHI-D with SOX9-, GATA4-, and insulin-positive cells reaching statistical significance, $P < 0.01$. By analysing regions of tissue each containing 20 000–30 000 cells we found that, on average, $4.3 \pm 0.1\%$ of the CHI pancreas was proliferative ($n=3$ cases) compared to $36.3 \pm 8\%$ of the foetal pancreas. CDK6 was detected in the cytoplasm of control islets where it colocalised with insulin. By comparison, in CHI-D, CDK6 was strongly nuclear in islet-, exocrine- and a sub-fraction of ductal-cells. **Conclusion:** CHI-D retains high rates of proliferation in SOX9-, GATA4-, and insulin-positive cell types compared to age-matched controls. Detection of nuclear-localised CDK6 in these cells supports a role for CDK6 in inappropriate cell proliferation.

FC9.2

Characterising the Immunohistochemical Expression of Dipeptidyl Peptidase-4 in Pancreatic Tissue from Patients with Diffuse and Focal Congenital Hyperinsulinism

Sofia Rahman, Maha Sherif, Sophia Tahir, Khalid Hussain

Developmental Endocrinology Research Group, UCL Institute of Child Health, Great Ormond Street Children's Hospital NHS Foundation Trust, London, UK

Background: Congenital hyperinsulinism (CHI) is the commonest cause of persistent hypoglycaemia and is due to the unregulated secretion of insulin from the pancreatic β -cells. The role of glucagon like peptide-1, gastric inhibitory polypeptide (GLP1/GIP), and dipeptidyl peptidase-4 (DPP4), is currently unknown in patients with CHI. **Objective and Hypotheses:** To understand the expression pattern of DPP4 in focal and diffuse disease CHI. **Method:** Using formalin-fixed paraffin embedded (FFPE) intra-operative pancreatic sections; immunofluorescence of DPP4 localisation in α -, β -, and δ -cells was carried out in five patients with either focal (F-CHI) or diffuse CHI (D-CHI) with relatively normal tissue sections taken from around the focal lesion as controls. Additionally, using the proliferative marker, Ki67, we attempted to identify the islet-cells that were proliferating. **Results:** We identified expression of DPP4 with insulin, glucagon, and somatostatin in their respective cell subtypes. Both F-CHI and D-CHI sections showed an increase in Ki67 expression. In comparison to control tissue, D-CHI showed an increase in β -cell DPP4 expression. However, this was absent in the focal lesions. **Conclusion:** In conclusion, this is the first study to show that DPP4 expression profiles are histologically different in F-CHI and D-CHI patients. Therefore, DPP4 might have a role in the pathophysiology of D-CHI and this knowledge might be useful for potential therapeutic applications.

FC9.3

In Search for New Monogenic Diabetes Genes: PCBD1

Deimante Simaite^{a,b}, Julia Kofent^a, Maolian Gong^{a,b}, Franz Rüschemdorf^a, Shiqi Jia^a, Pamela Arn^c, Kristi Bentler^d, Carolyn Ellaway^e, Peter Kühnen^f, Georg Hoffmann^g, Nenad Blau^{g,h}, Francesca Spagnoli^a, Norbert Hübner^a, Klemens Raile^{b,f}

^aMax Delbrück Center for Molecular Medicine, Berlin, Germany; ^bExperimental and Clinical Research Center, Berlin, Germany; ^cNemours Children's Clinic, Jacksonville, Florida, USA; ^dAmplatz Children's Hospital, University of Minnesota, Minneapolis, Minnesota, USA; ^eRoyal Alexandra Hospital for Children, Westmead, New South Wales, Australia; ^fCharité University Medicine, Berlin, Germany; ^gUniversity Children's Hospital, Heidelberg, Germany; ^hUniversity Children's Hospital, Zürich, Switzerland

Background: Mutations in more than 20 genes are described to cause monogenic diabetes. Nevertheless, numerous families with diabetes of unknown etiology and suspected genetic defect have no molecular diagnosis. This not only impedes our understanding of disease mechanisms but also prevents from predicting the clinical course of the patients and applying the pathogenesis-oriented treatment. **Objective:** To identify novel gene(s), causing monogenic adolescent-onset diabetes. **Methods:** Whole-genome sequencing (WGS), linkage analysis, Sanger sequencing, systematic recall of the patients present in BIoDEF (International Database of Tetrahydrobiopterin Deficiencies) and

gene expression studies in frog and mouse embryos and mouse insulinoma cell line were applied to identify, validate and characterize the novel disease-causing gene. **Results:** We identified a novel frameshift deletion in *PCBD1* (pterin-4 alpha-carbinolamine dehydratase/dimerization cofactor of hepatocyte nuclear factor 1 alpha), a gene that has recently been suggested as a possible cause of diabetes. Subsequent reexamination of the patients with mild transient neonatal hyperphenylalaninemia due to homozygous mutations in *PCBD1* included in the BIoDEF database revealed three additional cases that developed *HNF1A*-like diabetes in puberty, indicating an early pancreatic beta cell failure. We found that *Pcbd1* was not only expressed in the developing pancreas of both *Xenopus* and mouse embryos, but was enriched in endocrine progenitors and colocalized with insulin, too. Notably, gene knockdown approach in *Xenopus* showed that early pancreatic fate specification was dependent on *Pcbd1* activity within the endoderm. **Conclusions:** We provide the first genetic evidence that *PCBD1* mutations cause non-autoimmune *HNF1A*-like adolescent-onset diabetes which can be treated with sulphonylureas instead of insulin. Moreover, patients at risk can be indicated through the newborn screening for phenylketonuria. Furthermore, our findings suggest *Pcbd1* role in the pancreatic progenitor pool establishment during embryogenesis, which might lead to reduced pancreatic beta cell mass in the adult.

FC9.4

Clinical Characteristics and Molecular Genetics Analysis of 20 Patients with Neonatal Diabetes Mellitus from a Single Centre of the South-Eastern Region of Turkey

Huseyin Demirbilek^{a,c}, Ved Bhushan Arya^{a,b}, Mehmet Nuri Ozbek^c, Jayne Houghton^d, Riza Taner Baran^c, Selahattin Tekkes^e, Deborah Mackay^f, Sarah E Flanagan^d, Sian Ellard^d, Khalid Hussain^{a,b}

^aDepartment of Paediatric Endocrinology, Great Ormond Street Hospital For Children NHS Trust, London, UK; ^bInstitute of Child Health, University College London, London, UK; ^cDepartments of Paediatric Endocrinology, Children State Hospital, Diyarbakir, Turkey; ^dInstitute of Biomedical and Clinical Science, University of Exeter Medical School, Exeter, UK; ^eDepartment of Medical Biology and Genetics, Dicle University, Diyarbakir, Turkey; ^fFaculty of Medicine, Princess Anne Hospital, University of Southampton, Southampton, UK

Background: Neonatal diabetes mellitus (NDM), either transient (TNDM) or permanent (PNDM), is a rare form of monogenic diabetes, and usually presents in the first 6 months of life. **Objective and Hypotheses:** To describe the clinical characteristics and molecular genetics of a large Turkish cohort of NDM from a single centre. **Method:** NDM patients presenting to Diyarbakir Children State Hospital between 2010 and 2013 were prospectively recruited and phenotyped. Molecular genetic analysis (conventional or targeted next generation analysis, tNGS) was performed **Results:** Twenty patients (60% males) presented with NDM (five TNMD and 15 PNMD) during this

period. In 5 (100%) TNDM and 13 (86.7%) PNMD patients families were consanguineous. Molecular genetic analysis identified the cause of NDM in 18 (90%) patients. In 13 PNMD patients, 11 homozygous (*GCK* ($n=4$), *EIF2AK3* ($n=3$), *PTF1A* ($n=3$), and *INS* ($n=1$)) and two heterozygous (*KCNJ11*) mutations were identified. All patients with an *EIF2AK3* mutation had liver dysfunction and/or skeletal dysplasia. Pancreatic exocrine dysfunction was observed in the three patients with mutations in the distal enhancer region of *PTF1A*. One patient with a *KCNJ11* mutation responded well to oral sulphonylureas whilst the second patient with the same mutation was unable to transfer from insulin. A genetic diagnosis was possible for all five TNDM patients. Three had 6q24 methylation abnormalities and 2 patients were homozygous for mutations in *ABCC8* and *INS*. A variable phenotype was associated with the c.-331C>A *INS* mutation, which was identified in both a PNMD and TNDM patient. **Conclusion:** We present the largest cohort of NDM from a single paediatric centre. Homozygous mutations in *GCK*, *EIF2AK3* and the distal enhancer region of *PTF1A* were the commonest causes of NDM in our cohort. The underlying genetic cause could be established in up to 90% of NDM patients. This high pick-up rate is likely to reflect enrichment for consanguinity within our cohort.

FC9.5

Transient Neonatal Diabetes in Adulthood: Metabolic and Neurodevelopmental Outcomes

Fleur Le Bourgeois^{a,b}, Kanetee Busiah^{a,b}, Sawsan Abu-Amara-Olivieri^d, Nadège Bachere^e, Anne-Marie Bertrand^f, Olivier Bourron^{g,h,i}, Paul David^j, Fabienne De Boisvilliers^k, Bernard Deumier^l, Liat deVries^m, Stéphanie Jellimanⁿ, Claire Le Tallec^o, Amélie Martin-Dessila^p, Paul Nimri^m, Anne Paoli^q, Mireille Perrin^r, Chantal Stuckens^s, Hubert Ythier^t, Nathalie Pouvreaux^u, Christine Bellané-Chantelot^v

^aDepartment of Paediatric Endocrinology, Gynaecology, and Diabetology, Necker Enfants-Malades Teaching Hospital, Assistance Publique-Hôpitaux de Paris, IMAGINE affiliate, Paris, France; ^bFaculty of Medi, Paris, France; ^cINSERM U1016, Université Paris Descartes, Sorbonne Paris Cité, Paris, France; ^dDepartment of Endocrinology and Diabetology, Montélimar Hospital, Montélimar, France; ^eDepartment of Paediatric, Mont de Marsan Hospital, Mont de Marsan, France; ^fDepartment of Paediatric, Besançon Hospital, Besançon, France; ^gDepartment of Diabetology, La Pitié Salpêtrière Teaching Hospital, Assistance Publique-Hôpitaux de Paris, France; ^hFaculty of Medicine Pierre et Marie Curie, Paris, France; ⁱINSERM_UMRS1138, Centre de Recherche des Cordeliers, Paris, France; ^jDavid Grant USAF Medical Center, Fairfield, California, USA; ^kDepartment of Diabetology, Montpellier Teaching Hospital, Montpellier, France; ^lDepartment of Endocrinology and Diabetology, Cholet Hospital, Cholet, France; ^mThe Jesse Z and Sara Lea Shafer Institute of Endocrinology and Diabetes, The National Center for Childhood Diabetes, Schneider Children's Medical Centre of Israel, Petah Tikva, France; ⁿDepartment of Paediatric, Nancy Teaching Hospital, Nancy, France; ^oDepartment of Paediatrics, Paediatric Teaching Hospital, Toulouse, France; ^pDepartment of Pediatric, Castres Hospital, Castres, France; ^qDepartment of Internal

Medicine, Robert Bisson Hospital, Lisieux, France; ^dDepartment of Endocrinology, Roanne Hospital, Roanne, France; ^eDepartment of Paediatrics, Jeanne de Flandre Teaching Hospital, Lille, France; ^fDepartment of Paediatric, Children Hospital, Roubaix, France; ^gDepartment of Genetics, Robert-Debré Teaching Hospital, Assistance Publique-Hôpitaux de Paris, Paris, France; ^hDepartment of Genetics, La Pitié Salpêtrière Teaching Hospital, Assistance Publique-Hôpitaux de Paris, Paris, France

Background: Transient neonatal diabetes mellitus (TNDM) is a rare genetic β -cell dysfunction leading to hyperglycaemia that resolves in early childhood. About 80% of patients relapse during adolescence or adulthood. Some of these patients suffer from neurodevelopmental defect. Long-term outcome has been poorly investigated. **Objective and Hypotheses:** To investigate metabolic and neurologic outcomes in adults affected with TNDM. **Method:** The patients originated from the French Neonatal Diabetes Study Group cohort. We selected those with TNDM who were 18 years or more in September 2013. We assessed data on their glucose metabolism and neurodevelopmental outcomes from the medical reports and direct interviews. **Results:** We included 24 individuals (seven males and 17 females). We identified 6q24 abnormalities ($n=8$, 33%), mutations in *ABCC8* ($n=8$, 33%) and *KCNJ11* ($n=4$, 17%) genes. 4 (17%) patients had no identified molecular defect. 23 (96%) patients relapsed their diabetes at a median age of 14.7 years (9.0–45.5). Mode of recurrence, detailed for 18 patients was polyuria–polydipsia ($n=8$), hyperglycaemia without ketoacidosis during an infectious disease ($n=4$) and during follow-up ($n=6$). Follow-up median duration after recurrence was 11.9 years (2.3–40.7) and median HbA1c after relapse 6.6% (5.8–13%). After recurrence, treatments were insulin ($n=13$), oral antidiabetic drugs ($n=8$) or both ($n=2$). Despite frequent observance failure (treatment stopped, $n=5$ and frequent oversight, $n=6$), only one patient suffered from ketoacidosis. Long-term diabetes complications occurred (retinopathy, $n=3$ and nephropathy, $n=1$). Neurodevelopmental outcomes revealed academic difficulties ($n=12$, 50%, who repeated a class at least once before the age of 16 years), difficulties interfering with reading achievement ($n=8$) and spatial disabilities ($n=7$), whatever the molecular aetiologies. **Conclusion:** Our study suggests a partial insulin secretion defect in adulthood and a high incidence of neurodevelopmental difficulties. These results underscore the importance of performing a complete clinical and biological evaluation throughout adulthood in all patients affected with TNDM.

FC9.6

Sulfonylurea Therapy Corrects Hypotonia, Attention Deficits, Improves Complex Neuropsychological Functions and Motricity in Patients with Neonatal Diabetes Secondary to Mutation in Potassium Channel Subunits, Through a CNS Effect

Jacques Beltrand^{a,b}, Laurence Vavre-Douvret^{b,d}, Kanetee Busiah^{a,b}, Emmanuel Fournier^{e,m}, Nathalie Boddaert^{b,h}, Myriam Vera^a,

Nadia Bahi-Buisson^{b,i}, Emmanuel Bui-Quoc^f, Isabelle Ingster-Moati^g, Isabelle Flechtner^a, Albane Simon^{a,j}, Raphael Scharfmann^c, Helene Cave^j, Caroline Elie^k, Michel Polak^{a,b}

^aService Endocrinologie, Gynécologie et Diabétologie Pédiatrique, Hôpital Universitaire Necker Enfants Malades, Paris, France; ^bFaculté de Médecine Paris Descartes, Université Sorbonne Paris Cité, Paris, France; ^cInserm U1016, Institut Cochin, Paris, France; ^dInserm UMR-S0669, Université Paris Sud et Paris Descartes, Service de Pédiopsychiatrie, Paris, France; ^eCentre de Référence des Canalopathies Musculaires, Hôpital La pitié Salpêtrière, Paris, France; ^fService d'Ophtalmologie, Hôpital Universitaire Robert Debré, Paris, France; ^gService d'Ophtalmologie, Hôpital Universitaire Necker Enfants Malades, Paris, France; ^hService d'Imagerie Médicale, Hôpital Universitaire Necker Enfants Malades, Paris, France; ⁱService de Neurologie Pédiatrique, Hôpital Universitaire Necker Enfants Malades, Paris, France; ^jService de Génétique, Hôpital Universitaire Robert Debré, Université Denis Diderot, Paris, France; ^kUnité de Recherche Clinique, Centre d'Investigation Clinique, Hôpital Universitaire Necker Enfants Malades, Paris, France; ^lService de Pédiatrie, Centre Hospitalier de Versailles, Paris, France; ^mDépartement de Neurophysiologie Clinique, Université Pierre et Marie Curie, Paris, France

Background: Sulfonylurea therapy (SU) allows a better metabolic control than insulin in patients with neonatal diabetes secondary to mutation in potassium channel subunits (ND-K). Most of these patients have neurological and neuromotor developmental impairments whose changes under SU has not been studied in a systematic and prospective way in a large cohort. **Objective and Hypotheses:** To demonstrate the beneficial effect of SU on neuropsychological functioning in patients with ND-K. **Method:** 18 patients (15 boys, 0.1–18.5 years). Neurological (MRI, electroencephalogram, electromyography (EMG)) and quantitative neuropsychological and neuropsychomotor evaluations were performed before and 12 months after the switch from insulin to SU. **Results:** SU allowed a dramatic improvement of HbA1c (mean, -1.55% ; range, -3.8 to 0.1% ; $P<0.0001$). 17 patients presented neuro-motor developmental delay or defect (hypotonia, developmental coordination or attention disorders). One showed pyramidal signs and epilepsy. MRI was abnormal in 12 patients (periventricular white matter abnormalities, multiple punctate white matter or brainstem hyper intensities). At M12, hypotonia was corrected in 12 out 15 affected patients and visual attention deficits in ten out 13. In all patients younger than 3 years ($n=8$), global motricity impairments were corrected and fine motricity in 3. In older patients ($n=10$), gesture conception and realization were also improved (two hands praxia improved in four out eight affected patients, imitation of gesture and body spatial integration in six). Motor and sensitive nerve conduction and membrane excitability studies with EMG were normal at baseline and at M12. SU didn't significantly improved intelligence score. **Conclusion:** SU therapy in ND-K allows a measurable improvement of neuropsychomotor impairments that seems to be greater in younger patients. EMG shows that it is not a peripheral but rather a central effect. All efforts should be made for an early genetic diagnosis allowing a rapid switch to SU in ND-K.

FC10.1

A Role for Delta-Like Homologue 1 in a Secretory Placental Population and Implications for Foetal Growth

Muriel Meso^{a,b}, Harshini Katugampola^{a,b}, Helen Storra^{a,b}, Leo Dunkel^{a,b}, Marika Charalambous^{a,b}

^aWilliam Harvey Research Institute, Centre for Endocrinology, Queen Mary University of London, London, UK; ^bDepartment of Pathology, Royal London Hospital, Barts Health NHS Trust, London, UK

Background: Delta-Like Homologue 1 (DLK1) is a gene encoding a transmembrane protein, which may also be secreted into the circulation. DLK1 levels are known to rise in maternal serum during late gestation and our genetic studies in the mouse have shown that this DLK1 arises from the conceptus. However, the cell population that secretes DLK1 into the maternal circulation has not been identified. Since DLK1 has been shown to be differentially expressed in intrauterine growth restricted when compared with normal human placentas, it may be an important biomarker of placental function and foetal development. **Objective and Hypotheses:** Our objective is to find the source population of DLK1-secreting cells in the placenta. We hypothesise that maternal serum levels of DLK1 derived from the conceptus may reflect indices of foetal and placental growth. **Method:** 45 women were recruited from our obstetric department and followed up prospectively. Measurements of foetal growth parameters (abdominal circumference (AC), femoral length, and biparietal diameter), maternal clinical information and maternal serum samples were collected at 20, 28, 34, and 38 weeks gestation. DLK1 ELISA analyses were performed on the serum samples. DLK1 immunohistochemistry was carried out on placental samples in combination with histological and immunocytochemical markers of placental cell populations. **Results:** We were able to localise DLK1 expression to multiple cell populations within the mature placental villi including the foetal endothelium and the trophoblast compartments. Maternal DLK1 levels rise during gestation and fall post-delivery. The rate of this rise is seen to be highest between 28 and 34 weeks gestation, coincident with the increase of the foetal AC. **Conclusion:** We localised DLK1 in the term placenta to an endocrine cell population, consistent with its secretion into the maternal circulation from this tissue. In addition, our longitudinal study of DLK1 in maternal serum during normal pregnancy suggests that DLK1 levels reflect rates of foetal growth.

FC10.2

Stk11 Expression in Adipose Tissue Following Fetal Growth Restriction: Relation to Catch-Up Growth and Visceral Fat Mass

Gemma Carreras-Badosa^{a,b}, Xavier Remesar^c, Anna Prats-Puig^{a,b}, Estíbaliz Platero-Gutiérrez^{a,b}, Francis de Zegher^d, Lourdes Ibañez^e, Judit Bassols^{a,b}, Abel López-Bermejo^{a,b}

^aGirona Institute for Biomedical Research, Girona, Spain; ^bDr Josep Trueta Hospital, Girona, Spain; ^cUniversitat de Barcelona, Barcelona, Spain; ^dUniversity of Leuven, Leuven, Belgium; ^eSant Joan de Déu Children's Hospital, Esplugues, Barcelona, Spain

Background: *STK11* regulates glucose and lipid metabolism. In adult rats, excessive fat deposition and dysfunctional metabolism are related to low *STK11* expression in adipose tissue. It is unknown if low *STK11* expression in adipose tissue relates also to catch-up growth and fat deposition after intrauterine growth restriction. **Objective and Hypotheses:** To assess the expression of *STK11* in adipose tissue and its relation to body weight gain and visceral fat mass in prenatally growth-restricted rats. **Method:** We used a Wistar rat model of intrauterine growth retardation induced by calorie restriction throughout gestation. Dams fed *ad libitum* delivered control pups (C), and dams on a 50% calorie-restricted diet delivered growth-restricted pups with low birth weight (R). Restricted offspring fed a standard rat chow after birth showed catch-up growth (RC) whereas restricted offspring kept on a calorie-restricted diet did not show catch-up growth (RR). Body weight gain, visceral fat mass and relative expression of *STK11* in retroperitoneal white adipose tissue (WAT) were postnatally assessed in the offspring ($n=10$ pups/group) at day 42. **Results:** Postnatal body weight gain was higher in RC pups compared with RR and control pups ($P<0.0001$). RC pups showed higher percentages of visceral fat mass ($P<0.0001$) and retroperitoneal WAT ($P<0.0001$) and lower *STK11* expression in adipose tissue ($P<0.005$) than RR pups. In RC pups, *STK11* expression in adipose tissue was negatively related to postnatal body weight gain ($r=-0.652$, $P=0.012$), visceral fat mass ($r=-0.584$, $P=0.028$) and retroperitoneal WAT ($r=-0.682$, $P=0.007$). **Conclusion:** Impaired *STK11* expression in adipose tissue could be among the mechanisms involved in catch-up growth and fat mass accumulation following fetal growth restriction in rats. If *STK11* expression in adipose tissue is also reduced in low-birthweight children, then this may be one of mechanisms underpinning the beneficial effects of metformin therapy that are observed in such children.

FC10.3

Genetic and Epigenetic Defects at the GNAS Locus Lead to Opposite Patterns of Fetal and Postnatal Growth

Virginie Grybek^a, Stéphanie Maupetit-Méhouas^b, Wolfgang Hogler^c, Harald Jüppner^d, Caroline Silve^e, Agnès Linglart^e

^aINSERM U986-Hôpital Bicêtre, Université Paris Sud, 94276 Le Kremlin Bicêtre, France; ^bLaboratoire GReD P. Arnaud Team, CNRS 6293-Clermont Université-INSERM U1103, 63001 Clermont-Ferrand, France; ^cDepartment of Endocrinology and Diabetes, Birmingham Children's Hospital, Birmingham, UK; ^dEndocrine Unit and Pediatric Nephrology Unit, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts 02114, USA; ^eCentre de Référence des Maladies Rares du Métabolisme du Calcium et du Phosphore, Service d'Endocrinologie

Table 1 (for Abstract 10.3).

	PseudoPHP (n=4)	PHP1A (n=38)	AD-PHP1B (n=9)	sporPHP1B (n=22)
Birth length (SDS)	-2.89 (-3.04; -1.52)	-0.94 (-2.09; 1.01)	0.00 (-1.16; 0.85)	0.24 (-1.09; 3.26)
Height at 1y (SDS)	-0.79 (-1.79; 1.13)	-0.64 (-3.04; 1.54)	1.36 (0.96; 2.58)	2.16 (0.56; 3.83)
BMI at 1y (SDS)	-0.76 (-2.19; 0.39)	2.62 (-3.25; 5.12)	1.5 (0.22; 2.75)	1.74 (-1.74; 5.02)
Height at 18y (SDS)	-1.64 (-3.25; -0.04)	-3.25 (-4.23; -2.18)	0.57 (-0.25; 1.39)	0.17 (-1.67; 3.83)

et Diabétologie de l'Enfant, Université Paris Sud, Hôpital Bicêtre, APHP, 94270 Le Kremlin Bicêtre, France

Background: Pseudohypoparathyroidism (PHP) is characterized by proximal tubular resistance to PTH and, in some disease variants, by Albright osteodystrophy. PHP is caused either by mutations in those regions of *GNAS* encoding *Gsα* (PHP1A and PseudoPHP) or by *GNAS* methylation defects (autosomal dominant (AD) and sporadic (spor) PHP1B). Phenotypic differences in fetal growth, post-natal growth and metabolism are observed in the different PHP types. **Objective and Hypotheses:** Our study aimed at understanding the contribution of the different *GNAS* transcripts to the growth pattern. **Method:** We recorded height and weight (birth-18y) of patients with PHP and *GNAS* mutations or epimutations. *GNAS* methylation and transcript expressions were measured through pyrosequencing and qRT-PCR from blood and fibroblasts of patients, respectively. **Results:** Fetal growth (median(min;max)) was severely and moderately impaired in patients with PseudoPHP and PHP1A. In contrast, it was normal or enhanced in patients with AD-PHP1B and sporPHP1B, and these displayed postnatal overgrowth. Birth length correlated with the methylation at the four differentially methylated *GNAS* regions, whereas weight correlated with A/B and *XLαs* promoter methylation. In addition, we showed that methylation of the A/B promoter controls the quantitative expression of A/B transcripts in patients' fibroblasts and lymphocytes. **Conclusion:** Our data suggest that the relative expression of the *GNAS* transcripts is critical for fetal and postnatal growth.

FC10.4

Influence of Newborn and Maternal Factors on Neonatal Body Composition

Laura Breij, Anita Hokken-Koelega

Department of Pediatrics, Subdivision of Endocrinology, Erasmus University Medical Center/Sophia Children's Hospital, Rotterdam, The Netherlands

Background: There is increasing evidence that body composition in early life has both immediate and long-term influence on health. Air-displacement plethysmography creates the opportunity to study the effect of prenatal and early postnatal factors on neonatal body composition. Prenatal maternal factors, such as pre-pregnancy BMI and gestational weight gain, might also influence neonatal body composition. **Objective and**

Hypotheses: We hypothesized that newborns with a similar birth weight have different fat mass percentages (FM%), related with gender, gestational age and the pre-pregnancy BMI and gestational weight gain of the mother. **Method:** The study population comprised 200 healthy newborns, with a gestational age between 35.2 and 42 weeks, born in Erasmus MC – Sophia Children's Hospital. Within 3 days after birth, weight, crown-to-heel length, head circumference and whole-body composition were assessed using air-displacement plethysmography (PEA POD, Infant Body Composition System, COSMED). Maternal data, i.e. weight before and at end of pregnancy, height and parity were obtained from medical records. **Results:** The newborns showed a large range in FM% (1.4-19.9%). There was a large variation in FM%, even in children with the same weight. Weight was strongly related with fat mass in kg ($r=0.70$ $P<0.001$). Mean fat mass in kg increased with gestational age ($r=0.22$, $P=0.001$), but FM% did not. The pre-pregnancy BMI of the mother correlated with the FM% of the newborn ($r=0.14$, $P=0.04$), but gestational weight gain of the mother did not correlate with the FM% of the newborn. **Conclusion:** Our study has generated accurate FM% and fat mass reference data in a large population of healthy newborns. Newborn infants showed a large variation in FM%, which was associated with mother's pre-pregnancy BMI and surprisingly not with the weight gain during pregnancy.

FC10.5

Contrasting Associations of Maternal Smoking and Alcohol Intake in Late Pregnancy and Offspring Body Composition in Childhood

Rebecca Moon^{a,b}, Stefania D'Angelo^a, Justin Davies^b, Elaine Dennison^a, Sian Robinson^a, Hazel Inskip^a, Keith Godfrey^{a,c}, Nicholas Harvey^{a,c}, Cyrus Cooper^{a,d}

^aMRC Lifecourse Epidemiology Unit, University of Southampton, Southampton, Hampshire, UK; ^bPaediatric Endocrinology, University Hospital Southampton NHS Foundation Trust, Southampton, Hampshire, UK; ^cNIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, Hampshire, UK; ^dNIHR Musculoskeletal Biomedical Research Unit, University of Oxford, Oxford, Oxfordshire, UK

Background: There is increasing recognition that the *in utero* environment might influence obesity risk. **Objective and Hypotheses:** We explored the hypothesis that smoking and alcohol consumption in pregnancy are associated with offspring

body composition using the Southampton Women's Survey mother-offspring birth cohort study. **Method:** At 34 weeks' gestation, maternal smoking and any alcohol intake in the preceding 12 weeks were determined by interview. At birth and 6 years of age, body composition was assessed by whole body DXA. **Results:** 1075 children were assessed at 6 years; 474 of these children also had a DXA at birth. 11% of mothers had smoked, and 77% consumed alcohol. The relationships between maternal smoking and offspring body composition differed between birth and 6 years: at birth, infants of smokers weighed less ($\beta = -0.30SD$, $P=0.001$) and were less adipose (total fat mass (FM) $\beta = -0.43SD$, $P=0.005$; %FM: $\beta = -0.41SD$ $P=0.006$). In contrast, at 6 years, children of smokers were heavier ($\beta = 0.31SD$, $P=0.001$) and had greater total FM ($\beta = 0.36SD$, $P < 0.0001$) and %FM ($\beta = 0.38SD$, $P < 0.0001$). Total lean mass (LM) was also higher, but %LM lower. Although offspring body composition at birth did not differ by maternal alcohol intake, at 6 years, the associations contrasted with those observed with smoking. Thus, offspring of mothers who had consumed alcohol were of similar weight, but had greater LM ($\beta = 0.23$, $P = 0.002$) and %LM ($\beta = 0.15SD$, $P = 0.052$) than children of mothers who abstained. Total FM was similar. These associations were robust to mutual adjustment and for multiple maternal and offspring confounders. **Conclusion:** Offspring of mothers who smoked in late pregnancy were lighter at birth, but heavier and more adipose at 6 years of age. In contrast, offspring of mothers who consumed alcohol had greater LM at 6 years. The underlying mechanisms are unknown, but could result from a combination of long-lasting epigenetic modifications during the perinatal period, and postnatal environmental factors.

FC10.6

The PremAldo Study: Impaired Aldosterone Signaling Worsens Renal Sodium Loss in Preterm Infants

Laetitia Martinerie^{a,b}, Eric Pussard^{a,c}, Nadya Yousef^d, Claudine Cosson^e, Ingrid Lema^{a,c}, Sebastien Murf, Pascal Boileau^g, Marc Lombes^{a,h}

^aUnité Inserm 693, Le Kremlin Bicetre, France; ^bService Endocrinologie Pédiatrique, Hôpital Robert Debre, Paris, France; ^cService de Génétique Moléculaire, Pharmacogénétique et Hormonologie, Hôpital Bicêtre, Le Kremlin Bicetre, France; ^dService de Réanimation Pédiatrique et Néonatale, Hôpital Bicêtre, Le Kremlin Bicetre, France; ^eService de Biochimie, Hôpital Bicêtre, Le Kremlin Bicetre, France; ^fService de Réanimation Néonatale, CHRU, Lille, France; ^gService de Réanimation Néonatale, Hôpital Poissy, Poissy, France; ^hService d'Endocrinologie et Maladies de la Reproduction, Hôpital Bicêtre, Le Kremlin Bicetre, France

Background: Tubular immaturity, responsible for sodium wasting, is critical during the neonatal period, particularly in preterm neonates. This relates to partial renal aldosterone resistance (Martinerie, *Ped Res* 2009), coincident with low tubular expression of the mineralocorticoid receptor in newborns (Martinerie, *Endocrinology* 2009). **Objective and methods:** Our clinical trial (NCT01176162) aimed to assess aldosterone

resistance in neonates according to gestational age and during a 1-year postnatal follow-up period, by measuring urinary aldosterone concentration (UAC) and its correlation to the urinary Na/K ratio as an index of renal aldosterone sensitivity. **Results:** We enrolled 170 newborns prospectively, classified into three groups: <33 GW (gestational weeks) (52 patients), 33–36 GW (69 patients), >37 GW (49 patients). Plasma aldosterone levels measured from umbilical cord blood samples were very high in the >37 GW group (1001 ± 98 pg/ml) and decreased significantly with gestational age (583 ± 48 and 380 ± 55 pg/ml in the 33–36 and <33 GW groups, respectively, $P < 0.0001$). This was associated with an increase in renin levels (from 81 ± 10 pg/ml in the >37 GW group to 135 ± 22 pg/ml in the <33 GW group), suggesting an aldosterone biosynthesis/secretion defect in preterms. UAC followed a similar pattern (from 20.2 ± 3.2 g/mmol urinary creatinine in term neonates to 8.8 ± 1.2 in preterms, $P < 0.0001$) significantly correlated with plasma aldosterone levels in all groups ($P < 0.0001$), demonstrating its accuracy as a non-invasive index of aldosterone secretion. Renal aldosterone resistance was demonstrated in all groups given the lack of correlation between UAC and the urinary Na/K ratio, and high sodium wasting at birth in very preterm infants. Renal aldosterone responsiveness appears in term infants at 1 month of age ($P = 0.02$) while renal aldosterone insensitivity persists in the preterm groups beyond 3 months. **Conclusion:** These results uncover the mechanism of sodium wasting in preterm neonates and underscore new potential therapeutic management based on UAC measurement.

FC11.1

Abnormal Sonic Hedgehog Signalling in Adamantinomatous Craniopharyngiomas and its Association with CTNNB1/ β -Catenin Mutations

Debora C Gomes, Soraya A Jamra, Leticia F Leal, Leandro M Colli, Carlos E Juca, Marina L Campanini, Ricardo S Oliveira, Carlos E Martinelli Jr, Paula C L Elias, Fabiano Saggiaro, Helio R Machado, Ayrton C Moreira, Luciano N Serafini, Margaret Castro, Sonir R Antonini

Ribeirao Preto Medical School- University of Sao Paulo, Ribeirao Preto -SP, Brazil

Background: The sonic hedgehog pathway (SHH) regulates CNS development and mutations or abnormal expression of the SHH pathway genes have been identified in epithelial tumors. SHH pathway interacts with Wnt/ β -catenin signalling. To date, CTNNB1/ β -catenin mutations are the sole molecular abnormality found in adamantinomatous craniopharyngiomas (ACPs). **Objective and Hypotheses:** To analyze the expression pattern of SHH pathway genes in ACPs and its association with CTNNB1 mutations and clinical outcome in patients with ACPs. **Method:** Eighteen patients (ten females) with ACPs were analyzed. Mean age at diagnosis was 16.4 years (6–30). Control tissues included seven normal anterior pituitaries. The mRNA expression of SHH pathway components SHH, PTCH1, SMO, GLI1, GLI2, GLI3 and SUFU was evaluated by qPCR in tumoral and control tissues.

Immunohistochemistry (IHC) evaluated SMO, GLI1, GLI3, SUFU, β -catenin and Ki67 expression in ACPs. CTNNB1 gene was directed sequenced on tumoral DNA. **Results:** Somatic CTNNB1/ β -catenin mutations were found in eight ACPs. Compared to normal pituitary, ACPs presented higher mRNA expression of SHH (+400-fold change-FC; $P < 0.01$), GLI1 (+102 FC; $P < 0.001$) and GLI3 (+5.1 FC; $P < 0.01$). Interestingly, ACPs harboring CTNNB1/ β -catenin mutations presented higher expression of GLI1 (+10.2 FC; $P = 0.03$) and SMO (+4.3 FC; $P = 0.02$) than WT tumors. Higher expression of SMO mRNA associated with disease progression ($P < 0.01$) while lower SMO mRNA expression was associated with longer disease free survival ($P < 0.01$; HR = 0.14, 95%CI = 0.03–0.54). Moreover, GLI1 staining was detected in the typical palisade ACPs cells and co-localized with Ki67 staining, which is a marker of cell proliferation. **Conclusion:** These results show that the deregulation of the SHH signalling may be an important pathogenic event in ACPs, being associated with disease progression. These abnormalities appear to be more prominent in CTNNB1/ β -catenin mutated ACPs. Therefore, inhibition of the SHH pathway may be a novel potential target in adjuvant therapy for ACPs patients.

FC11.2

Novel SOX2 Mutation: Identification of New Molecular Mechanisms of SOX2 Action and Interactions

Kyriaki S. Alatzoglou^a, Cynthia L. Andoniadou^b, Daniel Kelberman^c, Hyoong-Goo Kim^d, Edward Botse-Baidoo^d, Jennifer Pedersen-White^d, Lawrence Layman^d, Juan Pedro Martinez-Barbera^b, Mehul T. Dattani^a

^aDevelopmental Endocrinology Research Group, UCL Institute of Child Health, London, UK; ^bNeural Development Unit, UCL Institute of Child Health, London, UK; ^cDevelopmental Biology Unit, Ulverscroft Vision Research Group, UCL Institute of Child Health, London, UK; ^dSection of Endocrinology, Diabetes and Metabolism, Department of Medicine, The Medical College of Georgia, Augusta, USA

Background: SOX2 is an early developmental transcription factor implicated in pituitary development; heterozygous SOX2 mutations have been reported in patients with a severe ocular phenotype and hypogonadotrophic hypogonadism (HH) with/without associated abnormalities. SOX2 physically interacts with β -catenin, a member of the Wnt-signalling pathway, via its carboxyl-terminus and it represses *in vitro* β -catenin mediated activation. **Objective and Hypotheses:** We report a novel SOX2 mutation (c.G261T, p.K87N) in a female patient with bilateral congenital anophthalmia and developmental delay, who first presented at the age of 21 years with primary amenorrhoea. She had hypogonadotrophic hypogonadism (FSH 1.0 IU/L, LH 0.6 IU/L, Oestradiol <15 pg/mL) and thinning of the corpus callosum on MRI. The mutation occurred in the high-mobility group (HMG) DNA-binding domain. We studied its functional consequences, revealing a distinct mechanism of action. **Method:** In vitro luciferase reporter assays, immunostaining and electrophoretic mobility shift assay (EMSA). **Results:** Luciferase reporter

assay showed that, unlike other mutations affecting the HMG domain, mutant p.K87N SOX2 had comparable transactivation to wild type (WT) SOX2 and it retained its ability to bind to a consensus DNA probe on EMSA. Nuclear localisation was confirmed by immunostaining. However, co-transfection of p.K87N SOX2 with a constitutively active form of human β -catenin (S33Y) in the TOPFLASH reporter assay, failed to repress β -catenin mediated activation. Neither WT nor p.K87N SOX2 bind to a TCF/LEF consensus probe on EMSA. Therefore, failure to repress β -catenin mediated activation *in vitro* may result from altered direct interaction β -catenin. **Conclusion:** We report a novel SOX2 mutation in the HMG domain that, unexpectedly, fails to repress β -catenin mediated activation suggesting that the HMG domain is critical for the interaction with β -catenin. We report, for the first time to our knowledge, that clinical phenotypes may result from altered interaction between SOX2 and β -catenin.

FC11.3

Early-Onset Central Diabetes Insipidus is Associated with De Novo Arginine Vasopressin-Neurophysin II or Wolfram Syndrome 1 Gene Mutations^{*}

Anna Elsa Maria Allegri^a, Natascia Di Iorgi^{a,b}, Silverio Perrotta^c, Fulvio Della Ragione^d, Saverio Scianguetta^c, Adriana Borriello^d, Marcella Ferraro^c, Claudia Santoro^c, Annalisa Calcagno^a, Flavia Napoli^a, Marta Giaccardi^{a,b}, Marco Cappa^e, Maria Carolina Salerno^f, Mohamad Maghnie^{a,b}

^aDepartment of Pediatrics, Istituto Giannina Gaslini, Genoa, Italy; ^bUniversity of Genoa, Genoa, Italy; ^cDipartimento della Donna, del Bambino e di Chirurgia Generale e Specialistica, Second University of Naples, Naples, Italy; ^dDepartment of Biochemistry, Biophysics, and General Pathology, Second University of Naples, Naples, Italy; ^eUnit of Endocrinology and Diabetology, Bambino Gesù Children's Hospital, Rome, Italy; ^fPediatric Endocrinology Unit, Department of Translational Medical Sciences, University 'Federico II' of Naples, Naples, Italy

Background: Children with familial forms of central diabetes insipidus (CDI) display polyuria and polydipsia within the first years of life. **Objective and hypotheses:** We hypothesize that children with an early-onset idiopathic CDI might be affected by *de novo* genetic mutations. **Method:** Eleven children aged between 1 month and 7 years with polyuria and polydipsia and negative family history were enrolled. In nine of them with CDI the arginine-vasopressin-neurophysin II (AVP-NPII) and Wolfram genes (WS1) were sequenced. **Results:** Two patients carried a mutation in AVP-NPII gene: a heterozygous G to T transversion at nucleotide position 322 of exon 2 (c.322G>T) resulting in a stop codon at position 108 (p.Glu108X), and a novel deletion from nucleotide 52 to 54 (c.52_54delTCC) producing a deletion of a serine residue at position 18 (p.Ser18del) of the AVP pre-prohormone signal peptide. A third patient carried two heterozygous mutations in the WFS1 gene, each localized on a different allele. The first change was A to G transition at nucleotide 997 in exon 8 (c.997A>G), resulting in the change of valine at position 333 in place of isoleucine (p.Ile333Val). The second novel

mutation was a 3 bp insertion in exon 8, c.2392-2393insACG that gave origin to the addition of a third consecutive aspartic acid at position 797 and the maintenance of the correct open reading frame (p. Asp797_Val798insAsp). While no changes of WS1 protein level were evidenced in the fibroblasts from healthy individuals as well as from the patient and his parents, a major sensitivity to staurosporine-induced apoptosis was observed only in the fibroblasts of the patient, as demonstrated by increased poly(ADP-ribose polymerase) cleavage and caspase 3 activation. **Conclusion:** Early-onset idiopathic CDI is associated with *de novo* mutations of *AVP-NP11* gene and with never reported hereditary changes of *WFS1* gene. These findings have valuable implications for genetic counseling.

*Nominated for a Presidential Poster Award.

FC11.4

Management of Hyperhydration in a Child with Syndrome of Inappropriate Antidiuretic Hormone Secretion (Siadh) Using a Selective Vasopressin Receptor Agonist

Violeta Delgado-Carballar, Ajay Thankamony, Ruben Willemsen, Daniela Elleri, David Dunger

Department of Paediatrics, University of Cambridge, Cambridge, UK

Background: Management of SIADH is challenging and no optimal therapies are available in children. We present a case of an 11 years old boy with severe SIADH resistant to 30% fluid restriction in the context of an intracranial suprasellar high grade B-cell lymphoma who requires hyperhydration for chemotherapy protocol. Tolvaptan is an oral highly selective arginine vasopressin V2 receptor antagonist, which has been approved for use in SIADH in adults. **Objective and Hypotheses:** The aim was to

use Tolvaptan in a patient with SIADH to treat hyponatremia and enable hyperhydration. **Method:** Tolvaptan was started at a dose of 0.14 mg/kg once a day and titrated up to 0.28 mg/kg twice a day based on fluid requirements and serum sodium levels. Frequent monitoring of serum/urine electrolytes and osmolality, fluid input/output with adjustment were needed to avoid rapid correction of hyponatremia. **Results:** Following tumor diagnosis serum sodium levels dropped from 132 to 118 mEq/l despite fluid restriction up to 30% and administration of furosemide. Hyponatremia was corrected gradually with Tolvaptan administration allowing liberalization of fluid intake and hyperhydration (twice the fluid maintenance rate, chart). The fluid intake was altered based on serum sodium levels and fluid balance. After 5 days of hyperhydration, when the methotrexate was cleared, Tolvaptan doses and frequency was decreased to achieve normal fluid intake and acceptable sodium levels. **Conclusion:** Tolvaptan is a safe and effective treatment for severe SIADH when fluid restriction is not possible or effective. However, close monitoring is important to avoid rapid correction of hyponatremia.

FC11.5

Endocrine Features of a Large Cohort of Children with Septo-Optic Dysplasia and Congenital Multiple Pituitary Hormonal Deficiencies

Manuela Cerbone, Maria Güemes, Tessa Kasia, Mehul T Dattani

London Centre for Paediatric Endocrinology and Diabetes, University College London and Great Ormond Street Hospitals, London, UK

Introduction: Septo-optic dysplasia (SOD) is characterized by a combination of midline forebrain, pituitary and eye abnormalities. We aimed to evaluate endocrine features of patients with SOD, and multiple pituitary hormone deficiencies (MPHD). **Design:** Retrospective data were collected from 130 patients: 102 SOD and 28 MPHD followed at a single tertiary centre. SOD were divided into two groups: with pituitary hormone deficiencies (SOD+, $n=83$) and with normal pituitary function (SOD-, $n=19$). To assess the degree of pituitary dysfunction the endocrine morbidity score (EMS) was calculated by attributing one point for each pituitary deficit presented. **Results:** The first pituitary deficit occurred earlier in MPHD compared to SOD+ ($P<0.03$). The most prevalent hormonal deficiency in SOD+ was GH, whilst TSH and GH were most prevalent in MPHD. The EMS was significantly higher in MPHD ($P=0.002$). The prevalence of TSH deficiency was higher in MPHD compared to SOD+ ($P=0.005$). At diagnosis 11.6% of the SOD+ and 16% of the MPHD had high TSH concentrations (ranging between 6.8 and 16.1 mU/l). DI was the least frequent endocrinopathy in both groups. In three SOD+, DI evolved after the age of 7.3 years. Undervirilized external genitalia were present at birth in 27.5 and 35.7% of SOD and MPHD males respectively. Of patients who received an HCG test during minipuberty, MPHD showed lower 3 day and 3 week testosterone responses ($P<0.05$). Of those who underwent an

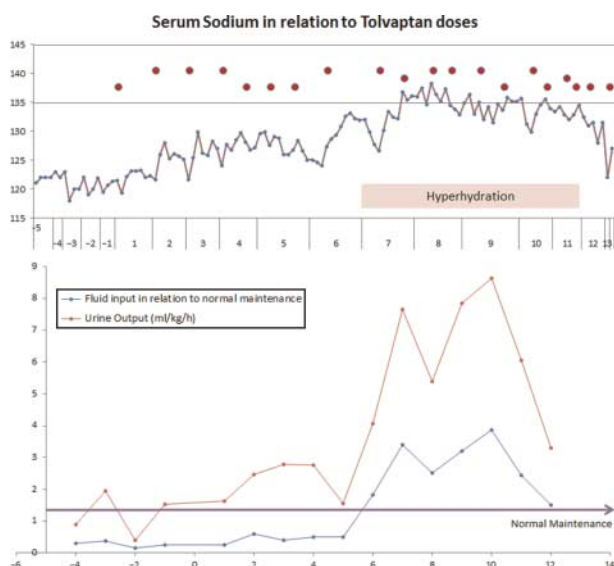


Figure 1

LHRH test during minipuberty an LH response < 5 IU/l ($P=0.003$) and undetectable gonadotrophins ($P<0.0008$) were present more frequently in MPHD. 4.9% of SOD and 14.3% of MPHD required induction of puberty. Treatment for cessation of puberty was needed in 20% of SOD. **Conclusions:** Our data suggest striking differences in endocrine features between SOD and MPHD patients. Further understanding of the aetiology and the natural history of these conditions may aid in their clinical management.

FC11.6

Clinical and Neuroradiological Characteristics in Children and Adolescents with Septo-Optic Dysplasia, Multiple Pituitary Hormone Deficiencies and Optic Nerve Hypoplasia: Experience from a Single Tertiary Centre

Maria Güemes^{a,b}, Manuela Cerbone^{a,b}, Manolis Bagkeris^c, L C Gregory^d, Tessa Kasia^d, Mehul Dattani^{a,d}

^aDepartment of Endocrinology, Great Ormond Street Hospital for Children, London, UK; ^bPaediatrics and Adolescent Service, University College London Hospital, London, UK; ^cStatistics Department, Institute for Child Health, London, UK; ^dDevelopmental Endocrinology Research Group, Epigenetics and Genetics in Health and Disease Section, Genomics and Genetic Medicine Programme, London, UK

Background: Septo-optic dysplasia (SOD) is an important cause of hypopituitarism, although less common than multiple pituitary hormone deficiency (MPHD). Children with optic nerve hypoplasia (ONH) are at risk of hormone and neurocognitive disturbances. **Objective and Hypotheses:** We describe clinical and neuroradiological findings of these three overlapping conditions, aiming to understand their pathophysiology. **Method:** Retrospective analysis of clinical and neuroimaging data in 140 patients with hypopituitarism (MPHD, SOD) and ONH, collected at a tertiary endocrinology centre between 2000 and 2013. **Results:** Male/female ratio in SOD ($n=102$), MPHD ($n=28$) and ONH ($n=10$) was 1.37, 1.33 and 0.66, respectively. There was no significant difference between the three groups in terms of birth characteristics. Given the mean age at last appointment in all groups (8.32–8.42 years), the majority of patients remained prepubertal and pre-adrenarcheal, although spontaneous puberty, in those who were of an appropriate age, had started in 86.6% SOD (26/30), 62.5% MPHD (5/8) and in all ONH (4/4). Abnormal male genitalia at birth was found in 27.5% SOD (16/59), 37.5% MPHD (6/16) and in none ONH (0/4). Obesity at last appointment was present in 25.5% SOD (26/102), 32.1% MPHD (9/28) and 30% ONH (3/10). Oral glucose tolerance tests (OGTT) revealed insulin insensitivity in 5/7 SOD patients with metformin administered to four of them. SOD was associated with hearing abnormalities (12.8%), hyposmia (2.9%), cardiovascular accidents (2%), hip dislocation (7.8%), autistic spectrum disorder (24.5%) and sleep

disturbances (35.3%). Neurodevelopmental delay was more prevalent in ONH (90%). MPHD had a higher prevalence of certain pituitary abnormalities; hypoplastic adenohypophysis (89.3%), ectopic neurohypophysis (67.9%) and absent stalk (21.4%). SOD more frequently had abnormalities of the septum pellucidum (36.2%), corpus callosum (44.2%), optic chiasm (48.1%) and cortical dysplasia (9.9%). **Conclusion:** SOD, MPHD and ONH patients show highly variable phenotypes, but shared clinical characteristics suggest that these conditions form a spectrum of midline brain abnormalities.

FC12.1

High-Fat Diet Rapidly Triggers Circadian De-Synchronization of Clock Genes, Neuropeptides and Inflammation Mediators in the Hypothalamus of C57BL Mice

Francisco Hernández-Nuño^a, Mariano Ruiz-Gayo^a, Francisca Díaz^{b,c}, Jesús Argente^{b,c}, Julie A Chowen^{b,c}

^aFacultad de Farmacia, Universidad CEU-San Pablo, Madrid, Spain; ^bDepartment of Endocrinology, Hospital Infantil Universitario Niño Jesús, Madrid, Spain; ^cDepartment of Pediatrics, CIBERobn Instituto Carlos III, Universidad Autonoma de Madrid, Madrid, Spain

Background: Circadian disorganization of feeding behavior evoked by high fat diet (HFD) intake is suggested to be involved in the resulting weight gain and development of associated metabolic alterations and hypothalamic inflammation. **Hypothesis:** We hypothesized that this circadian alteration might be a consequence of rapid de-synchronization of different gene clusters relevant for metabolic control. **Methods:** We analyzed the circadian pattern of clock (*Clock*, *Per2*), neuropeptide (*Npy*, *Agrp*, *Pomc*) and inflammation-related interleukin (*IL1 β* , *IL6*) hypothalamic gene expression and serum metabolic factors in male C57BL mice placed on a HFD or control diet at 0600, 1200, 1800 or 2400 and killed 48 h later. **Results:** HFD increased weight gain ($P<0.01$) and energy intake ($P<0.01$). Insulin levels were increased by HFD at all time-points, with leptin only being increased at 1800 and 2400. Hypothalamic *clock* expression decreased ($P<0.01$), being significant at 1800 and 2400. *Per2* changed over time, with no effect of HFD. HFD reduced the orexigenic neuropeptides *NPY* ($P<0.05$) and *AgRP* ($P<0.05$) and abolished their circadian rhythm of expression. *POMC* expression changed over time and was unaffected by HFD. HFD also mitigated the circadian changes in *IL6* ($P<0.05$) and *IL1 β* ($P<0.05$) expression. **Conclusion:** HFD rapidly modulates metabolic hormones and expression of hypothalamic neuropeptides. The loss of circadian variation in orexigenic neuropeptide expression could be associated with the observed modification in the pattern of food intake. Interestingly, the HFD-induced loss of rhythmicity in *IL1 β* and *IL6* expression levels results in these mice having more, less or similar levels of these interleukins compared to controls depending on the time of day. Thus, any eventual synchronicity between zeitgeber-related genes, food intake and inflammation is disrupted by HFD.

FC12.2

Obesity in Childhood and Adolescence is Associated with Shorter Leukocyte Telomere Length

Agaristi Lamprokostopoulou^a, George Moschonis^b, Yannis Manios^b, George P Chrousos^{a,c}, Evangelia Charmandari^{a,c}

^aDivision of Endocrinology and Metabolism, Biomedical Research Foundation of the Academy of Athens, Athens, Attiki, Greece;

^bDepartment of Nutrition, Harokopio University of Athens, Athens, Attiki, Greece; ^cFirst Department of Pediatrics, 'Aghia Sophia' Children's Hospital, University of Athens Medical School, Athens, Attiki, Greece

Background: Obesity in adulthood is associated with shorter leukocyte telomere length, a marker of biological age that is also associated with age-related disorders, including cardiovascular disease and type 2 diabetes mellitus. **Objective and Hypotheses:** To investigate the relation between BMI in childhood and adolescence and telomere length, by determining the mean telomere length of leukocytes. **Patients and Method:** Seven hundred forty-four ($n=744$) children and adolescents aged 11.3 years (mean \pm S.E.M., 11.31 ± 0.05 years; boys: 370, girls: 374) participated in the study. Depending on their BMI, patients were classified as obese ($n=91$), overweight ($n=212$), normal ($n=411$) or underweight ($n=15$). Two hundred thirty-three ($n=233$), children were prepubertal and 502 pubertal. The telomere length of leukocytes was determined by monochrome multiplex quantitative real-time PCR (MMQRTPCR). Telomere length was compared among groups and correlated with selected anthropometric parameters. **Results:** Obese children and adolescents had significantly shorter leukocyte telomere length compared with children and adolescents with normal BMI (0.94 ± 0.37 vs 1.16 ± 0.45 , $P=0.007$). Telomere length was inversely related to BMI ($r=-0.247$, $P<0.001$), triglycerides concentrations ($r=-0.119$, $P=0.001$), waist to hip ratio ($r=-0.164$, $P<0.001$) and high-sensitivity C-reactive protein ($r=-0.126$, $P=0.003$) concentrations. There was no significant correlation with total, HDL or LDL cholesterol concentrations. No significant difference in leukocyte telomere length was noted between boys and girls. **Conclusions:** Obese children and adolescents have significantly shorter leukocyte telomere length compared with their normal counterparts. These findings indicate that the increase in BMI in childhood and adolescence may be associated with an advanced biological age compared with the chronological age, and may have an adverse impact on future health.

FC12.3

Increased Resting Energy Expenditure in Girls with Turner Syndrome

Gerhard Bindera^a, Laura Frank^a, Gunnar Blumenstock^b, Roland Schweizer^a

^aUniversity-Children's Hospital, Paediatric Endocrinology, Tuebingen, Germany; ^bDepartment of Clinical Epidemiology and Applied Biometry, University of Tuebingen, Tuebingen, Germany

Background: There is no knowledge of the energy metabolism in the presence of X chromosome aneuploidy or structural aberrations. Recently, an abnormal muscle metabolism was observed in girls with Turner syndrome (TS). **Objective and Hypotheses:** Resting energy expenditure was prospectively estimated by indirect spirometry in 92 short prepubertal girls at the start of GH therapy. **Method:** The diagnoses were TS ($n=23$), GH deficiency (GHD) ($n=41$) and SGA short stature (SGA) ($n=28$). Mean ages were 8.2 years (TS), 7.0 years (GHD) and 6.8 years (SGA). Mean heights (Prader reference) were -2.90 SDS (TS), -3.31 SDS (GHD) and -3.68 SDS (SGA). In TS, karyotypes were 45,X ($n=15$), 45,X/46,XX ($n=3$), 46,X,i(Xq) ($n=1$) and other X chromosome abnormalities ($n=4$). GHD was defined by growth failure, bone age retardation, low IGF1 and two GH test peaks <10 $\mu\text{g/l}$. SGA was defined by birth length or weight <-2 SDS and an actual height <-2.5 SDS. Spirometry (Vmax Encore 229) was performed under fasting conditions in the morning in a lying position. Body composition was measured by DXA simultaneously in 36 girls (TS, $n=9$). **Results:** Girls with TS had significantly higher resting energy expenditure (mean \pm S.D.; 1114 ± 215 kcal/day) than the other girls (820 ± 169 kcal/day) ($P<0.0001$). In multiple linear regression analysis, the presence of TS was a strong independent predictor of resting energy expenditure ($P<0.001$) besides age ($P<0.001$) and BMI ($P=0.034$). GHD was no predictor ($P=0.822$). Mean lean body mass (DXA) was 15.2 kg (69%) in TS, 13.2 kg (73%) in GHD and 12.2 kg (81%) in SGA. **Conclusion:** In short girls with TS the resting energy expenditure is significantly increased in comparison to short girls with GHD or SGA. The underlying mechanisms are unknown. High lean body mass and altered muscle metabolism in TS may play a role.

FC12.4

Pediatric Reference Values for Insulin from oGTT and Prevalence of Hyperinsulinemia in Obese Children

Antje Körner^{a,c}, Kathrin Scheuermann^a, Madlen Neef^a, Elena Sergejeva^a, Mandy Vogel^b, Jürgen Kratzsch^b, Wieland Kiess^a

^aCenter for Pediatric Research, University Hospital for Children and Adolescents Leipzig, University of Leipzig, Leipzig, Germany;

^bLaboratory Medicine and Molecular Diagnostics, Institute of Clinical Chemistry, University of Leipzig, Leipzig, Germany;

^cMedical Center Adiposity Diseases (IFB), University of Leipzig, Leipzig, Germany

Background: Evaluation of glucose metabolism is currently based on 2 h glucose during an oral glucose tolerance test (oGTT) or fasting glucose and insulin or A1c, as these are the only parameters where cutoff values exist. This does, however, not adequately reflect the degree of hyperinsulinemia due to insulin resistance in obese children. **Objective and design:** From frequent glucose and insulin levels during an oGTT of 64 healthy lean children (aged 7.7–18.8 years, BMI SDS -0.25 ± 0.76) we aimed i) to established reference values for insulin secretion in normal children. ii) We compared insulin and glucose dynamics with data of 99 obese children (aged 6.1–17.9 years, BMI SDS

2.43 ± 0.50). iii) We then applied these reference data to assess the prevalence of insulin resistance in an extended cohort of 1.085 obese children. **Results:** i) From the healthy lean controls, we defined the maximal observed peak insulin (986 pmol/l) and minimal Matsuda ISI (3.154) as cutoffs. In lean children, pubertal status significantly affected fasting plasma (FPI) and Matsuda ISI. ii) In obese children, integral and 2 h glucose levels were significantly increased independent from age, gender and pubertal stage. However, particularly insulin parameters were markedly elevated, with peak and integral insulin levels doubled in obese compared to lean controls. The puberty effect seen in lean controls was overridden by BMI SDS when obese peers were included into multiple regression analyses, which explained 36.5% (peak insulin), 43.8% (FPI), 43.8% (Matsuda ISI) of variance. iii) Applying the obtained reference values to our extended obesity cohort, 47.3% of obese children had hyperinsulinemia and 49.2% were insulin resistant based on peak insulin and Matsuda ISI, respectively, while prevalence rates of impaired glucose tolerance (13.8%) and impaired fasting glucose (18.2%) were much lower. **Conclusion:** We provide reference values for insulin secretion during an oGTT from healthy lean children. Compared to lean children, insulin secretion is doubled in obese children and almost 50% of obese children already present hyperinsulinemia as a sign of insulin resistance.

FC12.5

Low Circulating Levels of DKK-1 Protein in Obese Children Indicate Suppression of Canonical Wnt Signaling

Christina Kanaka-Gantenbein^a, Evangelos Terpos^b,
George Chrousos^a, Ioannis Papassotiropoulos^c

^aFirst Department of Pediatrics, University of Athens School of Medicine, Athens, Greece; ^bDepartment of Clinical Therapeutics, University of Athens School of Medicine, Athens, Greece;
^cDepartment of Clinical Biochemistry, 'Aghia Sophia' Children's Hospital, Athens, Greece

Background: Secretion of Wnt-proteins by adipose cells plays an important role in the control of adipogenesis. The Wnt-antagonist, dickkopf-1 (DKK-1), is secreted by human pre-adipocytes and influences adipocyte maturation and growth. DKK-1 mRNA increases 6 h after onset of human adipogenesis followed by an increase in DKK-1 protein. Of note, DKK-1 protein has been implicated also in bone remodeling pathways. **Patients and Methods:** In this study we measured the circulating DKK-1 levels in 16 lean and 25 obese girls using immunoenzymatic techniques and we investigated possible correlations of DKK-1 levels with parameters of anthropometric evaluation; insulin resistance; adipose tissue secretory molecules (adiponectin, leptin, retinol-binding-protein-4 (RBP-4) and lipocalin-2); bone remodeling biomarkers (osteoprotegerin (OPG), receptor-activator of NF-κB ligand (RANKL), osteocalcin, C-terminal-cross-linking telopeptide of collagen type-I (CTX), bone-alkaline-phosphatase (bALP) and tartrate-resistant-acid-phosphatase-isoform-5b (bone-TRACP-5b) and a low grade inflammation marker

(hs-CRP)). **Results:** We found that: i) DKK-1 levels were significantly higher in lean than obese girls 37.5 ± 18.0 vs 18.6 ± 2.4 pg/ml, $P=0.009$, ii) BMI and HOMA index values correlated negatively with DKK-1 levels ($r=-0.508$, $P<0.001$ and $r=-0.380$, $P<0.01$, respectively), iii) logDKK-1 values correlated significantly only with adiponectin levels ($r=-0.404$, $P=0.008$), iv) DKK-1 and RANKL levels correlated positively with each other, ($r=0.492$, $P<0.001$) and v) hs-CRP and DKK-1 levels correlated, negatively with each other ($r=-0.371$, $P=0.01$). **Conclusion:** Our preliminary findings suggest that indices of metabolic syndrome such as obesity, insulin resistance, low adiponectin and low grade inflammation are negatively associated with circulating DKK-1 protein levels in children. Obesity is characterized by inappropriate expansion of adipose cells (hypertrophic obesity) and is caused by an inability to recruit and differentiate new precursor cells. Thus, the impairment of adipogenesis observed in obesity appears to be due mainly to suppression of canonical Wnt signaling via induction of DKK-1. The latter might connect obesity with increased osteoclastogenesis.

FC12.6

Resveratrol Inhibits Inflammation-Induced Production of Cytokines in Human Adipocytes

Ivana Zagotta^a, Alexandra Killian^a, Jennifer Haas^a,
Thomas Kietzmann^b, Klaus-Michael Debatin^a, Martin Wabitsch^a,
Pamela Fischer-Posovszky^a

^aUniversity Medical Center Ulm, Ulm, Germany; ^bUniversity of Oulu, Oulu, Finland

Background: Upon excessive expansion, adipose tissue is infiltrated by macrophages and shows increased production of inflammatory cytokines. This chronic low grade inflammation of adipose tissue is involved in the pathogenesis of insulin resistance. A supplementation with resveratrol can reverse the metabolic disturbances of human obesity, in part by mimicking the effects of caloric restriction. **Objective and Hypotheses:** We hypothesized that the beneficial effects of resveratrol might be mediated by an anti-inflammatory effect on adipose tissue. **Method:** To mimic adipose tissue inflammation we incubated SGBS adipocytes with THP-1 macrophage conditioned medium (MacCM). Cultures were treated with 100 μM resveratrol or vehicle (DMSO). Interleukin-6 and 8 (IL6, IL8) and monocyte chemo-attractant protein 1 (MCP1) production was studied by qPCR and ELISA. **Results:** Treatment of adipocytes with 10% MacCM resulted in upregulation of IL6 mRNA by ~50-fold, IL8 by ~500-fold and MCP-1 by ~25-fold after 48 h. Co-treatment with resveratrol completely abolished this effect of MacCM. Comparable results were found on the protein level. To elucidate the molecular pathway involved, we took advantage of small molecule inhibitors. Inhibition of NFκB with SC-514 (100 μM) prevented the MacCM-induced upregulation of IL6, IL8 and MCP1 production. Interestingly, inhibition of PI3K with Ly294002 (20 μM) did not interfere with IL6 and IL8, but downregulated mRNA expression of MCP1. However, we detected significantly lower amounts of IL6, IL8 and MCP1 secreted to the media supernatants upon

inhibition of PI3K. **Conclusion:** We show that resveratrol inhibits the inflammation-induced cytokine production in human adipocytes, mediating its anti-inflammatory effect by inhibiting NFκB activity and the PI3K/Akt pathway. Taken together, our results demonstrate that resveratrol has health beneficial effects on human adipocytes. Preventing proinflammatory conditions in adipose tissue might be a useful strategy to prevent the development of insulin resistance in the obese state.

FC13.1

Massive Sequencing of Thyroidal Genes Reveals Unexpected Polygenic Defects in Dyshormonogenic Hypothyroidism

A Iglesias^a, M García^a, P Ventura^f, J Pozo^b, M Clemente^c, L Audí^c, R Corripio^d, K Garikano^a, M Polak^e, A del Pozo^a, T J Visser^f, J C Moreno^a

^aInstitute for Medical and Molecular Genetics (INGEMM), La Paz University Hospital, Madrid, Spain; ^bPaediatric Endocrinology Service, Niño Jesus University Hospital, Madrid, Spain; ^cPaediatric Endocrinology Service, Vall d'Ebron Hospital, Barcelona, Cataluña, Spain; ^dPaediatric Endocrinology Service, Parc taulí Sabadell Hospital, Sabadell, Barcelona/Cataluña, Spain; ^ePaediatric Endocrinology Service, Necker-Enfants Malades Hospital, Paris, France; ^fErasmus Medical Center, Rotterdam, The Netherlands

Background: Dyshormonogenic hypothyroidism is classically a monogenic disease with recessive inheritance. Thyroid dysgenesis showed a multigenic origin in a mouse model of double-heterozygous deletions of *Nkx2.1/Pax8* transcription factor genes, suggesting a possible polygenic nature of certain cases of human hypothyroidism. **Objective and Hypotheses:** To investigate genetic traits of polygenic involvement in dyshormonogenic hypothyroidism, using next generation sequencing (NGS). **Methods:** Endocrine and genetic characterization of four pedigrees with thyroid dyshormonogenesis. NGS of 18 thyroidal genes including *TG*, *TPO*, *DUOX2/DUOXA2* and *DEHAL1*. Pathogenicity prediction and H₂O₂-generation testing of mutants. **Results:** Three families (F1–F3) were consanguineous. All patients showed positive perchlorate discharge (PD). In F1, two siblings with congenital hypothyroidism (TSH > 200 mu/l) had elevated thyroglobulin (> 1600 ng/ml) and 100% PD. NGS revealed a homozygous frameshift mutation in *TPO* (p.S756fsX75) in both brothers. Additionally, one presented a heterozygous nonsense mutation in *DUOX2* (p.K530X). In F2, two sisters were born with increased neonatal TSH (200 and 800 mu/l). Both were homozygotes for a nonsense *TG* mutation (p.R296X) but also were respectively heterozygote and homozygote for a pathogenic *TPO* mutation (p.G667S). In F3, index patient presented neonatal TSH > 800 mu/l, thyroglobulin > 300 ng/ml and 30% PD. NGS revealed a yet described pathogenic homozygous *TPO* mutation (p.G493S) and a rare heterozygous *TG* change (p.G653D) predicted as highly pathogenic. In non-consanguineous F4, two sisters had pubertal euthyroid/hyperthyrotropinemic goiters and 25% PD. Both were heterozygotes for a known pathogenic *TPO* mutation (p.N425S), but one also presented a heterozygous

DUOXA2 mutation (p.G294E) which reduced 50% the *in vitro* capacity of H₂O₂ generation by *DUOX2-DUOXA2* pair. **Conclusion:** Targeted NGS reveals unexpected mutations additional to typical homozygous defects in consanguineous children with thyroid dyshormonogenesis. These additional mutations occur in genes also involved in iodide organification (*DUOX2*, *TPO*, *TG*, *DUOXA2*), had not been identified by standard 'one-gene-approach' sequencing and may account for the intra-familial phenotypic variability of dyshormonogenic hypothyroidism.

FC13.2

Thyroid Agenesis and Severe Thyroid Hypoplasia Caused by a New Inactivating TSH Receptor Mutation Ala579Val

Theda Wessel^a, Daniela Handke^b, Gunnar Kleinau^b, Franziska Winkler^b, Annette Grüters^{a,b}, Peter Kühnen^{a,b}, Heiko Krude^{a,b}, Heike Biebermann^b

^aDepartment of Paediatric Endocrinology, Charité University Children's Hospital, Berlin, Germany; ^bInstitute of Experimental Paediatric Endocrinology, Charité University, Berlin, Germany

Background: Congenital thyroid dysgenesis usually occurs sporadically and may even be discordant in monozygotic twins. However, when caused by inactivating mutations in the TSH receptor (TSHR) it can be inherited recessively, typically resulting in thyroid gland hypoplasia. We present a new familial case of thyroid dysgenesis with two siblings of consanguineous parents. The daughter was identified in neonatal screening with severely elevated TSH and thyroid agenesis on ultrasound. Only when her brother was affected by CH and thyroid hypoplasia and a third child was found to have a hyperthyrotropinemia the diagnosis of a TSHR-mutation was considered. **Objective and Hypotheses:** To perform sequencing and functional analysis of the TSHR in the affected family members. **Method:** The identified variant p.Ala579Val was tested in cell-systems for signalling capabilities and cell surface expression compared to WT. Furthermore, tight interactions of Ala579 to residues of the second extracellular loop (ECL2) were suggested by a structural TSHR model. This hypothesis was tested by different side chain variations at position 579. **Results:** We demonstrated a new TSHR-mutation with complete loss of cAMP and IP signalling and decreased cell surface expression down to 30% affecting the tight interaction within the receptor conformation. Substitutions with more bulky and branched side chains compared to alanine resulted in a complete loss of cAMP and IP signalling. The homozygote clinical phenotype ranged from thyroid agenesis and nearly undetectable thyroglobulin levels in one sibling to a hypoplastic thyroid gland and normal thyroglobulin levels in the other. **Conclusion:** The newly identified TSHR-mutation Ala579Val widens the phenotypical spectrum of thyroid dysgenesis to agenesis of the thyroid gland. TSHR-mutations need to be considered also in cases with athyreosis, especially in a consanguineous family. The TSH receptor seems to play a critical role in thyroid development as shown by the variable manifestation in this family.

FC13.3

Overexpression of Suppressor Tumoral PTEN, but not DREAM, was Detected in Multinodular Goiter in Humans

Amanda Shinzato^a, Antonio M Lerario^a, Debora S Danilovic^a, Suemi Marui^a, Chin J Lin^b, Ericka B Trarbach^a

^aLaboratorio de Endocrinologia Celular e Molecular – LIM25, HCFMUSP, Sao Paulo/Sao Paulo, Brazil; ^bLaboratorio de Patologia Cardiovascular – LIM22, Sao Paulo/Sao Paulo, Brazil

Background: A high proliferative status of thyroid follicular cells and goiter were observed in mutants mice with *Pten* –/– or *Dream* overexpression. In humans, patients with Cowden disease have goiters or other thyroid abnormalities associated with germ-line *PTEN* mutations. **Objective and Hypotheses:** The aim of this study was to investigate the tissue expression of *PTEN* and *DREAM*, as well as germ-line and somatic *PTEN* and somatic *DREAM* mutations, in patients with multinodular goiter (MNG) to evaluate the role of these genes in goitrogenesis. **Methods:** We investigated 60 MNG patients (55 females). Relative quantification of *PTEN* and *DREAM* mRNA from hyperplastic thyroid tissue was evaluated by real-time PCR. *PTEN* and *DREAM* over and lower expression were respectively defined by value ≥ 2.0 - and ≤ 0.5 -fold. Mutations analyses were performed by PCR amplification followed by automatic sequencing. RQM, relative quantification median. **Results:** We observed a high expression of *PTEN* in 56.7% of MNG with RQM of 3.3 (s.d. = 1.4), and only one case with lower expression (RQ = 0.27). In the remaining cases (41.7%), *PTEN* expression was normal (RQM = 1.30; s.d. = 0.33). In fact, *PTEN* had been shown to be overexpressed in benign proliferative and typical endometrium hyperplasia, with loss expression related only to carcinomas and precancerous lesions. For the *DREAM* gene, the most cases of MNG (63.4%) had normal expression with RQM of 1.21 (s.d. = 0.37). Over and lower expression of this gene were observed in 28.3% (RQM = 3.5; s.d. = 5.7) and 10% (RQM = 0.4; s.d. = 0.14) of the cases, respectively. Regarding *PTEN* and *DREAM* mutations analysis, only previously described intronic polymorphisms were observed in DNA from blood and/or thyroid hyperplastic tissue. **Conclusions:** Our results demonstrated that *PTEN* expression is higher in MNG suggesting that this gene is overregulated (or at least has its expression maintained) in this benign hyperplastic thyroid lesions. No evidence for the involvement of *DREAM* in pathogenesis of human goiters was observed.

FC13.4

The Prevalence of Congenital Malformations in Infants with TSH Elevation on Newborn Screening: the Importance of Distinguishing Between True and Transient Congenital Hypothyroidism

Yasmine Ouarezki^a, Chourouk Mansour^b, Jeremy Jones^c, Abubaker alghanay^d, Sarah Smith^e, David Stone^c, Malcolm Donaldson^c

^aEPSP BARAKI, Algiers, Algeria; ^bHopital Universitaire A.Harouchi, Casablanca, Morocco; ^cChild Health Glasgow School of Medicine, Glasgow, UK; ^dUniversity Hospital of Wales, Cardiff, UK; ^eScottish Newborn Screening Laboratory, Glasgow, UK

Backgrounds: The prevalence of congenital malformations (CM) is higher in infants referred with capillary (c) TSH elevation on newborn screening. However, establishing the prevalence of CM \pm dysmorphic syndromes in true congenital hypothyroidism (CH) requires careful distinction between true and transient CH. **Objective:** To determine the prevalence of CM \pm dysmorphic syndromes in all infants referred with TSH elevation on newborn screening in Scotland since 1979 according to strictly defined diagnostic categories and dividing infants with CM into cardiac, extra-cardiac, cardiac and extra-cardiac \pm associated syndromes (including Down (DS) and unclassified (UC)); and infants with syndromes without accompanying CM. **Methods:** The diagnostic categories were: i) Definite CH: thyroid dysgenesis or dysmorphogenesis on imaging, or venous (v) TSH > 50 mu/l and TT₄/fT₄ subnormal in an otherwise healthy term infant, or vTSH > 10 mu/l on LT₄ replacement after first year of life; ii) Probable CH – vTSH > 50 mu/l with normal TT₄/fT₄ in a healthy term infant; iii) status uncertain – criteria for true and probable CH not met, infant unwell \pm CM and/or dysmorphism; iv) Transient TSH elevation – cTSH elevation with subsequent normal thyroid function off treatment. **Results:** Between August 1979 and March 2014 903 infants were referred with cTSH elevation and categorised as Definite (548), Probable (41) CH, status uncertain (97), and Transient TSH elevation (182) (data insufficient in 35). Breakdown of CM in the Definite CH group was: cardiac 7 (1.2%) (1 DS); extra-cardiac 14 (2.5%), cardiac and extra-cardiac 2 (0.4%), syndromes 8 (1.4%) (Pendred (2), PTH resistance (2), Sotos, Beckwith, Translocation 14/15, UC); for the Status Uncertain group: cardiac 17 (17.5%) (11 DS, DiGeorge, Williams), extra-cardiac 6 (6%), cardiac and non-cardiac 9 (9%) (6 DS, trisomy 18, UC), six syndromes (all DS); and for the Transient TSH elevation group: cardiac 7 (3.8%) (2 DS), extra-cardiac 19 (10.4%) (DS 2, UC), cardiac and extra-cardiac 6 (3.3%) (DS 2, UC), syndromes 3 (1.6%) (Turner, Kabuki, UC). **Conclusion:** The prevalence of cardiac and all CM for true CH in Scotland is 1.2 and 5.6% compared with 0.8 and 2.6% for European population. This is much lower than for Transient TSH elevation (19.2%) and Status Uncertain (39%) and underlines the need for rigorous diagnosis, with retesting of doubtful cases after 3 years of age.

FC13.5

The Ultrastructural Changes in Thyroid Cells in the Course of Damage in Hashimoto's Thyroiditis

Iwona Ben-Skowronek^a, Leszek Szewczyk^a, Elzbieta Korobowicz^b

^aMedical University Department of Paediatric Endocrinology and Diabetology, Lublin, Poland; ^bMedical University Department of Pathomorphology, Lublin, Poland

Background: The development of the Hashimoto's thyroiditis is the result of the damage to thyrocytes, apoptosis, and

autoimmune cytotoxic action of lymphocytes. **Objective and Hypotheses:** The aim of the study is to present ultrastructural changes in thyroid cells in the course of damage in Hashimoto's thyroiditis. **Method:** The study involved 40 children: 20 children with Hashimoto's thyroiditis and 20 children as a control group. Specimens for ultrastructural investigations were obtained during thyroidectomy. Ultrathin sections were contrasted with uranyl acetate and lead citrate and examined under the EM 900 Zeiss Germany Electron Microscope. **Results:** In the control group, the thyroid follicular cells were cuboidal or cylindrical and were lying on a thin basement membrane. Varied degrees of apoptosis were observed in the Hashimoto's thyroiditis patients. The basement membrane of the follicles was thickened by deposition of numerous collagen fibres. The thyrocytes had irregular cell nuclei and an increased number of mitochondria in the basal pole. Different stages of thyrocyte necrosis were visible at the sites of contact between lymphocytes or plasma cells and thyrocytes. The nuclei of dying thyroid cells were deformed, the cisterns of the endoplasmic reticulum were swollen, and the cell membrane disrupted. **Conclusion:** Ultrastructural examinations of thyroid sections sampled from patients with Hashimoto's thyroiditis suggest the following stages of process thyrocyte damage: thickening of the basement membrane caused by collagen deposition, thyrocyte apoptosis, stimulation of lymphocytes and plasma cells to cytotoxic reactions, and necrosis of thyrocytes damaged by the cytotoxic reaction.

FC13.6

Abnormal Thyroid Hormone Metabolism in Patients with THRA Mutations due to Impaired Expression of the Type 3 Deiodinase

Anja van Gucht^a, Alies van Mullem^a, Sigrun Horn^b, Marcel Meima^a, Douglas Forrest^c, Ramona van Heerebeek^a, Edward Visser^a, Heike Heuer^b, Robin Peeters^a, Theo Visser^a

^aErasmus University Medical Center, Rotterdam, The Netherlands; ^bLeibniz Institute for Age Research/Fritz Lipmann Institute, Jena, Germany; ^cLaboratory of Endocrinology and Receptor Biology, NIDDK, NIH, Bethesda, Maryland, USA

Background: Patients with a mutation in the thyroid hormone (TH) receptor TR α 1 are characterized by growth retardation, delayed bone development, mild cognitive defects and constipation. They also have abnormal TH levels: low FT₄, high T₃, and low rT₃ levels, suggesting an altered peripheral TH metabolism by deiodinases. The type 3 deiodinase (D3) inactivates TH by catalyzing the degradation of T₃. D3 is importantly expressed in brain under positive control of T₃. **Objective and Hypotheses:** From this perspective we hypothesized that changes in serum TH levels in TR α 1 patients are due to dysregulation of D3 activity. Our objective was to investigate the role of TR α 1 in the regulation of D3 in brain by T₃. **Method:** We determined the activity of brain D3 as well as serum TH levels in WT mice, mice with a

heterozygous dominant-negative mutation in TR α 1 (TR α 1PV), mice deficient in TR α 1 (TR α 1KO), mice deficient in TH (PAX8KO), and mice lacking both TH and TR α 1 (PAX8/TR α 1DKO). In addition, we studied the D3 promoter activity *in vitro*. **Results:** Compared with WT mice, both TR α 1PV and PAX8KO mice showed a 45% reduction in brain D3 activity. D3 activity was 37% higher in TR α 1KO than in WT mice. Additional deletion of PAX8 in the TR α 1KO background only reduced brain D3 activity by 18%, indicating that D3 activity is predominantly regulated by TR α 1. In cultured neurons, transfection of WT TR α 1 increased D3 promoter activity in the presence of T₃, whereas transfection of TR α 1 with the patient's mutation or of the TR β 1 isoform had no effect. **Conclusion:** These findings show that TR α 1 plays a major role in the positive regulation of D3 by TH in brain. This suggests that the changes in TH levels in patients with a TR α 1 mutation are at least in part due to an impaired D3 activity.

FC14.1

Brain Structure and Function in Gender Dysphoric Adolescents

Sabine Hannema^a, Sebastian Schagen^{a,b}, Eline Hoekzema^c, Baudewijntje Kreukels^b, Dick Veltman^b, Peggy Cohen-Kettenis^b, Julie Bakker^{c,d}, Henriette Delemarre-van de Waal^a

^aLeiden University Medical Centre, Leiden, The Netherlands; ^bVU University Medical Centre, Amsterdam, The Netherlands; ^cNetherlands Institute for Neuroscience, Amsterdam, The Netherlands; ^dUniversité Liège, Liège, Belgium

Background: Gender dysphoria is characterised by an incongruity between the perceived gender identity and the biological sex. The cause of gender dysphoria is unclear and environmental as well as genetic factors may be important. It is well known that during sexual differentiation sex steroids control not only the differentiation of the internal and external genitalia but also the sexual differentiation of the brain. Structural as well as functional differences have been shown between the male and female brain. **Objective and Hypotheses:** We hypothesised that this sexual differentiation of the brain may be atypical in children and adolescents with gender dysphoria. **Method:** We analysed brain MRI scans of 91 gender dysphoric adolescents (54 female-to-male and 37 male-to-female) for differences in gray matter volume using voxel based morphometry. Data of gender dysphoric individuals were compared to controls (44 boys and 52 girls). In addition fMRI scans were acquired of gender dysphoric adolescents and controls while performing cognitive tasks (mental rotation and tower of London). **Results:** Voxel based morphometry showed six sexually dimorphic areas, three male and three female dominant. The gray matter volume in these areas in gender dysphoric individuals was in between male and female values, showing a pattern of volumes being larger in females than female-to-males than males-to-females than males, or *vice versa*. Performance on the cognitive tasks was similar in males and

females. fMRI scans did however show sexually dimorphic activity levels in certain brain areas. Again, activity levels in these brain areas in gender dysphoric individuals were in between those of males and females. **Conclusion:** Structural and functional differences between the male and female brain are already obvious in adolescence. In individuals with gender dysphoria subtle differences in brain structure and function were identified compared to controls of the biological sex.

FC14.2

Infancy Growth Rate Predicts Timing of Puberty Both in Girls and Boys

Banu Kucukemre Aydin^a, Esra Devecioglu^b, Sezin Kisabacak^a, Alev Kadioglu^c, Gulbin Gokcay^b, Firdevs Bas^a, Sukran Poyrazoglu^a, Ruveyde Bundak^a, Nurcin Saka^a, Feyza Darendeliler^a

^aPediatric Endocrinology Unit, Department of Pediatrics, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey; ^bSocial Pediatrics Unit, Department of Pediatrics, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey; ^cALKA Radio-diagnostics Center, Istanbul, Turkey

Introduction: Rate of weight gain during early childhood may have an effect on timing of puberty in girls. Biological mechanisms underlying this condition are not fully understood. Studies examining this association in boys report contradictory results. Our aim was to examine the effects of growth rate during the first years of life on the onset of puberty both in girls and boys. **Description of methods:** 159 children aged between 6 and 9 years who were attending the Well Child Clinic between the ages of 1 month and 5 years were included in the study. Anthropometric measurements during the follow-up were obtained from children's files. Weight, height, waist and hip circumferences were measured and pubertal staging was done at the time of investigation at a mean age of 7.6 ± 0.9 years. Blood samples for LH, FSH and estradiol/testosterone were collected. Breast and pelvic ultrasonography was done. **Results:** 21.2% of girls had breast enlargement before the age of 8 years, 17.6% had breast enlargement between 8 and 9 years, and 7.1% had premature pubarche. 12.2% of boys had testicular enlargement starting before the age of 9 years and 7.1% had premature pubarche. The average BMI SDS and waist circumference SDS of girls demonstrating findings of puberty were significantly higher ($P=0.001$ and $P=0.03$). Girls having an accelerated weight gain between 6 and 15 months of age demonstrated precocious puberty signs more often ($P=0.007$) and at the ages of 6–9 years their average BMI SDS were higher compared to the peers ($P=0.01$). Boys having an accelerated linear growth between 9 and 15 months of age demonstrated pubertal findings more frequently ($P=0.004$). **Conclusions:** Our results suggest that early growth acceleration is important for the timing of puberty in both sexes but the girls and boys with precocious puberty showed different growth patterns and probably different mechanisms.

FC14.3

Novel Genetic Variants in a Cohort of Paediatric and Adolescent Patients with Hypogonadotrophic Hypogonadism and Kallmann Syndrome

Louise Gregory^a, Mark McCabe^a, Rodrigo Bancalari^b, Vaya Tziaferi^a, Helen Spoudeas^c, Mehul Dattani^{a,c}

^aUCL Institute of Child Health, London, UK; ^bPediatrics Department of Universidad Catolica de Chile, Santiago, Chile; ^cGreat Ormond Street Hospital for Children, London, UK

Background: Hypogonadotrophic hypogonadism (HH) is a complex developmental disorder characterized by a reduction in gonadotrophins (LH, FSH) released from the anterior pituitary. LH and FSH stimulate the ovaries or testes to release sex hormones that cause the onset of puberty, therefore delay in onset or complete absence of puberty is seen in the phenotype, often accompanied by short stature and genital abnormalities. When anosmia accompanies HH in the phenotype it is termed Kallmann syndrome (KS). **Objective and Hypotheses:** We screened 63 HH/KS patients in our cohort for variants in *KAL1*, *PROKR2*, *FGFR1* and *FGF8*. **Method:** Using PCR and direct sequencing analysis. **Results:** We identified four variants in *KAL1* and *FGFR1*, two of which were novel. A hemizygous missense substitution, *KAL1* c.257G>A, p.C86Y, was identified in a male KS patient. A heterozygous base pair deletion causing a frameshift, *FGFR1* c.915delG, p.(Leu305LeufsX6), was identified in two siblings with KS: one male with cleft lip/palate, anosmia and short stature and one female with anosmia and microform cleft lip. The father is the heterozygous carrier, and is clinically unaffected. Two previously described variants, with unknown functional consequence, have also been identified in our cohort: a hemizygous early stop codon, *KAL1* c.1267C>T, p.R423X, in a KS patient and a heterozygous missense substitution, *FGFR1* c.2059 G>A, p.G687R in a male HH patient. His mother had primary amenorrhoea and carries the variant. All four variants are located at highly conserved residues across multiple species and absent from any control databases. **Conclusion:** We report two novel and two previously described variants in two different candidate genes in a cohort of HH/KS patients. The potential genetic cause remains unknown in 94% of this cohort, signifying the need for further investigation into genes involved in GnRH neuronal development and migration and potentially responsible for the pathogenicity. Studies are currently on-going.

FC14.4

Development of Pubertal Gynaecomastia: a Longitudinal Cohort Study

Mikkel G Mieritz, Casper P Hagen, Anders Juul

Department of Growth and Reproduction, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

Background: Pubertal gynaecomastia (PG) is considered a clinical sign of an oestrogen–androgen imbalance at the breast

tissue level although little evidence exists. PG occurs in 40–60% of adolescent Caucasian boys, and in most cases however, no underlying endocrinopathy can be identified. Very few longitudinal studies on PG exist. **Objective and method:** As a part of the longitudinal COPENHAGEN Puberty Study we followed 110 healthy Danish boys (aged 5.8–16.4 years) in a prospective cohort over 7 years with semi-annual examinations including blood samples (FSH, LH, testosterone, estradiol, SHBG, and IGF1), to assess the development of pubertal gynaecomastia by palpation. The boys each had from two to 14 examinations. Anthropometry and pubertal stages (PH1–6 and G1–5) were evaluated, testicular volume was determined using Prader's orchidometer, and the presence of gynaecomastia was assessed. **Results:** A total of 949 examinations were carried out and PG was present at 107 of the examinations. 50 of the boys (45%) of the boys developed gynaecomastia during the 7 years period. Median age at first examination with PG was 13.3 years (ranging from 10.8 to 15.3 years), and the median genital stage was G3 (ranging G2–G5). The average testicular volume at presentation was 12 ml (ranging from 4 to 25 ml). In addition two boys G1 but pubic hair stage PH2 presented with gynaecomastia at age 12.0 and 12.5 years, respectively. Twelve of the boys had intermittent gynaecomastia with one or more intermediate examinations without the presence of gynaecomastia follow by examinations with palpable gynaecomastia. To our knowledge this is the first report of a 'coming and going' breast phenomenon in adolescent boys, which may result from difficulties in palpation of glandular breast tissue, especially in obese boys, but could also reflect a biological phenomenon due to fluctuating sex steroid levels.

FC14.5

Fertility of Women Treated During Childhood for Precocious Puberty with Triptorelin: PREFER Retrospective Study

Jean-Claude Carel^a, Jacques de Mouzon^b, Joëlle Blumberg^c

^aDepartment of Paediatric Endocrinology and INSERM CIE-5, Paris, France; ^bINSERM Hôpital Bicêtre, Le Kremlin Bicêtre, France; ^cIpsen Pharma, Paris, France

Introduction: There are few published large-cohort studies examining the long-term impact of GnRH analogue treatment for precocious puberty (PP) on fertility in women. The PREFER study analysed fertility in a large cohort of women treated during childhood for PP with triptorelin. **Methods:** PREFER was a longitudinal, descriptive, non-comparative, epidemiological study conducted in 23 centres in France between February 2007 and November 2009. Women aged ≥ 18 years (in 2006) treated during childhood for PP with triptorelin were included, and their fertility was examined during the 2 years prior to inclusion and during the 12-month follow-up period. Primary endpoints were the proportion of women wanting a pregnancy but not pregnant 6 and 12 months after stopping contraception, and waiting time to pregnancy (WTP; time between stopping contraception and

becoming pregnant). Secondary endpoints will also be presented. Endpoints were measured via self-reported questionnaires. **Results:** 212 women aged (mean \pm s.d.) 24.2 ± 3.0 years were included. They had received triptorelin therapy for 2.4 ± 1.2 years during childhood. At least 57 (26.9%) women were pregnant before or during the study; 64 pregnancies were described, of which 60% were wanted pregnancies. In the 2 years before inclusion, the proportion of pregnancies with a < 1 -year WTP (32/37, 86.5%–59.5% and 45.9% occurred within 6 and 3 months, respectively) was similar to that published for couples without PP trying to conceive ($\sim 85\%$). At 12-month follow-up, 108/109 (99.1%) respondents had not consulted a physician in the preceding 6 months regarding difficulties conceiving; one (1/107; 0.9%) woman received treatment to become pregnant. **Conclusion:** PREFER is a large cohort study looking at the long-term effects on fertility of triptorelin treatment for PP. The pregnancy rate for women treated during childhood for PP with triptorelin suggests that PP or its treatment do not impact subsequent fertility in adulthood.

FC14.6

Quality of Life in Patients with Congenital Hypogonadotropic Hypogonadism

Tero Varimo^a, Matti Hero^a, Eeva-Maria Laitinen^a, Harri Sintonen^c, Taneli Raivio^{a,b}

^aChildren's Hospital, Helsinki University Central Hospital, Helsinki, Finland; ^bInstitute of Biomedicine/Physiology, University of Helsinki, Helsinki, Finland; ^cDepartment of Public Health, University of Helsinki, Helsinki, Finland

Background: Little is known about the burden of disease, as evaluated by health related quality of life (HRQoL), in patients with congenital hypogonadotropic hypogonadism (CHH). We characterized the (HRQoL) in a relatively large and well-characterized population of patients with CHH using the 15D, a comprehensive preference-based generic instrument in sampling dimensions for the construct of HRQoL. 15D covers most of the 'domains of health' emphasized in the WHO International Classification of Functioning, Disability and Health (ICF). **Objective and Hypotheses:** To evaluate the HRQoL in CHH. **Method:** We investigated the HRQoL in 40 subjects (31 men and 9 women) with CHH using the Finnish 15D instrument. The mean age in men was 38.1 (range 16–61) and in women 32.7 (16–45) years. Kallmann syndrome was diagnosed in 30 (75%) and normosmic CHH in 10 (25%) patients. The results of CHH patients were compared with those of age- and sex-matched general population. $P < 0.01$ was considered statistically significant. **Results:** CHH patients had significantly lower scores in the depression and distress domains as compared to general population controls (Fig. 1). **Conclusion:** As compared with general Finnish population, CHH is associated with decrements in depression and distress dimensions of HRQoL. Our findings support the inclusion of screening for depression in the medical

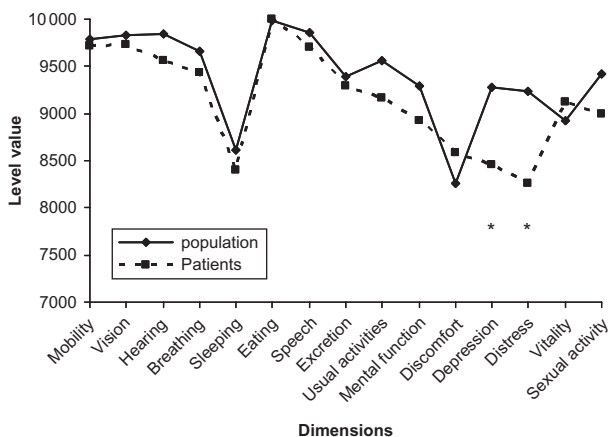


Figure 1 15D dimension scores in CHH patients and age- and sex-matched population controls. The scale ranges from 0 to 1. The smaller the level value, the more severe problems. The difference of 0.03 is considered clinically significant. $(P < 0.01)$.

follow-up of patients with CHH. Longitudinal studies of HRQoL in CHH are needed for confirming our finding, and for evaluating whether factors such as poor adherence to hormone replacement therapy or problems with transition to adult services increase the risk of poor HRQoL.

FCLB1

Top Line Results of Once-Weekly, CTP-Modified Human GH (MOD-4023): Phase 2 Dose Finding Study in Children with GH Deficiency

Zvi Zadik^a, Ron Rosenfeld^b, Klaudziya Radziuk^d, Nataliya Zelinska^e, Oleg Malievsky^f, Violeta Iotova^c, Julia Skorodok^f, Ronit Koren^b, Leanne Amitzi^b, Gili Hart^b, Oren Herskovitz^b, Eyal Fima^b

^aKaplan Medical Center, Rehovot, Israel; ^bOPKO BIOLOGICS, Nes Ziona, Israel; ^cUMHAT 'Sv. Marina', Varna, Bulgaria; ^d2nd Children City Clinic, Minsk, Belarus; ^eUkrainian Children Specialized Clinical, Kyev, Ukraine; ^fSt Petersburg State Pediatric Medical Academy, St Petersburg, Russia; ^gBashkir State Medical University, Ufa, Russia

Objective: 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 for once-weekly administration in GH deficient (GHD) adults and children. Pharmacokinetics (PK), pharmacodynamics, (PD) efficacy and safety analysis of weekly treatment with MOD-4023 in GHD naïve children was performed and compared to daily hGH. **Design and methods:** A randomized, controlled Phase 2 study was conducted in up to 56 pre-pubertal, naïve GHD children receiving S.C. injections of one of MOD-4023 doses as a once-weekly regimen (range: 0.25–0.66 mg/kg per week) or daily hGH (34 µg/kg per day) as a control arm. MOD-4023 and IGF1 levels were monitored throughout the study. Annualized Height Velocity (HV) assessment was evaluated at 6, 9 and 12 months.

Results: The baseline characteristics were comparable between all groups. PK/PD profile following administration of MOD-4023 demonstrated a significantly extended half-life as reflected by a 12- and 50-fold increase in T1/2 and AUC respectively. A dose dependent PK/PD (IGF1) response was observed between MOD-4023 dose cohorts, reaching steady state with no accumulation or excessive levels. All cohorts demonstrated expected 'catch-up' growth, in line with reported age- and GHD severity-matched data. All cohorts demonstrated 6 m annualized HV above 12 cm/year, correlated with the PK/PD profile in those patients. No unexpected adverse events were observed. **Conclusions:** This is the first report describing PK, PD, efficacy and safety results of extended treatment with MOD-4023 in pediatric patients with GHD. MOD-4023 administration to GHD children further confirmed its long acting properties. This study further affirmed that a single weekly injection of MOD-4023 has the potential to replace seven consecutive daily injections of currently marketed hGH in pediatric GHD patients and provided data for dose selection for the company's upcoming Phase 3 trial.

FCLB2

Sonic Hedgehog is Required for Cell Specification of Rathke's Pouch Progenitors During Normal Development and is Over-Expressed in Adamantinomatous Craniopharyngioma

Gabriela Carreno^a, Cynthia Andoniadou^b, Wendy Heywood^a, Kevin Mills^a, Mehul Dattani^a, Juan Pedro Martinez-Barbera^a

^aUniversity College London, London, UK; ^bKings College London, London, UK

Background: Mouse studies have demonstrated the necessity of Sonic Hedgehog (SHH) for normal proliferation of Rathke's pouch (RP) precursors. However, the possible function of SHH in pituitary cell specification remains to be assessed. Additionally, evidence suggests that SHH may be relevant in human adamantinomatous craniopharyngioma (ACP), a histologically benign, but clinically aggressive childhood tumour associated with high morbidity. **Objective and Hypotheses:** To determine the function of SHH during normal pituitary development and in human ACP. Specifically, we aim to test whether:

i) SHH is relevant for cell specification during pituitary development. ii) SHH is expressed in human ACP and involved in its pathogenesis. **Method:** i) Conditional deletion of *Shh* in the developing pituitary and ii) murine models of human ACP as well as chemical inhibition of *Shh* in the ACP models. **Results:** We firstly show that the conditional deletion of *Shh* in the hypothalamus causes a severe arrest of RP development with complete loss of pituitary tissue by 12.5 days post coitum. Molecular analyses have shown that *Shh* is not only required for normal proliferation as previously suggested, but in addition, its plays a critical role in the specification of RP precursors. In the absence of hypothalamic SHH signalling, expression of *Lhx3* and *Lhx4* is not activated, whilst *Islet 1* and *Pitx1* are normally

expressed in RP. Secondly, we show by *in situ* hybridisation analysis on more than 20 ACP samples that *SHH* is expressed in the β -catenin-accumulating cell clusters, whilst *PTCH1*, a direct target of the pathway, is expressed in surrounding tumour cells. Moreover, using a novel multiple-reaction-monitoring tandem mass spectrometry-based assay, SHH protein is detected in human ACP, strongly suggesting that biologically active SHH is present within the tumours. **Conclusion:** SHH is required for cell specification of RP precursors and is expressed in human ACP.

FCLB3

Parent-of-Origin Specific Allelic Associations Among 106 Genomic Loci for Age at Menarche

John Perry^a, Felix Day^a, Cathy Elks^a, Patrick Sulem^b, Kari Stefansson^b, Joanne Murabito^c, Ken Ong^a

^aUniversity of Cambridge, Cambridge, UK; ^bdeCODE Genetics, Reykjavik, Iceland, Boston; ^cUniversity School of Medicine, Boston, Massachusetts, USA

Background: Age at menarche in girls varies widely between individuals, is a heritable trait and is associated with risks for adult obesity, type 2 diabetes, cardiovascular disease, breast cancer and all-cause mortality. **Objective and Hypotheses:** The mechanisms that determine pubertal timing and underlie its links to later disease remain unclear. **Method:** We performed a genome-wide association study meta-analysis of genome-wide or dense custom-genotyping arrays in up to 182 416 women of European descent from 57 individual studies. Evidence for parent-of-origin specific allelic associations at imprinted loci was tested in a unique cohort of 35 377 women whose allelic parental origins had been determined by a combination of genealogy and long-range phasing. **Results:** We found robust evidence ($P < 5 \times 10^{-8}$) for 123 independent signals at 106 genomic loci associated with age at menarche. Many loci were associated with other pubertal traits in both sexes, and there was substantial overlap with genes implicated in BMI and various diseases, including rare disorders of puberty. Menarche signals were enriched in imprinted gene regions compared to published genome-wide-significant signals for all other traits (6/123, 4.8% vs 75/4332, 1.7%; $P = 0.017$). Three imprinted menarche loci (*DLK1/WDR25*, *MKRN3/MAGEL2*, and *KCNK9*) demonstrated parent-of-origin specific associations concordant with their known parental expression patterns. Other findings implicated lysine-specific histone demethylases and nuclear hormone receptors, particularly retinoic acid and γ -aminobutyric acid-B2 receptor signalling, among novel mechanisms that regulate pubertal timing in humans. **Conclusion:** Our findings indicate both BMI-related and BMI-independent mechanisms that could underlie the epidemiological associations between early menarche and higher risks of adult disease. Of note, only few parent-of-origin specific allelic associations at imprinted loci have been described for complex traits. Our findings implicate differential pubertal timing, a trait with putative selection advantages, as a potential additional target for the evolution of genomic imprinting.

FCLB4

Does Severity of Hypothyroidism at Birth Contribute to Abnormal Cortical Development among Children with Congenital Hypothyroidism?

Joanne Rovet^{a,b}, Hayyah Clairman^b, Jovanka Skocic^b

^aUniversity of Toronto, Toronto, Ontario, Canada; ^bHospital for Sick Children, Toronto, Ontario, Canada

Background: Despite early detection and treatment, children with Congenital Hypothyroidism show subtle persisting deficits in various cognitive abilities. Degree and type of deficit reflect CH severity at time of diagnosis. We reported (Rovet *et al.*, ATA, 2012) children with CH had abnormal cortical morphology, consistent with animal evidence showing early thyroid hormone (TH) insufficiency affects cortical development. It is not known, however, whether these cortical abnormalities reflect hypothyroidism severity at diagnosis. **Objective:** To correlate indices of cortical morphometry and CH severity at birth. **Method:** 41 CH and 42 controls matched for age and sex (age = 9–16 years) were assessed for intelligence and memory and received a 1 h MR scan. Scans were analyzed using FreeSurfer to determine cortical thickness (CT) levels; CT values were correlated with TSH and T₄ levels at diagnosis, compared by CH etiology, and correlated with test results. **Results:** Lower T₄ and higher TSH at diagnoses were associated with i) cortical thinning in the right superior and middle frontal gyrus, left superior temporal gyrus, right inferior parietal gyrus and parieto-occipital sulcus, and left lateral fissure and ii) cortical thickening in left superior frontal gyrus and middle frontal sulcus, right postcentral gyrus, right inferior temporal sulcus, left calcarine sulcus. Children with athyrotic etiology showed thinning of right occipital gyrus and thickening of left middle frontal and inferior parietal gyri relative to ectopic etiology. Lower IQ was associated with thickening or left middle frontal gyrus and superior frontal gyrus and poorer delayed visual memory performance with thickening of left superior frontal and temporal gyri and right superior parietal and occipital gyri. **Conclusion:** Early TH insufficiency in CH prior to treatment onset contributes to abnormal cortical morphology in critical brain regions for intellectual and other cognitive functions.

FCLB5

CB2 Polymorphism Could Modulate the Relationship Between Childhood Obesity and Age at Menarche

Anna Grandone, Giulia Bellini, emanuele Miraglia del Giudice, Laura Perrone, Francesca Rossi

Second University of Naples, Naples, Italy

Background: There is an emerging evidence that the ovary may be an important site where genes such as *LIN28b*, whose polymorphisms has been strongly associated to age at menarche, could modulate the timing of puberty. Recent data suggest that the

endocannabinoid system plays a role in folliculogenesis and ovulation, through cannabinoid receptor 2 (CB2) expressed in the ovary. On the other hand childhood obesity is associated with increased likelihood of early menarche, probably for the increased bioavailability of sex hormones. **Objective and Hypotheses:** We aimed to investigate the association of the functional variant Q63R of CB2 in influencing age at menarche in obese girls. **Method:** We studied 240 girls (age, 11.9 ± 3 years; BMI z-score, 2.8 ± 0.8). Age at menarche was recorded at the time of the visit if already occurred or asked by phone-call. The *CNR2* rs35761398 variant has been detected by TaqMan assay. **Results:** One hundred and five patients were homozygous for R allele (R63), 113 were Q63R and 22 were Q63. Variance analysis showed a significantly earlier age of menarche in subjects carrying the Q allele, also adjusting for BMI z-score (11 ± 1.2 vs 11.6 ± 1.2 years; $P: 0.0016$). Logistic regression analysis showed that carriers of the Q allele had 2.05 times higher risk (OR 2.05; CI: 1.21–3.45; $P: 0.0068$) to present with an early menarche (age at menarche, < 12 years). **Conclusion:** We demonstrated for the first time the association between rs35761398 polymorphism in *CNR2* gene and age at menarche in a cohort of Italian obese girls. We hypothesize that the CB2 receptor may be part of the pathway that mediates the ovary response to peripheral estrogens and the more functional variant (Q63) could enhance the ovary response to estrogens. In obese girls this mechanism may contribute in determining early menarche both affecting the initiation of puberty and the rate of progression through puberty.

FCLB6

Global Consensus Recommendations on Prevention and Management of Nutritional Rickets

Craig Munns^a, Nick Shaw^b, Mairead Kiely^c, Bonny Specker^d,
Thomas Thacher^e, Wolfgang Hogler^b

^aThe Children's Hospital at Westmead, Sydney, New South Wales, Australia; ^bBirmingham Children's Hospital, Birmingham, UK;

^cUniversity College, Cork, Ireland; ^dSouth Dakota State University, Brookings, South Dakota, USA; ^eMayo Clinic, Rochester, New York, USA

Background: Vitamin D and/or calcium deficiency are very common in many areas worldwide, causing nutritional rickets, osteomalacia, hypocalcaemic seizures, cardiomyopathy, and muscle weakness. Nutritional rickets is defined as impaired mineralization at the growth plate. Untreated rickets leads to bone deformity, disability, obstructed labor, and reduced quality of life. The prevalence of nutritional rickets is increasing globally. **Objective and methods:** 33 nominated experts in paediatric endocrinology, pediatrics, nutrition, epidemiology, public health, and health economics were allocated to working groups with assigned topics and specific questions. A systematic literature search was conducted to identify key articles relating to the definition, diagnosis, risk factors and strategies for prevention and management of nutritional rickets and osteomalacia. Each group evaluated the evidence using the GRADE system and met for a multi-day conference at the end of May 2014 to reach a global evidence-based consensus. **Results:** The consensus group established definitions for rickets, vitamin D and calcium deficiency; intakes of vitamin D and calcium required for prevention and treatment of rickets and osteomalacia including women of childbearing age, pregnancy and lactation, and identification of risk groups who benefit from screening and supplementation. The group also developed a number of recommendations. Women of childbearing age, particularly during pregnancy, should meet their recommended intakes of calcium and vitamin D. All infants should be supplemented with 400 IU/day of vitamin D until 12 months of age, and calcium-rich foods should be introduced no later than 6 months. Food fortification with vitamin D is recommended to increase average population intakes to 400 IU/day, a level that would eradicate rickets and osteomalacia. **Conclusion:** Nutritional rickets, a fully preventable disorder, is on the rise worldwide and should be regarded as a global epidemic. We advocate for eradication of rickets and osteomalacia through implementation of international vitamin D supplementation and food fortification programs.

Poster Presentations

P1-D2-1

Allelic Frequencies of CYP21A2 Variants and Genotype–Phenotype Correlations in a Cohort of 660 CAH Patients from Germany and Austria[☆]

Stefan Riedl^{a,b}, Friedrich-Wilhelm Röhl^c, Susann Empting^d,
Walter Bonfig^e, Helmuth-Günther Dörrf, Reinhard Holl^g,
Klaus Mohnike^d

^aSt Anna Children's Hospital, Medical University of Vienna, Vienna, Austria; ^bDepartment of Pediatric Pulmology, Allergology, and Endocrinology, Medical University of Vienna, Vienna, Austria; ^cInstitute of Biometry and Medical Informatics, Otto-von-Guericke University Magdeburg, Magdeburg, Germany; ^dDepartment of Pediatrics, Otto-von-Guericke University Magdeburg, Magdeburg, Germany; ^eDepartment of Pediatrics, Technical University Munich, Munich, Germany; ^fDepartment of Pediatrics and Adolescent Medicine, Friedrich-Alexander University Erlangen-Nuremberg, Erlangen, Germany; ^gInstitute of Epidemiology and Medical Biometry, University of Ulm, Ulm, Germany

Background: Congenital adrenal hyperplasia (CAH) due to a CYP21A2 defect (autosomal recessive) leads to salt wasting (SW), simple virilizing (SV), or non-classical (NC) phenotypes basically depending on residual 21-hydroxylase (21-OH) function on the least affected allele. **Objective and Hypotheses:** To test prediction of CAH phenotype based on genotype classification. **Method:** Patient data from 37 centers were retrieved from a central data base as part of a German quality assurance program (AQUAPE) within the German Association for Pediatric Endocrinology and Diabetes (DGKED). Allelic frequency and distribution of the 11 most common CYP21A2 mutations and deletions/conversions were analysed in 660 homozygous or compound heterozygous CAH patients. Clinical phenotypes as classified by the treating physician were compared with predicted phenotypes derived from genotype classification according to magnitude of residual 21-OH function (group null=0%; group A=0–2%; group B=2–5%; and group C=20–60%). **Results:** Allelic frequency of mutations was comparable to previous studies, with deletions/conversions (29.6%) and I2G (29.2%) being the most common, followed by I172N (13.1%). Complete genotype–phenotype data sets were available in 547 patients. Severe genotypes (null and A) correlated well with clinical phenotype (SW in 97 and 91% respectively), whereas weaker genotypes (B and C) showed poor correlation with expected phenotype (SV in 45% and NC in 57% respectively), underestimating clinical severity, specifically associated with I172N and P30L. In C genotypes, this was underlined by the degree of virilization (Prader stage > 1 in 28%). In A and B genotypes, a null-mutation on the second allele increased the risk of a more severe phenotype significantly. **Conclusion:** In our large cohort comprising 660 patients, phenotype prediction was unreliable in weaker

genotypes. Rather than clearly classifiable, CAH severity has to be regarded as a continuum requiring flexibility in clinical management.

[☆]Nominated for a Presidential Poster Award.

P1-D2-2

Functional Characterization of a Novel Heterozygous Point Mutation in the Human Glucocorticoid Receptor Gene Causing Primary Generalized Glucocorticoid Resistance

Nicolas C Nicolaidis^a, Dimitris Vlachakis^b, Amalia Sertedaki^c,
Sophia Kossida^b, George P Chrousos^{a,c}, Evangelia Charmandari^{a,c}

^aDivision of Endocrinology and Metabolism, Biomedical Research Foundation of the Academy of Athens, Athens, Attiki, Greece; ^bBioinformatics and Medical Informatics Team, Biomedical Research Foundation of the Academy of Athens, Athens, Attiki, Greece; ^cDivision of Endocrinology, Metabolism and Diabetes, First Department of Pediatrics, Aghia Sophia Children's Hospital, University of Athens Medical School, Athens, Attiki, Greece

Background: Primary generalized glucocorticoid resistance (PGGR) or Chrousos syndrome is a rare familial or sporadic condition caused by mutations in the hGR gene, which reduce tissue sensitivity to glucocorticoids. A new case of PGGR caused by a novel heterozygous point mutation in the hGR gene, which resulted in threonine (T) to isoleucine (I) substitution at amino acid position 556 in the ligand-binding domain of the receptor, was recently reported in a patient with an adrenal incidentaloma. **Objective and Hypotheses:** To delineate the molecular mechanisms of action of the natural mutant receptor hGR α T556I. **Methods and results:** Compared with the WT receptor (hGR α WT), the mutant receptor hGR α T556I demonstrated a 22% reduction in its ability to transactivate the glucocorticoid-inducible MMTV promoter in response to dexamethasone, and did not exert a dominant negative effect upon the hGR α WT. Western blot analyses showed equal protein expression of hGR α WT and hGR α T556I. Dexamethasone-binding assays showed that the affinity of the mutant receptor hGR α T556I for the ligand was 50% lower than that of the hGR α WT (21.3 ± 4.09 vs 10.8 ± 0.99 nM). In subcellular localization and nuclear translocation studies, both the hGR α WT and hGR α T556I were predominantly localized in the cytoplasm of cells in the absence of ligand. Addition of dexamethasone resulted in slower translocation of the hGR α T556I into the nucleus (50 min), compared to the hGR α WT (15 min). The 3D molecular modeling study of the T556I mutation revealed that the —OH moiety of T556 established strong hydrogen bonding interactions with the =O group of P637 backbone. The T556I mutation led to the disruption of the hydrogen bond and significant relocation of the P637 bearing loop, thus affecting mildly the local 3D arrangement of the receptor and hence the electrostatic surface of the region. **Conclusions:** The natural mutant receptor hGR α T556I alters glucocorticoid signal transduction through multiple molecular mechanisms.

P1-D2-3

Transient Generalized Glucocorticoid Hypersensitivity: Clinical Manifestations, Endocrinologic Evaluation, and Transcriptomic Profile: the Potential Role of $\text{nf-}\kappa\text{b}$

Nicolas C Nicolaides^a, Agaristi Lamprokostopoulou^a, Alexandros Polyzos^b, Tomoshige Kino^c, Eleni Katsantonid^d, Panagiota Triantafyllou^e, Athanasios Christophoridis^e, George Katzos^e, Maria Drakopoulou^f, Amalia Sertedaki^f, George P Chrousos^{a,f}, Evangelia Charmandari^{a,f}

^aDivision of Endocrinology and Metabolism, Biomedical Research Foundation of the Academy of Athens, Athens, Attiki, Greece; ^bInstitute of Molecular Biology, Biomedical Research Foundation of the Academy of Athens, Athens, Attiki, Greece; ^cUnit on Molecular Hormone Action, Program in Reproductive and Adult Endocrinology, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland, USA; ^dDivision of Hematology, Biomedical Research Foundation of the Academy of Athens, Athens, Attiki, Greece; ^eFirst Pediatric Department, Aristotle University Medical School, Thessaloniki, Greece; ^fFirst Department of Pediatrics, Aghia Sophia Children's Hospital, University of Athens Medical School, Athens, Attiki, Greece

Background: Transient generalized glucocorticoid hypersensitivity 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 molecular mechanisms that underlie its pathophysiology have not been elucidated as yet. Adenovirus 36 has been reported to cause obesity in various animal species. **Objective and Hypotheses:** To present the clinical manifestations, endocrinologic evaluation and transcriptomics profile in a rare pediatric case of transient generalized glucocorticoid hypersensitivity. **Patient, methods, and results:** A 9-year-old girl presented with an 8-month history of clinical manifestations suggestive of Cushing's syndrome, including central obesity, moon facies, buffalo hump, purple skin striae, hypertrichosis, and decreased growth velocity. Endocrinologic evaluation revealed undetectable 0800 h ACTH (< 1 pg/ml) and cortisol (0.025 $\mu\text{g}/\text{dl}$) concentrations, which remained decreased throughout a 24 h period of study and did not respond to stimulation with ovine CRH (1 $\mu\text{g}/\text{kg}$). The disease gradually resolved spontaneously over the ensuing 3 months. Sequencing of the human glucocorticoid receptor gene revealed no mutations or polymorphisms. Transcriptomic (RNA sequencing) analysis in white blood cells in the disease and post resolution phases identified 903 differentially expressed genes. Of these, 106 genes were up-regulated and 797 were down-regulated in the disease compared with the resolution phase. Bioinformatic analysis on the differentially expressed gene networks revealed nuclear factor- κB as the predominant transcription factor influencing the expression of the majority of these differentially expressed genes, suggesting an active inflammatory reaction. RNA-sequencing showed no enrichment of adenovirus 36 sequence in our patient. **Conclusions:** Our findings indicate that a transient post-receptor defect or a virus-encoded molecule may have interfered with glucocorticoid signal transduction

leading to transient generalized glucocorticoid hypersensitivity in our patient. The changes in the transcriptome in the active phase of the disease point toward a transient exogenous insult, probably an infectious agent.

P1-D2-4

Mineralo and Glucocorticoid Deficiency in Early Infancy are Caused by a Founder Novel Mutation in the Nicotinamide Nucleotide Transhydrogenase Gene

Abdulsalam Abu-Libdeh^a, Ariella Weinberg-Shukron^{b,c}, Sharon Zeligson^b, Fouad Zhadeh^d, Liran Carmel^b, Paul Renbaum^{b,c}, Ephrat Levy-Lahad^{b,c}, David Zangen^a

^aDivision of Pediatric Endocrinology, Hadassah Hebrew University Medical Center, Jerusalem, Israel; ^bMedical Genetics Institute, Shaare Zedek Medical Center, Jerusalem, Israel; ^cHadassah Medical School, Hebrew University, Jerusalem, Israel; ^dEdmond J. Safra Campus, Department of Genetics, The Hebrew University of Jerusalem, Jerusalem, Israel

Background: Nicotinamide nucleotide transhydrogenase (NNT) gene mutations have been recently shown to cause familial glucocorticoid deficiency (FGD), by decreasing reactive oxygen species (ROS) detoxification in adrenocortical cells. Affected infants present within the first few months with isolated glucocorticoid deficiency. **Objective and Hypotheses:** To study the genetic etiology of four cases presenting uniquely with neonatal Addisonian crisis (both mineralo and glucocorticoid deficiency). **Clinical presentation and method:** Palestinian male infant with normal external genitalia born to consanguineous parents, presented neonatally with Na: 118, K: 6 mmol/l, decreased basal and ACTH stimulated cortisol and 17-hydroxyprogesterone, normal infantile testosterone, and elevated plasma renin activity (> 15 ng/ml per h). Two female cousins and another unrelated female neonate presented with similar manifestations. Whole exom next generation sequencing was performed on two affected cousins from the first kindred. Functional assessment of ROS detoxification capacity by was performed on skin biopsy derived cultured fibroblasts using the ⁷2dichlorodihydrofluorescein (DCF) method. **Results:** Whole exom sequencing revealed a G200S homozygous mutation in NNT gene. The homozygous variant found segregated with the disease in both unrelated families, and all four pairs of parents were heterozygous. Haplotype analysis revealed a founder effect while the mutation was not found in 100 alleles from ethnically matched controls. Expression studies of the ROS detoxification capacity in fibroblasts revealed an increase in ROS production in the fibroblasts derived from affected patients when compared to controls. **Conclusion:** The founder and novel G200S mutation in the very recently described NNT gene causes uniquely early-infantile-severe mineralo and glucocorticoid deficiency. NNT mutations should be added to the differential diagnosis of neonatal Addisonian crisis. ROS detoxification capacity is reduced in patients with the

G200S NNT mutation. Given the ubiquitous nature of NNT, further studies of various mutations are required to elucidate the specific target organs prone to develop pathologies in relation to their impaired antioxidant defense.

P1-D2-5

Carbohydrate Metabolism in Children and Adolescents with Classical Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency

Helmuth G Dörr, Carolin Pichl, Michaela Marx, Nadine Herzog, Daniela Klaffenbach, Thomas Völkl

Department of Pediatrics, University of Erlangen, Erlangen, Germany

Background: Reports on obesity, high blood pressure and reduced insulin sensitivity in children with classical congenital adrenal hyperplasia (CAH) indicate an increased cardiovascular risk. **Objective and Hypotheses:** To evaluate potential mechanisms, we analysed various parameters of the carbohydrate metabolism in children and adolescents with CAH. **Method:** Out of 86 patients with classical CAH, $n=41$ (21 m, 20 f; ages: 6.9–17.9 years) gave their consent to attend the study. All patients were healthy except for their underlying disease and did not take any other medication besides their substitution therapy. All children had an overnight fasting blood sample between 0800 and 0900 h and an oral glucose tolerance test. The study had been approved by the Ethical Committee and was not accompanied by a control group; for data comparison we used published reference values. The quality of glucocorticoid medication was classified in 'good' ($n=22$; 11 m, 11 f) and 'bad' (under-dosed: $n=19$; 10 m, 9 f) according to laboratory and urinary parameters. **Results:** (mean \pm s.d.): The parameters fasting insulin, insulin 120 min, max insulin, total insulin, FGIR, HOMA-IR, Matsuda index, and QUICKI showed no statistically significant correlation with the quality of the metabolic control. The HbA1c, fasting blood glucose levels and 120 min glucose levels were within the normal range in all patients. However, we found 11 patients (5 m, 6 f; nine in puberty) with an elevated fasting insulin level (23.1 ± 13.9 μ U/ml). These patients had also higher insulin levels at 120 min (124.8 ± 48.8), a lower fasting glucose/insulin ratio (FGIR) of 4.9 ± 1.7 , and higher HOMA-IR values (4.4 ± 2.6) in comparison with CAH patients ($n=30$) with normal fasting insulin (7.0 ± 2.4), Ins 120 min (71.1 ± 51.6), FGIR (13.3 ± 5.5), and HOMA-IR (1.44 ± 0.5). The 11 CAH patients had also a statistically significant higher BMI-SDS (1.55 ± 0.97 vs 0.38 ± 1.19 ; $P < 0.01$). **Conclusion:** Our data show that already 26.8% of the CAH children and adolescents participating have reduced insulin sensitivity which is correlated with a higher BMI. We found no correlation with severity of CAH, genotype, gender, glucocorticoid medication, or quality of current metabolic control. We suggest that the prevention of overweight/obesity in CAH children and adolescents is of outstanding importance.

P1-D2-6

Descriptive Analyses of Turner Syndrome

Clemens Kamrath, Michaela Hartmann, Claudia Boettcher, Stefan Wudy

Justus-Liebig University, Giessen, Germany

Background: One major issue of newborn screening programs for 21-hydroxylase deficiency (21OHD) is the high rate of false-positive results, especially in preterm neonates. Urinary steroid analysis using gas chromatography-mass spectrometry (GC-MS) is used as a confirmatory diagnostic tool. **Objective and Hypotheses:** The objective of this study was to analyze diagnostic metabolite ratios in neonates and infants with and without 21OHD using GC-MS with emphasis on glucocorticoid metabolism, and to publish reference values for the diagnosis of 21OHD in the largest cohort so far. **Method:** We analyzed urinary steroid hormone profiles determined by GC-MS of 95 untreated 21OHD neonates and infants (1–148 days), and 261 neonates and infants (100 preterms) without 21OHD (0–217 days). **Results:** Metabolites of 17α -hydroxyprogesterone showed specificities below 98%, whereas the 21-deoxycortisol metabolite pregnanetriolone clearly separated 21OHD from non-21OHD subjects. The best diagnostic ratio for 21OHD was pregnanetriolone to 6α -hydroxy-tetrahydrocortisone. The lowest value of this ratio in the 21OHD group (0.47) was at least eight times higher than the highest values in the non-21OHD group (0.055). **Conclusion:** We have given appropriate reference values for steroid metabolite ratios in the largest 21OHD cohort so far. Consideration of glucocorticoid metabolism, especially the use of typical neonatal 6α -hydroxylates metabolites, leads to improvement of diagnostic metabolite ratios.

P1-D2-7

A Novel Founder Mutation of CYP21A2 in Patients with CAH due to 21-Hydroxylase Deficiency

Aysenur Ökten^{a,b}, Gülay Karagüzel^{a,b}, Bayram Toraman^{a,c}, Ersan Kalay^{a,c}, Tuğba Dincer^{a,c}

^aSchool of Medicine, Karadeniz Technical University, Trabzon, Turkey; ^bDepartment of Pediatric Endocrinology, Trabzon, Turkey; ^cDepartment of Medical Biology, Trabzon, Turkey

Background: Mutations in *CYP21A2* are the most common cause of congenital adrenal hyperplasia (CAH). Even though disease linked mutations are rarely classified as founder, in this study, we describe a novel founder mutation, c.2T>C (p.M1?), inactivating the translation initiation codon. **Objective and Hypotheses:** We aimed to investigate genotype-phenotype correlation and population based origin of this novel mutation in CAH patients with 21-hydroxylase deficiency. **Method:** Mutation analyses of *CYP21A2* were performed by long PCR-RFLP and Southern blot for detecting large rearrangements. In addition, DNA sequencing was done for detection of point mutations in all patients who live in the northern coastal region of the Black Sea in Turkey. **Results:** We describe a novel founder

mutation, c.2T>C (p.M1?), inactivating the translation initiation codon. This founder mutation was found as homozygous in ten patients who belong to seven families. All families were from the same small town of whom six of them had consanguinity. Among ten patients, nine of the patients had severe salt-wasting form of CAH and one had simple-virilising form. **Conclusion:** Most of our patients have had severe salt-wasting form of disease, which was thought to be consistent with the severe nature of this novel mutation. Though one of the patients who also was homozygous for this mutation, had simple-virilising form of the disease. The genotype–phenotype discordance of this patient requires further explanation.

P1-D2-8

Normal Value of Steroids in Amniotic Fluid by LC–MS/MS Method

Ingrid Plotton^{a,b}, Severine Ruet^a, Chantal Rigaud^a, Marianne Till^d, Damien Sanlaville^{c,d}, Yves Morel^{a,c}

^aHormonology and Endocrinology Molecular, Hospices Civils de Lyon, Bron, France; ^bU846, University Claude Bernard Lyon, Lyon, France; ^cUniversity Claude Bernard Lyon, Lyon, France; ^dCytogenetique, Hospices Civils de Lyon, Bron, France

Background: Determination of steroids in amniotic fluid (AF; Forest *et al.*, *J Clin Endocrinol Metab*, 1980) has been essentially used in the three past decades for the prenatal diagnosis of 21-OH deficiency. With the recent advances of ultrasound technology (US) and the widespread use of amniocentesis, prenatal diagnosis of DSD appears more common especially if a mismatch between karyotype and external genitalia detected by US occurs. An accurate and specific determination of normal value of steroids in AF appears essential to evaluate DSD during this prenatal period. **Objective:** Determination of the pattern of reference value for 17OHP, Δ 4-A and testosterone by liquid chromatography–tandem mass spectrometry (LC–MS/MS method) according to sex. **Method:** UPLC was performed on an Agilent Technologies 1290 Infinity using a Poroshell C18 4.6×50 2.7 μ m coupled to an Agilent Technologies triple quadrupole 6460. In the sample preparation, internal standard deuterium are added in calibration curve and AF before supported liquid extraction (SLE). This method separated the steroids was validated according the Norm (linear response, CV < 2% for the repeatability, < 15% for the reproducibility and correlation with RIA $R^2 > 0.93$ but the value was lower than in RIA). The lower limit of quantification is for Δ 4A: 0.13, testosterone: 0.05, and 17OHP: 0.11 nmol/l. **Materials:** Steroids were quantified in 133 AF with normal karyotype from women having amniocentesis, with informed consent. The amniocentesis was performed at 14.2 and 23 weeks of amenorrhea for increased maternal serum markers. No morphological abnormality (US) has been observed. **Results:** The measurement of these steroids allows the determination of normal range: Testosterone is significantly higher in male foetus. The lower values determined by LC–MS/MS vs chromatography–RIA should be due to a more specific determination (absence of cross-reaction

	17OHP (mean \pm S.D.) nmol/l	Δ 4-A (mean \pm S.D.) nmol/l	Testosterone (mean \pm S.D.) nmol/l
46,XX (n=74)	3.55 (\pm 1.37)	0.86 (\pm 0.47)	0.08 (\pm 0.31)
46,XY (n=59)	3.31 (\pm 1.36)	1.46 (\pm 0.84)	0.57 (\pm 0.31)

with the antibody). **Conclusion:** We report a rapid, sensitive and accurate method for simultaneous measurement of three steroids in AF. Moreover, pathological values for DSD (defect of steroid biosynthesis, ...) were in progress.

P1-D2-9

Mast Cells in Human Adrenal Gland During Fetal Development

Alexandre Naccache^{a,b}, Céline Duparc^a, Estelle Louiset^a, Hervé Lefebvre^{a,c}, Mireille Castanet^{a,b}

^aINSERM U982, Institute for Biomedical Research and Innovation, University of Rouen, Rouen, France; ^bDepartment of Pediatrics, University Hospital of Rouen, Rouen, France; ^cDepartment of Endocrinology, University Hospital of Rouen, Rouen, France

Background: We previously found that mast cells are present in the human adult adrenal gland with a possible role in the regulation of aldosterone secretion in both physiological conditions and aldosterone-producing adrenocortical adenomas responsible for primary hyperaldosteronism. **Objective and Hypotheses:** The aim of the present study was to investigate the presence of mast cells in the human fetal adrenal gland, and to provide arguments in favor of their implication in its development. **Method:** Paraffin-embedded human fetal adrenal samples were studied at 13 different stages of development from 16 weeks of gestation (WG) to the term. **Results:** Immunopositive cells for the mast cell marker tryptase were firstly detected at 20 WG with a peak of density at 28–31 WG. Double immunostaining with antibodies against the steroidogenic enzymes 3 β HSD, characterizing the definitive and transition zones, and 17 α -hydroxylase (17-OH; CYP17), characterizing the transition and fetal zones, revealed that mast cells are mainly located in the vicinity of steroidogenic cells in the subcapsular definitive zone. There was no correlation, in term of timing of expression, with either 17-OH, which was present at all studied stages, or 3 β HSD firstly detected quite earlier at 18 WG. **Conclusion:** We demonstrated for the first time that mast cells are present in the human fetal adrenal gland from the second trimester of pregnancy. However, no clear evidence of relationship was found with the kinetics of steroidogenic enzymes expression. Further studies need to be performed, such as investigation of CYP11B2 expression, to assess an eventual role of mast cells in aldosterone production and to better understand the role of these intra-adrenal mast cells in the fetal development.

P1-D2-10

An Unusual Presentation of Isolated ACTH-Deficiency Secondary to TBX19 Mutation Revealed by Late Onset Hypoglycemia Seizure

Cecile Valentin^a, Alexandru Saveanu^c, Jacques Beltrand^{b,e}, Irene Netchine^{a,d}

^aAP-HP, Hôpital Armand Trousseau, Explorations Fonctionnelles Endocriniennes, Paris, France; ^bUnité d'Endocrinologie, Gynécologie et Diabétologie Pédiatrique, Hôpital Universitaire Necker-Enfants-Malades, Paris, France; ^cCRN2M UMR 6231, Faculté de Médecine Nord, Centre National de la Recherche Scientifique, Université de la Méditerranée, Marseille, France; ^dUniversité Pierre et Marie Curie-Paris 6, Paris, France; ^eFaculté de médecine Paris Descartes - Université Sorbonne Paris Cité, Paris, France

Background: Congenital isolated ACTH deficiency (IAD) is a rare inherited disorder that is clinically and genetically heterogeneous. Patients are characterized by low or absent cortisol production secondary to low plasma ACTH despite normal secretion of other pituitary hormones and the absence of structural pituitary defects. Mutations in the TBX19 gene, a T-box factor selectively expressed in developing corticotroph cells, have been identified so far only in cases of neonatal-onset complete IAD. **Objective and Hypotheses:** Identify the IAD etiology. **Method:** We present the case of a 23-month-old boy with a severe hypoglycemia and a generalized seizure during a viral episode with fever and vomiting. His cortisol and ACTH were undetectable. Other pituitary hormones were in the normal range and the brain MRI showed no pituitary defect. He was born full term to related Tunisian parents. The mother had gestational diabetes. He had a hypoglycemia few hours after the delivery thought to be secondary to the gestational diabetes with no detected recurrence in the first months of his life. He had a medical history of asthma with multiple hospitalizations, included one at 15 months with a long-fasting hypoglycemia noted. He has a regular growth. His older brother diagnosed with a combined pituitary hormone deficiency at 2 months, deceased at 24 months in a probable context of hypoglycemia. **Results:** The TBX19 gene direct sequencing showed a homozygous recessive splicing site mutation previously described: IVS5 + 1G > A, leading to mRNA targeted for nonsense mediated decay and absence of protein expression. **Conclusion:** This is a rare case with a late IAD diagnosis secondary to a TBX19 mutation. A TBX19 anomaly should not be rule out in patients without a neonatal diagnosis of IAD but still life threatening given its severity.

P1-D2-11

Identification of a Novel Large CYP17A1 Deletion by Multiplex Ligation-Dependent Probe Amplification Analysis in Patients with Classic 17-Hydroxylase Deficiency

T Guran^a, D Turkkahraman^b, H Ivison^a, A Griffin^a, R Vijzelaar^c, N Krone^a

^aSchool of Clinical and Experimental Medicine, University of Birmingham, Birmingham, UK; ^bAntalya Education and Research Hospital, Antalya, Turkey; ^cMRC-Holland, Amsterdam, The Netherlands

Background: Steroid 17-hydroxylase deficiency (17OHD) (OMIM 202110) is a rare form of congenital adrenal hyperplasia caused by loss-of-function mutations in the 17 α -hydroxylase (CYP17A1) gene. CYP17A1 is a key enzyme in the biosynthesis of adrenal and gonadal steroid hormones facilitating both 17 α -hydroxylase and 17,20-lyase activities. The CYP17A1 gene is located on chromosome 10 and has eight coding exons. Herein, the molecular basis of 17OHD in a Kurdish family has been defined. **Objective and hypotheses:** To characterize a partial CYP17A1 deletion in a family with 17 α -hydroxylase deficiency by multiplex ligation-dependent probe amplification (MLPA). **Method:** The index patient presented with amenorrhea and absence of secondary sexual characteristics. Further investigations established the diagnosis of 46,XY disorder of sex development (DSD). She is the daughter of consanguineous parents and has two sisters with similar clinical signs and symptoms. **Results:** All patients had elevated concentrations of ACTH, gonadotropins, progesterone, in combination with decreased concentrations of cortisol, renin, testosterone and oestradiol. The molecular genetic analysis by PCR suggested a deletion spanning exons 1–6 of the CYP17A1 gene. MLPA analysis confirmed partial CYP17A1 deletion in patients and parents in homozygous and heterozygous state, respectively. **Conclusion:** This is the first report employing MLPA as mutation analysis for the analysis of partial deletion of CYP17A1 gene affecting multiple exons in three patients with classic 17-hydroxylase deficiency. It appears important to consider large partial CYP17A1 deletions in 17OHD in addition to point mutation analysis in cases where no segregation analysis is possible to determine the correct genotype.

P1-D3-12

Adrenal Rest Tumors in Patients with Primary Adrenal Insufficiency[☆]

Zehra Yavas Abali^a, Nurcin Saka^a, Oguz Bulent Erol^b, Banu Kucukemre Aydin^a, Tulay Guran^c, Firdevs Bas^a, Sukran Poyrazoglu^a, Ruveyde Bundak^a, Feyza Darendeliler^a

^aPediatric Endocrinology Unit, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey; ^bDepartment of Radiology, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey; ^cPediatric Endocrinology Unit, Marmara University, Istanbul, Turkey

Background: Gonads containing adrenal rests may enlarge in response to chronic overstimulation by ACTH in diseases with ACTH hypersecretion such as poorly controlled congenital adrenal hyperplasia (CAH), Addison's disease and Nelson's syndrome. Testicular adrenal rest tumors (TART) are present in childhood in CAH patients and frequency in adults may be up to 50–95%. Ovarian adrenal rest tumors (ART) are less frequently detected. TART is described less in patients other than CAH.

Objective and Hypotheses: To investigate the presence of ART in patients with primary adrenal insufficiency excluding CAH. **Method:** Twenty-four patients (9F, 15M); ages between 0.5 and 18.3 years (mean \pm s.d.; 8.6 ± 4.5 , median 7.5 years) at the time of evaluation, were included. ACTH resistance was the diagnosis of 23 patients (two of them were Allgrove syndrome). The other patient had autoimmune Addison's disease. Frequency of consanguinity was 75%. Mean duration of follow-up was 5.7 ± 4.1 years (median: 4.9 years, range: 0.17–18.3). Boys were screened by scrotal ultrasonography (US) and girls by suprapubic pelvic US. **Results:** One of the boys had bilateral TART (6.7%). No ovarian ART was detected in girls. The boy who had TART, was diagnosed as ACTH resistance at age 2 years, and was receiving hydrocortisone replacement therapy. He was 6.5 years old when US performed, at this time ACTH level was >1250 pg/ml. Totally four adrenal rest tissues were detected, in right testes one (3.5×3.5 mm), in left three (largest one 9.5×7 mm). Additionally testicular microlithiasis was detected in four patients (three of them were siblings) ($n=4$, 26.7%). **Conclusion:** In patients with primary adrenal insufficiency overstimulation by ACTH may predispose to TART. Additionally testicular microlithiasis has been found at high frequency similar to CAH patients. Especially in patients with primary adrenal insufficiency who have ACTH resistance accompanied with high ACTH levels, we recommend that the patients should be followed for ART by periodic ultrasonographic evaluation.

*Nominated for a Presidential Poster Award.

P1-D3-13

Assessment of Blood Pressure and Left Ventricular Parameters in Children with Classical CAH-due to 21 Hydroxylase Deficiency*

Shereen Abdelghaffar^a, Reem Ibrahim^a, Osama Abdelaziz^a, Mona Hafez^a, Mona Mamdouh^a, Abeer Alashmawy^a, Fatma Elmougy^b, Sahar Abdelaty^b, Amany Ibrahim^a, Hend Mehawed^a, Isis Ghaly^a

^aDepartment of Pediatrics, DEMPU, Cairo University, Cairo, Egypt;

^bDepartment of Chemical Pathology. Cairo University, Cairo, Egypt

Background: Patients with congenital adrenal hyperplasia (CAH), due to 21 hydroxylase (OH) deficiency may develop an adverse cardiovascular risk profile as reported by few previous studies. **Objective and Hypotheses:** Blood pressure (BP) and echo parameters in children with CAH due to 21-OH deficiency were evaluated. **Method:** This cross-sectional study included 53 children. BP, echocardiographic left ventricular functions as well as growth parameters were compared to results of 30 healthy control children. Association of results with androgen levels as well as with glucocorticoids (GCs), and mineralocorticoids (MCs) treatment doses were studied. **Results:** By using BP International centiles, 23 (43.3%) patients had hypertension. BP levels in cases were positively correlated with GCs doses and negatively correlated with 17-hydroxyprogesterone (OHP) levels. Fifteen (28.8%) patients were obese (>2 SDS), and generally, cases had significantly higher BMI-SDS than controls. Growth velocity (GV)-SDS was negatively correlated with MCs dose and plasma renin activity

(PRA level. By echocardiography, mean left ventricular mass (LVM) and left ventricular mass index (LVMI) (when compared to published paediatric criteria: $LVMI > 38.6 \text{ g/m}^{2.7}$) were found to be elevated. In cases, inter ventricular septum in diastole (IVSd) and left ventricular posterior wall in diastole (LVPWd) were statistically significantly increased while Left ventricular internal dimension in systole (LVIDs) and left ventricular mass index (LVMId) were statistically significantly decreased ($P < 0.05$). Multivariable linear regression showed that glucocorticoid dose was a predictor of hypertension and that age and hypertension were predictors of left ventricular (LV) hypertrophy (as evidenced by IVS, LVM, and LVMI) ($P < 0.05$ for all). **Conclusion:** Patients with CAH due to 21 OH deficiency can suffer from hypertension as well as affection of left ventricular functions. The systematic monitoring of BP, height, BMI, and echocardiographic parameters are important to prevent cardiovascular morbidity in adult CAH patients.

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P1-D3-14

Clinical, Biological and Genetic Characteristics of 48 Pediatric Patients with Micronodular Adrenal Hyperplasia (MAH)*

Anya Rothenbuhler^a, Evgenia Gourgar^{b,c}, Maya Lodish^b, Constantine Stratakis^b

^aService d'Endocrinologie Pédiatrique, Université Paris-Sud 11, Hôpital Bicêtre, 94270 Le Kremlin-Bicêtre, France; ^bSection on Endocrinology and Genetics (SEGEN), Program on Developmental Endocrinology and sGenetics (PDEGEN), Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), Nation, Bethesda, Maryland 20892, USA; ^cDivision of Pediatric Endocrinology, Georgetown University Hospital, Washington, District of Colombia 20016, USA

Background: Micronodular adrenal hyperplasia (MAH) is a rare disease. **Objective:** Describe the clinical, biological and genetic characteristics of micronodular adrenal hyperplasia (MAH) in children. **Method:** Retrospective study based on medical records (from the NIH and Bicêtre Hospital) of 47 pediatric patients (age <18 years at first signs of disease) with ACTH-independent Cushing syndrome (AICS) due to MAH proven histologically. Thirty-three girls and 15 boys were studied. **Results:** AICS appeared at a median age of 9.6 ± 4.6 years (comparable in both sexes) and two cases were neonatal. Six patients presented with cyclical CS. Seven patients presented with cardiac myxomas of which six had at least one re-occurrence; in two cases the cardiac myxoma was revealed by a vascular embolism. Twenty patients had characteristic dermatological findings of Carney Complex (lentigines, blue nevi, cutaneous myxoma). 21 patients presented with isolated AICS. All patients (when explored during an active phase) had high UFC's, high midnight cortisol levels, low ACTH and a paradoxical response to dexamethasone (Liddle's test); 25 cases were sporadic and 23 familial (in 16 familial cases the child was the index case). 20 patients had a PRKAR1A mutation, of which 14 were familial and

Table 1. (for abstract P1-D3-15)

	Patients	Age (Years)	Testicular volume (ml)	Inhibin B (pg/ml)	AMH (ng/ml)
CAH with TART	7	14.55 (10.41;17.93)	5.98 (3.79;6.84)	103.15 (60.71;166.10)	8.11 (4.07;13.17)
CAH without TART	21	12.82 (11.73;15.13)	8.37 (4.48;10.61)	187.45 (154.97;224.26)	8.16 (6.47;21.6)
Control group	18	14.5 (14.00;17.00)	10.95 (8.33;12.24)	249.12 (204.04;343.19)	8.38 (5.81;10.00)

six were sporadic cases. All studied patients that had a cardiac myxoma had a PRKAR1A mutation. **Conclusion:** Forty-five percent of pediatric cases of MAH presented as isolated AICS and 55% of patients had Carney Complex.

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P1-D3-15

Testicular Adrenal Rest Tumors and Sertoli Cell Function in Adolescents with CAH

Igor Chugunov, Maria Kareva, Elizaveta Orlova, Elvira Kuznecova, Sergey Bogolubov

Endocrinology Research Center, Moscow, Russia

Background: Infertility is one of the major problems in adult males with congenital adrenal hyperplasia (CAH), associated with the development of testicular adrenal rest tumors (TART). Sertoli cell dysfunction could be diagnosed not only in adults but in adolescence. **Objective and Hypotheses:** To study Inhibin B and AMH levels in adolescents with CAH and TART and its diagnostics value in access of Sertoli cell function. **Method:** We studied 28 CAH (16 with salt-wasting form (SW) and 12 simple virilizing (SV) form) and 18 healthy adolescents. TARTs have been detected in seven CAH patients with SW form. CAH patients were divided into two groups according to TART development. CAH and control groups were comparable in chronological age ($P=0.61$) and puberty stage ($P=0.61$). CAH patients with and without TART had no differences in chronological age ($P=0.53$), puberty stage ($P=0.72$) or testicular volume ($P=0.11$). **Results:** Patients with CAH had lower testicular volume compared to the control group ($P=0.002$). Lower values for inhibin B ($P=0.003$) but not AMH ($P=0.6$) were observed in the CAH patients. Inhibin B was significantly lower in patients with TART ($P=0.02$) in comparison to the patients without TART. There were no differences in AMH values between patients with or without TART. **Conclusion:** Low levels of inhibin B in CAH patients indicates Sertoli cell dysfunction especially in patients with TART.

P1-D3-16

A Novel Mutation in Exon 5 of TP53 Gene in a Familial Adrenocortical Carcinoma

Enver Simsek, Cigdem Binay, Baran Tokar, Emine DüNDAR, Meliha Demiral

Eskisehir Osmangazi University School of Medicine, Eskisehir, Turkey

Background: Adrenocortical carcinoma (ADCC) is a rare cancer in children and differs significantly in epidemiology, clinical characteristics, and biologic features from their counterparts in adults. Germline mutations of the TP53 tumor suppressor gene are associated with cancer predisposition in families with the Li-Fraumeni syndrome. **Aim:** To report a young girl with family a history of ADCC who presented with severe virilisation secondary to ADCC, and to investigate the possibility the germline p53 tumour suppressor gene mutation in patient and the other family members. **Subjects and methods:** In 2002, the first daughter was diagnosed with an ADCC at the age of 24-month-old. More than a decade later (2013), the second daughter presented with the

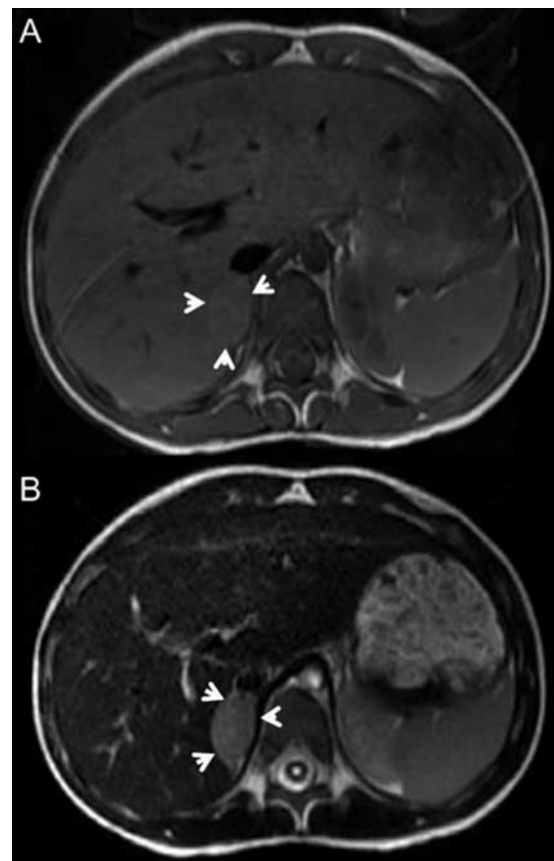


Figure 1 Right surrenal gland magnetic resonance imaging showing hypointense mass on T1 sequence (A), and hyperintense mass (2.0×2.5 cm) on T2 sequence after radiocontrast injection.

symptoms and signs of severe virilisation at the age of 38-month-old and she was also diagnosed with an ADCC. Because of this family history, all of the family members underwent testing for a genetic mutation that is associated with increased cancer formation. Full sequencing of the coding exons (2 – 11) and associated splice junctions of the *p53* gene was performed on patients and their healthy family member. **Results:** Sequencing analysis showed a heterozygous GCACCCG deletion in exon 5 of *TP53* gene (c.461_467delGCACCCG), which configures the mutation p.G154A.fs*14. This mutation has never been described in association with ADCC and was found in the proband and her affected sister. In addition, the same mutation was detected in two other siblings and father who have not yet developed any malignancy. **Conclusion:** This observation of germline *TP53* mutation in this family associated with ADCC confirms that genetic counselling and germline testing for *TP53* should be offered to all pediatric patients with ADCC. These cases also highlight the need for close surveillance of patients and first degree relatives with *TP53* gene mutation for malignancies

P1-D3-17

Aldosterone/Renin Ratio as Key Player in the Diagnosis of Primary Hypoaldosteronism in Newborns and Infants

Beate Ruecker^a, Mariarosaria Lang-Muritano^a, Katharina Spanaus^b, Maik Welzel^c, Dagmar Lallemand^d, Franziska Phan-Hug^e, Daniel Konrad^a, Claudia Katschnig^a, Paul-Martin Holterhus^c, Eugen Schoenle^a

^aDepartment of Endocrinology/Diabetology, University Children's Hospital Zurich, Zurich, Switzerland; ^bDepartment of Clinical Chemistry, University Hospital Zurich, Zurich, Switzerland; ^cDepartment of Endocrinology, University Children's Hospital Kiel, Kiel, Germany; ^dDepartment of Endocrinology, Children's Hospital St Gallen, St Gallen, Switzerland; ^eDepartment of Endocrinology, University Hospital Lausanne, Lausanne, Switzerland

Background: Primary hypoaldosteronism (PA) is a rare inborn disorder with life-threatening symptoms in newborns

and infants due to an aldosterone synthase defect. As plasma aldosterone concentration (PAC) can remain in the normal range, interpretation of the laboratory findings could be difficult and might lead to delayed initiation of therapy. **Objective and Hypotheses:** This study aims to show that PAC/PRC (plasma renin concentration) ratio can be used as a reliable diagnostic tool for PA in newborns and infants. Up to now this method is only validated to diagnose random conditions of disorders of the renin-angiotensin-aldosterone axis in adults. **Method:** Ten patients with diagnosed PA were included. In 9/10 diagnosis was genetically confirmed by detecting pathogenic mutations in the *CYP11B2* gene. The homozygous mutation T185I (8/10) and a compound heterozygous mutation with heterozygosity for T185I and for c.1398+1 G>A (1/10) were detected. In one patient the genetic result is pending. PACs and PRCs were available in 8/10. For those the PAC/PRC ratio was calculated in (pmol/l)/(mU/l). As patients were included from three different centres, the analytic methods differed. In order to enable a valid comparison of the values, PACs and PRCs were correlated to reference methods. **Results:** In eight patients the PAC/PRC ratio was <1 (pmol/l)/(mU/l) (min: 0.0001–0.6538, mean: 0.1382). In one patient renin was noted as plasma renin activity (PRA). The PAC/PRA ratio was with 4.8 (pmol/l)/(ng/ml×h) also clearly decreased. In one patient no values for aldosterone and renin were available. **Conclusion:** It was already shown in adults that a PAC/PRC ratio <1 (pmol/l)/(mU/l) and a PAC/PRA <28 (pmol/l)/(ng/ml×h) helps to identify patients with primary hypoaldosteronism. Due to our results this seems to be a very reliable screening tool in newborns and infants with aldosterone synthase deficiency as well. Thus we propose its introduction as a standard diagnostic tool.

P1-D3-18

Zenhale Inhaled Corticosteroid Therapy: Useful Second Line Therapy for Asthma in Children but be Wary of Adrenal Suppression

Rebecca Perry^a, Wendy Schwarz^a, Karen Stosky^b, Jonathan Dawrant^a, Daniele Pacaud^a, Mary Noseworthy^b, Mark Anselmo^b

^aDivision of Endocrinology, Department of Pediatrics, University of Calgary, Alberta, Canada; ^bDivision of Respiratory Medicine, Department of Pediatrics, University of Calgary, Alberta, Canada

Table 1. (for abstract P1-D3-18)

Median (range)		0800 h Plasma Cortisol (nmol/l)	Peak cortisol on LDST (nmol/l)	Age (years)	Zenhale dose (µg/day)	
*P<0.01 vs no suppression (n=86)	n					
Low 0800 h Cortisol and/or AI symptoms	Adrenal suppression	15	13 (2–255)	204 (11–385)	5.2 (3.2–12.6)*	800 (400–800)*
	No adrenal suppression	15	88.5 (3–233)	631 (482–890)	9.1 (3.2–13.2)	400 (400–800)
Normal 0800 h Cortisol and no AI symptoms		71	372 (203–747)	NA	10.8 (2.5–18)	400 (200–800)
No screening performed yet		69	NA	NA	10.2 (2.3–17.6)	400 (200–800)

Background: Children with Asthma who do not respond to first-line therapy may need inhaled corticosteroid-long-acting beta agonist combination (ICS-LABA) therapy. Adrenal insufficiency (AI) due to adrenal suppression is a recognized but relatively uncommon side effect of ICS. An increase in suspected cases of AI associated with one particular ICS-LABA, mometasone-formoterol (Zenhale) was observed at a tertiary care Asthma clinic over a 6-month period. **Objective:** To identify the prevalence of AI in children treated with Zenhale. **Methods:** After confirmation of AI in the index patients by low-dose synthetic ACTH stimulation (LDST) all children on Zenhale are being screened for AI symptoms along with an 0800 h plasma cortisol. Children with symptoms suggestive of AI and/or low morning cortisol (<200 nmol/l) undergo a LDST by endocrinology. **Results:** 170 children in the Asthma clinic were prescribed Zenhale. Screening has been completed in 101 children to date; 30 had LDST of which 15 (14.8%) had AI (see Table). In the <6y sub-group, nine of 18 children screened (50%) had AI. **Conclusion:** Zenhale therapy in children can cause adrenal suppression. Those with AI were younger and on higher doses. We will present the age and dose with highest odds of AI after ROC and give likelihood ratios. Meanwhile, we suggest caution in the use of Zenhale in children <6y and doses >400 µg/day. Children/adolescents using Zenhale under 12y or on high daily doses (>500 µg) should be advised about the signs and symptoms of AI and to avoid abruptly stopping Zenhale therapy and to discuss any dose changes with their Asthma team.

P1-D3-19

Development of Scotland Wide Process for Management of Acute Adrenal Insufficiency

Barbara S Wardhaugh^a, Jacquie Reid^b

^aRoyal Hospital for Sick Children, Edinburgh, UK; ^bRoyal Aberdeen Childrens Hospital, Aberdeen, UK

Background: The Scottish Paediatric Endocrine Managed Clinical Network is committed to providing equity of care across Scotland. A key role identified by the nurses group is developing information leaflets supporting patient care. It was recognized that there was no local unified approach to the management of adrenal insufficiency, especially in the home, community and acute setting. Of particular concern was the lack of a pathway of care from home to hospital and involvement of ambulance staff. **Objective:** To develop a national system to improve management of acute adrenal insufficiency. **Method:** All patients with known adrenal insufficiency are recorded on a local Hospital Alert System. In conjunction with the Scottish Ambulance Service a national Hazard Alert System has been established. A standard information sheet was designed and piloted. If an Ambulance is requested the crew attending are alerted that the child is at risk of an adrenal crisis and may require administration of i.m. hydrocortisone.

Policy remains that ideally parents administer i.m. hydrocortisone prior to arrival of ambulance. In addition a number of information leaflets and teaching guides to improve knowledge and support families in the acute management of adrenal insufficiency have been developed. Information Booklet on Adrenal Insufficiency for Patient/Carer, Information booklet for Schools on Adrenal Insufficiency, Steroid Replacement management plan. Adrenal Insufficiency emergency treatment information card and i.m. injection teaching package. **Conclusion:** We now have improved education for Patients and Carers and developed an emergency plan with Scottish Ambulance Service for those children at risk of Adrenal Crisis.

P1-D3-20

Salivary Cortisol as a Diagnostic Tool of Hypercortisolism in Primary Pigmented Nodular Adrenocortical Disease (ppnad)

Ayrton Moreira, Paula Elias, Marcelo Bittar, Carlos Eduardo Martinelli Jr, Sonir Antonini, Margaret Castro

Ribeirao Preto Medical School, University of Sao Paulo, Ribeirao Preto - SP, Brazil

Background: Hypercortisolism due to PPNAD may be cyclical, atypical and may develop suddenly or progressively. **Objective and Hypotheses:** The performance of salivary cortisol (SF) in this rare cause of Cushing's syndrome (CS) is lacking. **Method:** Ten patients (nine F/one M) with PPNAD (two sporadic; eight Carney complex) were evaluated. Among these, six had CS family history, while in two the diagnosis was confirmed by germline PRKARIA mutation. Median age at CS diagnosis was 13.5 years (range 4–28). Seven patients presented overt CS, two developed symptoms during follow-up, and one still has no clinical CS. Saliva samples for cortisol assay (RIA) were collected at 0900 and 2300 h (LNSF) and after overnight 1-mg dexamethasone suppression test (DST). Baseline plasma ACTH and cortisol after DST were obtained. In three patients without CS at presentation, longitudinal LNSF were evaluated during 16 months to 5 years follow-up. **Results:** Baseline LNSF of all patients (mean ± s.d.) was 890 ± 674 ng/dl. In 7/10 patients LNSF levels were above the cutoff level (≥350 ng/dl or 9.8 nmol/l). In three patients, there was a progressive increase of LNSF during longitudinal evaluation. After 1-mg DST, mean SF was 962 ± 1149; all patients had SF above the cutoff level (>150 ng/dl or 4.2 nmol/l). Mean plasma cortisol after 1-mg DST was 17.4 ± 12 µg/dl; all patients had values above the cutoff level (≥2.0 µg/dl or ≥55 nmol/l). Baseline plasma ACTH was 13.4 ± 2.8 pg/ml (range <5–17), and undetectable ACTH was observed in 5/10 patients. Nine patients with overt CS underwent bilateral adrenalectomy; PPNAD was confirmed by histopathology. **Conclusion:** Our data confirm that plasma or salivary cortisol after 1-mg DST are the most useful tools for the diagnosis of hypercortisolism in children and adults with sporadic or

Table 1. (for abstract P1-D3-21)

Cases	Age at dx (years)	17OHP (0') (ng/ml)	17OHP (60')	Cortisol (0') (µg/dl)	Cortisol (60')	Genotype
1	10.6	17	> 25	13.5	16.1	p.Val282Leu/p.Ile173Asn
2	5	24.3	> 25	9.66	16.05	p.Val282Leu/p.Arg357Trp
3	4.7	19	11.89	7.7	12	p.Val282Leu/p.Ile173Asn
4	8.8	14.1	49.9	8.6	11.2	p.Val282Leu/p.Ile173Asn
5	9.5	37.6	45	13.1	15.03	p.Val282Leu/655G
6	6.2	5.6	49.9	6.49	11.5	p.Val282Leu/p.Arg357Trp
7	9	16.9	32.4	14.5	17.1	p.Val282Leu /p.Arg357Trp
8	6.5	40.8	81.6	7.19	8.57	'Polimorph' c.735GTA/del-conv
9	7.3	8.2	31.9	12.5	17.8	p.Val282Leu/del-conv exon3-4

Carney complex PPNAD. Of note, LNSF may provide information on the temporal development of hypercortisolism in PPNAD. In addition, in PPNAD, normal ACTH levels do not exclude CS.

P1-D3-21

How to Interpret Cortisol Responses to Acth in Patients with Non-Classic Congenital Adrenal Hyperplasia

M Belen Roldan Martin, Yoko Oyakawa Barcelli, Raquel Barrio Castellanos, Maria Martin Frias, Daniel Alonso Martin, Milagros Alonso Blanco

Hospital Universitario Ramon y Cajal, Madrid, Madrid, Spain

Background: Recent clinical guidelines recommend that all patients with non-classic congenital adrenal hyperplasia (NCCAH) on glucocorticoid therapy (GC) need to be informed about stress doses and suggest the use of GC in the subgroup of patients with low cortisol response during periods of stress even though they are not on GC. **Objective and Hypotheses:** To study the response of cortisol to ACTH 250 µg i.v. (Synacthen[®], Novartis) in patients with NCCAH and to evaluate the need of GC in periods of stress in patients with subnormal response of cortisol to the test. **Method:** Descriptive, retrospective study in 46 patients with NCCAH. **Results:** The ACTH test was performed in 44/46 patients with NCCAH. Cortisol response to ACTH was determined in 34 patients. Nine patients (26%) had a response of cortisol <18 µg/dl and eight of them were treated with hydrocortisone. According to previous clinical guidelines for NCCAH, the patients on substitutive doses of GC did not use GC stress doses and they all tolerated well infectious or stress situations. **Conclusion:** About one third of our patients with NCCAH presented subnormal response of cortisol to ACTH. The patients did not present signs or symptoms of an adrenal crisis during periods of stress. The need of increased doses of GC in patients without significantly suppressed adrenal function may require confirmation in larger series of patients.

P1-D3-22

Clinical Utility of Urinary Steroid Metabolite Ratios in Children Undergoing Investigations for Suspected Disorders of Steroid Synthesis

Angela Lucas-Herald^a, Martina Rodie^a, Laura Lucaccioni^a, Karen Rankin^b, Guftar Shaikh^a, Jane McNeilly^c, David Shapiro^b, Faisal Ahmed^a

^aDevelopmental Endocrinology Research Group, University of Glasgow, Glasgow, UK; ^bDepartment of Biochemistry, Glasgow Royal Infirmary, Glasgow, UK; ^cDepartment of Biochemistry, Southern General Hospital, Glasgow, UK

Background: Calculation of a urinary steroid metabolite ratio (uSMR) may be a useful method of improving diagnostic yield when investigating disorders of steroid hormone synthesis. Our aim was to investigate the range of uSMR in children with suspected disorders of steroid hormone synthesis. **Methods:** Ten ratios were calculated on steroid metabolite data analysed by GC-MS in urine samples collected between 2008 and 2010 from 94 children who were undergoing investigations. To obtain reference data, urine samples were also analysed in 252 children with no background of endocrine concerns. **Results:** Of the 94 cases, 38 (40%) were male and the median age at the time of the test was 6.5 years (range 1 day–18 years). The most common indication for urinary steroid analysis was to investigate early puberty (22%). Of the 252 controls, 115 (46%) were male and the median age at the time of the test was 10 years (range 1 month–18 years). 40 (43%) had at least one ratio >2SDS above the mean for the reference range. The number of ratios per case which were >2SDS ranged from 1 to 6 (median 0). A high THS/(THE + THF + 5αTHF) was the most commonly abnormal ratio and found to be >2SDS in 18 cases. A total of 9/94 (10%) cases were diagnosed with a steroid hormone disorder (true positives); 4 (44%) with 21-hydroxylase deficiency, 2 (22%) with 11β-hydroxylase CAH, 2 (22%) with 5α-reductase deficiency and 1 (11%) with Cushings disease. All except one of these patients had at least 1 ratio >2SDS. The case with the normal steroid hormone ratios was later diagnosed with 5α-reductase deficiency. **Conclusions:** Abnormal urinary steroid metabolite ratios are commonly encountered in children undergoing investigations for disorders of steroid synthesis. On the other hand, the use of ratios may not identify all disorders of steroid synthesis, especially 5α-reductase deficiency.

P1-D2-23

Analysis of Zinc Transporter ZnT8 Autoantibodies in Children and Adolescents with Autoimmune Thyroid Diseases[☆]

Artur Bossowski^a, Hanna Borysewicz-Sanczyk^a, Barbara Glowinska-Olszewska^a, Beata Sawicka^a, Anna Bossowska^b, Justyna Michalak^a, Jadwiga Furmaniak^c

^aDepartment of Pediatric Endocrinology, Diabetology with Cardiology Division, Medical University, Bialystok, Poland;

^bDivision of Cardiology, Internal Affairs Ministry Hospital in Bialystok, Bialystok, Poland; ^cFIRS Laboratories, RSR Ltd based at Parc Ty Glas, Llanishen, Cardiff, UK

Background: Recent studies have revealed the presence of zinc and the expression of zinc transporter (ZnT) family members in most endocrine cell types. Moreover it was demonstrated that ZnT family plays an important role in the synthesis and secretion of many hormones. ZnT8 autoantibodies (ZnT8 Ab) next to glutamic acid decarboxylase antibodies (GAD Ab), insulin autoantibodies (IAA), and islet antigen-2 antibodies (IA-2 Ab) have been described as markers of autoimmune process in patients with type 1 diabetes mellitus. **Objective and hypotheses:** Since autoimmune disorders are known to be the pathophysiological factor in development of type 1 diabetes mellitus as well as thyroid diseases, we wanted to estimate in our study, the prevalence of ZnT8 Ab in patients with autoimmune thyroid diseases (AITDs). **Method:** The study was performed in the group consisting of 14 Graves' disease patients (mean age, 13.3±5.7), 13 Hashimoto's thyroiditis patients (mean age, 16.5±2.3), and 83 with DT 1 (mean age, 14±4.7). Patients were recruited from the Endocrinology Outpatient Clinic. GAD, IA-2, IAA, and ZnT8 antibodies' concentration was evaluated in the peripheral blood. **Results:** In our study we observed the presence of ZnT8 Ab in one patient (7.14%) in the case of Graves' disease patients while one patient (7.14%) in this group was positive for GAD Ab. In the case of Hashimoto's thyroiditis patients three patients (23%) were positive for ZnT8 Ab. One of ZnT8 Ab positive HT patients had additionally positive GAD Ab, IA-2 Ab, and IAA. In patients with DT1 we identified positive ZnT8 Ab (65.06%), GAD Ab (57.83%), and IA2 (49.4%) antibodies. **Conclusion:** In conclusion, these results may suggest that the presence of ZnT8 antibodies might not only be a marker of type 1 diabetes mellitus but also can be associated with other autoimmune diseases especially Hashimoto's thyroiditis.

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P1-D2-24

Final Height and BMI in English and Italian Adult Survivors of Childhood Acute Lymphoblastic Leukemia Treated without Cranial Radiotherapy[☆]

Patrizia Bruzzi^a, Assunta Albanese^d, Stephen Nussey^e, Barbara Predieri^b, Lorenzo Iughetti^b, Alison Leiper^c

^aPediatric Department, Azienda Ospedaliera-Universitaria Policlinico, Modena, Italy; ^bPediatric Department, University of Modena and Reggio Emilia, Modena, Italy; ^cHaematology Unit, Great Ormond Street Hospital for Children, London, UK; ^dPaediatric Oncology Unit, Royal Marsden Hospital, Sutton, UK; ^eEndocrine Unit, St Georges Hospital, London, UK

Background: Adult survivors of childhood Acute Lymphoblastic Leukemia (ALL) treated with protocols including cranial radiotherapy (CRT) demonstrate a persistent increased BMI and a reduced final height (FH). **Objective and hypotheses:** We investigated the effect of chemotherapy alone (CT) on BMI and FH in an international cohort of childhood ALL survivors. **Method:** English patients (61% female) treated on UKALL XI protocol without CRT and 107 Italian patients (46% female) treated on AIEOP 87-2000 protocols were included in the study. Height- and BMI-SDS were collected at: diagnosis (dT); end of CT (eT); FH. All Italian survivors and 54% of English population were exposed to i.v. high dose methotrexate (MTX). **Results:** Although survivors were not clinically short at FH, all Italian patients and English females experienced a loss of height-SDS during CT not followed by a complete catch-up growth (height-SDS: Italian female: dT 0.60±1.05, eT 0.19±1.09° (°significant difference vs dT), FH 0.07±1.25°; English female: dT 0.22±1.05, eT 0.00±0.90°, FH -0.02±0.84°; Italian male: dT 0.62±1.05, eT 0.30±1.09°, FH 0.27±1.03°; English male: dT 0.17±1.17, eT 0.10±1.13, FH 0.11±1.04). BMI-SDS increased during CT in all females and Italian males (BMI-SDS: Italian female: dT -0.12±1.31, eT 0.29±1.36°, FH 0.54±0.96°; English female: dT 0.14±1.25, eT 0.71±1.11°, FH 0.41±1.43; Italian male: dT 0.39±1.30, eT 0.82±1.29°, FH 0.49±1.09; English male: dT 0.48±1.38, eT 0.75±1.07, FH 0.25±1.38). Only Italian females showed a significant increase in BMI-SDS at FH compared with dT. **Conclusion:** CT alone minimizes the loss in FH SDS together with the increase in BMI SDS in adult survivors of childhood. Females seem more susceptible to CT effects, especially when exposed to high dose MTX.

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P1-D2-25

Autoimmune Polyendocrinopathy Candidiasis Ectodermal Dystrophy: New Insights into Phenotype and Genotype[☆]

Mariella Valenzise^a, Tommaso Aversa^a, Alessandra Fierabracci^b, Paolo Porcelli^c, Corrado Betterle^d, Filippo De Luca^a

^aUOC Pediatria, Messina, Italy; ^bOPBG, Roma, Italy;

^cEndocrinology Unit, Palermo, Italy; ^dEndocrinology Unit, Padova, Italy

Background: Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal-Dystrophy (APECED) is a rare autosomal recessive disease, caused by mutations of AIRE gene on chromosome 21. It is characterized by three main diseases: chronic mucocutaneous candidiasis (CMC), chronic hypoparathyroidism (HP) and

Addison's disease (AD). **Objective and hypotheses:** In this paper we review the clinical phenotypes and the genotypes of pediatric Sicilian population affected by APECED in order to: i) describe the peculiarities of this population with respect to those described in the literature; ii) to give an overview on the genetic epidemiology of APECED in Sicily and iii) to report new mutations of AIRE gene. **Method:** Fifteen Sicilian APECED patients were followed at our Department. **Results:** presented CMC, 15/15 presented HP and 13/15 presented AD. One patient of our series presented the triad of the syndrome very early (2.4 years). 5/15 presented gastrointestinal disease with tryptophan hydroxylase antibodies positivity. R203X was the most common mutation in our population (30% of alleles), followed by R257X (20%); other mutations were A21V (13%) and W78R (7%), which are typical of Campania and Apulia, respectively. Two brothers presented a new mutation (IVS13+2T) on intron 13, never described in APECED populations. **Conclusion:** On the basis of our experience we can infer that: i) the clinical manifestation that can be considered as connotative of APECED in Sicilian patient is HP (100% of cases); ii) the most frequent mutation in Sicilian APECED patient is R203X, that is peculiar of our population, but other mutation could be present as W78R, typical of Apulian cases and A21V typical of Campania; iii) the triad of the syndrome may appear very early in the life as observed in one patient of our series; for this reason the clinicians should be vigilant of diagnosis in order to initiate treatment very early.

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P1-D2-26

Abstract withdrawn.

P1-D2-27

Late Endocrine Effects Despite Reduced Intensity Chemotherapy for Bone Marrow Transplantation in Children

Jonathan Howell^a, Kasiani Myers^b, Adam Lane^b, Gregory Wallace^b, Sonata Jodele^b, Susan Rose^a

^aEndocrinology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA; ^bBone Marrow Transplantation and Immune Deficiency, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA

Background: Bone marrow transplantation (BMT) is known to affect endocrine function, most commonly causing primary hypothyroidism and hypogonadism in children. Newer reduced intensity conditioning (RIC) uses less myeloablative chemotherapy and no irradiation. Our study goal was to evaluate endocrine effects at 1 year post BMT in pediatric patients who received RIC. **Methods:** Retrospective, IRB-approved chart review was performed on 121 patients (44 females) who underwent a single RIC BMT to treat immune disorders (HLH, SCID, IPEX, and XLP),

genetic syndromes (Shwachman, Hurler, Seckel, and ALD), or malignancy (ALL and CML), and survived at least a year. Data recorded included dates, age, gender, diagnosis, height SDS, weight, and endocrine hormone results. **Results:** Among the study population, 43 patients, aged 2–17, had height and weight data both prior to and at least 1 year following BMT. The mean interval between first and last values was 20.5 months. Height SDS and BMI z-scores (BMI-Z) were examined separately using linear mixed effects models. There was a significant decrease in post-BMT height SDS compared to pre-BMT values (-1.26 ± 1.42 vs -0.94 ± 1.55 , $P=0.0471$). BMI-Z was also significantly reduced following BMT (0.28 ± 1.45 vs 1.02 ± 1.49 , $P=0.0028$). When grouped by diagnosis, there was no significant difference in height SDS or BMI-Z among immune disorders ($n=21$) vs all others ($n=22$). Thyroid function testing was performed on 78 patients following BMT, and 63 (81%) had normal TSH and free T₄. Among the remainder, 11 (14%) had evidence of primary hypothyroidism and 4 (5%) of these received hormone replacement. Four patients (5%) had evidence of primary hyperthyroidism or central hypothyroidism. Of the 67 patients with 25-OH vitamin D levels, 46 (69%) were normal (≥ 30 ng/ml), while 21 (31%) were low. **Conclusions:** Despite RIC, children undergoing BMT still have significant late endocrine effects following transplant. Prospective follow up for early detection of endocrine deficiencies after BMT is needed in these children. Further analysis is required in order to compare the degree of post-transplant endocrine effects with patients undergoing standard chemotherapy protocols.

P1-D2-28

Immune Changes are Observed After Radioiodine Treatment for Hyperthyroidism in Graves' Disease Patients

Sarah Côté-Bigras^a, Jean Verreault^b, Diane Rottembourg^a

^aDepartment of Pediatrics, Faculty of Medicine, University of Sherbrooke, Sherbrooke, Quebec, Canada; ^bDepartment of Nuclear Medicine and Radiobiology, Faculty of Medicine, University of Sherbrooke, Sherbrooke, Quebec, Canada

Background: Graves' disease (GD) involves autoimmunity against TSH receptor (TSHR) bearing cells, leading to hyperthyroidism and often orbitopathy. When hyperthyroidism is treated with radioactive iodine (RAI), exacerbation of the orbital disease can occur. **Objective and hypotheses:** We hypothesized that RAI has immune effects affecting the balance between autoreactive T cells and T cells with regulatory properties. **Method:** We monitored lymphocyte populations in peripheral blood of GD patients, patients with non-autoimmune goiter (NG), and healthy controls. **Results:** Circulating T cell interferon gamma production in the presence of TSHR peptides was measured in ten GD patients and ten healthy controls. Significant response to at least one peptide was measured in 2/10 and 4/10 GD patients before and after RAI therapy, respectively, and in none of the controls. Regulatory CD4⁺CD25^{high}FOXP3⁺T cells (Tregs) and

V α 24⁺V β 11⁺CD3⁺ natural killer T cells (NKT) were counted by flow cytometry in 16 GD patients and in five NG patients before and 1 month post-RAI treatment, as well as in seven untreated healthy subjects over the same time period. Variance of Tregs and NKT cells before and after RAI therapy was greater in GD patients compared to NG (Treg: $P=0.0053$; NKT: $P=0.0117$) and to controls (Treg: $P<0.0001$; NKT: $P=0.0217$). Post-RAI therapy, frequency of Tregs was positively correlated with NKT cells numbers in GD patients ($P=0.0422$). **Conclusion:** Collectively, RAI therapy has a mild effect on auto-reactive T cells specific to thyroid peptides. However, variation in Tregs and NKT cells after thyroid radiation appears to be greater in Graves' disease patients.

P1-D2-29

Standard Population Screening for Diabetes Mellitus has Low Sensitivity in Identifying Diabetes in Adult Survivors of Childhood Bone Marrow Transplantation with Total Body Irradiation

Christina Weja^{a,b}, Rebecca Unsworth^a, Nikki Davis^{a,c}, Ruth Elson^a, Karin Bradley^{a,d}, Michael Stevens^{a,d}, Elizabeth Crowne^{a,d}

^aUniversity Hospitals Bristol NHS Foundation Trust, Bristol, UK;

^bSt Georges Hospital, St Georges Health Care NHS Trust, London, UK; ^cUniversity Hospital Southampton NHS Foundation Trust, Southampton, UK; ^dUniversity of Bristol, Bristol, UK

Background: Adult survivors of childhood leukaemia treated Bone marrow transplantation with total body irradiation (BMT/TBI) have an increased risk of diabetes mellitus (DM) disproportionate to their level of adiposity or other recognised risk factors. Post prandial hyperglycaemia due to reduced β -cell reserve after irradiation will be missed by fasting glucose (FG) levels. However, the UK National Institute of Clinical Excellence (NICE) screening guidelines recommend the use of fasting glucose (FG) >7 mmol/l and/or HbA1c >48 mmol/mmol for the diagnosis of DM and, FG 5.5–6.9 mmol/l or HbA1c 42–47 mmol/mmol to indicate high risk. **Objective:** To evaluate sensitivity of the UK national screening criteria in the diagnosis of DM in survivors of childhood BMT/TBI. **Method:** Subjects: 37 ($M=19$) BMT/TBI survivors from a single UK centre 2006–2013, mean age (s.d.) 18.9 (3.1) years treated for acute lymphoblastic leukaemia ($n=31$) and acute myeloid leukaemia ($n=6$) by BMT/TBI at 7.9 (3.8) years of age. Outcome measures: demographic and treatment details, results of OGTT and HbA1c, prevalence of hypertension ($>130/85$), hypertriglycerides (>1.7 mol/l) and reduced high density lipoprotein(HDL) ($M<1.03$, $F<1.29$ mmol/l). **Results:** OGTT results revealed 6 (16.2%) with DM (120 minute glucose >11.1 mmol/l), 13 (37.1%) with impaired glucose tolerance (120 min glucose 7.8–11.1 mmol/l) and 2 (5%) with impaired FG (>7 mmol/l). NICE screening criteria for DM with FG (>7 mmol/l) or HbA1c (>48 mmol/mmol) identify 2/6 (33%) patients with DM. The lower cut-offs recommended for higher risk patients with FG >5.5 mmol/L and HbA1c >42 mmol/mmol identify 3/6 (50%) and 2/6 (33%) with DM respectively. In addition, only 1/13 (7.7%) with impaired glucose tolerance had a FG of >5.5 mmol/l and

none had HbA1c >42 mmol/mmol. BMT/TBI survivors had a high prevalence of hypertension (16%), hypertriglyceridaemia (62%), and reduced HDL (35%). **Conclusions:** There is a high prevalence of abnormal glucose tolerance and metabolic abnormalities in BMT/TBI survivors. Standard screening criteria under NICE with FG and HbA1c will miss 67% of those with DM and therefore do not identify those at risk. Screening of DM in BMT/TBI survivors requires standard OGTTs although the optimal frequency needs ongoing evaluation.

P1-D2-30

Managing Children with Thickened Pituitary Stalk and/or Idiopathic Central Diabetes Insipidus: a Single Centre Experience on 63 Children

Manuela Cerbone^a, Ash Ederies^b, Laura Losa^a, Carolina Moreno^a, Kristi Sun^a, Helen A Spoudeas^a

^aNeuroendocrine Division, London Centre for Paediatric Endocrinology, University College and Great Ormond Street Hospitals, London, UK; ^bNeuroradiology Department, Great Ormond Street Hospital, London, UK

Background and objective: Children with Thickened pituitary stalk (TPS) and/or Idiopathic central diabetes insipidus (ICDI) present to different (endocrine, oncology, and ophthalmology) specialists. Their rarity, absence of agreed radiological criteria or consensus guidance, make their management problematic. Biopsy is too dangerous and cases may remain undiagnosed or evolve over decades. We aimed: i) to longitudinally characterize a large childhood cohort presenting with TPS and/or ICDI ii) to assess radiological, clinical, visual, and endocrine correlates over time. **Method:** We searched the terms 'thickened pituitary stalk' or 'idiopathic diabetes insipidus' in electronic radiology and clinical document libraries at our centre over the last 30 years. 63 retrospective longitudinal data sets in patients with either TPS and/or ICDI were collected and MRI scans reviewed. In nine patients the diagnosis was clear at presentation. Within the remaining 54 occult cases: ten had TPS, 18 ICDI, and 26 TPS + ICDI. **Results:** Patients with TPS were older (TPS: 9.8 ± 4.9 years) at presentation than those with ICDI (5.5 ± 4.4 years) and TPS + ICDI (6.2 ± 3.4 years) ($P<0.04$). TPS + ICDI patients were more likely (38.5%) than ICDI (5.6%) and TPS (none) to have histiocytosis. Tumours were identified in 26.9% TPS + ICDI and 27.9% ICDI, 1.0 ± 1.4 and 1.9 ± 2.4 years later respectively, but not in TPS. 80% TPS cases remained unexplained (vs 61.1% ICDI and 34.6% TPS + ICDI) at a shorter follow-up (2.5 vs 5.2 and 5.8 years). Multiple anterior pituitary deficits evolved with time across groups (GHd, 45–58%, TSHd 19–30%, ACTHd 13–21%, and GnRHd 7–17%) but visual deficits, present in 8–23% at presentation, increased only in TPS + ICDI (7.6–34.6%). **Conclusion:** Longitudinal endocrine assessment of all patients with TPS and ICDI is important. ICDI is a negative prognostic factor for malignant disease, whilst the combination with TPS is more often associated with histiocytosis. TPS alone is unlikely to lead to malignancy but should be prioritized for endocrine follow-up.

P1-D2-31

Primary Pancreatic Insulinomas: Clinical, Morphological, and Genetic Characteristics of 12 Children

Maria Melikyan^a, Larisa Gurevich^b, Sergey Makarov^c, Alexey Stepanov^c, L Friis-Hansen^d, Valentina Peterkova^a, Henrik Christesen^e

^aEndocrinology Research Center, Moscow, Russia; ^bM. F. Vladimirovsky Regional Clinical Institute, Moscow, Russia; ^cRussian Children's Clinical Hospital, Moscow, Russia; ^dCopenhagen University Hospital, Copenhagen, Denmark; ^eH. C. Andersen Children's Hospital Odense University Hospital, Odense, Denmark

Background: Insulinomas are extremely rare tumors in children and an uncommon first manifestation of the MEN1 syndrome. An early clinical and genetic diagnosis is very important for the appropriate medical assessment and family counseling. In children, insulinomas are usually benign tumors with only a few reports of malignant cases. **Objective and hypotheses:** To investigate clinical features, genetic and morphological characteristics of 12 children with primary pancreatic insulinomas. **Method:** Insulinomas were diagnosed biochemically and by imaging and verified histopathologically. Detailed clinical and biochemical examination was performed in all children. Sequencing of the *MEN1* gene was performed in 11 patients using bidirectional direct sequencing and MLPA deletion analysis. Follow up (mean age 16.6 years) included screening for signs of MEN1 (hormonal, imaging) and screening for metastases in case of malignant tumors. **Results:** Twelve children aged 8–16 years were diagnosed to have primary pancreatic insulinoma. Seizures and weight gain were the most common symptoms of hyperinsulinemic hypoglycemia (83.3 and 66.6% respectively). Five children (41.6%) had hypoglycemic coma before the diagnosis was established. Eight patients (66%) were erroneously diagnosed with epilepsy. Four out of 11 children investigated (36.3%) were found to have mutations in the *MEN1* gene and developed hyperparathyroidism and hyperprolactinemia during the following 10 years. One patient with normal *MEN1* analysis developed hyperparathyroidism. In the two patients with *MEN1*, relatives revealed the biochemical spectrum of MEN1 components, but with no clinical symptoms. Histopathological studies revealed G2 differentiation stage (ENETs grade) in five of 12 cases (41.6%), distant metastases were seen during follow up in two patients. **Conclusion:** Late diagnosis of insulinoma is typical, probably due to unspecific symptoms and the disease rareness. MEN1 syndrome should be suspected in all cases of pediatric insulinomas, even in cases with no other clinical features of MEN1 and absence of suspicious family history. In our study a high incidence of malignant insulinomas was seen at follow up.

P1-D2-32

Papillary Thyroid Cancer After Hematopoietic Stem Cell Transplantation in Young Age

Marta Snajderova^a, Petra Keslova^b, Pavla Sykorova^c, Petr Sedlacek^b, Renata Formankova^b, Jan Stary^b

^aDepartment of Paediatrics, 2nd Faculty of Medicine, Charles University in Prague and University Hospital Motol, Prague, Czech Republic; ^bDepartment of Paediatric Haematology and Oncology, Charles University in Prague and University Hospital Motol, Prague, Czech Republic; ^cDepartment of Nuclear Medicine and Endocrinology, Charles University in Prague and University Hospital Motol, Prague, Czech Republic

Background: Increasing number of survivors following hematopoietic stem cell transplantation (HSCT) leads to necessity to focus also on careful monitoring for late effects. High dose chemotherapy and total body irradiation (TBI) is used for conditioning regimen in many patients. Thyreopathies belong to the most frequent among late endocrinopathies. **Objective:** Aim of the study was to evaluate incidence of secondary thyroid malignancies after HSCT in young age, especially after TBI. **Population and methods:** We analysed data (fT₄, TSH, thyroid antibodies, thyroid function, and ultrasound imagine) of 288 (110F, 178M) surviving patients transplanted within the period 1989–2012 at median age 8.2 years (range 0.2–20.5) evaluated at age 17.9 years (1.8–40.5), after HSCT 8.5 years (1.3–24.3). Of them 177 subjects were treated for malignant diagnosis, TBI (10–14 Gy) was used in 91 patients. **Results:** Papillary thyroid carcinoma (PTC) micronodular, T1 or T2 stage was diagnosed in 4/288 patients (2F, 2M) 8.7 years (5.3–15.2) after HSCT. Of them three were previously treated for autoimmune thyroid disease (AITD) and one for hypothyroidism. All but one had HSCT for malignant disease, in all TBI was used. Another nine patients (of them seven after TBI; *n*=4 treated for AITD) have been monitored for nodular goiter (FNAB confirmed benign thyroid nodule). In total 83/288 (29%) patients were treated for hypothyroidism or AITD. **Conclusions:** Risk of secondary malignancies after HSCT is increasing within the time. Long-life late effects monitoring as an important part of post-transplant care is necessary. Regular sonographic evaluation of thyroid gland and neck is very important especially more than 5 years after HSCT and namely in all patients after TBI. Regular monitoring of thyroid function, laboratory parameters and ultrasound is highly recommended.

P1-D2-33

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

Flavia Napoli^a, Annalisa Calcagno^a, Natascia di Lorgi^a, Anna Elsa Maria Allegri^a, Marianna Vannati^a, Laura de Miglio^a, Roberta Biancheri^b, Isabella Ceccherini^c, Yael Hacohen^d, Leslie Jacobson^d, Angela Vincent^d, Mohamad Maghnie^a

^aDepartment of Pediatrics, Istituto G. Gaslini, Genova, Italy;
^bDepartment of Neuroscience, Istituto G. Gaslini, Genova, Italy;
^cLaboratorio di Genetica Molecolare, Istituto G. Gaslini, Genova, Italy; ^dNuffield Department of Clinical Neurosciences, Oxford, UK

Background: ROHHADNET syndrome affects children with normal development until 2–4 years of age. **Objective and hypotheses:** Aim of this study was to evaluate a possible role of autoimmunity in this disorder. In spite of a suspicion for genetic etiology, disease-associated genetic variations have not been identified. A paraneoplastic/autoimmune etiology has been suggested mainly because of the association with neural crest tumors. **Method:** Six patients with ROHHADNET underwent clinical and neuroradiologic studies; serum levels of several antibodies against neural receptors (NMDAR, LGI1, CASPR2, dopamine receptor, AMPAR, ganglionic AChR, VGKC, and VGCC) were assessed. CSF was tested for oligoclonal bands in 2/6 patients. **Results:** All patients had uneventful history until 2–4 years, when they developed rapid weight gain, hyperprolactinemia, water/salt balance disruption and behavioral problems or EEG alterations (five patients). Central apnoeas were diagnosed in four patients and non-invasive ventilation was started. Central adrenal insufficiency was found in three patients; all patients had GH deficiency, two patients had central precocious puberty, five patients had central hypothyroidism. Brain MRI was normal or not significant in all patients. A retroperitoneal mass was found in four patients. The above mentioned serum autoantibodies were undetectable in all patients. CSF tested positive for oligoclonal bands in patient. **Conclusion:** In this study we aimed to evaluate whether the autoantibodies responsible for immune mediated encephalitis could be detected in serum of patients with ROHHADNET, whose possible autoimmune etiology has been suggested based on the frequent association with neural crest tumors, the finding of extensive infiltrates of lymphocytes and histiocytes in the hypothalamus of some patients and a partial response to intravenous immunoglobulin, or immunosuppressants. The results of our study were negative, but CSF tests have shown autoimmune activation in one patient so far. Additional studies are ongoing to further evaluate the autoimmune status of these patients.

P1-D2-34

High Prevalence of Low Bone Mass in Adolescents with Non-Transfusion Dependent Hb E/ β -thalassemia^{*}

Pairunyar Nakavachara, Jaturat Petchkul, Gritta Jeerawongpanich, Vip Viprakasit

Division of Pediatric Endocrinology, Department of Pediatrics, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand

Background: Hb E/ β -thalassemia is the most common β -thalassemia disorder in Southeast Asia. Children with Hb E/ β -thalassemia vary greatly in red cell transfusion requirement. Some are transfusion dependent (TD) whereas others are non-TD (NTD). Iron-overload associated with transfusion dependency causes endocrinopathies such as delayed puberty, short stature and low bone mass. The prevalence of these complications are high in TD patients with iron overload. While NTD thalassaemic patients are considered to have low risks of developing endocrine complication. As yet, the prevalence of short stature, delayed puberty and low bone mass in NTD thalassaemic patients is unknown. **Objective:** To evaluate prevalence of short stature, delayed puberty, low bone mass in adolescents with NTD HbE/ β -thalassemia. **Method:** We investigated the prevalence of short stature, delayed puberty and low bone mass among 22 adolescents aged 13.2–20 years old with NTD Hb E/ β -thalassemia by assessing their growth, pubertal status and BMD measured by DXA. BMD values were adjusted for bone age (BA). **Results:** The prevalence of short stature, delayed puberty, and low bone mass are 9.1, 9.1, and 63.6% respectively. Mean hemoglobin and serum ferritin levels were 8.9 ± 0.9 g/dL and 211.6 ± 145.4 ng/mL, respectively. The percentage of patients with hemoglobin levels of ≥ 8.5 g/dl in patients with normal BMD is significantly higher than patients with low bone mass (86.7 vs 28.6%, $P=0.014$). Average hemoglobin level correlates significantly with L2-4 and total body BMD Z-score adjusted for BA. **Conclusion:** This is the first study to show that low bone mass is highly prevalent in adolescents with NTD Hb E/ β -thalassemia. Anemia seems to contribute to low bone mass in this study. Our findings have important implications for the clinical management of these NTD patients. Whether raising hemoglobin levels by more intensive transfusion in NTD thalassaemic patients will ameliorate low bone mass needs to be further investigated.

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P1-D2-35

Assessment of Quality of Life Data After 4 Monthly s.c. Doses of a Human Monoclonal Anti-Fibroblast Growth Factor 23 Antibody (KRN23) in Adults with X-linked Hypophosphatemia^{*}

Mary Ruppe^a, Xiaoping Zhang^b, Erik Imel^c, Thomas Weber^d, Mark Klausner^b, Takahiro Ito^b, Maria Vergeire^b, Jeffrey Humphrey^b, Francis Glorieux^e, Anthony Portale^f, Karl Insogna^g, Munro Peacock^c, Thomas Carpenter^g

^aThe Methodist Hospital, Houston, Texas, USA; ^bKyowa Hakko Kirin Pharma, Inc., Princeton, New Jersey, USA; ^cIndiana University School of Medicine, Indianapolis, Indiana, USA; ^dDuke Clinical Bone Laboratories, Duke University Medical Center, Durham, North Carolina, USA; ^eShriners Hospital for Children, Montreal, Quebec, Canada; ^fUniversity of California, San Francisco, California, USA; ^gYale Center for X-Linked Hypophosphatemia, Yale University School of Medicine, New Haven, Connecticut, USA

Objectives: In X-linked hypophosphatemia (XLH), abnormally elevated serum Fibroblast growth Factor 23 (FGF23) results in low renal maximum threshold for phosphate reabsorption, low serum phosphorus, inappropriately normal 1,25-dihydroxyvitamin D, and development of rachitic deformities. The effect of KRN23 on health-related quality of life (HRQL) was assessed. **Methods:** Open-label KRN23 was given s.c. every 28 days up to four doses to 28 adults with XLH (26 completers). KRN23 doses were given in a stepwise dose escalation algorithm: 0.05 to 0.1–0.3 to 0.6 mg/kg. HRQL (SF-36v2 and WOMAC) was measured at baseline and day 120. Eight SF-36v2 scales were evaluated: physical functioning (PF), role limitations due to physical health (RP), social functioning (SF), bodily pain (BP), general health perceptions (GH), vitality (VT), role limitations due to emotional problems (RE), and mental health (MH). Physical component summary (PCS) and mental component summary (MCS) scores were derived. WOMAC scales included Pain, stiffness and physical functioning. Significance was declared for $P < 0.05$. **Results:** At baseline, mean BP, PF, RP, and PCS were far below those of the general USA population. At endpoint, mean MH and MCS became significantly higher than US norms; RP normalized; and PCS, BP, and PF remained below the norm. Scores for other domains remained comparable to the norm. Mean scores for all SF-36v2 domains increased and those for WOMAC decreased, indicating improvement in HRQL. Increases in RP, BP, and PCS (SF-36v2) and decreases in physical functioning and stiffness (WOMAC) were significant. At baseline, only GH, BP, and SF scores for XLH patients were significantly higher than a population with osteoarthritis; others were not significantly different. At endpoint, all mean SF-36v2 scores increased significantly relative to the osteoarthritis population for all except PF and RE. **Conclusions:** Four monthly doses of KRN23 resulted in significantly improved patient HRQL.

*Nominated for a Presidential Poster Award.

to inadequate vitamin D levels which impair bone health. Moreover, numerous studies linked decreased sunlight exposure to non-skin cancer incidence or survival. **Objective and hypotheses:** To compare sun habits in a cohort of paediatric patients with a history of malignancy to healthy controls. We hypothesized that sun exposure will be decreased in the study group since patients are firmly instructed to avoid sun exposure during therapy. Secondly, we assessed calcium intake of both groups. **Method:** Sun habits, as well as calcium intake, were assessed by validated questionnaires in 143 children with a history of malignancy (aged 11.2 ± 4.6 years, male=68, mean interval from diagnosis 4.4 ± 3.8 years) and 150 healthy controls (aged 10.4 ± 4.8 years, male=67). Pertinent clinical data of patients were obtained from their charts. **Results:** Patients and healthy controls reported a similar time of sun exposure during weekdays (94 ± 82 min/day vs 81 ± 65 min/day; $P=0.83$). However, during the weekend patients spent significantly less time outside compared to controls (103 ± 85 min/day vs 124 ± 87 min/day; $P=0.015$). Time elapsed from diagnosis was positively correlated with time spent outside both during weekdays ($r=0.194$, $P=0.02$) and weekends ($r=0.217$, $P=0.009$). Patients were more likely than controls to wear a hat when in the sun (34.5 vs 20.7% reporting 'always' or 'frequently'; $P=0.009$). There was no difference between the two groups regarding other sun protection habits such as using sunscreen, wearing a shirt covering the shoulders, staying in the shade or wearing sunglasses. Daily calcium intake of both groups was suboptimal, reaching only 52% of the RDA in adolescents, with no significant difference between patients and controls. **Conclusion:** Sun exposure of children with a history of malignant disease is decreased compared to healthy control. The combination of sunlight avoidance and inadequate calcium intake might have deleterious implications for their bone health.

*Nominated for a Presidential Poster Award.

P1-D2-36

Sun Protection Habits and Calcium Intake in Children with Malignancy^{*}

Yael Levy-Shraga^{a,b}, Orit Pinhas-Hamiel^{a,b}, Michal Ben Ami^{a,b},
Yonatan Yeshayahu^{a,b}, Vered Temam^c, Rinat Cohen^d,
Dalit Modan-Moses^{a,b}

^aPediatric Endocrinology unit, The Edmond and Lily Safra Children's Hospital, Chaim Sheba Medical Center, Tel-Hashomer, Ramat Gan, Israel; ^bThe Sackler School of Medicine, Tel-Aviv University, Tel Aviv, Israel; ^cDepartment of Pediatric Hematology–Oncology and BMT, The Edmond and Lily Safra Children's Hospital, Chaim Sheba Medical Center, Tel-Hashomer, Ramat Gan, Israel; ^dMeuhedet Health Services, Tel Aviv, Israel

Background: U.V. radiation exposure is the major environmental risk factor for skin cancers. However, sun avoidance leads

P1-D2-37

Vitamin D Levels and Effects of Vitamin D Replacement in Children with Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Cervical Adenitis (PFAPA) Syndrome^{*}

Perla Scalini, Stefano Stagi Stagi, Chiara Iurato, Camilla Menchini,
Cristina Manoni, Giulia Anzillotti, Maurizio de Martino,
Salvatore Seminara

Health Science Department, Anna Meyer Children's University Hospital, University of Florence, Florence, Italy

Background: The periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome, is an autoinflammatory disease characterised by regularly recurrent fever episodes, due to seemingly unprovoked inflammation. **Objective and hypotheses:** The aim of the study was to assess serum 25-hydroxy cholecalciferol (25(OH)D) concentrations in children with PFAPA and to evaluate longitudinally the effect of wintertime

supplementation on 25(OH)D status and the immune response in these children. **Method:** We have evaluated 25 Italian patients (19 males, six females, aged 2.4–5.3 years) who fulfilled the Euro-Fever PFAPA criteria. For each patient, we recorded demographic and anthropometric data, clinical manifestations, serum calcium, phosphate, and 25(OH)D. After 400 UI 25(OH)D supplementation, clinical, and auxological characteristics, calcium and phosphate, and 25(OH)D concentrations were re-evaluated. Data were compared with a sex- and age-matched control group (74 males, 39 females, mean age 4.9 ± 1.3 years, range 2.1–8.3 years). **Results:** PFAPA patients showed very reduced 25(OH)D levels than controls ($P < 0.0001$). Regarding the effect of the different seasons on 25(OH)D status, 25(OH)D levels in winter were significantly reduced in respect to those of the summer ($P < 0.005$), these values were significantly lesser than controls ($P < 0.005$). However, 25(OH)D levels correlated with episodes of fever ($P < 0.005$) and CRP ($P < 0.005$). After vitamin D₃ supplementation, PFAPA patients displayed significantly increased 25(OH)D levels, showing a significative reduction of febrile episodes and its characteristics (mean duration of fever episodes, $P < 0.05$ and number of febrile episodes for year, $P < 0.005$). **Conclusion:** Deficient and insufficient vitamin D serum levels were found in most children with PFAPA. Hypovitaminosis D can be significant risk factor for PFAPA recurrence. In fact, 25(OH)D supplementation seems significantly to reduce PFAPA episodes and fever duration, disclosing the importance of vitamin D as immunoregulatory factor in this syndrome.

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P1-D2-38

Increased Rates of Infantile Hypercalcaemia Following Guidelines for Antenatal Vitamin D₃ Supplementation

Lisa A Amato^{a,b}, Kristen A Neville^{a,b}, Shihab Hameed^{a,b}, Wei Shern Quek^b, Charles F Verge^{a,b}, Helen J Woodhead^{a,b}, Chris P White^{b,c}, Andrea Rita Horvath^c, Jan L Walker^{a,b}

^aSydney Children's Hospital, Sydney, New South Wales, Australia;

^bUniversity of New South Wales, Sydney, New South Wales,

Australia; ^cPrince of Wales Hospital, Randwick, New South Wales, Australia

Background: Consultations for infantile hypercalcaemia have increased at Sydney Children's Hospital since guidelines for vitamin D₃ supplementation during pregnancy were introduced in 2006. Recent nationwide shortages of low-calcium formula (LCF) suggest this problem may be widespread. **Aim:** To determine if infantile hypercalcaemia is occurring more commonly, identify potential aetiologies and clinical significance. **Methods:** De-identified, first-measured serum calcium from all infants <6 months ($n = 5796$) measured in our laboratory, were grouped by years 2005–2007 ($n = 1516$), 2008–2010 ($n = 1945$), and 2011–2013 ($n = 2335$). We analysed 13 infants treated by our

department for idiopathic infantile hypercalcaemia (IIH) from 2011 to 2013. **Results:** Rates of hypercalcaemia (> 2.75 mmol/l) increased from 2011 (1.1 vs 1.3 vs 8.7%, $\chi^2 P < 0.001$). Rates of hypocalcaemia (< 2.25 mmol/l) fell steadily (42.4 vs 32.3 vs 24.8%, $\chi^2 P < 0.001$). Twelve mothers of our 13 infants with IIH received antenatal vitamin D₃ supplementation. One infant also received 400 units/day Vitamin D₃ postnatally. At diagnosis, median age was 13 days (range 4–50), 77% were breast-fed, 54% were symptomatic, and 25% had nephrocalcinosis. Median initial calcium was 3.00 mmol/l (range 2.84–4.03) and phosphate 2.04 mmol/l (1.1–3.33). PTH was not elevated (median 1.0 pmol/l (< 0.3 –3.1)), urinary calcium:creatinine ratio not suppressed (median 2.3, (0.4–9)), 25OHVitD low-normal (median 44 nmol/l (17–218)) and 1,25(OH)₂VitD elevated (median 232 pmol/l (64–720)). In 7/10 infants with data available, treated with LCF for median 95 days (range 25–310), median PTH rose to 17.1 pmol/l ((8.2–49.3), $P = 0.02$) with a trend to lower 25OHVit D (median 23 nmol/l (< 10 –108), $P = 0.09$) despite continued high-normal calcium levels (median 2.66 mmol/l (2.11–2.75)). **Conclusion:** IIH was associated with significant morbidity. Concurrent changes in rates of hyper and hypocalcaemia suggest antenatal vitamin D₃ supplementation as an aetiological factor. Our patients' biochemistry raises variations in vitamin D metabolism or calcium set-point as potential associated factors. Monitoring treatment with LCF should not be based on calcaemia alone.

P1-D2-39

Continuous s.c. Recombinant PTH¹⁻³⁴ Pump Therapy in Congenital Hypoparathyroidism Associated with Malabsorption

Vrinda Saraff, Wolfgang Högl

Department of Endocrinology, Birmingham Children's Hospital, Birmingham, UK

Background: Congenital hypoparathyroidism (CH) is a rare disease that usually responds well to conventional therapy with active vitamin D and calcium supplementation. The successful use of continuous s.c. recombinant parathyroid hormone (rhPTH¹⁻³⁴) infusion as a hormone replacement has been demonstrated in cases of CH caused by autosomal dominant hypoparathyroidism or autoimmune polyendocrine syndrome type 1. **Objective and hypotheses:** We report the successful use of s.c. rhPTH pump therapy in the management of CH resistant to conventional therapy due to severe malabsorption. **Method:** This now 13-year-old boy, born to consanguineous Asian parents, was diagnosed with CH in infancy, which was initially managed on conventional treatment with oral calcium supplements and vitamin D analogues. He was subsequently diagnosed with sensory neural deafness, developmental delay and cryptogenic liver disease requiring liver transplant at the age of 2 years. He was also noted to have persistent diarrhoea with hypoalbuminaemia,

lymphopenia and developed recurrent severe hypocalcaemia. Video capsule endoscopy confirmed extensive intestinal lymphangectasia which was not amenable to surgery. Despite alfacalcidol doses of 200 ng/kg and oral calcium supplements of 300 mg/kg per day, serum calcium remained between 1.26 and 1.98 mmol/l. He had repeated hospital admissions with either hypocalcaemic seizures or symptomatic refractory hypocalcaemia requiring i.v. calcium infusions. He was started on a continuous s.c. infusion of rhPTH¹⁻³⁴ (teriparatide) delivered via a Medtronic pump on a dose of 0.16 mg/kg per day. **Results:** He was successfully weaned off alfacalcidol, oral calcium and magnesium supplements and his serum calcium normalised and stabilised within days of commencing s.c. PTH. The dose of teriparatide is titrated against serum calcium and urinary calcium excretion. **Conclusion:** We describe the first case of successful use of continuous s.c. rhPTH¹⁻³⁴ therapy in a patient with CH and associated severe malabsorption.

P1-D2-40

Effects and Limitations of Cinacalcet Therapy in Neonatal Severe Hyperparathyroidism

Ulla Doehnert^a, Wolfgang Goepel^b, Wolfgang Hoepfner^c, Olaf Hiort^a

^aDepartment of Pediatric Endocrinology, University of Luebeck, Luebeck, Germany; ^bDepartment of Neonatology and Pediatric Intensive Care, University of Luebeck, Luebeck, Germany; ^cFa. Bioglobe, Hamburg, Germany

Background: Neonatal severe hyperparathyroidism (NSHPT) has been associated with inactivating mutations of the calcium-sensing receptor (CASR) gene. Impaired inhibition of PTH secretion by extracellular ionized calcium and decreased urinary excretion of calcium leads to severe hypercalcemia in the first days of life. Calcium responsiveness of the CaSR is amplified by type 2 calcimimetic agents like cinacalcet, which has been able to normalize PTH and calcium levels in cases of NSHP and postpone parathyroidectomy. **Case report:** A full-term female newborn presented with severe respiratory distress due to thoracic and pulmonary hypoplasia at birth and hypotonia and failure to thrive in the following weeks. On the sixth day of life the serum calcium level was elevated to 3.27 mmol/l. Further evaluation showed hyperparathyroidism in the presence of low urinary calcium excretion. Sequence analysis of the CASR gene revealed a *de novo* heterozygous mutation in exon 4 (c.554G>A; p.R185Q). Forced diuresis and a single dose of pamidronate did not improve hypercalcemia. While cinacalcet therapy normalized PTH secretion and increased urinary excretion of calcium, serum calcium levels remained elevated above 3.27 mmol/l and the patient developed progressive nephrocalcinosis. **Discussion:** The mutation above has been associated with NSHPT that has successfully been treated with cinacalcet experimentally. A dosage has not been established for this indication and long-term side effects are unknown. In the presence of normal PTH levels and

increased urinary calcium excretion other gene mutations have been discussed to additionally impair calcium sensing in patients who do not reach eucalcemia. **Conclusion:** Cinacalcet offers an option to treat NSHPT resulting from inactivating mutations in the CASR gene. Laboratory parameters and ultrasound of the kidneys have to be closely monitored in order to prove the effect of the therapy and avoid side effects. Additional factors affecting hypercalcemia and calcium sensing should be considered.

P1-D2-41

Young Adults with Klinefelter Syndrome and Congenital Anorchia Treated with Testosterone Have Normal Bone and Muscle Mass but Increased Central Adiposity

S C Wong^a, D Scott^b, S Tandon^a, P Ebeling^b, M Zacharin^a

^aDepartment of Endocrinology, The Royal Hospital for Sick Children, Melbourne, Victoria, Australia; ^bAustralian Institute for Musculoskeletal Sciences, Melbourne, Victoria, Australia

Background: Decreased bone density using DXA is reported in mixed cohorts of testosterone treated and testosterone naïve men with Klinefelter syndrome (KS). Bone mass and body composition in men with congenital anorchia (CA) have never been previously reported. **Objective and hypotheses:** Men with KS and CA treated with testosterone from adolescence have normal bone mass and body composition. **Method:** Whole-body DXA and tibial (66%) and radial (4%) pQCT were performed in 20 hypogonadal men (12 KS and eight CA), treated with long term maintenance testosterone from adolescence, compared with 20 age-matched healthy controls. Results expressed in median (range). **Results:** Age, height, and BMI were not different between groups. No significant differences were seen between patients and controls for the following: DXA total body BMD z score -0.7 (-2.4, +3.0) vs -0.6 (-2.3, +1.2) ($P=0.93$); pQCT total density z score at 4% radius -1.1 (-3.2, +2.6) vs -1.4 (-3.5, +1.4) ($P=0.13$), cortical density 469.5 mg/cm³ (301, 753.1) vs 466.1 mg/cm³ ($P=0.28$) and trabecular density 223.7 mg/cm³ (151.9, 334) vs 198.6 mg/cm³ (147, 263.9) ($P=0.06$). DXA total body BMD z score showed modest but significant associations with pQCT total density z score ($r=0.68$, $P<0.0001$) and trabecular density z score ($r=0.69$, $P<0.0001$). DXA lean mass, lean mass for height, lean mass for fat mass were not different between groups. pQCT muscle density and area at 66% tibia were not different between patients and controls: 77.4 mg/cm³ (56.7, 80.4) vs 77.4 mg/cm³ ($P=0.86$) and 8079 cm² (6486.4, 1922.6) vs 8122.2 cm² (5429.1, 10258.6) ($P=0.92$). DXA percentage fat was similar in both groups but trunk: leg fat 1.53 (0.88, 3.0) vs 1.17 (0.78, 2.42) ($P=0.01$), visceral adiposity mass 464.9 g (156.5, 981.5) vs 289.3 g (137.2, 582.2) ($P=0.006$) and visceral adiposity volume 502.6 cm³ (169.2, 1061.1) vs 312.8 cm³ (148.3, 629.4) ($P=0.006$) were significantly higher in patients. **Conclusion:** This first preliminary report of bone assessment using pQCT and DXA in adults with KS and CA treated from adolescence demonstrates

BMD similar to healthy controls, with no deficits in cortical and trabecular bone. However despite androgen replacement, increased central adiposity was seen and this requires further exploration.

P1-D2-42

Decreased Bone Density in Boys with Klinefelter Syndrome: Results of a Placebo-Controlled Clinical Trial Using Low-Dose Androgen Treatment for 2 Years

Judith Ross^a, Hans Henrik Thodberg^b, Martha Bardsley^a, Ania Gosek^a

^aThomas Jefferson University, Philadelphia, Pennsylvania, USA;

^bVisiana, Holte, Denmark

Background: Klinefelter syndrome (KS) is a male genetic disorder defined by the karyo type 47,XXY. Adult males with KS are at increased risk for osteoporosis, based on androgen deficiency. Androgen replacement is standard in adolescent and adults with KS, but has not been used earlier in childhood. We performed a clinical trial to study the effects of childhood, low-dose androgen replacement on bone density in boys with KS. **Objective and hypotheses:** To measure baseline (BL) bone density and fracture risk in boys with KS and to determine the effects of androgen treatment for 2 years on these measures. **Method:** This double-blind, placebo-controlled clinical trial (2005–2011, NCT00348946) randomized 93 boys with KS, ages 4–12 years, to two groups: oxandrolone (Ox, 0.06 mg/kg daily, oral) ($n=46$) or placebo (Pl) ($n=47$). Study visits occurred every 6 months for 2 years and included determination of history of prior fractures and a bone age X-ray. Bone density SDS were derived from the pediatric bone health index (BHI). BHI utilizes automated radiogrammetry from hand X-rays to measure cortical thickness. Statistical analysis included repeated measures ANCOVA. **Results:** 93 boys enrolled and 80 (86%) subjects completed the 2-year study. BL bone density SDS was on average mildly reduced (-0.4 ± 1.1). 7/93 boys (ages 4–10) had a history of prior fractures at BL, which is twice the population rate of fractures. Their mean bone density SDS was significantly less than the group with no prior fractures (-1.6 ± 1.3 vs -0.3 ± 1.0 , $P < 0.004$). Over the 2-year study, BHI SDS increased more in the Ox than in the Pl group (change from BL: 0.4 ± 0.7 (Ox) vs -0.2 ± 0.5 (Pl), $P < 0.001$), indicating increased treatment-associated cortical bone mass in the Ox group. **Conclusion:** Boys with KS and a prior history of fractures had decreased bone density (BHI). This technique of assessing cortical bone thickness may be a clinically relevant screen for increased fracture risk in KS. In the 2-year clinical trial, cortical

bone mass by BHI increased significantly more in the Ox vs Pl group. Therefore, in a cohort at risk for osteoporosis, age-appropriate androgen replacement should be considered to optimize bone density in boys with KS.

P1-D2-43

Study of Mineral and Bone Metabolism in Pediatric Patients with Inflammatory Bowel Disease

María Aguilar-Quintero^a, Javier Caballero-Villarraso^b, María Dolores Cañete^c, Alicia Romero-Urrutia^a, Ramon Cañete^a

^aUnidad de Endocrinología Pediátrica, Hospital Universitario Reina Sofía, IMIBIC, Córdoba, Spain; ^bServicio de Análisis Clínicos, Hospital Universitario Reina Sofía, IMIBIC, Córdoba, Spain; ^cGrupo PAIDI CTS-329, Universidad de Córdoba, IMIBIC, Córdoba, Spain

Introduction: Knowledge of changes in bone-mineral metabolism in patients with inflammatory bowel disease (IBD) is of particular interest, since in many patients bone metabolic disease is an epiphenomenon of the underlying pathology. Impaired bone mineralisation and diminished spinal bone mineral density (BMD) are reported in children with IBD, together with increased incidence of vertebral fracture. The short- and long-term implications of reduced BMD are especially important in pediatric patients. **Material and methods:** A descriptive, transversal, case-control study of 39 children with IBD and 46 healthy children, aged 3–17. The following were recorded: clinical histories, bioimpedance, BMD, whole blood count, glucose, urea, creatinine, calcium and phosphor ions, magnesium, alkaline phosphatase, uric acid, PTH, osteocalcin, T_4 , TSH, cortisol, insulin, albumin, prealbumin, proteins, iron and lipid metabolism, CRP, orosomucoid, β -CrossLaps, vitamin D, leptin and its soluble receptor, IL6, FGF23, osteoprotegerin, sclerostin, and RANK ligand. Data were analysed using the SPSS 15.0 Statistical Software Package. **Results:** The bone-mineral biochemical profile of children with IBD differed from that of the control group, with lower blood calcium and total alkaline phosphatase levels and higher RANKL values. A positive correlation was observed in the IBD group, but not in the control group, between 25(OH)-vitamin D and serum iron and albumin levels and total proteins. A negative correlation was observed with activity markers, suggesting that vitamin D has an anti-inflammatory and immunomodulatory role. Findings confirmed the adverse effect of a greater activity index and higher corticoid dose-rates on bone tissue (according to the BMD z-score). The latter appears to be the most harmful factor for bone. **Conclusion:** In pediatric patients, IBD prompts changes in bone metabolism with implications in other areas.

P1-D2-44

Vitamin D Deficiency: a National Threat to Adolescent Health in Saudi Arabia

Mohammed Al Dubayee^{a,b}, Fadia Albuhairan^{a,b}, Ibrahim Alalwan^{a,b}, Suleiman Al Shahri^c, Hani Tamim^b, Mohieldin Magzoub^b, Walid Al Tamim^{a,b}, Nasreldin Ahmed^b

^aKing Abdulaziz Medical City, Riyadh, Saudi Arabia; ^bKing Saud Bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia;

^cMinistry of Education, Riyadh, Saudi Arabia

Background: Vitamin D has a key physiological role in many metabolic process and neuromuscular activities. The peak bone mass accrual occurred during adolescence, where about 51% of bone mass is gained during puberty and about 37% of the bone mineral density (BMD) of adults is reached. Vitamin D deficiency has long-term negative implications including increased risk of osteomalacia and osteoporosis. Severe hypovitaminosis D appears to be most common in the Middle East and African, where the highest rates of rickets worldwide are recorded. **Objective and hypotheses:** To determine the national and regional prevalence of vitamin D deficiency among adolescents in Saudi Arabia and to identify the factors associated with vitamin D deficiency. **Method:** This is part of the national study on adolescents 'JEELUNA'. School-based cross-sectional study was conducted in all regions of Saudi Arabia. Multistage, stratified, clustered random sampling was carried out to select intermediate and secondary male and female schools. Self-administered questionnaire addressing socio-demographic information and lifestyle behaviors including health risk behaviors was taken. Anthropometric measurements were obtained and blood samples were collected to determine serum 25-OH vitamin D levels for students. **Results:** A total of 12 584 students participated in the study 54% were male and 53% were in secondary school. 4843 had their blood sampled for vitamin D levels; 95% had vitamin D deficiency (25-OH Vit D < 50 nmol/l). Females are 7.4 times as likely as males to experience vitamin D deficient ($P < 0.0001$). School exercise decrease the chance of vitamin D deficiency by 72% ($P < 0.0001$). Missing breakfast increased the chance of vitamin D deficiency by 74% ($P = 0.01$). Physically inactive adolescents are twice as likely as active adolescents to have vitamin D deficiency ($P < 0.0001$). **Conclusion:** Vitamin D deficiency is major public health concern. Public health approaches and health policy are needed to optimize adolescent health.

P1-D2-45

Longitudinal Changes of Bone Mineral Content in Children with Cystic Fibrosis

Adela Chirita-Emandi^{a,b}, Sheila Khanna^a, Andreas Kyriakou^a, Jane McNeilly^c, Anne Devenny^d, Faisal Ahmed^a

^aDevelopmental Endocrinology Research Group, School of Medicine, University of Glasgow, Glasgow, UK; ^bGenetics

Department, University of Medicine and Pharmacy 'Victor Babes', Timisoara, Romania; ^cDepartment of Clinical Biochemistry, Southern General Hospital, Greater Glasgow and Clyde NHS Trust, Glasgow, UK; ^dDepartment of Respiratory Medicine, Royal Hospital For Sick Children, Yorkhill, Greater Glasgow and Clyde NHS Trust, Glasgow, UK

Background: A quarter of young adults with cystic fibrosis (CF) may have osteoporosis. However, children with CF do not seem to have an increased risk of fractures. **Objective:** We aimed to examine the factors that may determine longitudinal changes in bone mineralisation in children with CF. **Method:** 101 children (51 females) had DXA performed and the data were expressed as expected bone mineral content for bone area SDS (BMCSDS). Of them, 49 children had a second DXA, 24 had three DXA, during the 10-year period. Markers of disease, anthropometry, bone biochemistry and DXA parameters were collected retrospectively. Vitamin D deficiency was defined as levels < 50 nmol/l and insufficiency as levels between 50 and 72.5 nmol/l. **Results:** Median age at baseline was 12 years (range 8–18). 17 children (35%) were vitamin D deficient on one occasion, 18 (37%) on two occasions and 1 (2%) was deficient on three occasions. 18 children (37%) were vitamin D insufficient on one occasion, 5 (10%) in two occasions and 1 (2%) on three occasions. PTH status has worsened for seven children (14.3%), if the value changed from ≤ 7.5 to > 7.5 pmol/l at the next assessment. PTH was considered static in 79.6% children. Baseline LS BMCSDS in the 101 children, was > 0.5 in 13.9% patients; was between -0.5 and 0.5 , in 51%; while 35% had $SDS \leq -0.5$. Median LS BMCSDS decreased from baseline to subsequent assessments (-0.3 ; -0.4 ; and -0.5 ; $P = 0.053$). Assessment of factors that may influence bone mineralisation change by ANOVA, the longer the time between DXA assessments, the higher the likelihood of decreased BMC. Children with worsened BMC had lower FEV1%, had a lower BMI SDS, and a higher chance to have a low vitamin D associated with high PTH. **Conclusion:** Bone mineralisation as assessed by DXA decreases with time in children with CF. Lower FEV1%, poorer nutritional status and low vitamin D with high PTH were factors found to be associated with worsening BMC.

P1-D3-46

Loss of Function CYP24A1 Mutations in Patients with Hypercalcemia and Low Pth level: an Autosomal Dominant or Recessive Trait?[☆]

Arnaud Molin^a, Roseline Baudouin^b, Nadia Coudray^a, Marie-Lucille Figueres^c, Glennville Jones^d, Marie-Laure Kottler^a

^aCHU, Caen, France, ^bCHU, Bordeaux, France, ^cCHU, Nantes, France, ^dQueen's University, Kingston, Canada

Background: Homozygous or compound heterozygous mutations of gene CYP24A1 have recently been reported to cause idiopathic infantile hypercalcemia due to increased intestinal

absorption of calcium. However, an autosomal dominant transmission with partial penetrance of the trait was also suggested. **Objective and hypotheses:** Evaluation of the frequency of *CYP24A1* mutation and evaluation of the impact of heterozygous mutation on calcium metabolism. **Methods:** We screen for *CYP24A1* mutation in a cohort of 90 probands presenting with hypercalcemia (>2.6 mmol/l) and low PTH levels (<20 pg/ml) and 35 relatives. Biochemical data were obtained with routine methods. Calcium absorption studies were performed in eight family members using PAK test that consists in the evaluation of calciuria after oral calcium administration. Serum 25-hydroxyvitamin D and 24,25-dihydroxyvitamin D were assessed by liquid chromatography tandem mass spectrometry (LCMSMS). **Results:** Bi-allelic mutations were found in 21 patients (23%) and seven patients were heterozygous (7%). Fifteen mutations have never been described. In eight asymptomatic relatives carrying heterozygous *CYP24A1* mutations, we observed normal P/Ca/PTH level. However, five patients had high $1,25\text{-}(\text{OH})_2\text{D}$ level. Digestive absorption of calcium was at the upper limits of normal in three patients. Blood samples were tested with LCMSMS in 14 patients without mutations, 17 with heterozygous mutation and three with bi-allelic mutations. Low 24,25-dihydroxyvitamin D level and high ratio of 25-hydroxyvitamin D: 24,25-dihydroxyvitamin D ($M=102$) were found in 3/3 patients with bi allelic mutation. There is no difference between patients carrying heterozygous mutation ($M=14.3$) and patients with hypercalcemia without *CYP24A1* mutations ($M=19.8$), but heterozygous carriers exhibit higher 25-hydroxyvitamin D levels than subjects without mutation. **Conclusion:** Taken together, these elements do not suggest an increased risk of hypercalcemia for heterozygous patients, but seem to indicate a protective factor for vitamin D deficiency.

*Nominated for a Presidential Poster Award.

and the end of the 6 months' treatment, peripheral blood samples were collected to test serum amino-terminal proC-type natriuretic peptide (NTproCNP), IGF1 and procollagen type 1 amino-terminal propeptide (P1NP) concentrations. Comparisons were made among height velocity (HV), the improvement of predicted adult height (PAH) and the changes of serum NTproCNP, IGF1, P1NP concentrations between two groups. **Results:** After 6 months' treatment, the height velocity and PAH of the girls treated with rhGH and GnRHa were statistically higher compared with control group ($P<0.01$). Serum NTproCNP ((10.5 ± 4.9) pmol/l vs (9.6 ± 2.9) pmol/l), IGF1 and P1NP concentrations were not significantly different between the beginning and the end of the 6 months' treatment in the rhGH-combined group ($P>0.05$). In contrast, the girls treated with GnRHa alone showed a significantly decrease of both serum NTproCNP ((10.5 ± 3.6) pmol/l vs (6.9 ± 1.5) pmol/l) and P1NP levels ($P<0.05$), but no significant change of serum IGF1 level. **Conclusions:** In the CPP or EFP girls who are in mid/late puberty and at great bone ages, the combined treatment with rhGH and GnRHa may accelerate linear growth and improve predicted adult height. This growth-accelerating effect of rhGH could in part be induced by the increase production of CNP.

*Nominated for a Presidential Poster Award.

P1-D3-48

Paternal Isodisomy and Sporadic Pseudohypoparathyroidism I-b

Cindy Colson, Anne Claire Brehin, Geneviève Abeguile, Matthieu Decamp, Nicolas Richard, Marie-Laure Kottler

University Hospital, Caen, France

Background: Patients affected by pseudohypoparathyroidism type 1b (PHPI-b) develop resistance to PTH leading to hypocalcemia and hyperphosphoremia, which is often associated with resistance to TSH. PHP-Ib is associated with methylation changes at one or several differentially methylated regions (DMRs) within the *GNAS* complex locus, located at 20q13.2–13.3. This locus gives rise to several different transcripts (NESP55, XL, A/B), with varying patterns of imprinted expression depending on the methylation status of the specific exon 1 promoters. PHP-Ib may follow an autosomal dominant pattern of maternal inheritance (AD-PHPI-b), or it can occur as a disorder that appears to arise sporadically (SPO-PHP I-b). **Objective and hypotheses:** Epigenetic changes observed in genomic DNAs from SPO-PHP-Ib mimic the paternal-specific methylation pattern. Uniparental disomy (UPD) is a condition in which a chromosomally disomic individual inherited both copies of a chromosome from one parent only. Thus, paternal UPD20 without maternal contribution is a plausible cause of PHP1b. **Method:** We screened a cohort of 57 unrelated patients presenting with SPO-PHP1b and broad *GNAS* epigenetic changes to evaluate the frequency of patUPD20. Comparative genomic hybridization (CGH) combined with SNP-array (Agilent 4x180K sureprint G3 Cancer) was used to

P1-D3-47

Relation Between CNP Signaling Pathway and the Effect of Combined Treatment with GnRHa and rhGH on the Linear Growth in Mid/Late Pubertal Girls at Great Bone Ages with CPP or EFP*

Hua-mei M A, Zhe S U, Yin-ya L I

Sun Yat-sen University, Guangzhou, China

Objectives: To evaluate the effect of combined treatment with GnRH analogue (GnRHa) and recombinant human GH (rhGH) on the linear growth in mid/late pubertal girls at great bone ages with central precocious puberty (CPP) or early and fast puberty (EFP). To investigate the relation between C-type natriuretic peptide (CNP) signaling pathway and GH's effect on linear growth in these girls. **Methods** 22 girls were diagnosed as CPP or EFP, whose bone ages were older than 11.5 years, and received different therapies as follows: 11 girls received the combined treatment with rhGH and GnRHa, another 11 girls matched for auxological characteristics were treated with GnRHa alone. At the beginning

identify copy number variant and loss of heterozygosity (LOH). To confirm LOH, single nucleotide polymorphisms or short tandem repeats were studied along chromosome 20 in the proband and compared to his two parents. **Results:** Because GCH arrays required high quality DNA only 20 samples were tested. We found four patients (20%) with patUPD20: two patients with complete patUPD, one patient with patUPD of the long arm of chromosome 20 and one patient with a large interstitial UPD including *GNAS* locus. We also detailed the phenotype and the DNA methylation pattern of these patients. **Conclusion:** This study suggests that patUPD20 is a frequent cause of PHP1b that should be tested in the evaluation of patients with sporadic PHP1b.

P1-D3-49

Vertebral Fracture Assessment in a Paediatric Population using Dual-Energy X-ray Absorptiometry

Andreas Kyriakou, Sheila Shepherd, Guftar M Shaikh, Syed Faisal Ahmed, Avril Mason

Developmental Endocrine Research Group, University of Glasgow, Glasgow, UK

Background: Vertebral fractures (VF) are recognised as an important aspect of bone health in children and adolescents, yet most of them are not clinically apparent. The clinical utility of vertebral fracture assessment (VFA) using dual-energy X-ray absorptiometry (DXA) for vertebral morphometry has not been evaluated in the paediatric population. **Method:** VFA was performed independently by two non-radiologist observers in 110 patients (52M/58F) as part of their investigation for low bone mineral density. The median age of the patients was 13.6 years (3.6,19.2). Lateral DXA images of the spine from T6 to L4 were obtained using Lunar Prodigy DXA device. The diagnosis of VF was performed according to the extent of the difference in height ratios from 100% using Genant Semi-quantitative Method. **Results:** Interobserver agreement in vertebral readability was 95% (κ ,0.78). The vertebral bodies not readable by both observers were 210/1210 (17%) and 174 (83%) were located from T6 through T8. Conversely, 844/880 (96%) of vertebral bodies from T9 through L4 were adequately visualized ($P < 0.0001$). Among the visualized vertebrae by both observers, 47 (4.7%) in 31 (28%) patients and 57 (5.7%) in 34 (31%) patients were classified as VF by observer 1 and by observer 2 respectively. Both observers detected a total of 46VF in 28 (26%) patients and 13 (28%) of them were classified as moderate or severe. The anatomical distribution of VF was biphasic with peaks located on T9(odds ratio, 2.1(1.2, 4.4)) and L4 (odds ratio, 1.7(1.0, 3.6)). Interobserver per-vertebra agreement for the presence of a fracture was 98.8%(κ , 0.88) and for the grade of the fracture was 98%(κ , 0.76). Interobserver per-patient agreement for the presence of a fracture was 92%(κ , 0.8). **Conclusion:** VFA with DXA reach an excellent level of agreement between observers in identifying reduction of vertebral heights in paediatric population. The readability of vertebral bodies from

T6 to T8 is suboptimal and interpretation at this level should be exercised with caution.

P1-D3-50

Genetic Study of Osteogenesis Imperfecta: Two Novel Mutations in *COL1A1* and *COL1A2*

Lidia Castro-Feijóo^a, Lourdes Loidi^b, Nuria Quiroga^c, Paloma Cabanas^d, Claudia Heredia^d, Rosaura Leis^e, Francisco Barros^b, Manuel Pombo^d, Jesús Barreiro^d

^aUnidad de Endocrinología Pediátrica y Crecimiento, Dpto. de Pediatría, Fundación Ramón Domínguez, Hospital Clínico Universitario de Santiago de Compostela, Universidad de Santiago de Compostela, Santiago de Compostela. A Coruña, Spain; ^bFundación Pública Galega de Medicina Xenómica, Santiago de Compostela, A Coruña, Spain, ^cDpto de Pediatría, Hospital Clínico Universitario de Santiago de Compostela, Santiago de Compostela, Spain; ^dUnidad de Endocrinología Pediátrica y Crecimiento, Dpto de Pediatría, Hospital Clínico Universitario de Santiago de Compostela, Universidad de Santiago de Compostela, Santiago de Compostela, A Coruña, Spain; ^eUnidad de Investigación en Nutrición y Desarrollo Humano de Galicia, Dpto de Pediatría, Hospital clínico Universitario de Santiago de Compostela, Universidad de Santiago de Compostela, Santiago de Compostela, A Coruña, Spain

Background: Osteogenesis imperfecta (OI) is a clinically and genetically heterogeneous rare disorder characterized by variable symptoms including predisposition to fractures. OI has been associated with mutations affecting the synthesis of type I collagen. However, the new technologies have permitted the identification of other responsible genes which are in the collagen metabolic pathway, while others are not. **Objective:** Characterize the genotype of patients with OI. **Methods:** Study by Next Generation Sequencing (5500XL SOLID) the OI related genes: *COL1A1*, *COL1A2*, *CRTAP*, *FKBP10*, *LEPRE1*, *PPIB*, *SERPINF1*, *SERPINH1* and *SP7* and confirmation of the identified mutations by PCR and Sanger sequencing. **Results and discussion:** Patient 1 (male with severe phenotype of OI). Heterozygous carrier of the *COL1A2* mutation NM_000089.3: c.1207G > T (p.Gly403Cys). This mutation has not been previously described. The theoretical predictors suggest pathogenicity, which is consistent with the clear phenotype of OI in this patient. Patient 2 (girl with mild phenotype of OI). Heterozygous carrier of the *COL1A1* mutation NM_000088.3: c.572G > C (p.Gly191Ala). This mutation appears in The Human Gene Mutation Database associated with cervical artery dissection and the missense predictions indicate pathogenicity. Patients 3 and 4 (siblings with moderate phenotype of OI). Both girls are heterozygous carriers of the *COL1A1* mutation NM_000088.3: c.2T > C (p.Met1?). This mutation has not been previously described and there is not data of associated phenotype. This variation affects the translation initiation codon of the mRNA which indicates pathogenicity. **Conclusion:** The genetic analysis confirmed the diagnosis of OI in all the patients studied. These results allowed a better classification of patients and permitted an adequate genetic counselling. One *COL1A1* and one *COL1A2* novel mutations are described.

P1-D3-51

Bone Geometry, Volumetric Density, Microarchitecture and Estimated Bone Strength Assessed by HR-pQCT in Adult Patients with Hypophosphatemic Rickets

Vikram v. Shanbhogue^{a,b}, Stinus Hansen^{a,b}, Lars Folkestad^{a,b}, Kim Brixen^{a,b}, Signe Sparre Beck-Nielsen^{b,c}

^aDepartment of Endocrinology, Odense University Hospital, Odense, Denmark; ^bInstitute of Clinical Research, University of Southern Denmark, Odense, Denmark; ^cDepartment of Pediatrics, Hospital of Southwest Denmark, Esbjerg, Denmark

Background: Hypophosphatemic rickets (HR) are rare, inheritable disorders caused by excessive renal phosphate wasting. Despite a generalized mineralization defect, patients with HR are reported with a lower risk of fracture. **Objective and hypotheses:** The aim of this study was to evaluate the effect of bone -geometry, -microarchitecture and volumetric BMD (vBMD) on the estimated bone strength in adult patients with HR using high-resolution peripheral quantitative computed tomography (HR-pQCT). As evaluations of BMD in children with HR may be confounded by differences in bone size and bone maturation challenging comparisons with either age- or height matched normal children, only adults with HR were studied. **Method:** A total of 29 patients with HR (21 women and eight men, median age 46, range 19–79 years), of which 26 had genetically proven X-linked HR, were included. Patients with HR were age and gender matched with 29 healthy controls. **Results:** The patients with HR had significantly higher total bone cross-sectional areas (radius 36%, tibia 20%; both $P < 0.001$) with significantly higher trabecular bone areas (radius 49%, tibia 14%; both $P < 0.001$) compared with controls. In addition, the patients with HR had lower total vBMD (radius -20% , tibia -14% ; both $P < 0.01$), cortical vBMD (radius -5% , $P < 0.001$), trabecular number (radius -13% , tibia -14% ; both $P < 0.01$) and cortical thickness (radius -19% ; $P < 0.01$) compared with controls. The patients with HR had greater trabecular spacing (radius 18%, tibia 23%; $P < 0.01$) and a more inhomogeneous trabecular network (radius 29%, tibia 40%; both $P < 0.01$) compared with controls. Estimated bone strength at both sites was similar between the groups. **Conclusion:** In conclusion, in patients with HR, the negative impact of lower vBMD and trabecular number on estimated bone strength seemed compensated by an increase in bone cross-sectional area resulting in HR patients and controls having similar estimates of bone strength.

P1-D3-52

Opposing Effects of Childhood Obesity on Radial and Tibial Bone Microstructure

Paul Dimitri^{a,c}, Richard Jacques^a, Margaret Paggiosi^b, David King^a, Jennifer Walsh^b, Nick Bishop^c, Richard Eastell^c

^aSheffield Children's NHS Foundation Trust, Sheffield, South Yorkshire, UK; ^bSheffield Teaching Hospitals NHS Foundation

Trust, Sheffield, South Yorkshire, UK; ^cThe University of Sheffield, Sheffield, South Yorkshire, UK

Background: Bone mass is low in obese children when measured by conventional techniques. However, these imaging modalities cannot quantify alterations in bone microstructure and strength. High resolution peripheral quantitative computed tomography (HRpQCT – isotropic voxel size 82 μm) provides the resolution required to determine 3-dimensional *in-vivo* bone microstructure; microfinite element (microFE) analysis of HRpQCT images provides insight into skeletal biomechanical properties. **Method:** Children aged 8–15 years matched by gender and pubertal stage were recruited into lean and obese groups (18 pairs). Bone micro-structural parameters were quantified using HRpQCT. MicroFE was used to determine bone stiffness, estimated failure load, load carried by the trabecular and cortical bone, and the average Von Mises stresses. Bone strength index was calculated using $(\text{BSI} (\text{mg}^2/\text{mm}^4) = \text{Density}_{\text{total}}^2 \times \text{Area}_{\text{total}})$. Lean and fat mass were measured by DXA. **Results:** Lean and obese children were 12.9 ± 2.0 and 12.6 ± 1.9 years ($P = 0.23$) respectively. There was no difference in height SDS between the groups (1.12 ± 1.34 vs 0.96 ± 1.41 , $P = 0.67$). Radial cortical porosity (mean difference -0.01 (95% CI: -0.02 , -0.004), $P = 0.003$) and cortical pore diameter (mean difference -0.005 mm (95% CI: -0.009 , -0.001), $P = 0.01$) were lower in obese children. Tibial trabecular thickness was lower (mean difference -0.009 mm (95% CI: -0.014 , -0.004), $P = 0.003$) and trabecular number was higher (mean difference $0.23/\text{mm}$ (95% CI: 0.08 , 0.38), $P = 0.004$) in obese children. There was no difference in radial and tibial bone strength proxies. Subtotal fat mass % positively correlated with radial cortical thickness ($r = 0.43$, $P = 0.008$) and density ($r = 0.36$, $P = 0.02$) whereas lean mass correlated with radial cortical ($r = 0.44$, $P = 0.007$) and trabecular ($r = 0.55$, $P = 0.007$) area. Subtotal fat mass % negatively correlated with tibial trabecular density ($r = -0.37$, $P = 0.03$) and thickness ($r = -0.62$, $P < 0.001$). **Conclusion:** Obesity in children has a positive effect on cortical microstructure at the distal radius and a negative impact on trabecular microstructure at the distal tibia. However, these changes were not sufficient to impact on bone strength.

P1-D3-53

Bone Mineral Density Evaluation in Children with Gaucher Disease

Maria Silvia Larroude, Guillermo Drelichman, Hamilton Cassinelli, Lucia Richard, Alba Ruiz, Paola Reicher, Fernanda Cuello, Victoria Lanza, Ramiro Fernandez, Alejandra Maro, Marcela Corrales, Adriana Arizo, Nicolas Fernandez Escobar, Cristina Rapetti, Hugo Donato, Juan Jose Chain, Sandra Zirone, Alejandra Cedola, Julieta Bietti, Maia Sweri

Argentine Group of Gaucher Disease Study, Buenos Aires, Argentina

Background: Bone involvement is described as a relevant sign in patients suffering Gaucher disease (GD). **Objective and hypotheses:** To analyze the long-term effect of enzyme

replacement therapy on bone mineral density, a retrospective observational study was conducted in a cohort of 34 GD pediatric patients (14 males, 20 females, median age 11.3 years). **Method:** Lumbar spine (LS) (L2–L4, N: 34) and total body (TB) (N: 24) bone mineral density (BMD) (determined by dual-energy X-ray absorptiometry (DXA) (GE Lunar), were performed and expressed as Z-scores. According to the International Society of Clinical Densitometry guidelines, a Z-score ≤ -2.0 was considered pathological. Results were expressed in $X \pm s.d.$. Patients received imiglucerase infusions (57.7 ± 17.4 IU/kg), during a period of 7.7 ± 4.5 years. They were divided in two groups: pre pubertal (G1) and pubertal (G2), both for boys (G1B–G2B) and girls (G1G–G2G). **Results:** Mean BMD were normal in the whole group: -0.26 ± 1.4 and 0.11 ± 1.3 in LS and TB respectively. Only two patients had LS BMD below -2.0 Z-score, but none in TB BMD. BMD was: G1B: LS -0.6 ± 1.28 ; G2B: -0.15 ± 1.4 , TB -0.07 ± 1.4 and 0.58 ± 1.2 ; and G1G: LS: -0.23 ± 1.4 , G2G -0.56 ± 1.9 ; TB G1G -0.08 ± 0.9 , G2G 0.05 ± 1.9 respectively. **Conclusion:** Patients with GD receiving therapy with imiglucerase have normal BMD during. It seems that the pubertal groups are better than de pre pubertal, reflecting the action of sexual steroids on bone. A longitudinal study is needed to confirm this.

demonstrated a Gaussian distribution (Shapiro-Wilk $z = -1.685$, $P = 0.95$, kurtosis = 2.77, skewness = 0.13), with no significant difference between patients and controls (51.56 ± 12.05 vs 50.98 ± 13.55 pmol/l, $P = 0.84$). Lower values were found in girls (49.1 ± 12.7 vs 53.9 ± 12.3 pmol/l, $P = 0.05$) and in prepubertal children (47.3 ± 11.6 vs 53.3 ± 12.9 pmol/l, $P = 0.02$). In both patients and controls sclerostin values significantly and gradually increased in children through pubertal Tanner stages 1 to 3, then they were reduced in stage 4 adolescents and were increased again in pubertal stage 5 adolescents (ANOVA $F = 4.56$, $P = 0.0024$). Sclerostin levels were positively correlated with logCTX ($r = 0.41$, $P < 0.001$), logOsteocalcin ($r = 0.33$, $P = 0.004$), total body BMD ($r = 0.34$, $P = 0.0018$) and BMD Z-score ($r = 0.27$, $P = 0.015$). Total body BMD was not significantly different between patients and controls. **Conclusion:** T1DM children and adolescents had similar sclerostin levels and total BMD with controls. In both patients and controls, sclerostin was correlated with both resorption and formation markers and also with bone mass indices, gender and pubertal stage. The decrease in sclerostin values observed in pubertal stage 4 adolescents coincides with the concurrent growth spurt, and is consistent with sclerostin physiology as an inhibiting signal of bone formation.

P1-D3-54

Correlation of Sclerostin Levels with Bone Metabolism Markers and Bone Mineral Density in Children and Adolescents with Type 1 Diabetes Mellitus (T1DM)

Charalampos Tsentidis^a, Dimitrios Gourgiotis^b, Lydia Kossiva^a, Antonios Marmarinos^b, Asteroula Papathanasiou^a, Artemis Doulgeraki^c, Kyriaki Karavanaki^a

^aDiabetic Clinic, Second Pediatric Department University of Athens 'P&A Kyriakou' Children's Hospital, Athens, Attica, Greece;

^bBiochemistry Laboratory, Second Pediatric Department, University of Athens, 'P&A Kyriakou' Children's Hospital, Athens, Attica, Greece; ^cDepartment of Bone and Mineral Metabolism, Institute of Child Health, 'Aghia Sophia' Children's Hospital, Athens, Attica, Greece

Background: Sclerostin is an inhibitor of the Wnt/b-catenin bone metabolic pathway. Increased sclerostin levels and reduced bone mineral density (BMD) have been documented in adult patients with diabetes mellitus (DM), predominantly in those with T2DM. No relevant data exist on childhood T1DM. **Objective and hypotheses:** Our aim was to study plasma sclerostin concentration in children and adolescents with T1DM and controls and to correlate sclerostin levels with metabolic bone markers and BMD. **Method:** Forty children and adolescents with T1DM were evaluated (mean \pm s.d. age: 13.04 ± 3.53 years, T1DM duration: 5.15 ± 3.33 years), along with 40 healthy matched controls (mean \pm s.d. age 12.99 ± 3.3 years). Sclerostin, osteocalcin, C-telopeptide crosslinks-CTX, electrolytes, PTH, total 25(OH) D and total body BMD were measured. **Results:** Sclerostin levels

P1-D3-55

Increased Osteoclast Activity in Children and Adolescents with Type 1 Diabetes Mellitus Indicated by Higher Levels of Osteoprotegerin and s-RANKL may Predispose to Lower Bone Mass

Charalampos Tsentidis^a, Dimitrios Gourgiotis^b, Lydia Kossiva^a, Artemis Doulgeraki^c, Antonios Marmarinos^b, Triantafillia Sdogou^a, Kyriaki Karavanaki^a

^aDiabetic Clinic, Second Pediatric Department, University of Athens, 'P&A Kyriakou' Children's Hospital, Athens, Attica, Greece;

^bBiochemistry Laboratory, Second Pediatric Department, University of Athens, 'P&A Kyriakou' Children's Hospital, Athens, Attica, Greece; ^cDepartment of Bone and Mineral Metabolism, Institute of Child Health, 'Aghia Sophia' Children's Hospital, Athens, Attica, Greece

Background: Several bone metabolic pathways seem to be disrupted in patients with type 1 diabetes mellitus (T1DM), leading to reduced bone mass. **Objective and hypotheses:** Our aim was to study bone metabolism markers in children and adolescents with T1DM and their correlation with bone mineral density (BMD). **Method:** We evaluated 40 patients (mean \pm s.d. age 13.04 ± 3.53 years, mean \pm s.d. T1DM duration 5.15 ± 3.33 years) and 40 healthy age- and gender-matched controls (mean \pm s.d. age 12.99 ± 3.3 years). Osteoprotegerin (OPG), receptor activator of nuclear factor-KappaB ligand (s-RANKL), osteocalcin, C-telopeptide crosslinks-CTX, electrolytes, PTH, total 25(OH)D were measured. Total body (TB) and lumbar spine (LS) BMD were evaluated with dual energy X-ray absorptiometry (DXA). **Results:** Patients had significantly higher levels of OPG than controls

(6.15 ± 1.56 vs 5.01 ± 1.5 pmol/l, $P < 0.001$) and s-RANKL (logS-RANKL 5.97 ± 0.63 vs 5.51 ± 0.84 , $P = 0.004$). Patients also had lower levels of PTH (logPTH 3.25 ± 0.52 vs 3.43 ± 0.33 , $P = 0.036$) and magnesium (1.88 ± 0.12 vs 2.03 ± 0.12 mg/dl, $P < 0.001$) and higher ALP levels ($\sqrt{\text{ALP}}$ 14.07 ± 4.13 vs 12.6 ± 3.24 , $P = 0.05$). Patients and controls had comparable 25(OH)vitD levels, while one third of both groups had low 25(OH)vitD levels (< 20 ng/ml). Osteocalcin was highly correlated with CTX in both groups ($r = 0.75$, $P < 0.001$), indicating coupling of bone resorption and formation. OPG and s-RANKL were significantly associated in controls ($R^2 = 0.15$, $P = 0.021$), but not in patients ($R^2 = 0.006$, $P = 0.64$), possibly indicating an osteoclastic disorder. Bone formation was not significantly affected. Although BMD was not significantly different between patients and controls, it had greater variance in patients. Longer T1DM duration was associated with lower BMD Z-scores (TB-BMD $r = -0.41$, $P = 0.009$, LS-BMD $r = -0.34$, $P = 0.043$). **Conclusion:** RANKL/OPG axis seems to be significantly activated in children and adolescents with T1DM. These changes could indicate abnormal osteoclast function and could be associated with the lower bone mass, found in patients with longer disease duration.

P1-D3-56

Effect of a Vibration Based Rehabilitation Concept On Bone and Muscle Development in Children with Osteogenesis Imperfecta

Oliver Semler^{a,c}, Heike Hoyer-Kuhn^a, Christina Stark^{a,c}, Nora Struebing^b, Oranna Goebel^a, Eckhard Schoenau^{a,b}

^aChildren's Hospital, University of Cologne, Cologne, Germany;

^bUnireha GmbH, Paediatric Rehabilitation Center, University of Cologne, Cologne, Germany; ^cMedical Faculty, Cologne Center for Musculoskeletal Biomechanics, University of Cologne, Cologne, Germany

Introduction: Osteogenesis imperfecta is a rare disease leading to immobility by recurrent fractures, hyperlaxity of ligaments, short stature and muscular weakness. Beside drug treatment and surgical procedures physiotherapy is one of the most important treatment approaches to increase mobility. The objective of our analysis was to evaluate the effect of a new standardized 12 months physiotherapy concept including whole body vibration over 6 months on motor function and bone mineral density in children with osteogenesis imperfecta. **Description of methods/design:** In a retrospective data analysis 37 children (24 male; mean age: 8.57 years, bisphosphonate treatment $n = 30$; OI type 1 $n = 3$; OI type 3 $n = 12$; OI type 4 $n = 22$) were analyzed. The 12 months concept included a period of 6 months of whole body vibration and concomitant physiotherapy, resistance training and treadmill training. The concept is structured in two in-patient stays and two periods of 3 months home-based vibration training. Primary outcome parameter was the Gross Motor Function Measure before and after 12 months. iDXA (GE) was used to analyze muscle and bone parameters. **Results:** A significant increase of gross motor

function between start and after 12 months was seen (GMFM66 score (mean \pm s.e.m.) 54.48 ± 2.41 vs 57.59 ± 2.77 ; $P = 0.0007$). Bone mineral content and lean mass (total body less head (g corrected for cm body height)) increased significantly from 2.08 ± 0.3 to 2.54 ± 0.33 and 0.1027 ± 0.0053 to 0.1072 ± 0.006 ($P < 0.0001$ and 0.0013), respectively. Height (s.d.) and BMI (s.d.) did not change significantly after 12 months. **Conclusions:** The physiotherapy concept including whole body vibration leads to a significant improvement on gross motor function, lean mass and bone mineral content in children with Osteogenesis imperfecta. Therefore this therapeutic approach should be considered as part of an integrated treatment concept in children with OI.

P1-D3-57

No Correlation Between 25OHD Status and Pro or Anti-Inflammatory Cytokines in Obese Children and Normal Weight Controls

Aoife Carroll^{a,b}, Chike Onwuneme^{a,b}, Malachi McKenna^{b,d}, Philip Mayne^{e,f}, Eleanor Molloy^{c,f}

^aDepartment of Endocrinology, Children's University Hospital, Temple St, Dublin, Ireland; ^bUniversity College Dublin School of Medicine and Medical Services, UCD, Dublin, Ireland; ^cDepartment of Neonatology, National Maternity Hospital, Holles St, Dublin, Ireland; ^dDepartment of Endocrinology, St. Vincent's University Hospital, Dublin, Ireland; ^eDepartment of Biochemistry, Children's University Hospital, Temple St, Dublin, Ireland; ^fRoyal College of Surgeons, Dublin, Ireland

Background: While the primary function of vitamin D relates to calcium and bone metabolism, it is now recognised that vitamin D is a potent immunomodulator. *In vitro*, 1,25(OH)₂D has been shown to suppress pro-inflammatory cytokines, such as TNF- α and IL6, while up regulating synthesis of anti-inflammatory cytokines, IL10 and IL4. Previous *in vitro* studies have yielded inconsistent results on the relationship between 25OHD and cytokines in adults and preterm infants. **Objective and hypotheses:** To examine if vitamin D status altered the cytokine profile in different groups of children; obese children and lean healthy control children. **Method:** Healthy children attending a single tertiary paediatric hospital for minor medical or surgical illnesses were recruited. Obese children (BMI > 98 th centile) attending a weight management course were also recruited. Each had 25OHD level measured along with a cytokine panel (TNF- α , IL4, IL6, IL10 and adiponectin). **Results:** We studied 46 healthy children (28 females) ranging in age from 4.4 to 15.6 years. The mean (s.d.) for 25OHD was $44.7(24.6)$ nmol/l and 54% had 25OHD levels < 50 nmol/l. In the obese cohort there were 13 children (nine females) ranging in age from 7.6 to 5.8 years. The mean (s.d.) 25OHD level was $29.2(17.0)$ nmol/l and 92% had 25OHD levels < 50 nmol/l. There was no correlation between the cytokines examined and 25OHD levels. Cytokine concentrations did not differ between individuals with 25OHD

levels above or below 50 nmol/l. **Conclusion:** We believe this is the first study examining the relationship between 25OHD status and pro and anti-inflammatory cytokines in healthy children. We found no correlation. This may be a reflection of the different settings in which the research was performed (*ex vivo* vs *in vivo*) but it is also possible that the 25OHD levels of our patients were below the threshold required for 25OHD to exert its immunomodulatory effects.

P1-D1-58

A Leu402pro Mutation of the Non-hla Gene *il18rap* in Aggressive Neonatal Type 1 Diabetes Mellitus[☆]

Mirjam Dirlewanger^a, Jean-Louis Blouin^b, Jeremy Bevilard^{a,b}, Federico Santoni^{a,b}, Valérie Schwitzgebel^a

^aPediatric Endocrine and Diabetes Unit, Children's University Hospital, Geneva, Switzerland; ^bGenetic Medicine and Development, University Medical Center, Geneva, Switzerland

Background: Neonatal diabetes mellitus is defined by severe hyperglycemia appearing before 6 months of age. It occurs in about one in 200 000 live births and most cases are known to be of monogenic origin. Classical autoimmune type 1 diabetes mellitus (DM) is exceptional in this age group. **Objective and hypotheses:** Recently non-HLA type 1 DM susceptibility genes, such as *IL18RAP*, influencing the rate of progression to diabetes among children with multiple autoantibodies have been described. **Method:** We report a case of severe ketoacidosis in a 3 months old boy, born at term with a normal birth weight. **Results:** HbA1c was 6.4%. The anti-GAD65 antibody (14.9 EI/ml, $n < 10$) was positive and increased to 328 IE/ml after 2 months. The mother's islet autoantibodies were negative. Pancreatic ultrasound and fecal elastasis level were within normal limits, as well as thyroid function tests. HLA genotyping confirmed a high risk for diabetes with homozygosity for HLA DR3-DQ2. No mutation was found by direct sequencing of *KCNJ11*, *ABCC8*, *INS*, and *FOXP3* genes. Whole exome analysis revealed a highly damaging p.Leu402Pro mutation of *IL18RAP*. **Conclusion:** We concluded that our patient has a type 1 DM, based on increasing anti-GAD antibodies and high-risk HLA genotyping. A monogenic form of neonatal DM secondary to a K_{ATP} channel, insulin or *FOXP3* mutation could be excluded. This case illustrates an extremely early and rapid onset of diabetes in infancy by the combined presence of a novel mutation in the type 1 DM susceptibility gene *IL18RAP* and a high-risk HLA genotype. The exact functional effect of this Leu402Pro mutation has not been analyzed yet, but could involve IFN γ production. The identification of this characteristic signature of rapid progression in a very young child with an islet autoantibody-positive type 1 DM supports the hypothesis that characteristic antibodies and gene profiles could further help to identify high-risk phenotypes.

[☆]Nominated for a Presidential Poster Award.

P1-D1-59

A Randomized, Crossover Pilot Study Comparing Glycemic Control and Satisfaction with an Indwelling Catheter (I-PORT Advance) for Insulin Administration in Children and Adolescents with Type 1 Diabetes on Basal-Bolus Treatment[☆]

Giulio Maltoni, Anna Lisa Martini, Alessandra Rollo, Annamaria Perri, Stefano Zucchini

Pediatric Unit, Endocrinology Program, Department of Medical and Surgical Sciences, S. Orsola-Malpighi Hospital, Bologna, Italy

Background: Intensive insulin treatment allows a good metabolic control and prevents long-term complications. Basal-bolus regimen is the best treatment for children with type 1 diabetes T1D but requires several insulin injections a day. The needle-fear and discomfort felt by the child and parents/caregivers for insulin administration is one of the main obstacle to good compliance. **Objective and hypotheses:** To compare glycemic control and satisfaction with a new injection port (I-PORT), through which insulin can be injected subcutaneously from a syringe/pen without repeated needle punctures of the skin, to multiple daily insulin administration (MDI). **Method:** Twenty subjects (5 M, mean age 9.5 ± 2.6 years, mean T1DM-duration 3.1 ± 2.3 years) were enrolled. They were randomly assigned to group A (starting using I-PORT) and B (on traditional MDI). Participants were trained to change the device every 3 days and to inject both basal and bolus insulins through it. Subjects were invited to move to a strict basal-bolus regimen (requiring more insulin injections for meals, snacks, and hyperglycaemic peaks). After 8 weeks the two groups switched to the other arm. HbA1c was detected at baseline, before the cross-over and at the end of the study (16 weeks). A questionnaire was provided to collect satisfaction about the new device. **Results:** Two participants dropped out and were excluded from the analysis. Mean baseline HbA1c was $8.02 \pm 1\%$ (64 ± 11 mmol/mol), mean HbA1c after I-PORT period $7.53 \pm 0.7\%$ (58 ± 8 mmol/mol) whereas mean HbA1c on traditional MDI $7.92 \pm 0.9\%$ (63 ± 9.3 mmol/mol) ($P=0.09$). No dka or severe hypoglycaemic episodes occurred. At the end of the study 15/20 (75%) of participants appreciated I-PORT and decided to maintain it. **Conclusion:** In this pilot study I-PORT has proven to be safe and seems to improve metabolic control in children during real-life setting. Attenuating the discomfort of multiple injections through the device allowed to follow more strictly basal-bolus regimen. Children and adolescents seem to tolerate and appreciate this device.

[☆]Nominated for a Presidential Poster Award.

P1-D1-60

Activity of Neutral Alfa-Glucosidase in the Urine of Children and Adolescents with Type 1 Diabetes Mellitus and Diabetic Nephropathy[☆]

Akidahon Sadykova, Gulnara Rakhimova

Aim: To identify clinical significance of enzymuria in early diagnosis of DN in children and adolescents with type 1 diabetes mellitus. **Materials and methods:** We examined 112 patients (47males/55 females) with type 1 diabetes mellitus. By the DN severity the patients were divided into following groups: with normoalbuminuria (NAU) ($n=47$), with microalbuminuria (MAU) ($n=44$) and with marked proteinuria (MP) ($n=19$). Ten healthy subjects of the same age were included into the control group. Activity of neutral urinary alfa-glucosidase (alfa-GL) was measured by intensity of glucose formation from maltose after its incubation in potassium phosphate buffer containing 0.2 mmol/l of maltose at 37 °C. **Results and discussion:** The study showed confident increase in the urinary protein level with DN progression. As compared with the NAU persons there was a 6-time increase of the urinary protein in patients with MAU (13.6 ± 0.7 vs 77 ± 9.5), in patients with MP the protein increase being 32 times higher as compared with those with NAU (13.6 ± 0.7 vs 416.8 ± 50.78). In patients with NAU prior to MAU appearance activity of neutral alfa-GL confidently increases by 36 times (0.01 ± 0.032 vs 0.52 ± 0.041), in patients with MAU there was a 1.5-time increase as compared with NAU persons (0.36 ± 0.032 vs 0.52 ± 0.041), in the group with MP the parameter increasing by 1.2 times as compared with the patients having MAU (0.52 ± 0.041 vs 0.61 ± 0.04). **Conclusions:** In children and adolescents with type 1 diabetes mellitus increase in the activity of the urinary neutral alfa-glucosidase was established associating with disturbance of both renal tubular and glomerular apparatuses to correlate with the proteinuria and DN severity. As DN severity enhances the activity of the urine neutral alfa-GL is shown to increase. An early marker in DN diagnosis activity of the urinary neutral alfa-GL is found diagnostically significant at the early stages of diabetes mellitus progression.

*Nominated for a Presidential Poster Award.

P1-D1-61

Evaluation of S-100B, Antioxidant and Oxidative Capacity Before and After the Treatment in Children with Diabetic Ketoacidosis^{*}

Cemil Kaya^a, Ali Atas^a, Nurten Aksoy^b

^aDepartment of Pediatric Endocrinology, University of Harran, Sanliurfa, Turkey; ^bDepartment of Biochemistry, University of Harran, Sanliurfa, Turkey

Background: Diabetic ketoacidosis is a serious condition with high rates of morbidity and mortality in children with type 1 diabetes mellitus. Calcium-binding protein S100B is a cell damage marker glycopeptide that is mainly produced by astrocytes. Oxidative stress might be defined as an imbalance between anti-oxidative defense of the body and free radical production

responsible for peroxidation of lipid layer of cell walls. **Objective and hypotheses:** In patients with diabetic ketoacidosis, high blood glucose concentration may increase oxidative stress and consequent changes in neurotransmitter by which may increase the level of S100B. In this study we aimed to investigate S100B protein levels, oxidant and antioxidant capacity in children with diabetic ketoacidosis. **Methods:** 49 healthy children and 49 children with diabetic ketoacidosis included into this study. Peripheral venous bloods were taken for tests during diabetic ketoacidosis and after recover diabetic ketoacidosis. Measurement of serum S100B was performed by ELISA Kits. Total antioxidant status (TAS), Total oxidant status (TOS), and oxidative stress index (OSI) were studied at peripheral venous blood by Erel method. **Results:** Comparing pretreatment and post-treatment of TAS, TOS, S100B levels were significantly higher in patients with diabetic ketoacidosis than healthy control group ($P < 0.05$). There was no significant difference in the levels of S100B and OSI ($P > 0.05$). In our study there was also a positive correlation between S100B with the TOS and OSI values (respectively $r: 0.235$, $r: 0.244$; $P: 0.006$, $P: 0.005$). **Conclusions:** In diabetic ketoacidosis, increase of oxidative stress and S100B may be depending on high glucose level. Increasing concentrations of these factors in blood may be therefore indicative for either neuronal damage, impaired blood brain barrier function, or both.

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P1-D1-62

Effect of Adjunctive Therapy with Cholecalciferol on Residual β -Cell Function in Recent-Onset Type 1 Diabetes Mellitus: a Prospective Pilot Study

Ana Laura Fitas, Ana Filipa Almeida, Catarina Limbert, Lurdes Lopes
Hospital de Dona Estefânia, CHLC-EPE, Lisbon, Portugal

Background: Several studies have suggested that vitamin D supplementation in early childhood is successful in decreasing the risk of type 1 diabetes (T1D) through a complex immunomodulatory role. However, Intervening in disease once clinical symptoms have appeared and autoreactive immune responses are active might be more challenging. Controlled trials with vitamin D supplementation in recent-onset T1D have shown mixed results. **Objective and hypotheses:** The aim of this pilot trial was to investigate whether supplementation with cholecalciferol in subjects with recent-onset T1D is able to protect residual β -cell function (C-peptide) and to improve metabolic control (HbA1c, insulin requirement). **Method:** Twenty-eight subjects with recent-onset T1D and basal C-peptide > 0.2 nmol/l were randomized in a prospective non-blinded controlled trial to supplementation with oral cholecalciferol 1332 IU/day ($n=14$) or standard therapy ($n=14$). C-peptide, HbA1c and 25-hydroxy-vitamin D (25HOD) levels were measured at baseline and after a mean period of 13.4 months (s.d. = 2.5). Insulin requirements were

evaluated by total daily dose (U/kg per day). SPSS 20 was used for data analysis. **Results:** Mean age at T1D diagnosis was 7.9 years (s.d.=3.9). At baseline, the majority of patients had inadequate 25OHD levels: insufficiency (21–29 ng/ml) (48,5%) and deficiency (≤ 20 ng/ml) (12.1%). On the follow-up evaluation, the cholecalciferol supplementation group had significantly higher 25OHD (mean 59.72 vs 37.67 ng/ml, $P=0.05$) and C-peptide levels (mean 0.32 vs 0.062 nmol/l, $P=0.007$) when compared to the standard therapy group. The cholecalciferol supplementation group needed lower insulin daily dose (0.58 vs 0.66 U/kg per day) and had lower HbA1c (7.54 vs 7.71%) than the control group, on the follow up evaluation, even though statistical significance was not reached. **Conclusions:** This pilot study suggests that cholecalciferol supplementation in recent-onset T1D might prolong endogenous insulin production, and possibly improve glycemic control with lower insulin requirements.

P1-D1-63

Th17 Cells in Children with New Onset Type 1 Diabetes

Robert Piekarski^a, Iwona Ben-Skowronek^a, Agnieszka Bojarska-Junak^b, Jacek Tabarkiewicz^b, Leszek Szewczyk^a

^aDepartment of Pediatric Endocrinology and Diabetology, Medical University of Lublin, Lublin, Poland; ^bDepartment of Clinical Immunology, Medical University of Lublin, Lublin, Poland

Background: A recent data indicates a complex mechanism of β -cell destruction in type 1 diabetes in which despite Th1/Th2 bias different other populations of immune cells like Th17 with specific IL17A secretion with proinflammatory action will mediate β cells autoreactivity. In humans, the relevance of Th17 cells in new onset T1DM is still controversial. **Objective and hypotheses:** The aim of our study was to evaluate circulating Th17 in children with new onset type 1 diabetes and comparison to a group of healthy children. **Method:** The study group comprised 53 children, mean age 10.2 ± 5.5 years, with newly diagnosed type 1 diabetes. In all children were assessed C-peptide and anti-GAD and anti-IA2 antibodies to confirm autoimmune pathogenesis of disease and cell subpopulations were examined using flow cytometry. The reference group consisted of 20 healthy children. The percentage of circulating CD4+IL17A+ and CD4+/CD3+/IL17A+T cells with expression of Th17-related transcription factor ROR γ t have been analyzed. **Results:** Comparison between T1DM children and healthy counterparts showed no statistically significant difference in average percentage of circulating Th17 cells but there was significant difference in mean fluorescence intensity (MFI) between studied groups ($P<0.01$). Interestingly, as we evaluated TH17 cells at different time points of disease progression during initial phase of diabetes (6, 30, and 60 days from diagnosis of DM) we have noted gradual statistically significant decrease ($P<0.05$) in the absolute number of Th17 cells with positive correlation with

insulin requirement (total daily insulin dose). There were no correlation between the percentage of CD4+IL17A+ and CD4+/CD3+/IL17A+T cells and C-peptide and HbA1c level. **Conclusion:** Based on these findings more detailed analysis of the observed dependence is needed but it seems that observed changes in population of Th17 cells may be due to accumulation in the target organ during the initial effector phase of type 1 diabetes.

P1-D1-64

Biomarkers of Subclinical Inflammation in an Infant-Juvenile Population with Type 1 Diabetes

Maria Bazan^a, Sofia Casella^a, Santiago Lopez^a, Teresita Carrizo^b, Maria Velarde^b, Elba Diaz^b, Adela Abregu^b

^aMedicine Faculty, National University of Tucuman, Tucuman, Argentina; ^bBiochemical Faculty, National University of Tucuman, Tucuman, Argentina

Background: Diabetes is associated with increased risk of vascular disease. In children and adolescents with type 1 diabetes (T1D), clinical manifestations of vascular complications are infrequent; however, a pro-inflammatory state and endothelial disturbance could appear early. A subclinical inflammation state result in increased plasma levels of adhesion molecules, inflammatory cytokines as tumor necrosis factor alpha (TNF α), and acute phase proteins as C-reactive protein (CRP) and fibrinogen (Fg). **Objective and hypotheses:** The objective of this work was study plasma levels of soluble E-selectin (sE-S), VCAM1, TNF α , high sensitivity CRP (hsCRP) and Fg in a pediatric population with T1D, without clinical evidence of vascular complications; and the relationship with glycemic control and disease evolution. **Method:** Forty-two T1D patients and 20 control children, age 8–13 years, were studied. Biochemical parameters evaluated were: white blood cell count (WBC), sE-S and VCAM1, TNF α , hsCPR, and plasma Fg. Retinopathy and nephropathy was discarded cart by ophthalmic exam and microalbuminuria determination respectively. **Results:** In diabetic patients compared with the control group found increased levels of sE-S (108 (69–150) vs 68 (52–86) ng/ml, $P=0.003$), VCAM1 (785 (732–835) vs 712 (658–758) ng/ml, $P=0.04$), and hsPCR (1.00 (0.67–1.70) vs 0.20 (0.18–0.87) mg/l, $P=0.01$). No significant differences on WBC, TNF α , or Fg values between diabetics and controls were found. When diabetic patients were grouped according glycemic control degree (A1c < 8 and $\geq 8\%$) and disease evolution (≤ 3 and > 3 years), no differences were found in the studied molecules. hsCPR correlated with glucose ($r=0.54$, $P=0.001$), A1c ($r=0.41$, $P=0.01$), sE-S ($r=0.47$, $P=0.004$), and VCAM1 ($r=0.41$, $P=0.02$). **Conclusion:** The increased levels of hsPCR and adhesion molecules suggest that a proinflammatory state associated with endothelial activation are present in children with T1D, enhancing the risk of cardiovascular disease.

P1-D1-65**Glycaemic Control and Acute Complications in European Children, Adolescents, and Young Adults With Type 1 Diabetes in the Teens Study**

Moshe Phillip^a, Lori Laffel^b, Catherine Domenger^c, Marie-Paule Dain^c, Valerie Pilorget^d, Christophe Candelas^d, Thomas Danne^e, Carmen Mazza^f, Barbara Anderson^g, Ragnar Hanas^h, Sheridan Waldronⁱ, Roy Beck^j, Chantal Mathieu^k

^aInstitute for Endocrinology and Diabetes, National Center for Childhood Diabetes, Schneider Children's Medical Center of Israel, Petah Tikva, Israel; ^bPediatric, Adolescent and Young Adult Section, Joslin Diabetes Center, Boston, Massachusetts, USA; ^cSanofi, Paris, France; ^dSanofi, Chilly Mazarin, France; ^eKinder und Jugendkrankehaus 'Auf der Bult', Hannover, Germany; ^fNutrition Department, Hospital de Pediatría J P Garrahan, Buenos Aires, Argentina; ^gSection of Psychology, Department of Pediatrics, Baylor College of Medicine, Houston, Texas, USA; ^hNU Hospital Group, Department of Pediatrics, Uddevalla and Sahlgrenska Academy, Gothenburg University, Gothenburg, Sweden; ⁱHosted by West Midlands Strategic Clinical Network, Birmingham, UK; ^jJaeb Center for Health Research, Tampa, Florida, USA; ^kUniversity Hospitals (UZ), Leuven, Belgium

Aims: The TEENS study is an international, cross-sectional observational study aiming to assess type 1 diabetes (T1D) management and psychosocial parameters in children, adolescents, and young adults, to identify approaches to optimise glycaemic control and outcomes. Results from 11 European countries are presented. **Methods:** 111 centres providing diabetes care to young T1D patients collected data by participant interview, medical record review and participant/parent surveys from 2943 European youths (47.9% female) in three age groups: children (8–12 years old (y/o), $n=887$), adolescents (13–18 y/o, $n=1451$), and young adults (19–25 y/o, $n=605$). A1c was measured uniformly using A1c now (Bayer) (reference range 4–6%); target A1c defined as $<7.5\%$ for ≤ 18 y/o (ISPAD) and $<7\%$ for 19–25 y/o (ADA). **Results:** Median T1D duration was 6.5 years (interquartile range 3.7–9.9). Most participants (66.1%) received basal-bolus insulin therapy. Overall, mean A1c was $8.1 \pm 1.6\%$ (65.0 ± 17.5 mmol/mol), and varied by age: $7.9 \pm 1.4\%$ (62.8 ± 15.3 mmol/mol) in 8–12 y/o, $8.2 \pm 1.7\%$ (66.1 ± 18.6 mmol/mol) in 13–18 y/o, and $7.9 \pm 1.5\%$ (62.8 ± 16.4 mmol/mol) in 19–25 y/o. One-third of participants (1015 (34.5%)) achieved A1c targets (39.4% in 8–12 y/o, 36.5% in 13–18 y/o and 22.6% in 19–25 y/o). In the 3 months prior to the study, 72 (3.7%) of those not at A1c target and 20 (2.0%) of those at target had ≥ 1 diabetic ketoacidosis (DKA) episode, while 22 (1.1%) and 14 (1.4%), respectively, had ≥ 1 severe hypoglycaemic event (leading to seizure or loss of consciousness). Overall, occurrence of DKA was higher in children and adolescents (3.3% in both age groups) than young adults (2.5%), and severe hypoglycaemic events occurred in 1.5, 1.0, and 1.5% of 8–12, 13–18, and 19–25 y/o respectively. **Conclusions:** Overall, in European youths, diabetes outcomes remain sub-optimal, with mean A1c above target for two-thirds of participants and many youth experiencing acute complications, supporting the need for further improvements. Study sponsored by Sanofi.

P1-D1-66**Metabolic Consequences of Antipsychotic Medication in Youths with Type 1 Diabetes: Analysis from the Prospective Nationwide German and Austrian Diabetes Survey DPV**

Angela Galler^a, Esther Molz^b, Michael Meusers^c, Bela Bartus^d, Andrea Näge^e, Holger Haberland^f, Edith Schober^g, Reinhard W Holl^h

^aCharité - Universitätsmedizin Berlin, Berlin, Germany; ^bInstitute of Epidemiology and Medical Biometry, University Ulm, Ulm, Germany; ^cGemeinschaftskrankenhaus Herdecke, Child and Adolescent Psychiatry, Herdecke, Germany; ^dFilderklinik, Filderstadt, Germany; ^eUniversity Carl Gustav Carus Dresden, University Hospital for Children and Adolescents, Dresden, Germany; ^fSana Hospital Berlin Lindenhof, Hospital for Children and Adolescents, Berlin, Germany; ^gMedical University Vienna, University Hospital for Children and Adolescents, Vienna, Austria

Background: The use of antipsychotic medication in medical practice is increasing in Europe. Antipsychotics have serious adverse effects like weight gain. **Objective:** Aim was to explore metabolic risk factors and glycaemic control in youths with type 1 diabetes treated with typical or atypical antipsychotics. **Design and methods:** Data of children, adolescents, and young adults with type 1 diabetes up to the age of 25 years and with diabetes duration of more than 6 months registered in the prospective, nationwide German/Austrian computer-based diabetes survey (DPV) were included in the analysis. BMI SDS, HbA1c, prevalences of dyslipidaemia, microalbuminuria, and retinopathy, and frequencies of hypoglycaemia and diabetic ketoacidosis (DKA) in subjects treated with typical or atypical antipsychotics were compared to those without antipsychotic medication and analysed by regression analysis. **Results:** A total of 291 patients with type 1 diabetes (age 17 years, 60% males, diabetes duration 7.2 years) received antipsychotic medication (most commonly risperidone). Subjects treated with antipsychotics had a significant higher BMI SDS ($P=0.004$) and dyslipidaemia was more frequent ($P=0.045$) compared to subjects without antipsychotic medication. Frequencies of severe hypoglycaemias and DKA were significantly higher in patients receiving antipsychotics ($P<0.001$). Prevalences of microalbuminuria, and retinopathy were not different. In subjects treated with antipsychotics, glycaemic control did not differ compared to patients without antipsychotic medication. **Conclusions:** This analysis demonstrated that treatment with antipsychotic medication was associated with higher BMI SDS and higher rates of acute diabetic complications in youths with type 1 diabetes.

P1-D1-67**Protective Effects of Combined Intervention with Adenovirus Vector Mediated il10 and igf1 Genes on Endogenous Islet β Cells in Nonobese Diabetes Mice with Onset of Type 1 Diabetes Mellitus**

Tang Li^a, Lijuan Zhang^a, Yanyan Chen^b, Cheng Li^a, Xiaojie Lin^a

^aAffiliated Hospital of Medical College, Qingdao University, Qingdao, China; ^bPeople's Hospital of Rizhao, Rizhao, China

Introduction: To investigate the protective effects of combined intervention with adenovirus vector mediated interleukin 10 (IL10) and IGF1 genes on islet β cells in nonobese diabetes (NOD) mice with type 1 diabetes mellitus (T1D) at early stage. **Methods:** Twenty-four female NOD mice at onset of diabetes and aged 17–20 weeks old were randomly divided into four groups. Mouse 1, 2, and 3 groups were i.p. injected 0.1 ml of Ad-mIGF1, Ad-mIL10, and combined Ad-mIGF1 and Ad-mIL10 respectively. Mouse four group were used as diabetes control. In addition, six age- and sex-matched non-diabetic NOD mice were i.p. injected 0.1 ml of PBS and assigned five group as normal controls. All mice were weekly monitored for body weight, urine glucose and blood glucose, and sacrificed 3 weeks after injection. Their serum levels of IL10, IGF1, IFN γ , IL4 and C-peptide were measured and the degree of insulinitis and the local expression of IGF1 and IL10 gene were observed. **Results:** i) IL10 and IGF1 levels in serum and pancreas were enhanced in 1, 2, and 3 groups; ii) serum INF- γ level was decreased while serum IL10 and IL4 levels were increased in 1, 2, and 3 groups, and these alterations were more significant in three group than 1 and 2 groups ($P < 0.01$); iii) C-peptide level was not enhanced in 1 group, but significantly increased in 2 and 3 groups, and these increases were more significant in the latter ($P < 0.01$); and iv) three weeks later, the body mass of mice in two and three groups decreased significantly ($P < 0.05$). **Conclusion:** The administration of adenovirus vector mediated IL10 and/or IGF1 gene showed limited immune regulatory and protective effects on islet β -cells in NOD mice with T1D at early stage, and no significant reduction in insulinitis, blood glucose, and body weight.

P1-D1-68

Evaluation of Bone Geometry, Quality, and Bone Markers in Children with Type 1 Diabetes

Silvia Longhi^a, Roberto Franceschi^b, Vittoria Cauvin^b, Giuseppe Gallo^b, Fiorenzo Lupi^a, Petra Reinstadler^a, Giorgio Radetti^a

^aDepartment of Pediatrics, Regional Hospital of Bolzano, Bolzano, Italy; ^bDepartment of Pediatrics, Santa Chiara Hospital of Trento, Trento, Italy

Background: Several studies have examined the relationship between type 1 diabetes and bone mass, which reported contradictory data on BMD, bone remodelling markers, and bone quality. Nevertheless an increased prevalence of osteopenia was observed among patients with duration of disease of > 6 years. **Objective and hypotheses:** The aim of the study was to investigate the potential negative impact of type 1 diabetes on bone status in a group of children with type 1 diabetes, by evaluating bone geometry, quality, and bone markers. **Method:** 51 children (25 m, 26 f), mean age 10.31 ± 3.16 years height SDS, 0.17 ± 0.79 ;

and BMI SDS, 0.48 ± 0.81 with a mean duration of type 1 diabetes of 5.03 ± 3.11 years were studied. Bone geometry was evaluated on digitalized X-rays at the level of the second metacarpal bone. The following parameters were investigated: outer diameter (D), inner diameter (d), cortical area (CA) and medullary area (MA), meanwhile bone quality was evaluated by ultrasound performed at the phalangeal diaphysis of the non-dominant hand and expressed as amplitude dependent speed of sound (Ad-Sos) and bone transmission time (BTT). Bone markers (P1NP and CTX), sclerostin, Dkk-1, PTH, and 25OHD were also assessed. Data were converted to SDS and evaluated according to the bone age. Differences in bone geometry and quality were evaluated against zero, while the biochemical values of the patients were compared with a control group of 40 subjects of normal weight and height, which did not suffer of any chronic diseases. **Results:** D (-0.98 ± 0.95), d (-0.34 ± 0.98), CA (-0.88 ± 0.74) and MA (-0.39 ± 0.90) were all significantly smaller than in controls ($P < 0.01$) while Ad-Sos (-0.08 ± 1.06) and BTT (-0.12 ± 0.88) were not significantly reduced. The bone markers were similar in children with type 1 diabetes and controls. **Conclusion:** Type 1 diabetic children show a bone of reduced size but with conserved proportion and quality.

P1-D2-69

Activation of Insulin/IGF1 Signaling Could Increase Hypothalamic Lipid Anabolism in Non-Diabetic IRS2-Deficient Mice^{*}

Vicente Barrios^{a,b}, Eva Baquedano^{a,b}, Sandra Canelles^{a,b}, Águeda González-Rodríguez^{c,d}, Emma Burgos-Ramos^e, Julie A Chowen^{a,b}, Laura M Frago^{a,b}, Ángela M Valverde^{c,d}, Jesús Argente^{a,b}

^aEndocrinology, Hospital Infantil Universitario Niño Jesús, Madrid, Spain; ^bCentro de Investigación Biomédica en Red de Fisiopatología Obesidad y Nutrición, Madrid, Spain; ^cInstituto de Investigaciones Biomédicas Alberto Sols, CSIC/Universidad Autónoma de Madrid, Madrid, Spain; ^dCentro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas, Madrid, Spain; ^eMolecular Pathology Programme, Centro Nacional de Investigaciones Oncológicas, Madrid, Spain

Background: Insulin/IGF1 signaling plays a critical role in central glucose bioavailability and lipid metabolism. An increase in glucose disposal can generate reducing agents through the pentose-phosphate pathway necessary for the synthesis of free fatty acids (FFA). Disturbances in lipid synthesis are related to the appearance of insulin resistance and diabetes. The insulin receptor substrate 2 (IRS2) deficient mice (IRS2^{-/-}) is an excellent model to study the development of diabetes as a high proportion of them present an abrupt increase in glycemia, showing similarities with type 1 diabetes. However, the molecular mechanisms involved in the onset of diabetes in IRS2^{-/-} mice remain to be elucidated. **Objective and hypotheses:** We hypothesized that alterations in insulin/IGF1 signaling could be related to the incidence of diabetes

in IRS2^{-/-} mice. Thus, we analyzed the changes in hypothalamic signaling and its relationship with hypothalamic lipid synthesis in this model. **Method:** We studied 18 mice including controls (C), non-diabetic IRS2^{-/-} (ND) and diabetic IRS2^{-/-} (D) mice. We analyzed serum concentrations of FFA by a colorimetric method, insulin and IGF1 by enzyme immunoassay, insulin/IGF1 signaling by multiplexed bead immunoassay and immunoprecipitation/western blot and enzymes involved in glucose oxidation and lipid anabolism by western blot. **Results:** Serum insulin was increased in both D and ND, with higher levels in ND, whereas IGF1 and FFA concentrations were augmented only in ND mice. Hypothalamic levels of glucose transporter 2, IGF1 receptor, IRS1 and association of p85 subunit of PI3 kinase to IRS1 were augmented only in ND mice. Among the studied enzymes, acetyl-CoA carboxylase was inhibited in D mice, whereas levels of malic enzyme and fatty acid synthase were increased in the hypothalamus of ND mice. **Conclusion:** Increased hypothalamic insulin/IGF1 signaling might be a triggering factor for the occurrence of diabetes in IRS2^{-/-} mice.

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P1-D2-70

Evaluation of Subclinical Atherosclerosis by Non-Invasive Radiological Methods and its Relation with Endoglin and Nitric Oxide Levels^{*}

Hamdi Cihan Emeksiz, Aysun Bideci, Nurullah Çelik, Özge Yüce, Esra Döğür, Çağrı Damar, Öznur Boyunağa, Orhun Çamurdan, Peyami Cinaz

Gazi University, Ankara, Turkey

Background: Endothelial dysfunction is thought to be a key event in the development of atherosclerosis. Demonstration of increased endoglin expression in atherosclerotic plaques suggested participation of endoglin in atherogenesis. Endoglin expression was also related to nitric oxide (NO) production in endothelium.

Objective and hypotheses: Aim of the study was to evaluate the subclinical atherosclerosis in adolescents with type 1 diabetes mellitus (T1DM) by non-invasive radiological methods including flow-mediated dilation (FMD) of the brachial artery and measurement of intima-media thickness (CIMT) of the carotid arteries along with serum endoglin and plasma nitric oxide levels.

Method: 58 patients with moderately controlled T1DM (57% male, age 15.34 ± 1.79, and diabetes duration 6.71 ± 0.49) and 29 healthy controls (51% male, age 15.03 ± 2.00) participated in the study. Serum endoglin, plasma NO, FMD, and CIMT were measured and compared between study and control groups. Patients with microvascular complications (MiC) were further compared with those without, and controls. Serum endoglin was measured by ELISA Kit and plasma NO by colorimetric assay kit.

Results: Mean serum endoglin and plasma NO levels were found significantly increased in adolescents with diabetes as compared to the control group (2.61 ± 0.67 vs 1.97 ± 0.45 µg/ml, $P=0.001$; 4.68 ± 2.01 vs 3.74 ± 1.64 µg/ml, $P=0.033$ respectively). CIMT and

FMD (%) insignificantly differed between patient and control groups ($P>0.05$). Diabetic patients with MiC had lower endoglin level than the patients without MiC whereas higher endoglin level than the control group. CIMT was found significantly higher in patients with MC than diabetic patients without MC and controls. Significantly higher NO level was found in patients with MC as compared to the control group. **Conclusion:** Subclinical atherosclerosis should be investigated in diabetic adolescents particularly with microvascular complications. The levels of biomarkers reflecting endothelial dysfunction may change during the progression of the disease. Further studies are warranted to clarify cause-effect relationship.

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P1-D2-71

Identification of Novel Candidate Gene Variants for Mody by Whole Exome Sequencing in Korean Mody Families^{*}

Un Mi Cho, Yae Ji Shim, Byung Ho Choi, Cheol Woo Ko

Kyungpook National University Hospital, Daegu, Republic of Korea

Background: Maturity-onset diabetes of the young (MODY) is one of monogenic diabetes caused by a single gene defect. To date, 13 MODY genes have been identified. However, there is big discrepancy in genetic locus between the Asian MODY patients and Caucasian's one. **Objective and hypotheses:** We conducted the whole exome sequencing in Korean clinical MODY families to identify novel variants for MODY and compare the result with Caucasian's one. **Method:** The six clinical MODY probands and their family members were included for exome sequencing. To identify the disease causing mutations, the variants in dbSNP135 and TIARA database for Korean and the variants with minor allele frequencies > 0.5% of the 1000 g were excluded. We selected only the functional variants (gain of stop codon, frameshifts, and nonsynonymous SNV resulting in disruption of canonical splice sites) and conduct a case-control comparison in the family members. The selected variants were scanned for the interested gene list for MODY. **Results:** All exonic regions were 18 981–20 178 in six probands. After filtering, the functional variants were 224–250. After case-control method, variants with possibility of causing the disease were 31–63 in each one side pedigree. After scanning for the interested gene list for MODY, three novel variants, c.620C>T; p.Thr207Ile in *PTPRD*, c.559C>G; p.Gln187Glu in *SYT9*, and c.1526T>G; p.Val509Gly in *WFS1* were identified in three families respectively. **Conclusion:** We could not find any disease causative alleles among known MODY 1–13 genes. We confirmed again that there is huge discrepancy between Asian and Caucasian races in the case of generic variants of MODY. Further evaluation is necessary about the role of *PTPRD*, *SYT9*, and *WFS1* in glucose metabolism and normal insulin release from pancreatic beta cell in the future.

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P1-D2-72

Abstract withdrawn.

P1-D2-73**A Novel Mutation of *wfs1* Gene in a Japanese Infant of Diabetes Mellitus, Deafness, and Congenital Cataract**

Shuntaro Morikawa^a, Akie Nakamura^{a,b}, Katsura Ishizu^a, Satoru Kumaki^c, Toshihiro Tajima^a

^aDepartment of Pediatrics, Hokkaido University School of Medicine, Sapporo, Japan; ^bDepartment of Molecular Endocrinology, National Research Institute for Child Health and Development, Tokyo, Japan; ^cDepartment of Pediatrics, Teine Keijinkai Hospital, Sapporo, Japan

Introduction: Wolfram syndrome (WS) is a rare autosomal recessive disorder characterized by the association of early-onset, insulin-dependent diabetes mellitus (DM), diabetes insipidus, deafness, and progressive optic atrophy. The disease is caused by mutations of *wfs1* located on 4p16 encoding peptide that is called wolframin. Wolframin is a component of the endoplasmic reticulum (ER) membrane. It is considered that mutant Wolframin might cause increased misfolded and unfolded proteins in ER followed by cell apoptosis. Here, we report a Japanese female patient with DM, deafness, and congenital cataract. **Case report:** The patient was admitted to our hospital for poor weight gain and DM. Her growth failure was evident at 3 months old and congenital cataract was noticed at 7 months old. In addition, auditory brainstem response (ABR) test revealed her severe bilateral hearing loss. Her psychomotor development was also delayed. Based on these findings, she was suspected to have WS. **Methods:** The *wfs1* exon was amplified by PCR and direct sequencing was performed. The functional consequence of the mutant *wfs1* identified in this study was analysed using GPR78-luciferase vector *in vitro*. **Results:** Sequence analysis showed a heterozygous 12 bases deletion in exon 8 (c.973_984del12), resulting in three amino acids in-frame deletion. As her parents did not have the deletion, the mutation presumably occurred *de novo*. *In vitro* analysis revealed that the mutant *wfs1* lost the suppression activity of ER stress response compared with the wild type *wfs1*, resulting in the increase of ER stress. **Conclusion:** We identified a novel non-inactivating mutation of *wfs1* in a Japanese patient with WS.

P1-D2-74**Transient Hyperglycaemia Preceded by Neonatal Hyperinsulinaemic Hypoglycaemia in an Infant with a Novel *HNF1A* Mutation**

Barbora Obermannova, Klara Rozenkova, Petra Dusatkova, Stepanka Pruhova, Zdenek Sumnik, Jan Lebl

Department of Paediatrics, 2nd Faculty of Medicine, Charles University in Prague and University Hospital Motol, Prague, Czech Republic

Background: The phenotype associated with heterozygous *HNF1A* gene mutations has recently been extended to include neonatal hyperinsulinaemic hypoglycaemia (HH) in addition to maturity-onset diabetes of the young (HNF1A-MODY). **Objective and hypotheses:** The baby boy was born at 38th week of gestation; BW 4110g; BL 53 cm (LGA). The mother had gestational diabetes; her father is treated for diabetes mellitus from the age of 50 years. The boy developed hypoglycaemia since the first day of life that required i.v. glucose administration; during hypoglycaemia (2.0 mmol/l) the level of insulin was not suppressed (4.2 mIU/l) confirming HH. After the neonatal period, hypoglycaemias resolved spontaneously. At age 10 months, the boy developed acute respiratory failure during viral pneumonia with severe dyspnoea; tachypnoea, and dehydration. At admission, he had hyperglycaemia 18 mmol/l prior to the first administration of corticosteroids and mild acidosis with dominant respiratory component. His HbA1c was 34 mmol/mol, and he had no history of polyuria and polydipsia. During the subsequent therapy with high-dose corticosteroids and mechanical ventilation, he required continuous insulin infusion for 7 days. Insulin therapy could be discontinued after the respiratory stabilization, afterwards the glycaemias remained normal. At the age of 12 months, HbA1c is in normal range (32 mmol/mol) without antidiabetic treatment. **Method:** We performed molecular genetic testing of *HNF4A* and *HNF1A* genes using direct sequencing. **Results:** In the proband a novel heterozygous mutation (L254Q) within the *HNF1A* gene was found. Mutation segregated with diabetes in three generations. **Conclusion:** To our knowledge, this is the first observation of HNF1A-MODY with history of neonatal hypoglycaemia followed by transient stress hyperglycaemia in infancy. This suggests that the capacity of β -cells to respond to high demands on insulin secretion may be impaired since an early age.

P1-D2-75**Lpl Gene Mutation and Polymorphism of Apoc2 and Apoc5 Genes in a Patient with Diabetes Mellitus Type 1**

Julita Nocon-Bohusz, Beata Wikiera, Aleksander Basiak, Anna Noczynska

Medical University, Wroclaw, Poland

Background: The rise of TG in patients with ketoacidosis is connected with the impairment of lipoprotein lipase activity – the enzyme strictly dependent on insulin. **Objective and hypotheses:** The authors present a case report of 2.5 years old boy in whom diabetes manifestation was connected with severe metabolic disorders: ketoacidosis and extreme hyperlipidaemia. **Method:** The child without any significant medical history, admitted because of features of dehydration and ketoacidosis

connected with a newly diagnosed diabetes mellitus type 1. **Results:** The laboratory results were as follows: glucose 850 mg/dl, pH 7.27, Na 100.5 mmol/l, K 4.0 mmol/l, TG 13 496 mg/dl, and Ch 734 mg/dl. A milky serum caused the reliable results difficult to achieve. The child was referred to intensive care unit after i.v. fluid administration. Insulin therapy and parenteral nourishment caused normalization of glucose levels and gradual normalization of metabolic status. On admission to endocrine unit: body weight 11 kg, normal gas analysis, HbA1c 11.6%, Ch 337 mg/dl, TG 766 mg/dl, and HDL 24 mg/dl. On abdominal ultrasound examination: the liver enlargement and its echogenicity increase – the picture of steatosis. Genetic analysis confirmed heterozygous mutation in exon 6 *LPL* gene and polymorphism of *APOC2* and *APOC5* genes. The same mutation in *LPL* gene was found in the patient's mother. **Conclusion:** So escalated lipid disturbances in a young child with diabetes mellitus were not reported in medical literature so far. *LPL* deficiency or its lower activity, and deficit of apolipoprotein C2 (*apoC2*) essential to *LPL* activation constitute the main genetic reasons of a primary increase of triglycerides level in the reported patient.

P1-D2-76

Determinants of Serum Osteocalcin Concentrations in 12-Year-Old Children Born Small or Appropriate for Gestational Age

Sirpa Tenhola^{a,b}, Satu Seppä^{a,c}, Raimo Voutilainen^{b,c}

^aKymenlaakso Central Hospital, Kotka, Finland; ^bKuopio University Hospital, Kuopio, Finland; ^cUniversity of Eastern Finland, Kuopio, Finland

Background: Osteocalcin (OC) is an osteoblast derived marker of bone turnover, but it has also been linked to glucose metabolism. Specifically, the undercarboxylated form of OC has been proposed to act as a hormone that links bone to glucose homeostasis. **Objective and hypotheses:** Our aim was to study whether serum total OC associates with insulin sensitivity in 12-year-old children. **Subjects and methods:** A total of 192 children (109 girls) were studied at the mean age of 12.25 years (range 12.01–12.73). Seventy-eight of them had been born as appropriate for gestational age (AGA), 70 as small for gestational age (SGA, birth weight or length < -2 SDS), and 44 from preeclamptic (PRE) pregnancies as AGA. Pubertal development was assessed according to the Tanner scale. Fasting serum total OC, high molecular weight adiponectin (HMW-adipo), leptin, insulin, IGF1, IGFBP1, IGFBP3, and blood glucose were measured. Quantitative Insulin Sensitivity Check Index (QUICKI) was calculated. Mann–Whitney *U* and Spearman tests, and logistic regression statistical analyses were used. **Results:** The means of serum OC, HMW-adipo, leptin, insulin, IGF1, IGFBP1, IGFBP3, blood glucose, and QUICKI did not differ between the children born as SGA, AGA or from PRE pregnancies ($P > 0.05$ for all). In the whole study population, serum OC correlated negatively with BMI, leptin, HMW-adipo, and positively with

IGF1, IGFBP1, and IGFBP3 ($P < 0.01$ for all). The highest OC concentrations were found in midpuberty (Tanner B/G stage 3). The children in the highest OC tertile ($n = 64$) had lower leptin, HMW-adipo and BMI, higher IGF1, IGFBP1, and IGFBP3 than the subjects in the lowest OC tertile ($P < 0.01$ for all). The QUICKI means did not differ between these OC tertiles. In a logistic regression analysis, low leptin ($P = 0.008$), HMW-adipo ($P = 0.040$), and high IGF1 ($P = 0.021$) associated independently with high OC (adjusted by BMI, pubertal stage, sex, SGA, or maternal PRE pregnancy history). **Conclusion:** Serum OC was not associated with insulin sensitivity (QUICKI) or history of SGA. Instead, high OC was associated with low leptin and HMW-adipo. The relationship between high OC and IGF1 may reflect the fast pubertal growth phase.

P1-D2-77

Molecular Genetic Analysis of Maturity Onset Diabetes of the Young (Mody) Genes in Children by Using Targeted Next-Generation Sequencing

Ahmet Anik^a, Gönül Çatlı^a, Hale Ünver Tuhan^a, Ayhan Abacı^a, Hüseyin Anil Korkmaz^c, Behzat Özkan^c, Erkan Sari^d, Ediz Yesilkaya^d, Ayça Altıncı^e, Sefa Kızıldağ^b, Ece Böber^a

¹Department of Pediatric Endocrinology, School of Medicine, Dokuz Eylül University, Izmir, Turkey; ²Department of Molecular Biology and Genetics, School of Medicine, Dokuz Eylül University, Izmir, Turkey; ³Department of Pediatric Endocrinology, Behcet Uz Children's Hospital, Izmir, Turkey; ⁴Department of Pediatric Endocrinology, Gulhane Military Medical Academy, Ankara, Turkey; ⁵Denizli State Hospital, Denizli, Turkey

Background: MODY is an autosomal dominant inherited type of diabetes with significant genetic heterogeneity. To date, there are mutations in more than ten different genes that result in the MODY phenotype and new mutations causing MODY are still being found. **Objective and hypotheses:** In this study, we aimed to perform a molecular analysis of pediatric MODY patients by next-generation sequencing which enables the simultaneous analysis of multiple genes in a single test and to assess genotype–phenotype relationships. **Method:** Patients who were aged between 0 and 18 years and diagnosed as having MODY in four different pediatric endocrinology clinics were enrolled in the study. Molecular analysis of *GCK*, *HNFI1A*, *HNFI4A*, *HNFI1B*, *IPFI1*, *NEUROD1*, *KLF11*, *CEL*, *PAX4*, *INS* and *BLK* genes were performed on genomic DNA using next-generation sequencing. A pathogenicity for novel mutations were assessed by bioinformatic prediction softwares programs and segregation analyses. **Results:** Forty-two children with a diagnosis of MODY (mean age; 10.3 ± 4.2 years, 22 males) were enrolled in the study and mutations were identified in 15 cases (36%). *GCK* mutations were detected in eight cases, *HNFI1B* mutation in two, and *HNFI1A*, *IPFI1*, *PAX4*, *INS* and *BLK* mutations in each of five. We identified six novel missense mutations we believe causing MODY – three

mutations in *GCK* (V338M, C252S and V86A), one mutation in *HNF1A* (C241X), one mutation in *IPF1* (G55D) and one mutation in *PAX4* (R182C). **Conclusion:** The results of this study showed that i) genetic diagnosis could be made in 36% of patients, ii) six novel mutations were identified, and iii) it would be possible to establish novel mutations with further larger molecular studies given that the advantages of next-generation sequencing analysis with regard to cost and time.

P1-D2-78

Hormonal and Lipid Profile in Correlation with Anthropometric Measurements Among Offspring of Diabetic Mothers

Nancy Elbarbary, Mohammed AboElAsrar, Eman El-Hadidy, Marwa Maghrabi

Ain Shams University, Cairo, Egypt

Objective: This study was designed primarily to estimate whether there is an association between neonatal anthropometric parameters on one hand and cord blood levels of insulin, leptin, IGF1 and lipid profile on the other hand in offspring of diabetic mothers. **Method:** A total of 60 full term infants of diabetic mothers and 40 healthy infants of non-diabetic women participated in the study. Detailed anthropometric assessment of the newborn, head circumference, abdominal circumference, triceps skin fold thickness and sub scapular skin fold thickness was performed. Laboratory investigations including cord blood levels of insulin, leptin, IGF1 and lipid profile as markers for intrauterine growth were also assessed. **Results:** Significant differences between infant of diabetic mothers (IDDM) and the control group were detected regarding all anthropometric measures. As IDDM showed significantly higher mean birth weight (3.9 ± 0.48 vs 3.2 ± 0.4 kg), mean neonatal ponderal index (3.1 ± 0.32 vs 2.7 ± 0.46), mean abdominal circumference (30.8 ± 1.9 vs 28.5 ± 1.32 cm), mean triceps skin fold thickness (3.5 ± 0.58 vs 2.2 ± 0.28 mm) and sub scapular skin fold thickness when compared to control group (3.57 ± 0.6 vs 2.47 ± 0.56 mm, $P < 0.0001$ for all). Regarding the different laboratory parameters of the studied groups cord blood levels of biochemical growth factors were significantly higher in IDDM when compared to control group; insulin (70.4 ± 56.4 vs 4.48 ± 3.7 μ IU/ml), leptin (40.4 ± 14.85 vs 12.5 ± 6.7 ng/ml and IGF1 (131 ± 44.8 vs 77.3 ± 21.9 ng/ml, $P < 0.0001$ for all). As regard fetal lipid, mean HDL was lower in infants of diabetic mothers (21.4 ± 0.6) when compared to control group (32.8 ± 11.5 mg/dl, $P = 0.02$) whereas other lipid profile were the same between both groups. **Conclusion:** Exposure to maternal diabetes in fetal life results in characteristic changes in neonatal anthropometric measurements and caused abnormalities of lipid and biochemical growth factors (insulin, leptin and insulin-like growth factor-1) which may lead to metabolic and cardiovascular complications in later life.

P1-D2-79

Sequence Analysis of 11 Known Causative Genes in Clinically Diagnosed Children as Maturity Onset Diabetes of Youth by Next Generation Sequencing

Sebahat Yilmaz Agladioglu^a, Zehra Aycan^a, Semra Cetinkaya^a, Veysel Nijat Bas^a, Asan Onder^a, Havva Nur Peltek Kendirci^a, Haldun Dogan^b, Serdar Ceylaner^a

^aDr Sami Ulus Children's Health and Disease Training and Research Hospital Clinics of Pediatric Endocrinology, Ankara, Turkey;

^bIntergen Genetic Centre, Ankara, Turkey

Introduction: Maturity-onset diabetes of the youth (MODY), is a genetically and clinically heterogeneous group of diseases in the pancreatic β -cell that impair insulin secretion. It mostly caused by heterozygous mutations in one of 11 different genes associated with β -cell function. The aim of this study is detection of the distribution of both known and novel point mutations of these genes in Turkish population. **Patients and method:** This study includes patients diagnosed as MODY by clinical criteria. 43 children was included this study. Primers were designed for all coding regions and intron-exon boundaries for 11 known genes given in Online Mendelian Inheritance in Man Database (OMIM) (*HNF4A*, *GCK*, *HNF1A*, *PDX 1*, *TCF2*, *NEUROD1*, *KLF11*, *CEL*, *PAX4*, *INS*, *BLK*). **Results:** Twenty-six of patients were males (61%) and 17 were (39%) females. Family history of 29 patients (67.4%) presents typical three generation diabetes. Thirty six of them (83.7%) has an affected parent. Ages of diagnosis were within 1-20 years (10.1 ± 4.5). Mean of diabetes ages were calculated as 2.46 ± 2.01 . Thirty-four out of 43 patients (79%) have point mutations. Eighteen patients have *GCK* mutations (53%), six have (17%) *KLF11*, four have (12%) *HNF1A*, two have (6%) *NEUROD1*, one has (3%) *HNF1B*, one has (3%) *HNF4A*, one has (3%) *PDX1* gene variations. One patient has (3%) both *HNF1A* and *HNF4A* heterozygote mutations. Clinical features, mutations, numbers of patients were summarized. Twenty different mutations were detected in 34 patients. Eleven of them are proven and previously reported mutations while 15 patients have novel highly likely pathogenic mutations (44%). **Conclusions:** The most common types in our group is MODY 2. The known mutations are not found in 55% of our patients. This situation have been interpreted as evidence known mutations do not compose all the patients, and MODY distribution vary between communities.

P1-D2-80

Methylmalonic Acidemia (MMA) with Unusual Presentation Mimicking Diabetic Ketoacidosis

Prapai Dejkharnon^a, Karn Wejaphikul^a, Kamornwan Katanyuwong^a, Kevaluee Unachak^a, Duangrurdee Wattanasirichaigoon^b, Pranoot Tanpaiboon^c

^aChiang Mai University, Chiang Mai, Thailand; ^bMahidol University, Bangkok, Thailand; ^cChildren's National Medical Center, Washington, District of Columbia, USA

Background: Hyperglycemic ketoacidosis is an acute, life threatening condition requiring early etiologic recognition and management to prevent serious morbidity/mortality. The most common cause is diabetic ketoacidosis (DKA). Organic acidaemias (OAs) are inheritable metabolic disorders caused by defects in protein metabolism resulting in acid accumulation. Patients with metabolic decompensation usually present with lactic and/or ketoacidosis, with/without hypoglycemia. Hyperglycemia is a very rare manifestation. At least 16 cases of OAs presenting with hyperglycemia have been reported. Six/16 died from late diagnosis or poor compliance. **Objective and hypotheses:** We described a 2-year-old Thai girl presented with hyperglycemia, high gap acidosis and ketosis; pH 7.0, anion gap 26, glucose 283 mg/dl, and ketonemia. She has underlying delayed development, seizures, optic atrophy and poor growth. An initial diagnosis with DKA was made and standard treatment with fluids and insulin was started. After 4 h of treatment, blood sugar decreased but high gap acidosis and ketonemia persisted. Other causes of impaired response to insulin e.g. infection, errors in insulin preparation were not identified. HbA1c was 4.8%. **Method:** Due to persistent acidosis, investigations to rule out OAs were performed. **Results:** Markedly elevated urinary methylmalonic acid consistent with MMA was demonstrated. Molecular and enzyme analyses confirmed the diagnosis with MMA. Insulin was discontinued, specific treatment for MMA including protein restriction, high caloric fluid, carnitine and vitamin B12 was promptly started. Acidosis was normalized in 4 days. Patient was discharged a few days later. **Conclusion:** Majority of patients with DKA shows excellent response with standard therapy; therefore other etiologies of acidosis/hyperglycemia should be investigated in poor responders. OAs should be included in differential diagnosis especially in countries that national newborn screening is not implemented. Unusual findings e.g. hyperammonemia, lactic acidosis, delayed development may indicate underlying OAs. Determining the etiology of hyperglycemic ketoacidosis is importance and can lead to good outcome.

P1-D3-81

mHealth app for Young People with Diabetes Type 1 Transferring from Pediatric to Adult Care[☆]

Grete Teilmann^a, Kirsten Boisen^b, Eva Hommel^c, Birthe Olsen^d, Ulrik Pedersen-Bjergaard^e, Pernille Castensøe-Seidenfaden^a

^aDepartment of Children and Adolescents, Nordsjællands Hospital, University of Copenhagen, Hillerød, Denmark; ^bCenter of Adolescent Medicine, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; ^cSteno Diabetes Center, Gentofte, Denmark; ^dChildrens Department, Herlev Hospital, University of Copenhagen, Herlev, Denmark; ^eDepartment of Cardiology Endocrinology Nephrology, Nordsjællands Hospital, University of Copenhagen, Hillerød, Denmark

Background: Managing diabetes requires self-care, knowledge and support – especially when moving from pediatric to adult care. Finding ways to empower young people in transition and transfer is therefore important. **Objective:** To develop, test and evaluate a mHealth app for young people with diabetes type 1 transferring from pediatric to adult care. **Method:** Development: We developed an app-prototype based on rapid prototyping and participatory design. 13 young people aged 16–22 years old with type 1 diabetes, seven parents and seven health care professionals participated in workshops. Test: 25 young people with type 1 diabetes, seven parents and 21 health care professionals tested the app for 2 months. Evaluation: We did six individual interviews. 53 completed an electronic questionnaire. **Results:** Based on user driven innovation, we developed a mHealth app with information about: being young with diabetes; diabetes in general; the new adult department; others experiences with diabetes. Evaluation showed that 80% of the young people and 71% of parents used the app to get information about diabetes and being young with diabetes. 86% of the parents and 24% of the young people used the app to get information about their new adult department. The app gave some of the young people more knowledge of their own disease so they felt less dependent of their nurse and doctor. **Conclusion:** mHealth apps are well received by young patients, parents and staff. Prototypes can be designed, tested and evaluated within a short period of time. Especially needs of information and others experiences emerged. Future research should focus on the possible role for apps to support chronically ill young people during transition in randomized controlled trials.

[☆]Nominated for a Presidential Poster Award.

P1-D3-82

Holding the Horses of Insulin Pump Infusion: Usage and Effectiveness of the Low Glucose Suspend Feature During Fasting in Ramadan Among Adolescents with Type 1 Diabetes Mellitus to Prevent Hypoglycemia[☆]

Nancy Elbarbary

Ain Shams University, Cairo, Egypt

Background and aim: Severe hypoglycemic episodes during the daytime of Ramadan fasting is the most feared complication. Sensor-augmented pump therapy with insulin in combination with automatic insulin shutoff (low glucose suspend (LGS)) can be used to reduce hypoglycemia. In a prospective observational study, we investigated the effect of the LGS algorithm on the frequency of hypoglycemia in adolescents with type 1 diabetes who wished to fast Ramadan 2013. **Subjects and Methods:** Thirty-seven patients (23 males and 14 females, 15.6 ± 3.3 years, duration of diabetes 4.9 ± 4.2 years, pump therapy for 1.8 ± 1.1 years, used the Paradigm[®] Veo system (Medtronic) and were divided into two groups: first ($n=21$): those who wished to wear the sensor and use LGS feature. Second ($n=16$): those who did not want to wear

sensor and measured their BG level regularly. **Results:** A total of 2,314 LGS alerts occurred, and 70% began in the afternoon between 1400 and 1700 h. The mean duration of LGS events was 26.55 min, 38% lasted for <5 min, and 7% lasted for 120 min. Among these episodes, the mean sensor glucose was 61.3 ± 9.4 mg/dl at LGS activation, rose to 110.7 ± 34.6 mg/dl by the end of the LGS episode (when insulin delivery was automatically resumed), and was 163.33 ± 42.1 mg/dl at 240 min. Compared to the second group, LGS usage significantly reduced the number of BG readings <70 mg/dl ($P=0.001$) and >250 mg/dl ($P=0.03$). Non of the LGS group broke their fast vs 8 in the second group ($P=0.02$). No episodes of severe hyperglycemia or DKA were observed in both. **Conclusions:** This confirms the advantages provided by insulin pump with LGS feature used in diabetic patients who wishes to fast Ramadan. Use of the LGS significantly reduced exposure to hypoglycemia without compromising safety.

*Nominated for a Presidential Poster Award.

P1-D3-83

DKA During Diabetes Therapy: Multinational Comparison with 59 191 Pediatric Patients from England, Wales, The United States, Austria and Germany

Justin Warner^a, Julia Hermann^b, Thomas Kapellen^c, Sabine Hofers^a, Stephanie Dubose^e, Des Schatz^f, Roy Beck^e, Claudia Schweiger^h, David Maahs^d, Reinhard Holl^b

^aChildren's Hospital for Wales, on behalf of the National Paediatric Diabetes Audit and the Royal College of Paediatrics and Child Health, Cardiff, UK; ^bUniversity of Ulm, Ulm, Germany; ^cUniversity of Leipzig, Leipzig, Germany; ^dBarbara Davis Center for Childhood Diabetes, Denver, Colorado, USA; ^eJAEB Center, Tampa, Florida, USA; ^fUniversity of Florida, Florida, USA; ^gUniversity of Innsbruck, Innsbruck, Austria; ^hParacelsus Medical University, Salzburg, Austria

Background: DKA in children and adolescents with established type 1 diabetes (T1D) is a major problem with considerable cost to patients, families and health care systems. Many consider it as a quality of care indicator and a failure of relationship between the care provider and the family/patient. Considerable variability in rates are recognized. We analyzed multicenter registry and audit data from five countries with similarly advanced, yet differing, health care systems. **Objective and hypotheses:** Data from 59 191 individuals <18 years with T1D from the T1D exchange ($n=13\ 966$, United States), the National Pediatric Diabetes Audit ($n=18\ 963$, England and Wales) and the DPV initiative ($n=26\ 262$, Austria and Germany) were pooled. DKA was defined as ≥ 1 hospitalization with a pH<7.3 during the prior year. Data were analyzed using multivariable logistic regression models for the whole population. **Results:** The mean rate for DKA was 5.3% with differences amongst countries (6.2% US, 6.0% England, 4.5% Germany, 4.4% Wales, 3.3% Austria) which persisted after demographic adjustment ($P<0.0001$). Risk of DKA was highest

in adolescents (14–18 years: 5.8%) compared to younger children (6–10 years: 3.4%; $P<0.0001$). DKA increased with longer duration of diabetes from 3.5% (<2 years) to 5.9% (≥ 2 years, $P<0.0001$). DKA was higher in girls compared to boys (OR=1.34 (1.24–1.44)). DKA was more prevalent in patients with ethnic minority status (OR=1.32 (1.21–1.43)). Additionally, DKA risk was lower in patients on insulin pumps (OR=0.88 (0.81–0.96)).

Conclusion: These multicenter data demonstrate important differences in DKA in childhood T1D across five nations. Benchmarking data such as these are important so countries can learn from each other to better understand where to target interventions in order to improve quality of care.

P1-D3-84

Children and Adolescents with Type 1 Diabetes have Higher Plasma Visfatin Levels than Healthy Controls

Julia Höntzsch^a, Hildegard Jasser-Nitsche^a, Marlene Grillitsch^a, Elisabeth Suppan^a, Gudrun Weinhandl^a, Regina Riedl^b, Christine Barowitsch^c, Martin Borkenstein^a, Elke Fröhlich-Reiterer^a

^aDepartment of Pediatrics, Medical University of Graz, Graz, Austria; ^bInstitute for Medical Informatics, Statistics and Documentation, Medical University of Graz, Graz, Austria; ^cDepartment of Radiology and Nuclear Medicine, Medical University of Graz, Graz, Austria

Background: The aim of this study was to examine plasma visfatin levels in pediatric patients with type 1 diabetes (T1D). Visfatin, a novel adipokine, is predominantly secreted by visceral adipose tissue and seems to have insulin-mimetic effects. It has not been studied in children and adolescents with type 1 diabetes (T1D) yet. **Objectives:** We studied 124 subjects; 62 patients with T1D: 31 girls, mean age 13.7 ± 3.7 years; mean duration of diabetes 5.9 ± 3.5 years; mean insulin dosage 0.9 ± 0.3 U/kg per day; mean BMI 20.2 ± 3.2 kg/m² and 62 age-matched healthy controls (HC): 32 girls, mean age 13.5 ± 3.7 years; mean BMI 20.6 ± 4.6 kg/m². **Results:** The mean plasma level of visfatin was 17.5 ng/ml (range 10.6–104.5 ng/ml) in the T1D-group and 12.5 ng/ml (range 4.6–68.6 ng/ml) in the HC-group. An unadjusted comparison between the T1D-group and the HC-group showed a significant difference between visfatin levels ($P<0.001$). After adjustment for gender, BMI and pubertal status, the adjusted mean visfatin level remained significantly higher in the T1D-group (19.2 vs 11.9 ng/ml, $P<0.001$). There was no significant correlation between visfatin levels and BMI, HbA1c, duration of diabetes, fasting blood glucose, pubertal status, total cholesterol, LDL cholesterol and triglycerides, but we found a correlation between HDL cholesterol and visfatin levels ($r=0.39$, $P=0.002$), (adjusted: $P=0.38$, $P=0.003$). **Conclusion:** Children and adolescents with T1D have higher plasma visfatin levels compared to HC, suggesting an influence on glucose metabolism in insulin-deficient patients, independent of BMI. Furthermore, we could find a correlation between visfatin and HDL in pediatric T1D.

P1-D3-85

Algorithm-Based Cholesterol Monitoring in Children with Type 1 Diabetes

K Otfried Schwab^a, Juergen Doerfer^b, Christa Scheidt-Nave^c, Bärbel-Maria Kurth^d, Andreas Hungele^e, Nicole Scheuing^f, Andreas Krebs^g, Axel Dost^h, Tilman R Rohrerⁱ, Edith Schober^j, Reinhard W Holl^k

^aUniversity Hospital, Freiburg, Baden-Württemberg, Germany; ^bUniversity Hospital, Freiburg, Baden-Württemberg, Germany; ^cRobert-Koch-Institute, Berlin, Germany; ^dRobert-Koch-Institute, Berlin, Germany; ^eUniversity Ulm, Ulm, Baden-Württemberg, Germany; ^fUniversity Ulm, Ulm, Baden-Württemberg, Germany; ^gUniversity Hospital, Freiburg, Baden-Württemberg, Germany; ^hUniversity Hospital, Jena, Thuringia, Germany; ⁱSaarland University, Homburg, Saarland, Germany; ^jUniversity Hospital, Vienna, Austria; ^kUniversity Ulm, Ulm, Baden-Württemberg, Germany

Background: Lipid profiles of type 1 diabetic children are influenced by age, sex, BMI- and HbA1c-values. There is a discrepancy between increased cholesterol levels and the management required. Thus, 26% of patients have dyslipidemia but only 0.4% of them receive lipid lowering medication. **Objective and hypothesis:** To facilitate child-specific and diabetes-related cholesterol control, we developed a monitoring algorithm derived from population-based reference values. **Method:** LDL-, non-HDL-, and HDL cholesterol percentile values were calculated for children with type 1 diabetes and non-diabetic peers within algorithm-based categories of sex, age: 1–10 vs >10–<18 years, BMI: <90th vs ≥90th percentile, and HbA1c <6%, 6–<7.5%, 7.5–9%, >9%. Analyses included 26 147 patients sampled from a German/Austrian population-based registry for type 1 diabetes (DPV) and 14 057 non-diabetic peers participating in the national health interview and examination survey for children and adolescents (KiGGS) in Germany. **Results:** HDL-C values are almost higher in diabetic children than healthy peers. Very good controlled children with diabetes (HbA1c <7.5%) have a less atherogenic lipid profile compared to healthy peers. However, pubertal, overweight diabetic girls with a poor diabetes control show the most atherogenic lipid profile. HbA1c values influence the lipid profile most markedly, less in prepubertal than in pubertal children. **Conclusion:** The population-based algorithmic approach applied to LDL-, non-HDL-, and HDL cholesterol allows referencing diabetic children with regard to their non-diabetic peers and, if necessary, suggesting corrections of glycemic control to optimize long-term cholesterol monitoring. Pubertal overweight girls with a poor diabetes control need the most careful monitoring.

P1-D3-86

Implementation of Effective Transition from Paediatric to Adult Diabetes Care with an Outpatient Transition Nurse

Eglantine Elowe-Gruau^a, Marie-Paule Aquarone^a, Virginie Schlüter^c,

Sophie Stoppa-Vaucher^a, Franziska Phan-Hug^a, Andrew Dwyer^b, Nelly Pitteloud^{a,b}, Michael Hauschild^a

^aDivision of Pediatric Endocrinology and Diabetology, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland; ^bEndocrinology, Diabetes and Metabolism Service, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland; ^cCantonal Diabetes Program, Vaud, Switzerland

Background: Diabetes mellitus (DM) is a chronic metabolic disorder requiring daily care to prevent both acute and chronic complications. Intensive support to facilitate coping and self-care skills is advocated. Healthcare providers are challenged to manage the transition of adolescents from paediatric to adult diabetes services. **Objective and hypotheses:** While centres providing structured integrated paediatric and adult care seem optimal, many patients opt for ambulatory care in community-based medical practices. These patients are in need of transition programs to prevent discontinuities in specialized care. **Method:** In collaboration with the governmental health service, we developed a transition program for adolescents with DM. A specialized outpatient transition nurse (TN) meets patients and their parents in the paediatric diabetes center and plans the transfer to regional specialized adult health care services. DM related issues are recorded in a specially developed 'diabetes health passport' used by the patient. The TN accompanies the patient through the transition process, providing anticipatory guidance, ongoing assessment of psychosocial issues and promotes self-care in collaboration with both paediatric and adult healthcare providers. **Results:** 75 DM patients have successfully been transitioned from paediatric to adult care, 100% are followed by an adult diabetologist. 75% are followed in private practice, and 25% in the hospital setting. Continuity of care was provided by the TN who held between 2 and 30 annual visits per patient depending on individual needs. Patients and the parents alike report high satisfaction with the program. At least three hospital admissions related to decompensated diabetes have been avoided due to successful home management by the TN. **Conclusion:** We report on the successful implementation of a structured program for adolescents with DM transitioning from paediatric to adult care. This process includes focus on providing patient-centered care to promote autonomy and individuation. Our systematic approach appears to provide a structure for ensuring continuity of care and effective transition.

P1-D3-87

The Natural Evolution of Impaired Glucose Homeostasis Among Obese Adolescents in a High – Risk Diabetes Prone Population

Nehama Zuckerman-Levin^{a,b}, Idit Pasternak^c, Sami Najjar^d, Doron Hermoni^a, Naim Shehadeh^b

^aClalit Health Services, Sharon-Shomron district, Israel; ^bPediatric Diabetes Clinic, Rambam Medical Center, Haifa, Israel; ^cPediatrics Department, Carmel Hospital, Haifa, Israel; ^dClalit Health Services, Jisr A-Zarka clinic, Israel

Background: Obesity is increasing worldwide among adults, children and adolescents. The increase in obesity rates facilitated the development of several morbidities including impairment in glucose homeostasis. T2DM is described mainly among minority groups, and in Israel it is more frequent among the Arab population. **Objective and hypotheses:** We hypothesized that a correlation exists between the degree of obesity and impaired glucose homeostasis among Arab obese children and adolescents. As such, the aim of the study was to investigate whether this correlation exists in a high – risk diabetes prone Arab population. **Method:** 329 children and adolescents aged 10–18 years (mean 13.5 ± 2 y) from an Arab village in Israel with a high incidence of obesity and T2DM, were investigated. 117 (75 girls, 42 boys) obese patients were compared to 212 (131 girls, 81 boys) normal weight controls. Obese patients (BMI percentile >95) were evaluated clinically and their body composition and metabolic status was studied. **Results:** Obese patients had a mean BMI of 32.4 ± 6 vs. 20.8 ± 3 in the controls ($P < 0.00001$). Mean fasting blood glucose in the obese sample was 92.8 ± 8 mg/dl and 87.9 ± 6.3 in controls ($P < 0.00001$). Two girls were diagnosed with T2DM, 16.8% had impaired fasting glucose, and 56.7% had pre diabetes by HbA1C definition (>5.7%). Insulin resistance as assessed with the homeostatic model was increased in 80% of patients (6.3 ± 2.5). Lipid profile was normal for age; however C-reactive protein was increased (0.86 ± 0.3). While in the control participants BMI was stable with age (correlation of 0.05), the obese group demonstrated increased BMI with age, with a significant difference between younger and older patients ($P < 0.0001$). **Conclusion:** Increased degree of obesity predisposes children and adolescents from a high- risk population to impairment of glucose homeostasis. Identifying these children can prevent future morbidity.

P1-D3-88

Improved Health-related Quality of Life with Insulin Therapy in Children with Cystic Fibrosis-related Diabetes: a Prospective Cohort Study

Sherly George^{a,h}, Hilary M C V Hoey^{b,d}, Colm Costigan^c, Nuala Murphy^e, Edna F Roche^{b,d}, Stephen M P O'Riordan^{f,g}

^aUniversity College Dublin, Dublin, Ireland; ^bTrinity College Dublin, Dublin, Ireland; ^cOur Lady's Hospital for Sick Children, Crumlin, Dublin, Ireland; ^dAdelaide and Meath Hospital Incorporating National Children's Hospital, Tallaght, Dublin, Ireland; ^eThe Children's University Hospital, Temple Street, Dublin, Ireland; ^fCork University Hospital, Cork, Ireland; ^gUniversity College Cork, Cork, Ireland; ^hCoombe Women and Infants University Hospital, Dublin, Ireland

Background: Cystic fibrosis-related diabetes (CFRD) is a common complication in cystic fibrosis (CF). CFRD symptoms and treatment may impose additional burden and adversely affect their QoL. **Objective and hypotheses:** Assess HRQoL in CF children with normal glycaemia (CFN) and CFRD and evaluate the change in HRQoL over 1 year period along with clinical

changes. **Method:** A prospective study was undertaken including children aged 10–18 years attending the three paediatric CF clinics in Dublin. Collected clinical and demographic data at baseline and at 12 months. Based on the paired OGTT and CGMS patients were classified as CFRD and CFN. HRQoL was assessed using KIDSCREEN-10 and DISABKIDS CFM questionnaires. Total score ranged 0–100, higher the score better HRQoL. **Results:** A total of 103 patients (55 males) were recruited, mean age (14 ± 2.6) years and BMI (18.7 ± 3.0) kg/m². At baseline 12 (12%) CFRD patients were on insulin. They were older (16 vs 14, $P < 0.01$), with lower FEV1% predicted (48 vs 70, $P < 0.005$), but no difference in BMI. After 1 year, 24 (24%) CFRD patients were on insulin. CFRD group had lower overall HRQoL than CFN at baseline (50.3 ± 9.2 vs 53.6 ± 10.6) and follow-up (48.1 ± 10.2 vs 53.4 ± 10.2) and significantly decreased over 1 year ($P < 0.01$). The impact score was significantly lower in CFRD in both assessments (51 ± 33.8 vs 70.4 ± 22.1 , $P < 0.01$) and (54.2 ± 25 vs 67.3 ± 25 , $P < 0.05$). This improved after 1 year in CFRD but not in CFN. CFRD group had better treatment scores at baseline (68.1 ± 26.3) than impact score; this was higher than the CFN group (67.2 ± 21.3). This improvement in treatment score was correlated to the reduction in symptoms once insulin was started over the 12 months study period. **Conclusion:** CFRD adversely affects patient's QoL. Insulin therapy improves symptoms and thus improved QoL. Further regression analysis is warranted to assess the independent predictors of QoL.

P1-D3-89

Nutritional Status and Respiratory Function in Patients Affected by Cystic Fibrosis and Glucose Metabolism Derangements after 4 Years of Insulin Therapy with Glargine

Enza Mozzillo^{a,b}, Valeria Raia^a, Valentina Fattorusso^a, Carla Cerrato^a, Elena De Nitto^a, Fabiola De Gregorio^a, Angela Sepe^a, Giuliana Valerio^b, Adriana Franzese^a

^aSection of Pediatrics, Department of Translational Medical Science, University of Naples Federico II, Naples, Italy; ^bDepartment of Movement Sciences, Parthenope University of Naples, Naples, Italy

Background: The glucose metabolism derangements (GMD) can have an important impact on nutritional status and respiratory function in patients with cystic fibrosis (CF). **Objective and hypotheses:** The aim of our study is to evaluate the effects of 4 years of glargine therapy in patients affected by CF and GMD. **Method:** All CF patients attended to the Center of Cystic Fibrosis of our department were screened by oral glucose tolerance test. All CF subjects showing the following GMD were enrolled into a protocol of treatment with insulin glargine: cystic fibrosis related diabetes (CFRD), patients with glycemia at T0' >126 mg/dl and/or T120' >200 mg/dl; impaired glucose tolerance (IGT), patients with glycemia at T120' >140 mg/dl; abnormal glucose tolerance (AGT), patients with glycemia at T30' and/or T60' and/or T90' >140 mg/dl. The starting dose was 0.2 UI/kg per day.

Table 1. (for abstract P1-D3-89)

	- 2 years	- 1 years	0	+ 1 years	+ 2 years	+ 3 years	+ 4 years	P
BMI	16.3 ± 2.5	16.5 ± 2.4	17.1 ± 2.5	18 ± 2.7	18.7 ± 2.6	19.1 ± 2.5	19.4 ± 2.5	<0.05
BMIz-s	-0.3 ± 1.1	-0.3 ± 0.9	-0.2 ± 0.8	-0.1 ± 0.9	-0.07 ± 0.8	-0.1 ± 0.7	-0.2 ± 0.7	ns
FEV1%	95.3 ± 3.4	93.1 ± 17.8	91.6 ± 19.2	94.7 ± 19	91.9 ± 18.3	91.1 ± 21.6	94.3 ± 15.3	ns
Exac/year	2 ± 1.4	1.9 ± 1.5	1.5 ± 1	1.3 ± 1.1	1.5 ± 1.2	1.3 ± 1.3	1.1 ± 1.2	<0.05

Eighteen patients with GMD (6-CFRD, 6-IGT, 6-AGT), mean age 10.7 ± 2.4 years at the beginning of the study, completed 4 years of treatment with glargine (average dose: 0.22 IU/kg per day, range: 0.11–0.24). BMI, BMI Z-score, forced expiratory volume in the first second (FEV1%) and number of respiratory exacerbations/year were assessed longitudinally by 2 years before the beginning of therapy to 4 following years. **Results:** Longitudinal alterations of analysed parameters (mean \pm s.d.) are in the table. **Conclusion:** Glargine treatment seems to reduce the number of pulmonary exacerbations in patients affected by CF and GMD; moreover it seems to retard the decay of nutritional parameters and of respiratory function.

($r=0.111$, $P=0.040$; $r=0.122$, $P=0.024$). Obese patients with vitamin D deficiency have a significantly higher risk of disturbing the glucose metabolism, such as IFG, ITG, IFG plus ITG, either IFG or ITG, for its OR 3.198 (95%CI 1.467–6.97), 5.443 (95%CI 1.863–15.897), 5.560 (95%CI 1.212–25.502), 4.007 (95%CI 2.017–7.962). **Conclusion:** 25(OH)D deficiencies or insufficiency are common in obese children and adolescents in Zhejiang, China. Obese patients with 25(OH)D deficiency (<30 nmol/l) are at higher risk for abnormal glucose metabolism.

P1-D3-90**The Relationship of Serum 25-Hydroxyvitamin D with Glucose Homeostasis in Obese Children and Adolescents in Zhejiang, China**

You-Jun Jiang, Ke Huang, Jun-Fen Fu, Jian-Feng Liang, Hong Zhu, Zhi-Wei Zhu, Li-Fei Hu, Guan-Pin Dong, Xue-Feng Chen

Children's Hospital of Zhejiang University School of Medicine, Hangzhou, China

Background: Evidence of the association between vitamin D, insulin resistance and oral disposition index (oDI) in obese children and adolescents is limited. **Objective and hypotheses:** We investigated serum 25(OH)D levels in obese children and adolescents in Zhejiang, China, and determined the relationship between serum 25(OH)D and glucose metabolism. **Method:** A cross-sectional design was used. All together 348 obese and 445 non-obese children and adolescents (aged from 6 to 16 years old) were enrolled in this study. Obese children were divided into four subgroups: normal glucose tolerance (NGT), isolated impaired fasting glucose (IFG), isolated impaired glucose tolerance (IGT), combined IFG and ITG (IFG + ITG) according to the oral glucose tolerance test. We measured serum 25(OH)D levels and calculated the homeostasis model of insulin resistance (HOMA-IR), the whole body insulin sensitivity index (WBISI), the product of β -cell function and insulin sensitivity by the disposition index (DI). **Results:** The levels of 25(OH)D in obese group were significantly lower than those of non-obese group; serum 25(OH)D level in obese with NGT group was higher than that of the other three subgroups, and it was significantly inversely correlated with LogHOMA-IR ($r=-0.114$, $P=0.035$), positively correlated with LogWBISI, LogHOMA₀DI after control for age, sex, season, puberty stage

P1-D3-91**Feasibility and Acceptability of Robot Assistant in Self-management of Type 1 Diabetes in Children**

Majid Al-Taeaa, S Abooda^a, Christopher Garrett^b, Pratik Choudhary^b, Ritika R Kapoor^c

^aSchool of Computing and Information Systems, Kingston University London, London, UK; ^bKing's College London School of Medicine, London, UK; ^cKing's College Hospital NHS Trust, London, UK

Background: Robot assisted therapy has the potential to provide emotional and educational support to young patients with type 1 diabetes (T1DM). **Objective:** To investigate the attitudes of children and young people with T1DM and that of their parents towards the concept of utilising a humanoid robot as an assistant in the management of their diabetes. **Methods:** A humanoid robot programmed to help self-management of T1DM at home was introduced to 37 participants (aged 6–16 years) during their routine clinic visit. The children and parents were given the opportunity to interact with the robot, participate in an educational session provided by the robot and understand the potential utility of the robot in self-management at home. The participants then completed a questionnaire including ten questions, giving feedback on the various features of the robot. Mean scores for each question was calculated. **Results:** Overall acceptability amongst the 18 males and 19 females was high at 86.7%, with no significant gender difference. The younger participant group (6–9 years) consistently scored all features of the robot higher than the older participant groups (10–12 and 13–16 years). Features of the robot that were highly desirable, amongst all age groups included ability of the robot to give advice on identified patterns of blood glucose (BG) (90.6%) and its ability to relay BG readings to their medical team (89%).

Interestingly, the highest scoring feature was the ability to deliver education around diabetes (100% amongst 6–9 years old). 98.0% of the participants <10 years and 83.4% of participants >10 years expressed an interest in taking the robot home. **Conclusions:** Use of robots as a new device to support diabetes self-management in children was highly rated by participants. There is potential to develop this novel technique to help children with T1DM, especially in delivering education to the younger patients.

P1-D3-92

Mutations Involving *FIBULIN2* are a Novel Cause of 46,XY DSD^{*}

Anu Bashamboo^a, Chiara Palka^c, Angelika Mohn^c,
Valentina Chiavaroli^c, Francesco Chiarelli^c, Raja Brauner^b,
Ken McElreavey^a

^aInstitut Pasteur, Paris, France; ^bUniversité Paris Descartes and Pediatric Endocrinology Unit, Fondation Ophtalmologique Adolphe de Rothschild, Paris, France; ^cDepartment of Paediatrics, G. d'Annunzio, University of Chieti, Chieti, Italy

Background: The genetic causes of disorders of sex development (DSD) are difficult to identify since these conditions are refractory to classic genetic approaches. In particular the underlying genetic mutations of most cases of 46,XY DSD is unknown. **Objective and hypotheses:** Using an exome sequencing approach we aimed to identify new genetic factors involved in 46,XY gonadal dysgenesis. **Method:** Exon enrichment was performed using Agilent SureSelect Human All Exon V4. Paired-end sequencing was performed on the Illumina HiSeq2000 platform. Read files were generated from the sequencing platform via the manufacturer's proprietary software. Reads were mapped using the Burrows–Wheeler Aligner and local realignment of the mapped reads around potential insertion/deletion (indel) sites was carried out with the GATK version 1.6. SNP and indel variants were called using the GATK Unified Genotyper for each sample. SNP novelty was determined against dbSNP137. Candidate pathogenic mutations were confirmed by Sanger sequencing. **Results:** We identified different missense mutations in the gene encoding the extracellular matrix protein *FIBULIN2* (*FBLN2*) in association with 46,XY gonadal dysgenesis. These included three members of a familial case of 46,XY gonadal dysgenesis and two sporadic cases of 46,XY gonadal dysgenesis. None of these mutations were found in large series of ancestry-matched control samples. *FBLN2* is highly expressed in Sertoli cells following *SRY* expression and it is repressed in the developing ovary by *FOXL2* and *WNT4*. It has previously been proposed as a mammalian sex-determining gene. **Conclusion:** We demonstrate that mutations involving *FBLN2* are a new cause of 46,XY DSD.

^{*}Nominated for a Presidential Poster Award.

P1-D3-93

Ex vivo Culture of Human Fetal Gonads: Manipulation of Meiosis Regulation Affects Testis Development

Anne Jørgensen^a, John E Nielsen^a, Signe Perlman^b, Lene Lundvall^b,
Anders Juul^a, Ewa Rajpert-De Meyts^a

^aDepartment of Growth and Reproduction, Copenhagen University Hospital, Copenhagen, Denmark; ^bDepartment of Gynaecology, Copenhagen University Hospital, Copenhagen, Denmark

Background: Alterations in the timing or expression level of players involved in sex determination and differentiation can cause disorders of sex development, gonadal dysgenesis and germ cell neoplasms later in life. The mitosis–meiosis switch is one of the first manifestations of female sex differentiation and we hypothesise that a conflict between meiosis-inhibiting (male pathway) and meiosis-inducing signals (female pathway) is one of the possible mechanisms for disruption of gonocyte differentiation in dysgenetic fetal testes. **Objective and hypotheses:** To establish an experimental model that allows studies of germ cell–somatic niche interactions in human fetal gonad cultures and determine effects of manipulating signaling pathways involved in meiosis regulation. **Method:** Fetal gonadal tissue from first trimester induced abortions was isolated and set-up in 'hanging drop' cultures for 2 weeks with and without addition of 1 μM retinoic acid (RA). Samples were subsequently formalin-fixed and protein expression was investigated by immunohistochemistry. **Results:** An *ex vivo* model for normal fetal testes and ovaries was successfully established, with continued cell proliferation and lack of apoptosis for 2 weeks of culture. This model enabled manipulation studies resulting in specific outcomes related to meiosis regulation. In cultured fetal ovaries treated with RA we found a higher number of oogonia positively stained with the meiosis marker γH2AX, thereby confirming that RA induces meiosis. In fetal testes treated with RA we found a decrease in the number of proliferating gonocytes, decreased expression of the immature Sertoli cell marker AMH and disrupted seminiferous cord formation. **Conclusion:** Culture of human fetal gonads in 'hanging drops' maintains normal tissue morphology, proliferation of germ- and somatic-cells and preserves signaling activity within the niche. RA-induced stimulation of meiosis in fetal testes results in a phenotype that resembles gonadal dysgenesis. Further studies of effects on the expression of pluripotency factors are in progress.

P1-D3-94

Prenatal Exposure to Phthalates and Phenols in Relation to Anogenital Distance at Birth in Male Infants

Benjamin G Fisher^a, Ajay Thankamony^a, Ken K Ong^b,
David B Dunger^a, Ieuan A Hughes^a, Carlo L Acerini^a

^aDepartment of Paediatrics, University of Cambridge, Cambridge, UK; ^bMRC Epidemiology Unit, Institute of Metabolic Science, Cambridge, UK

Introduction: Increasing incidence of male reproductive disorders may be due to fetal exposure to putative endocrine disruptor chemicals (EDCs), such as phthalates and phenols. Anogenital Distance (AGD) is a biomarker of fetal androgen action in animals, and has recently been linked to testicular dysgenesis syndrome in humans. **Objective:** To examine the relationship between prenatal phthalate and phenol exposure and birth AGD in male infants. **Method:** Serum samples were collected from pregnant women between 10 and 12 weeks of gestation as part of a larger prospective study ($n=334$). 27 EDCs (16 phthalate monoesters, and nine phenols) were measured using liquid chromatography/tandem mass spectrometry. Statistical analyses excluded EDCs detectable in $<45\%$ of mothers. Birth AGD in males (measured from centre of anus to base of scrotum) was recorded ($n=151$). **Results:** Six phthalate monoesters (MEP, MiBP, MnBP, MEHP, MECPP, and MCiOP) and three phenols (BPA, TCS, and BP-3) were detectable in $\geq 45\%$; median concentrations were 1.57, 3.77, 1.30, 1.17, 0.52, 0.19, 1.78, 0.75 and 0.30 $\mu\text{g/l}$, respectively. Summed levels were calculated for di(2-ethylhexyl)phthalate metabolites (ΣDEHPm), dibutylphthalate isomer metabolites ($\Sigma\text{MBP}_{(i+n)}$), and all phthalate metabolites ($\Sigma\text{all.phth.m}$). Mean \pm s.d. birth AGD was 19.5 ± 5.5 mm. AGD was negatively correlated with ΣDEHPm ($\rho = -0.188$, $P=0.021$) and $\Sigma\text{all.phth.m}$ ($\rho = -0.203$, $P=0.012$), but no other EDCs. In a multiple regression model, potential confounding factors (maternal age, BMI, gestation, birth weight, and birth length) explained 4.5% of variance in birth AGD; entry of EDC levels (MEP, $\Sigma\text{MBP}_{(i+n)}$, ΣDEHPm , MCiOP, BPA, TCS, and BP-3) explained an additional 7.1%. In this model, only ΣDEHPm ($\beta = -0.210$, $P=0.019$) and BMI ($\beta = 0.177$, $P=0.043$) were significant. In a separate analysis, $\Sigma\text{all.phth.m}$ explained an additional 4.5% of variance in AGD when potential confounders were controlled for ($\beta = -0.213$, $P=0.014$). **Conclusion:** These results suggest that exposure to phthalates during the first trimester (specifically DEHP, and possibly others in

combination), but not phenols, adversely affects male reproductive development.

P1-D3-95

Ovarian Development and Hormonal Feedback Mechanism in a 46XX Patient with *cyp19a1* Deficiency Under Low Dose Estrogen Replacement

Marie-Anne Burckhardt^a, Verena Obmann^b, Marco Janner^a, Primus E Mullis^a

^aPaediatric Endocrinology, Diabetology and Metabolism, University Children's Hospital, Inselspital, Bern, Switzerland; ^bDepartment of Diagnostic, Interventional and Paediatric Radiology, Inselspital, Bern, Switzerland

Background: Ovarian and uterine development in relation to hormonal feedback mechanisms (E_2 , LH, FSH, and inhibin) has rarely been studied. Therefore, the age specific and longitudinally adequate replacement dose of estradiol to achieve normal maturation in terms of ovarian and uterine development during infancy, childhood and adolescence remains not well known. However, aromatase deficiency offers an excellent model to study the relevant estradiol dose needed to achieve a normal maturation so important for a natural development such as puberty, growth and bones. **Objective and methods:** We studied the impact of oral 17β -estradiol treatment on ovarian and uterine development in relation to FSH and inhibin B in the long-term follow-up of a girl compound heterozygote for two point

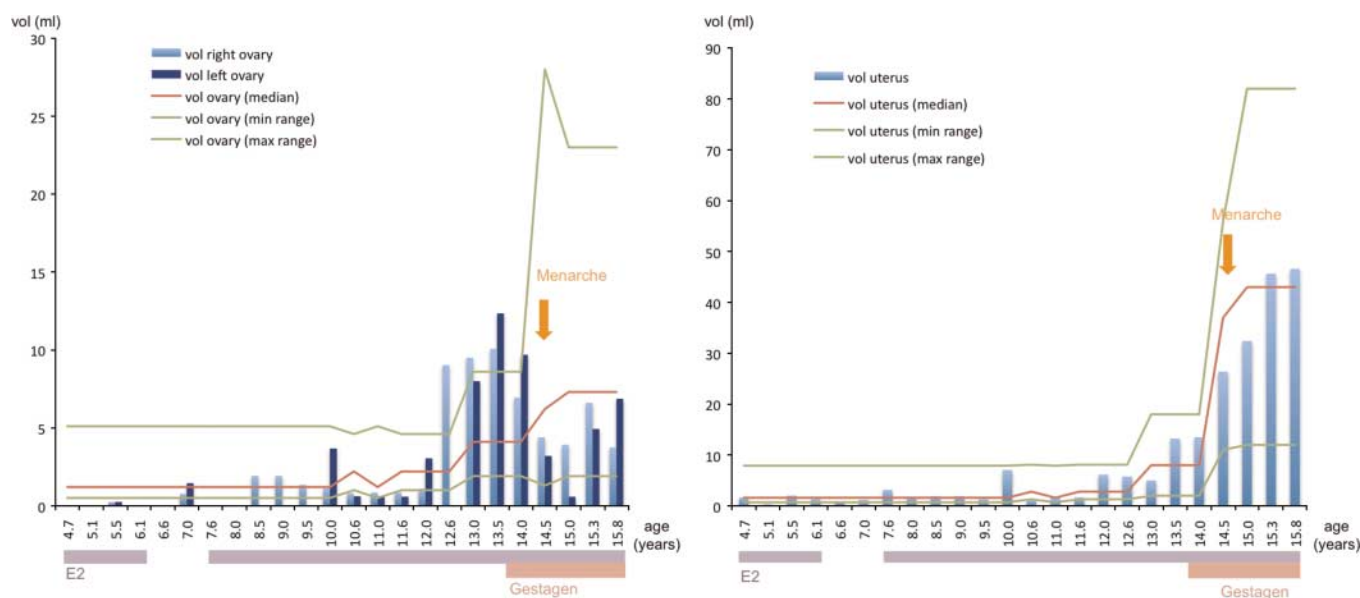


Figure 1 Ovarian and uterine development compared to literature (2). (for abstract P1-D3-95).

mutations within the CYP19A1 gene (1). **Results:** At the beginning (early childhood) low doses of oral 17 β -estradiol (starting with 0.1 mg daily) were given. In the follow-up doses were adequately increased to ensure normal height velocity and bone age maturation. During prepuberty, this treatment resulted in an almost normal development of ovarian volume and both number and size of follicles. Only at the beginning of puberty we found a minimal increase of ovarian volume compared to literature, normalizing when gestagen replacement was added in late puberty (Figure 1). Regarding hormonal feedback mechanism of the ovaries, inhibin B levels were in the upper normal range. On the contrary, low dose of estradiol replacement was not sufficient to achieve physiological gonadotropin levels in late prepuberty and puberty. **Conclusion:** In summary, this girl suffering from a complete aromatase deficiency provides an excellent model of how ovarian and uterine development in relation to E₂, LH, FSH and inhibin feedback progresses from infancy to adolescence. In addition, the estradiol doses to use can be deduced from this experiment of nature, which may help to treat our patients in a more appropriate way.

P1-D3-96

Isolated Hypospadias and Exposure to Endocrine Disrupting Chemicals During Pregnancy: a Multi-Institutional Controlled Study in a High Prevalence Area

Nicolas Kalfa^{a,b}, Pascal Philibert^b, Sylvie Broussous^a, Taieb Chouikh^a, Mohamed Masmoudi^a, Françoise Audran^b, Françoise Paris^b, Nadège Servant^b, Charles Sultan^b, Mattea Orsini^c, Amel Zahhaf^c, Jean Pierre Dures^c, Hélène Lehors^d, Jean Michel Guys^d, Rachel Reynaud^f, Pierre Alessandrini^e, Florence Bastiani^g, Jean Yves Kurzenne^g, Kathy Wagner^h, Gérard Morisson Lacombeⁱ

^aService de Chirurgie et Urologie Pédiatrique, Hôpital Lapeyronie, Montpellier, France; ^bService d'Endocrinologie, Hôpital Lapeyronie, Montpellier, France; ^cInstitut Universitaire de Recherche Clinique, Montpellier, France; ^dService de Chirurgie et Urologie Pédiatrique, Hôpital la Timone, APHM, Marseille, France; ^eService de Chirurgie et Urologie Pédiatrique, Hôpital Nord, APHM, Marseille, France; ^fUnité d'Endocrinologie et Diabétologie Pédiatriques, Hôpital la Timone, APHM, Marseille, France; ^gService de Chirurgie et Urologie Pédiatrique, Hôpital Lenal, Nice, France; ^hService de Pédiatrie, Hôpital Lenal, Nice, France; ⁱService de Chirurgie et Urologie Pédiatrique, Hôpital Saint-Joseph, Marseille, France

Background: Numerous studies focused on the association between hypospadias and Endocrine Disrupting Chemicals (EDC) exposures. The wide variability of phenotypes included in these studies, the absence of comparison groups representative of the populations and the absence of concomitant genetic testing to rule out another cause make the results questionable. **Objective and hypotheses:** We performed a prospective

phenotype-specific analysis of patients with Isolated Hypospadias (IH) after exclusion of genetic defects to identify the role of EDC exposures. **Method:** 700 boys were prospectively included in a multi-institutional study. After exclusion of genetic defects (androgen receptor and 5- α -reductase genes) and familial forms (vertical transmission), 300 IH were included and 302 normal children were used as controls. The parents' domestic and professional exposures to EDC were evaluated by a standardized detailed questionnaire and by a previously validated job-exposure matrix for EDC. The environmental exposition was estimated through the zip code of the pregnancy, type of surrounding hazards and straight distance from it. **Results:** Maternal occupational exposition to EDC was more frequent during pregnancy in case of IH (35.11 vs 17.55%, $P < 0.001$) mainly to paints/solvents/adhesive (16.05%), detergents (11.04%), pesticides (9.03%), cosmetics (5.69%). Exposed jobs (cleaners, hairdressers, beauticians, laboratory) were more frequently performed by hypospadiac boys' mothers than controls' one (19.73 vs 10.26%, $P = 0.0019$). The paternal professional exposition around the time of fertilization was more frequent in IH (40.13 vs 27.48%, $P = 0.02$). Regarding environmental exposure, industrial or intensive agriculture area were more frequently encountered in a 3 km radius around the place of pregnancy giving birth to a hypospadiac boy (13.31 vs 6.46%, $P < 0.0001$) or (19.47 vs 14.64%, $P = 0.0137$) respectively. **Conclusion:** In an homogenous cohort of patients with IH and no genetic defect, the maternal exposure to EDC during pregnancy is more frequent compared to controls. Both occupational and environmental exposure may be considered as risk factors.

P1-D3-97

46, XX Ovotesticular Disorder of Sex Development: Potential Role of 13q31.1

Céline M Girardin, Mirjam Dirlwanger, Frédérique Bena, Serge Nef, Anne-Laure Rougemont, Jacques Birraux, Valérie M Schwitzgebel
Geneva University Hospital, Geneva, Switzerland

Background: The origins of 46,XX ovotesticular DSD remains unclear in the majority of the cases. New genetic tools can help identifying genes and loci involved in gonadal development and differentiation. **Objective and hypotheses:** We report the results of the genetic investigations performed in a 15 years old African adolescent with SRY-negative 46,XX ovotesticular DSD. **Method:** Clinical evaluation, imaging studies, surgical exploration, histological analysis and genetic investigations including 1 mio Complete Genome Hybridization (CGH)-array were performed to characterize the origin of the DSD. **Results:** The patient, who was raised as a boy, was addressed to our consultation at age 15 years. Tanner stages were B4 PH4. External genitalia showed a 4 cm-long phallic structure with penoscrotal hypospadias, completely fused labioscrotal folds, the right one with rugae and containing a palpable gonad, the left one smooth and empty.

A common sinus led to the urinary bladder anteriorly and to a vagina posteriorly. Laparoscopy revealed on the right side a hemi uterus, a fallopian tube and an intra-abdominal gonad. The latter was removed: histology revealed an ovary without testicular tissue. Histology of the scrotal gonad was compatible with an ovotestis. Leucocyte and fibroblast karyotype was 46,XX. No *SRY* could be detected in different tissues, including in leucocytes and gonadal tissue. Mosaicism, chimerism and anomalies in *SOX9*, *WNT4* and *R-spondin1* were excluded. CGH-array revealed a heterozygous deletion of 1.7 kb in region 13q31.1 between base pairs positions 81 270 158 and 81 287 901 that was not present in the mother. This non-coding region is highly conserved between species.

Conclusion: To date, the mechanisms leading to ovotesticular DSD are not fully understood. The discovery of a deletion in the highly conserved region 13q31.1 in our patient suggests that this locus could be implicated in the pathogenesis of 46,XX ovotesticular DSD, probably through the regulation of genes implicated in gonadal differentiation.

P1-D3-98

A Novel NR5A1 Mutation with Preserved Fertility

Hiroko Yagi^a, Masaki Takagi^a, Yukihiko Hasegawa^a, Maki Igarashi^b, Masafumi Kon^b, Maki Fukami^b

^aTokyo Metropolitan Children's Medical Center, Tokyo, Japan;

^bNational Research Institute for Child Health and Development, Tokyo, Japan

Background: The common phenotype caused by *NR5A1* mutations of 46,XY is gonadal dysgenesis without adrenal deficiency. Preserved fertility of the affected males was described in two patients with different mutations. No functional analysis of these two mutations has been done. Here we report brothers with isolated hypospadias who carries a novel heterozygous mutation of c.910G>A, E304K in *NR5A1* gene. Their asymptomatic father carries the same nucleotide change in heterozygous state, indicating fertility. **Objective:** To clarify the molecular mechanism of preserved fertility in the family. **Case:** A 3-month-old boy presented penoscrotal hypospadias at birth. He had no other manifestations including adrenal deficiency. His karyotype was 46,XY. His elder brother also presented hypospadias at birth with no other manifestations. At present, younger and elder brothers are 13 and 16 years old, respectively. Spontaneous puberty developed in both brothers. Because both brothers were affected, we analyzed candidate genes for hypospadias and identified the novel mutation described above. **Methods:** We generated *NR5A1* expression vector containing WT and E304K, which were transiently transfected in COS-1 cells. Using the constructs, western blot analysis, immunofluorescence assay, electrophoretic mobility shift assay and Luciferase assay were performed. **Results:** WT and E304K proteins were expressed in comparable amounts and localized exclusively to the nucleus.

DNA binding affinity of E304K was decreased. Transcriptional activity of E304K was diminished down to 40% compared to WT in Luciferase assay. No dominant negative effect was observed. **Conclusion:** E304K showed residual DNA binding affinity and transcriptional activity. We assume that those residual functions led to preserve fertility.

P1-D3-99

Development of a Next Generation Sequencing Panel for Disorders of Sex Development

Graham A Fewes^a, Lowri Hughes^a, Kirsten McKay Bounford^a, Trevor Cole^b, Nils Krone^{c,d}, Fiona Madonald^a

^aWest Midlands Regional Genetics Laboratory, Birmingham Women's NHS Foundation Trust, Birmingham, UK;

^bWest Midlands Clinical Genetics Service, Birmingham Women's NHS Foundation Trust, Birmingham, UK; ^cSchool of Clinical and Experimental Medicine, University of Birmingham, Birmingham, UK; ^dBirmingham Children's Hospital, Birmingham, UK

Background: Disorders of sex development (DSDs) refer to congenital disorders where the chromosomal, gonadal or anatomical sex is atypical. Patients typically present neonatally with ambiguous genitalia preventing immediate gender assignment or during adolescence where atypical sexual development becomes apparent. Genetic testing is key in establishing a diagnosis, allowing for personalised patient management and may significantly reduce the period of uncertainty for families regarding the sex of rearing of their child. Cytogenetics may provide guidance on possible causes and where further investigation is indicated, however a definitive molecular diagnosis is only made in around 20% of cases. Current DSD molecular testing strategies are not ideal, as tests for only a few of the many associated genes are currently available and require sequential testing. **Objective and hypotheses:** To develop a targeted next generation sequencing (NGS) approach for the investigation of DSDs. This allows for multiple genes to be investigated simultaneously at a reduced cost compared to the current sequencing strategies. In addition, the time to diagnosis in many cases would be reduced. **Method:** A TruSeq custom amplicon panel has been designed covering 32 genes associated with 46,XX and 46,XY DSD's and across the sex development and steroid biosynthesis pathways. Sequencing is performed using the Illumina MiSeq. **Results:** Assay validation has correctly identified the mutation status in 27 individuals. In addition a previously undiagnosed pathogenic mutation in the *AR* gene has been identified in one family. **Conclusion:** The development of a DSD gene panel has increased the number of genes available for analysis in a diagnostic setting. The simultaneous testing allows for a streamlined and cost effective testing strategy. This DSD gene panel is now available on a diagnostic basis.

P1-D3-100

Quality of Life in a Large Cohort of Adult Brazilian Patients with 46,XX and 46,XY Disorders of Sex Development from a Single Tertiary Centre

Rita Amaral^a, Marlene Inacio^a, Vinicius Brito^a, Tania Bachega^a, Ari Oliveira Jr^a, Sorahia Domenice^a, Francisco Denes^b, Maria Helena Sircilli^b, Ivo Arnhold^a, Guiomar Madureira^a, Larissa Gomes^a, Elaine Costa^a, Berenice Mendonca^a

^aUnidade de Endocrinologia do Desenvolvimento, Laboratório de Hormônios e Genética Molecular LIM/42, Disciplina de Endocrinologia, Hospital das Clínicas da Faculdade de Medicina da Universidade de São, Sao Paulo/SP, Brazil; ^bDisciplina de Urologia, Departamento de Cirurgia Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, São Paulo, Brazil

Background: Few studies have focused on the quality of life (QoL) of patients with disorders of sex development (DSD). **Objective and hypotheses:** Our aim was to evaluate QoL in DSD patients with defined diagnoses followed until adulthood in a single tertiary centre. **Method:** Subjects: adult DSD patients (56 patients with 46,XX DSD – 49 with female social sex and seven with male social sex as well as 88 patients with 46,XY DSD – 54 with female social sex and 34 with male social sex). Measurement: quality of life evaluation using WHOQOL-Bref questionnaire. **Results:** Both 46,XX and 46,XY DSD patients had similar QoL scores on the WHOQOL-Bref, comparable to the scores of the Brazilian general population. The chronological age at the start of treatment was negatively and significantly associated with general QoL score. Male social sex DSD patients had better scores on the psychological domain than female social sex DSD patients, as found in the Brazilian general population. In addition, among the 46,XY DSD group, the male social sex patients had better QoL compared to the female social sex patients. There was a positive and significant correlation between sexual performance and general QoL, although it explained only 4% of the variability of the general QoL score. The most influencing variables were general health, positive feelings and spirituality, religion and personal beliefs, each of them contributing with 18% of the variability of the general QoL score. **Conclusion:** Our large cohort of adult DSD patients, which was followed by a multidisciplinary team in a single tertiary centre, had good QoL in adulthood; in addition, late treatment compromised the QoL of DSD patients, whereas sexual performance has little influence on QoL.

P1-D3-101

Subjective Need for Psychological Support in Parents of Children with dsd: Results from the German Clinical Evaluation Study

Elena Bennecke^a, Knut Werner-Rosen^a, Heiko Krude^a, Ute Thyen^b, Anke Lux^c, Eva Kleinemeier^b, Martina Jürgensen^d, Birgit Köhler^a, Group DSD Network Working^a

^aCharité, Paediatric Endocrinology, Berlin, Germany; ^bHospital for Children and Adolescents, Universität zu Lübeck, Lübeck, Germany; ^cInstitute for Biometrics and Medical Informatics, University Magdeburg, Lübeck, Germany; ^dInstitute for Social Medicine and Epidemiology, University Lübeck, Lübeck, Germany

Introduction: The diagnosis of a disorder/difference of sexual development (dsd) is an exceptional psychosocial situation. As the diagnosis is often made in childhood, the parents are the primary communication partners. In some cases, the impossibility of immediate sex determination of the child can be a traumatic experience with a negative impact on the relationship between the parents and the child, the couple and members of the entire family. It has been recommended by the Chicago DSD Consensus Group (2005) and the German Ethical Committee (2012) that interdisciplinary care should include a psychologist. **Methods:** The subjective need for psychological support in parents ($n=317$) of children with dsd was investigated in the German Clinical Evaluation Study (2003–2008). Diagnoses were classified into dsd-46-X or 46-XY without (c) or with partial (P) androgen effects, and female (F) or male (M) sex of rearing. Factors influencing parental need for psychological support were investigated. **Results:** 40.4% of the parents of children with dsd expressed a need for psychological support and 77.3% of these reported not having received psychological care as needed. Parents of children included in the diagnostic subgroup dsd-46-XY-P-F (XY dsd with partial androgen effects) expressed significantly more need for psychological support (58.7%). Moreover, hormonal puberty induction, taking a photo of the child's genitalia, laparotomy and gonadal biopsy were associated with an increased need for psychological support (55.1%; 49.0%; 66.7%; 56.7%). Further results will be presented. **Discussion:** The special situation of having a child with dsd is associated with a high parental need for psychological support. Considering fears of stigmatization by psychotherapy, an even higher need for psychological counselling can be assumed. Factors such as the diagnosis of dsd 46-XY-P-F and invasive medical procedures lead to a higher need for psychological support. This might be due to more insecurities and fears of the parents induced by these factors.

P1-D3-102

Four Cases of Isolated Partial Gonadal Dysgenesis Due to nr0b1 (dax1) Locus Duplication Inherited in a Large Family

Kathy Wagner Mahler^a, Caroline Devos^a, Jean Yves Kurzenne^a, Frederique Gastaud^a, Marie Hoflack^a, Delphine Mallet^b, Houda Karmous Benailly^c, Fabienne Giuliano^c, Gilbert Simonin^d, Damien Sanlaville^a, Yves Morel^b

^aHôpitaux Pédiatriques CHU and CHU-Lenval, Nice, France; ^bUniversité de Lyon and Hospices Civils, Lyon, France; ^cCytogenetic Department CHU, Nice, France; ^dPaediatric Department CHU,

Background: Isolated gonadal dysgenesis due to NR0B1 locus duplication is a rare cause of 46,XY DSD. Almost reported cases were a total gonadal dysgenesis with complete female phenotype associated with primary amenorrhea. Only two unrelated cases of isolated partial gonadal dysgenesis with molecular characterization have been reported. The risk of gonadoblastoma is high. **Objective and hypotheses:** Phenotype correlation study (clinical, hormonal, and histological) and genotype size DAX1 duplication could be decisive of the degree of gonadal dysgenesis and oncological risk. **Method:** Description of four cases of a family with several cases are known to six generations. All four cases had hypomasculinisation of external genitalia. The age of diagnosis were 14 years, 11 years and two in antenatal period. The absence of Mullerian structure was observed. The sex rearing differs: one was reared as girl but changed as boy at puberty (14 years old) and deceased at 70 years old; two reared as girl; the latest reared as boy after a collegiate decision. Biological data in neonatal period two cases have confirmed the diagnosis of partial gonadal dysgenesis with low AMH, but normal testosterone response to hCG test. Bilateral gonadectomy have been done in patients reared as girl. At 13 months, gonads were hypoplastic and showed subnormal testicular structure, at 11 years the gonads (V.1) were more dysplastic. **Results:** This duplication of the NR0B1 gene detected by MLPA and bordered by CGH array was about of 452 kb including NR0B1 and four MAGEB genes, but not CXorf21 and GK genes. The phenotype of our cases is that of partial gonadal dysgenesis. **Conclusion:** The explanation of the isolated partial gonadal dysgenesis vs pure gonadal dysgenesis with high risk of gonadoblastoma could be the location and the extent of this NR0B1 duplication. These data suggested the screening of this duplication in all cases of partial 46,XY gonadal dysgenesis.

P1-D1-103

TNF-Related Apoptosis-Inducing Ligand Induces a Pro-Inflammatory Secretion Profile in Human Adipocytes*

Verena Zoller, Muad Abd El Hay, Jan-Bernd Funcke, Klaus-Michael Debatin, Martin Wabitsch, Pamela Fischer-Posovszky
University Medical Center Ulm, Ulm, Germany

Background: Obesity is tightly associated with adipose tissue inflammation. Tumor necrosis factor- α (TNF α) has been identified as a key player in this inflammatory process and has been linked to the development of obesity-associated insulin resistance. Our group studies the involvement of TNF superfamily members in obesity-induced alterations in adipose tissue. **Objective and hypotheses:** Here, we aimed to identify the effects of the TNF superfamily member TNF-related

apoptosis-inducing ligand (TRAIL) on cytokine production in human adipocytes. **Method:** SGBS adipocytes on day 8 of adipogenic differentiation were treated with increasing doses of TRAIL for 6, 12, and 24 h. The production of several pro-inflammatory cytokines (IL6, IL8, and MCP1) was analyzed by qPCR and ELISA. **Results:** In SGBS adipocytes, TRAIL increased the expression of IL6, IL8, and MCP1 in a dose-dependent manner. After 6 h of treatment, we observed a 3.7-fold increase in IL6, a 15-fold increase of IL8 and 3.8-fold increase of MCP1 mRNA compared to vehicle-treated control cells. Comparable results were observed on the protein level. We next sought to identify the molecular events causing these changes in gene expression. Upon TRAIL stimulation, we observed a rapid cleavage of caspases. Treatment with the pan-caspase inhibitor zVAD.fmk abolished the upregulation of IL6, but not that of IL8 or MCP1. In contrast, genetic ablation of caspase-8 by shRNA negated the TRAIL-induced upregulation of all three cytokines. This suggests that the presence and activation of caspase-8 is important for the TRAIL-induced upregulation of IL6, whereas only the presence of caspase-8 is necessary for mediating TRAIL's effect on IL8 and MCP1 expression. **Conclusion:** TRAIL increases the production of pro-inflammatory cytokines in human adipocytes in a caspase-dependent manner. Our findings suggest that in the context of obesity, TRAIL might be an important player modulating the adipocyte secretion profile.

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P1-D1-104

Coexistence of Elevated Chitinase 3-Like Protein 1 and von Willebrand Levels in Prepubertal Obese Children

Ioannis Kyrgios, Charilaos Stylianou, Eleni Kotanidou, Assimina Galli-Tsinopoulou

4th Department of Pediatrics, Faculty of Medicine, Papageorgiou General Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece

Introduction: Obesity as a chronic inflammatory disease is associated with impaired prothrombotic state leading to atherothrombosis. A variety of prothrombotic factors have been implicated in the pathophysiology of this phenomenon, especially the von Willebrand factor (vWF) produced in endothelium, megakaryocytes and subendothelial connective tissue. The aim of this study was to investigate any possible association between the new inflammatory marker chitinase 3-like protein 1 (YKL-40) and vWF levels in obese children. **Methods/design:** Forty-one obese prepubertal children and 41 age- and gender-matched lean controls were included in the study. Children were classified as obese or non-obese according to international age- and gender-specific BMI cutoff points. In all participants, fasting levels of YKL40 were measured by a commercial ELISA Kit. The coagulation state was evaluated in obese children by assessment of vWF, plasminogen activator inhibitor -1 (PAI1), and fibrinogen

levels. **Results:** Obese children as compared with controls had higher YKL-40 and vWF ($P < 0.01$) levels. A statistically significant correlation between these two parameters was also noted ($r = 0.467$, $P = 0.016$). No association was found between YKL-40 and PAI1 or fibrinogen levels. The children with vWF levels above median as compared to those with vWF below median also tended to present higher YKL-40 ($P = 0.09$), indicating more severe inflammation. By contrast, although children with PAI1 or fibrinogen levels above median differed regarding YKL-40 as compared to those with PAI1 or fibrinogen below median, these differences did not reach the level of statistical significance. **Conclusions:** Higher levels of vWF are more common among obese children that have higher YKL-40 levels. The coexistence of elevated levels of these markers may have a synergistically aggravating effect on atherosclerosis even in childhood obesity.

P1-D1-105

Being Overweight During the Peripubertal Period Modifies the Leptin Induced Changes in Hypothalamic Neuropeptides Involved in Metabolism but not those Involved in Pubertal Onset

David Castro-González^{a,b}, Esther Fuente-Martín^{a,b}, Miguel A Sánchez-Garrido^{b,c}, Pilar Argente-Arizona^{a,b}, Manuel Tena-Sempere^{b,c}, Julie A Chowen^{a,b}, Jesús Argente^{a,b}

^aDepartment of Endocrinology, Hospital Infantil Universitario Niño Jesús, Department of Pediatrics, Universidad Autónoma de Madrid, Madrid, Spain; ^bCIBERobn Instituto Carlos III, Madrid, Spain; ^cUniversidad de Córdoba, IMIBIC/HURS, Córdoba, Spain

Background: Leptin is suggested to be a permissive factor in the onset of puberty by signaling at the level of the hypothalamus to indicate adequate energy stores. Overweight female rats due to increased neonatal nutrition have been shown to develop puberty before normal weight rats. **Objective and hypothesis:** We hypothesized that this permissive effect may be due not only to increased leptin levels, but also to increased hypothalamic sensitivity to this hormone before pubertal onset. **Methods:** On the day of birth Wistar rats were arranged into litters of four (neonatal overnutrition (NO)) or 12 (control (Ct)) pups and weaned on postnatal day (PND) 21. On PND30 all rats remained prepubertal although NO rats weighed more than Ct rats and had higher serum leptin levels. They then received an i.p. injection of leptin (3 µg/g bodyweight) or vehicle and were sacrificed 2 h later. **Results:** Both Ct and NO rats had a rise in hypothalamic phosphorylated STAT3 levels, but this rise was significantly greater in NO rats ($P < 0.05$). Basal hypothalamic neuropeptide Y mRNA levels were higher in NO rats, with levels in both Ct and NO rats decreasing in response to leptin, with a greater decline in NO rats ($P < 0.05$). Proopiomelanocortin mRNA levels were not different at baseline, but the leptin induced rise was significantly greater in NO rats ($P < 0.01$). There were no baseline differences between Ct

and NO rats in GnRH, Kisspeptin, or Kiss receptor mRNA levels and leptin had no significant effect in either group. **Conclusion:** There is an increased response of metabolic neuropeptide systems in overweight peripubertal female rats to an acute rise in leptin levels. However, leptin induced no changes in reproductive neuropeptides in control or overweight rats. Thus, during the peripubertal period the response of hypothalamic neuronal systems may be differentially affected by changes in leptin.

P1-D1-106

Natural Antibiotics: New Biomarkers of Childhood Obesity

Anna Prats-Puig^{a,b}, Montserrat Gispert-Saüch^a, Gemma Carreras-Badosa^{a,b}, Ferran Díaz-Roldán^{a,b}, Francis de Zegher^c, Lourdes Ibáñez^{d,e}, Judit Bassols^{a,b}, Abel López-Bermejo^{a,b}

^aDr Josep Trueta Hospital, Girona, Spain; ^bGirona Institute for Biomedical Research, Girona, Spain; ^cDepartment of Development and Regeneration, University of Leuven, Leuven, Belgium; ^dSant Joan de Déu Children's Hospital, Barcelona, Spain; ^eCIBERDEM, Barcelona, Spain

Background: The innate immune system is one of the first lines of host defense against invading pathogens. Pro-inflammatory α -defensins (mainly DEFA1-3) and anti-inflammatory bacterial/permeability-increasing protein (BPI) are antimicrobial peptides predominantly produced by neutrophils which have been recently related to obesity, type 2 diabetes and cardiovascular risk. **Objective and hypotheses:** The aim of our study was to test whether α -defensins and BPI could be new biomarkers of obesity and cardiovascular risk in children. **Method:** We performed a cross-sectional and longitudinal study in asymptomatic prepubertal Caucasian children. Plasma α -defensins and BPI (ELISA), BMI, waist circumference, systolic blood pressure (SBP), carotid intima media thickness (cIMT), HOMA-IR, and HMW-adiponectin were cross-sectionally assessed in 250 children at age 7 years (50% girls, 21% overweight subjects). α -defensins and BPI were also longitudinally assessed in a subset of these children ($n = 89$) at age ~ 10 years. **Results:** In the cross-sectional study, higher α -defensins concentrations were associated with a poorer cardiometabolic profile, showing positive associations with BMI, waist, SBP, cIMT, HOMA-IR, and negative correlations with HMW adiponectin (all between $r = 0.191$ and $r = 0.377$; $P < 0.01$ and $P < 0.0001$). Conversely, higher plasma BPI concentrations were associated with a better cardiometabolic phenotype showing negative associations with BMI, waist, SBP, cIMT, HOMA-IR, and positive correlations with HMW adiponectin (all between $r = -0.124$ and $r = -0.329$; $P < 0.05$ and $P < 0.0001$). In the longitudinal study, plasma concentrations of α -defensins, but not of BPI, at age 7 were associated with BMI ($\beta = 0.189$, $P = 0.002$; overall $R^2 = 0.847$) and waist ($\beta = 0.241$, $P = 0.001$; overall $R^2 = 0.754$) at age ~ 10 years. **Conclusion:** We suggest that α -defensins and BPI may be new biomarkers of childhood obesity. Increased concentrations of α -defensins may predict weight gain and abdominal fat deposition in prepubertal children.

P1-D1-107

Evidence of Early Alterations in Adipose Tissue Biology and Function in Obese Children

Kathrin Landgraf^{a,b}, Denise Rockstroh^{a,b}, Isabel Wagner^{a,b}, Roy Tauscher^a, Julian Schwartze^a, Ulf Bühlig^c, Holger Till^c, Magdalena Wojan^c, Jürgen Kratzsch^d, Wieland Kiess^a, Matthias Blüher^e, Antje Körner^{a,b}

^aCenter for Pediatric Research Leipzig (CPL), Hospital for Children and Adolescents, University of Leipzig, Leipzig, Germany; ^bMedical Center Adiposity Diseases (IFB), University of Leipzig, Leipzig, Germany; ^cDepartment of Pediatric Surgery, University of Leipzig, Leipzig, Germany; ^dInstitute of Laboratory Medicine, Clinical Chemistry and Molecular Diagnostic, University Leipzig, Leipzig, Germany; ^eDivision of Endocrinology, Department of Medicine, University of Leipzig, Leipzig, Germany

Background: Accumulation of fat mass in the development of obesity may result from hypertrophy and/or hyperplasia and is frequently associated with adipose tissue (AT) dysfunction in adults. However, the onset and mechanisms of AT dysfunction are not entirely understood. **Objective and hypotheses:** We assessed composition, function, lipolysis, and inflammation in 171 AT samples from lean and obese children and adolescents (aged 0 – 18 years) to evaluate early alterations in AT biology with the development of obesity in children. **Results:** In normal lean children, both adipocyte size ($R=0.62$) and number ($R=0.76$) gradually increased with age. Beginning in early childhood, obese children have significantly enlarged adipocytes (by 17%) compared to lean children, and adipocyte number is 2.6-fold increased. The proliferation rate of stromal vascular cells is threefold enhanced in obese children, whereas the differentiation potential remained unchanged. These alterations in AT composition in obese children were accompanied by increased macrophage infiltration and formation of crown-like structures. Macrophage infiltration was associated with age ($R=0.23$), BMI-SDS ($R=0.35$), and adipocyte size ($R=0.41$) in univariate analyses, but was largely dependent on adipocyte size in multivariate analyses. Furthermore, expression of extracellular matrix marker genes (COL6A1 and SPARC) was upregulated in AT of obese children indicating the early development of AT fibrosis. Finally, we detected a significant decrease in basal lipolytic activity up to ~60% in obese children. **Conclusion:** In summary, we showed that adipocyte hypertrophy and hyperplasia is linked to functional metabolic impairment and increased inflammation in AT from obese children thereby providing evidence that obesity-associated AT dysfunction develops in early childhood.

P1-D1-108

The Impact of Antibiotic Exposure During Infancy on Weight and Height

Antti Saari^a, Lauri Virta^b, Ulla Sankilampi^c, Harri Saxen^d, Leo Dunkel^e

^aUniversity of Eastern Finland, Kuopio, Finland; ^bSocial Insurance Institution, Turku, Finland; ^cKuopio University Hospital, Kuopio,

Finland; ^dUniversity of Helsinki and Helsinki University Central Hospital, Helsinki, Finland; ^eQueen Mary University of London, London, UK

Background: Antibiotics have direct effects on human gut, and infant's intestinal microbiota is particularly vulnerable for perturbation. In mice it was shown that antibiotics increased body fat mass due to changes in composition of the intestinal microbial community. Therefore, antibiotic exposure during infancy could be associated with increase in body mass also in man. **Objective and hypotheses:** To evaluate impact of antibiotic exposure, and its timing and type during infancy on weight and height at the age of 24 months or over. **Method:** Retrospective longitudinal weight and height data were obtained for healthy 5.562 boys and 5.418 girls aged ≥ 24 months, and BMI z-scores (zBMI) were calculated. Data on antibiotic administration from birth until 23 months of age was obtained from the Drug Purchase Register. Weight and height data in exposed and non-exposed children were compared using linear mixed models with perinatal factors as covariates. **Results:** Exposed boys and girls were on average heavier (zBMI difference 0.13 s.d. (95% CI 0.07–0.19, $P<0.001$) and 0.05 s.d. (0.01–0.12, $P<0.05$) respectively) than non-exposed children at the age of ≥ 24 months. The most pronounced increase in zBMI was found in children with the first exposure before the age of 6 months (for boys 0.22 s.d. (0.13–0.31), and for girls 0.09 s.d. (0.00–0.19)) respectively. This effect was mainly due to exposure to macrolide antibiotics both in boys and girls (for boys 0.30 (0.14–0.46), and for girls 0.23 (0.04–0.42)). **Conclusion:** Antibiotic exposure before 6 months of age has an increasing effect on body mass seen at ≥ 24 months of age both in boys and girls.

P1-D1-109

Identification of Brown Adipocyte Progenitor Marker Genes in Progenitor Cells from Human Deep Neck and Subcutaneous Adipose Tissue by Gene Array Analysis

Daniel Tews^a, Verena Schwar^a, Theresia Weber^a, Marc Scheithauer^a, Tobias Fromme^b, Martin Klingenspor^b, Thomas F Barth^a, Peter Möller^a, Pamela Fischer-Posovszky^a, Martin Wabitsch^a

^aUniversity Medical Center Ulm, Ulm, Germany; ^bMolecular Nutritional Medicine, Technical University Munich, Munich, Germany

Background: Studies in animal models revealed that brown and white adipocytes derive from different progenitor cells. Molecular characteristics of these cells have not been investigated in detail in humans. **Objective and hypotheses:** To identify novel markers of human brown adipocyte progenitor cells. **Method:** Progenitor cells from human paired deep neck and subcutaneous adipose tissue samples were obtained from $n=12$ subjects and progenitor cells were isolated. A subset of cells was differentiated into adipocytes *in vitro*. Expression profile of

progenitor cells was assessed by gene array analysis. Real-time PCR was performed to assess mRNA expression of selected genes. **Results:** According to marker gene expression, deep neck progenitor cells differentiated into brown adipocytes *in vitro*. Compared to subcutaneous progenitor cells, cells from the deep neck adipose tissue show marked differences in gene expression pattern including 355 differentially regulated (>1.5-fold) genes. Analysis of highest regulated genes revealed that STMN2, MME, ODZ2, NRN1, and IL13RA2 genes were specifically expressed in white progenitor cells, whereas expression of LRRC17, CNTNAP3, CD34, RGS7BP, and ADH1B marked brown progenitor cells. **Conclusion:** The ability of human adipocyte progenitor cells to differentiate into brown-like adipocytes is depot-specific and is based on intrinsic differences in gene expression. Our data provide potential molecular targets involved in the genetic determination of brown adipocyte precursor cells.

P1-D1-110

Free Fatty Acids Activate Hypothalamic Astrocytes in a Sexually Dimorphic Manner

Pilar Argente-Arizón, Esther Fuente-Martín, Francisca Díaz, Alejandra Freire-Regatillo, Jesús Argente, Julie A Chowen

Department of Endocrinology, Hospital Infantil Universitario Niño Jesús, Department of Pediatrics, Universidad Autónoma de Madrid, CIBERobn Instituto Carlos III, Madrid, Spain

Introduction: Obesity is known to associate with chronic systemic inflammation. However, hypothalamic inflammation also occurs in response to high fat diet (HFD)-induced obesity and is proposed to participate in central insulin/leptin resistance and the perpetuation of weight gain and systemic affectation. The weight gain and central responses to HFD differ between males and females. As hypothalamic glial cells are implicated in the central inflammatory response we hypothesized that their response to free fatty acids (FFAs) differs between the sexes. **Methods:** Primary astrocyte cultures from male and female Wistar rats (2 days of age) were used. Cells were treated with a mixture of palmitic and oleic acids at 1 and 2 mM or vehicle for 24 h. Nitrates and nitrites, as a marker of oxidative stress, released to the media and mRNA levels of CPT1a, glial fibrillary acidic protein (GFAP), glucose transporter (GLUT)2, IL6, IL1 β , and TNF α were quantified. **Results:** After 24 h of treatment CPT1 α increased ($P < 0.001$) and the amount of nitrites and nitrates released by astrocytes rose in a dose responsive manner in both sexes ($P < 0.0001$). GFAP mRNA levels were decreased in males at a concentration of 1 \times , while in females a higher concentration was needed. Basal GLUT2 levels were higher in females ($P < 0.01$), with FFA increasing them in males and having no effect in females. Basal levels of IL1 β , IL6, and TNF α were higher in male cultures compared to females ($P < 0.0001$). In response to FFAs, IL6 increased in males and females ($P < 0.0001$). However, IL1 β and TNF α only increased in male astrocytes ($P < 0.0001$). **Conclusion:** FFAs have a direct effect on astrocytes, inducing cytokine production and oxidative

stress, suggesting that these glial cells participate in the response to a HFD. Moreover, astrocytes from males are more sensitive to FFAs, indicating that this might be involved in their increased sensitivity to HFD.

P1-D1-111

A Multiplatform Non-targeted Metabolomics Approach to Investigate Insulin Resistance Associated to Obesity in Childhood

Annalaura Mastrangelo^a, Gabriel Martos-Moreno^b, Antonia García^a, Francisco Rupérez^a, Julie Chowen^b, Luis Pérez-Jurado^c, Coral Barbas^a, Jesús Argente^b

^aCEMBIO, Facultad de Farmacia, Universidad CEU San Pablo, Campus Montepríncipe, Boadilla del Monte, Madrid, Spain;

^bHospital Infantil Universitario Niño Jesús, Universidad Autónoma de Madrid, Pediatrics and Pediatric Endocrinology, Instituto de Investigación La Princesa, Centro de Investigación Biomédica en Red de fi, Madrid, Spain; ^cDepartment of Genetics, Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Hospital del Mar Research Institute (IMIM), Universitat Pompeu Fabra, Barcelona, Spain

Background: Childhood obesity is often associated with insulin resistance (IR), which is a key risk factor for the development of comorbidities. The etiologic relation between insulin resistance and obesity is still not completely understood. **Objective:** In this study a multiplatform metabolomics approach was applied for the first time to elucidate the metabolic alterations in obese children with or without IR. Metabolomics is the revolutionary strategy of the last century capable of interpreting the interaction of the genetic and environmental factors by studying the final effectors of a process. **Methods:** Plasma from 60 prepubertal obese children between 5 and 13 years, 30 males and 30 females, which were insulin ($n = 30$) or non-insulin resistant ($n = 30$) were analyzed by using LC-ESI-MS-QTOF, GC-EI-MS-Q and CE-ESI-MS-QTOF (Agilent, USA) in a non-targeted approach. Together the three techniques provided information about several thousand compounds. **Results:** Once the valuable information from the analytical data was mined, the two groups were compared and 85 significant differences (P value < 0.05) were unveiled. Subtle differences existed between groups that were magnified when comparisons between sexes were made. Bile acids and their derivatives represented the most prominent changes indicating the influence of the gut microbiota on the host metabolism. In addition, branched-chain amino acids, lactic acid, pyruvic acid, lysophosphocholine, and decanamide were significantly different. These are usually altered in obesity and our results suggest they may have a possible function in the predisposition towards complications such as IR. **Conclusion:** This study reveals the potential of metabolomics to highlight unexpected pre-pubertal sex differences and to detect subtle differences between two conditions highly linked but not unequivocally correlated to the onset of comorbidities, which could help to elucidate processes in their early stage where the preventive action could play an essential role.

P1-D1-112

Mir-146a and -155 are Involved in FOXO1 Regulation and Non Alcoholic Fatty Liver Disease in Childhood Obesity

Luisa Montanini^a, Pietro Lazzeroni^a, Chiara Sartori^a, Valerio Nobili^b, Pellegrino Crafa^a, Sergio Bernasconi^a, Maria E Street^a

^aUniversity Hospital of Parma, Parma, Italy; ^bBambino Gesù Children's Hospital, IRCCS, Rome, Italy

Background: Non alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in childhood, in obese subjects and associated with insulin resistance. FOXO1 is a key regulator in insulin signalling and in intracellular adipogenesis, and is implicated in liver steatosis. We have previously identified that a group of miRNAs are involved in its epigenetic regulation. **Objective and hypotheses:** We aimed to assess in liver tissue and in serum whether two of these miRNAs were differentially expressed and showed relationships with NAFLD. **Method:** MiR-146a and -55 were extracted from paraffin embedded liver biopsies, quantified by TaqMan microRNA assays and normalized with respect to RNU48 in ten young subjects having NAFLD, and from normal liver tissue of comparable subjects. Both were overexpressed in NAFLD. We enrolled obese children with (11.89 ± 0.86 years; BMI-SDS: 3.41 ; 8M, 8F), and without liver steatosis at ultrasound (11.81 ± 1.0 years; BMI-SDS: 3.15; 5 M, 4F). Pubertal stages were similar. The HOMA-IR index, the waist circumferences (Wtc), and the waist to height ratios (Wt/Ht) were significantly higher in the subjects with NAFLD. miRNA-146a and -155, purified from serum were quantified by TaqMan microRNA assays and normalized with respect to miR-16, and -93, as housekeeping miRNAs. dCts were normalized with respect to an appropriate pool of dCt controls of comparable age, sex, and pubertal stage (N.11 pubertal stage 1 and N.12 pubertal stages 3-5) and expressed as fold change (Log_{10}). **Results:** Both miR-146a and -155 (0.85 ± 0.59 vs -1.15 ± 1.74 , $P < 0.05$) were increased in the obese children having NAFLD. In the entire group, miR-146a was correlated with Wtc ($R: 0.65$; $P: 0.01$) and with Wt/Ht ($R: 0.52$; $P: 0.05$), and miR-155 with BMI-SDS ($R: 0.55$; $P: 0.04$), Wtc ($R: 0.71$; $P: 0.004$), and Wt/Ht ($R: 0.64$; $P: 0.01$). MiR-146a and -155 were also correlated ($R: 0.47$; $P: 0.04$). **Conclusion:** Both miR-146a and -155 were over-expressed in NAFLD both in tissue and in serum and showed relationships with adipose fat distribution. Both have been previously described in tumours and inflammation, besides insulin-insensitivity by us, recently. Obesity is a chronic inflammatory disease and the prevalence of tumours is increased. Further investigation is ongoing to verify whether these miRNAs could become markers of disease.

P1-D2-113

Prenatal Maternal Weight and Weight Status and Lipid Profile of the Offspring

Isolina Riaño-Galan^a, Cristina Rodriguez-Dehli^a, Ines Olaya Velázquez^a, Ana Fernández-Somoano^b, Damaskini Valvis, Marisa Rebagliato^d, Jesus Ibarluzea^e, Adonina Tardon^b

^aHospital San Agustín Pediatría, Aviles, Spain; ^bCIBERESP and Oviedo University, Preventive Medicine, Oviedo, Spain; ^cCIBERESP and Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain; ^dCIBERESP and Unit of Environment and Health, Centre for Public Health Research (CSISP/FISABIO), Valencia, Spain; ^eCIBERESP and BioDonostia Health Research Institute, Donostia, Spain

Background: Childhood obesity is a serious public health concern. To identify risk for obesity in early childhood is important. **Objective:** To analyse association of pre-pregnancy maternal weight with BMI and metabolic profile at 4 years. **Methods:** 2604 pregnant mothers and 1960 children from the Spanish population-based cohort study Environment and Childhood (Infancia y Medio Ambiente) Project (INMA). Research protocol was approved by the Ethics Committee. We analysed maternal BMI, gestational weight gain (GWG), BMI at 4 years and prevalence of overweight (OW) and obesity (OB) according to IOTF. Lipid profile was determined in a subgroup of children. **Results:** 4.6% mothers were underweight (BMI < 18.5 kg/m²), 68.8% normal (BMI 18.5-24.9 kg/m²), 18.7% had OW (BMI 25-29.9 kg/m²) and 7.9% OB (BMI ≥ 30 kg/m²). GWG was as recommended in 37.9% pregnant mothers, low in 24.2% and high in 37.9%. 20.2% children had OW or OB at 4 years. There are positive association between pre-pregnancy BMI and BMI at 4 years (P -trend < 0.001). Maternal pre-pregnancy OW/OB increases the risk of child OW/OB by 1.3 (95% CI: 1.2-1.4). Table 1 shows lipid profile at 4 years (mean (s.d.)). **Conclusions:** High prevalence of OW/OB maternal and at 4 years was detected. Correlation between them was found. An adverse metabolic profile is associated with overweight and obesity in 4 years-old children. Childhood obesity prevention must be started from pregnancy and infancy. Global cardiovascular risk prevention program focused on obesity prevention must be applied early in life. Table 1

Table 1.

	Normal weight (n=413)	Overweight (n=70)	Obese (n=35)	P (trend)
Total cholesterol (mg/dl)	163.9 (27.2)	168.1 (24.9)	171.9 (24.8)	0.050
C-HDL (mg/dl)	54.5 (12.2)	51.4 (11.2)	51.9 (9.2)	0.042
Triglycerides (mg/dl)	78.9 (40.4)	85.8 (42.2)	98.5 (52.2)	0.005

P1-D2-114

Pro-Inflammatory (M1) and Anti-Inflammatory (M2) Profiles in Adipose Tissue of Lean and Obese Children and Adolescents

Alexia Karvela^a, Aikaterini Avgeri^a, Eleni D Vlotinou^b, George Georgiou^c, Dionysios J Papachristou^b, Bessie E Spiliotis^a

^aResearch Laboratory of the Division of Pediatric Endocrinology and Diabetes, Department of Pediatrics, University of Patras School of Medicine, Patras, Greece; ^bDepartment of Anatomy- Histology- Embryology, Faculty of Medicine, University of Patras, Patras, Greece; ^cDepartment of Pediatric Surgery, Karamandaneio Childrens Hospital, Patras, Greece

Background: Childhood obesity predisposes to metabolic disorders. Low grade inflammation of adipose tissue (AT) associated with macrophage infiltration may lead to metabolic complications. Two macrophage activation states M1 (pro-inflammatory) and M2 (anti-inflammatory) exist in AT with surface markers CD40 (M1), CD206 (M2) and CD163 (M2). M1 polarization correlates with metabolic complications. **Objective and hypotheses:** To study the expression of CD40, CD163 and CD206 in AT of lean and obese children and adolescents. **Method:** Paraffin embedded subcutaneous AT microarrays were developed from surgical biopsies of 33 lean (BMI < 85%) and 29 obese (BMI ≥ 95%) prepubertal children (Groups A: 2mos-7 years and B: 8-12 years) and adolescents (Group C: 10-15 years). The intensity and distribution of CD40, CD163 and CD206 were studied with immunohistochemistry and mean adipocyte size and total adipocyte number were estimated by image analysis (adiposoft). **Results:** CD206: Most children of all age groups showed CD206⁺ macrophages: Group A lean showed a higher distribution vs their respective obese ($P=0.024$). CD163: High intensity was observed in 33.3% of lean A, 100% of lean and obese B, 71.4% of lean C and 50% of obese C ($P=0.012$), whereas all of the obese A showed low intensity. CD40: High intensity was observed in 50% of lean and obese A, 70% of lean B, 40% of obese B and 50% of lean C ($P=0.015$). CD40 was also expressed on the adipocytes and was at high intensity only on the adipocytes of lean A (37.5%) and obese A (33.3%), ($P=0.012$). **Conclusion:** Our study confirms the presence of both M1 and M2 macrophages in early childhood. The high distribution of CD206⁺ macrophages and high intensity of CD163 in the younger lean prepubertal children possibly reflects a strong anti-inflammatory profile in this young age group. The high intensity of CD40 in the obese A, together with the lower distribution of CD206 and lower intensity of CD163, may put them at a higher risk for metabolic complications. The lack of CD40⁺ macrophages in the obese adolescents alongside the positive staining for CD206 and CD163 may maintain an anti-inflammatory protective environment in these adolescents.

P1-D2-115

Important Links Between Fat Derived Proteins and Bone Remodeling Factors in Lean and Obese Girls

Christina Kanaka-Gantenbein^a, Evangelos Terpos^b, George Chrousos^a, Ioannis Papanastasiou^c

^aFirst Department of Pediatrics, University of Athens School of Medicine, Athens, Greece; ^bDepartment of Clinical Therapeutics, University of Athens School of Medicine, Athens, Greece; ^cDepartment of Clinical Biochemistry, 'Aghia Sophia' Children's Hospital, Athens, Greece

Background and aims: Fat and bone are linked by a multitude of pathways supporting a skeleton appropriate for the mass of adipose tissue of the organism. We aimed to investigate the relations of adipose tissue hormones such as leptin, adiponectin, retinol-binding-protein-4 (RBP-4) and lipocalin-2 along with the low grade inflammation marker hs-CRP with markers of bone metabolism such as osteoprotegerin (OPG), receptor-activator of NF- κ B ligand (RANKL), osteocalcin, C-terminal-cross-linking-telopeptide of collagen type-I (CTX), bone-alkaline-phosphatase (bALP) and tartrate-resistant-acid-phosphatase-isoform-5b (bone TRACP-5b) in girls with various degrees of BMI. **Method:** Eighty girls (aged 9–15 years) were enrolled in the study divided by their BMI-SDSs into four groups of 20 girls each: overweight 1.8 ± 0.4 ; obese 2.2 ± 0.4 ; morbidly obese 3.6 ± 0.4 and lean controls -0.11 ± 0.4 , in whom adipocytokines, hs-CRP and bone markers were measured by means of immunoenzymatic techniques. **Results:** We found that: i) OPG, RANKL and bALP levels decreased significantly as BMI-SDSs increased ($P=0.03$, $P=0.03$ and $P<0.01$ respectively), while osteocalcin, CTX and bone TRACP5 show no relations ($P>0.60$); ii) leptin correlated negatively with bALP, bone TRACP-5b, osteocalcin, OPG and RANKL ($P<0.05$, $P=0.02$ and $P=0.006$ respectively); adiponectin correlated positively with CTX and OPG ($P=0.004$ and $P=0.04$ respectively); RBP-4 correlated positively with OPG and bALP ($P<0.01$ and $P=0.002$ respectively), while NGAL correlated positively with bALP ($P<0.001$); iii) obesity-related systemic inflammation expressed as hs-CRP correlated positively only with OPG. **Conclusion:** Our findings suggest that there are important links between adipose tissue-derived proteins and bone remodeling factors. Bone turnover was altered in obese girls mainly due to decreased OPG levels. There were significant correlations of OPG with leptin, adiponectin and hs-CRP, indicating that, probably, the bone mass is regulated by adipokines, as well as by low grade inflammation in obese children.

P1-D2-116

Characterizing the Metabolically Obese Normal Weight Phenotype in Youth

Melanie Henderson^a, Marie-Eve Mathieu^a, Andrea Benedetti^c, Tracie Barnett^b

^aUniversity of Montreal, Montreal, Quebec, Canada; ^bConcordia University, Montreal, Quebec, Canada; ^cMcGill University, Montreal, Quebec, Canada

Background: Although metabolically obese normal weight (MONW) adults are at increased risk of type 2 diabetes and cardiovascular disease (CVD), little is known regarding MONW children. **Objective and hypotheses:** To characterize lifestyle habits and insulin dynamics of MONW children. **Method:** Caucasian youth ($n=630$) aged 8–10 years, with at least one obese biological parent, were studied (QUALITY cohort). We defined MONW children as having normal weight and at least one of: triglycerides >1.2 mmol/l, fasting glucose >6.1 , HDL-cholesterol <1.04 , blood pressure (BP) >95 th percentile for age and sex and height, or waist circumference >90 th percentile for

age and sex ($n=53$). Fitness was measured by VO_{2peak} , moderate to vigorous physical activity (MVPA) using accelerometry. Sedentary behavior indicators included average hours daily of self-reported screen time (SB_{ST}), and average minutes daily at <100 counts/min from accelerometry (SB_{acc}). Insulin sensitivity and secretion were measured with Matsuda-insulin sensitivity index (ISI) and the ratio of the area under the curve of insulin to glucose (AUC I/G 30 min) over the first 30 min of an OGTT respectively. We compared MONW children to normal weight youth with no risk factors ($n=182$) using t -tests. **Results:** No normal weight youth ($n=235$) met criteria for metabolic syndrome, while 47/235 children had one CVD risk factor, and 6/235 had two risk factors. Children with at least one risk factor (22.6%) vs those without had: i) lower MVPA (57 vs 48 min/day, $P=0.03$); ii) higher SB_{ST} (3.1 vs 2.3 h/day, $P=0.006$). There were no differences between the groups in terms of age, sex, fitness, SB_{acc} , Matsuda-ISI or AUC I/G 30 min. **Conclusion:** Further research is warranted to better understand what characteristics distinguish normal weight youth without CVD risk factors from MONW youth, towards the development of early CVD prevention strategies.

P1-D2-117

Ratio of Triglycerides to High-Density Lipoprotein Cholesterol Compared with Homeostasis Model Assessment Insulin Resistance Indexes in Screening the Metabolic Syndrome in Chinese Obese Children

Jianfeng Liang, Junfen Fu, Jinling Wang, Youjun Jiang, Guanping Dong

Children's Hospital of Zhejiang University School of Medicine, Hangzhou, China

Background: IDF-2007 MS definition (MS-IDF2007) for children and adolescents has been challenged frequently in clinical practice and should be improved further. Therefore, it becomes imminent to explore an accessible and effective tool to screen obese children with the metabolic syndrome components. **Objective and hypotheses:** To investigate the optimal cut-off values and compare the accuracy for the triglycerides and HDL cholesterol ratio and homeostasis model assessment insulin resistance indexes to identify the metabolic syndrome in obese pediatric population in China. **Method:** 976 children from 6–16 years old were recruited and went through a series of medical assessments including a physical examination and investigations of total cholesterol, HDL, LDL, triglycerides, insulin, glucose and an oral glucose tolerance test to identify the components of metabolic syndrome. The validity and accuracy between TG/HDL-C ratio and HOMA-IR were compared by receiver operating characteristics analysis. **Results:** TG/HDL-C ratio achieved a larger ROC area under curve ($AUC=0.843$) than HOMA-IR indexes (0.640, 0.625 for HOMA1-IR, HOMA2-IR respectively) to screen the metabolic syndrome. The cut-off values for MS were: TG/HDL-C ratio >1.25 (sensitivity: 80%; specificity: 75%),

HOMA1-IR >4.59 (sensitivity: 58.7%; specificity: 65.5%) and HOMA2-IR >2.76 (sensitivity: 53.2%; specificity: 69.5%). The results kept constant after stratification by gender, age group and pubertal stage. **Conclusion:** TG/HDL-C ratio proved to be a better index than HOMA-IR in screening MS for obese children and adolescents. A cutoff of 1.25 for TG/HDL-C ratio might be used in detecting the potential MS in Chinese obese pediatric population.

P1-D2-118

Plasminogen Activator Inhibitor-1(Pai-1) Levels, Pai-1 Gene Polymorphism, and Family History of Cardiovascular Disease in Relation to Metabolic Parameters in a Sample of Obese Children

Zacharoula Karabouta^{a,b}, Areti Makedou^{a,b}, Anagnostis Argiriou^{a,b}, Dimitrios Papandreou^{a,b}, Eleni Xanthopoulou^{a,b}, Vasiliki Bisbinas^{b,c}, Fani Athanassiadou-Piperopoulou^{a,b}, Israel Rousso^{a,b}

^a2nd Academic Paediatric Department, AHEPA General University Hospital, Thessaloniki, Greece; ^bInstitute of Applied Biosciences Centre for Research and Technology, Thessaloniki, Greece; ^cAristotle University Medical School, Thessaloniki, Greece

Background: Obesity is a metabolic disorder associated with increased PAI-1 levels in the circulation. This increase is related to insulin resistance and cardiovascular disease (CVD). In adults the relationship between plasma PAI-1 levels and the 4G/5G gene polymorphism in the PAI-1 gene has been demonstrated, but few data exist in children. **Objective and hypotheses:** To assess the relationship between PAI-1 plasma levels and the PAI-1 4G allele gene polymorphism with family history of CVD, anthropometric and metabolic parameters in a sample of Greek children and adolescents. **Method:** 195 subjects, 106 obese/overweight (median age 10.7 years, range 2.25–17.41) and 89 non-obese controls (median age 10 years, range 3.72–17.51) were studied. Serum levels of glucose, insulin, PAI-1 levels were measured, homeostasis model assessment of insulin resistance (HOMA-IR) was calculated, and the PAI-1 4G/5G gene polymorphism was studied by PCR-restriction fragment length polymorphism. Family history of cardiovascular disease (CVD) was obtained from all participants. **Results:** The prevalence of insulin resistance (HOMA-IR) in the obese/overweight group was significantly higher (17.9%) than in the normal-weight group (7.8%) ($P<0.05$). Frequencies of the PAI-1 gene polymorphisms were 36.8% (4G/4G), 28.3% (4G/5G), 18.8% (5G/5G) in the obese/overweight group and 22.5% (4G/4G), 21.7% (4G/5G), 31.4% (5G/5G) in the control group. FH of CVD was positive in 67.9% (obese/overweight group) compared to 66.2% (controls), and statistically significant ($P<0.05$) in relation to the PAI-1 gene 4G/4G and 4G/5G polymorphisms (36.8, 28.3 and 22.5, 21.7% respectively). HOMA-IR and PAI-1 plasma levels were also significantly correlated in the obese/overweight group compared to controls ($P<0.05$). **Conclusion:** In our obese children with FH of CVD and any feature of metabolic syndrome, the frequency of 4G/4G and 4G/5G genotype was significantly higher than the 5G/5G genotype in the PAI-1 gene. In this group of children high HOMA-IR value is an extra risk factor for developing vascular disease in adult life.

P1-D2-119

How Production of Vascular Endothelial Growth Factor Influences Formation of Vascular Disorders in Children with Obesity

Olena Budreiko, Nataly Shlyachova, Larisa Nikitina, Svitlana Chumak, Anna Kosovtsova

State Institution 'Institute of Children and Adolescents Health Care of NAMS of Ukraine', Kharkov, Ukraine

Background: Vascular Endothelial Growth Factor (VEGF) is largely produced by adipose tissue and is an important regulator of physiological and pathological angiogenesis in adults with obesity. **Objective and hypotheses:** To determine the nature of VEGF production and its connection to the formation of vascular complications in patients with childhood obesity. **Method:** In 87 children (42 boys and 45 girls) 9–17 years old with obesity and 35 healthy peers (17 boys and 18 girls) with normal weight serum levels of VEGF were measured by ELISA. The presence of insulin resistance (IR) was estimated using HOMA Calculator v.2.2. We evaluated the presence of microcirculatory disorders (MD) using capillaroscopy and arterial hypertension (AH) by measuring blood pressure (BP). **Results:** We found significantly higher levels of VEGF in obese children compared with healthy peers (350.14 ± 30.81 vs 135.82 ± 16.38 pg/ml, $P=0.045$), especially in the presence of IR (518.88 ± 68.65 vs 296.06 ± 27.19 pg/ml, $P=0.003$). Increased association of IR and VEGF production was observed at concentrations of VEGF > 320 pg/ml (OR=5.44, $P<0.004$), especially at the level of VEGF > 450 pg/ml (OR=13.14, $P<0.0001$). The growth was accompanied by an increase in the degree of MD indicator VEGF (from 234.98 ± 31.21 pg/ml to 361.71 ± 45.05 pg/ml and 432.26 ± 67.28 pg/ml, $P=0.02$). No significant differences in VEGF production were found depending on the level of BP in obese children, except for a trend towards an increase in AH compared with patients without AH (397.90 ± 56.91 vs 244.26 ± 44.38 pg/ml, $P=0.07$). **Conclusion:** We discovered an increased production of VEGF in obese children, as well as its relation to IR and the formation of MD, but not AH.

P1-D2-120

RANKL and Osteoprotegerin Serum Levels in Obese Children and Adolescents

Maria Felicia Faienza^a, Maria Rosaria Vulpi^a, Laura Piacente^a, Annamaria Ventura^a, Antonella Lonero^a, Vincenza Luce^a, Fabrizia De Palma^a, Angelo Acquafredda^a, Clara Zecchino^a, Antonio Minenna^b, Maurizio Delvecchio^c, Maria Grano^d, Luciano Cavallo^a, Giacomina Brunetti^d

^aSection of Pediatrics, Department of Biomedical Sciences and Human Oncology, University of Bari, Bari, Italy; ^bEndocrinology Section, ASL Bari, Bari, Italy; ^cIRCCS Casa Sollievo della Sofferenza, Pediatrics Unit, San Giovanni Rotondo, Foggia, Italy; ^dSection of Human Anatomy and Histology, Department of Basic Medical Sciences, Neurosciences and Sense Organs, University of Bari, Bari, Italy

Background: There is growing evidence of a correlation between fat and bone metabolism at both the clinical and molecular levels, although the systemic regulators have not been clearly identified. The receptor activator of nuclear factor κB ligand (RANKL) and its soluble decoy receptor, osteoprotegerin (OPG), are involved in bone resorption and vascular calcification. OPG levels has been related with insulin resistance in adult obese subjects. **Objective and hypotheses:** i) To evaluate RANKL and OPG serum levels in obese subjects and healthy lean controls; ii) to investigate correlation between metabolic alteration and OPG levels; iii) to correlate OPG and RANKL levels with bone status assessed by QUS. **Method:** Twenty-five subjects (16 males, median age 10.8 ± 2.6), BMI for age and sex > 95th centile, were enrolled. Waist circumference was assessed in all subjects. As control group were recruited 28 non-obese subjects (18 males, median age of 10.8 ± 2.6 years), age- and sex-matched. Bone status was assessed by QUS through BTT-Z-score and Ad-Sos-Z-score evaluation. **Results:** Obese children have higher RANKL ($P=0.01$) and lower OPG ($P<0.006$) serum levels compared with controls; thus, RANKL to OPG ratio was significantly higher in patients than controls ($P<0.001$). However, these serum levels did not correlate with BTT-Z-score and Ad-Sos-Z-score, although obese patients had significantly reduced QUS parameters compared to the controls ($P<0.01$). Interestingly, in patients BTT-Z-score and Ad-Sos-Z-score inversely correlated with serum LDL levels ($P<0.04$ and $P<0.01$ respectively) whereas RANKL and RANKL to OPG ratio correlated with serum cholesterol levels ($P<0.05$). Parallel results demonstrated that OPG serum concentrations significantly correlate with waist circumference ($P<0.05$), SDS-BMI ($P<0.05$), insulin levels and HOMA-IR ($P<0.04$). **Conclusion:** Our results pointed out to a complex alteration in obese children involving adipose tissue, bone and glucose metabolism, which is orchestrated by RANKL and OPG, two cytokines which function is cell-tissue specific.

P1-D2-121

Sex-, Age- and Height-Specific Reference Curves for the 6-min Walk Test in Healthy Children and Adolescents

Vrinda Saraff^a, Johanna Schneider^b, Valeria Colleselli^b, Monika Ruepp^b, Sabrina Neururer^c, Markus Rauchenzauner^d, Ralf Geiger^{b,e}, Wolfgang Högler^a

^aDepartment of Endocrinology & Diabetes, Birmingham Children's Hospital, Birmingham, UK; ^bClinical Division of Cardiology, Department of Pediatrics, Pulmonology, Allergology and Cystic Fibrosis, St Vinzenz Hospital, Zams, Austria; ^cDepartment of Medical Statistics, Informatics, Health Economics, St Vinzenz Hospital, Zams, Austria; ^dDepartment of Pediatrics, St Vinzenz Hospital, Zams, Austria; ^eDepartment of Pediatrics, Bruneck Hospital, Bruneck, Italy

Background: The 6-min walk test (6MWT) is a simple, accurate and safe method to measure functional exercise capacity. The 6MWT is increasingly used in children to predict morbidity

and mortality from cardiopulmonary disease, to assess functional capacity and measure disease progression in chronic childhood conditions such as muscular dystrophy. **Objective and hypotheses:** To provide smooth reference curves for the 6-min walk distance (6MWD) in healthy children aged 4–19 years and to enable calculation of sex-, age- and height-specific Z-scores for use in clinical practice. **Method:** 696 healthy Caucasian children and adolescents (328 girls) aged 4–19 years were included in the study. The modified 6MWT measures the distance walked by the participant in 6-min using a measuring wheel with interchangeable handlebars. Smooth sex-specific 6MWD centile charts for age and height were created using the Altman model. **Results:** Sex-specific centile curves were created from the best fitting equations, showing the 2nd, 50th and 98th centiles for age and height. In age specific centile curves for girls, the 6MWD increased between 4 and 11 years of age, plateaued thereafter and dipped slightly in those aged 15 years and above. In boys, the 6MWD increased from 4 to 19 years of age with the maximum rise between 6 and 14 years of age. Overall boys covered greater 6MWD in comparison to girls. **Conclusion:** Our study provides smooth reference curves for the 6MWT in a large cohort of healthy Caucasian children aged 4–19 years for easy use in clinical practice, and enables the calculation of sex-, age- and height- specific Z-scores. These centile charts help in assessing exercise capacity, measure disease severity and response to intervention.

P1-D2-122

Predictive Value of Excess Body Weight in Childhood and Adolescence Compared to BMI and Waist to Height Ratio

David Petroff^{a,b}, Katrin Kromeyer-Hauschild^c, Susanna Wiegand^d, Dagmar L'Allemand-Jandere^e, Gerhard Binder^f, Karl Otfried Schwaba^g, Rainer Stachow^h, Wieland Kiessⁱ, Elke Hammer^j, Sirid Sturm^k, Reinhard Holl^l, Susann Blüher^a

^aLeipzig University Medical Center, IFB AdiposityDiseases, Leipzig, Germany; ^bClinical Trial Centre, Leipzig, Germany; ^cInstitute of Human Genetics, Jena University Hospital, Friedrich-Schiller-University, Jena, Germany; ^dDepartment of Pediatric Endocrinology and Diabetology, Charité Universitätsmedizin Berlin, Berlin, Germany; ^eEastern Swiss Children's Hospital, St Gallen, Switzerland; ^fPediatric Endocrinology and Diabetology, University Children's Hospital, University of Tuebingen, Tuebingen, Germany; ^gPediatric Endocrinology and Diabetology, Centre for Child and Adolescent Health, University of Freiburg, Freiburg, Germany; ^hChildren's Hospital Sylt, Westerland, Germany; ⁱDepartment of Women and Child Health, University Hospital of Leipzig, Leipzig, Germany; ^jChildren's Hospital Wilhelmsstift, Hamburg, Germany; ^kSANA Hospital Lichtenberg, Berlin, Germany; ^lInstitute of Epidemiology and Medical Biometry, University of Ulm, Ulm, Germany

Background: Weight status in children is commonly defined using BMI (SDS), but this measure is problematic due to the

skewness of the BMI distribution and its age-dependant increase. In addition, it is difficult for physicians or parents alike to grasp what a certain value means. Excess body weight (EBW) is frequently used in adult patients in the context of bariatric surgery. **Objective and hypotheses:** An appropriate definition for the paediatric population is not available. A simple definition for EBW in children/adolescents is introduced with median weight as a function of height, age and gender as a robust reference point. The relationships between EBW, BMI-SDS, waist to height ratio (WHtR) and metabolic parameters are examined. **Method:** $EBW(\%) = 100 \times (\text{weight} - \text{median weight}) / \text{median weight}$. Correlations are analyzed in 14,362 children aged 11–18 (7553 overweight/obese children from the APV data base which collects data from German/Swiss/Austrian obesity outpatient centres; 6809 representative German children from the KiGGS survey covering all weight ranges). **Results:** In both cohorts, BMI-SDS correlates strongly with EBW (linear correlation coefficients ≥ 0.93) and to a lower extent with WHtR (linear correlation coefficients ≥ 0.76). The relationships of all three measures with metabolic (triglycerides, HDL-cholesterol, fasting glucose) and clinical (systolic/diastolic blood pressure) parameters are quite similar to each other, and the strongest linear correlation of all measures can be found with HDL-cholesterol and systolic blood pressure. BMI-SDS, EBW and WHtR are similar in terms of their ability to predict metabolic risks, based on area under the curve from receiver operating characteristic (ROC) analyses. **Conclusion:** EBW is a novel four-dimensional marker, comparing individual weight to a gender, age and height related ideal weight. BMI-SDS, WHtR and EBW have similar predictive values for metabolic comorbidities in the pediatric population. As EBW is valid even in extremely obese patients, it would make a very useful addition to existing anthropometric tools in paediatric obesity.

P1-D2-123

Cardiovascular Risk Markers in Metabolically Healthy and Metabolically Unhealthy Obese Adolescents

Tetyana Chaychenko

Kharkov National Medical University, Kharkiv, Ukraine

Background: The theory of 'Metabolically healthy obese individuals' is become very popular in researchers across the world. Nevertheless, obese persons are at increased risk for adverse long-term outcomes compared with metabolically healthy normal-weight individuals. **Objective:** To determine the obesity-related cardiovascular comorbidities in metabolically healthy obese adolescents comparatively to lean and metabolically unhealthy ones. **Methods:** 208 obese adolescents aged 10–17 were examined with an analysis of body composition, lipid and carb parameters, evaluation left ventricular (LV) geometry and function, 24-h BP monitoring, carotid intima-media thickness (CIMT). IDF criteria were used for grouping for metabolically healthy (MH) and metabolically unhealthy (MUH). Control group – 27 lean healthy (LH) subjects. Standard statistical methods were used for the

data analysis. **Results:** BMI in MUH group was greater than in MH ($P=0.019$) due to fat mass ($P=0.020$), despite of the same values of waist to height ratio ($P=0.071$) and lean mass ($P=0.124$). Interestingly the upper arm circumference to lean mass ratio was greater in MUH vs MH ($P=0.031$). Clearly lipid parameters (TC, TG, HDL, FFA) were higher in MUH vs MH ($P<0.001$ for all) and in MH vs LH ($P<0.001$ for all). Fasting insulin levels and HOMA-IR were similar ($P=0.431$; $P=0.364$), but greater vs LH. LV mass indexed was increased in all obese subjects: LH vs MH and MUH ($P=0.013$; 0.002), but without difference MH vs MUH ($P=0.469$). CIMT higher in obese ($P<0.001$) and no distinction MH vs MUH ($P=0.199$). SBP gradually growing from lean to MUH (LH vs MH $P<0.001$; MH vs MUH $P=0.014$). DPB didn't reveal any difference with a lean group. **Conclusion:** Our data suggests the presence of independent cardiovascular risk markers such as myocardial hypertrophy, thickening carotid vessels and systolic hypertension in both metabolically healthy and unhealthy individuals. Considered the lipid flux between fat and lean body compartments at the insulin resistance background plays the key role in risk development.

P1-D2-124

A Dual Role of Fetuin A on Cardiovascular Risk in Obese Children and Adolescents

Susanna Wiegand, Mareike Buermann, Andrea Ernert, Silvia Briese, Ann-Madeleine Bau, Heiko Krude

Institut Exp.Päd. Endocrinologie, Charite-University Medicine-Beröin, Berlin, Germany

Background: Cardiovascular diseases are most relevant for morbidity and mortality in obese patients. Because metabolic complications already start in childhood obesity one may expect an early manifestation of cardiovascular disease in this group as young adults. In adults fetuin A was shown to promote adipocyte inflammation and metabolic syndrome and subsequently vascular damage. **Objective and hypotheses:** We evaluated the role of fetuin A in the vascular pathogenesis in an obese childhood and adolescent cohort. **Method:** As part of the weight intervention trial MAINTAIN we measured a variety of obesity associated parameters including lipids, HOMA, leptin, fetuin A and intima media thickness (IMT) in 136 obese children and adolescents. **Results:** While leptin was strongly correlated with BMI-SDS, fetuin A was not correlated with BMI-SDS, waist circumference or fat-mass. Neither was fetuin A correlated with GOT, GPT or triglycerides. However we found a weak correlation of fetuin A with HOMA ($r=0.189$, $P=0.029$). In contrast fetuin A was negatively and significantly correlated with IMT ($r=0.308$, $P<0.000$). **Conclusion:** We found a dual role of fetuin A in obesity comorbidity parameters in a well characterized children and adolescent obesity cohort. While fetuin A was positively – however weakly- correlated with HOMA as it was expected from the so far available data in obese adult cohorts, fetuin A was negatively correlated with IMT. This negative correlation with

IMT suggest that in younger obese patients the known protective role of fetuin A to inhibit vascular calcification might still be more relevant compared to the negative influence on vascular pathogenesis triggered by pro-inflammatory effects as described in adult cohorts.

P1-D3-125

Impairment of Adipose Tissue in Prader-Willi Syndrome Rescued by GH Treatment

Thomas Cadoudal^{a,b}, Gwenaëlle Diene^c, Coralie Sengenes^{a,b}, Catherine Molinas^{c,e}, Flavie Desneulin^d, Sanaa Eddiry^e, Françoise Conte Auriol^{d,e}, Daniele Daviaud^{a,b}, Anne Bouloumie^{a,b}, Jean Pierre Salles^{c,e}, Philippe Valet^{a,b}, Maithe Tauber^{c,e}

^aINSERM, UMR 1048, Institut des Maladies Métaboliques et Cardiovasculaires I2MC, Toulouse, France; ^bUniversité Paul Sabatier, UMR 1048, Toulouse, France; ^cUnité d'Endocrinologie, Obésité, Maladies Osseuses, Génétique et Gynécologie Médicale. Centre de Référence du Syndrome de Prader-Willi, Hôpital des Enfants, Toulouse, France; ^dAxe Pédiatrique du CIC 9302/INSERM, Hôpital des Enfants, Toulouse, France; ^eINSERM, UMR 1043, Toulouse, France

Background: Prader-Willi syndrome (PWS) results from abnormalities in the genomic imprinting process leading to hypothalamic dysfunction with an alteration of GH secretion. PWS is associated with early morbid obesity and short stature which can be efficiently improved with GH treatment. **Objective and hypotheses:** Our aims were to highlight adipose tissue structural and functional impairments in young children with PWS and to study the effect of GH treatment. **Method:** Adipose tissue (AT) biopsies were obtained during scheduled surgeries from control lean children ($n=15$, age= 40.6 ± 5.9 months), untreated lean PWS children ($n=7$, age= 19.6 ± 3.8 months) or PWS children under GH treatment for at least 1 year ($n=8$, age= 103.6 ± 20.1 months). This study is part of a prospective national multicenter study evaluating both *in vivo* and *in vitro* GH sensitivity in PWS approved by the Local Ethical Committee (no. EUDRACT 2008-004612-12). **Results:** Analysis of biopsies revealed that in stromal vascular fraction of AT, adipose progenitor cells (CD34⁺/CD31⁻/CD14⁻ cells) were significantly reduced in untreated PWS AT when compared to control samples (75 000 cells/g of control AT to 40 000 cells in the same amount of PWS tissue). GH treatment tended to restore this population of progenitor cells in AT. Isoprenaline strongly activated lipolysis in control adipocytes (maximal 12-fold increase of basal lipolysis) whereas this β -adrenergic agonist effect was partially lost in adipocytes from PWS children (maximum fourfold activation). In contrast, isoprenaline-induced stimulation over basal lipolysis was stronger in GH-treated than untreated PWS adipocytes. **Conclusion:** Herein, we report adipose tissue dysfunctions in children with PWS which may be partially restored by GH treatment.

P1-D3-126**Dysautonomia and Acyl Ghrelin in Prader–Willi syndrome**

Ohn Nyunt^{a,c}, Sinead Archbold^b, Jennifer Donnelly^b,
Penelope Jeffery^{d,e}, Andrew Cotterill^{a,b}, Peter Davies^a, Mark Harris^{a,b}

^aThe University of Queensland, Brisbane, Queensland, Australia;

^bMater Children's Hospital, Brisbane, Queensland, Australia, ^cRoyal North Shore Hospital, Sydney, New South Wales, Australia,

^dQueensland University of Technology, Brisbane, Queensland, Australia, ^eMater Research Institute, The University of Queensland, Brisbane, Queensland, Australia

Background: Poor temperature regulation in Prader–Willi syndrome (PWS) suggests dysautonomia probably secondary to hypothalamic dysfunction. Autonomic nervous system (ANS) has control over orexigenic ghrelin. **Objective and hypotheses:** We aim to assess ANS function in PWS and its association with acyl ghrelin. **Method:** We recruited 16 genetically-confirmed children with PWS and 16 controls. Exclusion criteria were diabetes mellitus, psycho-trophic medications, and other hypothalamic pathologies. Subsidized GH therapy for children with PWS became available before the study and became an unavoidable confounder for the study. We performed a mixed meal study to assess ANS and ghrelin statuses. Orthostatic change in pulse rate (PR), and blood pressure (BP) expressed as per cent change of PR (% Δ PR), BP (% Δ BP) were used to assess ANS function. PR and BP increase soon after standing from recumbent position by increasing sympathetic vasomotor tone. Sympathetic and parasympathetic nervous systems are stimulated after a meal. We examined % Δ PR and % Δ BP at 15 and 30 s after standing from a lying, at fasting, and post-prandial periods. We measured plasma gastrin, catecholamines (Pcat) and urinary catecholamines (Ucat) to complement cardiovascular data. **Results:** Post-prandial % Δ PR at both 15 and 30 s were significantly lower in PWS group than controls. % Δ systolic BP and diastolic BP were not different in both groups. Post-prandial plasma gastrin and Ucat were higher in PWS group than controls but Pcat were not different in two groups. Fasting plasma acyl ghrelin (AG) was higher in PWS but it decreased to similar level of controls at 120 min after a meal. Fasting AG is negatively correlated to fasting % Δ PR at 30 s ($r = -0.52$, $P = 0.04$). **Conclusion:** In PWS, there is measureable sympathetic dysfunction indicated by poor orthostatic pulse change. Higher gastrin and Ucat suggest poor vagal function similar to post-vagotomy state. Because of ANS dysfunction, fasting ghrelin was high.

P1-D3-127**Infancy Lipidomic Analyses and Associations with Early Nutrition and Growth**

Philippa Prentice^a, Albert Koulman^b, Lee Matthews^b, Carlo Acerini^a,
Ken Ong^a, David Dunger^a

^aUniversity of Cambridge, Cambridge, UK; ^bMRC Human Nutrition Centre, Cambridge, UK

Background: Links between early life exposures and long-term health outcomes may in part be due to nutritional programming, and suggested benefits of breast feeding during infancy include reduced risk of obesity and metabolic disease. Mechanisms remain unexplained but potential differences in lipid exposures during infancy may be involved. **Objective and hypotheses:** To explore the effects of breast- or formula-feeding on lipidomic profiles we used recently established high-resolution mass-spectrometry (HRMS) methods to interrogate dried blood spot (DBS) samples from a large representative birth cohort study. **Method:** Lipidomic profiles were analysed in 3.2 mm DBS collected at ages 3 months ($n = 241$) and 12 months ($n = 144$) using HRMS. Lipid species were compared between infants exclusively breast-fed, formula-fed or mixed-fed, and associations with 12-month infancy weight were investigated. Data analysis used supervised multivariate statistics (PLS-DA) and univariate analysis with Bonferroni's correction for multiple testing. **Results:** Three-month lipidomic profiles differed widely between breast- and formula-fed infants; mixed-fed infants showed intermediate profiles. Lipidomic characteristics of breast-fed infants included: higher total phosphatidylcholines (PC), with lower short chain unsaturated PC and higher long chain polyunsaturated PC; higher cholesterol esters and sphingomyelins differences. 12-month lipidomic profiles were markedly different to those at 3 months, but effects of earlier breast/formula/mixed-feeding were no longer seen. However, several of the 3-month lipid differences associated with breast-feeding, such as lower PC 34:1 and PC-O 34:1, and higher PC 38:4, were associated with higher or lower 12 month infant weight respectively. **Conclusion:** State of the art HRMS methods with DBS showed striking differences in lipidomic profiles between breast-fed and formula-fed infants, and changes with age. Links between lipidomic profiles reflecting association with breast-feeding at 3 months and 12-month weight may indicate that this approach could inform future neonatal nutritional interventions.

P1-D3-128**Acylated and Unacylated Ghrelin Levels in Children and Young Adults with Prader–Willi Syndrome**

Renske Kuppens^{a,c}, Gwenaëlle Diène^c, Nienke Bakker^{a,b},
Catherine Molinas^c, S Faye^c, Marc Nicolino^d, Delphine Bernoux^d,
Patric Delhanty^e, Aart Jan van der Lelije^e, Soraya Allas^f,
Michiel Julien^f, Thomas Delale^f, Maïthé Tauber^c,
Anita Hokken-Koelega^{a,b}

^aDutch Growth Research Foundation, Rotterdam, The Netherlands;

^bDepartment of Pediatric Endocrinology, Erasmus Medical Center-Sophia Children's Hospital, Rotterdam, The Netherlands;

^cPrader–Willi Reference Center, INSERM U563, Children's Hospital Toulouse, Toulouse, France; ^dDivision of Pediatric Endocrinology, University of Lyon, Hôpital Femme-Mère-Enfant, Bron/Lyon,

Background: Prader–Willi syndrome (PWS) is characterized by a switch in early childhood from failure to thrive to excessive weight gain and hyperphagia with impaired satiety. The underlying mechanism for this switch may involve hyperghrelinemia, but only poor data exists regarding levels of acylated ghrelin (AG), unacylated ghrelin (UAG), and the AG/UAG ratio in PWS. **Objective and hypotheses:** To investigate plasma levels of AG and UAG in PWS, compared with the levels of obese and lean controls. To investigate associations in PWS between AG and UAG levels, and BMI and eating behaviour. **Method:** The AG and UAG levels of 138 children and young adults with PWS (range 0.2–29.4 years) are compared with age-matched obese (50) and lean (39) controls. AEBSE, inhibitor of des-acylation of AG, was added to the blood samples. **Results:** AG levels were significantly higher in PWS than in lean controls. UAG levels in PWS were similar to lean controls, which resulted in a significantly raised AG/UAG ratio. Obese controls had lowest AG and UAG levels compared with PWS and lean controls. UAG is more decreased than AG in obese controls, which resulted in the highest AG/UAG ratio of the three groups. We found no difference in gender or genetic subtype of PWS. In PWS, age and BMI SDS were strongly correlated with nutritional phases according to Miller (both $P < 0.000001$). In these patients, AG, UAG levels, and AG/UAG ratio were inversely associated with the nutritional phase ($P = 0.004$, $P < 0.00001$ and $P = 0.015$, respectively). Raised BMI was associated with lower UAG levels, even after adjustment for age and gender ($P = 0.008$). **Conclusion:** Our findings provide a rationale for a role of an abnormal AG/UAG ratio in eating behavior in PWS.

P1-D3-129

The Effect of Honey on Plasma Glucose and Insulin Concentrations in Obese Prepubertal Girls

Ioanna Farakla^a, Georgios E. Papadopoulos^a, Eleni Koufi^a, Jessica Arditi^a, Paraskevi Moutsatsou^b, Maria Drakopoulou^a, Ioannis Papassotiriou^c, George P. Chrousos^a, Evangelia Charmandari^a

^aDivision of Endocrinology, Metabolism and Diabetes, First Department of Pediatrics, University of Athens Medical School, 'Aghia Sophia' Children's Hospital, Athens, Attiki, Greece;

^bDepartment of Biological Chemistry, University of Athens Medical School, Athens, Attiki, Greece; ^cDepartment of Clinical Biochemistry, University of Athens Medical School, 'Aghia Sophia' Children's Hospital, Athens, Attiki, Greece

Background: Honey is known for its medicinal and health promoting properties. It contains phytochemicals with high phenolic and flavonoid content, which contribute to its high antioxidant activity. Recent studies performed in adult healthy subjects suggest that honey has a beneficial effect on plasma glucose and serum insulin concentrations compared with monosaccharides and disaccharides from different sources.

Objective/hypotheses: To compare the effects of oral honey (OHTT) and glucose tolerance test (OGTT) solutions on plasma glucose and serum insulin concentrations in obese prepubertal girls. **Methods:** Thirty healthy obese prepubertal girls aged 11.59 (\pm S.E.M.: 0.4) years with a BMI above the 90th centile for age (27.60 ± 1.38 kg/m²) underwent initially a standard OGTT and an OHTT 2 weeks later. Both solutions contained 75 g of glucose. Plasma glucose and serum insulin concentrations were determined before the solution administration and at 30 min intervals thereafter for a total of 3 h. Subsequently, subjects were randomized to either receive 15 g of honey or 15 g of marmelade daily, while both groups complied with dietary instructions. Six months later all subjects were re-validated with an OGTT and an OHTT. **Results:** Upon initial evaluation, plasma glucose concentrations at 120 min were significantly lower at the OHTT than the OGTT (91.00 ± 2.58 vs 104.44 ± 2.99 mg/dl, $P = 0.001$). At the end of the study, all subjects demonstrated a significant reduction in BMI (26.59 ± 1.38 vs 27.60 ± 1.38 kg/m², $P < 0.001$). Serum insulin concentrations at 0 min (21.48 ± 4.57 vs 41.23 ± 7.47 μ IU/ml, $P < 0.01$) and at 120 min (45.47 ± 6.35 vs 71.79 ± 11.99 μ IU/ml, $P = 0.007$) were significantly lower at OHTT than the OGTT. **Conclusions:** Honey had a beneficial effect on stimulated plasma glucose and serum insulin concentrations compared with the standard OGTT solution. These findings indicate that honey might delay or prevent the development of insulin resistance, impaired glucose tolerance and diabetes in obese children.

P1-D3-130

Features of Neuroendocrine Status in Children with Different Forms of Obesity

Anzhalka Solntsava^a, Olga Zagrebaeva^a, Hanna Mikhno^a, Helena Dashkevich^b, Alexandr Sukalo^{a,c}, Katsiaryna Konchyts^a

^aBelarusian State Medical University, Minsk, Belarus; ^b10th State Clinic, Minsk, Belarus; ^cNational Academy of Sciences of Belarus, Minsk, Belarus

Background: The relationship of obesity and emotional disorders is confirmed in many studies. It is known that one of the substances responsible for the emotional status is dopamine. **Objective:** To study the features of neuroendocrine status in obese children. **Methods:** We examined 285 children (206 obese, age 14.56 ± 2 years, BMI 32.86 ± 5.1 kg/m²; 79 normal weight (control), 14.51 ± 2.2 years ($P = 0.95$), 19.9 ± 2.5 kg/m² ($P = 0.0001$)), observed in the Endocrinology Department of University clinic (Minsk) in 2013–2014. Obese children were divided into subgroups: simple (14.35 ± 2 years, BMI < 35 kg/m²) and morbid obesity (15.6 ± 1.6 years, > 35 kg/m²). The levels of dopamine (D), neuropeptide Y (HY), leptin, insulin were examined in all children. Results were processed using SPSS 18.0. **Results:** Obese children showed a significant D increase compared with control (median (Me) simple 12.1 (4.2–50.2) ng/ml, Me morbid obesity 61.1 (10.8–163.7) ng/ml, and Me control 5.96 (3.1–16) ng/ml) ((ps-c = 0.012), (pm-c = 0.0001), and (pm-s = 0.009)). The positive correlation with D and BMI were

observed in all obese children ($r_s=0.36$; $P=0.044$). Leptin levels in children with morbid (Me 24.4 (10.7–58.6) ng/ml) and simple (Me 18.7 (8–37.3) ng/ml) obesity were significantly higher than control (Me 4.46 (1.4–18.4) ng/ml) ($p_s-c=0.0001$), ($p_m-c=0.0001$), and ($p_m-s=0.0001$). Leptin levels were positively correlated with insulin concentrations ($r_s=0.3$; $P=0.0001$) and BMI ($r_s=0.56$; $P=0.0001$). The reduced levels of NY were noticed in children with morbid (Me 80.7 (61.4–116.2) pmol/ml) and simple (Me 89.6 (56.9–124.8) pmol/ml) obesity compared with control (Me 108.4 (75.7–143.9) pmol/ml) ($p_m-c=0.0001$), ($p_s-c=0.0001$), and ($p_s-m=0.1$). There were negative correlation between NY and BMI ($r_s=-0.18$; $P=0.022$) in children with different forms of obesity compared with control. **Conclusions:** Obese children had higher levels of dopamine and leptin with the reduction of NY concentrations. Increased dopamine levels revealed the violation of its binding to dopamine receptors and greater risk of developing emotional disorders in children with different forms of obesity.

P1-D3-131

Under-Diagnosed Beckwith–Wiedemann Syndrome Among Early-Onset Obese Children

Gabriel Á Martos-Moreno^{a,b}, Clara Serra-Juhé^{c,d},
Luis A Pérez-Jurado^{c,d}, Jesús Argente^{a,b}

^aHospital Infantil Universitario Niño Jesús; Endocrinology Department IIS La Princesa, Universidad Autónoma de Madrid; Pediatrics Department, Madrid, Spain; ^bInstituto de Salud Carlos III, CIBER Fisiopatología de la Obesidad y Nutrición, Madrid, Spain; ^cUniversitat Pompeu Fabra, Genetics Unit, Hospital del Mar Research Institute (IMIM), Program in Neurosciences, Barcelona, Spain; ^dInstituto de Salud Carlos III, Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Barcelona, Spain

Background: Beckwith–Wiedemann Syndrome (BWS) is a clinical and genetically heterogeneous entity encompassing overgrowth and variable manifestations. Early diagnosis of BWS is crucial due to the increased risk for developing embryonal malignancies (mainly below 5 years of age). **Objective:** We aimed to screen the presence of underdiagnosed BWS among ‘non-syndromic’ obese children. **Method:** We studied 159 children (95 males/64 females) diagnosed with early-onset (<5 years) severe (BMI-SDS > +3 SDS) obesity. A custom-made methylation-specific multiple-ligand-probe-assay (MS-MLPA), with HhaI as a methylation-sensitive restriction enzyme, was used to analyze blood cell DNA methylation at the 11p15.5 region. The assay contains 11 probes, including one for the imprinting-center 1 (IC1) locus (*H19*) and one for IC2 (*KCNQ1*). Probes located at fully unmethylated loci were included as technical controls, as well as probes without the HhaI recognition site for methylation quantification. **Results:** Hypomethylation at *KCNQ1* locus was identified in two patients (60 and 33% methylation decrease respectively). None of them fulfilled the minimum

criteria proposed for diagnosing BWS. The patient with 60% methylation impairment, presented no major nor minor criteria for BWS, with suitable birth anthropometry and height and bone age according to her target height and chronological age, respectively. In contrast, the patient with a 33% methylation impairment, presented a more severe, predominantly abdominal obesity (BMI > +8SDS), with pre- (birth length and weight 53 cm and 4.0 kg, respectively) and postnatal macrosomy (height +2.7 SDS), gestational polyhydramnios, diastasis recti and advanced bone age (> +1.5 years over chronological age) among proposed BWS diagnostic criteria (one major+three minor). No liver or kidney ultrasonographic abnormalities nor elevation in plasma α -fetoprotein levels were found, but patients had never been tested before their molecular diagnosis. **Conclusion:** Some overgrowth syndromes, particularly BWS, can present clinically as early-onset obesity leading to misdiagnosis and misclassification as ‘common’ obesities.

P1-D3-132

Impact of Maternal and Fetal Inflammatory Markers on Neonatal and Infant Adiposity

Jean M Donnelly^a, Jennifer M Walsh^{a,b}, Mary Horan^a, Eleanor J Molloy^{c,d}, Fionnuala Mc Auliffe^a

^aUniversity College Dublin, Dublin, Ireland; ^bNational Maternity Hospital, Dublin, Ireland; ^cRoyal College of Surgeons of Ireland, Dublin, Ireland; ^dOur Lady’s Childrens Hospital Crumlin, Dublin, Ireland

Background: The effect of maternal obesity and the associated maternal inflammation on neonatal and paediatric health and wellbeing over the early childhood years is not fully understood. **Objective and hypotheses:** This study aimed to determine the impact of maternal and fetal inflammatory factors on infant anthropometric measurements. **Method:** 265 mother–infant pairs from an RCT assessing the effect of a low glycaemic index diet on birth weight (ROLO study) were analysed. Maternal interleukin 6 and TNF α were measured at booking and 28 weeks and fetal levels assessed in cord blood. Birth weight and anthropometric measurements were recorded at birth and at 6 months. Abdominal circumference and various skinfolds were measured. The sum of subscapular+triceps skinfolds was used as a marker of general adiposity and the ratio of these as a marker of central adiposity. **Results:** IL 6 in early pregnancy and fetal samples was found on simple linear regression to influence general adiposity at birth. A correlation was also found between fetal IL6 and birth length. At 6 months of age IL-6 was found to influence triceps skinfolds predominantly in late pregnancy. TNF α in early pregnancy was found to influence general adiposity and various skinfolds. Early, late and fetal TNF α were also found to correlate with various markers anthropometry at 6 months. **Conclusion:** Maternal inflammatory markers have a significant role to play in the determination of neonatal and infant anthropometry. This data emphasises the importance of the antenatal inflammatory markers

in the prediction of neonatal and infant anthropometry. They exert their influence throughout the antenatal period and it persists beyond the neonatal period and therefore may play a role in the predisposition towards early childhood obesity.

P1-D3-133

Can We Predict the Risk of Obesity?

Antonio de Arriba^a, Javier Pascual^b, Mario de Francisco^b, Marta Ferrer^a, Ignacio Martínez^b, José Ignacio Labarta^a, Ángel Ferrández^c

^aPediatric Endocrinology Unit, Miguel Servet Hospital, Zaragoza, Spain; ^bGodday Solutions SL, Zaragoza, Spain; ^cAndrea Prader Foundation, Zaragoza, Spain

Background: Recognizing the risk of developing obesity is essential to implement preventive measures to avoid the increasing prevalence of obesity in adulthood. **Objective:** To evaluate predictive factors that may be associated with overweight and obesity in early adulthood. **Method:** A regression analysis of different variables of body composition in a normal population have been done. The sample consisted of 122 boys and 120 girls followed longitudinally from birth to adulthood. Simple data and their variations in different periods of time have been used (from birth to 3 years measured every 3 months). Variables studied: weight, height (H)/length, sitting height (SH), BMI, waist circumference, waist to hip (WH), skin folds (tricipital (TS) and subscapular (SS)), cephalic perimeter (CP), arm perimeter (AP), thigh circumference (TC), biacromial diameter (BD) and biiliac diameter. Overweight threshold has been established for each time period depending on the values of BMI and waist circumference of the total sample when both parameters were $> +1$ S.D. **Results:** Two different predictive models have been obtained (for boys and girls) that can predict at 3 years of age the risk of being overweight in early adolescence.

Women:

$$P(\text{overweight}) = 1/(1 + e^{(-25,4662 \times \text{BMI} - 3 - 19,1074 \times \text{BMI}_{2.75} - 3,3415 \times \text{SH}_{1.5} - 10,9374 \times \text{WH}_0 + 2,6447 \times \text{TS}_{0.75} + 1,6515 \times \text{BD}_{0.75} + 2,5140 \times \text{BD}_2))})$$

Men:

$$P(\text{overweight}) = 1/(1 + e^{(-27,3543 + 27,9645 \times \text{BD}_{0.75} - 23,7834 \times \text{WH}_{0.5} + 4,8652 \times \text{BD}_{1d} + 12,2667 \times \text{TC}_2 + 75d_{0.25} - 7,8747 \times \text{BD}_{0.5d} - 34,3391 \times \text{SS}_{2.25d} + 48,9172 \times \text{SS}_{2.5d} - 0,8233 \times \text{TC}_{1.5d} - 3,0773 \times \text{BD}_{0.75d} - 2,5331 \times \text{SH}_1 \times \text{TS}_{0.25d}))})$$

The variables with the greatest impact on risk estimation were BMI index at 3 years of age in girls, and the interaction of the variation presented by the subscapular skinfold between 2 and 2.25 years of age associated with the difference between thigh circumference measured at 2.5 and 2.75 years of age in boys. These formulas have a sensitivity of 92.13% for females and 91.86% for males and a specificity of 91.3% for females and 92.59% for males. **Conclusions:** Longitudinal studies provide great information about the growth and development of populations, which allow to design predictive models of developing overweight/obesity in

adulthood. 2. A formula for each sex has been achieved with high sensitivity and specificity that can predict the risk of being overweight from 3 years old. However, these models are of great complexity that limits its application in the daily practice and therefore easier formulas must be obtained.

P1-D3-134

Can Hypothalamic Obesity be Treated with Stimulants?

Friederike Denzer, Belinda Lennerz, Christian Denzer, Martin Wabitsch

Division of Pediatric Endocrinology und Diabetes, University Hospital for Pediatric and Adolescent Medicine, Ulm, Germany

Background: Published case reports and anecdotal experience suggest a positive effect of dexamphetamine on impetus and weight in patients with hypothalamic obesity. **Objective and hypotheses:** We aimed to observe these effects in our patients who are offered off-label treatment with dexamphetamine. **Method:** Between 2010 and 2013, patients starting dexamphetamine treatment were enrolled in a prospective observation study. BMI-SDS was determined and impetus was rated on a scale from 1 to 5 at baseline and every 3 months. A retrospective chart review was conducted to establish BMI-SDS development prior to treatment initiation. Dexamphetamine administration was initiated at a single dose of 5 mg/day, and titrated to effect up to a dose of 20 mg/day in two to three single doses. Side effects were recorded in a standardized fashion. **Results:** Six patients, two males, four females, age 17.5 years on average (range: 14.5–23.8) were included in the study. The primary diagnosis was craniopharyngeoma in five patients, and neonatal meningitis in one patient. Time from initial CNS insult to initiation of dexamphetamine treatment was 6.6 years on average (range 2.7–17.4 years). All patients demonstrated a steady increase in BMI-SDS from the time of initial diagnosis up until the initiation of treatment. Baseline BMI-SDS was +3.1 (1.9–4.1). After an average treatment duration of 1.6 years (0.2–3.0), all patients experienced a sustained increase in impetus and a stabilization or reduction in BMI-SDS by 0.3 (0–0.8). No significant side effects were reported. **Conclusion:** Dexamphetamine lead to improved impetus and stabilization or reduction of BMI-SDS in a cohort of six patients with hypothalamic obesity. Considering the projected increase in BMI-SDS according the natural course of the disease, these findings are promising and warrant further study.

P1-D1-135

The Association Between Adipocytes and Growth is Mediated by Growth and Differentiation Factor 5[☆]

Biana Shtai^{a,b}, Nitzan Dror^c, Meytal Bar-Maisels^{a,c}, Moshe Phillip^{b,c}, Galia Gat-Yablonski^{a,c}

^aFelsentein Medical Research Center, Petah Tikva, Israel; ^bSackler Faculty of Medicine, Tel Aviv University, Petah Tikva, Israel; ^cSchneider Children's Medical Center of Israel, Petah Tikva, Israel

Background: The association between nutrition and growth is common knowledge but the mechanism is still unelucidated. Several reported cases in the literature describe growth without GH, that in most cases were associated with obesity, suggesting that the adipocytes might have a role in regulating linear growth. **Objective and hypotheses:** The aim of the study was to search for a skeletal growth factor that is secreted by adipocytes. **Method:** 3T3L1 cells were induced to differentiate into adipocytes and their conditioned medium (CM) was added to metatarsals bone culture. Studying the differentially expressed growth factors identified growth and differentiation factor 5 (GDF5) as a possible mediator. **Results:** CM of adipocytes significantly increased metatarsals bone elongation. GDF5 was found to be expressed 700 fold higher by adipocytes compared to non differentiated cells and to be secreted into their CM. The presence of BMPRI on metatarsal bone was confirmed. GDF5 significantly increased metatarsal length in culture. **Conclusion:** In this study we showed that CM of the 3T3L1 adipocytes directly stimulates growth of metatarsal bones in culture. Specifically we found that GDF5, a growth factor that plays an important role in limb mesenchymal cell condensation and chondrogenesis is a possible mediator of this stimulation. These results add a new understanding of the interaction between nutrition and growth.

*Nominated for a Presidential Poster Award.

normal pituitary at MRI. At first evaluation, low IGF1 and IGFBP3 levels, in addition to decreased GH peak to hypoglycemia test (4.8 ng/ml by RIA), were found in all siblings. At adulthood IGF1 and IGFBP3 were low as well as GH peak at hypoglycemia tests (2.5–2.8 ng/ml – IFMA). Nucleotides –123T and –161C are within a highly conserved region among species and predicted binding sites for POU1F1/SP1 and NF1 respectively. Functional study was performed aiming to check the effect of these variants on the phenotype. **Methods:** DNA–protein interaction was evaluated by EMSA. In order to perform transient transfection and dual luciferase reporter assay, three plasmids were constructed containing both positions WT (WTWT) or mutated (MUTMUT) or only mutated for –161 position (–161MUT). **Results:** EMSA demonstrated less affinity of GH3 nuclear extract to –161C>T variant and normal affinity of POU1F1 protein and GH3 nuclear extract for –123T>C variant. The transfected WTWT mean values were significantly higher compared to MUTMUT (20.2 ± 2.24 vs 11.1 ± 2.7 , $P < 0.01$), and to –161MUT (11.3 ± 2.1 vs 5.2 ± 0.8 , $P < 0.01$). **Conclusion:** To our knowledge, c.–161C>T is the first point mutation in the GH1 promoter that leads to short stature due to IGHD.

*Nominated for a Presidential Poster Award.

P1-D1-136

A Homozygous Point Mutation in the GH1 Promoter (–161T>C) Leads to Reduced GH Expression in Siblings with Isolated GH Deficiency[☆]

Joao Madeira^a, Regina Martin^a, Luciana Montenegro^a, Marcela Franca^a, Everlayny Costalonga^a, Fernanda Correa^a, Aline Otto^a, Ivo Arnhold^a, Helayne Freitas^b, Ubiratan Machado^b, Berenice Mendonca^a, Alexander Jorge^a, Luciani Carvalho^a

^aDivision of Endocrinology, University of Sao Paulo Medical School, Sao Paulo, Sao Paulo, Brazil; ^bDepartment of Physiology and Biophysics, Institute of Biomedical Science, University of Sao Paulo, Sao Paulo, Sao Paulo, Brazil

Introduction: Mutations in the GH1 promoter are a rare cause of isolated GH deficiency (IGHD). In order to find the molecular cause of short stature due to IGHD, three siblings (2 M) born to consanguineous parents without mutations in the GHRHR and GH1 coding regions were screened for mutations in the GH1 promoter and locus control region. All patients harbored two variants (c.–123T>C and –161C>T) in homozygous state in the GH1 promoter, not found in 100 controls. The parents and a brother with normal stature were carriers. Patients presented proportionate short stature (height SDS from –4.1 to –5.8) and

P1-D1-137

Growth Differentiation Factor 15 and Fibroblast Growth Factor 21: Novel Biomarkers for Mitochondrial Diseases

Shuichi Yatsuga, Yasutoshi Koga

Department of Pediatrics and Child Health, Kurume, Fukuoka, Japan

Background: Multiple organ dysfunction occurs in mitochondrial diseases (MDs). MDs are sometimes difficult to diagnose, because patients have solitary and/or combination of various symptoms including short stature, diabetes, myopathy, and seizure. Since plasma levels of lactate and pyruvate are not always the perfect biomarker for MDs, there are many pseudo-mitochondrial patients who are suspect for MDs. Diagnosis for MDs often requires muscle biopsy, gene analysis, and measurement of mitochondrial enzyme activity. In 2011, serum fibroblast growth factor 21 (sFGF21) was launched as a biomarker to diagnose muscle-featured MDs. Owing to this, it is now possible to differentiate MDs from similar other diseases using sFGF21.

Objective and hypotheses: We investigated whether sFGF21 is useful as a good biomarker for MDs in Japanese. Furthermore, we investigated whether serum growth differentiation factor 15 (sGDF15) can be a more specific biomarker for MDs. **Method:** Blood was extracted from 52 MDs patients and 149 controls. Serum FGF21 (sFGF21) and serum GDF15 was measured using ELISA (Biovendor, Czech and R&D systems, USA). Mann–Whitney *U* test and ROC analysis were performed using JMP (SAS Institute, Inc., USA) **Results:** As previously reported, sFGF21 was higher in MDs (median 661.4 ng/ml (7–8,854 ng/ml)) than in

control (median 108.2 pg/ml (7–1645 pg/ml)) ($P < 0.001$). sGDF15 was also significantly higher in MDs (1,807 pg/ml (333.9–5295 pg/ml)) than in control (median 370.7 pg/ml (152.5–1,010 pg/ml)) ($P < 0.001$). When sFGF21 was over 240.4 pg/ml, sensitivity and specificity were 80.77 and 78.08% for MDs in ROC analysis. Interestingly, when sGDF15 was over 707.2 ng/ml, sensitivity and specificity were 93.48 and 95.21% for MDs in ROC analysis, that was much higher sensitivity and specificity compared with sFGF21. **Conclusion:** We investigate that GDF15 is the new and useful biomarker for MDs, which is more advantage for diagnostic tool than that in sFGF21.

P1-D1-138

A Novel Homozygous Mutation of the IGF1 Receptor Gene (*igf1r*) in Two Siblings with Severe Short Stature, Intellectual Disability, Congenital Malformations, and Deafness

Isabelle Maystadt^{a,b}, Shayne F Andrew^c, Jean De Schepper^d, Nathalie Wauters^e, Geert Mortier^f, Valerie Benoît^g, Pascal Joset^g, Beatrice Oneda^g, Ron G Rosenfeld^c, Anita Rauch^g, Vivian Hwa^c

^aInstitut de Pathologie et de Génétique, Center for Human Genetics, Gosselies, Charleroi, Belgium; ^bFaculty of Medicine, Université Namur, Namur, Belgium; ^cDepartment of Pediatrics, Oregon Health and Science University, Portland, Oregon, USA; ^dDepartment of Paediatric Endocrinology, Ghent University Hospital, Ghent, Belgium; ^eDepartment of Pediatrics, Hôpital Civil de Charleroi, Charleroi, Belgium; ^fCenter for Medical Genetics, University of Antwerp, Antwerp, Belgium; ^gInstitute of Medical Genetics, University of Zurich, Zurich-Schwerzenbach, Switzerland

Background: Heterozygous mutations in the IGF1 receptor (*IGF1R*) are often associated with congenital IGF1 resistance, causing variable degrees of intrauterine growth retardation (IUGR) and postnatal short stature. To date, only one homozygous *IGF1R* mutation has been reported, in a child presenting with severe growth failure, mild intellectual impairment, microcephaly, dysmorphic features, and cardiac malformations. **Objective:** We now report the clinical and functional characteristics of a second novel homozygous *IGF1R* mutation, identified in two siblings. **Patients and methods:** The two siblings, an 11-year-old girl and a 7-year-old boy, with similar dysmorphic features, born from healthy consanguineous short Yemenite parents (mother's height, 145 cm and father's height, 160 cm), presented with severe IUGR (birth weight and length, -6 SDS) and postnatal growth failure (height, -5.5 SDS). Genetic causality (exome sequence analysis) and functional impacts of the mutation were evaluated. **Results:** A moderate delayed bone age and epiphyseal abnormalities, normal basal growth hormone, elevated IGF1 and normal IGFBP3 concentrations were found. Severe microcephaly (head circumference, -7 SDS), mild intellectual disability, deafness, cardiac malformations, and a partial vermis hypoplasia were also documented in

both patients. Fasting glucose levels were normal, but an impaired glucose tolerance without an hyperinsulinemic response were documented at OGTT. Exome sequencing identified a novel homozygous, in-frame p.711_714delAEKE deletion in *IGF1R*. Flow-cytometric analysis by FACS of live fibroblasts derived from the patients demonstrated normal expression and cell surface localization of the mutant IGF1R, which exhibited significantly reduced, but not abrogated, IGF1-induced signal transduction. **Conclusion:** Homozygous *IGF1R* mutations that do not completely ablate IGF1R expression/functions can result in severe pre- and postnatal growth failure comparable to *IGF1R* compound heterozygotes. While a disturbed glucose tolerance appears a common finding, insulin reserve and bone maturation can be variable. Cardiac anomalies were observed in patients carrying homozygous, but not heterozygous, *IGF1R* mutations.

P1-D1-139

Functional Characterization of Three Novel Mutations in the IGF1R Gene

Matias Juanes, Gabriela Guercio, Roxana Marino, Esperanza Berensztein, Marta Ciaccio, Silvia Gil, Marco A Rivarola, Alicia Belgorosky

Hospital de Pediatría Garrahan, Buenos Aires, Argentina

Background: *IGF1R* gene mutations have been associated with varying degrees of intrauterine and postnatal growth retardation, and microcephaly. We have previously reported three novel variants in the *IGF1R* gene: *de novo* p.Arg1256Ser, *de novo* p.Asn359Tyr and p.Tyr865Cys (ENDO 2013, OR20-2). **Aim:** To characterize the functional effects of the novel *IGF1R* gene allelic variants. **Methods:** *In silico* tools were used to predict the pathogenicity of the variations. Functional effects were evaluated by two *in vitro* assays: i) IGF1 dependent DNA synthesis in fibroblast cell primary cultures from patients and two control subjects (C1 and C2) were analyzed by ³[H]thymidine incorporation into DNA treated with IGF1 (50 ng/ml) for 16, 20, and 24 h and ii) PI3K/Akt pathway phosphorylation by phospho Akt (Ser473) STAR ELISA Kit (Millipore) assay in fibroblast cultures from patients and two controls (C3 and C4) stimulated with 100 ng/ml of IGF1 for 10 min. Protein concentration for each well was measured by Bradford assay. **Results:** *In silico* prediction models indicated that the substitutions probably affect protein function. Proliferation assay showed that IGF1 significantly induced DNA synthesis in C1 and C2 at 20 h (5.15 ± 0.67 and 6.37 ± 1.00 fold increase over '0' dose respectively, $P < 0.05$ by ANOVA and Bonferroni tests) and also Akt phosphorylation was significantly stimulated in C3 and C4 after 10 min of treatment with IGF1 ($P < 0.05$ by ANOVA and Bonferroni tests). However, no significant increase was observed in any of the three patients in both functional studies. **Conclusion:** We characterized three novel heterozygous mutations in the *IGF1R* gene that inhibit cell proliferation induced by IGF1 and affect IGFR signal transduction in patients' fibroblast cultures. These findings strongly suggest

that these mutations lead to failure of the IGF1R and cause the phenotype of pre and postnatal growth retardation and microcephaly.

P1-D1-140

Severe Short Stature and GH Insensitivity Due to a De Novo Heterozygous *STAT5B* Missense Mutation

Jürgen Klammt^a, David Neumann^b, Shayne F Andrew^c, Marcela Drahosova^b, Heike Stobbe^a, Kyle Buckham^c, Ron G Rosenfeld^c, Roland Pfäffle^a, Vivian Hwa^c

^aHospital for Children and Adolescents, University of Leipzig, Leipzig, Germany; ^bDepartment of Pediatrics and Department of Clinical Immunology and Allergology, University Hospital Hradec Kralove, Hradec Kralove, Czech Republic; ^cDepartment of Pediatrics, CDRC, Oregon Health and Science University, Portland, Oregon, USA

Background: GH insensitivity is caused by disturbances of GH receptor function or inability to transduce the hormone signal. Affected children are severely growth retarded and may also present immune complications when the transducer *STAT5B* is defective. Only autosomal-recessive *STAT5B* mutations have been described to date. **Clinical case:** Two male 14.5 year monozygotic twins presented with heights of 131.5 cm (−5.3 SDS). Bone age of the index patient was retarded by 4.9 years. Endocrine evaluation revealed normal stimulated GH concentrations (16.2 ng/ml) but borderline IGF1 level (56 µg/l) indicative of GH resistance. rhIGF1 therapy was commenced (0.12 mg/kg twice daily). At 17.1 years his height was 149.0 cm (−4.33 SDS) and weight 42.0 kg (−3.49 SDS). Biochemical re-evaluation indicated reduced IGF1 (102.7 µg/l, −5.13 SDS) and ALS levels (418 pmol/l, normal: 986–1678); IGFBP3 (2.33 mg/l, −1.69 SDS), prolactin (290.6 mU/l, RR: 86–324), GHBP were normal. In addition to severe short stature, the proband also presented with eczema but was otherwise healthy. Immunological phenotyping was unremarkable, except IgE concentration (340.0 kU/l, normal <114). Evaluation of the twin brother yielded similar results. Molecular analysis revealed a novel heterozygous variant in the *STAT5B* gene (c.530A>C, exon 5; p.Gln177Pro) that was not found in the parents, suggesting a *de novo* germline mutation, nor was the variant listed in >6000 individuals (Exome Sequencing Project; <https://esp.gs.washington.edu/drupal/>). No additional variant(s) was identified in the *GHI*, *GHR*, *IGFALS*, *IGF1*, or *IGF1R* genes. Functional evaluation of FLAG-*STAT5B*p.Gln177Pro (HEK293 reconstitution system) indicated protein expression and GH-induced phosphorylation comparable to WT FLAG-*STAT5B*, but transcriptional functions were compromised as the FLAG-*STAT5B*p.Gln177Pro could not translocate to the nucleus, and limited nuclear localization of the WT *STAT5B*. **Conclusion:** We describe a novel heterozygous p.Gln177Pro *STAT5B* mutation with potential dominant-negative properties conferring clinical manifestations comparable to reported *STAT5B* deficient patients but with less severe co-morbidities.

P1-D1-141

Whole Exome Sequencing is an Efficient Approach to Screen for Changes in Growth-Relevant Genes in Primary IGF1 Deficiency

Greta Grosse^{a,b}, Alina Hilger^a, Markus Draaken^c, Michael Ludwig^d, Heiko Reutter^e, Joachim Woelfle^b

^aInstitute of Human Genetics, University of Bonn, Bonn, Germany; ^bPediatric Endocrinology Division, Children's Hospital, University of Bonn, Bonn, Germany; ^cDepartment of Genomics Life and Brain Center, Bonn, Germany; ^dDepartment of Clinical Chemistry and Pharmacology, University of Bonn, Bonn, Germany; ^eDepartment of Neonatology, Children's Hospital, University of Bonn, Bonn, Germany

Background: Primary IGF1 deficiency (PIGFD) is a rare disease defined by low IGF1 levels, GH sufficiency and absence of secondary causes of growth failure. Whereas some members of the GH-IGF axis have been shown to be implicated in the severe syndromic forms of PIGFD due to GH insensitivity, genetic causes of less severely affected patients are mostly unknown. **Objective and hypotheses:** The aim of the present study was to systematically investigate frequencies of mutations/deletions in selected growth-relevant genes (*GHR*, *PTPN-11*, *STAT5B*, *IGFALS*, *IGF1*, *IGF2*, *IGFBP1-4*, *CUL-7*, *IRS1*, *IRS2*, *AKT1-3*, *SOCS2/3*, *JAK2*, *SHP2*, *SH2-B*, *SHOX1*, and *SHOX2*) in patients with PIGFD. **Method:** We performed whole-exome sequencing (WES) in three complete case-parent-trios and eight single patients with PIGFD. **Results:** We identified six novel missense mutations with a frequency below 1% in the general population in four different patients. Of these two different missense mutations were identified in *SHOX2* (one *de novo* and one homozygous respectively), two different missense mutations were identified in *IRS1* in two different patients, two missense mutations were identified in *IGFBP4* and *SOCS3*. Furthermore we identified one known missense mutation in *GHR*. The mutation in *GHR* was transmitted from an affected mother; the mutation in *SOCS3-3* was transmitted from an affected father. **Conclusion:** Preliminary WES analysis in our patient cohort with PIGFD identified putative disease causing mutations in three patients (twice transmitted from an affected parent, once *de novo*). The identification of four additional novel missense mutations warrants segregation analysis in the parents as soon as DNA will be available. WES provides an efficient method to identify putative disease causing mutations in growth-relevant genes in subjects with PIGFD.

P1-D1-142

Parental Gonadal Mosaicism for a BRAF Mutation in Cardiofaciocutaneous Syndrome

Sarah Geoghegan^a, Rose Morrissey^a, Jeniffer Shorto^b, Simon Ramsden^b, Stephen O'Riordan^a, Andrew Green^c, Susan O'Connell^a

^aDepartment of Paediatrics and Child Health, Cork University Hospital, Cork, Ireland; ^bGenetic Medicine, St Mary's Hospital,

Background: Cardiofaciocutaneous syndrome (CFCS) is a rare autosomal dominant (AD) condition characterized by cardiac abnormalities, a distinctive craniofacial appearance and short stature. Endocrine manifestations include GH deficiency and precocious puberty. CFCS is part of the RASopathy group including Noonan, LEOPARD, and Costello syndromes. The four associated genes are BRAF (~75%), MAP2K1 and MAP2K2 (~25%), and KRAS (<2%). Most individuals represent new sporadic mutations. To date one family with transmission of an AD germline mutation (*MAP2K2*) through multiple generations has been reported. **Objective and hypotheses:** To describe a sibling pair with CFCS due to gonadal mosaicism. **Method:** Two brothers presented for paediatric management of failure to thrive (FTT) and developmental delay. The parents are healthy, unrelated with one unaffected daughter.

The first boy was born at term with a normal birth weight (50th centile). There was polyhydramnios, intrauterine growth restriction and right sided hydronephrosis on antenatal scans. He had FTT and gastro-oesophageal reflux disease in the neonatal period. A phenotype suggestive of Noonan syndrome with short stature, pulmonary stenosis, global developmental delay, and sensorineural hearing loss became apparent. Fifteen months later his brother was born at term with a normal birth weight (50th centile). Echocardiogram showed concentric left ventricular hypertrophy. He has a similar phenotype to his brother. **Results:** Mutation analysis of the *PTPN11*, *MEK1*, and *MEK2* genes were normal. Mutation analysis of the BRAF gene showed heterozygosity for a pathogenic mutation in BRAF c.770A>G (p.Gln257Arg) in both brothers. Neither healthy parent had the BRAF mutation in their blood DNA. **Conclusion:** The likely explanation for these findings is that one or other parent has mosaicism for the BRAF mutation at least in their gonadal tissue. There could be up to a 50% chance of the parents having another affected child. This is the first reported family with CFCS due to gonadal mosaicism for a pathogenic BRAF mutation.

P1-D1-143

Mitochondrial DNA in Placenta: Associations with Fetal Growth and Superoxide Dismutase Activity

Marta Díaz^{a,b}, Gemma Aragonés^{a,b}, David Sánchez-Infantes^{a,b}, Judit Bassols^c, Francis De Zegher^d, Abel López-Bermejo^c, Lourdes Ibáñez^{a,b}

^aPediatric Endocrinology, Hospital Sant Joan de Deu, University of Barcelona, Esplugues de Llobregat, Barcelona, Spain; ^bCIBERDEM, Instituto de Salud Carlos III, Barcelona, Spain; ^cPediatrics, Hospital Dr. Josep Trueta and Institute for Biomedical Research, Girona, Spain; ^dPediatric Endocrinology, University Hospital, Leuven, Belgium

Background: Prenatal growth restraint associates with increased oxidative stress – as judged by mitochondrial dysfunction – in pregnancies complicated by preeclampsia or diabetes, but it is uncertain whether this is also the case in uncomplicated pregnancies. **Objective and hypotheses:** To assess the link between fetal growth restraint and placental mitochondrial dysfunction, as reflected by changes in mitochondrial DNA content and superoxide dismutase activity. **Method:** Placentas ($n=48$) were collected at term delivery of singleton infants whose gestations were uncomplicated and who were appropriate- or small-for-gestational-age (24 in each subgroup). Placentas were weighed at delivery, and placental tissue was obtained from the maternal side. Placental mitochondrial DNA content was assessed by real-time PCR, placental superoxide dismutase activity by colorimetry, and citrate synthase activity – to determine mitochondrial mass – by the spectrophotometric method. **Results and conclusion:** Placentas of small-for-gestational-age infants had a lower mitochondrial DNA content ($P=0.015$) and a higher superoxide dismutase activity ($P=0.001$) than those of appropriate-for-gestational-age controls. These differences were maintained after normalization of the mitochondrial DNA content by citrate synthase activity. In placentas of small-for-gestational-age infants, there was a negative association between mitochondrial DNA content and superoxide dismutase activity ($r=-0.58$, $P=0.008$), suggesting that fetal growth restraint is accompanied by adaptive changes in mitochondrial function of placenta, also in uncomplicated pregnancies.

P1-D1-144

Genetics of Growth Failure in Small for Gestational Age Children

Romy Keppler, Natascha van der Werft-Grohmann, Karl Otfried Schwab, Ekkehart Lausch

Department of Pediatrics, Freiburg University Hospital, Freiburg, Germany

Background: Small for gestational age (SGA), defined as ≤ -2.0 SDS birth length or weight, is a condition seen in up to 3% of all newborn. Most SGA children catch up height in postnatal life. In a significant number (~10%), however, height remains below the third centile. Recombinant GH therapy is indicated when growth failure continues to 4 years of age. The pathophysiological basis of SGA is complex: monogenic disorders and/or fetal programming by environmental factors like placental-fetal insufficiency all have the same clinical presentation and may act together. Importantly, no predictors are known for the efficacy of GH therapy. Preliminary evidence indicates that a significant fraction of SGA patients may carry genetic aberrations of the IGF hormone-receptor system. **Objective and hypotheses:** In our study, we aimed for a detailed clinical, genetic, and molecular characterization of SGA children refractive to GH therapy. In a cohort of 62 selected SGA children,

we screened for mutations in a gene panel of the GH/IGF1 axis to provide the molecular basis for future functional studies and therapeutic intervention. **Method:** Clinical, biochemical, and molecular characterization of SGA patients by next generation sequencing (NGS) panel on a semiconductor-based platform and Sanger confirmation analysis. **Results:** Our analysis included the genes *CUL7*, *OBSL1*, *CCDC8*, and *FBXW8*, which are associated with 3M syndrome. In seven of 62 SGA patients, recessive mutations in either of these disease genes were found, in one case presenting as compound digenic variants in *CUL7* and *OBSL1*. None of the patients responded to GH therapy. *CUL7* is a ubiquitin ligase of IRS1, a transducer of IGF1 receptor signalling. **Conclusion:** Thus, 3M is a disorder of GH/IGF1 axis that has an unexpectedly high prevalence in non-GH responsive SGA children. Therefore, we performed functional characterization of IGF1 signalling in 3M syndrome as a step towards an adjusted therapy for these patients.

P1-D1-145

Genotype-Phenotype Relationship in Patients with SHOX Region Rearrangements Detected by MLPA in the French Population

Julie Auger^a, Amandine Baptiste^b, Gaëlle Thierry^c, Jean-Marc Costa^d, Mélanie Amouyal^e, Marie-Laure Kottler^f, Renaud Touraine^g, Marine Lebrun^g, Bruno Leheup^a, Sébastien Schmitt^c, Valérie Cormier-Daire^h, Nicolas De Roux^e, Caroline Elie^b, Jean-Paul Bonnefont^h

^aService de Médecine Infantile et Génétique Clinique, Centre Hospitalier Universitaire de Nancy, et U954, Université de Lorraine, Vandoeuvre les Nancy, France; ^bUnité de Recherche clinique/Centre d'Investigation Clinique Paris Centre, Groupe Hospitalier Universitaire Necker-Enfants Malades, Paris, France; ^cCHU Nantes, Service de Génétique Médicale, Nantes, France; ^dUnité de Génétique Moléculaire, Laboratoire Cerba, Saint-Ouen l'Aumône, France; ^eLaboratoire de Biochimie-Hormonologie, Hopital Robert Debré, Université Paris Diderot, Paris, France; ^fService de Génétique, CHU de Caen, INSERM U1075, Caen, France; ^gService de Génétique, CHU de Saint-Etienne, Saint-Etienne, France; ^hUniversité Paris Descartes, IHU IMAGINE et Sce de Génétique Médicale, GH Necker Enfants Malades, Paris, France

Background: *SHOX* and enhancer regions on PAR1 disorders have variable phenotypic consequences such as idiopathic short stature (ISS) and Leri-Weill Dyschondrosteosis (LWD). **Objective and hypotheses:** The aim of this observational multicentric study was to describe phenotypes and genotypes of a large population with mutation on *SHOX* and adjacent regions and to identify a possible phenotype-genotype correlation. **Method:** Phenotypes and genotypes were collected between 2009 and 2013 in seven French laboratories using multiplex ligation-dependant PCR analysis (MLPA) routinely for diagnostic. Sequencing was performed to detect point mutation when MLPA was normal and the clinical description in favor of LWD. **Results:** 205 index cases (IC; 74% females) and 100 related cases (RC; 26% females) where diagnosed with *SHOX* anomalies, 91.3%

with LWD. Median age at diagnosis was 11.7 years in IC (Q1: 9.0; Q3: 15.9) and 38 years in RC (Q1: 14.1; Q3: 43.8). Median height SDS was -2.2 in IC (Q1: -2.9; Q3: -1.7) and -1.8 in RC (Q1: 2.4; Q3: -0.8). Girls were diagnosed earlier than boys (12.7 vs 15.2 years, $P=0.04$), were shorter (-2.4 s.d. vs -2.0 s.d., $P=0.007$) and presented more frequently with Madelung deformity (78.2 vs 21.7%, $P=0.0004$). Genetic anomalies were: 40.3% *SHOX*+/-*PAR1* deletions, 33.7% *PAR1* deletions, 5.9% *PAR1* duplications, 2.0% *SHOX*+*PAR1* duplications, and 18% point mutations. In girls, deletions were more frequently associated with Madelung deformity, short forearm and radiologic anomalies than duplications ($P=0.02$, $P=0.006$, and $P=0.008$ respectively). **Conclusion:** Our study is biological relevant since MLPA allows an easy access of patients to *SHOX* anomalies diagnosis before sequencing and allows identification of duplications and clinical relevant since we show that phenotypes in boys are less severe than in girls.

P1-D1-146

Analysis of GH Receptor Gene Expression in Idiopathic Tall Stature Children

Sara Pagani^a, Giorgio Radetti^b, Cristina Meazza^a, Mauro Bozzola^a

^aIRCCS Fondazione San Matteo, University of Pavia, Pavia, Italy; ^bRegional Hospital of Bolzano, Bolzano, Italy

Background: Growth is a multifactorial process involving genetic, nutritional and other environmental determinants. Because of a major proportion of ultimate stature is dependent upon an intact GH and IGF1 axis, much attention has been devoted to abnormalities related to these growth factors and their signalling pathways. **Objective and hypotheses:** At the tissue level, the action of GH result from the interaction of GH with a specific cell surface GH receptor (GHR). Thus, the ability of GH to exert biological effects is intimately linked to the number and function of GHRs in these tissue. **Method:** In this study we analyzed the GHR gene expression in peripheral blood mononuclear cells of 31 idiopathic tall children (age: 11.59 ± 0.53 years; height: 2.69 ± 0.13 SDS), and 46 age- and sex-matched control children of normal stature (age: 10.57 ± 0.42 years; height: -0.24 ± 0.12 SDS) by Real-time PCR. Normalization and validation of the data will be carried out using GADPH as housekeeping control gene and quantitative Real-time PCR data are expressed as $\text{agGHR}/5 \times 10^5 \text{ agGAPDH}$. We also measured circulating IGF1, by Immulite, in these children in order to investigate if a correlation between levels of this mediator and GHR gene expression level could exist. **Results:** We found a significantly ($P=0.029$) higher GHR gene expression value in tall children (976.85 ± 653.4) compared to control children (86.81 ± 19.48); also IGF1 value was significantly ($P=0.035$) higher in tall children (0.87 ± 0.11 SDS) than in control children (0.06 ± 0.19). **Conclusion:** In conclusion our preliminary data suggest that an up regulation of GHR gene expression could be responsible for the increased sensibility to GH in tall stature children.

P1-D1-147

The Role of SHOX Gene in Idiopathic Short Stature: an Italian Multicenter Study

R Minari^a, A Vottero^a, S Azzolini^b, D Barbaro^c, G Bindì^d, M Bozzola^e, C Burrai^f, G M Cardinale^g, D Cioffi^h, M Cisterninoⁱ, M S Coccioli^j, M Delvecchio^k, E Fabbrizi^l, M Ferrari^m, F Gallarottiⁿ, F Gallo^o, L Ghizzoni^p, M C Maggio^q, B Mainetti^r, R Montinaro^s, G Municchi^t, A Panariello^u, M Parpagnoli^v, L Perrone^w, M Petraroli^x, G Radetti^y, A F Radicioni^z, A Rossodivita^A, MC Salerno^B, S Savastaⁱ, S Seminara^v, L Tafi^c, M Tomat^D, A Tummolo^E, M Wasniewska^F, L Iughetti^G, S Bernasconi^a

^aDepartment of Clinical and Experimental Medicine, University of Parma, Parma, Italy; ^bPediatric Endocrinology and Adolescence Unit, Pediatric Department, University Hospital of Padua, Padua, Italy; ^cASL 6, Section of Endocrinology, Livorno, Italy; ^dUnit of Pediatrics, Pistoia Hospital, Pistoia, Italy; ^eUnit of Auxology, San Matteo Hospital, Pavia, Italy; ^fEndocrinology Unit, University Hospital of Sassari, Sassari, Italy; ^gUnit of Pediatrics, Ferrari Hospital, Casarano (LE), Italy; ^hAuxology and Endocrinology Units, Santobono Pausilipon Hospital, Naples, Italy; ⁱUnit of Pediatrics, San Matteo Hospital, Pavia, Italy; ^jUnit of Pediatrics, Camberlingo Hospital, Francavilla Fontana (BR), Italy; ^kPediatrics Unit, IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo (FG), Italy; ^lUnit of Pediatrics, Civili Hospital, Fermo, Italy; ^mAUSL 1, Department of Pediatrics, Massa Carrara, Italy; ⁿDepartment of Pediatrics, S. Croce e Carle Hospital, Cuneo, Italy; ^oUnit of Pediatrics, Perrino Hospital, Brindisi, Italy; ^pDivision of Endocrinology and Metabolism, Department of Internal Medicine, University of Turin, Turin, Italy; ^qUnit of Pediatrics, G.Di Cristina Hospital, Palermo, Italy; ^rUnit of Pediatrics, AUSL, Forlì, Italy; ^sUnit of Pediatrics, S. Caterina Novella Hospital, Galatina (LE), Italy; ^tPediatric Department, University of Siena, Siena, Italy; ^uDepartment of Pediatrics, San Salvatore Hospital, Pesaro, Italy; ^vDepartment of Pediatrics, Meyer Children Hospital, Florence, Italy; ^wPediatric 2 Unit Department Donna, Bambino e Chirurgia Generale e Specialistica, Second University of Naples, Naples, Italy; ^xUnit of Pediatrics, Santa Maria Nuova Hospital, Reggio Emilia, Italy; ^yDepartment of Pediatrics, Regional Hospital, Bolzano, Italy; ^zDepartment of Experimental Medicine, Sapienza University, Rome, Italy; ^ADepartment of Pediatrics, UCSC, Rome, Italy; ^BDepartment of Pediatrics, Federico II University, Naples, Italy; ^CAUSL 8, Department of Pediatrics, Arezzo, Italy; ^DUnit of Pediatrics, University Hospital of Udine, Udine, Italy; ^EClinical Genetics and Metabolic Diseases Unit, Children Hospital Giovanni XXIII, Bari, Italy; ^FDepartment of Pediatrics, University of Messina, Messina, Italy; ^GDepartment of Pediatrics, University of Modena and Reggio Emilia, Modena, Italy

Background: The short stature homeobox-containing (SHOX) gene, located in the telomeric pseudoautosomal region 1 (PAR1) on the short arm of both sex chromosomes, is important for linear growth. **Objective and hypotheses:** The aim of our study was to evaluate the presence of SHOX gene deletions/point mutations in children with short stature in order to understand the role of SHOX gene in idiopathic short stature (ISS) and estimate its frequency. **Method:** This study supported by the Eli Lilly Italia

and approved by the Italian Society for Pediatric Endocrinology and Diabetes (ISPED), is a multicenter study involving several Italian Pediatric Endocrinology Units. Out of a total number of 184 blood samples received, 128 were from patients with ISS. Genomic DNA was extracted and used for multiplex ligation-dependent probe amplification (MLPA) and sequencing analysis. MLPA was performed using the SALSA MLPA P018-F1 SHOX probemix kit. **Results:** Out of the 160 patients analyzed, ten presented a deletion of the SHOX gene. Among the remaining 150 patients, i) two patients showed deletion of two probes in the putative SHOX regulatory region, ii) one showed deletion of three probes in PAR1, and iii) six showed CRLE2 gene alterations. Three patients had a complex karyotype. Only two patients, with no suggestive clinical signs except for short stature, presented a point mutation in exon 3 (c.367A>G) and in exon 6 (c.701C>T) respectively. The WT genotype was present in 74 patients while for the remaining patients analysis is ongoing. **Conclusion:** If we exclude the patients with Leri-Weill syndrome who presented a SHOX gene deletion in 5.4%, in our cohort of patients with ISS the incidence of SHOX gene point mutations was very low (1.5%), suggesting that the presence of mesomelia, minor skeletal abnormalities, and eventually subtle radiographic signs are essential for requiring genetic analysis properly.

P1-D2-148

Beneficial Effects of Long-term GH Treatment on Adaptive Functioning in Infants With Prader-willi Syndrome[☆]

Sin Lo^{a,b}, Dederieke Festen^a, Roderick Tummers-de Lind van Wijngaarden^a, Philippe Collin^c, Anita Hokken-Koelega^{a,b}

^aDutch Growth Research Foundation, Rotterdam, The Netherlands; ^bSophia Children's Hospital/Erasmus University Medical Center, Rotterdam, The Netherlands; ^cde Koraalgroep, Sittard, The Netherlands

Background: Knowledge about the effect of GH treatment on adaptive functioning in children with Prader-Willi syndrome (PWS) is limited. **Objective and hypotheses:** The aim of this study was to investigate the effect of GH treatment on adaptive functioning in children with PWS. **Method:** Vineland Adaptive Behavior Scale (VABS) was assessed at start, at the end of the RCT, and after 7 years of GH treatment. In the RCT, 75 children (42 infants and 33 prepubertal children) with PWS were included. Subsequently, 53 children were treated with long-term GH 1 mg/m² per day. **Results:** Children with PWS were delayed in their adaptive skills in all domains. Older age and lower intelligence were associated with more delay in adaptive functioning compared to references. On short-term, no effect of GH treatment was found between the GH-treated and untreated group in the RCT, in both infants and prepubertal children. However, after 7 years of GH treatment, there was significantly less delay in adaptive functioning in infants of the former GH treatment group vs the former untreated group in all domains (communication: $P < 0.001$, daily living skills: $P < 0.001$, socialization: $P < 0.001$, motor skills: $P < 0.001$). An earlier age at start

of GH treatment during infancy (0–3.5 years) was associated with less developmental delay in communication ($P < 0.05$), daily living skills ($P < 0.05$), socialization ($P < 0.05$) and motor skills ($P < 0.005$), but in children who started GH treatment above the age of 3.5 years, this association was not found. **Conclusion:** Our study demonstrates a marked delay in adaptive functioning in infants and children with PWS. The earlier GH treatment was started during infancy, the better the adaptive skills on the long-term.

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P1-D2-149

Early Development, Growth and Puberty before and During Treatment of Congenital IGHD

Keren Samuel^{a,b}, Rivka Kauli^{a,b}, Zvi Laron^{a,b}

^aSchneider Children's Medical Centre, Petach-Tikva, Israel; ^bSackler Faculty of Medicine, Tel Aviv University, Tel-Aviv, Israel

Background: Congenital isolated GH deficiency (cIGHD) is a rare genetic disease occurring mostly in consanguineous families. It is caused by hGH-1 gene deletion or GHRH – receptor mutations. **Aim of study:** To collect retrospectively size at birth, developmental mile stones, linear and head growth and pubertal development before and during hGH treatment. **Subjects:** The medical charts of 37/41 patients with cIGHD (21 m, 16 f) contained pertinent data. 34 patients had hGH1 deletions, seven had GHRH-R mutations. **Methods:** The patients were diagnosed, treated, measured and followed in our clinic. **Results:** Mean birth length of 10/37 neonates was 48.3 ± 2.3 (44–50) cm. Mean birth weight of 32/37 neonates was 3290 ± 460 g (2400–4000 g) (m), 3090 ± 480 g, (2300–4000) (f). Neuromotor development was normal or slightly delayed. Age at referral for boys was 5.7 ± 4.2 (0.12–13.6)y and for girls 5.6 ± 3.8 (0.4–13.1)y. Mean age of hGH (35 µg/kg per day) treatment initiation for boys was 7.5 ± 4.8 , (0.8–15.5)y and of girls 6.8 ± 4.4 (0.8–16.6)y. Other changes during hGH treatment were :

Sex	Height SDS		Weight SDS		BMI		Head circumference SD	
	m	f	m	f	m	f	m	f
Before	-3.3	-3.1	-1.8	-1.8	15.8	15.5	-2.6	-2.7
After	-1.68	-1.61	-0.8	-0.48	20.6	20.4	-1.3	-2.3

Puberty was delayed in boys, less so in girls. Mean age of 1st ejaculation of 14 boys was 17.6 ± 2.2 (14–21)y. Mean age at menarche of 14 girls was 13.8 ± 1.2 (12–16)y. All reached full sexual development but the penile and testicular size were below normal.

Conclusion: Earlier initiation and longer duration of hGH treatment resulted in better results, but did not normalize height in all patients.

P1-D2-150

Cognitive Processing Speed as a Function of GH Treatment in Short Stature Children: a Multiple Regression Analysis

John Eric Chaplin^a, Berit Kriström^b, Björn Jonsson^c, Torsten Tuvemo^c, Kerstin Albertsson-Wikland^a

^aSahlgrenska Academy at University of Gothenburg, Institute of Clinical Science, Paediatrics, Gothenburg, Sweden; ^bInstitute of Clinical Science, Umeå University, Paediatrics, Umeå, Sweden; ^cDepartment of Women and Child Health, Uppsala University, Uppsala, Sweden

Background: Cognitive function has been shown to improve following GH treatment in adults. In children born small for gestational age (SGA) IQ scores were found to improve following 24 months of GH treatment. **Objective and hypotheses:** The aim was to observe cognitive function in pre-pubertal, short children with isolated GH deficiency (IGHD) or idiopathic short stature (ISS) during the first 24 months of GH treatment. Cognitive testing was carried out using the Wechsler Scales of Intelligence at baseline, 3, 12, 24 months. **Method:** A prospective, randomized multi-centre study in four centres in Sweden. 99 children (3–11 years/41 GHD; 58 ISS) fulfilling the per-protocol criteria were analysed. Multiple regression models were tested for the GHD and ISS populations. **Results:** A significant increase in full scale IQ ($P < 0.001$; Cohen's $d = 0.63$); performance IQ ($P < 0.001$; Cohen's $d = 0.65$) and Processing Speed Index (PSI) ($P < 0.005$; Cohen's $d = 0.71$) were found in the IGHD population. Only one regression model for PSI could be constructed in the IGHD population. GHmax entered into the model first followed by IGF1SDS at baseline; together they explained 40% (adj. R^2) of the variance. **Conclusion:** An association between GH treatment and increases in IQ variables was found. The greatest improvements were in the non-verbal IQ variables, mostly in the IGHD sub-population with PSI showing the greatest improvement. The regression analysis indicated that the children with the lowest GH levels were the most likely to gain a cognitive benefit from GH treatment.

P1-D2-151

Sequential Measurements of IGF1 Serum Concentrations in Patients With Severe Primary IGF1 Deficiency (SPIGFD) and Growth Failure Treated With Recombinant IGF1 (Increlex®)

Markus Bettendorfer^a, Klaus Kapelari^b, Carolin Kneppo^a, Hermann L Müller^c, Dirk Schnabel^d, Joachim Wölfle^e

^aUniversity Children's Hospital, Heidelberg, Germany; ^bUniversity Children's Hospital, Innsbruck, Austria; ^cUniversity Children's Hospital, Oldenburg, Germany; ^dUniversity Children's Hospital, Berlin, Germany; ^eUniversity Children's Hospital, Bonn, Germany

Introduction: Increlex® was approved as an orphan drug for treatment of growth failure in children and adolescents with

SPIGFD in 2007 with relatively little data available. Therefore sequential measurements of serum IGFI, glucose, insulin and potassium were performed in SPIGFD patients treated with Increlex[®] to evaluate their significance in safety and efficacy. **Design:** Blood samples were taken after meals before and 30, 60, 120, 180 and 360 min after s.c. Increlex[®] injections in seven patients (six male, one female) with idiopathic SPIGFD ($n=5$) or Laron syndrome ($n=2$). 23 sequences were performed at treatment start, dose escalation or dose adjustment. Serum IGFI was measured centrally by RIA (Mediagnost, Reutlingen). Written informed consent was obtained for all patients and the study approved by the ethics committee of Heidelberg University. **Results:** Median IGFI concentrations were 248 ($n=37$), 442 ($n=138$) and 410 ($n=46$) ng/ml for patients receiving 0.04–0.08, 0.08–0.12 or >0.12 mg/kg Increlex[®] respectively. Maximal IGFI concentrations were reached 2–3 h after injections and values were still higher 6 h after injections than at baseline. 21.3% of all and 48% of maximal IGFI concentrations were greater than +2 SDS (adjusted for bone age, retarded by 2.5 years). Height velocity correlated poorly with Increlex[®] dose but significantly with individual maximum serum IGFI (cm/year, $P<0.01$; SDS $P<0.002$). Insulin and glucose did not correlate to IGFI concentrations but serum K⁺ declined after injections (3.1–4.7 mmol/l) and showed a significant negative correlation with IGFI concentrations ($n=203$, $P<0.0001$). **Conclusions:** Sequential measurements of serum IGFI and serum glucose, insulin and potassium in SPIGFD patients may add to optimize and individualize Increlex[®] treatment. IGFI concentrations should be referenced using bone ages which better reflect biological ages. The inverse correlation of IGFI and serum K⁺ concentrations after injections of IGFI has not been reported before and warrants further consideration.

P1-D2-152

Longitudinal Growth of Healthy Preterm Infants Born Below 37 Gestation Weeks

Niina Hyvönen^{a,b}, Panu Kiviranta^c, Antti Saari^c, Leo Dunkel^d, Ulla Sankilampi^c

^aCentral Finland Central Hospital, Jyväskylä, Finland; ^bUniversity of Eastern Finland, Kuopio, Finland; ^cKuopio University Hospital, Kuopio, Finland; ^dQueen Mary University of London, London, UK

Background: The ideal pattern of postnatal growth for preterm infants is unknown. Existing preterm growth charts are based on cross-sectional birth size data, and fail to describe longitudinal growth adequately. **Objective and hypotheses:** We collected longitudinal growth data of healthy preterm infants and constructed growth references from birth to term equivalent age (TEA). Our aim was to describe optimal growth under contemporary neonatal care, in comparison to babies born at same gestational age. **Method:** Data of 3067 infants born at 24–36 gestation weeks (GW) were evaluated. Infants with pre- or postnatal conditions possibly affecting growth were excluded. The final study population consisted of 1303 preterm infants in three GW groups (80, 169, and 1,054 infants born at 24–27, 28–31,

and 32–36 GW, respectively, 55.0% boys) with 3807/3284 weight/length measurements. Data were converted to SD using contemporary birth size references. Longitudinal growth was summarized as median curves for each postmenstrual (PM) week until TEA. Median curves were fitted by a cubic smoothing spline in R-program. **Results:** Birth weight and length varied between –2.0 and 2.0SD. After birth, catch-down growth occurred in all GW groups apart from growth in length in infants born at 32–36 GW. Catch-up growth started after 34 PM weeks. At TEA, the median weights were –2.0/–1.8, –0.60/–0.50, –0.60/–0.50 SD and the median lengths were –2.3/–1.8, –0.40/–0.30, –0.10/0.20SD in boys/girls born at 24–27, 28–31, and 32–36 GW, respectively (Table 1). **Conclusion:** Despite modern neonatal care, still 30–40% of the healthy extremely preterm infants have extrauterine growth failure at TEA when compared to growth *in utero*. However, the ideal growth pattern of extrauterine growth in preterm infants may not be the same as the growth *in utero*.

Table 1

Gestation weeks	Percentage of infants with weight/length < –2SD at TEA	
	Weight (boys/girls)	Length (boys/girls)
24–27+6	36.0/38.9	56.0/36.8
28–31+6	12.3/6.7	8.8/2.3
32–36+6	1.1/2.1	0.4/0.4

P1-D2-153

Intima Media Thickness in Children Treated With GH

Caroline Knop, Barbara Wolters, Nina Lass, Rainer Wunsch, Thomas Reinehr

Vestische Hospital for Children and Adolescents Datteln, Datteln, Germany

Background: The cardiovascular risk for children receiving treatment with GH has hardly been investigated. Therefore, we studied the relationships between GH treatment and carotid intima media-thickness (IMT), which is predictive for the cardiovascular diseases. **Methods:** We measured carotid IMT (four values) in 100 children (mean age 11.6 ± 2.8 years, 63% male) treated with GH (GH deficiency 61%, SGA 31%, Turner syndrome 5%, SHOX deficiency 2%, Prader-Willi syndrome 1%) and 100 age- and gender-matched healthy children without GH treatment. Furthermore, we analyzed blood pressure, lipids, HbA1c, IGF1, and IGFBP3 in children treated with GH. The mean duration of GH treatment was 4.4 ± 2.2 years. This study has a power of 0.95 to detect differences in IMT with an α -error of 0.05 assuming an increase of IMT of 0.05 mm. **Results:** The mean and maximum IMT levels did not differ significantly between children with and without GH treatment (max IMT in median 0.50 (interquartile range (IQR) 0.40–0.50) mm vs 0.50 (IQR 0.40–0.50) mm, $P=0.506$, mean IMT in median 0.43 (IQR 0.40–0.50) vs 0.45 (IQR 0.40–0.50) mm, $P=0.582$). There were no significant differences in the maximal IMT ($P=0.941$) nor in the mean

IMT ($P=0.644$) between the different GH indication groups. In backwards linear regression analyses, mean IMT was significantly related to HbA1c (β coefficient: 0.06, 95% CI ± 0.05 , $P=0.017$, $r^2=0.05$), but not to age, gender, BMI, duration or doses of GH treatment, indication of GH treatment, IGF1, IGFBP-3 nor to any cardiovascular risk factor. Furthermore, maximal IMT was not related to age, gender, BMI, duration or doses of GH treatment, indication of GH treatment IGF1 levels, or to any cardiovascular risk factor. **Conclusions:** We found no evidence that GH treatment is associated with changes in the cardiovascular system measurable by IMT.

P1-D2-154

Clinical and Laboratory Parameters Predicting a Requirement for Reevaluation of GH Status During GH Treatment

Dogus Vuralli, Nazli Gonc, Alev Ozon, Ayfer Alikasifoglu, Nurgun Kandemir

Department of Pediatric Endocrinology, Hacettepe University, Ankara, Turkey

Background: Reevaluation of children diagnosed as GH deficiency (GHD) showed 25–75% of cases had normal GH responses in retests after cessation of therapy. Low reproducibility and high intra-individual variability of the tests are the important problems in diagnosis. Repeat evaluation during treatment may help detect cases with normal GH status earlier. **Objective and hypotheses:** We repeated stimulation tests following the first year of GH treatment to detect patients with normal responses, and analyzed clinical and laboratory features in order to define the characteristic findings that may point to patients who require reassessment of GH status. **Method:** One year after the onset of therapy, GH tests were repeated in 265 patients (MPHD 35.8%; isolated GHD-IGHD 64.2%). Auxological data, pubertal stage, IGF1, IGFBP3 levels, and imaging of the pituitary gland were analyzed. Final heights of cases with normal responses to retests in whom GH treatment was discontinued were recorded. **Results:** Retests showed normal GH response in 40.6% of cases with IGHD. None of the patients with MPHD had a normal response during retest. Puberty or sex steroid priming in prepubertal cases increased the probability of normal response. GH response was normal in 45.6% of IGHD cases with normal pituitary MRI (68/149), and in 4.8% of IGHD cases with structural pituitary defects (1/21). The most important factors distinguishing normal and low responses were peak GH level at diagnosis and height gain in the first year of therapy. Cases with a peak GH <5 ng/ml, and height gain >0.61 SDS are more likely to have permanent deficiency. In cases where GH was >10 ng/ml and therapy was discontinued, final heights were consistent with target heights. **Conclusion:** Patients with MPHD do not need reevaluation for GH status. Patients with IGHD who have the following features should be reevaluated:

- Peak GH >5 ng/ml at diagnosis.
- Normal/hypoplastic pituitary gland.
- Height gain <0.61 SDS during the first year of therapy.

P1-D2-155

Clinical Characteristics and Imprinting Analysis of Chinese Silver Russell Syndrome

Di Wu, Chunxiu Gong, Yang Zhao

Beijing Children's Hospital, Capital Medical University, Beijing, Beijing, China

Background: Silver Russell syndrome (SRS) is an imprinting defect disease. **Objective:** To study clinical characteristics and imprinting defects in Chinese children with SRS. **Methods:** Forty-nine SRS cases were studied retrospectively. Out of these 49 cases, 36 were available to be detected chromosome 11p15 imprinting defects and 21 cases were detected uniparental disomy of maternal chromosome 7 (UPD(7) mat). **Results:** There were 32 boys and 17 girls whose ages ranged from 3 m to 12 y. The main clinical characteristics of these SRS were: i) SGA and postnatal growth retardation (mean height SDS (HT SDS) was 2.25; ii) skeletal malformation including triangular-shaped face, small chin, irregular/crowded teeth, limbs asymmetry and fifth finger clinodactyly. Genetic analysis showed that ICR1 hypomethylation were 22/36 (61.1%) which were following: ten had hypomethylation in chromosome 11p15 imprinting control region 1 (ICR1) of the paternal allele; seven had both hypomethylation in ICR1 and ICR2; five had hypomethylation in ICR1 and hypermethylation in ICR2. And UPD7 (mat) positive is 1/21 (4.8%). Six patients had been treated with GH for 3–24 months. Growth rates ranged from 4 to 10.8 cm/year. **Conclusions:** This study demonstrated that Chinese children with SRS had more growth retardation than bone retardation and had classical skeletal malformation such as triangular faces, and limb asymmetry. Chromosome 11p15 imprinting defects contributed to over 60% of these cases and UPD7 (mat) positive is 4.8%.

P1-D2-156

Gender Difference in Secular Trend in Sweden

Anton Holmgren^{a,b}, Aimon Niklasson^a, Andreas F M Nierop^c, Lars Gelander^a, Agneta Sjöberg^d, Stefan Aronson^b, Kerstin Albertsson-Wikland^a

^aGP-GRC Department of Pediatrics, Institute of Clinical Sciences, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden, ^bDepartment of Pediatrics, Halmstad Hospital, Halmstad, Sweden, ^cMuvara bv, Multivariate Analysis of Research Data, Leiderdorp, The Netherlands, ^dDepartment of Food and Nutrition and Sport Science, University of Gothenburg, Gothenburg, Sweden

Background, objective and hypotheses: By using QEPS, a new mathematic growth model, different components of growth can be analyzed, comparing secular trends of prepubertal and pubertal growth in Swedish birth cohorts born 1974 and 1990. **Materials and methods:** Two birth cohorts followed to adult height (AH) born around 1974 (1691 boys; 1666 girls) and 1990 (1647 boys; 1501 girls) being healthy, Nordic and born term.

A subpopulation of 1974 (1177 boys; 1168 girls) and 1990 (989 boys; 919 girls) with > 10 height measurements evenly distributed during growth phases, and high data quality was used for comparison. The different components of the QEPS-model: (Q)uadratic, (E)xponential, (P)ubertal, and (S)top function were estimated with corresponding maximum values at AH and tempo adjusting 'time scale ratios' of E and P. Multivariate regression analyses were used for explaining the variation of AH. **Results:** Both boys and girls born 1990 compared to those born 1974 had at birth an increased length_{SDS} and weight_{SDS} and during infancy a more rapid growth (shorter E_{timescale}). Boys -1990 had increased prepubertal growth ($P < 0.0001$ for Q_{max} , $Q_{heightscale}$), their pubertal part of growth was not significantly changed. Their AH_{cm} increased 1.3 from 180.4 to 181.7; the variation in AH was explained to 44% by mid parental height (MPH) and birth characteristics, to 72% by adding Q_{max} , to 75% by pubertal onset age and to 99% by P_{max} . Girls -1990 had prepubertal growth increased ($P < 0.05$ for Q_{max} , $Q_{heightscale}$). Their pubertal gain was markedly increased ($P < 0.001$ for P_{max} ; $P_{heightscale}$), and duration decreased whereas mean menarche age remained 12.8 years. AH_{cm} increased 0.7 from 167.6 to 168.3. AH could be explained to 52% by MPH and birth characteristics, to 71% by adding Q_{max} , to 75% by pubertal onset, and to 99% by P_{max} . **Conclusion:** In cohorts born 16-years apart; a secular trend with increased AH_{cm} was found, 1.3 in boys, due to more prepubertal growth, 0.7 in girls, due to more pubertal growth, indicating gender specific underlying regulations.

P1-D2-157

Autoantibodies Against Some Selected Appetite-Regulating Peptide Hormones and Neuropeptides are Present in Serum of Short Children with *Candida Albicans* Colonisation and *Helicobacter Pylori* Infection

Renata Stawerska^a, Elżbieta Czkwianianc^b, Agnieszka Matusiak^c, Joanna Smyczyńska^a, Sylwia Prymus-Kasińska^b, Maciej Hilczer^{a,d}, Magdalena Chmiela^c, Andrzej Lewiński^{a,d}

^aDepartment of Endocrinology and Metabolic Diseases, Polish Mother's Memorial Hospital – Research Institute, Lodz, Poland; ^bDepartment of Pediatrics and Gastroenterology, Polish Mother's Memorial Hospital – Research Institute, Lodz, Poland; ^cDepartment of Immunology and Infectious Biology, Faculty of Biology and Environmental Protection University of Lodz, Lodz, Poland; ^dDepartment of Endocrinology and Metabolic Diseases, Medical University of Lodz, Lodz, Poland

Background: Peptide hormones synthesized in gastrointestinal tract (GI) and adipose tissues, in addition to neuropeptides, regulate growth and body weight in children. The GI microflora (i.e. *Candida albicans* – CA and *Helicobacter pylori* – HP) is an antigenic source. Based on the molecular mimicry hypothesis, intestinal microbe-derived antigens may trigger the production of

autoantibodies cross-reacting with regulatory peptides. **Objective and hypotheses:** The aim of the study was to assess whether in short children with CA colonisation and HP infection the autoantibodies anti selected neuropeptides (Ab anti-NP) are more prevalent than in the control group. **Method:** The study group comprised 77 short (height below – 2.0 SD), children (28 girls and 49 boys), mean age: 10.2 ± 3.6 s.d. years). The control group comprised 14 children with normal height (nine girls and five boys), mean age: 11.9 ± 3.8 s.d. years). In every child, serology to detect HP (anti-HP IgG and IgA) was performed and stool samples were cultured for CA. Moreover, the prevalence of anti-ghrelin, anti-leptin, anti-alfaMSH and anti-orexinA Ab was assessed. **Results:** In 42 out of 77 short children CA and/or HP infections were confirmed. In 15 of them (35.7%) anti-NP Abs were found. In seven out of 14 children from the control group CA and/or HP infections were confirmed and in two of them (28.6%) anti-NP Abs were found. Among short children without CA and/or HP infections, anti-NP Abs were detected in three cases only (out of 35) – 8.5%, while in the control group they were not found. **Conclusion:** In short children with CA colonisation and/or HP infection the incidence of antibodies against neuropeptides is elevated, which may be connected with the molecular mimicry phenomenon. It may be a reason of worse high velocity in these children due to disorders in neuropeptides activity. However, further studies are necessary to elucidate this issue.

P1-D2-158

Effects of Methylphenidate on Growth and Appetite in Attention-Deficit Hyperactivity Patients

Fatih Gurbuza^a, Berrak Bilginer Gurbuz^b, Gonca Celik^c, Veli Yildirim^d, Ahmet Ucakurturk^e, Eda Mengen^a, Ali Kemal Topaloglu^a, Bilgin Yuksel^a

^aCukurova University, Pediatric Endocrinology, Adana, Turkey; ^bNumune Training Hospital, Pediatrics, Adana, Turkey; ^cCukurova University, Pediatric Psychiatry, Adana, Turkey, ^dMersin University, Pediatric Psychiatry, Mersin, Turkey, ^eMersin Gynecology and Pediatric Hospital, Pediatric Endocrinology, Mersin, Turkey

Background: Attention-deficit hyperactivity disorder (ADHD) is one of the most common psychiatric problems of adolescent and childhood. Methylphenidate is a psychostimulant drug in use of attention-deficit hyperactivity treatment as a first choice modality. **Objective and hypotheses:** The aim of this study is to evaluate the levels of leptin, ghrelin and nesfatin-1 in relation to slowdown in growth and poor appetite. **Method:** Total of 89 male children at the age of 7–14 years in two groups was conducted in this study; 48 ADHD and 41 age-matched control group without any disorder. Leptin, ghrelin and nesfatin-1 levels were measured by ELISA together with anthropometric measurements before and after 3 months of the methylphenidate treatment. Additionally, IGF1 and IGFBP3 levels were evaluated. Results were expressed as mean \pm s.d., median (min-max), *n* (number of patients), and percent (%). **Results:** Lack of appetite was observed in 34 of 48 patients together with a significant

decrease in weight, weight SDS, BMI, and BMI SDS values. Interestingly, the height SDS was in trend of decreasing while statistically insignificant. In addition, serum IGF1 levels were remained unchanged while there was a significant decrease in IGF1 levels. Most significant data from the study were increased leptin levels and decreased ghrelin levels after methylphenidate therapy, but no change in nesfatin-1 levels. Interestingly, there was a positive correlation between leptin and nesfatin-1 values after the treatment. **Conclusion:** Methylphenidate therapy in ADHD patients has an effect on lack of appetite via an increase in leptin and decrease in ghrelin levels. Mechanisms underlying the growth and appetite status in ADHD patients in relation to treatment modalities were studied, in first in literature. Future studies could be designed to examine the mechanisms supported by our study.

P1-D2-159

How Precisely can we Measure Increments of Bone Age and Bone Health Index with an Automated Method in Boys with Klinefelter Syndrome?

Hans Henrik Thodberg^a, Martha Bardsley^b, Ania Gosek^b, Judith L Ross^b

^aVisiana, Holte, Denmark; ^bThomas Jefferson University, Philadelphia, Pennsylvania, USA

Background: The assessment of bone age increments is important when monitoring treatment in many conditions in pediatric endocrinology. However, manual rating suffers from significant rater variability. Automated bone age assessment could provide increased precision, and also assess increments of bone health index (BHI) from the same X-rays. **Objective and hypotheses:** To assess the precision of automated assessment of increments of bone age and BHI. **Method:** We included 77 boys aged 4–12 years with Klinefelter syndrome from NCT00348946 with X-rays of left and right hand at five visits separated by 6 months. Half of them were treated with oxandrolone. Bone age and BHI of each hand were obtained with BoneXpert. We assumed the bone age increments in the left and right hands to be the same if the measurements were ‘perfect’, so that the deviation between them is due to the imprecision of the measurements. **Results:** The s.d. between the increments was 0.24 y for bone age and 3.4% for BHI. The precision s.d. of the increment assessed in one hand was therefore 0.17 y and 2.4% respectively, and the precision of a single bone age or BHI assessment was 0.12 y (0.10 y; 0.14 y) 95% confidence, and 1.7% (1.4%; 2.0%) respectively. The results were the same on treated and untreated children and over the four periods. **Conclusion:** Bone age increments can be assessed much more precisely with the automated method than with manual rating. BHI can be determined from the same X-rays with a precision comparable to DEXA. In studies of normal children a typical annual increment in BoneXpert bone age in prepubertal boys is 1.0 y with an s.d. of 0.30 y. This can thus be decomposed in quadrature into 0.17 y from method imprecision and 0.25 y from

biological variation in speed of maturation; thus the automated method is well-suited for studying the relation of speed of maturation to puberty and hormonal development.

P1-D3-160

Final Height and Safety Outcomes in GH-Treated Children with Short Stature Homeobox-Containing Gene (SHOX) Deficiency: Experience From a Large, Multinational, and Prospective Observational Study^{*}

Christopher Child^a, Charmian Quigley^b, Alan Zimmermann^c, Judith Ross^d, Cheri Deal^e, Stenvert Dropf^f, Werner Blum^g

^aEli Lilly and Company, Windlesham, Surrey, UK; ^bSydney Children’s Hospital, Randwick, New South Wales, Australia; ^cEli Lilly and Company, Indianapolis, Indiana, USA; ^dThomas Jefferson University, Philadelphia, Pennsylvania, USA; ^eUniversity of Montreal and CHU Ste-Justine, Montreal, Quebec, Canada; ^fErasmus Medical Centre Sophia, Rotterdam, The Netherlands; ^gUniversity of Giessen, Giessen, Germany

Background: To date, one randomized, controlled, clinical trial (RCCT) demonstrated that GH-treated patients with SHOX deficiency (SHOX-D) had GH-mediated height gain comparable to that of girls with Turner syndrome (TS). No new safety concerns were identified, but the study was limited by small sample size. **Objective and hypotheses:** To examine long-term outcomes in patients treated in standard clinical practice, we assessed final height (FH) and safety outcomes in GH-treated patients diagnosed with SHOX-D using data collected in a multinational observational study (Genetics and Neuroendocrinology of Short Stature International Study (GeNeSIS)). **Method:** At time of analysis, 444 GH-treated patients with SHOX-D (59% girls), diagnosed by genetic analysis and/or investigator assessment, had baseline height available. FH (defined by one or more of the following: closed epiphyses, height velocity <2 cm/year, last bone age >14 years in girls/>16 years in boys) was available for 85 patients (72% girls). **Results:** Mean ± s.d. baseline age was 9.4 ± 3.1 years, and height SDS was -2.4 ± 0.8. Initial GH dose was 0.30 ± 0.10 mg/kg per week, increasing at FH by <10%. FH at age of 15.5 ± 1.5 years and after 4.2 ± 2.3 years of GH treatment was -1.6 ± 1.1 SDS; height gain from baseline was 0.9 ± 1.0 SDS. Of 434 patients with SHOX-D and ≥1 follow-up visit (2.9 ± 1.8 years follow-up), ≥1 adverse event was reported for 89 (21%) compared with 5214/18 929 (28%) for GeNeSIS overall and 710/1663 (43%) for TS. Adverse events reported for ≥1% of patients with SHOX-D were precocious puberty (3%), arthralgia (3%), hypothyroidism (1%), back pain (1%), and headache (1%). One death was reported, but no cases of malignancy or diabetes. IGF1 SDS was -1.8 ± 2.7 at baseline, increased to 1.2 ± 1.8 at 3 years of follow-up, and was >+2 s.d. for 26% of patients at ≥1 follow-up visit. **Conclusion:** In conclusion, ‘real-world’ data from a large cohort of GH-treated patients with SHOX-D support the RCCT findings, with significant height gain to FH and no additional safety concerns. ^{*}Nominated for a Presidential Poster Award.

P1-D3-161

Safety and Effectiveness of Increlex[®] Therapy in Children Enrolled in the Increlex[®] Growth Forum Database in Europe: 4 Years Interim Results[☆]

Michel Polak^a, Joachim Woelfle^b, Peter Bang^c, Aude Sicsic^d, Bruno Fiorentino^d

^aHôpital Necker Enfants Malades, AP-HP, Université Paris Descartes, Paris, France; ^bChildren's Hospital, University of Bonn, Bonn, Germany; ^cFaculty of Health Sciences, Linköping University, Linköping, Sweden; ^dIPSEN Pharma, Boulogne Billancourt, France

Background: The post-authorization registry, European Increlex[®] (Mecasermin (rDNA Origin) injection) growth forum database (EU-IGFD) was initiated in Dec 2008 to collect data on children with growth failure treated with Increlex[®]. **Objective:** To report 4-year safety and effectiveness data. **Methods:** Multicenter, open-label observational study, eCRF data collection. **Results:** As of 30/09/13, 195 patients were enrolled in nine countries: 34% female, 85% severe primary IGF1 deficiency, 81% pre-pubertal, and 67% growth treatment-naïve. Median age at first injection was 10.6 years. Mean (95% CI) treatment duration was 832 (762; 902) days. Median dose was 40 µg/kg BID at treatment initiation, 116 at year 1 and 120 from years 2 to 4. Effectiveness data are summarized by mean (s.d.) of height SDS and Δheight SDS.

Targeted adverse events were reported for 74 pts (39%), the most frequent (≥5%) being hypoglycaemia (18%), lipohypertrophy (11%), tonsillar hypertrophy (7%), headaches (6%), and injection site reactions (6%). Hypoglycaemia tended to be related to age at start of treatment (OR [95% CI]=0.92 (0.83; 1.01) by 1 year increment) and to whether the patient has Laron syndrome

All pts	n ^a	Height SDS	n ^a	ΔHeight SDS
Baseline	176	-3.50 (1.34)		
Year 1	151	-3.18 (1.37)	144	0.34 (0.42)
Year 2	104	-3.14 (1.58)	98	0.59 (0.64)
Year 3	66	-2.76 (1.78)	62	0.73 (0.74)
Year 4	25	-2.87 (1.75)	23	0.92 (0.80)
Treatment-naïve pre-pubertal pts				
Baseline	102	-3.35 (1.34)		
Year 1	71	-2.92 (1.33)	67	0.47 (0.38)
Year 2	41	-3.06 (1.59)	39	0.78 (0.64)
Year 3	22	-2.70 (2.00)	21	0.90 (0.79)

^aData available at the timepoint.

(OR [95% CI]=4.3 (1.8; 10.6)). **Conclusions:** The overall increase in height SDS was confirmed on a larger cohort, with better results in naïve pre-pubertal pts. The safety profile remains consistent with the product labeling.

[☆]Nominated for a Presidential Poster Award.

P1-D3-162

Infliximab Improves Growth in Paediatric Crohn's disease Only if Commenced Early in Puberty or Prior to the Onset of Puberty

Arundoss Gangadharan^a, Joanna Metcalf^b, Dinesh Giri^a, Sharon Irving^c, Marcus Auth^c, Krishnappa Venkatesh^c, Balaji Krishnamurthy^c, Joanne C Blair^a, Mohammed Didi^a

^aDepartment of Paediatric Endocrinology, Alder Hey Children's Hospital, Liverpool, UK; ^bLiverpool Medical University, Liverpool, UK; ^cDepartment of Paediatric Gastroenterology, Alder Hey Children's Hospital, Liverpool, UK

Background: Crohn's disease is a relapsing systemic inflammatory disorder with inflammatory bowel disease (IBD) due to up-regulation of pro-inflammatory cytokines including TNFα. More than 80% of newly diagnosed children present with growth failure Paediatric gastroenterology units in the UK submit data to the UK IBD database which can be accessed when required. One aim of current treatment protocols is to promote growth. Studies on the use of anti-TNFα antibodies like Infliximab have produced conflicting results with respect to growth. **Objective:** To determine whether Infliximab improves growth in paediatric Crohn's disease. **Method:** The UK IBD database was used to identify all Crohn's disease patients at Alder Hey Hospital, Liverpool, UK receiving Infliximab. Age, height, weight, and Tanner pubertal status were determined at commencement of Infliximab, 9–12 months later or at the latest assessment. The height and weight SDS were calculated. Paired *t*-test was employed to compare height and weight SDS at these time points for patients who were at Tanner stages 1–3 vs those at stages 4–5 at commencement of Infliximab therapy. **Results:** There were 31 patients (14 females). The median age at commencement of Infliximab treatment was 14.3 years (range 7.5–17.4 years). The median duration of follow-up since commencement of Infliximab therapy was 1.6 years (0.3–2.0). Twenty patients at Tanner stages 1–3 had median height SDS -0.45 (-1.88 to +1.86), at the second assessment which was significantly better than at commencement of infliximab (median -0.94 (-2.15 to +1.72)), (*P*=0.018). **Conclusion:** Infliximab improves growth in children with Crohn's disease who are in early stages of puberty. Pubertal hormones appear to modulate the TNFα availability for attack by a TNFα antibody.

P1-D3-163

Six Months Follow-Up Pharmacokinetics and Pharmacodynamics Profile of Once-weekly, CTP-modified Human GH (MOD-4023);: phase 2 Dose Finding Study in Children with GHD Deficiency

Gili Hart^a, Zvi Zadik^b, Klaudziya Kradziuc^c, Nataliya Zelinska^d, Oleg Malievsky^e, Violeta Iotova^f, Julia Skorodok^g, Ronit Koren^a, Leanne Amitzi^a, Eyal Fima^a

^aPROLOR Biotech, Nes Ziona, Israel; ^bKaplan Medical Center, Rechovot, Israel; ^c2nd Children City Clinic, Minsk, Belarus; ^dUkrainian Children Specialized Clinical Hospital, Kyev, Ukraine; ^eBashkir State Medical University, Ufa, Russia; ^fUMHAT 'Sv. Marina', Varna, Bulgaria; ^gSt. Petersburg State Pediatric Medical Academy, St Petersburg, Russia

Background: GH replacement therapy currently requires daily injections, which may cause poor compliance, inconvenience and distress for patients. CTP-modified hGH (MOD-4023) is being developed for once-weekly administration in GH deficient (GHD) children. In the present study the longer term pharmacokinetics (PK) and pharmacodynamics (PD) profile of MOD-4023 in GHD naïve children was assessed. **Objective and hypotheses:** To assess the long acting properties of MOD-4023 in GHD children. **Method:** A randomized, comparator-controlled Phase 2 study in up to 56 pre-pubertal, naïve GHD children receiving three MOD-4023 doses as once-weekly regimen (0.25, 0.48, and 0.66 mg/kg per week) or daily hGH (34 µg/Kg per day) as comparator arm subcutaneously. All patients randomized to receive MOD-4023 doses started treatment for 2 weeks with the low MOD-4023 dose and based on the patient's dose allocation, followed by a dose increase to the next dose level every 2 weeks until the final allocated dose was reached. MOD-4023, GH, IGF1, and IGFBP3 concentrations were measured monthly on day 3–4 post administration, PK–PD analysis was conducted. **Results:** MOD-4023 long acting properties were confirmed in GHD children treated for more than 6 months as compared to daily hGH. MOD-4023 demonstrated extended half-life, increased exposure and reduced clearance. Long term monitoring of pre-dose and trough levels indicated no accumulation of MOD-4023. Following 6 months of MOD-4023 treatment IGF1 SDS increased gradually at a dose proportional manner with no indication for excessive levels. As anticipated, IGFBP3 levels increased reaching the normal range but as anticipated, not at a dose sensitive manner. **Conclusions:** MOD-4023 once-weekly injections during the first six months of treatment demonstrated an excellent PK and PD profile supporting once weekly injection in pediatric GHD population and therefore can potentially promote proper growth. In addition, the changes observed in IGF1 and IGFBP3 demonstrate adequate stimulation of the GH–IGF1 axes which were shown to be comparable to that observed with daily hGH treatment.

P1-D3-164

Characterization of MOD-4023 Glycosylation, a CTP Modified Long Acting GH in Advanced Clinical Stages

Oren Herskovitz, Laura Moschovich, Rachel Guy, Yana Felikman, Eyal Fima

PROLOR Biotech, Nes Ziona, Israel

Background: Prolor Biotech, Inc. is a clinical stage public company developing long acting therapeutic proteins utilizing a technology called CTP. The technology involves fusion of the

terminus peptide of hCG, which is a highly O-glycosylated peptide, to the target protein. Manufacturing process was developed to generate a reproducible highly glycosylated CTP-modified long-acting hGH (MOD-4023), which supports a single weekly injection in GH deficient patients. MOD-4023 is manufactured as a non-viscous liquid formulation. **Objective and hypotheses:** Characterization of MOD-4023 drug substance glycosylation profile at different batches. **Methods:** MOD-4023 characterization was carried out by applying various acceptable analytical methods including glycosylation profiling including O-glycan/sialic acid content and serine site occupancy. **Results:** Glycoprofiling analysis of different batches shows that the major O-glycan structure in MOD-4023 is mono-sialylated core 1 with a comparable site occupancy of the O-glycans in MOD-4023 between different batches. Reproducible high levels at different GMP batches of O-glycan and sialic acid content were obtained. The high glycosylation levels contributes to the significant increased hydrodynamic volume of MOD-4023 as compared to recombinant hGH, which results in the elongated circulating time of MOD-4023. **Conclusion:** MOD-4023 manufacturing process is robust, producing a highly O-glycosylated product. Based on these findings and combined with its excellent safety profile and significant prolonged GH activity MOD-4023 has the potential to replace the daily injections of hGH now required for the treatment of GH deficiency with a weekly regimen.

P1-D3-165

Validating Genetic Markers of Response to Recombinant Human GH in Children with GH Deficiency or Turner Syndrome: Results From the PREDICT Validation Study

Pierre Chatelain^a, Adam Stevens^b, Chiara De Leonibus^b, Peter Clayton^b, Jerome Wojcik^c

^aDépartement de Pédiatrie, Université Claude Bernard, Lyon, France; ^bManchester Academic Health Sciences Centre, Royal Manchester Children's Hospital, Manchester, UK; ^cQuartz Bio, Geneva, Switzerland

Introduction: Genetic markers associated with the response to recombinant human GH (r-hGH) have been identified in Growth Hormone Deficiency (GHD) and Turner Syndrome (TS) children in the PREDICT long-term follow-up (LTFU) prospective study (NCT00699855).¹ A validation (VAL) study (NCT01419249) was conducted to confirm association. **Methods/design:** Inclusion criteria for GHD and TS children were identical in the LTFU and VAL studies (GHD defined as peak GH < 10 µg/l, prepubertal at start of r-hGH). The VAL patients were children who had already completed one r-hGH treatment year. Single nucleotide polymorphisms (SNPs) previously associated with GHD or TS (22 with GHD and 26 with TS) were tested. Patients (293 GHD and 132 TS) were recruited from 29 sites in nine countries. For each SNP, growth response (change in height (Ht) SDS or Ht velocity SDS)

was used as the dependent variable in a regression analysis and gender, age, GH peak during provocative testing (GHD), GH dose, distance to target Ht SDS, and mid-parental Ht SDS as covariates. **Results:** There were no differences in gender distribution (GHD) and SNP allele frequencies between LTFU and VAL but age, GH dose and distance to target Ht SDS were lower ($P < 1.2 \times 10^{-5}$), and GH peak (GHD, $P = 5.8 \times 10^{-5}$) and first year growth responses higher in VAL. Using regression modelling to control for differences in the studies and investigate interaction with covariates, we found GHD *SOS1* (rs2888586) associated with change in Ht SDS with GH peak as covariate ($P = 0.0036$ VAL; 6.4×10^{-5} LTFU), and in TS *ESR1* SNP rs2347867 associated with Ht velocity SDS ($P = 0.0304$ VAL; 6.2×10^{-6} LTFU). **Conclusions:** The PREDICT validation study confirmed in an independent cohort the association of genetic markers with growth response to r-hGH treatment in both pre-pubertal GHD and TS children, but only after controlling for covariates.

P1-D3-166

Short-Term Changes in Bone Formation Markers Following GH Treatment in Short Prepubertal Children with a Broad Range of GH Secretion

Björn Andersson^b, Diana Swolin-Eide^b, Per Magnusson^a, Kerstin Albertsson-Wikland^b

^aDivision of Clinical Chemistry, Linköping, Sweden; ^bInstitute of Clinical Sciences, Göteborg, Sweden

Background: GH promotes longitudinal growth and bone modeling/remodeling. The bone formation markers intact amino-terminal propeptide of type 1 procollagen (PINP), bone-specific alkaline phosphatase (BALP), and osteocalcin reflect different stages in bone formation, i.e. proliferation with collagen synthesis, matrix maturation, and mineralization. **Objective:** The purpose was to study the time course of different bone formation markers during GH treatment in prepubertal children with a broad range of GH secretion, and to study the bone markers relation to the first year growth response during GH treatment. **Methods:** The study group, out of clinical trials TRN 89-071, 88-080 and 88-171, comprised 115 short prepubertal children (boys = 99) mean \pm s.d., 9.38 ± 2.16 years, on GH treatment (33 ± 0.06 μ g/kg per day) for 1 year. Samples were taken at baseline, after 1 and 2 weeks, 1 and 3 months, and at 1 year following GH treatment. PINP, BALP, and osteocalcin were measured using the automated IDS-iSYS immunoassay system. **Results:** PINP, BALP, and osteocalcin, increased significantly during GH treatment (Fig). PINP increased after 1 week ($P = 0.00082$), whereas BALP and osteocalcin after 1 month ($P < 0.0001$ and $P = 0.0032$ respectively). PINP levels at 1 and 3 months correlated positively, whereas the osteocalcin levels at 1 week and the percentage change after 1 month correlated negatively with the first year growth response. Using multiple regression analyses, the variance of first year GH growth

response was explained to 16% using bone markers and auxological variables, to 30% after 2 weeks and to 26% after 3 months. Adding IGF1_{SDS} and IGFBP3_{SDS}, only IGFBP3_{SDS} improved the explained variance at start to 40% and at 3 months to 47%. **Conclusion:** The demonstrated short-term increase of the bone formation markers PINP, BALP, and osteocalcin showed different time patterns, reflecting different stages of bone formation, and correlated with the first year increase of growth response during GH treatment.

P1-D3-167

Aromatase Inhibitors in Girls: Anastrozole Combined to an LHRH Analogue is a Safe and Effective Strategy in Girls with Early or Precocious Puberty with Compromised Growth Potential

Dimitrios T Papadimitriou^{a,b}, Eleni Dermizaki^a, Vassiliki Papaevangelou^a, Anastasios Papadimitriou^a

^aDivision of Pediatric Endocrinology, 3rd Department of Pediatrics, Attikon University Hospital, Athens, Greece; ^bDivision of Pediatric Endocrinology, Athens Medical Center, Athens, Greece

Background: Third generation aromatase inhibitors have been used to increase predicted adult height (PAH) in boys but in girls only in McCune-Albright syndrome. **Objective and hypotheses:** We overcame the theoretical concern of secondary hyperandrogenism by combining anastrozole to an LHRH analogue in a 6-year prospective study to test whether the combination therapy could significantly improve PAH compared to inhibition of puberty alone. **Method:** Forty girls with idiopathic precocious or early puberty with PAH < -2 SDS or > 1 SDS lower than their target height (TH) were enrolled for 2 years. Twenty (age 8.85, height -0.16 , and PAH -2.61 SDS) started on anastrozole 1 mg/day p.o. + Leuprorelin/Triptorelin (group-A) and 20 (age 7.29, height $+0.45$, and PAH -1.91 SDS) on LHRH analogue only (group-B). **Results:** Groups A and B did not differ in BMI, TH nor bone age advancement (BAA) $+2.15$ vs $+1.91$ years. Group-B showed a small gain in height (SDS) for bone age $+0.29$ only at 12 months ($P = 0.01$) without further improvement: $+0.22$ at 24 months ($P = 0.24$) from -1.33 at inclusion, whereas group A showed a significant gain $+0.65$ at 12 months ($P < 0.001$) and furthermore $+0.76$ at 24 months ($P < 0.001$) from -1.96 at inclusion. This led to a significant improvement in PAH: $+4.5$ cm in group-A at 12 months vs $+2.23$ cm in group-B ($P = 0.02$) and even more $+6.4$ cm at 24 months vs $+2.05$ cm in group-B ($P = 0.03$), due to the significantly less BAA of group-A despite an initial drop in height velocity. None of the girls in group-A developed clinical/biochemical hyperandrogenism nor ovarian stromal hyperplasia/cysts and all had normal BMD and lumbar spine X-rays checked annually. **Conclusion:** The combination of anastrozole to an LHRH analogue is safe and effective in ameliorating PAH in girls with early or precocious or early puberty compared to inhibition of puberty alone.

P1-D3-168

Abstract withdrawn.

P1-D3-169**Recombinant Human GH Therapy Allows to Reach a Normal Final Adult Height in Coeliac Children with GH Deficiency due to Hypophysitis**

Lorenzo Iughetti^a, Laura Lucaccioni^a, Patrizia Bruzzi^a, Anna Rita Di Biase^a, Anna Maira De Bellis^b, Barbara Predieri^a

^aDepartment of Medical and Surgical Sciences of the Mother, Children and Adults, University of Modena and Reggio Emilia, Modena, Italy; ^bDepartment of Clinical and Experimental Medicine and Surgery 2, Chair of Endocrinology, Second University of Naples, Naples, Italy

Background: Coeliac disease (CD) can be associated with impaired growth in children after a prolonged period of Gluten-free diet (GFD). A small percentage of CD patients does not show catch-up growth during GFD because of GH secretion deficiency (GHD) that could be associated with antipituitary autoantibodies (APA). **Objective and hypotheses:** This study aims to evaluate the efficacy of recombinant human GH (rhGH) therapy on final adult height in children with CD and GHD associated with APA. **Method:** We evaluated six CD patients with persistent growth impairment after at least 1 year from the GFD initiation due to GHD. APA and/or antihypothalamus autoantibodies resulted positive at high titers in four out of six CD-GHD patients. They all started rhGH therapy at the recommended weekly dose of 0.233 ± 0.007 mg/kg s.c. for a mean period of 3.21 ± 1.88 years. **Results:** Patients showed a significant gain of height SDS from the onset of rhGH therapy to the stop time (-2.09 ± 0.35 vs -1.00 ± 0.43 , respectively; $P=0.0277$) and the final adult height SDS, evaluated after 1 year from the rhGH interruption, was within the target height (-0.81 ± 0.69 vs -0.57 ± 0.61 , respectively; $P=0.248$). Results did not change analysing data according to APA and/or AHA status (positive vs negative): final adult height was consistent with the target height. **Conclusion:** In patients with CD and GHD the association of GFD and rhGH treatment seems to allow an adequate catch-up growth and the achievement of height within target height and presence of LYH seems not to influence the efficacy of the treatment.

P1-D3-170**The ZOMATRIP Study: 4 Year Combination Therapy of GH and GnRH_a in Girls with a Short Predicted Adult Height During Early Puberty: Interim Results at the End of the Treatment Phase**

Raoul Rooman^{a,b}, Annick France^b, Claudine Heinrichs^c, Sylvie Tenoutasse^{a,c}, Cecile Brachet^c, Martine Cools^d, Kathleen De Waele^d, Guy Masa^e, Marie-Christine Lebrethon^f

Jean-Pierre Bourguignon^f, Inge Gies^g, Jesse Van Besien^g, Christine De Rycke^a, Jean De Schepper^{a,g}

^aBSGPE, Brussels, Belgium; ^bUniversity Hospital Antwerp, Edegem, Belgium; ^cHopital Universitaire des Enfants Reine Fabiola, Brussels, Belgium; ^dUniversity Hospital Ghent, Ghent, Belgium; ^eJessa Hospital, Hasselt, Belgium; ^fUniversity Hospital Liège, Liège, Belgium; ^gUniversity Hospital Brussels, Brussels, Belgium

Background: A combination of GH and a GnRH agonist is sometimes used to improve adult height in children with a poor height prediction, only few studies support this. **Study design:** In this multicenter study, 24 short girls in early puberty, with a bone age below 12.0 years, an adult height prediction below 151.0 cm and normal body proportions were treated with GH (Zomacton) transjections 50 µg/kg per day and triptorelin (Decapeptyl) i.m. (3.75 mg/month) for 4 years. Bone age was calculated by the Greulich and Pyle method and height predictions were made using the Bailey-Pinneau tables. **Results:** Eighteen girls completed the treatment phase per protocol (PP). Reasons to drop out were: doping concerns in sports (1), no wish to postpone puberty any further after 2.5 or 3 years (3), poor compliance (1), and premature stop of GH injections (1). In the PP group, height (mean \pm s.d.) increased from 130.9 ± 4.0 cm to 154.8 ± 4.7 cm so that height at the end of treatment surpassed their initial predicted height by 7.2 ± 3.9 . Bone age progressed by 2.4 ± 0.5 from 10.4 ± 0.6 to 12.8 ± 0.6 years. Final height prediction after 4 years of treatment (161.8 ± 5.1 cm) increased by 15.1 cm compared to the prediction at the start of treatment (147.6 ± 2.0 cm). Adverse events were restricted to injection site reactions (pain, bruising, and scarring) and common health problems for this age group. Mean IGF1 levels rose from 316 ± 124 to 695 ± 264 ng/ml (after 3 years of treatment). Fasting insulin levels increased 2.5-fold but fasting glucose and HbA1c levels remained within the normal range. **Conclusion:** A 4-year combination treatment of GH and triptorelin was safe and significantly increased height (7.2 cm or 1.2 SDS) above the predicted adult height after the treatment phase. The participants will be followed until final height to determine the full growth promoting effect of this intervention in comparison to historic matched untreated controls.

P1-D3-171**Safety and Efficacy Results of a 6 Month, Randomized, Multi-Center Trial of a Novel Long-Acting rhGH (VRS-317) in Naïve to Treatment, Pre-Pubertal Children with GH Deficiency**

George M Bright^a, Wayne V Moore^b, H Q Nguyen^c, Gad B Kletter^d, Bradley S Miller^{e,f}, Douglas G Rogers^g, Eric Humphriss^a, Jeffrey Cleland^a

^aVersartis, Inc, Redwood City, California, USA; ^bChildren's Mercy Hospital, Kansas City, Missouri, USA; ^cSierra Medical Research, Clovis, CA, USA; ^dSwedish Pediatric Specialty Clinics, Seattle, Washington, USA; ^eUniversity of Minnesota, Minneapolis, Minnesota, USA; ^fAmplatz Children's Hospital, Minneapolis, Minnesota, USA; ^gCleveland Clinic, Cleveland, Ohio, USA

Background: VRS-317, a novel fusion protein of rhGH, was safe and well tolerated in single dose studies of adults and children with growth hormone deficiency (GHD). **Objectives:** Conduct a 6-month study to determine the safety, tolerability, height velocity and IGF1 response in GHD children. **Methods:** 64 subjects were randomized into three arms to evaluate monthly, semi-monthly and weekly dosing. **Results:** At VRS-317 doses equivalent to daily rhGH of $\sim 30 \mu\text{g rhGH/kg}$ per day, repeat dosing of VRS-317 in phase 2a is safe and well tolerated in pre-pubertal GHD children and maintained mean IGF1 increases over baseline and within the therapeutic range without IGF1 overexposure. There have been no related serious adverse events or unexpected adverse events. Other related adverse events have been primarily mild and transient and of the type expected when rhGH is initiated in children naïve to rhGH treatment. With more than 1000 injections administered to date, discomfort at injection sites has been reported in a minority of patients and has been mild and transient. Nodule formation or lipatrophy has not been observed at injection sites. Peak IGF1 levels have been the greatest with monthly dosing but did not exceed 3 s.d. and in only three cases transiently exceeded 2 s.d. Mean trough IGF1 SDS levels remain above baseline at day 30 in all dosing groups. After 2 months of dosing, peak IGF1 levels have been generally higher than after the first dose, suggesting that repeat VRS-317 dosing may augment IGF1 responses. The mean annualized 3-month height velocities from GHD children in the phase 2a were comparable to the historical age-matched controls administered a comparable dose of daily rhGH ($33 \mu\text{g rhGH/kg}$ per day). **Conclusions:** Overall, results to date in the phase 2a clinical trial of GHD children indicate that VRS-317 has a comparable safety and efficacy profile to historical studies of daily rhGH administered at comparable doses.

P1-D3-172

Three-Years Height Outcome During rh-GH Therapy in Subjects with Achondroplasia and Hypochondroplasia

Francesco Massart^a, Francesco Vierucci^b, Mario Miccoli^c, Angelo Baggiani^a

^aMaternal and Infant Department, St Chiara University Hospital of Pisa, Pisa, Italy; ^bPediatric Unit, ASL2 Lucca Hospital, Lucca, Italy; ^cEpidemiology Unit, Department of Experimental Pathology M.B.I.E., University of Pisa, Pisa, Italy

Background: Achondroplasia (ACH) and hypochondroplasia (HCH) are the most common forms of chondrodysplasia. ACH is characterized by rhizomelic short stature, macrocephaly and lumbar lordosis. Because HCH is clinically milder, HCH is often goes unrecognized in childhood but is diagnosed in adult life when disproportionate short stature becomes obvious. **Objective:** Although episodic reports showed the recombinant human GH (rhGH) treatment may improve short-term height (Ht) in HCH or ACH subjects, poor data were available for long-term outcome. **Method and hypotheses:** After thorough search of pertinent English-language literature, meta-analysis evaluation of the efficacy of three-years rhGH treatment in patients with HCH or

ACH were performed. **Results:** In total ACH patients ($n=498$), mean Ht at rhGH therapy start was subnormal (Ht -5.069 SDS (95% CI -5.109 to -5.029)) in all the studies. For ACH subjects, Ht progressively improved during 12 months of rhGH treatment with low catch-up growth ($n=494$; Ht -4.325 SDS (95% CI -4.363 to -4.287); $P<0.0001$). Then, Ht trend of ACH subjects appeared constant until 36-months ($n=60$; -4.124 SDS (95% CI -4.190 to -4.059)). From baseline ($n=494$; SHtR -4.325 SDS (95% CI -4.363 to -4.287); $P<0.0001$), sitting Ht ratio (SHtR) was clinically unchanged in ACH subjects after 2-years ($n=45$; SHtR 64.637% (95% CI 59.931 to 69.344); $P<0.0001$). In HCH sample ($n=74$, pre-treated Ht -3.071 SDS (95% CI -3.779 to -2.362)), rhGH therapy progressively produced similar catch-up growth of ACH group at 12 months ($n=74$; -2.654 SDS (95% CI -3.043 to -2.264); $P<0.0001$); Then, rhGH-induced Ht was progressively improved until 36 months ($n=22$; -2.493 SDS (95% CI -2.870 to -2.116); $P<0.0001$). **Conclusion:** The rhGH treatment progressively improved Ht outcome of short children with ACH and HCH though with minor catch-up growth. Future studies using carefully titrated rhGH protocols are need to optimize treatment protocols.

P1-D1-173

A Girl with Beckwith–Wiedemann Syndrome and Pseudohypoparathyroidism Type 1B, a Unique Example of Multiple Imprinting Defects^{*}

Boudewijn Bakker^{a,b}, Laura Sonneveld^a, Claire Woltering^a, Sarina Kant^{a,b}

^aReinier de Graaf Hospital, Delft, The Netherlands; ^bLeiden University Medical Center, Leiden, The Netherlands

Background: Although multiple imprinting defects have been found by genetic analysis in a subset of patients with Beckwith–Wiedemann Syndrome (BWS), very few patients have been described with both genetic and clinical signs and symptoms of multiple diseases caused by imprinting defects. **Methods:** Methylation analysis of the *KCNQ1OT1* gene was performed by Southern blot, methylation analysis of the *GNAS* region was done by MLPA. **Case report:** A girl presented at the age of 6 months with morbid obesity (BMI $+7.5$ SDS) and a large umbilical hernia. Genetic analysis showed hypomethylation of the *KCNQ1OT1* gene, consistent with BWS. She had no signs of Albright hereditary osteodystrophy (AHO) and calcium homeostasis was normal (Ca. 2.75 mmol/l, P 1.99 mmol/l, and PTH 5.6 pmol/l). At the age of 10 years she presented with fatigue. Laboratory analyses showed marked hypocalcemia with signs of PTH resistance (high PTH, high phosphate, low urine phosphate, and normal alkaline phosphatase). The clinical picture of PTH resistance in a patient without AHO and with a known imprinting defect was suggestive of Pseudohypoparathyroidism Type 1B (PHP1B) due to defective imprinting of the *GNAS* region. Methylation analysis of the *GNAS* complex revealed hypomethylation ($<20\%$) of the *GNAS* exon 1A, *NESPAS* and *GNASXL* loci and 100% methylation of *NESP* locus, consistent with the clinical diagnosis of PHP1B. **Conclusion:** This unique patient shows that

multiple imprinting defects can cause multiple diseases in patients. Furthermore, symptoms of PHP1B may be absent at diagnosis. As prolonged subclinical hypocalcemia can have negative consequences (intracerebral calcifications, cardiomyopathy, etc.), on should be aware of multiple imprinting defects, especially PHP1B, in patients with BWS.

*Nominated for a Presidential Poster Award.

P1-D1-174

Use of Long Acting Somatostatin Analogue (Lanreotide) in Congenital Hyperinsulinism^{*}

Pratik Shah^{a,b}, Clare Gilbert^a, Kate Morgan^a, Louise Hinchey^a, Hannah Levy^a, Roberta Button^a, Niamh Landy^a, Rebecca Margetts^a, Senthil Senniappan^{a,b}, Emma Bascompta Santacreu^c, Carles Morte Marti^c, Carles Celma Lezcano^c, Rakesh Amin^{a,b}, Khalid Hussain^{a,b}

^aGreat Ormond Street Hospital for Children NHS Trust, London, UK; ^bInstitute of Child Health, University College London, London, UK; ^cKymos Pharma Services, S.L., Barcelona, Spain

Background: Congenital hyperinsulinism (CHI) is cause of severe hypoglycaemia. Octreotide (somatostatin analogue), given as four times daily s.c. injections or via a pump, is used as second line treatment in diazoxide unresponsive CHI patients. **Objective and hypotheses:** The aim of our study was to evaluate the use of a long acting somatostatin analogue (Lanreotide) in patients with CHI. **Method:** Diffuse CHI patients above three years of age, on high dose diazoxide (causing side effects) or daily octreotide injections were recruited. The starting dose of Lanreotide was 30 mg 4 weekly. Blood glucose was monitored when weaning diazoxide or octreotide after the first dose of Lanreotide. Every patient had their auxology, endocrinology and ultrasound abdomen monitored. Quality of life questionnaires were also completed. **Results:** 16 children (eight boys and eight girls) with CHI were recruited. The median age was 6 years (3–15 years). Lanreotide treatment was stopped in three children (one had atypical diffuse disease, one had profuse diarrhoea and one showed partial response and developed hypoglycaemic episodes despite increasing the dose to 60 mg). Out of the 13 patients on Lanreotide, ten were on daily octreotide injections and three on diazoxide. Seven (54%) and 5 (38%) patients came off their current treatment within 4 weeks and 8–12 weeks respectively after administering first Lanreotide injection. However, one patient continues to be on a small dose of diazoxide and on Lanreotide dose of 60 mg. Eight patients had mutations in *ABCC8/KCNJ11*. Two children have come off their continuous overnight feeds and five of them are currently being weaned. The preliminary data on the quality of life suggests that both parents and children are very satisfied with the response. **Conclusion:** Lanreotide is safe and an effective alternative to octreotide/diazoxide therapy in patients with diffuse CHI, offering an improved quality of life. However, some children may not show complete response and monitoring of

side effects is equally important. Also, long-term follow-up is necessary in this group of children.

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P1-D1-175

The Role of mTORC1/RagGTPase and IGF1R/mTORC2/Akt Pathways and the Response of Diffuse Congenital Hyperinsulinism to Sirolimus^{*}

Senthil Senniappan^{d,e}, Nina Tatevian^c, Pratik Shah^{a,d}, Ved Bhushan Arya^{a,d}, Sarah Flanagan^b, Sian Ellard^b, Robert Brown^c, Khalid Hussain^{a,d}

^aGreat Ormond Street Hospital, London, UK; ^bUniversity of Exeter Medical School, Exeter, UK; ^cThe University of Texas Health Science Center, Houston, Texas, USA; ^dUCL Institute of Child Health, London, UK; ^eAlder Hey Children's Hospital, Liverpool, UK

Background: The gene expression microarray and morpho-proteomics in diffuse congenital hyperinsulinism (CHI) revealed activation of the mammalian target of rapamycin (mTOR) pathway and the subsequent treatment of four diffuse CHI patients with sirolimus (mTOR inhibitor) avoided pancreatectomy. **Objective and hypotheses:** To further evaluate the mechanism of action of sirolimus by studying the expression of mTORC1/RagGTPase and IGF1R/mTORC2/Akt pathways in pancreases from four infants with diffuse CHI. The clinical use of sirolimus was further studied in eight infants with medically unresponsive diffuse CHI. **Methods:** Immunohistochemical probes were applied to detect the expression of p-mTOR, RagGTPase, p-Akt, insulin, and IGF-1R. Eight infants with diffuse CHI unresponsive to diazoxide and octreotide were trialled on sirolimus therapy. The genetic aetiology in these patients included homozygous *ABCC8* mutation (×3), maternal *ABCC8* mutation (×2), paternal *ABCC8* mutation (×1), compound heterozygous *ABCC8* mutation (×1), and no identified mutation (×1). **Results:** Morphoproteomic analysis revealed overexpression of p-Akt and IGF1R in the islets and plasmalemmal overexpression of p-mTOR and variable cytoplasmic expression of RagGTPase in the acinar cells. Seven out of the eight infants responded to sirolimus therapy and were able to come off intravenous fluids and glucagon infusions thereby preventing the need for a major surgery. Subsequent follow up (range 6–18 months) revealed that the patients were normoglycaemic on sirolimus (with or without concomitant octreotide therapy). One infant with homozygous *ABCC8* mutation did not respond to sirolimus therapy. **Conclusions:** The sirolimus-sensitive mTORC1 pathway is present in the exocrine pancreas and the relatively sirolimus-resistant IGF1R/mTORC2/Akt pathway is overexpressed in the β-cells, thereby suggesting that sirolimus is effective in treating diffuse CHI by reducing the transdifferentiation of exocrine elements to insulin-producing cells. The response to sirolimus is clinically more marked in patients with possible pancreatic β-cell hyperplasia than those with homozygous *K_{ATP}* channel mutations. ^{*}Nominated for a Presidential Poster Award.

P1-D1-176**A Novel Mutation of the PCSK1 Gene with Surprising Enzymatic Consequences Causes Proprotein Convertase 1/3 Deficiency and Consequent Endocrinopathies[☆]**

Abdulsalam Abu-Libdeh^d, Michael Wilschanski^a, Montaser Abbasi^a, Elias Blanco^b, Iris Lindberg^b, Michael Yourshaw^c, Itai Berger^e, Martin Martin^c, Orly Elpeleg^f, David Zangen^d

^aGastroenterology Unit, Division of Pediatrics, Hadassah University Medical Center, Jerusalem, Israel; ^bDepartment of Anatomy and Neurobiology, University of Maryland–Baltimore, Department of Pediatrics, Division of Gastroenterology and Nutrition, Mattel Children's Hospital and the David Geffen School of, California, USA; ^cDivision of Gastroenterology and Nutrition, Department of Pediatrics, Mattel Children's Hospital and the David Geffen School of Medicine, University of California Los Angeles, California, USA; ^dEndocrinology Unit, Division of Pediatrics, Hadassah Hebrew University Medical Center, Jerusalem, Israel; ^eNeurology Unit, Division of Pediatrics, Hadassah University Medical Center, Jerusalem, Israel; ^fMonique and Jacques Roboh Department of Genetic Research, Hadassah, Hebrew University Medical Center, Jerusalem, Israel

Background: Congenital diarrheal disorders (CDDs) are a large group of life-threatening genetic disorders that are frequently difficult to diagnose. We report four siblings from consanguineous kindred with persistent generalized malabsorptive diarrhea hypothyroidism, GH deficiency, intermittent diabetes insipidus, and monogenic obesity. **Objective and hypotheses:** To find the genetic etiology for the CDD in four cases from consanguineous family using homozygosity mapping and whole exom sequencing. **Method:** Following clinical presentation with CDD, homozygosity mapping and whole exom next generation sequencing were followed by Sanger sequencing. The mutated PC1/3 protein enzymatic activity was assayed in HEK293 and Neuro2A cells. **Results:** Homozygosity mapping identified five regions, comprising 337 protein-coding genes that were shared by the three affected siblings. Exome sequencing identified a novel homozygous N309K mutation in the *PCSK1* gene, encoding the neuroendocrine convertase 1 precursor (PC1/3) which was recently reported to cause CDD. The N309K mutation located in an evolutionarily conserved locus was not observed in the ~7500 individuals sequenced by the 1000 genomes and NHLBI exome projects, and was predicted to be deleterious by *in silico* analysis. The *PCSK1* mutation affected the oxyanion hole transition state-stabilizing amino acid within the active site, which is critical to proprotein maturation and enzyme activity. Unexpectedly, the N309K mutant protein exhibited normal prodomain removal and was efficiently secreted from both HEK293 and Neuro2A cells. However, the secreted enzyme showed no catalytic activity, and was not processed into the 66 kDa form in either cell line. **Conclusion:** The novel N309K mutation in the very recently characterized *PCSK1* gene causes a severe decrease in PC1/3 catalytic activity against *in trans* substrates. This results in a dysfunction of enteroendocrine and glandular endocrine cells, causing severe infantile diarrhea and endocrinopathies. Further studies are underway to elucidate the

mechanism for the late onset presentations of different endocrinopathies including monogenic (PC1/3) obesity.

[☆]Nominated for a Presidential Poster Award.

P1-D1-177**Growth and Puberty in Monozygotic Twins with Intra-Twin Birth-Weight Difference**

Sandra Schulte, Bettina Gohlke, Peter Bartmann, Charlotte Prinz, Lioba Wimmer, Joachim Woelfle

University Hospital, Bonn, Germany

Background: Low birth weight, unfavourable intrauterine conditions, and post-natal catch-up growth are associated with a subsequent impact on growth and pubertal development. Start of puberty is genetically determined but might be altered due to environmental influences. **Objective and hypotheses:** In a longitudinal study we observed genetically identical twins with intra-twin birth-weight (bw) differences from birth until puberty. **Method:** 30 pairs of monozygotic twins with intra-twin bw-differences were seen at birth, at a mean of 2.8, 9.8 (prepubertal), and 14.6 (during/post-puberty) years. Birth-weight difference of <1 SDS was defined concordant ($n=14$), bw-difference >1 SDS was defined discordant ($n=16$). **Results:** Auxiology: In all twin-pairs major catch-up growth occurred from birth to 2.8 years followed by only a slight further catch-up during puberty. However, a significant intra-twin difference for height-SDS remained until the age of 14.6 years ($P<0.001$). By analysing concordant and discordant twin-pairs separately, we found that concordant twin-pairs remained significantly different only concerning BMI-SDS ($P<0.05$) but not for height-SDS, whereas in the discordant twins significant differences were observed for height ($P<0.001$) and BMI-SDS ($P<0.01$). Puberty: In 63% (19/30) the former lighter twin started puberty before the co-twin, and in only 26% (8/30) the larger twin started first (3/8: no difference reported). In 77% of the girls (10/13) the former lighter twin experienced menarche before the co-twin. In the majority of the boys voice-breaking occurred earlier in the lighter twin. The observed differences were even more pronounced by analysing only the discordant twin-pairs: all lighter girls showed menarche first (median age 12.5 vs 12.8 years). **Conclusion:** In this special group of monozygotic twins presenting with different intra-twin bw, we could show that bw has an impact not only on growth but also on puberty. The already impaired height in some low bw infants might be additionally diminished by an early starting and fast progressing puberty.

P1-D1-178**Pubertal and Adrenal Hormones in Monozygotic Twins with Intra-Twin Birth-Weight Difference**

Sandra Schulte, Joachim Woelfle, Peter Bartmann, Michaela Hamm, Birgit Stoffel-Wagner, Felix Schreiner, Bettina Gohlke

Background: Low birth weight, unfavourable intrauterine conditions, and post-natal catch-up growth are associated with a subsequent impact on growth, pubertal development, and metabolic disturbances later in life. Although the start of puberty is genetically determined it might be altered due to environmental influences. **Objectives:** In a longitudinal study (birth to final height) we observed growth and pubertal development of genetically identical twins born with a significant intra-twin birth-weight (bw) difference. **Patients/method:** 30 pairs of monozygotic twins with intra-twin bw-differences were seen at birth, at a mean of 2.8, 9.8, and 14.6 years. We defined concordant: bw-difference <1 SDS ($n=14$), discordant: bw-difference >1 SDS ($n=16$). Fasting blood sampling was performed at the mean age of 9.8 (prepubertal) and 14.6 years (during puberty). **Results:** In the majority (67%) of the twin-pairs the former smaller twin started puberty earlier and progressed more rapidly through puberty than the co-twin. The difference was most pronounced in the discordant twins. At 9.8 years a significant intra-twin difference ($P<0.01$) was observed for DHEAS: mean DHEAS: 895 vs 1036 ng/ml in the former smaller co-twin. A similar – although not significant – difference was observed for androstendione (0.43 vs 0.72 ng/ml). At 14.6 years a significant difference was only found for those with discordant bw (1825 vs 2119 ng/ml, $P<0.05$).

A highly significant intra-twin correlation was found for sexual steroids during puberty (correlation-coefficient for testosterone: 0.9, $P<0.001$). However, neither prepubertal nor during puberty significant intra-twin differences were observed for gonadotropins, estradiol, and testosterone. **Conclusion:** The high intra-twin correlation coefficient confirms that puberty and sexual steroids are genetically determined. However, the increased adrenal androgen secretion of the smaller twin during late childhood could have effects on rate of maturation and puberty. This could further impair final height and increase the risk for the polycystic ovary syndrome and insulin resistance.

P1-D1-179

Variations in Protein Expression in Small-For-Gestational-Age Newborns

María Dolores Ruiz-González^a, María Dolores Cañete^b, José Luis Gómez-Chaparro^c, Juan Luis López-Barea^d, Ramón Cañete^e

^aUnidad de Neonatología, Hospital Universitario Reina Sofía, IMIBIC, Córdoba, Spain; ^bGrupo PAIDI CTS-329, IMIBIC, Córdoba, Spain; ^cZBS Alcolea, Córdoba, Spain; ^dDepartamento de Bioquímica y Biología Molecular, Universidad de Córdoba, Córdoba, Spain; ^eUnidad de Endocrinología Pediátrica, Hospital Universitario Reina Sofía, IMIBIC, Córdoba, Spain

Introduction: Small-for-gestational-age newborns (SGA-NB) may present subsequent comorbidities affecting their metabolism, growth, and development. Analysis of changes in serum proteome profile expression in SGA-NB may provide

physiopathological information and help to identify postnatal biomarkers. **Aim:** To compare serum proteome profiles in SGA vs AGA newborns, stratified by gestational age. **Study population and method:** The study included 43 SGA-NB vs 45 AGA-NB, divided into three groups (15 SGA/15 AGA, except group 1 with 13 SGA): Group 1: 29–32 weeks. Group 2: 33–36 weeks. Group 3: ≥ 37 weeks. Inclusion criteria: signed informed consent, birth weight <p10 (Carrascosa) and no genetic abnormalities malformations or congenital infections. Three samples were obtained: at birth, at 7–10 and at 28–30 days. Proteome profiling techniques (2-DE-PAGE) were used to measure protein expression; spots were analysed using the Proteomweaver v 4.0. Software package, and proteins were identified by MALDI-TOFF/TOFF. **Results:** Differences were found for nine proteins, of which eight were identified. Lysophosphatidinositol-acyltransferase 1 (LPIAT1) was detected in SGA-NB in all groups and at all times. Small-ubiquitin-related-modifier 3 (SUMO3) and apolipoprotein-L1 (APOL1) were found in AGA-NB in groups 1 and 3. Ig-lambda-light chain 6 (ICLC6) and putative β -defensin (DEFB108A) were occasionally detected in AGA-NB (at birth and at 1 week). Delayed expression of IGLC2 was noted at 1 week and 1 month in AGA-NB and SGA-NB respectively. The same pattern was recorded for keratin-type-I-cytoskeletal-9 (KRT9), though only in group 1. Coiled-coil-domain-containing-protein 51 (CCDC51), detected only in group 3, was present in all measurements for AGA-NB but only at birth for SGA-NB. **Conclusions:** Differences were recorded between AGA-NB and SGA-NB groups, as a function of sampling time and GA, in protein expression, in glycerophospholipid synthesis, protein sumoylation, lipid transport, antimicrobial activity, and the innate immune response. Expression of LPIAT1 in SGA-NB may represent an adaptive response to protect the brain in an adverse fetal environment.

P1-D1-180

Long-Term Cognitive Effects from Dexamethasone-Treated Pregnancies

Anna Shaytarova^a, Elena Khramova^b, Lyudmila Suplotova^b

^aTyumen Regional Clinic, Tyumen, Russia; ^bTyumen State Medical Academy, Tyumen, Russia

Background: In most countries of the world the prenatal glucocorticoid treatment to prevent reproductive losses in hyperandrogenic pregnancies has been found non-efficient. In Russia, up to present, dexamethasone has been listed in the standard therapy of pregnancy noncarrying risk of hyperandrogenic women. Simultaneously, during the last decade the safety of treating pregnant women with synthetic glucocorticoids has been the subject-matter of intense debates considering possible adverse effects on the foetus and child health in the future. **Objective and hypotheses:** To study possible long-term effects of prenatal glucocorticoid treatment on children cognition. **Method:** From 2002 to 2011 the children of the DEX-exposed group ($n=288$) were examined at the age of early childhood (mean 2.7 years) and up to the primary school age (mean 7.8 years) – ($n=90$). 57 infants of early childhood and 50 children of primary school age

were included into the controls. **Results:** The direct correlation has been established between quotients of intellectual development of primary school-aged children and the initiation date of prenatal dexamethasone treatment. The level of general intelligence of children whose mothers have been treated with dexamethasone in I and II trimesters of pregnancy is considerably lower than the controls. However, negative effects on speech development, verbal reasoning and logical thinking, maturity of volitional attention and ability of organizing and monitoring activities have been found. It is of special interest that examining children of the similar groups at an earlier age has not revealed any differences of their intellectual development. No differences of cognitive development between children, prenatally treated with dexamethasone in III trimester, and the controls have been observed. **Conclusion:** Prenatal DEX-exposure at an early gestation can result in significant negative effects on intellectual abilities of children in the future; the earlier the gestation period of prenatal DEX-exposure, the more well-marked the depression of children cognition.

P1-D1-181

The Prevalence and Outcome of Sex Chromosome Abnormalities Detected Prenatally in Scotland

Angela Lucas-Herald^a, Ruth McGowan^b, Fiona Cann^c, Lorna Crawford^c, Syed Faisal Ahmed^a

^aDepartment of Child Health, Royal Hospital for Sick Children, Glasgow, UK; ^bDepartment of Clinical Genetics, Southern General Hospital, Glasgow, UK; ^cDepartment of Clinical Genetics, Grampian, UK

Background: Prenatal diagnosis (PND) via amniocentesis or chorionic villus sampling may result in the identification of a sex chromosome abnormality, often as an incidental finding. **Objective and hypotheses:** The aims of this study were to ascertain the prevalence of sex chromosome abnormalities detected by prenatal diagnosis in Scotland and to determine the outcomes for these cases. **Method:** A retrospective review of all prenatal karyotypes performed in Scotland between 2000 and 2012 was conducted. Data linkage was performed to obtain information regarding maternal characteristics, pregnancy outcomes and outcomes for affected infants. More detailed outcome data were available for two regions of Scotland: the Grampian and West of Scotland areas. **Results:** Over the 12 years, 28 145 karyotypes were performed in Scotland. Records were available for 27 152 (96%) of these pregnancies. Karyotype abnormalities were identified in 8% of tests performed, with sex chromosome abnormalities being identified in 1% of all tests performed. The commonest sex chromosome abnormality was 45,X. A total of 126 cases of sex chromosome abnormalities were identified prenatally in the West of Scotland and Grampian areas. Of these, 54 (43%) progressed to live birth; 4 (4%) resulted in intrauterine death or stillbirth and 49 (46%) resulted in termination of pregnancy. 71% of pregnancies which progressed to live birth received genetic counselling vs 2% of those which progressed to termination of pregnancy. Of the 54 live births, 26 (48%) of the infants were clinically reviewed

during the study time period. Only 12/54 (22%) in the West of Scotland/Grampian areas had undergone an endocrine review. **Conclusions:** Sex chromosome abnormalities are identified in ~1% of all pregnancies undergoing a prenatal diagnosis. There is a need for an improved structured pathway for prenatal as well as postnatal care of the mother and the offspring.

P1-D1-182

Clinical and Histological Heterogeneity of Congenital Hyperinsulinism Due to Paternally Inherited Heterozygous *ABCC8/KCNJ11* Mutations

Ved Bhushan Arya^{a,b}, Maria Guemes^{a,b}, Azizun Nessa^a, Syeda Alam^b, Pratik Shah^{a,b}, Clare Gilbert^b, Senthil Senniappan^{a,b}, Sarah E Flanagan^c, Sian Ellard^c, Khalid Hussain^{a,b}

^aClinical and Medical Genetics Unit, UCL Institute of Child Health, London, UK; ^bLondon Centre for Paediatric Endocrinology, Great Ormond Street Hospital NHS Foundation Trust, London, UK; ^cInstitute of Biomedical and Clinical Sciences, University of Exeter Medical School, Exeter, UK

Context: Congenital hyperinsulinism (CHI) has two main histological types – diffuse and focal. Diffuse CHI is due to recessive or dominant mutations in *ABCC8/KCNJ11*. Focal disease is due to somatic maternal allele loss of 11p15 in pancreatic β -cells along with paternally inherited germline *ABCC8/KCNJ11* mutation. Fluorine-18 L-3, 4-dihydroxyphenylalanine positron emission tomography computerized tomography (¹⁸F DOPA-PET CT) scan and pancreatic venous sampling (PVS) can differentiate the two subtypes. Heterozygous paternally inherited *ABCC8/KCNJ11* mutations (depending upon whether recessive or dominant acting and occurrence of somatic maternal allele loss) can give rise to variable phenotype. **Objective:** To describe the variable clinical phenotype observed in CHI patients due to heterozygous paternally inherited *ABCC8/KCNJ11* mutations. **Design:** A retrospective case-notes review of the children diagnosed with CHI due to heterozygous paternally inherited *ABCC8/KCNJ11* mutations from 2000 to 2013 was conducted. **Results:** During this period, paternally inherited heterozygous *ABCC8/KCNJ11* mutations were identified in 53 patients. Of these, 18 (34%) either responded to diazoxide or resolved spontaneously. ¹⁸F DOPA-PET CT scan in 3/18 children showed diffuse disease. The remaining 35 (67%) children were diazoxide unresponsive and either had PVS (7) or ¹⁸F DOPA-PET CT (28) to differentiate between focal and diffuse disease. Diffuse disease was found in 12 (23%) and focal disease in 22 (42%) patients. Differentiation between focal and diffuse disease was not possible in one patient studied by PVS. No recurrence of hypoglycaemia was noticed in 95% (20/21) patients with focal CHI after removal of the focal lesion. Diazoxide-unresponsive diffuse CHI patients were managed with either near-total pancreatectomy (9) or octreotide therapy (3). **Conclusions:** Paternally inherited heterozygous *ABCC8/KCNJ11* mutations can manifest as a wide spectrum of CHI with variable PET/histological findings and clinical outcomes. Focal CHI patients were completely cured after surgery.

P1-D1-183**Molecular Genetic Analysis of Czech Patients with Congenital Hyperinsulinism: Surprisingly High Incidence of *HNF1A* Mutations**

Klara Rozenkova^a, Lenka Dusatkova^a, Petra Dusatkova^a, Jitka Kytarova^b, Barbora Obermannova^a, Blanka Rypackova^c, Zdenek Sumnik^a, Jan Lebl^a, Ondrej Cinek^a, Stepanka Pruhova^a

^aDepartment of Pediatrics, 2nd Faculty of Medicine, Charles University in Prague and University Hospital Motol, Prague, Czech Republic; ^bDepartment of Pediatrics, 1st Faculty of Medicine, Charles University in Prague and the General University Hospital in Prague, Prague, Czech Republic; ^cThird Faculty of Medicine, Charles University in Prague, Prague, Czech Republic

Background: Congenital hyperinsulinism of infancy represents a group of heterogeneous disorders characterized by over-secretion of insulin from pancreatic β cells causing severe hypoglycemia. Genetically, congenital hyperinsulinism is caused by defects in key genes regulating insulin secretion (*ABCC8*, *KCNJ11*, *GLUD1*, *GCK*, *HADH*, *SLC16A1*, *UCP2*, *HNF4A*, and non-constantly *HNF1A*). The aim of our project was to perform molecular genetic analysis of Czech patients with congenital hyperinsulinism. **Methods:** Since 2012 we have systematically collected clinical information and DNA samples from 38 Czech patients with the diagnosis of congenital hyperinsulinism (12 females, median age of diagnosis 2 months (0–6 months)). The DNA was investigated by direct sequencing of the above mentioned genes. **Results:** Out of 38 patients, 19 patients have been found to carry a causal mutation in genes associated with congenital hyperinsulinism. We found 11 mutations in *ABCC8* (seven novel), two novel mutations in *KCNJ11* (one patient carries heterozygote mutations in *ABCC8* and in *KCNJ11* simultaneously), one mutation in *GCK*, two novel mutations in *HNF4A* and four mutations in *HNF1A* - G31D, L254Q, R272H, and E508K (mutation L254Q is novel, mutations G31D, R272H and E508K have been described in connection with *HNF1A*-MODY diabetes). Clinically congenital hyperinsulinism caused by mutations in *HNF1A* gene is usually milder, manifests in the first weeks of life (second day, first week, third week respectively), presents with fetal macrosomy and is diazoxide-responsive. The patients are expected to develop *HNF1A*-MODY diabetes later in life. **Conclusion:** In comparison with other genetic studies of larger patient cohorts, the incidence of mutations in *HNF1A* gene in our Czech study is much higher. This confirms the role of *HNF1A* in pathogenesis of congenital hyperinsulinism and emphasizes the importance of molecular genetic testing of *HNF1A* gene in patients presenting with congenital hyperinsulinism.

P1-D1-184**Very Low Birth Weight < 1500 g is Associated with Reduced Sex-Typical Behaviour in Childhood**

Ulla Sankilampi^a, Melissa Hines^b, Annamarja Lamminmäki^a

^aKuopio University Hospital, Kuopio, Finland; ^bUniversity of Cambridge, Cambridge, UK.

Objective: Low birth weight and prematurity are linked to various behavioural outcomes. In addition, preterm (PT) infants show altered maturation of pituitary–gonadal axis, as demonstrated by its pronounced transient activation during the first postnatal months. Given that gonadal steroid hormones shape the basic processes of neural and behavioural sexual differentiation these elevated sex steroids in premature infants might affect the developing brain and alter subsequent sex-typical behaviour. The objective of this study was to determine whether very low birth weight is associated with differences in sex-typical behaviour in childhood. **Methods:** All PT children born with very low birth weight below 1500 g (VLBW), between 1st January 2003 and 31st December 2008 in Kuopio University Hospital, Finland ($n = 143$, mean gestation age, 28.8 weeks), and randomly selected cohorts of PT children with birth weight 1500 g or over ($n = 282$) and FT children ($n = 454$) were included in the study. Sex-typical behaviour was assessed using the 24-item standardized questionnaire, The Pre-school Activities Inventory (PSAI). The final cohort included 449 boys and 430 girls (mean age 4.9 years). **Results:** The mean PSAI score was 68.2 (s.d. 10.3) in all boys and 28.4 (s.d. 10.9) in all girls (in *t*-test *P* for difference < 0.0001). The VLBW boys had less male-typical PSAI scores than other boys (65.7 vs 68.6) and this difference remained significant in the multivariate linear mixed model adjusting for age at assessment, maternal age, exposure to antenatal corticosteroid and number of brothers and sisters ($B = -3.3$, $P = 0.02$). The VLBW girls had significantly less female-typical PSAI scores than other girls (30.8 vs 27.9, $B = 3.5$, and $P = 0.02$). **Conclusion:** Very low birth weight is associated with reduced sex-typical behaviour in childhood in both sexes. This finding may reflect differences in the postnatal hormonal milieu of VLBW infants. Further prospective studies are needed to verify these findings and further examine the mechanisms underlying them.

P1-D3-185**Early-Onset Central Diabetes Insipidus is Associated with *de novo* Arginine Vasopressin-Neurophysin II or Wolfram Syndrome 1 Gene Mutations^{*}**

Anna Elsa Maria Allegria^a, Natascia Di Iorgi^{a,b}, Silverio Perrotta^c, Fulvio Della Ragione^d, Saverio Scianguetta^c, Adriana Borriello^d, Marcella Ferraro^c, Claudia Santoro^c, Annalisa Calcagno^a, Flavia Napoli^a, Marta Giaccardi^{a,b}, Marco Cappa^e, Maria Carolina Salerno^f, Mohamad Maghnie^{a,b}

^aDepartment of Pediatrics, Istituto Giannina Gaslini, Genoa, Italy; ^bUniversity of Genoa, Genoa, Italy; ^cDipartimento della Donna, del Bambino e di Chirurgia Generale e Specialistica, Second University of Naples, Naples, Italy; ^dDepartment of Biochemistry, Biophysics, and General Pathology, Second University of Naples, Naples, Italy; ^eUnit of Endocrinology and Diabetology, Bambino Gesù Children's Hospital, Rome, Italy; ^fPediatric Endocrinology Unit, Department of Translational Medical Sciences, University 'Federico II' of Naples, Naples, Italy

Background: Children with familial forms of central diabetes insipidus (CDI) display polyuria and polydipsia within the first

years of life. **Objective and hypotheses:** We hypothesize that children with an early-onset idiopathic CDI might be affected by *de novo* genetic mutations. **Method:** Eleven children aged between 1 month and 7 years with polyuria and polydipsia and negative family history were enrolled. In nine of them with CDI the arginine-vasopressin-neurophysin II (*AVP-NPII*) and Wolframin genes (*WFS1*) were sequenced. **Results:** Two patients carried a mutation in *AVP-NPII* gene: a heterozygous G to T transversion at nucleotide position 322 of exon 2 (c.322G>T) resulting in a stop codon at position 108 (p.Glu108X), and a novel deletion from nucleotide 52 to 54 (c.52_54delTCC) producing a deletion of a serine residue at position 18 (p.Ser18del) of the AVP pre-prohormone signal peptide. A third patient carried two heterozygous mutations in the *WFS1* gene, each localized on a different allele. The first change was A to G transition at nucleotide 997 in exon 8 (c.997A>G), resulting in the change of valine at position 333 in place of isoleucine (p.Ile333Val). The second novel mutation was a 3 bp insertion in exon 8, c.2392-2393insACG that gave origin to the addition of a third consecutive aspartic acid at position 797 and the maintenance of the correct open reading frame (p. Asp797_Val798insAsp). While no changes of *WFS1* protein level were evidenced in the fibroblasts from healthy individuals as well as from the patient and his parents, a major sensitivity to staurosporine-induced apoptosis was observed only in the fibroblasts of the patient, as demonstrated by increased poly(ADP-ribose polymerase) cleavage and caspase 3 activation. **Conclusion:** Early-onset idiopathic CDI is associated with *de novo* mutations of *AVP-NPII* gene and with never reported hereditary changes of *WFS1* gene. These findings have valuable implications for genetic counseling.

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P1-D3-186

A Boy with Septo-Optic Dysplasia Identified a Mutation in *WDR11*^{*}

Hirohito Shima^a, Yoko Izumi^b, Ikumi Umeki^a, Akimune Kaga^a, Miki Kamimura^a, Akiko Saito-Hakoda^a, Junko Kanno^a, Maki Fukami^b, Ikuma Fujiwara^a

^aDepartment of Pediatrics, Tohoku University School of Medicine, Sendai, Japan; ^bDepartment of Molecular Endocrinology, National Research Institute for Child Health and Development, Tokyo, Japan

Background: Septo-optic dysplasia (SOD) is a rare disorder characterized by optic nerve hypoplasia, anterior midline abnormality and pituitary hormone deficiency. Mutations of several genes are known to cause SOD related condition, such as *HESX1*, *SOX2*, *SOX3*, and *OTX2*, but mutations of *WDR11* has not been reported in SOD. **Objective:** Reporting the first SOD patient identified a mutation in *WDR11*. **Method:** Genomic DNA was extracted from the patient, and 30 genes related to congenital hypopituitarism were screened by the Haloplex method (Agilent Technologies) on a MiSeq next generation sequencer (Illumina). The mutation indicated by the screening analysis was verified by Sanger sequencing. **Case report:** A 2-year-old boy suffered from hypoglycemia, dysopia, and mental retardation. Laboratory data

showed low serum IGF1 (23 ng/ml) and low free T₄ (0.69 ng/dl). We performed TRH test (peak TSH was 17.44 µIU/ml at 120 min and peak PRL was 89.15 ng/ml at 30 min), CRH test (peak ACTH was 68.2 pg/ml at 15 min and peak cortisol was 10.5 µcg/ml at 30 min), GRF test (peak GH was 13.60 ng/mL at 60 min), and arginine stimulation test (peak GH was 5.28 ng/ml at 90 min). A brain MRI confirmed pituitary hypoplasia, agenesis of anterior corpus callosum, and deficit of optic chiasm. We diagnosed him as SOD with combined pituitary hormone deficiency, and the hypoglycemic episodes were disappeared after the replacement therapy with hydrocortisone, L-thyroxine and GH. **Results:** We identified a heterozygous missense mutation in *WDR11* (p.A1076T). The analyses of the family members are currently underway. **Discussion and conclusion:** This is the first case reporting a *WDR11* mutation in SOD patients. *WDR11* was reported to interact with a transcription factor EMX1, and this protein-protein interaction, which was a part of the Sonic-Hedgehog-Patched-Gli signaling pathway, might lead to the malformation of hypothalamus.

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P1-D3-187

Quality of Life and Psychosexual Function in Young Adults with Childhood-Onset Hypopituitarism^{*}

Kung-Ting Kao^{a,b}, Robyn Stargatt^{b,c}, Margaret Zacharin^{a,b}

^aThe Royal Children's Hospital, Melbourne, Victoria, Australia;

^bMurdoch Childrens Research Institute, Melbourne, Victoria,

Australia; ^cLa Trobe University, Melbourne, Victoria, Australia

Introduction: Hypopituitarism has been reported to be associated with lower quality of life (QoL), marital rates, and sex-life satisfaction in adulthood in patients with GH deficiency. Very few studies have examined this in those with childhood-onset multiple pituitary hormone deficiency (COMPHD). **Aims:** To evaluate QoL in adults with COMPHD. **Subjects and methods:** All COMPHD patients aged (≥ 18 years) were identified from medical records and clinics of one author (m zacharin). Questionnaires were mailed to all potential participants who expressed interest. The World Health Organization QoL Questionnaire, Kessler psychological distress scale, Female Sexual Function Index (FSFI) and Male Sexual Quotient (MQ19) were used to measure QoL, psychological distress, female and male psychosexual function respectively. Age- and sex-matched controls were recruited for every patient. **Results:** 92 (68.1%) of 135 potential patients participated, 6 (4.4%) refused, and 37 (27.4%) did not respond. 51 (55%) male, 41 (45%) females, mean age 29.7 years (s.d. 8.18; range 18–61) completed the questionnaire. Mean age at diagnosis was 6.7 ± 4.9 years. COMPHD was caused by brain tumour in 63 (68.5%), congenital hypopituitarism 19 (20.1%), other cancers 7 (7.6%) and trauma 3 (3.3%). COMPHD patients were shorter, more overweight, experienced more behaviour problems in childhood, had significantly less education, more unemployment, lower income and marital rates and less children, compared to healthy controls (*P*<0.005 for each). Although they scored significantly lower

in all QoL domains ($P \leq 0.001$) and psychosexual function (FSFI, $P < 0.001$ and MQ19 $P = 0.004$), there was no difference in reported psychological distress ($P = 0.119$). Subgroup analysis of non-cancer patients showed significantly lower educational achievement ($P = 0.014$) and more behaviour problems in childhood ($P < 0.001$) than controls. There was a non-significant trend for lower QoL and psychosexual function scores in the cancer group. **Conclusion:** Adults with COMPHD have significantly lower QoL compared to normal peers. In addition to medical care of endocrine deficiencies, difficulties in psychosocial and psychosexual function need to be addressed.

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P1-D3-188

Butyrate Stimulates GH Secretion From Rat Anterior Pituitary Cells Via the G-Protein-Coupled Receptors GPR41 and 43

Maria Consolata Miletta^a, Vibor Petkovic^a, Andrée Eblé^a, Roland Ammann^b, Christa E Flück^a, Primus E Mullis^a

^aPediatric Endocrinology, University Children's Hospital, Inselspital, Bern, Switzerland; ^bDepartment of Hematology/Oncology, University Children's Hospital, Bern, Switzerland

Background: Butyrate is a short-chain fatty acid closely related to the ketone body β -hydroxybutyrate (BHB) considered as the major source of energy during prolonged exercise. During fasting, when the liver switches to fatty acid oxidation, a rise in serum GH occurs concomitantly with the accumulation of BHB and short chain fatty acids (SCFA) acetate, propionate and butyrate. Interactions between GH, ketone body and SCFA during the metabolic adaptation to fasting are poorly investigated. In this study, we examined the effect of butyrate, an endogenous agonist for the two G-protein-coupled receptor (GPCR) GPR41 and 43, on non-stimulated and GHRH-induced GH secretion. Furthermore, we investigated a potential role of GPR41 and 43 on the generation of butyrate-induced intracellular Ca^{2+} signal and its ultimate impact on GH secretion. **Methods:** Rat pituitary cell line stably expressing hGHRHR (GC-GHRHR cells) were transiently transfected with wt-hGH and treated with 10 nM GHRH and/or 5 mM butyrate. After 24 h, extracellular GH secretion was measured by DSL-GH ELISA in aliquots of culture medium while intracellular GH expression was analysed by western blot. Relative gene expression of *GPR41* and *43* and the degree of their silencing, obtained by using gene-specific siRNAs, was assessed by qRT-PCR. Measurements of intracellular Ca^{2+} rise were performed before and after *GPR41* and *43* silencing. **Results:** Treatment with butyrate promoted GH synthesis and improved basal and GHRH-induced GH-secretion. By acting through GPR41 and 43, butyrate enhanced intracellular free cytosolic Ca^{2+} . Gene-specific silencing of these receptors led to a partial inhibition of the butyrate-induced intracellular Ca^{2+} rise having a direct impact on extracellular GH-secretion. **Conclusion:** Our results indicate that by acting through GPR41 and 43, butyrate increases both, non-stimulated and GHRH-induced

GH synthesis and extracellular secretion suggesting its local and/or systemic role in the regulation of the GH axis function.

P1-D3-189

An Unusual Case of Hereditary Nephrogenic Diabetes Insipidus Affecting Mother and Daughter

Dinesh Giri^a, Caroline Jones^b, Ian Ellis^c, Renuka Ramakrishnan^a

^aDepartment of Paediatric Endocrinology, Alder Hey Children's Hospital, Liverpool, UK; ^bDepartment of Paediatric Nephrology, Alder Hey Children's Hospital, Liverpool, UK; ^cDepartment of Clinical Genetics, Alder Hey Children's Hospital, Liverpool, UK

Background: Hereditary Nephrogenic Diabetes Insipidus (HNDI) is an uncommon disorder due to a resistance to anti diuretic hormone (ADH) leading to a reduced urinary concentrating ability. The X-linked form is fully expressed in hemizygous male patients, but diabetes insipidus may also present in heterozygous females where it must be distinguished from autosomal and other secondary causes. **Objective and hypotheses:** We report a mother and daughter with HNDI due to a heterozygous deletion in exon 1 of the arginine vasopressin receptor 2 (*AVPR2*) gene not previously described. **Method:** A 5-year-old girl was referred for investigation of polyuria and polydipsia from her infancy. Her mother showed similar symptoms that had not been previously investigated. The patient had a water deprivation test elsewhere at age 3 that was inconclusive. Thyroid, cortisol, renal, and calcium profiles were normal. Hypertonic saline test was performed, the results of which are shown below. **Results:** AQP2 (Aquaporin) and initial *AVPR2* gene sequencing had not identified a mutation, but subsequent quantitative PCR analysis revealed a heterozygous large exon 1 deletion of the *AVPR2* gene. The same deletion was also found in the mother. Results of skewed X inactivation studies on mother and daughter are awaited. The patient's symptoms have significantly improved on appropriate treatment. **Conclusion:** It is important to note that the clinical phenotype of HNDI in a symptomatic female may be due to non-random X chromosome inactivation, thereby allowing expression of the mutant X chromosome. Deletions in *AVPR2* gene with skewed X inactivation, although rare, should be considered in symptomatic females with HNDI.

Table 1. Hypertonic saline test.

Plasma Osmolality (mosm/kg)	Plasma Sodium (mmol/l)	Urine Osmolality (mosm/kg)	ADH (pmol/l)
301	146		
307	149		
313	152	212	> 64
Post Desmopressin			
316	153	243	
313	149	190	

P1-D3-190

A Rare Cause of Diabetes Insipidus: Congenital Proprotein Convertase 1/3 Deficiency

Gülay Karagüzel^{a,b}, Murat Cakir^{a,c}, Ulas Akbulut^{a,c},
Andreas Janecke^{d,e}, Aysenur Ökten^a

^aSchool of Medicine, Karadeniz Technical University, Trabzon, Turkey; ^bDepartment of Pediatric Endocrinology, Trabzon, Turkey; ^cDepartment of Pediatric Gastroenterology, Hepatology and Nutrition, Trabzon, Turkey; ^dInnsbruck Medical University, Innsbruck, Austria; ^eDivision of Human Genetics, Department of Pediatrics, Innsbruck, Austria

Background: Proprotein convertase 1/3 (PC1/3) deficiency, an autosomal-recessive disorder caused by rare mutations in the proprotein convertase subtilisin/kexin type 1 (PCSK1) gene, has been associated with severe malabsorptive diarrhea and certain endocrine abnormalities. **Objective and hypotheses:** To date, only 13 subjects with PC1/3 deficiency have been reported, now we want to report a new patient who was diagnosed PC1/3 deficiency with novel PCSK1 mutation and diabetes insipidus. **Method:** A 3-month-old girl was referred to our clinic for the investigation of severe intractable diarrhea. She was the first child of non-consanguineous parents. She suffered from watery diarrhea started on the ninth postnatal day and persisted despite oral feeding with a variety of whole protein, hydrolysate, and amino acid-based infant formula feeds. There was no improvement on a therapeutic trial of pancreatic enzyme supplements. **Results:** She required long-term parenteral nutrition while establishing her on a hydrolyzed feed. She also had hypernatremic dehydration and polyuria at the presentation. Urine density was low and diabetes insipidus was diagnosed by DDAVP test. Serum levels of corticotropine, cortisol, GH, and free thyroxine were normal, proinsulin was high (81.07 pmol/l). We clinically diagnosed of the patient as PC1/3 deficiency and confirmed the diagnosis by demonstration of a novel homozygous PCSK1 mutation. **Conclusion:** PC1/3 is expressed richly in endocrine cells in the gut, in the arcuate and paraventricular nuclei of the hypothalamus, and β cells of the pancreas, where it has a well-defined role in processing proinsulin. Diabetes insipidus was also reported the previous eight patients. PC1/3 deficiency should be considered in patients presenting with intractable neonatal onset diarrhea and endocrinopathy like diabetes insipidus. Our case extends the clinical and molecular spectrum of human congenital PC1/3 deficiency.

P1-D3-191

Phenotypic Evaluation of Combined Pituitary Hormone Deficiency Caused By *prop1* Gene Mutation in Comparison to Pituitary Deficiency Caused by Other Factors

Agata Zygmunt-Górska^{a,d}, Jerzy Starzyk^{a,d}, Małgorzata Wójcik^{a,d},
Ewa Madetko-Talowska^{b,d}, Piotr Sucharski^{b,d},
Izabela Herman-Sucharska^c, Jacek J Pietrzyk^{b,d}

^aDepartment of Pediatric Endocrinology, Chair of Pediatr, Kraków, Poland; ^bDepartment of Medical Genetics, Kraków, Poland; ^cDepartment of Radiology, Medical College, Jagiellonian University, Kraków, Poland; ^dPolish American Pediatric Institute, Medical College, Jagiellonian University, Kraków, Poland

Background: Combine pituitary hormone deficiency (CPHD) may be caused by many factors. One – them is *PROPI* gene mutation, that causes maldevelopment of GH, TSH, LH, FSH prolactin but not ACTH, producing cells (CPHD-*PROPI*). **Objective and hypotheses:** The details of possible differences between phenotypes of CPHD-*PROPI* and CPHD of other reasons (CPHD-non*PROPI*) are not clear to date. The aim of the study was to determine the frequency of *PROPI* gene mutation in CPHD patients and to compare the phenotypes of patients with CPHD-*PROPI* and CPHD-non *PROPI*. **Method:** In 74 (32 ♀) CPHD patients retrospective analysis of growth pattern, puberty, hormonal function, MRI of pituitary, *PROPI* gene investigation were performed. **Results:** *PROPI* gene mutations were stated in 43 patients (58%), in remaining patients CPHD was caused by other inborn defects. CPHD-*PROPI* in comparison to CPHD-non *PROPI* patients presented with: higher birth weight (0.2 vs -0.3 SDS, $P=0.02$), perinatal abnormalities ($n=1$ vs 17), younger age at diagnosis (4.9 vs 8 years, $P=0.006$), less frequent neonatal hypoglycaemia ($n=0$ vs 4). At the moment of diagnosis there was no significant differences in height SDS (-4.1 vs -4.3), BMI SDS (0.22 vs 0.01). All patients presented with secondary hypothyroidism. The CPHD-*PROPI* in comparison to CPHD-non *PROPI* patients presented higher median GH peak value in stimulation tests (1.26 vs 0.87 ng/ml, $P=0.02$), less frequent secondary adrenal insufficiency (SAI) (2.4 vs 74%), however in 55% of CPHD-*PROPI* patients SAI was recognized at later age. 92% of CPHD-non *PROPI* and all CPHD-*PROPI* patients who reached the age of puberty presented with hypogonadotrophic hypogonadism. In all CPHD-*PROPI* patients MRI examination revealed smaller, normal or enlarged pituitary, ectopy of the posterior lobe in one CPHD-*PROPI* patient and in eight CPHD-non *PROPI*. **Conclusions:** *PROPI* gene mutation is the most common cause of CPHD in Polish population. Analysis of the birth, growth data, as well as hormonal status at the moment of diagnosis may indicate on *PROPI* gene mutation. *PROPI* gene investigation in CPHD patients might be helpful in order to anticipate SAI at later age.

P1-D3-192

Diencephalic Syndrome in Childhood Craniopharyngioma: Results of German Multicenter Studies on 485 Long-Term Survivors of Childhood Craniopharyngioma

Anika Hoffmann^a, Ursel Gebhardt^a, Anthe Sterkenburg^{a,b},
Monika Warmuth-Metz^c, Hermann L Müller^a

^aDepartment of Pediatrics, Klinikum Oldenburg, Oldenburg, Germany; ^bUMCG University Hospital, Groningen, The Netherlands; ^cDepartment of Neuroradiology, University Hospital, Würzburg, Germany

Background: Childhood craniopharyngiomas are known to be associated with an increased risk of excessive weight gain and hypothalamic obesity. Atypical clinical manifestations include the development of a diencephalic syndrome (DS) with a failure to thrive or weight loss. **Objective and hypotheses:** In a retrospective study we analyzed 21 of 485 childhood craniopharyngioma patients (4.3%) who presented with a low weight (<-2 BMI SDS) at time of diagnosis. 11 of 21 patients were identified with a DS due to proven hypothalamic involvement. **Method:** We demonstrate the clinical manifestations of DS and weight development before and after diagnosis in these 11 patients. **Results:** First significant differences between patients with low weight at diagnosis and normal weight patients at diagnosis are observed at an age of 5 years. Within the first 2 years after diagnosis, the weight of DS patients and normal weight patients converge to a similar level. Tumor size does not play a role in respect of DS development. Finally, MRI tumor properties of DS patients were compared with MRI scans of obese patients at time of diagnosis. A trend towards a lower rate of infiltrative growth within the hypothalamus might be related to DS patients. **Conclusion:** DS is a rare clinical manifestation in childhood craniopharyngioma but should be considered as a differential diagnosis in failure to thrive. DS at the time of diagnosis does not prevent weight gain after diagnosis of a craniopharyngioma with hypothalamic involvement.

P1-D3-193

A Novel Mutation of OTX2 Associated with Neonatally Diagnosed Combined Pituitary Hormone Deficiency and Bilateral Microphthalmia

Aya Shimada, Masaki Takagi, Yukihiro Hasegawa

Department of Endocrinology and Metabolism, Tokyo Metropolitan Children's Medical Center, Tokyo, Japan

Background: Orthodenticle/homeobox 2 (OTX2) is a transcription factor implicated in pituitary, ocular, and craniofacial development. To date, more than 30 mutations in OTX2 have been described in congenital hypopituitarism (CH) with or without ocular malformation. The pituitary phenotype varied from isolated GH deficiency (IGHD) to Combined Pituitary Hormone Deficiency (CPHD). However, CPHD including ACTH deficiency from neonatal period was rare among the previous reports. Here, we report a baby with GH, ACTH, TSH, LH, FSH deficiency, and bilateral microphthalmia, carrying a novel missense mutation in OTX2 (R89P). We showed that R89P-OTX2 had markedly decreased transcription activities. **Case:** The patient was born at 40 weeks of gestation to the non consanguineous Japanese parents with a healthy brother. He had congenital cardiac malformations, bilateral microphthalmia, and micropenis. At the age of 5 days, he was diagnosed as having CPHD on the basis of

multiple low anterior pituitary hormones. **Methods:** We sequenced all coding exons and flanking introns of OTX2. As a functional analysis, we performed western blotting, nuclear localization analysis, DNA binding analysis, and transactivation analysis. Transcriptional activity of the mutation was evaluated by using HESX1, POU1F1, and GnRH as promoters. **Results:** We identified a novel heterozygous mutation (c.266G>C, p.R89P) in the patient and in his healthy father. There were no differences in nuclear localization analysis between WT and R89P. In western blot analysis, WT and R89P proteins were detected at expected size in almost same concentrations. DNA binding capacity was lost only in R89P protein. Transactivational studies showed loss of transactivation activity of R89P to all the promoters. A dominant negative effect was observed only in analysis with POU1F1 promoter. **Conclusions:** We showed a case with severe ACTH deficiency from neonatal period, carrying a novel mutation in OTX2. OTX2 mutation carriers exhibit wide phenotypic variability and can present as clinically normal, even though they have a nonfunctional mutation.

P1-D3-194

Type 3 Congenital Multiple Pituitary Hormone Deficiency

Lucia Radillo^a, Antonella Fabretto^a, Alexandru Saveanu^b, Sergio Demarini^a, Giorgio Tonini^a, Elena Faleschini^a, Gianluca Tornese^a, Maria Chiara Pellegri^a

^aInstitute for Maternal and Child Health, IRCCS Burlo Garofolo, Via dell'Istria, 65/1, 34137 Trieste, Italy; ^bUnité Mixte de Recherche, Centre de Recherche en Neurobiologie et Neurophysiologie de Marseille, Faculté de Médecine de Marseille, Aix-Marseille Université, Marseille, France

Background: G, male, was born at 39 GW by emergency CS from non-consanguineous parents. Prenatal US showed growth at lower limits of normal from 22 GW, short limbs and polyhydramnios. Amniocentesis karyotype was 46,XY. At birth weight and length were <3rd percentile, head circumference was between 10 and 25th percentile. At physical examination: short limbs, short neck, cryptorchidism, and microphallus. Early the baby presented mild respiratory distress and a severe episode of hypoglycemia corrected with infusion of D10% through umbilical vein catheter. In the next days he presented recurrent episodes of hypoglycemia treated with corticosteroids and feeding via NG tube and jaundice, that requested prolonged phototherapy. Furthermore he was recalled at hypothyroidism screening. **Objective and hypotheses:** We speculate the hypotheses of congenital hypopituitarism. **Method:** We investigated pituitary gland function and morphology and excluded multiorgan involvement. We initiate also genetic evaluation. **Results:** US and radiological findings were negative for CNS, abdominal, cardiothoracic, and

skeletal abnormalities. Laboratory confirmed lack of all pituitary hormones but no morphologic alterations of pituitary gland and stalk were shown by brain MRI. Considering hypothyroidism, hypogonadism, hypocorticism, and hyposomatotropism diagnosis of congenital multiple panhypopituitarism (CMPHD) was made. G was started on L-thyroxine, hydrocortisone and rhGH replacement therapy. At 3 months he was diagnosed with bilateral sensorineural hearing loss. Genetic evaluations excluded gene PROP1 mutations (cause of CMPHD2) but showed a missense variant (p.Leu196Pro, CTG>GGG) in exon four of LHX3 gene not yet described responsible for CPHD3. Functional studies demonstrated that this variation determines the inability of the synthesized protein to bind to DNA altering activity of the normal protein. **Conclusion:** Because of the same mutation was detected in his mother, asymptomatic, the hypothesis that this mutation alone is the cause of baby G panhypopituitarism was discarded. SNP's array excluded hemizygoty so we speculated that his phenotype may be correlated with a digenic form.

P1-D3-195

Childhood Craniopharyngioma: Changes of Treatment Strategies in Multinational Trials During the Last 12 Years

Anika Hoffmann^a, Monika Warmuth-Metz^b, Ursel Gebhardt^a, Torsten Pietsch^c, Fabian Pohl^d, Rolf-Dieter Kortmann^e, Gabriele Calaminus^f, Hermann L Müller^a

^aDepartment of Pediatrics, Klinikum Oldenburg, Oldenburg, Germany; ^bDepartment of Neuroradiology, University Hospital, Würzburg, Germany; ^cInstitute for Neuropathology, University of Bonn, Bonn, Germany; ^dDepartment of Radiooncology, University Hospital, Regensburg, Germany; ^eDepartment of Radiooncology, University Hospital, Leipzig, Germany; ^fDepartment of Pediatric Oncology, University Hospital, Münster, Germany

Background: Despite high survival rates in childhood craniopharyngioma, prognosis is frequently impaired due to sequelae. Radical surgery was the treatment of choice for several decades. However, even at experienced surgical facilities radical surgery can result in hypothalamic disorders such as severe obesity. **Objective and hypotheses:** We analyzed, whether treatment strategies for childhood craniopharyngioma patients recruited in German studies (KRANIOPHARYNGEOM 2000/2007) have changed during the last 12 years. **Method:** We compared the grade of pre-surgical hypothalamic involvement, the treatment, degree of resection and grade of surgical hypothalamic lesions between patients recruited in KRANIOPHARYNGEOM 2000 ($n=120$; 2001–2007) and KRANIOPHARYNGEOM 2007 ($n=106$; 2007–2012). **Results:** The grade of initial hypothalamic involvement was similar in patients treated 2001–2007 and 2007–2012. The degree of resection was more radical ($P=0.01$) in patients recruited 2001–2007 (38%) when compared with patients

treated 2007–2012 (18%). In patients with pre-surgical involvement of anterior/posterior hypothalamic areas, the rate of hypothalamus-sparing operations resulting in no (further) hypothalamic lesions was higher ($P=0.005$) in patients treated 2007–2012 (35%) in comparison with the 2001–2007 cohort (13%). Event-free-survival rates were similar in both cohorts.

Conclusion: A trend towards less radical surgical approaches is observed, which was accompanied by a reduced rate of severe hypothalamic lesions. Event-free survival was not compromised by this development. Radical surgery is not an appropriate treatment strategy in patients with hypothalamic involvement. Despite previous recommendations to centralize treatment at specialized centers, a trend towards further decentralization was seen. Treatment should be confined to experienced multi-disciplinary teams.

P1-D3-196

Rathke Cleft Cysts and Endocrine Dysfunction in Children

Marie Dupre^a, Frederic Brioude^b, Laurence Berard^b, Blandine Esteve^b, Muriel Houang^b

^aCentre Hospitalier, Valenciennes, France; ^bHopital Armand Trousseau, Paris, France

Background: Rathke's cleft cysts (RCC) are benign lesions of the pituitary gland, remnants of Rathke's pouch. RCC have rarely been reported in children and adolescents and are usually known as asymptomatic but some cases may be associated with hormonal disturbances. **Objective and hypotheses:** The aim of the study was to assess the characteristics and frequency of endocrine disturbances in children with RCC. **Method:** We retrospectively reviewed the clinical, biological, and magnetic resonance imaging findings in all RCC cases seen in our institution from 2004 to 2014.

Results: We found ten children with RCC. Their age ranged from 14 months to 16 years old (median age at 13.5 years) at diagnosis. They were six males and four females. Common features at presentation were headaches (4/10), growth retardation (3/10), polyuria–polydipsia (1/10), visual disturbances (1/10), and one was asymptomatic. Six children had endocrine dysfunctions and four of them multiple deficiencies. There were five GH deficiencies (three complete GH deficiencies and two partial GH deficiencies), two TSH deficiencies, three ACTH deficiencies, one hypogonadotropic hypogonadism, and two diabetes insipidus. All cysts were in intrasellar position and two of them had a suprasellar portion. Five patients had a cyst longer than 10 mm. Two cases underwent surgical procedure; endocrine deficiencies remained after surgery.

Conclusion: RCC are rare and association with hypopituitarism or diabetes insipidus is higher than expected. This association is not fortuitous since we did not find any RCC in all MRI done for central precocious puberty during the last 10 years. Careful follow up is recommended; surgical procedures are required in case of visual disturbances, persistent headaches, or diagnostic doubt.

P1-D3-197**Congenital Nasal Pyriform Aperture Stenosis and Pituitary Abnormalities: Case Series of 20 Patients and a Management Guideline for Early Identification of Pituitary Insufficiency**

Suet Ching Chen^a, Helen McDevitt^b, W Andrew Clement^c, David M Wynne^c, Avril Mason^a, Malcolm Donaldson^a, S Faisal Ahmed^a, M Guftar Shaikh^a

^aPaediatric Endocrinology, Royal Hospital for Sick Children, Glasgow, UK; ^bNeonatology, Royal Hospital for Sick Children, Glasgow, UK; ^cPaediatric Otorhinolaryngology (ENT), Royal Hospital for Sick Children, Glasgow, UK

Introduction: Congenital nasal pyriform aperture stenosis (CNPAS) is an increasingly recognised cause of upper airway obstruction associated with holoprosencephaly, of which solitary median maxillary central incisor (SMMCI) is the least severe form. Studies have described pituitary abnormalities in up to 40%. We aimed to determine the use of baseline endocrine investigations and MRI brain in assessing endocrine dysfunction. **Method:** Retrospective casenote review of patients diagnosed with CNPAS between 2000 and 2013 in a tertiary paediatric unit. **Results:** 20 patients (13F:7M) were identified. Sixteen were diagnosed during the neonatal period at median (range) age 10 (1–28) days of whom 13 needed surgical correction; while four patients diagnosed later at age 2, 6, 11, and 60 months were all managed conservatively. SCMMI was detected in 12 (60%) patients. Baseline endocrine investigations were performed in the neonatal period in 11/20 and MRI brain in 12/20 patients with 7/20 having both. Hypoplastic/ectopic posterior pituitary was identified in one patient, who was also found to have panhypopituitarism. Two patients were referred later for evaluation of short stature and investigated at ages 3 and 5 years, of which one had an ectopic posterior pituitary together with abnormal baseline endocrine function (IGF1). The other patient had normal pituitary on MRI but was also diagnosed with GH deficiency. Available height SDS data at 1 year on 60% of our patients identified both the late-diagnosed GH deficient patients, with SDS of –2.6 to –3.6 respectively. **Conclusion:** CNPAS management requires a multi-speciality and consistent approach in evaluation of the endocrine axis. All CPNAS patients at diagnosis should have MRI brain and baseline endocrine investigations which will allow early recognition and treatment of pituitary insufficiency, minimising surgical risks. Growth monitoring for at least 1 year is recommended as height SDS at 1 year is a good predictor for pituitary function.

P1-D3-198**Spatial and Temporal Expression of Immunoglobulin Superfamily Member 1 in the Rat**

Sjoerd Joustra^a, Onno Meijer^a, Wilma Oostdijk^a, Charlotte Heinen^b, Isabel Mol^a, Gabriela Carreno^c, Daniel Bernard^d, Nienk Biermasz^a, Ans van Pelt^b, Geert Hamer^b, Jan Maarten Wit^a, Gerry Wagenaar^a

^aLeiden University Medical Center, Leiden, The Netherlands;

^bAcademic Medical Center, Amsterdam, The Netherlands; ^cInstitute of Child Health, London, UK; ^dMcGill University, Montréal, Canada

Background: Loss-of-function of immunoglobulin superfamily member 1 (IGSF1) results in an X-linked syndrome of central hypothyroidism and macroorchidism, variable prolactin deficiency, GH deficiency, increased fat percentage, and delayed puberty testosterone rise despite normal timing of testicular growth. **Methods:** We investigated the spatial and temporal expression of IGSF1 at the protein and mRNA levels in fetal, neonatal, and adult Wistar rats, using immunohistochemistry, *in situ* hybridization, and real-time RT-PCR. **Results:** High levels of IGSF1 immunoreactivity are observed in various brain regions, including the hypothalamus, but not to any major extent in neuroendocrine cell populations. In the pituitary gland, IGSF1 is present in the Pit1-cell lineage comprising GH, TSH, and PRL-producing cells, but not in gonadotrophs and corticotrophs. In the testis, IGSF1 is present in Sertoli cells (during stages XIII–VI of the seminiferous epithelium) and Leydig cells. IGSF1 is strongly expressed in hepatocytes of the fetal liver, but decreases rapidly to background levels immediately after birth. In all cases, specificity of IGSF1 protein expression was corroborated by *in situ* hybridization and real-time RT-PCR for the *Igsf1* mRNA. **Conclusion:** Our results represent the first comprehensive characterization of the organ specific expression profile of IGSF1 in rats. The expression pattern in the pituitary gland suggests a role for IGSF1 in the regulation of TSH, GH, and prolactin secretion. In contrast, IGSF1 is not expressed in the gonadotrophs, suggesting that the delayed puberty and macroorchidism in IGSF1-deficient patients is not likely caused by gonadotropin deficiency, but rather by a local defect in the testis. This is consistent with our observations that IGSF1 is expressed in Sertoli cells (the number of which determines testicular size) and Leydig cells. The results of our study provide a framework that will facilitate future research on IGSF1 function in relevant cells and tissues.

P1-D1-198**Stability Conditions in Estradiol Matrix Patches; *in vitro* Studies for Application in Pediatrics^{*}**

Carina Ankarberg-Lindgren^a, Theo Sas^{b,c}

^aDepartment of Pediatrics, Institute of Clinical Sciences, The Sahlgrenska Academy, Göteborg Pediatric Growth Research Center, University of Gothenburg, Göteborg, Sweden; ^bDepartment of Pediatrics, Albert Schweitzer Hospital, Dordrecht, The Netherlands; ^cDepartment of Pediatric Endocrinology, Sophia Childrens' Hospital/Erasmus Medical Center, Rotterdam, The Netherlands

Background: We have previously shown that estradiol (E₂) matrix patches for adults could be cut in smaller pieces to administer low doses for pubertal induction in girls with hypogonadism. With a slow increase of the patch size during a few years, serum E₂ levels in normal girls undergoing puberty can be closely mimicked. **Objective and hypotheses:** To evaluate storage conditions once the patch has been cut. **Method:** Evorel[®]

25 µg/24 h patches, containing 1.55 mg E₂ (Janssen-Cilag Pharmaceutica N.V.) were used. The outer edge on the patch were cut off and discarded. Two equal 1/7 pieces were cut, following the dotted marks on its cover. The cut pieces were stored together with the remaining patch in its foil-lined sachets, either i) in a plastic bag in the fridge ii) in a plastic bag in room temperature or iii) just in room temperature. Storage for 0, 1, 2, 3, 4, and 5 days were compared. E₂ concentrations were determined in the entire patch. The patch pieces were put in a solution of n-hexan + ethylacetat and put on slow shaking for 1 h. The samples were thereafter serially diluted. After totally evaporated, reconstitution was made using zero calibrator. E₂ concentrations were determined by RIA with lower limit of detection 9 pmol/l and total coefficient of variation (CV) 9% for 250 pmol/l and above. **Results:** In average, 1/7 pieces of a 25 µg patch contained 190 µg E₂ which is 86% of the expected concentration. No difference was seen either in time of storage, the way the patches were stored or how many edges that were cut. Total CV was 3%. **Conclusion:** *In vitro*, the patches contained the expected drug amount E₂ and it was evenly distributed on the surface. After cutting the patches, E₂ concentrations were stable for at least 5 days storage.

*Nominated for a Presidential Poster Award.

obesity, insulin resistance (IR), dyslipidemia, and hypertension. **Results:** TS patients had higher BMI and waist circumference than controls. The frequencies of dyslipidemia and homeostasis model assessment-insulin resistance were similar in both groups. The TS patients had higher hsCRP, BNP, and ANP levels than controls. Plasma aldosterone/PRA ratios, IGF1 and IGFBP3 were similar in both groups. The carotid intima media thickness (cIMT) SDS, β-index SDS, incremental modulus of elasticity (E_{inc}) SDS, BSA corrected left ventricle mass (LVM) and left atrial volume (LAV) were higher, and the distensibility coefficient (DC) SDS was lower in TS than in controls. Multivariable regression analyses revealed that BNP was associated with cIMT SDS (β=0.17, P<0.01), β-index SDS (β=0.62, P<0.01), E_{inc}SDS (β=0.39, P=0.01) and DC SDS (β=-0.53, P<0.01). IGF1 SDS was associated with cIMT SDS (β=0.81, P<0.01), β-index SDS (β=0.17, P<0.01). hs-CRP was associated with DC SDS (β=-0.16, P<0.01). LVM and LAV were not associated with biomarkers and IGF1 after correction for multiple testing. When the whole cohort was evaluated, TS was independently associated with increased arterial stiffness indices and LVM (β=0.420-3.424, P<0.001 for all, R²=0.06-0.31). **Conclusions:** Normotensive TS 'dippers' have increased arterial stiffness when compared with healthy controls. BNP, and to a variable extent, IGF1 and hsCRP are associated with arterial stiffness indices in TS. Further research is needed to clarify the causal inference of these relationships.

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P1-D1-199

Associations of Vascular Biomarkers and the Somatotrophic Axis with Carotid Ultrasound and Echocardiography Findings in Relation to Turner Arteriopathy[☆]

Ahmet Uçar^a, Fahrettin Özb^b, Firdevs Baş^a, Hüseyin Oflaz^b, Kemal Nişli^c, Melike Tuğrul^a, Feyza Darendeliler^a, Nurçin Saka^a, Şükran Poyrazoğlu^a, Rüveyde Bundak^a

^aPediatric Endocrine Unit, Istanbul Medical Faculty, Istanbul University, Istanbul, Turkey; ^bDepartment of Cardiology, Istanbul Medical Faculty, Istanbul University, Istanbul, Turkey; ^cPediatric Cardiology Unit, Istanbul Medical Faculty, Istanbul University, Istanbul, Turkey

Background: Turner syndrome (TS) is associated with increased arterial stiffness. To date, factors associated with the ontogeny of Turner arteriopathy remain unclear. **Objective and hypotheses:** To assess the associations of vascular biomarkers and the somatotrophic axis with arterial stiffness indices, and left heart size, in normotensive 'dipper' TS. **Method:** Sixty-one patients with uncomplicated normotensive 'dipper' TS with a mean age of 12.6 years (range 6.6-27.3 years) and body surface area (BSA) of 34 matched with healthy peers were compared using carotid ultrasound and echocardiography. We derived several arterial stiffness and left heart size indices in association with vascular biomarkers (high sensitivity C-reactive protein (hsCRP), B-type natriuretic peptide (BNP), Atrial NP (ANP), aldosterone/plasma renin activity (PRA)), IGF1 and IGF-binding protein 3 after correcting for metabolic syndrome antecedents such as

P1-D1-200

Testes in Infants with Prader-Willi Syndrome: hCG Treatment, Surgery, and Histology

Nienke Bakker^{a,b}, Katja Wolffenbuttel^c, Leendert Looijenga^d, Anita Hokken-Koelega^{a,b}

^aDutch Growth Research Foundation, Rotterdam, The Netherlands; ^bDepartment of Endocrinology, Children's Hospital Erasmus MC-Sophia, Rotterdam, The Netherlands; ^cDepartment of Urology, Children's Hospital Erasmus MC-Sophia, Rotterdam, The Netherlands; ^dDepartment of Pathology, Josephine Nefkens Institute, Erasmus MC, Daniel den Hoed Cancer Center, Rotterdam, The Netherlands

Background: Boys with PWS often have unilateral or bilateral cryptorchidism. Prospective studies on the treatment of cryptorchidism in boys with PWS are lacking and there is no treatment consensus among pediatricians and urologists. **Objective and hypotheses:** We hypothesized that hCG treatment would lead to a scrotal position of the testes in infants with PWS and cryptorchidism. We therefore evaluated the effects of hCG treatment on testis position. Additionally, in those who underwent orchidopexy, testis histology was studied. **Method:** Sixteen infants with PWS, median (IQR) age 1.6 (1.2-1.8) years, were treated with hCG. After a positive stimulation test, hCG treatment was initiated (i.m. injection, 250-500 IE depending on age, twice a week for

6 weeks). hCG treatment was defined successful in case of bilateral stable scrotal position. Indications for operation were patent processus vaginalis, non-scrotal position or non-stable scrotal position of the testis. **Results:** Thirty-one of the 32 testes had a non-stable scrotal position. All infants had a positive response to hCG stimulation, with a median (IQR) testosterone increase of 5.9 (3.5–9.2) nmol/l. After hCG treatment, 83% of testes had descended to a lower position, with seven to a stable scrotal position, not requiring orchidopexy. Twenty-four testes underwent orchidopexy. Of 15 obtained biopsies, two had more than 60% of germ cells, three between 30–60%, seven <30% and three showed Sertoli cell-only syndrome. In infants who underwent orchidopexy, a younger age, higher Inhibin B levels and higher testosterone increase after hCG stimulation were associated with a higher number of germ cells. Testis position before hCG treatment was not associated with the number of germ cells. **Conclusion:** Our study demonstrates that HCG treatment in infants with PWS results in a lower testis position. Nevertheless, 13 infants required an additional orchidopexy. A younger age at orchidopexy is associated with a better histological outcome.

P1-D1-201

The Effect of 17 β -Estradiol on Uterine Volume in Young Women with Turner Syndrome: a 5-Year Randomized Controlled Clinical Trial

Line Cleemann^a, Kirsten Holm^a, Eva Fallentin^b, Nini Møller^c, Bent Kristensen^{d,e}, Sven Oluf Skouby^f, Per Leth-Esbensen^d, Eva Mosfeldt Jeppesen^g, Claus Gravholt^{h,i}

^aDepartment of Pediatrics, 3400 Hillerød, Denmark; ^bDepartment of Radiology, 2100 Copenhagen, Denmark; ^cDepartment of Gynecology and Obstetrics, 3400 Hillerød, Denmark; ^dDepartment of Radiology, 3400 Hillerød, Denmark; ^eDepartment of Medical Research, 3400 Hillerød, Denmark; ^fDepartment of Gynecology and Obstetrics, 2730 Herlev, Denmark; ^gDepartment of Pediatrics, 2730 Herlev, Denmark; ^hDepartment of Endocrinology and Internal medicine, 8200 Aarhus, Denmark; ⁱDepartment of Molecular Medicine, 8200 Aarhus, Denmark

Background: The majority of Turner syndrome (TS) girls need exogenous estrogen treatment to induce normal uterine growth. The optimal estrogen treatment protocol has not been determined. **Objective and hypotheses:** To compare the effect of two different dosing regimens of oral 17 β -estradiol on uterine size with the hypotheses that most girls with TS would benefit from a higher dose. **Method:** A double-blind 5-year randomized controlled clinical trial. The lower-dose group (LD group) took 2 mg 17 β -estradiol/day orally and placebo. The higher-dose group (HD group) took 2 + 2 mg 17 β -estradiol/day orally. 20 young TS women (19.2 \pm 2.5 years, range 16.0–24.9) participated. The uterus was investigated by transabdominal ultrasound (US) and magnetic resonance imaging (MRI) at baseline and yearly thereafter. **Results:** A steep increase in uterine volume within the first

years of treatment was seen in the HD-group by US and MRI. In the LD-group a less steep increase in uterine volume was seen by US. In the LD-group the uterine volume remained statistically unchanged from baseline and throughout the follow-up by MRI. The uterine volume remained stable in the subsequent years in both groups and at the last visit there were no significant differences in uterine volume between the two groups. **Conclusion:** High dose oral 17 β -estradiol induces a steeper increase in uterine volume in young women with TS within the first years of treatment compared to the lower dose. The uterine growth potential seems to be the same in most young women with TS making the duration of treatment equally significant as estrogen dose.

P1-D1-202

Genetic Markers in the Study of Chromosome Y in the Population of Girls with Turner Syndrome

Aleksandra Rojek^a, Monika Obara-Moszynska^a, Barbara Rabska-Pietrzak^a, Zofia Kolesinska^a, Marek Niedziela^{a,b}

^a2nd Chair of Pediatrics, Department of Pediatric Endocrinology and Rheumatology, Poznan University of Medical Sciences, Poznan, Poland; ^bDepartment of Pediatric Endocrinology and Rheumatology, Karol Jonscher's Clinical Hospital, Poznan, Poland

Background: Turner syndrome (TS) is one of the most common chromosomal aberrations resulting from the total or partial absence of one of the X chromosomes in all or a portion of cells. The presence of genetic material of the Y chromosome in TS patients is a risk factor for the development of gonadoblastoma or dysgerminoma. **Objective and hypotheses:** The aim of this study was to detect the presence of fragments of the Y chromosome, which increase the risk of malignant transformation, what may be important for further proper surgical treatment (prophylactic gonadectomy). **Method:** The studies were carried out using PCR method. The following genetic markers located in different regions of the Y chromosome were selected: *SRY*, *DYZ1*, *DYZ3*, *DYS132*, *ZFY1*, and *TSPY* gene located within *GBY* locus (gonadoblastoma locus on the Y chromosome), which is associated with the risk of the development of gonadoblastoma. Additionally, *SRY* gene was analyzed using direct sequencing method. **Results:** 46 patients with TS with different karyotypes were studied. Based on our study 17/46 patients were chromosome Y-positive. 8/17 in the Y-positive group had Y chromosome in their karyotypes and they underwent prophylactic gonadectomy. In two of them histopathologic examination revealed gonadoblastoma and dysgerminoma respectively. Both patients were *TSPY*-positive. 9/17 in the Y-positive group did not have Y chromosome in their karyotypes. In 9/46 patients *TSPY* gene was detected – two of them did not have Y chromosome in their karyotypes. *SRY* gene was identified in 8/46 patients and there was no mutation in the coding region in these *SRY*-positive patients. **Conclusion:** Molecular tests for the presence of genetic material of the Y chromosome in TS, particularly *TSPY*, are the most precise ones, and may serve as important tools in cancer risk prediction as well as risk of virilization.

P1-D1-203

Girls with Turner Syndrome have Normal Muscle Force but Decreased Muscle Power

Ondrej Soucek^a, Jan Lebl^a, Jana Matyskova^a, Marta Snajderova^a, Stanislava Kolouskova^a, Stepanka Pruhova^a, Zdenek Hlavka^b, Zdenek Sumnik^a

^a2nd Faculty of Medicine, Charles University in Prague and Motol University Hospital, Prague, Czech Republic; ^bFaculty of Mathematics and Physics, Charles University in Prague, Prague, Czech Republic

Background: Turner syndrome (TS) associates with decreased bone mineral density and altered bone geometry, a risk factors leading to increased fracture rate. Although hypogonadism or SHOX gene haploinsufficiency are the probable causes, the exact mechanism remains unclarified. Particularly, the muscle function as an important determinant of bone strength has yet not been widely studied in TS patients. **Objective and hypotheses:** We hypothesised there is muscle dysfunction leading to increased fracture rate in TS patients. Secondary aim was to describe the influence of pubertal stage, hormone therapy, fracture history, and genotype. **Patients and methods:** All TS patients consenting to the study and having no other chronic disease were included (60 patients, age 13.7 ± 4.5 years). Age- and weight-specific Z-scores of muscle parameters were calculated based on control group of 432 healthy girls. A Leonardo Mechanograph[®] Ground Reaction Force Platform was used to assess muscle force (F_{max}) by the multiple one-legged hopping test and muscle power (P_{max}) by the single two-legged jump test. Muscle function parameters were related to body weight (F_{max}/BW) and body mass ($P_{max}/mass$), respectively. **Results:** While F_{max} and F_{max}/BW were normal (mean weight-specific Z-scores 0.11 ± 0.77 , $P=0.27$, and 0.046 ± 0.62 , $P=0.55$), P_{max} and $P_{max}/mass$ were decreased in TS patients (Z-scores -0.93 ± 1.5 , $P<0.001$, and -0.45 ± 0.58 , $P<0.001$) compared to healthy controls. The muscle function parameters were not significantly influenced by menarcheal stage, hormone therapy duration, fracture history or genotype (linear regression adjusted for age, weight and height; $P>0.05$ for all). **Conclusion:** F_{max} , a principal determinant of bone strength, is normal in TS. The changes in bone quality and structure in TS are thus not likely related to inadequate mechanical loading but rather represent a primary bone deficit. A decreased P_{max} represents a novel indicator of impaired muscle coordination in TS.

P1-D1-204

The Influence of GH Treatment on the Oral Disposition Index in Turner Syndrome Girls and in GH Deficient Children: 8 Years of Follow-Up

Federico Baronio^a, Fiorenzo Lupi^b, Benedetta Sirola^a, Silvia Longhi^b, Federica Tamburrino^a, Emanuela Scarano^a, Laura Mazzanti^a, Giorgio Radetti^b

^aDepartment of Medical and Surgical Sciences, Pediatric Unit, Program of Endocrinology, University of Bologna and S. Orsola-Malpighi Hospital, Bologna, Italy; ^bDepartment of Pediatrics, Regional Hospital of Bolzano, Bolzano, Italy

Background: GH has been shown to influence glucose homeostasis through a negative effect on insulin sensitivity followed by a compensatory increase of insulin secretion. However it has been recently reported, in animals and in humans, that GH might stimulate insulin secretion also through a direct effect on the growth and on the function of the pancreatic β cell. **Objective and hypotheses:** To study longitudinally the insulin sensitivity (HOMA-S), the insulin secretion (IGI) and the capacity of the β cell to adapt to the insulin sensitivity (oral disposition index (ODI)) in a group of girls affected by Turner's syndrome (TS) and in a group of GH deficient children (GHD). **Method:** We studied 92 TS (9.7 ± 2.95 years) and 99 GHD (62 m, 37 f) (8.9 ± 3.5 years for a median period of 7.32 years (range 2.04–13) in TS and 7.7 years (range 3.4–14.7) in GHD). Every year the children underwent an OGTT which was employed to calculate the HOMA-S ($1/((\text{insulin} \times \text{glucose})/22.5)$), the insulinogenic index, IGI ($\Delta I30/\Delta G30$) and the ODI (disposition index = $\text{HOMA-S} \times \text{IGI}$). **Results:** In TS no significant changes over the years were observed in term of HOMA-S, IGI, or ODI. On the contrary, in GHD children, despite HOMA-S remaining unchanged, an increase of IGI (1.25 ± 1.28 vs 2.35 ± 2.38) and ODI (0.57 ± 0.68 vs 1.23 ± 1.68) was observed, which became significant after 6 years of treatment. There was no difference before GH treatment between GHD and TS regarding HOMA-S, IGI, and ODI but IGI became significantly higher in GHD after 6 years. **Conclusion:** Our results suggest a positive influence of GH treatment on the β cell secretory capacity in children with GH deficiency, while no effect was observed in those (TS) with normal GH secretion. A different sensitivity to GH might explain the differences.

P1-D1-205

Abstract withdrawn.

P1-D1-206

Hypogonadotropic Hypogonadism in Patients with Congenital Adrenal Hypoplasia due to *NROB1* (*DAX1*) Mutations: Phenotype/Genotype Relationship

Marek Niedziela^a, Aleksander Jamsheer^b, Maciej R Krawczynski^b, Monika Obara-Moszynska^a, Aleksandra Rojek^a

^aDepartment of Pediatric Endocrinology and Rheumatology, Poznan University of Medical Sciences, Poznan, Poland; ^bDepartment of Medical Genetics, Poznan University of Medical Sciences, Poznan, Poland

Background: X-linked AHC is a rare disorder of the adrenal cortex caused by mutations in the *NROB1* (*DAX1*) gene. *NROB1* (*DAX1*) encodes for an orphan nuclear hormone receptor which is expressed in the adrenal, gonad, hypothalamus, and pituitary glands. Hypogonadotropic hypogonadism (HH) is the most frequently observed puberty disorder (absent or delayed puberty) caused by mutations in the *NROB1* (*DAX1*) gene and is due to impaired gonadotropin synthesis and release. **Objective and hypotheses:** The aim of the study was to investigate the clinical phenotype of eight boys with congenital adrenal hypoplasia due to *NROB1* (*DAX1*) mutation. **Results:** All patients had postnatally normal male external genitalia and intrascrotal location of testes apart from one unilateral (patient 6) due to anatomical reasons. A novel mutation c.315G>A (W105X) was detected in patients 1 and 2, a known mutation c.A1319>T (p.Asn440Ile) in exon 2 in patient 3 and a known mutation c.C109>T (p.Gln37X) in exon 1 in patient 4. In patients 5 and 6 a *NROB1* (*DAX1*) gene deletion coexisted with the deletion of other neighbouring genes (*MAGE* family genes). Boys 7 and 8 presented coexisting HH but manifested later by lack of spontaneous puberty. Patient 7 had a novel mutation c.T1118>G (p.Ile373Ser) in exon 1 and patient 8 had a known mutation c.A1319>T (p.Asn440Ile) in exon 2. Both had low peak levels of LH and FSH on LHRH test and both had GH deficiency. **Conclusion:** The onset of adrenal failure in our patients was in neonatal period but the clinical manifestation of HH was in pubertal period in two of them (six patients are still prepubertal). To date, there is no clear evidence for genotype-phenotype correlation in our group of patients. Genetic counseling in families with congenital adrenal hypoplasia (AHC) patients is mandatory to predict those at risk of HH manifestation later in life.

P1-D1-207

Analysis of the *WDR11* Gene in Patients with Isolated Hypogonadotropic Hypogonadism with and without Olfactory Defects

Leticia FG Silveira, Luciana R Montenegro, Elaine MF Costa, Ana C Latronico

Unidade de Endocrinologia do Desenvolvimento, Laboratório de Hormônios e Genética Molecular (LIM/42), Disciplina de Endocrinologia e Metabolgia, Hospital das Clinicas da Faculdade de Medicina da Univ, Sao paulo, SP, Brazil

Background: The *WDR11* gene was recently involved in the pathogenesis of isolated hypogonadotropic hypogonadism (IHH). In 2010, Kim *et al.* (1) identified five different heterozygous missense *WDR11* rare variants in six of 201 IHH patients (five normosmic IHH and one Kallmann syndrome), which were absent in more than 400 controls. Animal studies demonstrated that *WDR11* interacts with *EMX1*, a homeodomain transcription

factor involved in the development of olfactory neurons, and the missense alterations reduced or abolished this interaction. However, since this first description, no other mutations in this gene were associated with the IHH phenotype. **Objective and hypotheses:** To investigate the presence of *WDR11* rare variants in patients with IHH with and without olfactory defects. **Method:** We studied 129 Brazilian patients with sporadic or familial IHH, including 65 with normosmic IHH and 64 with Kallmann syndrome. Genomic DNA was extracted from peripheral leukocytes from all patients. All 29 exons and exon-intron boundary regions of *WDR11* were amplified by PCR using specific primer pairs and automatically sequenced. **Results:** No rare variants were identified in the patients studied. Only known polymorphisms were found: rs35692153, COSM147066, rs151162552, rs7899928, COSM147068, rs34567350, rs1652727, rs34567350, COSM147069, rs149486212, rs117848117, COSM1346180, and rs12268298. **Conclusion:** These results show that *WDR11* rare variants are not a common cause of IHH, and suggest that the role of this gene in the pathogenesis of this condition needs to be further investigated.

P1-D1-208

GH Therapy in Turner Syndrome Patients: the Effects on Nutritional Status, Adipokines, and Aortic Dilatation

Hanna Magnuszewska^a, Maria Gnacinska-Szymanska^b, Piotr Wisniewski^b, Piotr Potasz^c, Dorota Birkholz-Walerzaka^a, Maria Korpala-Szczyrska^a, Krzysztof Sworczak^b

^aDepartment of Paediatrics, Diabetology and Endocrinology, Medical University of Gdansk, Gdansk, Poland; ^bDepartment of Endocrinology and Internal Medicine, Medical University of Gdansk, Gdansk, Poland; ^cDepartment of Pediatric Cardiology and Congenital Heart Defects, Medical University of Gdansk, Gdansk, Poland

Background: Turner syndrome (TS) patients are at increased obesity risk. Additionally body composition in TS is distinctly altered. The percentage of body fat mass (BFM) is higher. Also adipokine dysregulation is observed. TS is associated with aortic dilatation, which is seen not only in patients with congenital aortic defects but also in patients without underlying pathology. Considering different co-morbidities common in TS, it's extremely important to evaluate wide spectrum of GH effects in these patients. Till now there are very few studies analyzing long-term effects of GH therapy on obesity and cardiovascular complications in TS. **Objective and hypotheses:** Assessment of long-term GH therapy effects on nutritional status and aortic dilatation in TS. **Method:** Fifty three TS patients with confirmed diagnosis. Group 1: *n* = 37, after GH therapy. Age 20.87 (\pm 3.69), age at start of GH therapy 11.73, treatment duration 4.83, interval between GH discontinuation and study 4.46 years. Group 2: *n* = 16, never treated with GH, age 23.16 (\pm 5.8) years. Exclusion criteria: diabetes mellitus, unbalanced thyroid pathology, aortic defects:

aortic coarctation and bicuspid aortic valve. Study protocol contained: measurements: height, weight, BMI, WHR; bioelectrical impedance analysis; laboratory tests: adiponectin, obestatin, omentin, wifatin; echocardiography, including different aortic diameters, which were indexed to BSA. **Results:** BMI, WHR didn't differ between groups. BFM was significantly lower in group 1 vs 2 (27.4 vs 31.8%, $P=0.03$). There was no difference in adipokines between groups. Also aortic diameters didn't differ. Negative correlation between aortic size index (ASI) and obestatin was noted ($r = -0.6117$, $P=0.0015$). ASI correlated with karyotype ($r = -0.4886$, $p=0.0083$) and didn't correlate with GH treatment duration. **Conclusion:** GH therapy in TS has beneficial impact on body composition. GH therapy has no direct effect on aortic dimension. However, the association between obestatin, negatively correlating with nutritional status, and aortic size, suggest that GH may decrease aortic dilatation risk in TS.

P1-D1-209

Evaluation of Sitting Height/Height SDS in Patients with Turner Syndrome

Mikayir Genens, Gamze Kaya, Ceren Melis Ulak, Sukran Poyrazoglu, Firdevs Bas, Ruveyde Bundak, Nurcin Saka, Feyza Darendeliler

Pediatric Endocrinology Unite, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey

Background: Short stature and gonadal dysgenesis are the main characteristics in Turner syndrome (TS). There are conflicting reports about the body proportions in TS. Some studies described a proportionate short stature, whereas others reported disproportionately short legs. It is known that body proportions are genetically controlled and are different in different populations or ethnic groups. **Objective and hypotheses:** To evaluate body proportions assessed by sitting height/height ratio in patients with TS with respect to national standards. **Method:** Ninety-two patients with TS were reviewed retrospectively. Disproportionate short stature was defined as sitting height (SH)/height (H) $SDS > 2$ SD above the mean for age and sex with respect to national standards. **Results:** The mean age of the patients was 11.9 ± 2.9 years (range: 6.0–17.7 years). The mean HSDS and SHSDS at presentation was -3.6 ± 1.2 and -3.4 ± 1.1 retrospectively. The frequency of abnormal body proportion at presentation was 15.3%. Karyotype distribution was 45,X in 52%; mosaicism in 28% and structural abnormalities in 20%. There was no difference in the body proportions according to karyotypes. The mean age of the onset of puberty (spontaneous and induced) was 14.5 ± 2.1 years and 22% of TS had spontaneous puberty. Thirty-two patients reached adult height. Twenty-two of them had been treated with GH. The frequency of abnormal body proportion at adult height was 9.4%. Treatment with GH did not

influence the body proportion. The frequency of abnormal body proportion was similar in patients who reached adult height with or without GH (9.1 and 10% respectively). **Conclusion:** The frequency of abnormal body proportion was low in our patients with TS. We could not find a confounding factor for disproportion.

P1-D2-210

Messenger Ribonucleic Acid Expression of Kiss-1 and Serum Level of Kisspeptin in Rat at Different Developmental Stages^{*}

Ah Reum Kwon^a, Duk Hee Kim^b, Jung Min Ahn^a, Kyungchul Song^a, Hyun Wook Chae^a, Ho-Seong Kim^a, Ye Jin Kim^a, Yong Hyuk Kim^a

^aYonsei University Severance Hospital, Seoul, Republic of Korea;

^bSowha Children's Hospital, Seoul, Republic of Korea

Background: KiSS-1 and its product, kisspeptin is necessary for puberty onset and proper adult gonadal function due to its stimulatory effect on the secretion of gonadotropin-releasing hormone (GnRH). Although the pathophysiological importance of KiSS-1 and kisspeptin is well known, the developmental patterns of expression of KiSS-1 genes and serum level of kisspeptin have not been explored to date. **Objective and hypotheses:** We report herein the expression profile of *KiSS-1* genes and serum level of kisspeptin in the rat at different developmental stages. **Method:** Sprague-Dawley (SD) strain female rats were used. To analysis expression of *KiSS-1* mRNA, samples were obtained from hypothalamus, pituitary and ovaries in female rats according to developmental stages. At the same time, blood samples were collected for analysis serum level of kisspeptin and luteinizing hormone (LH). The expression of *KiSS-1* mRNAs was assessed by RT-PCR and the serum levels of kisspeptin and LH were analyzed by ELISA. **Results:** The expressions of *KiSS-1* gene in hypothalamus and ovary were increased according to developmental stages and were peaked at prepubertal stage (at day 27, respectively, 0.88 ± 0.22 , 0.54 ± 0.25). However, there were no significant changes or correlations between developmental stages and *KiSS-1* gene expression in pituitary. Serum kisspeptin level was also increased according to developmental stages. However, peak level of kisspeptin (35.43 ± 3.60 pg/ml) was in pubertal stage at day 34. Serum LH level was also increased and peaked (23.29 ± 15.24 ng/ml) at pubertal stage (at day 38). However, an increasing pattern was little delayed than that of kisspeptin level. **Conclusion:** The expressions of *KiSS-1* mRNA in hypothalamus and ovary, serum levels of kisspeptin and serum LH levels were increased according to developmental stages in rat in regular sequence. Therefore, serum kisspeptin levels can be an indication of *KiSS-1* gene expression in hypothalamus and pubertal onset.

^{*}Nominated for a Presidential Poster Award.

P1-D2-211

The Incidence of Childhood Gonadoblastoma Over 15 Years in the Republic of Ireland

Susan M O'Connell^a, Sally-Ann Lynch^b, David Coyle^c, Michael McDermott^d, Maureen O'Sullivan^{d,f}, Edna Roche^{e,f}, Feargal Quinn^e, Declan Cody^g

^aDepartment of Paediatrics and Child Health, Cork University Hospital, Cork, Ireland; ^bNational Centre for Medical Genetics, Our Lady's Hospital Crumlin, Dublin, Ireland; ^cDepartment of Paediatric Surgery, Our Lady's Hospital Crumlin, Dublin, Ireland; ^dDepartment of Histopathology, Our Lady's Hospital Crumlin, Dublin, Ireland; ^eThe National Children's Hospital, Tallaght, Dublin, Ireland; ^fUniversity of Dublin, Trinity College, Dublin, Ireland; ^gDepartment of Paediatric Endocrinology, Our Lady's Hospital Crumlin, Dublin, Ireland

Background: Gonadoblastoma is a rare tumour of the gonads presenting in childhood or adolescence. It is a lesion composed of a mixture of germ cells at different stages of maturation, with low malignant potential. It is associated with disorders of sex development (DSD), most commonly Turner mosaic syndrome with Y chromosome material (TMSY), and 46XY gonadal dysgenesis (GD). Little is known about the natural history and incidence of this rare tumour. **Objective and hypotheses:** To determine the incidence and clinical features of gonadoblastoma presenting before age 16 years in the Irish Republic (RoI) from 1999 to 2013 inclusive. **Method:** A retrospective review of children and adolescents with a diagnosis of gonadoblastoma was undertaken using the records of the National Cancer Registry Ireland (NCRI) and the Departments of Endocrinology, Pathology and Surgery at the main children's hospitals. All children in Ireland requiring gonadectomy are referred to the same tertiary referral centre thus anticipating good case ascertainment. Clinical case notes and histopathological findings were reviewed. **Results:** Eight cases of gonadoblastoma were identified over the 15 year period. All were phenotypically female. Five cases had TMSY (age range gonadoblastoma diagnosis 6 months–14 years), bilateral in two cases. Three cases of 46 XY GD were aged 4 months, 8 and 9 years at diagnosis of gonadoblastoma (unilateral). In one case of 46 XY GD with SRY deletion, clinical symptoms (age eight) prompted gonadectomy. Histology showed unilateral dysgerminoma and contralateral gonadoblastoma. In all other cases gonadoblastoma was diagnosed on elective gonadectomy. **Conclusion:** The incidence of gonadoblastoma in RoI over the past 15 years is eight, giving a population incidence of 0.08 per 10 000 births. To our knowledge this is the first population incidence rate of GB in children reported. Due to the low age of gonadoblastoma cases observed in this cases series, the recommendation for elective gonadectomy in high risk conditions is supported.

P1-D2-212

A Novel MKRN3 Mutation Discovered in a Korean Girl with Central Precocious Puberty

Hae Sang Lee^a, Jung Sub Lim^b, Jin Soon Hwang^a, Eun Young Kim^c

^aAjou University School of Medicine, Suwon, Republic of Korea; ^bKorea Cancer Center Hospital, Seoul, Republic of Korea; ^cCollege of Medicine Chosun University, Gwangju, Republic of Korea

Context: It has recently been shown that mutations of *MKRN3*, the gene encoding makorin RING-finger protein 3, lead to central precocious puberty (CPP). The aim of this study was to investigate mutations of the *MKRN3* gene in Korean girls with CPP. **Methods:** Two hundred and sixty Korean girls with idiopathic CPP were included in this study. Auxological and endocrine parameters were measured. The entire *MKRN3* gene was directly sequenced. **Results:** The analysis of the *MKRN3* gene revealed one novel nonsense mutation (p.Gln281*) and six kinds of missense variants (p.Ile100Phe, p.Gly196Val, p.Ile204Thr, p.Gln226Pro, p.Lys233Asn, and p.Ser396Arg). The novel nonsense mutation (p.Gln281*) was a heterozygous C>T nucleotide change (c.841C>T) predicted to result in a truncated protein due to a premature stop codon in the *MKRN3* gene. The nonsense mutation (p.Gln281*) was identified in a girl. The girl's father had the same nonsense mutation, but her mother did not. **Conclusion:** We reported a novel *MKRN3* mutation (p.Gln281*) in a girl with CPP. The present study reveals that the *MKRN3* mutation appears to be associated with the progression of puberty.

P1-D2-213

The Association of Moebius Syndrome and Kallman Syndrome is Due to a Specific Mutation of TUBB3

Melanie Amouya^a, Patrice Bouvagnet^{b,c}, Galliane Rochette^{b,c}, Nicolas de Roux^{a,d}

^aINSERM U676, Robert Debre Hospital, Paris Diderot University, Paris, France; ^bCardiogenetic Laboratory, Biology and Pathology East Center, Lyon, France; ^cEA4173, Lyon 1 University and Northeast Hospitals, Lyon, France; ^dBiochemistry-Hormonology Laboratory, Robert Debre Hospital, Paris, France

Background: Between the 6000 monogenic disorders, only few are due to a single mutation. Recently, a specific mutation has been described in TUBB3, encoding tubulin beta 3, in the association of Moebius syndrome (MS) and Kallmann syndrome (KS). MS is a congenital paralysis of eye and face's muscles and can be caused by mutations of TUBB3. KS combines hypogonadotropic hypogonadism and anosmia. **Objective and hypotheses:** The combination of these two syndromes in the same patient is very rare. We report here a new case confirming that the association of MS and KS is due to the E410K mutation in TUBB3. **Method:** MS has been diagnosed in a boy at the end of his first month of life because he had a facial paralysis, a micro retrognathism and suction difficulties. The diagnosis has been confirmed by an electromyogram of eye muscles. The hypogonadotropic hypogonadism has been brought up because of a micropenis and unilateral chryptorchidism, and it was confirmed at 3 months of life, with low gonadotropins, low testosterone and a negative LHRH test. Other pituitary axes were normal. Later in life, a psychomotor retardation appeared, as well as an epilepsy and a growth retardation. No puberty occurred spontaneously and

the patient had an anosmia. **Results:** The association between MS and KS led us to sequence the 4th exon of TUBB3. The results showed that the patient has a heterozygous mutation c.1228G>A in TUBB3 leading to the E410K substitution, whereas his mother and sister did not bear the mutation. We suspect a *de-novo* mutation. **Conclusion:** The association of MS and KS is specifically due to a single mutation of TUBB3. Other mutations of TUBB3 cause MS only. The E410K substitution disturbs the tubulin beta 3 function in olfactory developing neurons whereas functional compensation occurs for other TUBB3 mutations in MS.

P1-D2-214

Early Medical Treatment of Children with Gender Dysphoria: an Empirical Ethical Study on Arguments of Proponents and Opponents Concerning Early Interventions

Martine de Vries^a, Lieke Vrouwenraets^b, Anne Wichmann^c, Maartje Schermer^d, Miranda Fredriks^b, Henriette Delemarre-van de Waal^a

^aDepartment of Pediatrics, Leiden University Medical Centre, Leiden, The Netherlands; ^bCurium-LUMC, Academic Centre for Child and Adolescent Psychiatry, Leiden, The Netherlands; ^cDepartment of Philosophy, VU University, Amsterdam, The Netherlands; ^dDepartment of Bioethics and Philosophy of Medicine, Erasmus Medical Center, Rotterdam, The Netherlands

Background: Both The Endocrine Society and the World Professional Association for Transgender Health (WPATH) published guidelines for the treatment of children and adolescents with gender dysphoria (GD). The guidelines recommend the use of GnRH agonists in adolescence to suppress puberty, and the use of cross-sex hormones starting around age 16 for eligible patients. In actual practice, there is no consensus whether to use these early medical interventions. The aim of our study was to gain insight in the contexts of treatment disagreements surrounding early medical interventions and the underlying considerations of proponents and opponents. **Methods:** i) Systematic literature review on treatment discussions in children with GD; ii) qualitative study (semi-structured interviews) to identify considerations of key-informants (pediatric endocrinologist, psychologist, psychiatrist, ethicist) of 14 treatment teams worldwide **Results:** The literature and the interviews show six fundamental topics that give rise to different, and even opposing, views on treatment of adolescents: i) the (non-)availability of an explanatory model for GD; ii) the nature of GD (normal variation, social construct or (mental) illness); iii) the role of physiologic puberty to form a consistent gender identity; iv) the role of comorbidity; v) ideas about harms of early medical interventions as well as of refraining from interventions; vi) ideas about decision making authority and child competence. Strikingly, the guidelines are debated both for being too liberal and for being too limiting. Many teams using the

guidelines are exploring the possibility of expanding the current age limits. **Conclusion:** Judgment on GD treatment is affected by fundamental ideas on the nature of gender and GD. There is an urgent need for systematic, interdisciplinary, multicenter research and debate, not only on long-term outcomes, but also on the nature of gender (dysphoria). The guidelines will only have a sound foundation once consensus is reached on these fundamental issues.

P1-D2-215

Serum Inhibin-B Values in Boys with Unilateral Cryptorchidism and Boys with Unilateral Vanished Testis

Dina Cortes^b, Jorgen Thorup^a

^aRigshospital, Copenhagen, Denmark; ^bHvidovre Hospital, Copenhagen, Denmark

Background: In some recent materials of blood samples from boys with cryptorchidism gonadotropins are higher and serum inhibin-B lower than normal. Inhibin-B is produced by the Sertoli-cells and to some extent serum values of inhibin-B reflect the state of germinative epithelium in cryptorchid testes. In boys with bilateral vanished testes the serum inhibin-B level is close to zero. **Objectives and hypotheses:** Aim of study was to evaluate the serum inhibin-B level in a large series of boys with unilateral cryptorchidism and compare with unilateral vanished testis. **Methods:** 236 blood samples from boys ¼ to 5 years were included. 171 blood samples were taken at time of orchiopexy from boys with unilateral cryptorchidism. 23 boys had unilateral vanished testis and 42 blood samples were taken from boys median 1 year after orchiopexy for unilateral cryptorchidism. Median ages of the groups were 15, 18 and 25 months. Serum inhibin-B levels were measured using a commercial available inhibin-B ELISA kit. Lower detection-limit: 5 pg/ml. The inhibin-B levels were related to age matched normal values. **Results:** In boys previously operated for unilateral cryptorchidism 88 and 40% of cases respectively had inhibin-B values above normal 2.5 and 50 (median) percentiles. This was significantly higher ($P < 0.0002$) than in unilateral cases at time of orchiopexy where 12% only had inhibin-B values above normal 50 (median) percentile. Serum inhibin-B values of boys with unilateral vanished testis (83 and 22% had serum values above normal 2.5 and 50 (median) percentiles) were not different from the serum values of unilateral cases with cryptorchidism at time of orchiopexy (78 and 12% had serum values above normal 2.5 and 50 (median) percentiles) ($P = 0.88$ and $P = 0.35$ respectively). **Conclusion:** As reflected by the serum inhibin-B values the germinative epithelium and Sertoli-cells have some ability of recovering after surgery for cryptorchidism. The low serum inhibin-B values in unilateral vanished testis cases may be explained by the impaired total number of Sertoli-cells.

P1-D2-216**IGSF1 Variants in Boys with Familial Delayed Puberty**

Sjoerd Joustra^a, Karoliina Wehkamp^b, Wilma Oostdijk^a,
Nienke Biermasz^a, Sasha Howards^c, Daniel Bernard^d,
Jan Maarten Wit^a, Leo Dunkel^c, Monique Losekoot^a

^aLeiden University Medical Center, Leiden, The Netherlands;

^bHelsinki University Central Hospital, Helsinki, Finland; ^cQueen Mary University of London, London, UK; ^dMcGill University, Montréal, Canada

Background: The immunoglobulin superfamily member 1 (*IGSF1*) gene encodes a plasma membrane glycoprotein enriched in pituitary and testes. Loss-of-function mutations in *IGSF1* cause an X-linked syndrome of central hypothyroidism (CeH), macroorchidism, and delayed pubertal rise of testosterone despite normal timing of testicular growth. This syndrome was discovered in patients with CeH; therefore, it is presently unknown whether *IGSF1* mutations also cause delayed puberty without CeH. **Methods:** We determined the prevalence of *IGSF1* sequence variants in 30 patients with familial constitutional delay of growth and puberty (CDGP) in an apparent maternally transmitted pattern of inheritance (pubertal delay in the index patient's siblings, mother, and/or siblings of mother). Isolated DNA was screened for mutations in *IGSF1* using Sanger sequence analysis. Functional effects of variants with unknown clinical significance were assessed by: i) *in silico* prediction of pathogenicity, and ii) transfecting heterologous HEK293 cells with expression vectors specific for each *IGSF1* variant, followed by cell surface biotinylation and immunofluorescence to determine plasma membrane expression of the resulting IGSF1 proteins. **Results:** In four families, we discovered three novel variants of unknown clinical significance (VUCSs) with possible pathogenicity predicted by *in silico* analysis. However, the genotype did not fully cosegregate with delayed puberty. All three VUCSs showed normal plasma membrane localization in transfected HEK293 cells. Besides delayed puberty, no other features of the IGSF1 deficiency syndrome were observed in family members carrying the VUCSs. Hyperprolactinemia was observed in one family. **Conclusion:** There is insufficient evidence that the three newly discovered VUCSs in *IGSF1* in 30 patients with maternally transmitted CDGP are associated with delayed puberty. Thus, it is unlikely that *IGSF1* mutations are a prevalent cause of CDGP. However, the limited size of the study group does not completely rule out such an association.

P1-D2-217**Reference Charts for Testicular Volume in Dutch Children and Adolescents**

Sjoerd Joustra^a, Evelyn van der Plas^b, Joery Goede^b, Wilma Oostdijk^a,
Henriette Delemarre - Van de Waal^a, Wilfried Hack^b,
Stef van Buuren^{c,d}, Jan Maarten Wit^a

^aLeiden University Medical Center, Leiden, The Netherlands;

^bMedical Centre Alkmaar, Alkmaar, The Netherlands; ^cNetherlands

Organisation for Applied Scientific Research TNO, Leiden, The Netherlands; ^dUniversity of Utrecht, Utrecht, The Netherlands

Background: Measurement of testicular volume is important when conditions associated with a delay or advance in the onset of puberty, or micro- and macroorchidism, are suspected. Measured testicular volumes must be compared with reference data, preferably expressed in s.d. curves using the LMS method, as is routinely done for many auxological measurements in pediatrics. The current study therefore aimed to construct LMS-smoothed age-reference charts for testicular volume in healthy children and adolescents. **Methods:** Data from a recently published large cross-sectional study on testicular growth in 769 healthy Dutch boys aged 0.5–19.0 years were used. Testicular volume was measured both with ultrasonography ($\pi/6 \times \text{length} \times \text{width} \times \text{height}$) and the Prader orchidometer (ellipsoid models ranging in volume from 1 to 25 ml). For each testis, the highest of three measurements was used, and the volumes of both testes were averaged. The reference distributions were fitted by the LMS method, which summarizes the distribution by three age-dependent smooth curves representing skewness (L curve), median (M curve) and coefficient of variation (S curve), and assumes that the data follow a standard normal distribution after a Box-Cox transformation. **Results:** Standardized reference charts, allowing the calculation of SDs, and reference curves, allowing easy follow-up of testicular volume in clinical practice, were constructed. The ratio between testicular size assessed with the Prader orchidometer and ultrasonography changed from 3.9 to 2.0 between 0.5–19.0 years. Based on these charts, no revision of the definition of male precocious or delayed puberty is warranted. **Conclusions:** This study allows clinicians and researchers to calculate age-corrected SDs for testicular volume measured either with ultrasonography or orchidometer. The results will aid in the diagnosis and follow-up of abnormalities in the timing and progression of male puberty, as well as micro- or macroorchidism.

P1-D2-218**High Incidence of Genetic Defects in a Cohort of 24 Male Adolescents with Persistent Pubertal Gynecomastia**

Françoise Paris^{a,b}, Laura Gasparia^c, Felicien MBou^e, Pascal Philibert^b,
Anna Lauber-Biason^d, Charles Sultan^{a,b}

^aDepartment of Pediatric Endocrinology, CHU Montpellier, Montpellier, France; ^bDepartment of Hormonology, CHU Montpellier, Montpellier, France; ^cDepartment of Pediatrics, CHU Nîmes, Nîmes, France; ^dDepartment of Pediatric Endocrinology, University Hospital, Fribourg, Switzerland; ^eDepartment of Pediatrics, CHU Fort de France, Fort de France, Martinique

Background: Pubertal gynecomastia is a common condition appearing in up to 65% of adolescent boys. However, if male breast development is over B3–B4 and lasts more than 2–3 years, persistent pubertal gynecomastia (PPG) may be the sign of serious endocrine disease and the source of considerable psychological

discomfort. **Objective and hypotheses:** We investigated a cohort of 24 adolescents with PPG followed at the Pediatric Endocrinology Unit over a 3-year period to determine whether PPG is associated with genetic disorders. **Method:** Clinical, endocrine and radiological investigations were performed in all patients. Genetic analyses were done in six patients with suspected genetic disorder. **Results:** The patients' mean age was 14.5 ± 0.8 years and the pubertal Tanner stage was >2 without genital abnormalities. Laboratory evaluation revealed no hormonal disturbance for 18 boys (75%), whereas two patients presented Klinefelter syndrome and three, partial androgen insensitivity syndrome (PAIS) due to AR gene mutation (p.Ala646Asp for twins and c.134C>G for the third). Although external genitalia were normal in these three adolescents, it is likely that PAIS manifested only as PPG. Another patient showed 17α -hydroxylase/17,20-lyase deficiency confirmed by CYP17A1 gene analysis, which revealed compound heterozygosity consisting of c.275C>A/WT in exon 1 (plus three known heterozygous SNPs) and c.887C>T/WT in exon 4, respectively leading to p.Pro35Thr(P35T) and p.Arg239Stop(R239X). To assess the functional consequence of this mutation, COS1 cells were transfected with the expression vector pcDNA3 containing either WT or mutant CYP17A1cDNA. The mutant protein bearing the premature stop codon R239X showed a complete loss of 17α -hydroxylase and 17,20-lyase activity. Compared with the WT protein, the mutant P35T seemed to retain 15–20% of 17α -hydroxylase and about 8–10% of 17,20-lyase activity at two different substrate concentrations. **Conclusion:** This work suggests that screening for genetic disorders (besides Klinefelter syndrome, PAIS, and CAH) should be systematic, as they may be the cause of up to 25% of PPG.

P1-D2-219

Mutation Analysis of the KISS1, KISS1R, LIN28A, LIN28B, TAC3, and TACR3 Genes in Girls with Central Precocious Puberty

Yoo-Mi Kim^a, Ja Hye Kim^b, Ja Hyang Cho^b, Jin-Ho Cho^b, Han-Wook Yoo^b

^aDepartment of Pediatrics, Pusan National University Children's Hospital, Yangsan, Republic of Korea; ^bDepartment of Pediatrics, Asan Medical Center Children's Hospital, University of Ulsan College of Medicine, Seoul, Republic of Korea

Background: Central precocious puberty (CPP) is mostly idiopathic, however, familial cases of CPP and evidence of genetic factors on pubertal timing by genome-wide association studies suggested genetic causes of CPP. **Objective and hypotheses:** Molecular defects in six genes (*KISS1*, *KISS1R*, *LIN28A*, *LIN28B*, *TAC3*, and *TACR3*) have been known to cause early activation of the hypothalamic-pituitary-gonadal axis. This study investigated genetic defects in these six genes in patients with idiopathic CPP. **Method:** This study included 73 girls with breast development before the age of 8 years. Forty-one of them (56.2%) had a family history of CPP. The GnRH stimulation test was performed in all patients and peak LH levels were > 5.0 mIU/ml. Also, they showed advanced bone age of at least 1 year relative to chronologic age.

Patients with organic brain lesion were excluded in this study. Mutation analyses of the *KISS1*, *KISS1R*, *LIN28A*, *LIN28B*, *TAC3*, and *TACR3* genes were performed using genomic DNA from peripheral blood leukocytes. **Results:** Of the 73 girls who underwent DNA analyses, only one girl (1/73 patients, 1.3%) harbored a heterozygous variant of p.L210I in *TACR3*, which is located in the third transmembrane domain of the neurokinin B receptor. The p.L210I variant was predicted to be detrimental by web-based prediction programs. It was not detected in the 1000 Genomes database and NHLBI exome variant server. There were no mutations in *KISS1*, *KISS1R*, *LIN28A*, *LIN28B*, and *TAC3*. **Conclusion:** This study investigated the mutations in candidate genes causing the premature activation of puberty, but only one subject with a heterozygous variant in *TACR3* was identified. This result indicates that mutations in these genes are a rare cause of CPP, even in patients with family members with early pubertal timing. Other genetic defects, modifier genes, or environmental influences may play a crucial role in pubertal timing.

P1-D2-220

Successful Treatment of Male Congenital Hypogonadotropic Hypogonadism with rFSH Pretreatment Followed by GnRH

Haruo Mizuno, Kohei Aoyama, Shinji Saitoh

Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

Background: Congenital hypogonadotropic hypogonadism (CHH) is a group of rare disorders responsible for insufficient secretion of the pituitary gonadotropins LH and FSH. We have observed CHH in men with poorer responses to human chorionic gonadotropin (hCG), or combined FSH and hCG for testicular maturation and fertility after adolescence. **Objective and hypotheses:** The purpose of this research is to clarify how best to tailor-make treatment according to the genotype by retrospectively analyzing the results of a treatment method based on exact gene diagnosis. rFSH pretreatment may become a successful means of treatment for men with CHH. **Method:** We investigated the clinical course of 11 male patients (aged 4–25 years) with CHH, including eight patients with Kallmann syndrome and two patients with CHARGE syndrome. All male patients with CHH were subjected to mutation assessment in 48 CHH-associated genes, using Ion Torrent next-generation sequencing. We then confirmed these mutations using Sanger sequencing. **Results:** Seven of the patients had bilateral cryptorchidism and micropenis, and three patients had micropenis only. All patients had no olfactory blub. Abnormal delay of secondary sexual characteristics was noted in the eight patients older than 15 years, who revealed no response in the hCG test. We discovered *KALI*, *FGFIR* mutations during the study. In one adolescence man with Kallmann syndrome and *FGFIR* mutation, testicular maturation was absent during continuous hCG injections for 6 months. His testes volume was < 1 ml. We administered rFSH 75 IU s.c. daily for 2 months, following which hCG 1000 IU s.c. and rFSH 75 IU s.c. were administered every other day. Consequently, his testes

became larger and his serum testosterone value reached a normal range. **Conclusion:** rFSH pretreatment followed by GnRH may be useful in enhancing testicular growth in men with CHH including Kallmann syndrome. However, further studies are needed to clarify whether rFSH pretreatment results in fertility.

P1-D3-221

The Uterine Artery Pulsatility Index as an Accurate Index for the Assessment of Puberty^{*}

Alessandra di Lascio, Caterina Colantoni, Silvia Laura Carla Meroni, Moira Gianninoto, Pierluigi Paesano, Gianni Russo

San Raffaele Scientific Institute, Milan, Italy

Background: The onset of physiological puberty in females is characterized by physical, hormonal, and genital changes. However, a single specific parameter to early identify these modifications does not exist; its identification could be extremely useful in the evaluation of pubertal development disorders. The uterine artery pulsatility index (PI), defined as systolic peak – diastolic peak/average speed of maximum flow, is an expression of vascular compliance in the uterine artery. Circulating estrogen reduce vascular resistance and, consequently, the PI values. **Objective and hypotheses:** The end-point was to assess the accuracy of the uterine artery PI in the evaluation of the pubertal status and to set a cut-off value to classify prepubertal vs pubertal girls. **Method:** 495 girls (mean age 8.6 ± 2.17 years) referring to our hospital from September 2005 to March 2013 for the evaluation of pubertal disorders were enrolled. Exclusion criteria were GnRH-independent puberty, Turner syndrome, Prader-Willi syndrome, and patients under GnRH-analogs treatment. Tanner score, LH peak measurement after GnRH stimulation, ultrasound uterine and ovarian diameters, and PI values were assessed. ANOVA and ROC analysis were performed. **Results:** PI values in the prepubertal ($n=207$), pubertal ($n=117$), and the CPP ($n=171$) groups were respectively: 6.3 ± 1.42 , 3.4 ± 1.10 , and 3.9 ± 1.48 ($P < 0.0001$). The best PI cut-off value to distinguish pubertal from prepubertal girls was 4.6 (sensitivity 83%, specificity 94%, PPV 95%, NPV 80%, and accuracy 87%). ROC area for LH peak and for combined PI-longitudinal uterine diameter were 0.9439 and 0.9272% ($P=0.7931$) respectively. **Conclusion:** The ultrasound uterine artery PI can be considered an accurate and non-invasive parameter for the diagnosis of pubertal activation.

^{*}Nominated for a Presidential Poster Award.

P1-D3-222

The Uterine Artery Pulsatility Index in Evaluation of the GnRH-Analog Treatment Efficacy in Central Precocious Puberty^{*}

Alessandra di Lascio, Caterina Colantuoni, Silvia Laura Carla Meroni, Moira Gianninoto, Pierluigi Paesano, Gianni Russo

San Raffaele Scientific Institute, Milan, Italy

Background: GnRH analogs (GnRHa) have been used in the management of central precocious puberty (CPP). The response to GnRHa treatment are evaluated by clinical, hormonal, and ultrasonographic criteria. However, a single parameter to define the adequacy of therapy is not defined. The uterine artery pulsatility index (PI), defined as systolic peak – diastolic peak/average speed of maximum flow, is an expression of vascular compliance in the uterine artery. Circulating estrogen reduce vascular resistance and, consequently, the PI values. **Objective and hypotheses:** We aimed to evaluate the PI accuracy in the monitoring of GnRHa treatment in patients with CPP. **Methods:** 56 girls referring to our hospital from September 2005 to March 2013 for CPP were enrolled. Tanner stage, LH peak measurement after GnRH stimulation, uterine and ovarian diameters and volumes, and PI values were compared at baseline and 6 months after treatment beginning. Paired *t*-test analysis was performed. **Results:** Before and after 6 months of treatment PI values were 3.9 ± 1.19 and 5.6 ± 1.44 ($P < 0.0001$), longitudinal uterine diameter (mm) were 41.3 ± 6.57 and 36.7 ± 5.4 ($P < 0.0001$), LH peak values (mU/ml) were 19.4 ± 12.8 and 0.8 ± 0.82 ($P < 0.0001$), and breast development were 2.75 ± 0.97 and 2.0 ± 1.17 . After 6 months of treatment PI increased in 48 patients (86%), longitudinal uterine diameter decreased in 46 patients (82%), LH peak value decreased ≤ 3 mU/ml in 54 patients (96%), and Tanner stage decreased or was stable in 53 patients (95%). **Conclusion:** The PI, together with longitudinal uterine diameter and clinical evaluation, could be an accurate and non-invasive parameter for the evaluation of the GnRH-analog treatment efficacy, avoiding the need for a stimulation test.

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P1-D3-223

Serum Bisphenol a Concentration and Premature Thelarche in Female Infants Aged 4-Month to 2-Year-Old

Fang Yanlan^a, Chen Lianhui^b, Liang Li^a

^aDepartment of Pediatrics, The First Affiliated Hospital of College of Medicine, Zhejiang University, Hangzhou, China; ^bChildren's Hospital of Zhejiang University School of Medicine, Hangzhou, China

Background: Bisphenol A (BPA) is one of high production-volume chemicals and used extensively in consumer products, including food containers and epoxy food-can coatings. The primary source of BPA exposure in adults is via food and beverages, while among infants breast milk and polycarbonate feeding bottles are the predominant source of BPA exposure. **Objectives and hypotheses:** To estimate the association between serum BPA A and premature thelarche in female infants aged 4-month to 2-year-old. **Method:** Case-control study. A total of 251 female infants (aged 4 months–2 years) with premature thelarche and 33 healthy age-matched control subjects. **Results:** The mean serum BPA A levels in the normal and premature thelarche groups were 5.27 and 7.84 ng/ml respectively. Serum BPA A concentration in the premature thelarche group was

significantly greater than that in the control group. There was no correlation between age and serum BPA level. Univariate logistic regression analysis showed that serum BPA concentration positively associated with premature thelarche, and the effect of BPA falls down as age growing. **Conclusions:** This hospital-based study implies that the association between serum BPA concentrations and premature thelarche. Additionally, the serum BPA levels are much higher than we ever thought in infants, and much more concerns should be raised in infants aged 4-month to 2-year-old.

P1-D3-224

Test on Kisspeptin Levels in Girls with Idiopathic Central Precocious Puberty and its Significance

Yu Yang, Xiang-Yu Xiong, Li Yang, Li-Ling Xie, Hui Huang

The Children's Hospital of Jiangxi Province, Nanchang, China

Objective: This paper is aimed to explore the significance of plasma kisspeptin level in diagnosis and therapeutic evaluation through the detection of kisspeptin level of girls diagnosed with idiopathic central precocious puberty (ICPP) before treatment and after 6-months of treatment and girls with simple premature thelarche (PT). **Methods:** A total of 70 girls including 24 girls diagnosed with ICPP, 21 girls with PT and 25 normal girls were enrolled. ELISA was adopted to detect plasma kisspeptin level. **Results:** The kisspeptin level of ICPP group before treatment (1.80 ± 0.13 ng/ml) was higher than those of other groups with significantly statistic difference. The kisspeptin level of ICPP group after 6-months of treatment (1.49 ± 0.21 ng/ml) was significantly lower than those before treatment ($P < 0.05$). **Conclusions:** We can conclude that plasma kisspeptin level is related with initiation of pubertal development, and it can be served as important parameter in ICPP diagnosis and therapeutic effect evaluation.

P1-D3-225

Treated and Untreated Women with Idiopathic Precocious Puberty: Long-Term General Health Status and Metabolic Outcome Between third and fifth decades

Joseph Meyerovitch^{a,b}, Yael Lebenthal^{a,b}, Felice Antebi^c, Shlomit Shalitin^{a,b}, Liat de Vries^{a,b}, Moshe Phillip^{a,b}, Liora Lazar^{a,b}

^aThe Jesse Z and Sara Lea Shafer Institute for Endocrinology and Diabetes, National Center for Childhood Diabetes, Schneider Children's Medical Center of Israel, Petah Tikva, Israel; ^bSackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; ^cResearch and Health Planning Department, Health Planning and Policy Division, Clalit Health Services, Tel Aviv, Israel

Context: Central precocious puberty (CPP), treated or untreated, may have clinical implications in adulthood. **Objective:** To assess the general health status and metabolic

outcome of former CPP women between the third and fifth decades of life. **Design:** Case-control study of an historical cohort using the computerized database of a health management organization. **Participants:** Study group - 148 CPP women aged 26-49 years (104 GnRH-analog (GnRHa)-treated; 44 untreated). Control group - 446 women randomly matched for age, year of birth, and community clinic (293 for the GnRHa-treated; 130 for the untreated). **Methods:** Extracted from the database were demographic data, medical history and medications dispensed, recorded anthropometric measurements and vital signs and laboratory data. **Outcome Measures:** Prevalence of obesity (BMI ≥ 30), hypertension, hyperlipidemia, diabetes, osteoporosis, and cancer. **Results:** The mean current age of the GnRHa-treated and untreated CPP women was 31.5 ± 3.1 and 35.4 ± 4.9 years respectively. The prevalence of obesity, hypertension, hyperlipidemia, and diabetes were similar in the former-CPP women and their controls: GnRHa-treated vs controls (13.9 vs 8.5; 1.9 vs 1; 10.6 vs 10.9; and 1.9 vs 1.7 respectively) and untreated vs controls (19.0 vs 20.0; 2.3 vs 3.1; 18.2 vs 20.8; and 6.8 vs 1.5% respectively), with no significant difference between CPP groups. Osteoporosis was not documented in the former-CPP women. Malignancy rate was low ($< 5\%$) and similar in both former-CPP and their controls, with no report of breast cancer among the former-CPP women. **Conclusion:** CPP (treated or untreated) is not associated with increased risk of metabolic derangements or malignancy rate in early and mid-adulthood. Health status of former-CPP women is comparable to that of the general population.

P1-D3-226

Serum Leptin, Ghrelin, and Adiponectin Levels in Relation to Body Composition in Rhythmic Gymnasts Entering into Puberty: a 3-year Follow-up Study

Vallo Tillmann^{a,c}, Kristel Vösaberg^b, Anna-Liisa Jürimäe^b, Meeli Saar^b, Toivo Jürimäe^b, Katre Maasalu^d, Inga Neissaar^b, Evelin Lätt^b, Jaak Jürimäe^b

^aDepartment of Paediatrics, University of Tartu, Tartu, Estonia;

^bInstitute of Sport Pedagogy and Coaching Sciences, Faculty of Exercise and Sport Sciences, University of Tartu, Tartu, Estonia;

^cChildren's Clinic of Tartu University Hospital, Tartu, Estonia;

^dDepartment of Traumatology and Orthopaedics, University of Tartu, Tartu, Estonia

The aim: Of this study was to describe longitudinal changes in body composition and serum leptin, ghrelin and adiponectin levels over 36-month period in prepubertal rhythmic gymnasts (RG) and their age-matched untrained controls (UC) entering into puberty. **Methods:** 35 RG (mean age 8.0 ± 0.6 years) and 33 UC (8.2 ± 0.6 years) were followed at 12-month intervals for the next 3 years. Height, weight, pubertal stage, body composition by DXA and serum leptin, ghrelin and adiponectin levels were measured at each time points. **Results:** The pubertal development over the next 36 months was slower in the RC group where only 4 out of 35 girls reached Ma 3 whereas in the UC there were 14 girls at Ma 3. At 36 month RC had significantly higher serum adiponectin levels than UC (12.9 ± 5.8 vs 9.8 ± 4.4 $\mu\text{g/ml}$; $P < 0.05$). Serum leptin

concentration per fat mass reached peak at 24 months in both groups being significantly lower in RC than in UC (0.52 ± 0.2 vs 0.7 ± 0.25 ng/ml per kg; $P < 0.05$). Thus, relative leptin deficiency may be the reason for delayed pubertal development in RC. Serum ghrelin levels were highest at the beginning of the study, after that it started to decline reaching the nadir at 36 months in RC and at 12 months in UC. In RC baseline leptin concentration was negatively correlated to the change in body fat % over study period ($r = -0.34$; $P < 0.05$). Change in BMI was negatively correlated with the change in serum adiponectin levels over the study period ($r = -0.43$; $P < 0.05$). **Conclusions:** The pubertal development in girls active in high-intensity rhythmic gymnastics is slower than in untrained girls. RC girls have relative leptin deficiency per their body fat mass. We speculate that relatively high serum leptin concentration at the beginning of puberty may predict those girls who do not increase their body fat % through coming years and therefore may have increased risk for delayed puberty. Further studies are necessary to confirm or reject our hypothesis.

P1-D3-227

Impact of BMI on GnRH Stimulated LH Provocation Peak in Girls with Central Precocious Puberty

Jun-Fen Fu, Ju-Hua Jin, Heranmaye C Prasad, Xue-Lian Zhou, Guan-Ping Dong, You-Jun Jiang

Children's Hospital of Zhejiang University School of Medicine, Hangzhou, China

Background: Excess adiposity may influence various aspects of pubertal development, including the timing of pubertal initiation and hormonal parameters during puberty. **Objective and hypotheses:** The aim of this study was to clarify the impact of BMI on LH secretion in response to GnRH stimulation test in girls diagnosed with central precocious puberty. **Method:** Girls with central precocious puberty, who underwent GnRH-stimulation test during the time period of 2008–2012 were recruited. Using a stratified random sampling method, we obtained 359 subjects. Subjects were classified as normal weight (5th percentile \leq BMI $<$ 85th percentile), overweight (85th percentile \leq BMI $<$ 95th percentile), and obese (BMI \geq 95th percentile) according to their BMI. We compared their pubertal development using the Tanner Scale, correlated sexual hormone parameters and LH secretion in response to GnRH stimulation test among the three groups. **Results:** Among the 359 girls with precocious puberty whose data were in the final analysis, 122 girls were of normal weight (34%), while 119 children (33%) were overweight, and 118 (33%) were obese. The mean age at diagnosis of each group was 7.20 ± 1.35 , 7.23 ± 0.87 , and 7.26 ± 0.68 years. The bone age for each group was 9.15 ± 1.44 , 9.79 ± 0.97 , and 9.89 ± 0.97 years respectively. Peak LH levels after GnRH stimulation test were much higher in the normal weight group 18.95 (16.30 – 23.70) mIU/ml compared with the overweight and obese subjects which were 7.50 (3.90 – 11.80) and 7.20 (3.8 – 11.50) mIU/ml respectively ($P < 0.001$ for all comparisons). By multivariate analysis, it was found that there was a significant negative association of BMI with peak stimulated LH level to the GnRH-stimulation tests ($r = -0.546$, $P < 0.001$). **Conclusion:** The higher BMI is

associated with lower LH response to the GnRH-stimulation test in girls experiencing precocious puberty. Recommendations for future studies in this regard include that BMI should be considered when interpreting GnRH-stimulation tests.

P1-D3-228

Impact of Bisphenol-A on the Puberty of Female Rats

Chen Linqi

Soochow Children's Hospital, Soochow, China

Background: It is now widely accepted that chemical pollutants in the environment can interfere with the endocrine system. The impact of endocrine disrupting chemicals on puberty disorders is concerned. bisphenol-A (BPA) has been measured in fetal plasma. There are different toxic effects with different doses of BPA. **Objective and hypotheses:** To observe vaginal opening day (VOD), hypothalamic kiss-1 gene and ovarian estrogen receptors (ER) gene expression level changes in neonatal rats exposure to different doses of BPA. **Method:** Neonatal female SD rats were randomly divided into six groups: control group, vehicle group, 17β -estradiol group (17β -estradiol (E2), $10 \mu\text{g}/\text{kg}$ per day), low-dose BPA group ($25 \mu\text{g}/\text{kg}$ per day), medium-dose BPA group ($50 \mu\text{g}/\text{kg}$ per day) and high-dose BPA group ($250 \mu\text{g}/\text{kg}$ per day). The rats got seven s.c. injections over postnatal day (PND) 0–6 and were sacrificed on the VOD and weighed. The VOD was recorded. The hypothalamus and ovaries were removed, weighed, and calculated the organ/body weight ratio. Real-time PCR were used to observe the mRNA level changes of hypothalamic kiss-1 gene and ovarian ER gene. **Results:** Data suggests that neonatal 50 and $250 \mu\text{g}/\text{kg}$ per day BPA exposure induced premature puberty of rat, but it may not result from the expression level changes of hypothalamic kiss-1 mRNA; neonatal $25 \mu\text{g}/\text{kg}$ per day BPA exposure did not induce premature puberty of rat. **Conclusion:** Neonatal 50 and $250 \mu\text{g}/\text{kg}$ per day BPA exposure induced premature puberty of rat. The premature puberty above mentioned was not caused by the changes of the hypothalamic kiss-1 mRNA and its protein expression. Neonatal $25 \mu\text{g}/\text{kg}$ per day BPA exposure did not induce premature puberty of rat.

P1-D3-229

The Role of Bisphenol A in Etiopathogenesis of Polycystic Ovary Syndrome in Adolescent Girls

Leyla Akin^a, Mustafa Kendirci^a, Figen Narin^b, Selim Kurtoglu^a, Recep Saraymen^b, Meda Kondolot^c, Selda Ozkan Kocak^a, Nihal Hatipoglu^a, Ferhan Elmali^d

^aDepartment of Pediatric Endocrinology, Faculty of Medicine, Erciyes University, Kayseri, Turkey; ^bDepartment of Biochemistry, Faculty of Medicine, Erciyes University, Kayseri, Turkey; ^cDepartment of Pediatrics, Faculty of Medicine, Erciyes University, Kayseri, Turkey; ^dDepartment of Biostatistics, Faculty of Medicine, Erciyes University, Kayseri, Turkey

Background: Polycystic ovary syndrome (PCOS) is a common endocrinological disorder of unclear etiopathogenesis characterized by hormonal and reproductive abnormalities which may coexist with metabolic disturbances. **Objective and hypotheses:** To investigate the role of endocrine disruptor bisphenol A (BPA) in etiopathogenesis of PCOS in adolescent girls. Additionally, we wished to investigate the relationship between BPA and metabolic parameters, insulin resistance and obesity in this population. **Method:** A total of 112 PCOS patients (52 obese and 60 lean) aged 13–19 years and 61 age-matched healthy controls (35 obese and 26 lean) were included in the study. Anthropometric measurements, hormonal and metabolic parameters and serum BPA levels were evaluated in all participants. BPA was measured by HPLC. An oral glucose tolerance test was performed in the groups of PCOS and obese controls. Insulin resistance was determined using HOMA-IR, QUICK1, fasting glucose/insulin ratio, Matsuda index, and total insulin levels during OGTT. **Results:** Adolescents with PCOS had markedly increased serum BPA levels (1.1 ± 0.4 ; 0.8 ± 0.3 ng/ml; $P=0.001$). BPA was significantly correlated with gynaecological age, total and free testosterone, DHEA-S, and Ferriman–Gallwey score ($r=0.29$; $r=0.52$; $r=0.44$; $r=0.37$; and $r=0.43$ respectively). There was no statistically significant difference between PCOS and control groups regarding serum glucose, lipids, transaminases, insulin, HOMA-IR, QUICK1, Matsuda index, and FGIR. **Conclusion:** Adolescent girls with PCOS have higher serum BPA levels than controls. Moreover, BPA concentrations are significantly correlated with androgen levels leading us to consider that BPA might have a potential role in etiopathogenesis of PCOS in adolescents.

P1-D3-230

Increasing Incidence of Premature Thelarche in the Central Denmark Region? Who Evolve into Precocious Puberty?

Mia Elbek Sømod, Esben Thyssen Vestergaard, Kurt Kristensen, Niels Holtum Birkebæk

Department of pediatrics, Aarhus University Hospital, Aarhus, Denmark

Background: Premature thelarche (PT) may evolve into precocious puberty (PP). The incidence of PP in girls has increased during the last two decades. The epidemiology of PT in the first years of life is less well described. **Objective and hypotheses:** We aimed to identify 0–6 year old girls referred to paediatric evaluation for PT in order to examine if the number of girls with PT is increasing, and to describe clinical characteristics of the girls with PT who evolve into PP. **Method:** Register-based retrospective follow-up study, including 0–6 year old girls referred with PT in the period 2006–2012 in the Central Denmark Region (population 1,277,538). PT was defined as isolated breast development Tanner stage \geq B2. Review of para-clinical data from patient files. **Results:** 121 girls met the inclusion criteria. The incidence proportion of PT for girls born in 2006 was 0.24%. The number of girls with PT increased during the years 2006 (7.4% of the cohort) to 2012 (20.7% of the cohort). 50.4% of the girls with PT were 1–2 years old at referral. 11 girls (9.1%) developed PP.

A GnRH test was performed in 45 girls at referral. The peak LH/FSH in response to the GnRH test was 0.38 (median) (range 0.09–2.67) in girls with PP and 0.19 (median) (range 0.06–1.25) in girls with PT. The girls with PP had a median bone age increase corresponding to 18.5 months (range – 2.5–40 months). 17 patients (14%) had a magnetic resonance imaging (MRI) of the brain. One PP patient had a tuber cinereum hamartoma. **Conclusion:** The referral rate of patients with PT increased over the years 2006–2012 indicating an increasing incidence. PT patients evolving into PP were characterized by an increased median peak LH/FSH ratio compared to patients not evolving into PP, and bone age was significantly increased in most patients with PP.

P1-D1-231

The Association between rs4684677 T/A Polymorphism in Preproghrelin Gene And predisposition to Autoimmune Thyroid Diseases in Children*

Artur Bosswski^a, Anna Moniuszko^b, Natalia Wawrusiewicz-Kurylonek^c, Anna Bossowska^d, Ewa Jakubowska^a, Adam Kretowski

^aDepartment of Pediatric Endocrinology, Diabetology with Cardiology Division, Medical University, Białystok, Poland; ^bDepartment of Infectious Diseases and Neuroinfections, Białystok, Poland;

^cDepartment of Endocrinology and Diabetes with Internal Medicine, Białystok, Poland; ^dDivision of Cardiology, Internal Affairs Ministry Hospital in Białystok, Białystok, Poland

Background: Ghrelin and obestatin are two gastrointestinal peptides obtained by post-translational processing of a common precursor, preproghrelin. mRNA expression for preproghrelin was found in autoimmune thyroid diseases (AITDs) in previous studies. There are papers, where a role of preproghrelin polymorphism on various immunological diseases was determined, but nothing is known about its influence on the AITDs. **Objective and hypotheses:** The aim of our study was to estimate the association of two polymorphism of preproghrelin gene with the predisposition to GD and HT in children. **Method:** The study was performed in the group consisting of 98 patients with GD (mean age \pm SD, 17.3 ± 6), 39 patients with HT (mean age \pm SD, 18 ± 4.5) sequentially recruited from the endocrinology outpatient clinic. Control group consisted of 158 healthy subjects. DNA was extracted from the peripheral blood leukocytes using a classical salting out method. The two SNPs rs4684677 (C_3151003_20) and rs4684677 (C_25607748_10) in the preproghrelin gene were genotyped by TaqMan SNP genotyping assay using the real-time PCR method. **Results:** In our study, rs4684677 T/A genotype was more frequent in patients with GD and HT (as one group) in comparison to healthy subjects ($P=0.04$) with OR=2.0 and 95% CI for OR: 1.02–4.5. We also observed rs4684677 T/A genotype to be more frequent in patients with HT in comparison to healthy subjects and patients with obesity and this difference was statistically significant ($P=0.02$) with OR=5.8 and 95% CI for OR: 1.2–139.4. **Conclusion:** Rs 4684677 T/A polymorphism in preproghrelin gene could contribute to autoimmune thyroid diseases development in children and T allele is the main risk factor. *Nominated for a Presidential Poster Award.

P1-D1-232

Chosen Polimorphisms in FoxP3 Gene in Children and Adolescents with Autoimmune Thyroid Diseases^{*}

Artur Bossowski^a, Hanna Borysewicz-Sanczyk^a, Natalia Wawrusiewicz-Kurylonek^b, Mieczysław Szalecki^c, Beata Wikiera^d, Ewa Barg^d, Malgorzata Mysliwiec^e, Anna Kucharska^f, Anna Bossowska^g, Joanna Gosciak^h, Katarzyna Zioraⁱ, Maria Gorska^b, Adam Kretowski^b

^aDepartment of Pediatrics, Endocrinology and Diabetes with a Cardiology Unit, Medical University in Białystok, Białystok, Poland; ^bDepartment of Endocrinology and Diabetes with Internal Medicine, Medical University in Białystok, Białystok, Poland; ^cClinic of Endocrinology and Diabetology Children's Memorial Health Institute, Warsaw, Poland; ^dDepartment of Endocrinology and Diabetology for Children and Adolescents, Wrocław Medical University, Wrocław, Poland; ^eDepartment of Pediatrics, Hematology, Oncology and Endocrinology, Medical University in Gdansk, Gdansk, Poland; ^fDepartment of Pediatrics and Endocrinology, Medical University in Warsaw, Wrocław, Poland; ^gDivision of Cardiology, Internal Affairs and Administration Ministry Hospital in Białystok, Białystok, Poland; ^hCentre for Experimental Medicine, Medical University of Białystok, Białystok, Poland; ⁱDepartment of Pediatrics, Silesian Medical University, Białystok, Poland

Background: Forkhead box P3 (Foxp3) is an important regulatory factor for the development and function of T regulatory cells (Tregs). Moreover it has been established that deficiency of the Foxp3 gene in Treg cells suppresses their regulatory function leading to the development of autoimmune diseases especially autoimmune thyroid diseases (AITDs). **Objective and hypotheses:** The aim of our study was to estimate the association of three polymorphism of FOXP3 gene with the predisposition to GD and HT in children and adolescents. **Method:** The study was performed in the group consisting of 145 patients with GD (mean age, 16.5 ± 2), 87 patients with HT (mean age, 15.2 ± 2.2) sequentially recruited from the endocrinology outpatient clinic and 161 healthy volunteers (mean age, 16.3 ± 3). DNA was extracted from the peripheral blood leukocytes using a classical salting out method. The three SNPs rs3761549 (-2383C/T), rs3761548 (-3279G/T) and rs3761547 (-3499T/C) in the FOXP3 gene were genotyped by TaqMan SNP genotyping assay using the real-time PCR method. The levels of thyroid hormones, TSH, and anti-thyroid autoantibody were determined using chemiluminescence method. **Results:** In our study the frequencies of rs3761549G/A genotype was more frequent in female patients with GD in comparison to healthy female ($P=0.03$). There were no differences in the distribution of other analyzed polymorphisms of FOXP3 gene between the studied groups. **Conclusion:** In conclusion, this result may suggest that rs3761548G/A polymorphism in Foxp3 gene may determine predisposition to GD.

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P1-D1-233

TSH Receptor Gene Variants in Pediatric Patients with Non Autoimmune Hyperthyrotropinemia^{*}

Paula Scaglia, Ana Keselman, Laura Gruñero Papendieck, Patricia Papendieck, Ignacio Bergadá, Horacio Domené, Ana Chiesa
Centro de Investigaciones Endocrinológicas "Dr. César Bergadá" (CEDIE), CONICET – FEI – División de Endocrinología, Hospital de Niños Ricardo Gutiérrez, Buenos Aires, Argentina

Context: Heterozygous mutations in TSH receptor (TSHR) have been described associated with mild TSH resistance characterized by non autoimmune hyperthyrotropinemia (NAH). The prevalence of this condition varies in different reports. **Objective:** To determine the prevalence of TSHR variants in pediatric NAH. **Subjects and methods:** Thirty-five non obese unrelated children with NAH (18 girls, aged 1–19 years) were enrolled. All presented at least two TSH >5mIU/l (median 8.8 mIU/l) with normal total and free thyroxine and negative thyroid antibodies. 18 patients were born small for gestational age (SGA). The coding sequence of TSHR (exons 1–10 and their intronic flanking regions) was PCR amplified from genomic DNA and automatically sequenced. Polyphen 2, SIFT, and Mutation Taster softwares were used for *in silico* prediction of gene variants effects. **Results:** Several polymorphic variants were found (allelic frequency, AF): p.P52T (4.3%), p.N187N (14.3%), p.A459A (1.4%), p.D727E (15.7%), and p.N744K (1.4%). Uncommon heterozygous variants were found in exon 10 in two patients, both non SGA. Patient 1 carried a novel missense variant, p.P407L (c.1220C>T), while patient 2 carried the p.I583T (c.1748T>C) variant, already reported in one NAH patient. This variant was less responsive to TSH stimulation *in vitro* than the WT receptor (1). Both variants were predicted as pathogenic by three different prediction software and were absent (p.I583T) or present with very low AF in public databases (1/13 005 for p.P407L). Nevertheless, *in vitro* expression of the novel p.P407L variant is required to establish its role in thyroid pathogenesis. **Conclusions:** The occurrence of ~6% of potential pathogenic variants of TSHR in a relative small cohort of pediatric NAH, confirms previous reports. Their deleterious effect on thyroid function needs further investigation but their identification might represent a useful tool in the clinical management of pediatric subclinical hypothyroidism.

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P1-D1-234

Association of Toll-Like Receptor-10 Polymorphisms with Autoimmune Thyroid Disease in Korean Children^{*}

Won Kyoung Cho, Yeon Jin Jeon, In Ah Jung, Shin Hee Kim, Jung-Pil Jang, Eun-Jeong Choi, Min Ho Jung, Tai-Gyu Kim, Byung-Kyu Suh

College of Medicine, The Catholic University of Korea, SEOUL, Republic of Korea

Background: The Toll-like receptors are germline-encoded receptors that play an essential role in initiating the immune

response against pathogens. **Objective and hypotheses:** We aimed to assess the association of TLRs polymorphism with autoimmune thyroid disease (AITD) in Korean children. **Method:** We define the polymorphism of TLR10, rs4129009, rs11096956, rs10004195 in 85 Korean AITD (GD=50, HD=35; M=16, F=69, mean age=12.9 3.1 years) and 183 controls. **Results:** The frequencies of the TLR10 (rs4129009) GG genotype were lower in AITD (OR=0.2, *cP*=0.01) and non-TAO (OR=0.2, *cP*=0.03) and A allele was higher in non-TAO (OR=6.4, *cP*=0.02) than normal group. The frequencies of the TLR10 (rs10004195) AA genotype in AITD (OR=0.4, *cP*=0.02), GD (OR=0.4 *cP*=0.02) and non-TAO (OR=0.3, *cP*=0.02) and A allele in AITD (OR=0.5, *cP*=0.03) and non-TAO (OR=0.4, *cP*=0.01) were lower and TT genotype in AITD (OR=2.0, *cP*=0.05) and non-TAO (OR=2.4, *cP*=0.02) and T allele in AITD (OR=2.7, *cP*=0.01) and non-TAO (OR=3.4, *cP*=0.01) were higher than normal group. **Conclusion:** Our results suggest that the polymorphism of TLR 10 might contribute to the pathogenesis of AITD.

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P1-D1-235

A Nonsense Thyrotropin Receptor Gene Mutation (R609X) is Associated with Congenital Hypothyroidism and Heart Defects*

Hakan Cangül^a, Veysel Nijat Bas^b, Yaman Sağlam^d, Michaela Kendall^e, Timothy G Barrett^f, Eamonn R Maher^g, Zehra Aycan^{b,c}

^aDepartment of Medical Genetics, Bahcesehir University School of Medicine, Istanbul, Turkey; ^bClinics of Pediatric Endocrinology, Dr. Sami Ulus Research and Training Hospital of Women's and Children's Health and Diseases, Ankara, Turkey; ^cYildirim Beyazıt University Medical School, Ankara, Turkey; ^dCentre for Genetic Diagnosis, Medical Park Goztepe Hospital, Istanbul, Turkey; ^eDivision of Clinical and Experimental Sciences, Department of Child Health, Faculty of, Southampton, UK; ^fSchool of Clinical and Experimental Medicine, Centre for Rare Diseases and Personalised Medicine, University of Birmingham, Birmingham, UK; ^gAcademic Department of Medical Genetics, University of Cambridge Clinical School, Cambridge, UK

Background: Congenital hypothyroidism, one of the most important preventable causes of mental retardation, is a clinical condition characterized by thyroid hormone deficiency in newborns. **Objective and hypotheses:** Congenital hypothyroidism is most often caused by defects in thyroid development leading to thyroid dysgenesis. TSH receptor (TSHR) is the main known gene causing thyroid dysgenesis in consanguineous families with congenital hypothyroidism. In this study, we aimed to determine the genetic alteration in a case with congenital hypothyroidism and heart defects coming from a consanguineous family. **Method:** We utilised genetic linkage analysis and direct sequencing to achieve our aim. **Results:** Our results revealed that the family

showed linkage to the TSHR locus, and we detected a homozygous nonsense mutation (R609X) in the case. **Conclusion:** Apart from other cases with the same mutation, our case had accompanying cardiac malformations. Although cardiac malformations are not uncommon in sporadic congenital hypothyroidism, here they are reported for the first time with R609X mutation in a familial case.

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P1-D1-236

Genome-Wide Promoter Methylation Analysis in Cytologically Indeterminate Thyroid Nodules*

Ericka B Trarbach^a, Amanda Shinzato^a, Chin J Lin^b, Suemi Marui^a, Antonio M Lerario^a

^aLaboratorio de Endocrinologia Celular e Molecular – LIM25, HCFMUSP, Sao Paulo/Sao Paulo, Brazil; ^bLaboratorio de Patologia Cardiovascular – LIM22, Sao Paulo/Sao Paulo, Brazil

Background: Differentiating potentially malignant thyroid nodules among those undetermined by cytology avoid unnecessary surgical procedures. Aberrant DNA methylation is ubiquitous in human cancers, including thyroid tumors. Biomarkers based on methylation profiles have been successfully used to diagnose early stage malignancy in many human cancers. **Objective and hypotheses:** To determine the genome-wide promoter methylation status of cytologically indeterminate thyroid nodules. **Methods:** We obtained genomic DNA from frozen samples of three classical (CV-PTC) and three follicular variant papillary (FV-PTC), two follicular adenomas (FA) and three adenomatous goiter (AG) removed from 11 unrelated patients. The DNA methylation fraction was enriched using methyl-DNA immunoprecipitation and interrogated on Affymetrix human promoter 1.0 array. For control, DNA from normal thyroid tissue patients' were also extracted and pooled in a single reaction. All array data analysis were performed using pre-defined tiling workflow in Partek[®] Genomics Suite[™] Software 6.4. In general, *P* values <0.05 were considered statistically significant. **Results:** We identified genes that are differentially hypermethylated in each thyroid tumor subtypes compared to normal tissue: 189 in CV-PTC, 192 in FV-PTC, 313 in FA, and 288 in AG. We also categorized thyroid tumors samples in two broad groups: benign (FA and AG) or malignant (CV-PTC and FV-PTC); 139 and 138 hypermethylated *loci* were exclusively observed in benign and malign tumors respectively. In addition, we further found that the tumor suppressor *RPS6* (ribosomal protein S6) and the *SLC5A4* (*solute carrier family 5 member 4*) genes were among selectively hypermethylated *loci* in malignant group. Subsequent analysis with large numbers of patients with thyroid cancer will be required to assess the usefulness of *RPS6* and *SLC5A4* promoter methylation as biomarkers of malignancy. **Conclusion:** Our findings confirmed previous results which demonstrated that DNA methylation signatures were only distinguished between well differentiated and non-differentiated thyroid cancers.

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P1-D1-237

Genetic Analysis of the Paired Box Domain Gene in a Cohort of Polish Patients with Primary Congenital Hypothyroidism

Malgorzata Kumorowicz-Czoch^a, Anna Madetko-Talowska^b, Adam Dudek^c, Dorota Tylek-Lemanska^d

^aJagiellonian University Medical College, Krakow, Poland, ^bChair of Pediatrics, Division of Medical Genetics, Polish-American Institute of Pediatrics, Jagiellonian University Medical College, Krakow, Poland, ^cPediatric Endocrinology Out-Patient Clinic, Provincial Hospital No2, Rzeszow, Poland, ^dDivision of Mass Screening and Metabolic Diseases, University Children's Hospital, Krakow, Poland

Background: The morphological and biochemical phenotype of Paired Box Domain Gene PAX8 mutation in patients with congenital hypothyroidism (CH) is variable. The contribution of mutations in PAX8 gene in children with CH and dysgenetic or orthotopic thyroid glands still remains a subject of interest of researchers. **Objective and hypotheses:** This study presents mutational analysis of the PAX8 gene in patients with primary CH. **Method:** 50 children (36 girls, 14 boys) with CH connected with thyroid ectopy ($n=18$), aplasia ($n=10$), hypoplasia ($n=2$), thyroid dysgenesis of unknown reason ($n=13$) or orthotopic thyroid ($n=7$) were enrolled. Study participants were born in south-eastern Poland in years 1993–2012 and selected in neonatal mass screening for CH. DNA was extracted from peripheral blood samples with the use of Master Pure DNA Purification Kit (Epicentre Biotechnologies). The 12 exons of the PAX8 gene along with their exon–intron boundaries were amplified and sequenced by Sanger method. Capillary electrophoresis was run on ABI 3500 (Applied Biosystems). **Results:** Two heterozygous transitions in exon 3 (c.68G>A) and in exon 5 (c.404A>G) were detected in a 3-year-old girl with a thyroid hypoplasia. One heterozygous transition in exon 5 (c.404A>G) was found in a 15-year-old girl with a thyroid aplasia. Additionally, a novel genetic variant in 3'UTR region of exon 12 (c.1971C>T) occurred in a 3-year-old boy with ectopic thyroid tissue. Well-described SNPs in exon 12 were revealed in 48 children. **Conclusion:** The study reports the occurrence of two novel missense substitutions in the PAX8 gene and also confirms a very low prevalence of PAX8 mutations in thyroid dysgenesis. Estimation of the contribution of the revealed mutation to the etiology of CH in two girls with hypoplastic and aplastic thyroid requires further functional analysis.

P1-D1-238

Homozygous Deletion of The TSH β Subunit Gene Causes Congenital Secondary Hypothyroidism in a Consanguineous Family of Turkish Descent

Pia Hermanns^a, Cherize Klotz^b, Robert Couch^c, Norma Leonard^b, Joachim Pohlenz^a

^aDepartment of Pediatrics, University Medical Center Mainz, Mainz, Germany; ^bUniversity of Alberta Hospital, Edmonton, Alberta,

Canada; ^cPediatric Endocrinology, Walter Mackenzie Health Sciences Centre, Edmonton, Alberta, Canada

Background: A 6-week-old male was admitted for investigation of prolonged jaundice. The pregnancy was unremarkable with a normal at term delivery. The neonatal screening was unremarkable. The boy was born to consanguineous parents of Turkish descent. **Objective and hypotheses:** At presentation serum levels of thyrotropin, T₄ and T₃ were low and prolactin slightly elevated. Venous TSH was undetectable low. Central hypothyroidism was diagnosed and a TSH beta gene mutation was hypothesized. **Method:** Using different PCR protocols, we were unable to amplify both coding exons of the boy's TSHbeta gene, which suggested a deletion of the coding sequence. An array comparative genomic hybridization (aCGH) was performed using specific probes around the TSHbeta gene locus on chromosome 1. **Results:** The proband was homozygous for a 6 kb deletion spanning all exons, as well as parts of the 5' UTR of the TSHbeta gene. Both parents were heterozygous for this deletion. **Conclusion:** This is the first report of a large deletion in the TSH beta gene. Isolated congenital secondary hypothyroidism (ICSH) is rare but important, since most patients with ICSH are diagnosed later in life, which results in severe growth failure and intellectual disability. Our study shows again that neonatal screening for both, fT4 and TSH is desirable. It would help to prevent symptoms of hypothyroidism in affected individuals.

P1-D1-239

Genotype and Phenotype Characterization of a Series of Italian Patients Affected with Idiopathic Central Hypothyroidism

Marco Bonomi^a, Paolo Duminuco^a, Alessandro Salvatori^b, Mario Maggi^c, Fabio Buzi^d, Alba Pilotta^e, Giorgio Radetti^f, Paolo Beck-Peccoz^g, Irene Campi^g, Nadia Schoenmakers^h, Sjoerd Joutstra^{i,j}, Jan Maarten Witⁱ, Daniel Bernard^k, Luigi Nespoli^b, Mauro Bozzola^l, Luca Persani^g

^aLaboratorio di Ricerche Endocrino-Metaboliche e Divisione di Medicina ad indirizzo Endocrino-Metabolico, Milano, Italy;

^bDipartimento di Pediatria, Università dell'Insubria, Varese, Italy;

^cDipartimento di Fisiopatologia Clinica, Università di Firenze, Firenze, Italy;

^dDipartimento di Pediatria, Ospedale A.Poma, Mantova, Italy;

^eDipartimento di Auxo-Endocrinologia, Spedali Civili di Brescia, Brescia, Italy;

^fDipartimento di Pediatria, Ospedale Regionale di Bolzano, Bolzano, Italy;

^gDipartimento di Scienze Cliniche e di Comunità, Università di Milano, Milano, Italy;

^hMetabolic Research Lab, Wellcome Trust-MRC Institute of Metabolic Science, Addenbrooke's Hospital, University of Cambridge, Cambridge, UK;

ⁱDepartment of Pediatrics, Leiden University Medical Center, Leiden, The Netherlands;

^jDepartment of Endocrinology and Metabolism and Center for Endocrine Tumors Leiden, Leiden University Medical Center, Leiden, The Netherlands;

^kDepartment of Pharmacology and Therapeutics, McGill University Montreal, Montreal, Quebec, Canada;

^lDipartimento Materno-infantile, Policlinico San Matteo, Pavia, Italy

Background: Central hypothyroidism (CeH) is a rare thyroid hormone deficiency due to an insufficient stimulation of a normal thyroid gland. Candidate genes for isolated CeH include TSH β , TRH receptor (TRHR) or IGSF1 genes while the combined pituitary hormone deficits (CPHDs) are the consequence of defects in embryonic pituitary transcription factors or in the prokineticin receptor 2 (PROKR2). **Patients series:** Here we report nine males (M) and 15 females (F), with CPHD in three cases and Isolated CeH in the remaining 21 and affected with low/normal TSH levels and low free T₄ levels. Familiarity was previously known in only two cases. **Results:** In 1M and 2F that were negative at neonatal TSH screening, severe congenital hypothyroidism was diagnosed at 44 or 81 days or 4 months, while other patients with milder forms were diagnosed during childhood or adulthood (2–58 years). All had a normal pituitary MRI, but two with a partial empty sella and other two with pituitary hyperplasia or a microlesion. Their history was invariably negative for traumatic or ischemic brain injuries. Thyroid ultrasound did not uncover any sign of thyroid autoimmunity and thyroid autoantibodies were negative in all cases. Among the eight cases presenting with blunted TSH responses to TRH stimulation but normal PRL increases we had detected two homozygous mutations in the TSH β gene (Q49X e IVS2+5) in two neonates (1F and 1M) associated with severe hypothyroidism. Two mutations of the TRHR gene (R17X) and two mutations in the IGSF1 gene (E1200fsX3; S770N) were found in 3M and 1F having an absent TSH/PRL responses after TRH stimulation. In all the three cases with CPHDs we identified a genetic cause: 2 cases were associated with PROP1 defects (1M was heterozygous for a novel variant, R104Q, whereas 1F was homozygous for the known R73H variant), whereas we identified a heterozygous PROKR2 variant (H20MfsX23) in a 58-year-old male patient. **Conclusion:** In the present series, we identified a genetic cause in eight out of 24 CeH subjects. Since genetic variations were identified in all three CPHD cases, the pathogenesis remains unexplained in the majority of patients with isolated CeH.

P1-D1-240

A Novel Mutation in the TITF1 Gene in a Child with Benign Hereditary Chorea

Viviana Dora Patianna^a, Barbara Predieri^a, Livia Garavelli^b, Carlo Fusco^c, Simona Filomena Madeo^a, Patrizia Bruzzi^a, Lorenzo Iughetti^a

^aPediatrics Unit, Department of Medical and Surgical Sciences Mother, Children and Adult, University of Modena & Reggio Emilia, Modena, Italy, ^bClinical Genetic Unit, Obstetric and Pediatric Department, S. Maria Nuova Hospital, Reggio Emilia, Italy, ^cChild Neurology Unit, Obstetric and Pediatric Department, S. Maria Nuova Hospital, Reggio Emilia, Italy

Introduction: Benign hereditary chorea (BHC) is a rare, autosomal dominant disorder, described as a non-progressive chorea of early onset. BHC can present as single neurologic disorder (13%), brain and thyroid disease (30%) or 'brain-lung-thyroid syndrome' with congenital hypothyroidism and neonatal respiratory distress syndrome (50%). **Case Report:** 18 months old

infant was admitted to the Endocrinology Outpatient Clinic with motor delay and gait disorder. He was the second son of healthy and non-consanguineous parents. Family history was uneventful. Perinatal history was unremarkable for pulmonary problems and screening test for congenital hypothyroidism was normal. He presented short stature (2nd perc, -1.99 SDS), normal weight, without significant dysmorphic features. Neurological examination showed hypotonic and joint laxity, axial dystonia, and choreic movements. No inherited metabolic disease was shown, array-CGH were normal, and IGF1 levels were at the lower limit. TSH (8.46 μ UI/ml) and fT₄ (11.1 pg/ml) were consistent with a state of subclinical hypothyroidism. Brain MRI showed mild abnormalities in peripheral regions, with a large cistern and dysmorphism of the hippocampal formations. This clinical complex together with thyroid disorders led us to formulate the diagnostic suspicion of BHC and to analyse the thyroid transcription factor 1 gene (TITF1). This hypothesis was confirmed by molecular test with the detection of a heterozygous substitution (Pro291Arg) in the gene TITF1, cr.14q13.3. **Conclusion:** The transcription factor 1 gene is essential for the organogenesis of the lungs and thyroid and in the development of the basal ganglia. The study of genotype/phenotype can be extremely complex in the presence of a highly variable disease expressivity. Mild alteration of TSH in presence of hypotonia, and choreic jerks has to take in account to suspect this rare condition. Our patient presented a 'de novo mutation' and the choreic jerks were subtle and were not the dominant clinical feature.

P1-D1-241

Twin Couples and/or Triplets Discordant for Congenital Hypothyroidism at Birth: the Importance of the Re-screening at 2–4 Weeks of Life

Antonella Olivieri^a, Emanuela Medda^a, Alessandra Cassio^b, Giovanna Webers^c, Pietro Costa^d, Francesca Calaciura^e, Maria Cristina Vigone^c, Valentina Di Russo^b, Cristina Fazzini^a

^aItalian National Institute of Health, Rome, Italy; ^bDepartment of Medical Sciences and Surgery, University of Bologna, Bologna, Italy; ^cVita-Salute University, IRCCS San Raffaele Hospital, Milan, Italy; ^dUniversity 'La Sapienza', Rome, Italy; ^eDepartment of Clinical and Molecular Biomedicine, Garibaldi Hospital, Catania, Italy

Background: A high risk of congenital hypothyroidism (CH) has been documented in multiple pregnancies. Over the years special screening procedures for preterm and twin babies (re-screening at 2–4 weeks of life) have been adopted by many screening laboratories worldwide. However, no extensive studies have been performed to verify how many co-twins with negative test at first screening (3–5 days of life) become positive at re-screening, and the utility of a long-term follow-up also in co-twin with negative test at screening and re-screening. **Objective and hypotheses:** The aims of this study were: i) to estimate the concordance rate for CH by the first month of life in twin couples/triplets discordant for CH at the first screening and ii) to verify whether a long-term follow-up of co-twins with negative test at screening and re-screening may be useful to verify the occurrence of thyroid hypofunction in these children during

development. **Method:** Twenty-four twin couples and two triplets discordant for CH at first screening (26 CH probands) were recruited for the study. The range of the long-term follow-up in the couples/triplets was 3 months–18 years. Pairwise concordance rate (PWCR), for CH by the first month of life and for the occurrence of thyroid hypofunction during development, was calculated as the proportion of concordant pairs over the sum of concordant and discordant pairs. **Results:** Among the couples/triplets discordant at first screening two co-twins resulted positive at re-screening. Therefore, the PWCR for CH was 7.1%. During the long-term follow-up a thyroid hypofunction was observed in three co-twins and a treatment with L-thyroxine was started at the age of 2 months, 9 months, and 12 years. The PWCR for thyroid hypofunction among couples discordant at screening was 11.7%. **Conclusion:** These preliminary results confirm the importance of the re-screening at 2–4 weeks of life in twins, and the possible benefit of a long-term follow-up also in co-twin with negative test at screening and re-screening.

P1-D1-242

Congenital Hypothyroidism and Tuberous Sclerosis: an Association or a Coincidence?

Francesco Gallo^a, Pietro Conte^a, Rosa Maria Alfano^b, Gaetano Bulfamante^b, Fulvio Moramarco^a

^aPediatric Unit of Perrino Hospital, Brindisi, Italy; ^bAnatomical Pathology Unit of Azienda Ospedaliera San Paolo, Milan, Italy

Background: Tuberous sclerosis (TS) is a polymorphic, dominantly inherited syndrome caused by an inactivating mutation in tumor suppressor genes, TSC1 or TSC2; they regulate mammalian target of rapamycin (mTOR), a key player in control of cellular growth and protein synthesis. The disease involves benign tumors in several distinct organs (such as the skin, kidneys, heart, and CNS), that can interfere with organ function. Rarely TS is associated with endocrine abnormalities, and almost never with congenital hypothyroidism. **Objective and hypotheses:** EG was a female newborn, positive at neonatal screening for congenital hypothyroidism (CH) (confirmed with venous sample). USgraphy and scintigraphy showed hypo-dysplasia of her thyroid (treated with L-thyroxine). As a part of diagnostic approach, we made echocardiography, founding several rhabdomyomas. These benign tumors are frequently associated with TS, so we searched for mutations of TSC1 and TSC2 genes. EG had also brain nuclear magnetic resonance (NMR) and abdominal organs echographies (normal). No skin lesions were found. **Method:** DHPLC and polymorphisms sequencing of TSC1 and TSC2 genes. **Results:** EG had heterozygosis in pLeu697Ser[^] of TSC2 exon 18 and p.Asn762Ser mutation of TSC1 exon 18. The same abnormalities were found in her father. The brain NMR showed a small altered signal in left front-insular white substance. EG had later seizures, so she had to begin therapy with valproic acid. **Conclusion:** Although the association of CH and TS in one patient may be merely coincidence, we speculate that the dysgenetic thyroid gland in this baby can be a 'hamartia' as a consequence of the tuberous sclerosis gene mutation.

P1-D1-243

Evaluation of Serum Cytokines IL-6 and Osteoprotegerin Measurements in the Diagnosis of Chronic Autoimmune Thyroiditis and Graves' Disease in Children

Hanna Mikos^a, Marcin Mikos^b, Marek Niedziela^a

^a2nd Chair of Pediatrics, Department of Pediatric Endocrinology and Rheumatology, Poznan University of Medical Sciences, 27/33 Szpitalna Street, 60-572 Poznan, Poland; ^b3rd Chair of Pediatrics, Department of Pneumology, Allergology and Clinical Immunology, Poznan University of Medical Sciences, 27/33 Szpitalna Street, 60-572 Poznan, Poland

Background: Chronic autoimmune thyroiditis (cAIT) and Graves' disease (GD) are the most common autoimmune disorders in children. Proinflammatory cytokine such as IL-6 has been generally associated with the induction of inflammation and autoimmunity. Osteoprotegerin, a soluble glycoprotein and a member of the tumor necrosis factor receptor (TNFR) family, play an important role in bone homeostasis and in vasculature. **Objective and hypotheses:** The aim of the study was to determine concentrations of IL-6 and OPG in autoimmune thyroid disease (AITD) in children. **Method:** We studied serum IL-6 and OPG (ELISA) in 22 newly diagnosed children with cAIT (mean: TSH 46.7 μ IU/ml \uparrow , fT₄ 0.54 ng/dl \downarrow , fT₃ 2.10 pg/ml; ATPO 2597 IU/ml \uparrow , and ATG 533 IU/ml \uparrow), 22 GD children (mean: TSH 0.01 μ IU/ml \downarrow , fT₄ 4.24 ng/dl \uparrow , fT₃ 19.01 pg/ml \uparrow ; TRAb 24 U/l \uparrow ATPO 2280 IU/ml \uparrow , ATG 426 IU/ml \uparrow) and 20 healthy subjects with normal fT₄, fT₃, TSH, and negative antithyroid Abs. **Results:** In our study no significant difference was observed between IL6 serum concentrations in studied groups ($P=0.48$; Kruskal–Wallis test). OPG concentrations were significantly higher (ANOVA $P=0.013$; Newman–Keuls $P<0.01$) in children with GD: (mean \pm s.d.) (4.48 \pm 2.01 pmol/l) compared to control group (3.02 \pm 1.17 pmol/l); whereas no significant difference between children with cAIT (3.79 \pm 1.28 pmol/l) vs control group (Newman–Keuls $P>0.05$) and cAIT vs GD (Newman–Keuls $P>0.05$) was observed. In children with hyperthyroidism we identified significant positive correlation between OPG and IL6 ($r=0.51$; $P<0.05$). ROC curve indicates good efficacy of OPG to discriminate groups of hyperthyroid and healthy children (AUC=0.716; $P=0.017$) at cut-off point of 4.54 pmol/l with low sensitivity (54.5%) but high specificity (95%). In these groups of children AUC of IL6 did not differ significantly from 0.5 ($P=0.435$). **Conclusion:** Based on performed study we suggest that OPG may be considered as a marker of hyperthyroidism in GD children.

P1-D2-244

Treatment of Graves' Disease with Methimazole in Children Alters the Proliferation of Treg Cells and T Lymphocytes^{*}

Maria Klatka^a, Ewelina Grywalska^b, Magdalena Wasiak^c, Jacek Rolinski^b

^aDepartment of Pediatric Endocrinology and Diabetology, Medical University, Lublin, Poland; ^bDepartment of Clinical Immunology and Immunotherapy, Medical University, Lublin, Poland; ^cDepartment of Otolaryngology and Laryngeal Oncology, Medical University, Lublin, Poland

Background: Graves' disease (GD) is almost always the cause of hyperthyroidism in children. Studies carried out for recent years confirm an important role of T regulatory cells (Tregs) in the development of autoimmune diseases. However, the interactions between T-cell response and Treg proliferation in GD is still poorly understood. **Objective and hypotheses:** The aim of this research was the assessment of the *in vitro* proliferation of Treg cells and T CD3+ lymphocytes in 50 children with GD before and after the treatment with methimazole (MMI). **Methods:** The study was conducted by means of a proliferation test which uses methyl-3H-thymidine. The relations between proliferation assays and selected clinical parameters were also described. **Results:** T CD3+ and T CD3+ with PMA lymphocyte proliferation rates before the treatment with MMI were significantly higher than after the treatment ($P < 0.0001$). Treg and Treg with PMA cell proliferation rates were significantly lower before the treatment ($P < 0.0001$). Moreover, we observed higher Treg ($P < 0.0001$) and Treg with PMA ($P < 0.05$) cell proliferation rates before the treatment as well as after the treatment in patients who had no relapse of hyperthyroidism. There was also observed a positive correlation between CD3+ lymphocyte proliferation rate before the MMI treatment and FT₃ as well as FT₄ concentration ($r = 0.839$, $P < 0.0001$ and $r = 0.375$, $P < 0.01$, respectively). Then T CD3+ lymphocyte proliferation rates before and after the treatment with MMI were positively correlated with TSI ($r = 0.968$, $P < 0.0001$ and $r = 0.522$, $P < 0.0001$, respectively). **Conclusions:** Co-cultures of Tregs and T CD3+ cells show that Tregs are not capable of inhibiting efficiently the proliferation of T CD3+ cells in these patients. Partly dysfunctional in Graves' disease Tregs seem to be suppressed by CD3+T cells. Our observations indicate that MMI treatment helps Treg cells to restore their suppressive function in autoimmune diseases indicating some immunomodulatory effects of methimazole.

*Nominated for a Presidential Poster Award.

P1-D2-245

Thyroid Dysfunction in Children After Hematopoietic Stem Cell Transplantation: Short Term Follow-Up for 12 Months*

Yeon Jin Jeon, In Ah Jung, Shin Hee Kim, Won-Kyoung Cho, Jae-Wook Lee, Kyoung Soon Cho, So Hyun Park, Nak-Gyun Chung, Min-Ho Jung, Bin Cho, Byung-Kyu Suh

Department of Pediatrics, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

Background: We evaluated 12 months follow-up of thyroid function in patients who underwent hematopoietic stem cell transplantation (HSCT) during childhood and adolescents. **Methods:** We studied 83 hematologic-malignancy patients

(46 boys and 37 girls, acute lymphoblastic leukemia = 25, acute myeloid leukemia = 51, chronic myelogenous leukemia = 7) who underwent HSCT between January 2006 and December 2011.

The mean age at HSCT was 9.78 ± 4.42 years. Thyroid function of the patients was evaluated before and 1, 3, 6, 9, 12 months after HSCT. The incidence and risk factors of overt hypothyroidism, subclinical hypothyroidism (SH) and euthyroid sick syndrome (ESS) were studied. The effect of conditioning regimen, graft-vs-host disease, use of steroid hormone or other clinical factors on thyroid dysfunction was investigated. **Results:** Forty-four patients (53.0%) had thyroid dysfunction during 12 months after HSCT. Thyroid dysfunction developed in 14 (17.3%), 10 (12.0%), 14 (17.3%) and 21 (24.1%) patients at 1, 3, 6, 9 and 12 months after HSCT. The incidence according to duration increased significantly (P for trend 0.035). ESS developed in 8(9.9%), 5(6.9%), 3(3.7%), 3(3.7%) and 2(2.4%) patients at 1, 3, 6, 9 and 12 months after HSCT. The incidence according to duration increased significantly (P for trend 0.00015). SH developed in 2(2.5%), 2(2.4%), 13(16.0%), 13(15.9%) and 12(14.5%) patients at 1, 3, 6, 9 and 12 months after HSCT. The incidence according to duration increased significantly (P for trend 0.031). A total of 11 patients (13.3%) needed thyroid hormone replacement; ten out of them had SH and one overt hypothyroidism. In univariate analysis, there was no significant risk factor of thyroid dysfunction at 12 months after HSCT. **Conclusion:** After HSCT during childhood and adolescence, a significant number of patients experience thyroid dysfunction including ESS and SH. Short-term and continuous follow-up for thyroid function after HSCT is important to provide timely and appropriate treatment.

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P1-D2-246

The Effect of L-Thyroxine Treatment on Left Ventricular Functions in Children with Subclinical Hypothyroidism

Gonul Catli^a, Mustafa Kir^b, Ahmet Anik^a, Nuh Yilmaz^b, Ece Bober^a, Ayhan Abaci^a

^aDepartment of Pediatric Endocrinology, Faculty of Medicine, Dokuz Eylül University, Izmir, Turkey; ^bDepartment of Pediatric Cardiology, Faculty of Medicine, Dokuz Eylül University, Izmir, Turkey

Background: Subclinical hypothyroidism (SH) is defined as an elevated serum concentration of TSH when serum free thyroxine (fT₄) concentration is within its reference range. Impaired myocardial contractility in overt hypothyroidism and left ventricular (LV) diastolic dysfunction in adults with SH as well as beneficial effects of thyroid hormone replacement on systolic and diastolic functions in adults with SH has been documented, however the presence of similar alterations in children with SH is still under debate. **Objective and hypotheses:** To evaluate cardiac functions of children with subclinical hypothyroidism (SH) before and after L-thyroxine (LT₄) replacement using M-mode and tissue Doppler echocardiography (TDE). **Method:** Children with SH together with age- and sex-matched healthy

children were enrolled in the study. At baseline and 6 months after euthyroidism was achieved M-mode and TDE were performed and left ventricular functions were evaluated. Pre-treatment data of the SH group was compared with those of controls and post-treatment parameters. **Results:** Thirty-one children with SH and 32 healthy children were enrolled in the study. In M-mode echocardiography interventricular septum thickness and left ventricle mass index were slightly increased in SH group than controls ($P < 0.05$). In the SH group none of the M-mode echocardiography-derived parameters have changed after LT_4 treatment ($P > 0.05$). In TDE, patients with SH had a significantly lower E_m' and a higher E/E_m' , isovolumic relaxation time (IVRT), isovolumic contraction time (IVCT) and myocardial performance index (MPI) than the control group ($P < 0.05$). Six months after euthyroidism was achieved TDE showed a significant increase in E_m' and a significant decrease in IVRT, IVCT and MPI. **Conclusion:** The result of this study showed that SH was associated with pre-clinical alterations in left ventricular function as compared to healthy individuals and LT_4 treatment improved left ventricular TDI functional parameters.

P1-D2-247

Urinary Iodine Concentrations in Mothers and their Term Newborns

Katerina Krylova^a, Radovan Bilek^b, Milan Bayer^a, Petr Dejmek^c, David Neumann^a

^aDepartment of Pediatrics, Faculty of Medicine in Hradec Kralove and University Hospital Hradec Kralove, Charles University in Prague, Hradec Kralove, Czech Republic; ^bInstitute of Endocrinology, Prague, Hradec Kralove, Czech Republic, ^cDepartment of Pediatrics, 3rd Faculty of Medicine and University Hospital Kralovske Vinohrady, Charles University in Prague, Hradec Kralove, Czech Republic

Background: The development of fetal thyroid gland and its function in fetus and newborn are influenced by maternal iodine supplementation and maternal disorders of thyroid gland. Pregnant and lactating women are considered a risk group, although the Czech Republic ranks among countries with sufficient iodine supply. In case of maternal iodine deficiency, fetus is more susceptible to other factors influencing fetal thyroid gland development and function and also its neurologic development during all phases of fetal growth. Iodine supplementation of a population is mainly detected through urinary iodine concentrations (UIC). **Objective and hypotheses:** Iodine status of pregnant women and newborns is still questionable even in countries with sufficient iodine supply. The study search actual data in a mid-european region. **Method:** In 2013, we examined concurrently 50 mothers without thyroid disorder and their 50 healthy term newborns. Iodine supplementation during pregnancy was recorded. UIC levels were measured on the day of birth (mothers) and on day 3 (mothers and newborns). **Results:** Only 46% of mother declared regular iodine supplementation in the

form of iodide or multivitamins with iodine. According to the UIC levels detected, 78% of mothers before delivery suffered from mild to moderate iodine deficiency, 78% of mothers on day 3 showed mild iodine deficiency. Newborn UIC levels on day 3 were in 54% of cases below 100 $\mu\text{g/l}$. **Conclusion:** The maternal UIC did not depend on their declared iodine supplementation. Individual differences in iodine needs cannot be excluded. Results do not prove a strong influence of maternal iodine supplementation on newborn UIC, although newborn iodine status was favourable in mothers with declared regular intake. Iodine substitution during pregnancy and lactation remains essential as prevention of maternal and neonatal health, even in countries with overall sufficient iodine supply.

P1-D2-248

Vitamin D in Adolescents with Hashimoto's Thyroiditis

Olga Gumeniuk^{a,b}

^aSaratov State Medical University, Saratov, Russia; ^bDepartment of the Peadiatric Endocrinology, University's Hospital, Saratov, Russia

Background: The results of several studies suggest that vitamin D could possibly decrease the risk of autoimmune diseases. **Objective:** To evaluate the efficiency of the vitamin D in adolescents with Hashimoto's thyroiditis (HT). **Methods:** The study included 32 adolescents (aged 12–17 years, mean age was 14.4 ± 1.3 years) with HT (normal range TSH, fT_3 , fT_4 and elevated antibodies). HT was diagnosed on the basis of thyroid peroxidase antibodies level and typical picture of thyroid ultrasound. Thyroid volume was estimated by using ultrasound (Medison Accuvix V20, Korea). We compared out thyroid volume results with recommended normal values established by WHO/ICCIDD. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS 16.0, USA). Data are expressed as median. The part of the patients (group I, $n = 16$) were treated with levothyroxine and vitamin D (400 IU/day) for a 6 months. Patients in the group II ($n = 14$) were treated with only levothyroxine for a 6 months. Patients in the group III, control group ($n = 12$) were not treated (only observation for a 6 months). **Results:** Thyroid volume was enlarged more than 30% above normal volume (97th percentiles) in all patients in group I and II. After 6 months of therapy with levothyroxine and vitamin D, in the group I the antibody levels (from 877.5 to 511.5 mIU/ml) and thyroid volume (from 14.8 to 8.7 ml decreased significantly ($P = 0.044$ and $P = 0.0089$ respectively). After 6 months of therapy with levothyroxine, in the group II the thyroid volume (from 15.3 to 10.8 ml) decreased significantly ($P = 0.01$). Among the untreated group III (control group), the antibody levels remained the same in 100% patients and thyroid volume rise in 87% patients. **Conclusion:** This study has shown that preventative vitamin D treatment in adolescents with Hashimoto's disease reduced the markers of autoimmune thyroiditis.

P1-D2-249

Capillary TSH Cut-off Levels for Congenital Hypothyroidism Screening: Evidence Against Adopting the UK Threshold of 10 mIU/l

Jeremy Jones, Guftar Shaikh, Avril Mason

Department of Endocrinology, Royal Hospital for Sick Children, Glasgow, UK

Background: The recommended capillary TSH cut-off level for neonatal screening for congenital hypothyroidism (CH) in the UK is 10 mIU/l. However several of the regional screening laboratories have adopted lower cut-off limits in order to increase detection sensitivity. There is now pressure to standardise the UK screening programme with universal adoption of the recommended cut-off. Scotland has been using a cut-off of 8 mIU/l since the adoption of AutoDELFIA TSH screening methodology in Autumn 2003. We wished to examine what difference this lower cut-off point has made to detection of congenital hypothyroidism. **Methods and design:** The national congenital hypothyroidism database was searched for cases in which the first or subsequent capillary TSH (cTSH) results fell between 8.0 and 10.0 mIU/l between January 2004 and 2014. The outcome of these cases was then examined. **Results:** There were 304 referrals for cTSH of any value in the study period. Twenty-five (8.2%) referrals were made because of a cTSH between 8.0 and 10.0 mIU/l. Of these, 13 (52%) have since proven to have had transient elevated TSH in the neonatal period. A further 6 (24%) cases have permanent forms of CH (two thyroid ectopia with compensated hypothyroidism, two dysmorphogenesis and decompensated hypothyroidism, two unknown cause: one decompensated pre-treatment; the other on 100 µg/day thyroxine at seven years of age). The remainder 6 (24%) have no final diagnosis, either because they are still awaiting diagnostic challenge ($n=2$), because the challenge was inconclusive ($n=2$) or data was not available. **Conclusion:** Less than 10% of referrals made were due to a cTSH of between 8.0 and <10.0 mIU/l. Unsurprisingly, a significant proportion of these referrals proved to be transient neonatal hyperthyrotropinaemia. However one quarter of all referrals made based on a cTSH of between 8.0 and <10.0 mIU/l had permanent forms of CH including both dysgenesis and dysmorphogenesis. Half of the referrals made in this group had decompensated CH at pre-treatment assessment. Thus we would find it difficult to adopt the recommended UK cut-off of 10 mIU/l.

P1-D2-250

In Patients with Chronic Autoimmune Thyroiditis, Investigation of the Effects of Functions of Regulatory T Cells and Vitamin D

Zeynep Siklar, Deniz Karatas, Figen Dogu, Pinar Kocaay, Bulent Hacıhamdioglu, Aydan İkinçioğulları, Merih Berberoglu

Ankara University School of Medicine, Ankara, Turkey

Background: Treg cells are characterized by expression of Foxp3 molecule that serve as keys in the maintenance of peripheral tolerance and in controlling the immune response. The exact role of Treg cells in the pathogenesis of CAT has not been recognized yet. **Objective and hypotheses:** It is suggested that vitamin D is one of the factors that can regulate the function of Treg cells. In this study, the relationship between Treg cells (levels and expression) and vitamin D levels was investigated in pediatric CAT patients. **Method:** Thirteen children and adolescents (ages: 5–18.4 years) with a diagnosis of CAT and 22 healthy subjects were enrolled to the study. Foxp3 expressing CD4+ CD25+ T cells were identified as Treg cells. Treg cells are measured by flow cytometry (Beckmancoulter the NAVIOS, USA) using intracytoplasmic staining with tree colors direct immunofluorescence method. At diagnosis, 25 OHD3 levels were determined all patients. Foxp3 expression was measured before and after vitamin D replacement therapy in patients having low levels of 25 OHD3. **Results:** In study group, Treg cell levels (%) did not differ from the control group, while Foxp3 molecule expression was lower. There was no statistically significant difference between the groups according to vitamin D levels. However, the patients having vitamin D deficiency and CAT who are given vitamin D replacement, the Treg cells level did not change and Foxp3 molecule expression were significantly increased (before and after vitamin D replacement were 70.46 ± 6.16 and 82.1 ± 14.88 µg/l respectively, $P=0.015$). **Conclusion:** In the pediatric age group, patients with CAT, FoxP3 expression is decreased. This reduction seems not associated with vitamin D levels, but in patients requiring vitamin D replacement, the expression of FoxP3 molecules showed an increase. This result suggests that vitamin D can play a role in enhancing natural Treg cells functions.

P1-D2-251

Triiodothyronine-Predominant Graves' Disease (T3-P-GD): Description and Management in Childhood

Julie Harvengt^a, Priscilla Boizeau^b, Delphine Zenaty^a, Anne Paulsen^a, Dominique Simon^a, Sophie Guilmin Crepon^a, Corinne Alberti^b, Jean-Claude Carel^a, Juliane Léger^a

^aDepartment of Pediatric Endocrinology, CRMERC, INSERM 1141, Hopital Robert Debré, Université ParisVII, Paris, France; ^bClinical Epidemiology Unit, INSERM CIE5, Hopital Robert Debré, Université ParisVII, Paris, France

Background: T3-P-GD, a severe, rare disorder well known in adults, has not previously been described in children. It is characterized by persistently high serum fT₃ concentration and normal, or even low, fT₄ concentration during drug treatment. This condition is associated with very high titers of TRAb and large goiters, but its pathogenesis remains unclear. The recognition of this form of GD in children is of particular importance, as higher antithyroid drug (ATD) doses are required for its management. We aimed to describe clinical characteristics and management of T3-P-GD in a paediatric population. **Methods:** All patients with GD followed for more than 1 year in our

department between 2003 and 2013 ($n=60$) were included, and patients with T3-P-GD (Group I) were defined as high fT_3 (>8.0 pmol/l) associated with normal fT_4 (<21.5 pmol/l) and undetectable levels of TSH during follow-up, at more than 1 month after ATD treatment initiation. **Results:** Eight of the patients with GD had T3-P-GD (13%), at a median of 6.3 (3.3–9.6) months after diagnosis ($n=4$) or 2.75 (2.0–11.9) months after relapse ($n=4$). At diagnosis, the Group I patients were younger than those of Group II (patients without T3-P-GD) (6.8 (4.3–11.0) vs 10.7 (7.2–13.7) years) and had a more severe form of the disease ($fT_4=92$ (64–99) vs 63 (44–83) pmol/l, $fT_3=31$ (30–46) vs 25 (17–31) pmol/l; TRAb 40 (31–60) vs 17 (8–25) IU/l) and a lower fT_4/fT_3 ratio (2.1 (2.0–2.5) vs 2.7 (2.2–3.1) for Group I vs II, respectively); $P<0.001$. fT_4/fT_3 ratio remained significantly lower for several months. During follow-up, a significantly higher dose of ATD was required (0.63 (0.52–0.96) vs 0.41 (0.28–0.56) mg/kg per day after 6 months; $P<0.001$). **Conclusion:** Severe hyperthyroidism and fT_4/fT_3 ratio at diagnosis may facilitate the identification of patients requiring higher ATD dosage during follow-up.

P1-D2-252

Autoimmune Encephalopathy in a Boy with Graves' Disease

Anna Kucharska, Katarzyna Kadziela, Beata Pyrzak

Department of Paediatrics and Endocrinology, Medical University of Warsaw, Warsaw, Poland

Background: Autoimmune encephalopathy is usually reported in patient with Hashimoto's thyroiditis and in Graves' disease is rather rare, especially in children. **Method:** We report a boy of 15 years diagnosed with Graves' disease and treated ineffectively with thyrostatics. After 2 years of the therapy he had recurrence of hyperthyroidism and underwent radical treatment with ablative dose of ^{131}I . After 2 weeks the patient suffered from tachycardia and weakness, increasing sleepiness and progressive qualitative and quantitative disorders of consciousness. Body temperature was normal. Laboratory examinations revealed severe thyrotoxicosis and increase of antithyroid antibodies in blood. Thyroid storm was suspected and typical treatment was administered, including steroids. Symptoms of thyrotoxicosis and consciousness disorders completely withdrew. After 6 weeks hypothyroidism developed and substitution with left- thyroxine was introduced to receive euthyroidism. Three months later again disorders of consciousness appeared again similarly to the previous episode. **Results:** Electroencephalography, CT and MR of the CNS were normal. The cerebro-spinal fluid lab evaluation was within normal reference values. In the serum high concentrations of antithyroid antibodies were found without hormonal dysfunction. Taking into account the encephalopathy associated with autoimmune thyroid disease, steroid therapy was administered (i.v. pulses and than orally). The fast improvement was observed with complete withdrawal of neurological

symptoms. **Conclusion:** Lack of thyroid dysfunction during the second episode, high levels of antithyroid antibodies, exclusion of CNS infectious diseases and very good response to steroids confirmed the diagnosis of autoimmune encephalopathy. Patient was treated with steroids for 8 months in decreasing doses without the recurrence of symptoms. During 3 years follow-up he remained in complete remission.

P1-D2-253

Maternal Hypothyroxinemia in Early Pregnancy is Associated with Poorer Arithmetic Performance in a School Test in Offspring at Age 5 Years

Anna Noten^a, Eva Loomans^b, Tanja Vrijkotte^c, Paul van Trotsenburg^d, Manon van Eijsden^b, Joost Rotteveel^a, Martijn Finken^a

^aDepartment of Pediatrics, VU University Medical Center, Amsterdam, The Netherlands; ^bPublic Health Service Amsterdam, Amsterdam, The Netherlands; ^cDepartment of Public Health, Academic Medical Center – University of Amsterdam, Amsterdam, The Netherlands; ^dEmma Children's Hospital – Academic Medical Center, Amsterdam, The Netherlands

Background: Subtle impairments in the thyroid function of pregnant women are associated with poorer scores on mental developmental scales in their children at age 2–3 years, and with reduced performance in a simple reaction time test at 5–6 years. However, associations with school performance estimates have never been studied. **Objective and hypotheses:** We aimed to assess the effect of normal variation in the maternal thyroid function during early pregnancy on school performance at age 5 years. **Method:** This was a longitudinal study that included the data of 1196 healthy children from the Amsterdam Born Children and their Development study. Maternal serum free T_4 and TSH were obtained at a median pregnancy duration of 90 (interquartile range: 83–100) days. School performance was based on scores obtained in arithmetic and language tests from the nationwide monitoring and evaluation system. Poor school performance was defined as a test result <25 th percentile and subnormal school performance as a test result <50 th percentile. Multivariable logistic regression analysis was used and analyses were repeated after adjustment for family background and perinatal variables. **Results:** Maternal hypothyroxinaemia (i.e., a maternal free T_4 in the lowest 10% of distribution) was associated with a 1.90 (95% CI: 1.26–2.87) –fold increased risk of subnormal performance in the arithmetic test ($P=0.002$). This relation persisted after statistical correction. Maternal hypothyroxinaemia was associated with a 1.79 (95% CI: 1.08–2.96) –fold increased risk of poor language performance ($P=0.02$) but statistical significance was lost after introduction of family background variables in the regression equation. No such relations were found with TSH. **Conclusion:** Maternal hypothyroxinaemia at the end of the first trimester was associated with poorer performance in an arithmetic test, but not in a language test, in offspring at age 5 years.

P1-D2-254

TSH: Different Normalization Methods, Very Different Normal Upper Limits

David Strich^a, Gilad Karavani^b, David Gillis^{b,c}

^aPediatric Specialists' Clinics, Clalit Health Services, Jerusalem, Israel and Shaare Zedek Medical Center, Jerusalem, Israel; ^bHebrew University Hadassah School of Medicine, Jerusalem, Israel;

^cPediatric Endocrine unit, Hadassah-Hebrew University Medical Center, Jerusalem, Israel

Background: Distribution of TSH levels is not normal. This is due to physiological changes that cause temporary increases in TSH during physiological events. Several methods are used to normalize the distribution when defining normal limits. **Objective and hypotheses:** To compare the normal limits defined by three normalization methods vs non-normalized distribution based on a large cohort with no known thyroidal illness. **Method:** Data were collected from a computerized data base of the Clalit health services in Jerusalem, Israel. Exclusion criteria were positive anti-thyroid antibodies and treatment with any drug. TSH values were normalized with the Hoffmann, Tukey and Tukey followed by tural log transformation (NLT) methods. The lower normal limits (LNL) i.e. the 2.5th percentile and the upper normal limits (UNL), i.e. the 97.5th percentile were defined. The clinical relevance of the limits was tested by calculating the mean FT₃ and mean FT₄ for results of TSH below, within and above the limits for each method. **Results:** We report the results of the 6–10 age group, based on 1450 subjects, as a representative example. According to the non-normalized, Hoffman, Tukey and Tukey followed by NLT, the limits were 0.98–6.87, 0.95–4.31, 0.97–5.55 and 0.97–5.55 IU/l respectively, i.e. maximal change from non-normalized data occurred for the UNL by the Hoffman method (–33%) and for the LNL also by the Hoffman method (+4%). There was no difference in average FT₃ or FT₄ between patients with TSH within, below or above the normal range for all four methods. **Conclusion:** i) As expected, normalization methods alter mainly the UNL but the difference between methods is more than 30%. ii) In individuals without thyroid illness, thyroid hormone values are stable over a wide range of TSH levels thus questioning the value of TSH as a screening test.

P1-D2-255

Usefulness of Second Screening Strategy for Congenital Hypothyroidism in LBW Neonates

Paolo Cavarzere^a, Florina Ion Popa^b, Monica Vincenzi^b, Marta Camilot^b, Francesca Teofoli^b, Lorella Morosato^b, Evelina Maines^b, Rossella Gaudino^b, Silvana Lauriola^b, Franco Antoniazzi^b

^aPediatric Division, University Hospital of Verona, Verona, Italy;

^bPediatric Clinic, Department of Life and Reproduction Sciences, University of Verona, Verona, Italy

Background: Thyroid function in preterm infants is often altered for various reasons. LBW or VLBW newborns frequently present a particular form of congenital hypothyroidism (CH) characterized by low FT₄ and delayed TSH elevation. The incidence of this disease is 1:250 for VLBW babies and 1:1589 for LBW newborns. In this condition, neonatal screening based solely on TSH can miss the diagnosis, therefore some screening programs have proposed to repeat the screening test 2 weeks after the first screening in preterm and/or LBW neonates. Nevertheless, in the literature there is disagreement about whether or not the retesting is necessary. **Objective and hypotheses:** To evaluate the incidence of CH with delayed TSH elevation in North-Eastern Italy, and the need for a second screening strategy in LBW neonates. **Method:** Since 2010, we have used a second screening strategy for newborns with birth weight <2500 g. First screening TSH cut-off was 9 mU/l, second screening TSH cut-off was 5 mU/l. Retrospective analysis of newborn thyroid screening data was performed. **Results:** Thirty-seven newborns presented an increased TSH level at the second screening. The data was confirmed at serum control for 26 neonates, who started a L-thyroxine treatment. The incidence of CH with delayed TSH elevation in North-Eastern Italy was 1:586 for LBW, 1:215 for VLBW and 1:107 for ELBW. Between them 50% was newborns with a birth weight higher than 1500 g. **Conclusion:** The second screening strategy for CH in preterm neonates proved useful in detecting newborns who otherwise would not be identified at first screening procedure. Moreover, it is interesting to note that more than a half of those who required a treatment had a birth weight higher than 1500 g. Finally the incidence of CH with delayed TSH elevation, in North-Eastern Italy, was superior to previous studies.

P1-D2-256

Screening for Congenital Hypothyroidism in the Russian Federation (1997–2012)

Olga Bezelepkina^a, Olga Chikulaeva^a, Olga Chumakova^b, Lyudmila Karavaeva^b, Alexey Bezelepkin^c, Valentina Peterkova^a

^aEndocrinological Research Center, Institute of Pediatric Endocrinology, Moscow, Russia; ^bMinistry of Healthcare of the Russian Federation, Moscow, Russia; ^cHigher School of Economics National Research University, Moscow, Russia

Background: Screening for congenital hypothyroidism (CH) in the Russian Federation started in 1994. A survey was conducted in 1994 on the basis of 32 laboratories, and since 2007 newborn screening is being carried out in 79 laboratories of 83 regions of the Russian Federation. **Objective and hypotheses:** To study the prevalence of CH in Russia and in different regions of the Russian Federation. **Method:** Official statistics on CH screening in Russia from Ministry of Healthcare of the Russian Federation was gathered and analyzed, data includes 1997–2012. **Results:** The average percentage of coverage of newborn screening CH in Russia in 1997 was 66.9%; by 2002 it had increased to 91.5 and to 99.6% by 2012. The number of detected cases of CH in Russia is growing

annually. It is connected not only with the increase of the percent coverage of newborn screening, but with the increase of the birth rate in Russia (2002 – 1 396 967 newborns; 2012 – 1 896 263 newborns). The total number of detected cases of CH in 1997 reached 273 newborns; in 2012 was 512 newborns. The prevalence of CH (at the screening of more than 90% newborns) decreased slightly from 1:3278 (2002) to 1:3689 (2012). During the analyzed period more than 21 951 000 children were born, over 19 620 000 newborns were examined by the screening programme, 5345 children with CH were identified. The prevalence of CH during the analyzed period varied across regions of Russia: Central Federal district – 1:3750; North-West Federal district – 1:4232; South Federal district – 1:4260; North-Caucasian Federal district – 1:4452; Volga Federal district – 1:3316; Urals Federal district – 1:2274; Siberian Federal district – 1:4010; Far-Eastern Federal district – 1:4495. **Conclusion:** Average frequency of CH in Russia is 1:3600 newborns. These values are comparable to data from the EU and the USA.

P2-D1-257

Growth Pattern in Infants with Congenital Adrenal Hyperplasia During the First Year of Life

Heba Elsedfy, Rasha Hamza

Ain Shams University, Cairo, Egypt

Background/aims: Several studies demonstrated rapid growth during the first year of life in infants with congenital adrenal hyperplasia (CAH) which has a considerable effect on final adult height. Whether decreased height potential is caused by inadequate suppression of adrenal androgens, excess steroid therapy or salt wasting itself is a matter of debate. Thus, we aimed to analyze growth pattern in infants with CAH during first year of life and the effect of therapy on those parameters. **Methods:** Seventy patients with CAH of different variants were subjected to history and clinical examination. Laboratory and imaging data were obtained from patients' records. Height, weight for height and mid parental height SDSs were calculated at diagnosis and at the end of first year. **Results:** The mean MPH SDS was -0.3 ± 0.9 . Length SDS at the start of treatment (-0.82 ± 0.1) decreased to -1.06 ± 0.11 at the end of first year ($P=0.001$) with adequate weight gain (height/weight SDS -0.41 ± 0.11 at diagnosis vs -0.16 ± 0.13 at the end of first year, $P=0.01$). The mean hydrocortisone dose did not differ at diagnosis (14.8 ± 0.4 mg/m² per day) and at the end of first year (14.98 ± 0.6 mg/m² per day). Patients required lower doses of fludrocortisone at the end of first year (0.46 ± 0.02 mg/m² per day at diagnosis vs 0.29 ± 0.01 mg/m² per day at the end of first year, $P<0.001$). **Conclusion:** At the end of first year, with proper adjustment of therapeutic doses, linear growth acceleration decreased and adequate weight gain occurred in infants with CAH.

P2-D1-258

ACTH and Cortisol Levels are Associated with Cardiovascular Risk in Pediatric Obesity: a Cross-Sectional Study in China

Jianfeng Liang, Junfen Fu, Jinling Wang, Youjun Jiang, Guanping Dong

Children's Hospital of Zhejiang University School of Medicine, Hangzhou, China

Background: The hypothalamic–pituitary–adrenal (HPA) axis, and cortisol in particular, has been reported to be involved in obesity-associated metabolic disturbances in adults and in specific populations of adolescents. **Objective and hypotheses:** To investigate the associations between serum ACTH and cortisol levels and cardiovascular risk factors in obese children and adolescents. **Method:** Of 1119 obese children and adolescents ACTH at 0800 h, cortisol at both 0800 h and 1600 h, cardiovascular risk factors and insulin resistance were evaluated. All analyses were adjusted for possible confounding factors, and odds ratios were determined. **Results:** ACTH was positively associated with fasting insulin and HOMA-IR but negatively with blood pressure, while cortisol was positively associated with systolic and diastolic blood pressure. Also, cortisol but not ACTH was positively associated with LDL. The diurnal cortisol rhythm, the ratio of cortisol at 0800 h/cortisol at 1600 h, was positively associated with ACTH. After adjustment for possible confounding factors, ACTH levels were significantly higher in subjects with HOMA-IR > 3 but lower in subjects with hypertension, and higher cortisol levels were found in subjects with high blood pressure (≥ 95 th percentile), hyperglycemia and high LDL-cholesterol (≥ 95 th percentile). However, the ratio of cortisol at 0800 h/cortisol at 16 h was significantly higher in subjects only with HOMA-IR > 3. **Conclusion:** In obese children and adolescents, high morning ACTH levels are only positively associated with HOMA-IR while high cortisol levels are associated with hypertension, hyperglycemia and high LDL-cholesterol although within the normal range. The flatter diurnal cortisol rhythm may be a feedback of insulin resistance. These specific relationships suggest complex mechanisms through which the HPA axis may contribute to metabolic impairments in obesity, and the interaction of between ACTH and the diurnal cortisol rhythm in the metabolic disorder merits further investigations.

P2-D1-259

Inadequate Cortisol Response to Tetracosactide (Synacthen®) Test in NCCAH Patients, an Exception to the Rule?

Athanasia Stoupa^a, Laura González Briceño^a, Graziella Pinto^{a,b}, Dinane Samara-Boustani^{a,b}, Isabelle Flechtner^{a,b}, Caroline Thalassinou^{a,b}, Maud Bidet^{a,b}, Albane Simon^c, Yves Morel^d, Christine Béllanné-Chantelot^{e,f}, Philippe Touraine^{f,g}, Michel Polak^{a,h}

^aService d'Endocrinologie, Diabétologie et Gynécologie Pédiatrique, Hôpital Necker-Enfants Malades, Paris, France; ^bCentre de Référence des Maladies Endocriniennes Rares de la Croissance, Paris, France; ^cService de Pédiatrie, Centre Hospitalier de Versailles, Le Chesnay, France; ^dEndocrinologie Moléculaire et Maladies Rares, CBPE, Lyon-Bron, France; ^eDépartement de Génétique, Hôpital Pitié-Salpêtrière, Paris, France; ^fUniversité Pierre et Marie Curie, Paris, France; ^gEndocrinologie et Médecine de la Reproduction, Hôpital Pitié-Salpêtrière, Paris, France; ^hUniversité Paris Descartes, Paris, France

Background: Non-classical congenital adrenal hyperplasia (NCCAH) may present during childhood, adolescence or even adulthood with various degrees of hyperandrogenism. Diagnosis is established through tetracosactide (Synacthen[®]) test and genotyping. Cortisol insufficiency has rarely been described in NCCAH. **Objective and hypotheses:** To describe cortisol response to tetracosactide test in NCCAH patients. **Method:** Retrospective study, comparing cortisol response after tetracosactide test (250 µg) in NCCAH patients and a control group (CG) with precocious pubarche and 17OHP response <3 ng/ml. NCCAH diagnosis was confirmed by genotyping. Adequate cortisol response was defined as a peak level ≥ 18 µg/dl. **Results:** NCCAH patients were included (26 girls and eight boys). Mean age at test: 7.0 years old (0.8–15.6). The CG consisted in 47 children (39 girls and eight boys), mean age: 7.2 years old (0.5–9.9). Basal cortisol in NCCAH patients was 12.8 µg/dl (4.3–22.2) vs 9.7 (4.2–16.2) in the CG ($P=0.0006$). Cortisol peak in NCCAH patients was 18.0 µg/dl (6.3–40) vs 24.9 (12–30.3) in the CG ($P<0.0001$). 21/34 of NCCAH patients (61.8%) had a low cortisol peak level, vs 1/47 in the CG (2.1%), with similar response between affected siblings. None of the NCCAH patients had symptoms of adrenal insufficiency, but some reported fatigue which improved under hydrocortisone treatment. Presence of one allele with 'severe mutation' was not predictive of cortisol response. **Conclusion:** We noted a suboptimal cortisol response in 61.8% of NCCAH patients. There is no current consensus regarding glucocorticoid replacement therapy in untreated NCCAH patients. We propose hydrocortisone treatment in case of stress, surgery, acute illness or fatigue in NCCAH patients with an insufficient cortisol peak following tetracosactide test. Fatigue should be objectively documented, and in case of introduction of hydrocortisone treatment, re-evaluation is necessary for assessment of its efficacy.

P2-D1-260

Genotype–phenotype Non-Concordance: How Prevalent is it? How to Explain it

Ahmed Khattab, Mabel Yau, Maria New

The Mount Sinai School of Medicine, New York, NY, USA

Background: The rate of direct genotype–phenotype correlation in 21 hydroxylase deficiency congenital adrenal hyperplasia

(CAH) is <50%. We report two cases of genotype/phenotype non-concordance, which has been explained by gene sequencing. Family 1: in a non-consanguineous family of Irish, German, and Italian ethnicity there are five children. Two of the boys have hormonal evidence of CAH owing to 21-hydroxylase deficiency. The third boy has no symptoms of CAH. The father had no mutations while the mother was heterozygous for a deletion of the *CYP21A2* gene. The genotype for the common mutations in the three boys only revealed a heterozygous mutation for the deletion transmitted by the mother yet the phenotype was that of a CAH patient. Family 2: in a non-consanguineous Ashkenazi Jewish family, the father's DNA analysis revealed no mutation in the *CYP21A2* gene. The mother was diagnosed with non-classical 21-hydroxylase deficiency and her genotype revealed an Ex7 mutation on one allele and a deletion of the *CYP21A2* gene on the other allele. Their born infant had clear hormonal evidence of being a patient with classic simple virilizing CAH. Initial genotyping revealed a heterozygous genotype with a deletion of the *CYP21A2* gene on one allele and no mutations on the other allele yet the infant was clearly a CAH patient and not a heterozygote. **Objective and hypotheses:** Identify rare mutations in the *CYP21A2* gene of families with hormonal evidence of CAH not explained by initial genotyping **Method:** Sequencing of *CYP21A2* gene. **Results:** Family 1: upon sequencing of the *CYP21A2* gene, a rare mutation (Ex8366H) was found in the father and the three boys indicating they were patients with a genotype Ex8366H/Del. Family 2: upon sequencing of the *CYP21A2* gene another rare mutation was found (p.Trp19x) in the child and father. This explained the diagnosis of classic CAH in the infant. **Conclusion:** These cases are emblematic of the need to search for rare mutations by sequencing in the *CYP21A2* gene when there is genotype/phenotype non-concordance.

P2-D1-261

Paradoxical Increase in Urinary Cortisol Excretion in Children with Primary Pigmented Nodular Adrenal Disease

Ana Beatriz Fraga, João Anselmo, Catarina Franco, Sara Vaz, Fernanda Gomes

Hospital Divino Espírito Santo, Ponta Delgada, Portugal

Background: Pediatric Cushings syndrome is a rare condition and its diagnosis is always a challenge to the clinicians. The hypercortisolism can be classified as ACTH-dependent (Cushings disease) and ACTH-independent. The latter group comprises several hereditary conditions. One of them is primary pigmented nodular adrenocortical disease (PPNAD) which occurs isolated or as part of Carney complex (CNC). It is known that adult patients with Cushings syndrome due PPNAD exhibited a paradoxical increase of urinary cortisol excretion in response to dexamethasone. However, this finding has been rarely described in children. **Case report:** Two 14-year-old twin girls belonging to a large Azorean family with CNC have been followed in our

outpatient consultation since the age of 4-years. Her mother died at age of 28-years due to adrenal carcinoma arising in the context of PPNAD. The children and her mother were heterozygous for the mutation S147G in the gene of PRKAR1A. Since early childhood, they present strong spotty skin pigmentation. At 13-year-old, one of the twins started complaining of oligomenorrhea and later on to amenorrhea. She gained 6 kg in <1 year. Her blood pressure was raised to 140/90 mmHg. The circadian cortisol variation was abolished and ACTH was below the lower limit of the assay. Oral administration of dexamethasone, 0.5 mg each 6 h for 48 h, produced a paradoxical increase in urinary cortisol excretion (100% over basal value). These findings were not found in the other twin. She was submitted to adrenalectomy and the histologic examination confirmed the diagnosis of PPNAD. **Conclusion:** As in most adults with Cushing's syndrome due to PPNAD, a paradoxical increase in urinary cortisol excretion in response to dexamethasone is also found in children. When this increase is over 100% it is pathognomonic of PPNAD.

P2-D1-262

Mutation Spectrum of CYP11B1 Gene in Turkish Patients with 11 β -hydroxylase Deficiency

Nurgun Kandemir^a, Didem Yucel Yilmaz^b, E Nazli Gonc^a, Z Alev Ozon^a, Ayfer Alikasifoglu^a, Ali Dursun^b, R Koksal Ozgul^b

^aHacettepe University Dept of Pediatric Endocrinology, Ankara, Turkey; ^bInstitute of Child Health Metabolism Unit, Ankara, Turkey

Background: Deficiency of 11 β -hydroxylase is the second most frequent type of congenital adrenal hyperplasia and more common in Turkey than other populations. **Objective and hypotheses:** The purpose of this study is to examine the spectrum of CYP11B1 gene mutations in Turkish population. **Method:** 17 patients from 13 families are included in this study. Diagnosis was based on virilisation and high levels of 11-deoxycortisol. 15 cases had classical and two cases had non-classical form. Mutation screening of nine exons in CYP11B1 gene was performed using direct sequence analysis. The CYP11B1 gene was specifically amplified avoiding simultaneous amplification of homologous CYP11B2 gene sequences. **Results:** The karyotype of nine cases out of 15 was 46,XX and the remaining was 46,XY. The age at diagnosis ranged 0.1-4.2 years. 46,XX cases presented with severe virilisation (Prader genital stages IV and V). Four of 46,XX patients were reared as male at presentation and three of them remained male due to establishment of male gender identity. Two siblings with late onset form were diagnosed at 4, 9, and 7 years. Overall mutation analyses revealed eight homozygous pathogenic mutations of four different types (two splicing, two duplication, two nonsense, and two missense). The detected nucleotide changes in patients resulted in five novel (c.1336G>A;p.G446S, c.563_566dupTCCA, c.1200+1G>A, c.1398+5G>C, c.1178-1179dupAG) and three previously reported mutations (p.A141X, p.L299P, and p.A384Q) in the CYP11B1 gene. Mutation prediction

software tools PolyPhen-2 and SIFT, both indicate that the novel mutations detected in this study are likely to be pathogenic. **Conclusion:** All detected mutations were scattered throughout the gene. The most common mutation in this group of Turkish patients was A141X with the allele frequency of 25%. All new and known mutations in the classical form led to severe virilisation. The missense novel mutation c.1336GA;p.GLY446Ser caused late onset form of the disease.

P2-D1-263

Genotype and Phenotype Characteristics of Patients with Nonclassical Congenital Adrenal Hyperplasia due to 21-hydroxylase Deficiency

Nese Akcan Tombalak^a, Oya Uyguner^b, Guven Toksoy^b, Esin Karakilic^a, Banu Aydin^a, Firdevs Bas^a, Nurcin Saka^a, Sukran Poyrazoglu^a, Ruveyde Bundak^a, Hulya Kayserili^b, Feyza Darendeliler^a

^aPediatric Endocrine Unit, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey; ^bDepartment of Medical Genetics, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey

Background: Nonclassical congenital adrenal hyperplasia (NCAH), which is generally presented with symptoms of androgen excess, is inherited autosomal recessive due to different kind of mutations in the CYP21A2. Recently, high frequency of copy number variations at CYP21A2 gene and predisposition of heterozygous duplicated CYP21A2 for *de novo* gene aberrations has been reported. **Objective and hypotheses:** To evaluate clinical and molecular characteristics of the patients with NCAH. **Method:** Twenty-one patients (19F, 2M), diagnosed as NCAH according to their clinical, hormonal, and molecular (biallelic or monoallelic mutations) findings, were included. Sequencing and multiplex ligation-dependent probe amplification (MLPA) were used for molecular analysis. **Results:** Mean age of the patients at presentation was 10.5 \pm 4.1 (3.1-17.2) years. The presenting symptoms were clinical hyperandrogenemia (hirsutism, acne, and hair loss) (*n*=10), premature adrenarche (*n*=6), precocious puberty (*n*=5), menstrual irregularity (*n*=2), and cliteromegaly (*n*=2). Mean of basal and peak 17-OH progesterone levels to ACTH stimulation were 12.8 \pm 13.0 and 27.2 \pm 19.5 ng/ml respectively. Cortisol responses to ACTH stimulation were normal. Nine different mutations, including one novel were detected in patients. Eight patients carried mutation in a single allele. Two had heterozygous p.Q319X mutation with active gene duplication. One patient carried two different (p.V282L and p.P454S) mutations in a single allele. The p.454S was *de novo* in *cis* position according to parental analysis and her father had active gene duplication with p.Q319X mutation which wasn't inherited. Other patient with homozygous p.V282L also had novel *de novo* heterozygous p.P214L mutation. **Conclusion:** As a result of complex structure of CYP21A2 locus, not only sequencing but also

MLPA or southern blot methods should be performed to both patients and parents. Much more comprehensive studies with new genetic methods, including both offspring and parents, should be designed to exhibit clinical effects of variety of mutations in NCAH.

P2-D1-264

LC-MSMS Profiling of Plasma Steroids in Different Types of Congenital Adrenal Hyperplasia

Alexandra E. Kulle^a, Thomas Reinehr^b, Halit Ilker Akkurt^c, Christian Commentz^d, Sabine Heger^e, Gunter Simic-Schleicher^f, Maik Welzel^a, Nadine C. Hornig^a, Paul-Martin Holterhus^a

^aUniversity Hospital Kiel, Kiel, Germany; ^bUniversity Witten/Herdecke, Datteln, Germany; ^cChildren's Hospital, Hamburg, Germany; ^dMVZ am Wilhelmstift, Hamburg, Germany; ^eChildren's Hospital 'Auf der Bult', Hannover, Germany; ^fHospital Bremen-Nord, Bremen, Germany

Background: Congenital adrenal hyperplasia (CAH) encompasses a group of autosomal recessive disorders which lead to impairment of steroid biosynthesis in the adrenals and gonads. 21-hydroxylase deficiency (21OHD) is the most common form of CAH (95%), followed by 11 β -hydroxylase deficiency (11OHD) and 3 β -dehydrogenase steroid dehydrogenase type 2 deficiency (3 β HSD2). LC-MSMS based steroid analysis has become an increasingly important method for steroid analyses in Paediatric Endocrinology in the last few years. **Objective and hypotheses:** Determination of plasma steroid profiles by LC-MSMS comprising adrenal and gonadal steroid hormones in different types of CAH. **Method:** LC-MSMS based plasma steroid profiling was performed in 18 cases with molecular proven CAH (21OHD, $n=11$; 11OHD, $n=4$; and 3 β HSD2, $n=3$). Steroid analyses were originally initiated because of either pathological screening, ambiguous genitalia or late onset hyperandrogenism. In addition to the determination of 12 adrenal and gonadal steroid hormones, 17-hydroxypregnenolone (17OHPreg) and DHEAS were measured. All values were compared to our previously established age- and sex-specific reference ranges. To allow for age independent evaluations and comparisons of steroid profiles, multiples of median (MOM) of the specific reference ranges were calculated. **Results:** In the 11 patients with 21OHD, a 30-fold MOM for 17-hydroxyprogesterone and a ten-fold MOM for 21-deoxycortisol was present. The four individuals with 11OHD showed a 100-fold MOM for 11-deoxycortisol and a ten-fold MOM for deoxycorticosterone. In the three patients with 3 β HSD2, a 100-fold MOM for 17-OHPreg and a ten-fold MOM for DHEAS was found. **Conclusion:** LC-MSMS based profiling of plasma steroids leads to characteristic steroid patterns and is a reliable tool for diagnosing different forms of CAH. Applying MOMs allows age-independent comparisons and easy identification of pathologic cases.

P2-D1-265

Two Brothers with Late Onset Apparent Mineralocorticoid Excess

Grazia Morandi, Evelina Maines, Francesca Malesani, Paolo Cavarzere, Rossella Gaudino, Franco Antoniazzi

Department of Life Sciences and Reproduction Sciences, Pediatric Clinic, 'Giambattista Rossi' Hospital, University of Verona, Verona, Italy

Background: Apparent mineralocorticoid excess (AME) is a rare congenital autosomal recessive disorder resulting from mutations in the HSD11B2 gene, which encodes the kidney isozyme of 11- β -hydroxysteroid dehydrogenase type 2, inactivating circulating cortisol to the less-active metabolite cortisone. Less than 100 cases of AME have been reported in the literature so far. Affected individuals have elevated renal concentrations of cortisol, which can cross-react and activate the mineralocorticoid receptor, leading to aldosterone-like effects in the kidney. AME is usually diagnosed within the first years of life in children presenting with failure to thrive, severe hypertension (HT), low renin and aldosterone levels, profound hypokalemia and hypernatremia. Measurement of urinary free tetrahydrocortisol and tetrahydrocortisone ratio (allo-THF + THF)/THE is important in the diagnosis. AME can also present later in life, in apparent healthy children or adolescents. **Case report:** We describe the case of two brothers, aged 14 and 7 years, which were diagnosed during a routine visit as suffering from HT (blood pressure values above the 95th percentile for gender and age; 160/110 mmHg in the first brother and 150/110 mmHg in the second one). They were in good general conditions and their clinical examination was normal. At echocardiography, the oldest one had a moderate left ventricular hypertrophy. As they had no risk factors for primary HT, we performed laboratory and instrumental exams to detect a secondary form of HT. We found hypokalemia (K 2.6 mmol/l) just in the older brother with low levels of both aldosterone (undetectable in both children) and renin. The urinary steroid profile revealed a marked increase in the (allo-THF + THF)/THE ratio (6.1; normal value <0.5). Children started spironolactone with a good response. **Conclusion:** Our cases suggest that it is important to think about AME also in apparent healthy children or adolescents affected by HT, because the disease can remain unrecognized until late childhood or adolescence. An early diagnosis and a prompt treatment of AME are important to prevent end-organ damage, sudden stroke, cardiac, and renal insufficiency.

P2-D1-266

Is Basal 17-Hydroxyprogesterone a Sensitive Marker for Diagnosis of Non-Classical Congenital Adrenal Hyperplasia?

Rachel Bello^a, Yael Lebenthal^{a,b}, Moshe Phillip^{a,b}, Liat de Vries^{a,b}

^aThe Jesse Z and Sara Lea Shafer Institute for Endocrinology and Diabetes, National Center for Childhood Diabetes, Schneider

Background: A basal 17-hydroxyprogesterone (17-OHP) plasma level of 6.0 nmol/l was suggested as a threshold for the diagnosis of non-classical congenital adrenal hyperplasia (NCCAH), particularly in children presenting with precocious pubarche (PP). **Objective:** The present study aimed to determine if this threshold could lead to underdiagnosis of NCCAH. **Method:** In a retrospective study the cohort of pediatric patients ($n=145$, 22 males) diagnosed as NCCAH (defined by a post-ACTH 17-OHP plasma level >30 nmol/l), was stratified according to morning basal 17-OHP levels, using the value of 6.0 nmol/l as a cut-off. Clinical and laboratory characteristics of patients with basal 17-OHP <6.0 nmol/l and of those with higher basal levels were compared. **Results:** Mean age at diagnosis was 8.35 ± 4 years. Basal 17-OHP was <6.0 nmol/l ($1.1-5.1$) in 18/145 (12.4%) patients and in 6/40 (15%) referred for PP. No differences between the groups stratified by basal level were found for age, height-SDS, weight-SDS and extent of bone age advancement at diagnosis. This held true for gender distribution, age at glucocorticoid treatment initiation, dose, basal and stimulated plasma cortisol and testosterone levels. For the entire cohort, patients with basal 17-OHP <6.0 nmol/l had significantly lower androstendione (2.2 ± 1.9 vs 4.6 ± 4.3 nmol/l, $P < 0.03$) and lower stimulated 17-OHP (68.5 ± 46.4 vs 122.1 ± 93.5 nmol/l, $P < 0.001$). Similarly, children referred for PP with basal 17-OHP <6.0 nmol/l had lower plasma levels of androstendione (1.7 ± 0.6 vs 5.0 ± 4.5 nmol/l, $P < 0.02$), testosterone (0.08 ± 0.16 vs 0.75 ± 0.77 nmol/l, $P < 0.02$), and stimulated 17-OHP (60.5 ± 48.4 vs 122.4 ± 63.8 nmol/l, $P < 0.02$). **Conclusion:** A selective strategy based on a 6.0 nmol/l basal 17-OHP plasma level threshold carries the risk of overlooking the diagnosis of NCCAH. The lower levels of androstendione and stimulated 17-OHP may reflect a milder impairment in enzymatic activity in patients with lower basal 17-OHP at diagnosis.

P2-D1-267

An adolescent with Hypertension Caused by Primary Hyperaldosteronism due to KCNJ5 Mutation

Annelieke van der Linde^a, Jaap Deinum^a, Yvette Konijnenberg^b, Mandy Keijzer-Veen^c, Hedi Claahsen-van der Grinten^a

^aRadboud University Medical Centre, Nijmegen, The Netherlands;

^bSt Jansdal Hospital, Harderwijk, The Netherlands; ^cUniversity Medical Center Utrecht Wilhelmina Children's Hospital, Utrecht, The Netherlands

Background: Primary aldosteronism (PA) is a rare form of secondary hypertension. In adults PA is often caused by unilateral adrenal adenoma which can be cured by unilateral adrenalectomy. However, in young patients hereditary causes of PA have to be considered with bilaterally affected adrenal glands.

Objective and hypotheses: We report on an adolescent with PA due to a recently described KCNJ5 mutation and want to point out the importance of performing mutation analysis in pediatric patients with PA. **Method:** A 16-year-old boy was referred to our clinic because of hypertension. Diagnostic work up revealed elevated aldosterone and low renin concentrations. A CT scan showed focal thickening of the left adrenal gland, without evidence for a clear adenoma. Adrenal venous sampling did not show lateralisation. Aldosterone was not suppressed by sodium loading which confirmed the diagnosis PA. We performed mutation analysis for CYP11B1/2 and the newly described KCNJ5 mutation. **Results:** Mutation analysis was negative for the hybrid CYP11B1/CYP11B2 gene that causes glucocorticoid-remediable aldosteronism but revealed a *de novo* germline missense mutation in the KCNJ5 gene (c.452G>A (p.Gly151Glu)). This mutation has only been described in seven families causing familial PA type III. Somatic mutations in the KCNJ5 gene are also present in about a third of aldosterone-producing adenomas. In our patient, treatment with an aldosterone antagonist was successful for blood pressure control without surgical intervention. **Conclusion:** PA is a rare cause of secondary hypertension, especially in children and adolescents. In hereditary forms of PA bilaterally elevated production of aldosterone can be expected. Therefore, surgery is not the first choice treatment. We recommend mutation analysis for CYP11B2 and KCNJ5 mutation in all children and adolescents with biochemically proven PA.

P2-D1-268

Analysis of Prospective Annual ACTH Stimulation Testing Among Survivors of Intracranial Tumor

Marjorie Golekoh^a, Manasa Mantravadi^a, Lindsey Hornung^b, Jane Khoury^b, Maryam Fouladi^c, Susan Rose^a, Sarah Lawson^a

^aDivision of Pediatric Endocrinology, Cincinnati Children's Hospital Medical Center and University of Cincinnati School of Medicine, Cincinnati, Ohio, USA; ^bDivision of Biostatistics and Epidemiology, Cincinnati Children's Hospital Medical Center and University of Cincinnati School of Medicine, Cincinnati, Ohio, USA; ^cDivision of Oncology, Cincinnati Children's Hospital Medical Center and University of Cincinnati School of Medicine, Cincinnati, Ohio, USA

Background: ACTH deficiency (ACTHD) is a potentially life-threatening condition observed in many childhood survivors of intracranial. Time from tumor diagnosis and therapy to development of ACTHD cannot be ascertained from previous studies. This lack of knowledge has led to annual surveillance using low-dose ACTH stimulation testing (LDST) for 10–15 years following completion of therapy. **Objective and hypotheses:** To identify the incidence and timing to ACTHD onset to allow development of an effective screening strategy among brain tumor survivors. **Method:** We performed a retrospective chart review of 77 children diagnosed with primary brain tumor in the optic (OP) or suprasellar (SS) regions, between 2002 and 2012. The outcome

of interest was ACTHD, defined as peak serum cortisol $< 18 \mu\text{g/dl}$ 20 min after $1 \mu\text{g/m}^2$ i.v. ACTH. Peak cortisol $> 20 \mu\text{g/dl}$ was defined as normal while $18\text{--}20 \mu\text{g/dl}$ was indeterminate. For random cortisol levels, ACTHD was defined as cortisol $\leq 12.9 \mu\text{g/dl}$ drawn at 0700–0900 h. A level ≥ 13 at any time of the day was considered normal. **Results:** Among this subset of 77 patients (52% female, mean age (\pm s.d.) 6.1 ± 4.5 years), 69% (53) had OP (mean age 4.8 ± 3.9 years) and 31% (24) had SS (mean age 9.0 ± 4.4 years). ACTHD was present in 6 (14.3% of those who had any ACTH testing, 7.8% of all patients), however 43% (33) have not had any testing. Two additional patients had indeterminate results. Of those with ACTHD, 33% (2/6) had OP. Among the 25% (19/77) who underwent cranial irradiation, 2 (11%) developed ACTHD. The time to onset of ACTHD from tumor diagnosis was 1.3 years (range: $-0.02, 4.26$) ($n=6$), and from irradiation -0.2 and 0.75 years ($n=2$). Among those who underwent LDST, $n=36$, the time from diagnosis to initial test was 2.2 years (-0.1 to 8.2) and from therapy was 1.4 years (-3.3 to 6.1). Concurrent endocrinopathies were found in 83% of those with ACTHD vs 61% of those without ACTHD. **Conclusion:** For patients with optic pathway or suprasellar tumors, monitoring for ACTHD should be done at the time of diagnosis, then annually thereafter. A follow up screening for ACTHD should be done 4–6 months after completion of cranial irradiation therapy.

P2-D1-269

Congenital Adrenal Hyperplasia Caused by 11 β -hydroxylase-Deficiency as a Rare Differential Diagnosis of Precocious Pseudo-Puberty and Hypertension

Vira Yakovenko^{a,b}, Anke Simon^a, Egbert Schulze^a,
Jürgen Grulich-Henn^a, Markus Bettendorf^a

^aUniversitätsklinikum Heidelberg Zentrum für Kinder- und Jugendmedizin, Heidelberg, Germany; ^bCrimean State Medical University, Simferopol, Ukraine

Background: 11 β -hydroxylase deficiency (HD) represents a rare cause of congenital adrenal hyperplasia (CAH) characterized by glucocorticoid deficiency and excess of mineralcorticoids and androgens. The CYP11B1 gene on chromosome 8q22 encodes the 11 β -hydroxylase. **Objective:** To report clinical, biochemical and molecular features of patients with 11 β -HD. **Results:** Four male patients of Turkish descent with 11 β -HD including two brothers were identified in our patient cohort. They were diagnosed between the ages of 1.4–3.3 years with tall stature (height SDS $2.58\text{--}5.02$), increased growth velocity (SDS $1.13\text{--}4.83$), advanced bone age (GP, 4–12 years), precocious pseudo-puberty (PPP) and hypertension (systolic RR > 95 th percentile). The sibling was diagnosed postpartum because of his family history. The plasma concentrations of 11-deoxycorticosterone ($525.8\text{--}3091.0$ ng/dl, ref. $2\text{--}34$), of 11-desoxycortisol ($14.5\text{--}58.0$, ref. $0.02\text{--}0.25$), testosterone ($129\text{--}298$ ng/dl, ref. $2\text{--}20$), and ACTH

($211\text{--}512$ pg/ml, ref. $10\text{--}50$) were elevated while plasma renin activity was suppressed. Treatment with high doses hydrocortisone was required to normalize steroid metabolism ($16.4\text{--}29$ mg/m² per day). Mutations were identified in exon 7 (c.1181insGA and c.1179_1180dupGA (p.Asn394Argfs*37) and 8 ((T \rightarrow C) 5* splice site) of the CYP11B1 gene leading to an almost complete loss of function of 11 β -hydroxylase. The c.1179 mutation had been described once in 1992, but not been included in the database (HGMD). The parents in each case are consanguineous and heterozygous carriers of a mutation. Testicular adrenal rest tumors (TART) developed in the two brothers. The youngest patient had sonographic signs of TART at the age of 4. **Conclusion:** Tall stature with advanced bone age, PPP and hypertension may be caused by CAH due to 11 β -HD, which is not detected in routine newborn screening. The therapy requires higher doses of hydrocortisone compared to those in the treatment of 21-HD. TART may be present as early as infancy or develop during the course of illness.

P2-D2-270

Osteoporosis in Triple A Syndrome: an Overlooked Symptom of Unexplained Etiology

Miroslav Dumic^a, Natasa Rojnic Putarek^a, Vesna Kusec^a,
Nina Barisic^a, Katrin Koehler^{a,b}, Angela Huebner^{a,b}

^aClinical Hospital Centre Zagreb, Zagreb, Croatia; ^bTechnische Universität Dresden, Klinik für Kinder- und Jugendmedizin, Universitätsklinikum Carl Gustav Carus, Dresden, Germany

Background: Triple A syndrome (alacrima, achalasia, adrenal failure, progressive neurodegenerative disease) is caused by mutations in the AAAS gene which encodes the protein ALADIN. Osteoporosis seems to be an overlooked symptom in triple A syndrome. **Objective and hypotheses:** To evaluate etiology of osteoporosis in six male and four female patients with triple A syndrome. **Method:** X-ray, dual X-absorptiometry (DXA) of the lumbar spine and hip, bone turnover markers, minerals, ALP, 25-OHD, 1,25-OH2D, PTH and adrenal androgens were measured. **Results:** At time of diagnosis osteoporosis was suspected on X-ray in eight of ten patients aged 2–11 years (DXA was not available) and normal levels of minerals and ALP were measured in ten patients. Seven to 30 years after introduction of 12 mg/m² per day hydrocortisone (at age 9–37 years) DXA showed low Z-score -2.1 in two children and osteoporosis in eight adults (T-score between -2.6 and -4). Normal levels of minerals, ALP, PTH, 1,25-OH2D, osteocalcin, crosslaps (CTX), procollagen 1 (P1CP) were found in ten patients. Low levels of DHEAS ($0.1\text{--}1$ $\mu\text{mol/l}$, NR 3–11) and androstenedione ($0.2\text{--}1$ $\mu\text{mol/l}$, NR 2–9) in all and low levels of 25-OHD ($18\text{--}44$ $\mu\text{mol/l}$, NR 50–150) were found in six patients. In all patients BMI was < 25 ct. for age and sex. Osteoporosis was not associated with sex or the type of the AAAS gene mutation. **Conclusion:** Appropriate glucocorticoid replacement probably had no detrimental effects on

BMD. Osteoporosis may be the consequence of low levels of adrenal androgens, the neurological impairment causing physical inactivity, inadequate sun exposure and protein malnutrition secondary to achalasia. Regarding ubiquitous ALADIN expression, osteoporosis may be phenotypic feature of the disease. Besides optimizing glucocorticoid dose, physical activity, adequate sun exposure, appropriate nutrition and vitamin D supplementation, therapy with DHEA could be considered.

P2-D2-271

The Results of CYP21A2 Mutation Analysis in Adolescent with Polycystic Ovary Syndrome

Elif Yaglı Çolakoglu^a, Derya Bulus^a, Nesibe Andiran^b, Ugur Ufuk Isin^c

^aDivision of Pediatric Endocrinology, Keçiören Research and Educational Hospital, Ankara, Turkey; ^bDivision of Pediatric Endocrinology, Keçiören Research and Educational Hospital, Yıldırım Beyazıt University, Ankara, Turkey; ^cDivision of Pediatric Endocrinology; Pediatrics Department, Keçiören Research and Educational Hospital, Ankara, Turkey

Background: Diagnosis of polycystic ovary syndrome (PCOS) in the adolescent is difficult due to high background rate of menstrual irregularity, high prevalence of polycystic morphology and hyper androgenic features in this population. Also late onset congenital adrenal hyperplasia (LOCAH) mimics PCOS in this period. It is important to distinguish these entities because of the differences in their therapy. The study aimed to find out the frequency of LOCAH in patients who diagnosed as PCOS by using CYP21A2 genetic analysis. **Objectives and hypotheses:** 66 patients who admitted to our clinics and prediagnosed as PCOS were evaluated. Following basal hormonal evaluation, all subjects underwent ACTH stimulating test and CYP21A2 genetic mutation analysis. Patients were divided into three diagnosis groups. The patients who diagnosed as LOCAH by genetic analysis were group A. Patients who had peak 17-OHP levels above 6 ng/ml on ACTH stimulation test were group B. And the others were group C. **Results:** CYP21A2 genetic mutations were found in 15 (22.7%) patients (Group A). The most common mutations were isolated as Q318X (10.6%) and V281L (9.1%) heterozygous mutations

Table 1. Genetic mutations frequency

Genetic Mutation Analysis	Number of Patients	Percent (%)
Negatif	51	77.3
Q318X	7	10.6
V281L	6	9.1
V281L+I172N	1	1.5
V281L+Q318X+I172N	1	1.5
Total	66	100

Table 2. Comparison of genetic analysis and ACTH stimulation test

Genetic analysis	ACTH stimulation test	
	-	+
-	49	2
+	12	3

(Table 1). In one patient there was a compound heterozygous mutation (V281L-I172N). In another patient three mutations were found together (V281L-Q318X-I172N). On ACTH stimulation test only 5 (7.6%) of all PCOS patients had 17-OHP levels above 6 ng/ml indicated 21 hydroxylase deficiency (Group B). In three of them, CYP21A2 mutations were also isolated (Table 2). Median (min-max) peak 17-OHP levels were 3.21 ng/ml (0.45–71.30) in group A, 7.87 ng/ml (6.68–71.30) in group B and 2.61 ng/ml (1.08–5.40) in group C. The difference between three groups is statistically significant ($P=0.001$, Kruskal–Wallis). This difference was based on group B (mWU). For the correct diagnosis of LOCAH according to the genetic analysis was calculated to be superior to ACTH stimulation test (OR:6.12, CI: 0.91–40.84). **Conclusions:** In the lights of these findings, in adolescents with PCOS, ACTH stimulation test could not be adequate for differential diagnosis of LOCAH. For exact diagnosis CYP21A2 genetic mutation analysis should also be performed.

P2-D2-272

Timing of precocious pubarche in girls: Does a contemporary subgroup exist?

Feride Tahmiscioglu, Oya Ercan, Bahar Ozcabi, Olcay Evliyaoglu
Cerrahpasa Medical School, Istanbul, Turkey

Background: In 2012, a phenomenon of early isolated gonadotropin-independent thelarche among contemporary girls was reported. **Objective and hypotheses:** We wanted to evaluate whether a contemporary isolated early pubarche also exists. One way of looking into this is by investigating the age of pubarche in a group of girls with premature pubarche (PP) over time. If some girls had earlier pubarche, then, we would expect a subgroup (i.e. those younger than 8 years) of individuals with earlier pubarche to constitute a subgroup of individuals with PP. **Method:** There were 268 girls with PP and without SGA referred between 1978 and 2013. 31 cases with precocious puberty and/or those given GnRH analogue treatment were excluded ($n: 268 - 31 = 237$). Of these 237 girls, seven had nonclassical CAH, one had ovarian tumour, one had adrenocortical carcinoma, one had SV CAH ($n: 237 - 10 = 227$). Of 227 girls, those with known pubarche age ($n: 200$) were grouped according to years of referral. 173 girls had serum DHEAS levels determined. Girls with PP and with increased serum levels of DHEAS for age were named as

premature adrenarche (PA) and those without as idiopathic PP (IPP). **Results:** Age of pubarche in 2006–2010 and 2011–2012 was significantly higher than in 1996–2000 (respectively P : 0.007 and 0.005). Age of pubarche after 2006 was significantly higher than that of before 2006 (P : 0.001). (< 1995 (n : 19) 5.82 ± 1.49 ; 1996–2000 (n : 22) 5.19 ± 1.89 ; 2001–2005 (n : 18) 5.54 ± 3.12 ; 2006–2010 (n : 102) 6.48 ± 1.45 ; 2011–2012 (n : 39) 6.72 ± 0.97 years). Although there was no significant difference between pubarche age of PA subjects before and after 2006, there was a significant difference between pubarche age of IPP subjects before and after 2006 respectively (6.22 ± 0.76 ; median 6.5, 6.63 ± 1.51 ; median 7 years; P : 0.004). **Conclusion:** Our findings suggest that there might be a contemporary subgroup of individuals with earlier pubarche in our group of PP girls, especially indicated by the presence of a higher proportion of 7–8 years old girls with IPP after 2006 than before 2006.

P2-D2-273

Nonclassic Lipoid Adrenal Hyperplasia with R272C STAR Mutation: a Case Report

Tatsuya Miyoshi^{a,b}, Masaki Takagi^a, Yukihiro Hasegawa^a

^aDivision of Endocrinology and Metabolism, Tokyo Metropolitan Children's Medical Center, Tokyo, Japan; ^bDivision of Pediatric Endocrinology and Metabolism, Shikoku Medical Center for Children and Adults, Kagawa, Japan

Background: The StAR protein is crucial for the transportation of cholesterol to the mitochondria, where it is converted to pregnenolone. Complete loss of StAR protein function impairs adrenal and gonadal steroidogenesis since the fetal period, called classic lipoid adrenal hyperplasia (CLAH). Nonclassic lipoid adrenal hyperplasia (NCLAH) is a recently recognized disorder, with partial StAR protein function, and several mutations causing NCLAH have been reported. **Objective:** To report clinical, biochemical, genetic, and functional data on a mutation of the STAR gene. **Patient:** A Japanese boy was born with normal male genitalia, and had hyperpigmentation. At 2 years of age, he experienced an episode of adrenal failure accompanied by infection, and his medical history was uneventful before this. Serum cortisol was undetectable, and did not respond to ACTH stimulation. Aldosterone showed a low response in the furosemide-upright test, and a CT scan showed normal-sized adrenal glands. At 11 years of age, he had normal pubertal development, but serum DHEA-S level was very low. **Methods:** STAR genetic analysis was performed. The ability of STAR mutations on the conversion of cholesterol to pregnenolone was assessed. **Results:** We identified compound heterozygous mutations K238fs and R272C. *In vitro* experiments showed that the R272C mutation retained 50% of the WT activity. Western blotting and visualization of mitochondria localization revealed no significant difference between the WT and the R272C mutant. **Discussion and conclusions:** Our patient presented with adrenal failure at 2 years of age and normal male external genitalia. This phenotype may be related to residual STAR protein activity. The

K238fs/Q258X mutation was previously reported in Japanese patients with CLAH, and the R272C/Q258X mutation was recently reported in a Japanese patient with primary adrenal failure without enzymatic defect. The frequency of these mutations may be high in Japanese patients.

P2-D2-274

Severe 21-Hydroxylase Deficiency Congenital Adrenal Hyperplasia and Congenital Hypothyroidism Due to Thyroglobulin Mutations in a Single Family: Two Distinct Genetic Disorders with Phenotypic Variability within a Single Family

Caroline Ponmani^{a,b}, Abigail Atterbury^b, Senthil Seniappan^c, Nadia Schoenmakers^d, Adeline K Nicholas^d, Krishna Chatterjee^d, Mehul Dattani^b

^aQueens Hospital Romford, London, UK; ^bGreat Ormond Street Hospital, London, UK; ^cAlderhey Children's Hospital, Liverpool, UK; ^dUniversity of Cambridge Metabolic Laboratories, Cambridge, UK

Background: 21-Hydroxylase deficiency due to mutations in CYP21A2 represents the commonest form of congenital adrenal hyperplasia (CAH). Dysshormonogenetic congenital hypothyroidism (CH) may be due to TPO, TG, DUOX2, DUOX2A2, IYD, SLC5A5 and SLC26A4 mutations. **Objective and hypotheses:** We report a kindred with three siblings born to unrelated parents manifesting with two different forms of CAH. The older siblings presented in the neonatal period with salt losing CAH due to compound heterozygosity in CYP21A2 gene (maternally derived intron 2 splice mutation, paternally-derived p.Ile172Asn). The third sibling, presented at the age of 7 years with premature pubarche, has a simple virilising form of CAH. CH was diagnosed in both older siblings by neonatal screening. Next generation sequencing recently demonstrated compound mutations in the thyroglobulin gene (TG): p.R277X and p.T1397Rfs*30. **Method:** The oldest sibling, a female now aged 17, has learning difficulties and is short (height SDS -2.60) with severe obesity (BMI 52.5), insulin insensitivity, severe virilisation, hirsutism, primary amenorrhoea, voice changes, and polycystic ovarian disease, due to poor compliance with medication. Her 13-year-old brother is currently on hydrocortisone, fludrocortisone and thyroxine (height SDS: -0.90, weight SDS: +1.39, BMI SDS: +2.63). His compliance is also erratic, and he is being treated with GnRH analogue for gonadotrophin-dependent precocious puberty. **Results:** Abdominal MRI in the older sibling revealed bilaterally enlarged adrenals with a probable right adrenal adenoma, probably due to chronic ACTH stimulation. **Conclusion:** In this unusual pedigree, three siblings manifested two different forms of CAH, and the older siblings show inheritance of two distinct genetic disorders, namely CAH and CH due to TG mutations. Finally, this case illustrates the importance of optimal disease control in CAH; poor compliance with chronically elevated ACTH concentrations may have resulted in an adrenal adenoma in the older sibling.

P2-D2-275

Non-virilizing Congenital Adrenal Hyperplasia in a Female Patient: Report of a Novel *HSD3B2* Mutation

Ursina Probst-Scheidegger^a, Christa Flück^b, Dagmar l'Allemand^a, Nürja Camats^b

^aChildren's Hospital of Eastern Switzerland, 9006 St Gallen, Switzerland; ^bUniversity Children's Hospital, 3011 Bern, Switzerland

Background: 3 β -Hydroxysteroiddehydrogenase (3 β -HSD) is a key enzyme in steroidogenesis, responsible for the conversion of Δ 5- to Δ 4-steroids. Deficiency in 3 β -HSD results in congenital adrenal hyperplasia (CAH). The molecular etiology of 3 β -HSD deficiency lies in a defect in *HSD3B2* gene. **Clinical case:** A healthy newborn girl was admitted on day of life (DOL) 8 due to increased 17-OH-progesterone (17OHP) in newborn screening. She was in no physical distress, feeding well, and gaining weight appropriately. External genitalia were female without virilization nor palpable gonads. Ultrasound revealed female internal genitalia. Labs: increased ACTH (549 ng/l), low cortisol (92 nmol/l), increased 17OHP (124 nmol/l), normal DHEA and 11-desoxycortisol, and increased renin (116 pg/ml). The patient was immediately started on hydrocortisone (HC). The following day, she developed salt loss (Na of 129 mmol/l, K of 6.1 mmol/l) and was therefore started on fludrocortisone (FC) and NaCl. Further evaluation at 7 months of age, 36 h after discontinuing HC and FC: increase in ACTH and renin, low cortisol and aldosterone, no increase in 17OHP, DHEA, Δ 4A, 11-desoxycortisol and testosterone, confirming glucocorticoid (GC), mineralocorticoid (MC) and androgen deficiency. **Molecular analysis:** Compound heterozygote for two mutations in *HSD3B2*: a previously described c.512G>A (W171X) mutation in the paternal allele, and a novel frameshift mutation c.503delC (A168Vfs*6) in the maternal allele. **Conclusion:** Our patient is compound heterozygote for two mutations in *HSD3B2* causing two shorter and aberrant peptides. This clinically causes a severe loss of 3 β -HSD II activity, leading to a nearly complete deficiency in GCs, MCs and sex steroids in our phenotypically non-virilized female CAH patient. One of the mutations is novel: c.503delC (A168Vfs*6).

P2-D2-276

Waist-to-Height Ratio, Waist-to-Hip Ratio, Waist Circumference, and BMI in Children and Adolescents with Classical Congenital Adrenal Hyperplasia Due to 21-Hydroxylase Deficiency (CAH)

Helmuth G. Dörr, Michaela Marx, Nadine Herzog, Katja Gassmann, Carolin Pichl, Thomas Völkl

Department of Pediatrics, University of Erlangen, Erlangen, Germany

Background: It has been reported that children with congenital adrenal hyperplasia (CAH) have higher BMI, increased body fat and greater waist-to-hip ratio (WHR) than control

children. **Objective and hypotheses:** Recently it was speculated that the screening potential of waist-to-height ratio (WHtR) and waist circumference (WC) for cardio-metabolic risk in adults is higher than WHR and BMI. **Method:** To review this hypothesis, we studied 43 children and adolescents with classical CAH (21 m, 22 f; ages: 6.9–17.9 years). All patients were healthy except for their underlying disease and did not take any other medication besides their substitution therapy. The study had been approved by the Ethical Committee and was not accompanied by a control group; for data comparison we used published reference values. **Results:** (Mean \pm s.d.): The BMI-SDS of all patients was 0.79 ± 1.29 . Sixteen patients (37.2%) had a BMI above the 90th percentile. The BMI SDS of both male and female patients was significantly correlated with the waist circumference (total: $r=0.793$, $P<0.001$). Twelve CAH patients (9 m, 3 f; 9 in puberty) had a significantly higher WC of 87.3 ± 15.7 cm and WHR of 0.99 ± 0.04 ($P<0.01$) in comparison with the other 31 CAH patients (WC: 69.4 ± 12.3 ; WHR 0.86 ± 0.05). Their BMI-SDS was also significantly higher (1.55 ± 1.06 vs 0.48 ± 1.25). The WHtR of all CAH patients was 0.48 ± 0.08 . Sixteen CAH patients (10 m, 6 f; 13 in puberty) had a significantly higher ($P<0.01$) WHtR of 0.57 ± 0.06 compared with 0.42 ± 0.02 ($n=27$ CAH patients). Their BMI-SDS was also significantly higher (2.13 ± 0.66 vs -0.12 ± 0.80). The BMI (>90.perc.) was elevated in 8/12 patients with an increased WC and WHR (66.7%), but elevated in all 16 patients with an increased WHtR (100%). **Conclusion:** Our data show a good correlation between BMI, WC, WHR and WHtR in children with CAH. All parameters can be used as screening parameters for overweight.

P2-D2-277

Psychological and Behavioral Outcome of Female Patients with Congenital Adrenal Hyperplasia

Abeer El Ashmawy^a, Amany Abdou^a, Mohamed Nasr^a, Sameh Tawfik^b, Shereen Abdelghaffar^a, Amany Ibrahim^a

^aKas Alini, Cairo, Egypt; ^bArmy Academy, Cairo, Egypt

Background: Children with congenital adrenal hyperplasia (CAH) may suffer from multiple psychological troubles. **Objective and hypotheses:** To assess the psychological and behavioral outcome of genetically females with classic CAH and to study the extent to which these behavioral changes could be attributed to high levels of androgens in the prenatal and postnatal periods. **Method:** 51 genetically females with CAH, representing Prader stages II–V at birth, aged 12 ± 4.7 years. Simple virilizing (SV) was 47% and salt-wasting (SW) was 53% of patients. Nine cases were assigned female, and eight cases were named as males after birth. Psychiatric history and examination were recorded, in addition to the Wechsler Intelligence Scale for children. The anxiety, depression, self-concept scales and the behavioral checklist for children were applied. **Results:** Significant degree of depression score was reported in 21 patients (41.2%), anxiety in 39 patients (76.5%), anxiety/depression in 18 cases (35.3%), low self-concept in 30 (58.8%). In addition, 48 cases were withdrawn

(94.1%) and 15 experienced sex problems (29.4%). Regarding prenatal androgen exposure, depression and anxiety were correlated with CAH type (SW or SV) ($P=0.03$, $r=0.4$ and $P=0.02$, $r=0.2$). Significant positive correlation of genital masculinization at diagnosis associated with self-concept ($P=0.002$, $r=0.476$). Depression was greater in females with SW-CAH than in females with SV-CAH ($P=0.04$). Patients had low early postnatal levels of androgen not associated with altered psychology and/or behaviour. Depression, anxiety, aggression, and sex problems were not associated with bone age advance as an indicator of growth advancement and late androgen excess. ($r(P)$: $-0.227(0.195)$, $-0.29(0.13)$, $-0.02(0.45)$, $0.26(0.15)$ respectively), except for the association with self-concept ($r=0.48$, $P=0.02^*$). **Conclusion:** Behavioral disturbances in girls with CAH result from high levels of androgens during fetal development and rather than postnatal life.

P2-D2-278

Do Neonates Need a Short Synacthen Test to Investigate the Adrenal Axis?

Usha Niranjana^a, Victoria Franklin^b, Imran Bashir^a, Sarah Martin^a, Alan Gibson^c, Neil Wright^a, Paul Dimitri^a

^aSheffield Children's Hospital, Sheffield, UK; ^bUniversity of Sheffield, Sheffield, UK; ^cSheffield Teaching Hospitals, Sheffield, UK

Background: There is limited evidence regarding the most appropriate method to investigate adrenal dysfunction in neonates. Our unit in Sheffield, UK measures a series of three serum cortisol levels to determine the need for a short synacthen test (SST). Other units use the SST as the first-line investigation in suspected adrenal insufficiency in neonates; however SST is more invasive with anaphylactic risk. **Objective and hypotheses:** To determine the proportion of neonates at risk of adrenal insufficiency who are likely to require SST. Our criteria was that two cortisol levels of >100 nmol/l or one level of >200 nmol/l would indicate normal adrenal function. **Method:** By retrospectively analysing a cohort of 154 neonates who underwent cortisol sampling over a 5-year period. **Results:** Out of 154 babies, 8(5.1%) had cortisol below the threshold and required SST (one abnormal). The mean random cortisol was 46.3 ± 8.1 and 491.6 ± 833.5 nmol/l for babies requiring and not requiring SST respectively ($P<0.0001$). Hypoglycaemia (27%), maternal steroids (23%), hypotension (16%) and suspected pituitary anomaly (10%) were the common reasons for adrenal-axis testing. To demonstrate normal adrenal function, 80%(123/154) of neonates required one cortisol and 10%(15/154) required two cortisol tests. Among neonates with hypoglycaemia only 7%(3/41) required two cortisol tests and one required SST (normal). All babies tested due to hypotension required only one cortisol. Of the 16% babies with suspected pituitary dysfunction or congenital adrenal hyperplasia, 8%(2/25) had significantly low cortisol levels requiring steroid replacement; only one of them had SST. Among babies tested due

to maternal steroids, 11%(4/36) required SST (normal) and one (3%) was started on steroid replacement prior to SST due to significantly low cortisol levels. **Conclusion:** Random cortisol measurement in suspected adrenal insufficiency is an appropriate screening test prior to SST assuming laboratory testing of cortisol is rapid. A SST is indicated if two cortisol measurements are <100 nmol/l.

P2-D2-279

Genotype-Phenotype Discordant Patients with Homozygous Intron 2 Mutation (IVS2) of CYP21 Gene

Emine Camtosun^a, Zeynep Siklar^a, Hatice Ilgin Ruhî^b, Nukhet Yurur Kutlay^b, Pinar Kocaay^a, Ajlan Tukun^b, Merih Berberoglu^a

^aDepartment of Pediatric Endocrinology, University of Ankara School of Medicine, Ankara, Turkey; ^bDepartment of Medical Genetic, University of Ankara School of Medicine, Ankara, Turkey.

Background: 21-Hydroxylase deficiency is the most common cause of congenital adrenal hyperplasia (CAH) and resulted from CYP21 gene mutations. Genotype and phenotype are usually concordant. Homozygous intron 2 splice mutation (IVS2/IVS2) is frequently associated with severe enzyme deficit, and causes classical CAH. Here, we present genotype-phenotype discordant members of two different families with IVS2/IVS2 mutation. **Family 1:** First child of family 1 was a girl diagnosed as salt wasting (SW) CAH, died at 6 days old and IVS2/IVS2 mutation of CYP21 gene was detected. Analysis of chorion villus sample showed 46, XX karyotype and IVS2/IVS2 mutation in the second pregnancy and mother received dexamethasone treatment. Postnatally, child was treated with hydrocortisone (HC) up to 21 months old. Due to suppressed hormone profile with low dose HC, treatment was discontinued. After this, she was admitted to our hospital at 25 months. She was followed-up for 3 years without medicine and she is still hormonally and clinically normal. The third child was diagnosed as SWCAH with IVS2/IVS2 mutation. **Family 2:** The daughter of family 2 was diagnosed Type 1 DM at 4.7 years old. On her follow-up at 8.17 years old, thelarche and axillary hair was detected. Her basal and stimulated 17-hydroxyprogesterone levels were high (7.5 and 18.4 ng/ml respectively), compatible with nonclassical CAH. Her genetic analysis revealed IVS2/IVS2 mutation. Asymptomatic brother also had the same mutation. Considering pseudogene state, molecular analysis of asymptomatic homozygous cases was reevaluated and the same result was observed. Sequence analysis still is going on. **Conclusion:** Although patients who have IVS2/IVS2 mutation can present with nonclassical CAH infrequently, asymptomatic patient as seen in our two cases have not been reported yet. In the CYP21 gene mutations, genotype-phenotype discordance is an issue still open for debate.

P2-D2-280

A 26-Day-Old Japanese Girl with Aldosterone Synthase Deficiency Caused by a Novel Mutation in the CYP11B2 Gene

Satomi Koyama^a, Tatsuo Tsuboi^a, Naoto Shimura^a, Akie Nakamura^b, Toshihiro Tajima^b, Osamu Arisaka^a

^aDepartment of Pediatrics, Dokkyo Medical University, Tochigi, Japan; ^bDepartment of Pediatrics, Hokkaido University School of Medicine, Hokkaido, Japan

Background: Aldosterone synthase deficiency (ASD) is a rare autosomal recessive disease, presenting with salt wasting and failure to thrive in early infancy. It is caused by inactivating mutations of the CYP11B2 gene. **Objective and hypotheses:** Our objective was to describe a Japanese patient with ASD, who presented with failure to thrive and salt wasting. **Method:** We present a case report and investigate molecular analysis of CYP11B2 gene. **Results:** A 26-day-old Japanese girl of unrelated parents was examined for poor weight gain, vomiting and dehydration. Her height and weight at birth were 46.0 cm and 2820 g with 39 weeks and 5 days gestation and her weight at 26 days old was 2515 g. She drank formula milk only about 400 ml/day and vomited once or twice a day. Laboratory findings showed hyponatremia (125 mEq/l), hyperkalemia (6.7 mEq/l) and metabolic acidosis (PH 7.306, BE-7.6 mmol/l). After infusion therapy started, her laboratory findings and weight gain had improved. But poor weight gain and hyponatremia appeared again at 38 days old after infusion therapy had stopped. At that time, the level of plasma renin activity (PRA) was 580 ng/ml per hour and aldosterone was 27.1 ng/dl. She had been suspected ASD because the normal level of aldosterone compared with highly elevated level of PRA and she had started taking fludrocortisone 0.075 mg/day and sodium chloride 1.8 g/day. Fludrocortisone replacement therapy effectively normalized growth and sodium balance. Sequence analysis of CYP11B2 gene revealed that she had a heterozygous mutation, a novel p.P108L mutation in exon 2 that was inherited from her father and a previously described p.R181W mutation in exon 3 from her mother. The novel p.P108L mutation was considered to lose the CYP11B2 activity because the result of protein function analysis by using Polyphen-2 was probably damaging. **Conclusion:** ASD is an important differential diagnosis of diseases associated with failure to thrive and salt wasting in early infants.

P2-D2-281

Nonclassic CYP21A2 Deficiency: Diagnosis and Clinical Evolution

Cristina Luzuriaga^a, María Laura Bertholt^a, Cristina Naranjo^a, Begoña Ezquieta^b

^aHospital Universitario Marques de Valdecilla, Santander, Spain;

^bHospital Gregorio Marañón, Madrid, Spain

Background: The nonclassic congenital adrenal hyperplasia (CAH) is often presented as isolated premature pubarche in childhood. Definitive diagnosis is genetic. **Objective and hypotheses:** To describe patients diagnosed in our hospital, clinical signs and laboratory results that lead to genetic study. To analyze adult height. **Method:** Descriptive retrospective study of our population with genetic confirmation. **Results:** Twenty patients: 14 girls and six boys. Reason of consultation: premature pubarche 16, family history 3 (three family, six patients), short stature 1 and clitoral hypertrophy 1. Different degree of bone acceleration. We separated into two groups: group 1 with no severe genetic mutation (two mild mutations) seven patients; group 2: 13 patients, mild-severe mutation. Comparing the two groups: age at diagnosis 7.3 ± 2.9 vs 7.6 ± 1.5 years. Bone age acceleration: 1.5 ± 1.3 vs 2.6 ± 1.0 years. 17O-HP 37.2 (7.8–70.0) vs 76.3 (21.0–162.0) ng/ml (significant). Treatment: no treatment two patients (group 1) vs three (group 2), hydrocortisone 4 vs 5; hydrocortisone + triptorelin 1 vs 3; triptorelin 0 vs 2. Twelve patients reached final height: 5 vs 7. Two patients exceed target height. Two under target height (one of group 1: untreated, another of group 2: treated). Only one patient with adult height $< p3$ (current Spanish population). No primary amenorrhea, two patients with functional ovarian hyperandrogenism. Two men with azoospermia (one patient group 1 and other group 2). Mutations found: p.Val282Leu + p.Val282Leu (six), p.Val282Leu + p.Pro454Ser (one), p.Val282Leu + c.293-13A/C > G (one), p.Val282Leu + (c.293-13A/C > G; c.332-339del)(1), p.Val282Leu + c.332-339del (two), p.Val282Leu + p.Gln319Stop (one), p.Val282Leu + (p.Gln319Stop; p.Ile173Asn) (one), p.Val282Leu + (p.Gln319Stop; p.Arg357Trp) (three), p.Val282Leu + gene conversion (three), p.Val282Leu + c.1205_1206delAT (one). **Conclusion:** In our study predominate presence of severe mutation, which must be taken into account for genetic counseling. Premature pubarche and advanced bone age are the main clinical signs. We got good results of adult height in both groups with hydrocortisone treatment, triptorelin or combined. Unable to ensure that no treatment deteriorate adult height. Larger studies are necessary. In this type of CAH we recommend monitoring reproductive function.

P2-D2-282

Steroid 11 β -Hydroxylase Deficiency Due to CYP11B1 Mutations in Females with Hyperandrogenemia

Christos Shammass^a, Stefania Byrou^a, Alexia AP Phedonos^a, Stella Nicolaou^b, Meropi Toumba^c, Nicos Skordis^{a,d}, Vassos Neocleous^a, Leonidas A Phylactou^a

^aThe Cyprus Institute of Neurology & Genetics, Nicosia, Cyprus;

^bMakarios III Hospital, Nicosia, Cyprus; ^cIasis Hospital, Paphos, Cyprus; ^dSt George's, University of London Medical School at the University of Nicosia, Nicosia, Cyprus

Background: More than > 90% of cases of congenital adrenal hyperplasia (CAH) are caused by 21-hydroxylase deficiency, steroid 11 β -hydroxylase deficiency accounts for 5–8% of cases.

Objective and hypotheses: To seek evidence on the prevalence of *CYP11B1* mutations in prepubertal girls, adolescents and adult females with clinical signs of hyperandrogenemia. **Method:** The study included 31 girls with premature adrenarche (PA) of whom 15 were identified heterozygotes for *CYP21A2* gene mutation and 25 adolescents and adult females with polycystic ovary syndrome (PCOS), of whom seven were heterozygotes for *CYP21A2*. The diagnosis of PCOS was based on the Rotterdam Criteria. Direct DNA sequencing was used to identify mutations in *CYP11B1*. **Results:** In the group of girls, who presented early with PA, 48.4% were heterozygotes and 51.6% had no identifiable mutations in *CYP21A2*. On the contrary, in the group of females with late onset hyperandrogenemia, the presence of one mutation was detected in 28%, whereas 72% carried no mutation. In the total group of 31 girls, who presented early with PA, 16 had no identifiable mutation both in *CYP21A2* or *CYP11B1*, 14 were identified as heterozygotes in *CYP21A2* only and one girl was identified with digenic inheritance in *CYP21A2* (p.Qln318stop) and the *CYP11B1* (p.Arg43Gln). In the group of 25 females with late onset hyperandrogenemia (PCOS), 17 had no identifiable mutation, seven were identified as heterozygotes in *CYP21A2* and one was identified in heterozygosity with the missense p.Arg43Gln in *CYP11B1*. No mutants were identified in the 3' and 5' untranslated region (UTR) of the *CYP21A2* and *CYP11B1* genes. **Conclusion:** The carrier status for *CYP21A2* may be an important factor in the variable phenotype of hyperandrogenism and a contributing factor for the early manifestation of the disease. Furthermore non-classic 11 β -hydroxylase deficiency is a rare disorder and it is not a significant factor of hyperandrogenemia in females with PA and PCOS.

P2-D1-283

Hypophosphatemic Rickets in Norwegian Children: Genotypes, Phenotypes, and Complications

Silje Rafaelsen^a, Helge Ræder^{a,c}, Stefan Johansson^{a,b}, Robert Bjercknes^{a,c}

^aInstitute of clinical science, University of Bergen, Bergen, Norway;

^bCenter of Medical Genetics and Molecular Medicine, Haukeland University Hospital, Bergen, Norway; ^cDepartment of Pediatrics, Haukeland University Hospital, Bergen, Norway

Background: Hereditary hypophosphatemic rickets (HR) is a group of rare diseases with disordered phosphate metabolism. The Norwegian cohort of HR patients has not previously been described. **Objective and hypotheses:** The aim of the study was to characterize the genotype, phenotype, and complications to treatment in a national cohort of Norwegian children HR. **Method:** For assessment of genotype, Sanger sequencing of *PHEX*, *FGF23*, *DMPI*, *ENPP1*, and *KL* were performed. Multiplex ligand-dependent probe amplification (MLPA) analysis was performed to detect larger duplications or deletions in *PHEX*. In one family, exome sequencing was performed to identify the genotype. For assessment of phenotype and complications to

treatment, the medical records were reviewed. **Results:** The prevalence of HR was one in 45 000 children. We identified 26 patients (17 females, nine males) from 17 families. There were 21 familiar and five sporadic cases. *PHEX* mutations were found in 21 subjects (81%). Two brothers had mutations in *FAM20C*. In three sporadic cases, no pathogenic mutation was identified. 11 of 18 X-linked HR (XLHR) patients had elevated levels of intact parathyroid hormone (iPTH) at the time of diagnosis, and all 18 patients developed hyperparathyroidism during follow-up. In patients with XLHR, the maximum level of iPTH was higher for patients with missense mutations than patients with other mutations. Nephrocalcinosis was observed in nine XLHR individuals, and was related to higher treatment doses of calcitriol and phosphate. The height Z-score at follow-up correlated negatively with age at start of medical treatment, but was not related to treatment doses of phosphate and calcitriol. **Conclusion:** A genetic diagnosis is important, as new anti-FGF23 treatment may become available in the future. Early diagnosis and medical treatment are probably more important than phosphate dosing to optimize growth and minimize the occurrence of complications.

P2-D1-284

Increased Fracture Rate in Children and Adolescents with Marfan Syndrome

Giuliana Trifirò^a, Susan Marelli^b, Stefano Mora^c, Alessandro Pini^b

^aAO Salvini P.O. Rho, Rho (Milan), Italy; ^bMarfanClinic-Cardiology Dpt Sacco Hospital, Milan, Italy; ^cLaboratory of Pediatric Endocrinology, San Raffaele Scientific Institute, Milan, Italy

Background: Marfan syndrome (MFS) is an autosomal dominant disorder of connective tissue. Cardinal features affect cardiovascular system, eyes and skeleton. It is caused by mutations of *FBN1* gene, which encodes the extracellular matrix protein fibrillin 1. The improper activation of TGF β , due to defective fibrillin-1, is the pathophysiological mechanism. The altered modulation leads to overgrowth of long bones (disproportionate stature) and altered bone morphology. **Objective:** Aim of our study was to investigate bone mineral density and risk of fracture in children with MFS. **Method:** Seventy-three patients (35 girls and 38 boys) were enrolled in the study from 2009 to 2013: all had a clinical diagnosis of MFS by revisited Ghent Criteria (2010). The mean age at examination was 10.2 (4.0) years in girls, and 9.8 (3.6) years in boys. The mean weight Z-scores was -0.01 (ranging from -3.2 to 3.5) and the mean height Z-score was 1.9 (-1.8-6.3). We measured bone mineral density (BMD) by dual-energy X-ray absorptiometry at the lumbar spine. Because MFS patients are taller than healthy peers, BMD measurements were corrected for height Z-scores, and expressed as BMD Z-score/height. **Results:** Mean BMD Z-score/height at lumbar spine was -1.9 (-6.7 to 1.0), significantly lower than average ($P < 0.0001$): in girls -1.8 (-4.2 to -0.27), in boys -2.1 (-6.7 to 1.06), $P < 0.0001$ in both. Nineteen patients (13 males and six females) reported to have had

one or more fractures: 17 patients had one fractures, one (boy) had two fractures, and one (boy) three fractures. Fractures were nine at wrist, three at forearm, two at humerus, two at finger hand bones, one at clavicle, two at tibia, one at ankle, one at toe, and one at pubic symphysis. Fractures occurred after mild or moderate traumatic injuries: fall playing (six) or during physical activity (five biking, two playing football, and one basket), slip (four), collision against a peer (two) or a corner (one), crash (one). Difficulties on fracture healing were not reported. Fractures were not correlated with BMD values. **Conclusion:** The prevalence of fractures (30%) in our patients is markedly higher than the reported average for children (in UK from 1.6–3.6% and in Lombardy, Italy 1.5%). Our study demonstrates a skeletal fragility in MFS children, increasing with age. The knowledge of the epidemiology may be useful to develop preventive strategies.

P2-D1-285

Mutations in IFITM5 Leading to Prenatal and Postnatal Signs of Dominant Osteogenesis Imperfecta

Heike Hoyer-Kuhn^a, Christian Netzer^b, Jutta Becker^b, Eckhard Schoenau^a, Oliver Semler^a

^aChildren's Hospital, University of Cologne, Cologne, Germany;

^bInstitute of Human Genetics, University of Cologne, Cologne, Germany

Introduction: Osteogenesis imperfecta (OI) is a hereditary disease characterized by a wide range of skeletal signs. Mutations in COL1A1/A2 have been known to cause dominant OI. Recently, a heterozygous mutation in the 5'-UTR of *IFITM5* (c. -14C>T) was identified as a new cause of dominant OI. We present three patients from three different families with two mutations in *IFITM5* with extremely different phenotypes. **Description of methods/design:** Patient 1 displayed at 20 weeks of gestation with bowing of the lower extremities. Postnatal, he showed white sclera, a hypoplastic thorax, bowing of the long bones. With 19 months the patient presented with a length of -4.8 SDS and a weight of -3.2 SDS. Bone resorption was increased despite antiresorptive bisphosphonate treatment (deoxypryridinoline/creatinine 63.9 nM/mM (19.5 ± 7.2)). Patient 2 and 3 were diagnosed with a moderate OI at the age of 1.7/8.7 years based on extremity fractures and hyperplastic callus formation. Bone mineral density was reduced with a DXA ap spine Z-score of -3.3/-2.8 before initiating i.v./oral bisphosphonate treatment. Sanger sequencing of *IFITM5* was performed. Written informed consent was given. **Results:** In patients 2/3 the *IFITM5* c. -14C>T mutation was identified causing the classical postnatal hallmarks of OI V. Patient 1 presented a new heterozygous mutation within the coding region of *IFITM5* (c.119C>T; p.S40L). This mutation resulted in severe OI with prenatal onset and extreme short stature. Characteristics of OI type V did not occur yet. **Conclusions:** Dominant mutations in the gene *IFITM5* are connected to the clinical hallmarks of moderate OI V but also can lead to severe OI with prenatal onset.

In patients suspected of OI, the entire gene *IFITM5* – and not only the 5'-UTR region – has to be analyzed to exclude a causal role of *IFITM5*. We propose that this should be part of the initial diagnostic steps as dominant mutations are most common in OI.

P2-D1-286

Musculoskeletal Health in Children with Crohn's Disease at Diagnosis: Dynamic Muscle Function, Tibia Cortical and Trabecular Bone Density and Vertebral Fracture Prevalence

Leanne M Ward^a, Frank Rauch^b, Jinhui Ma^c, Maya Scharke^c, Heather Cosgrove^c, Mary Ann Matzinger^d, Nazih Shenouda^d, Eric I Benchimol^a, David R Mack^a

^aDepartment of Pediatrics, Children's Hospital of Eastern Ontario, University of Ottawa, Ottawa, Ontario, Canada; ^bDepartment of Pediatrics, Shriners Hospital for Children, McGill University, Montréal, Québec, Canada; ^cChildren's Hospital of Eastern Ontario Research Institute, Ottawa, Ontario, Canada; ^dDepartment of Diagnostic Imaging, University of Ottawa, Ottawa, Ontario, Canada

Background: The bone mass deficit in pediatric Crohn's disease (CD) is associated with low total body lean mass and suppression of bone turnover. **Objective and hypotheses:** We examined at diagnosis whether the sarcopenia is associated with leg muscle hypofunction, changes in tibia muscle-bone indices as well as overt bone strength loss (vertebral fractures, VF). **Method:** 70% children with CD were studied within 2 weeks of diagnosis (64% boys; median age 13.9 years, range 7–17) including lateral spine radiograph for VF assessment by the Genant semi-quantitative and Algorithm-Based Qualitative methods. Muscle function was measured by peak jump power (PJP) on a two-legged jump by mechanography force plate. Muscle-bone structural indices were measured by peripheral quantitative computed tomography (pQCT) at 4, 38 and 66% tibia sites. PJP and pQCT results were converted to age-, gender- and tibia-length specific Z-scores (as appropriate). **Results:** 90% of children had moderate or severe CD, 36% were pre-pubertal, height and weight Z-scores were low (mean ± s.d. -0.3 ± 1.1, $P=0.046$ and -0.8 ± 1.3, $P<0.001$, both compared to the healthy average). Only one patient had VF (1%, 95% CI 0, 4) – a 16-year-old boy with severe CD and VF at T4/5 plus loss of end-plate parallelism at T12/L1. The following muscle-bone indices were reduced: PJP (Watts/kg, mean Z-score -1.9 ± 1.6, $P<0.001$), tibia trabecular density (-1.4 ± 1.4, $P<0.001$), cortical bone mineral content (BMC) (-0.9 ± 1.2, $P<0.001$) and muscle cross-sectional area (-1.5 ± 1.1, $P<0.001$). Cortical density at 38% was preserved (mean 0.2 ± 1.1, $P=0.171$). **Conclusion:** Leg muscle mass and dynamic function is reduced in newly diagnosed CD children. The tibia findings including low trabecular density, low cortical BMC but relative preservation of cortical bone density suggest a relatively recent insult affecting muscle and development. The VF prevalence, while low, highlights that children with CD at diagnosis are not exempt from overt bone strength loss.

Table 1. (for abstract P2-D1-287)

	Adj. S. calcium (2.2–2.79 mmol/l)	PTH (1.1–6.9 mmol/l)	S. phosphate (1.36–2.26 mmol/l)	Ca/Cr clearance ratio	Vitamin D (nmol/l)
Index case	3.22	2.1	1.44	0.003	47
Mother	2.91	2.6	1.06	0.004	32
Younger brother	3.05	5.1	1.57	0.01	77
Grandfather	2.69	9.7	0.84		
Father	2.46	4.8			

P2-D1-287**Case report: A Novel mutation in the Calcium Sensing Receptor in a Welsh Family with Hypercalcaemia**

Astha Soni, Carley Frerichs, Renuka Ramakrishnan, Poonam Dharmaraj

Alder Hey Childrens NHS Foundation Trust, Liverpool, UK

Background: Familial hypocalciuric hypercalcaemia (FHH) is an autosomal dominant disorder due to inactivating mutations in the calcium sensing receptor (CASR). FHH is generally benign with asymptomatic hypercalcaemia, low urinary calcium excretion and normal or mildly elevated PTH. **Objective and hypotheses:** We report a novel mutation in CASR in a family with three generations affected with hypercalcaemia. **Method:** A 15-month-old boy was found to have asymptomatic hypercalcaemia when admitted for elective tonsillectomy. Further investigations revealed normal PTH, phosphate and vitamin D levels. Urine calcium/creatinine (Ca/Cr) clearance ratio was low. A younger brother born a few months later also had asymptomatic hypercalcaemia and hypocalciuria. Investigation of family members showed raised calcium in the index case's mother and maternal grandfather, but not in his father or older brother. **Results:** CASR sequencing of the family has revealed a previously undescribed T to C nucleotide substitution in exon 4 of CASR (c.1342T>C (p.Ser448Pro)). The index case, younger brother, mother and grandfather are all heterozygous for this unclassified variant (Table 1). **Conclusion:** We describe a novel mutation in the CASR gene in three generations of the same family with biochemical diagnosis of FHH.

P2-D1-288**A New Missense Mutation in FGF23 Gene in a Male with Hyperostosis-hyperphosphatemia Syndrome**

Farzaneh Abbasi^{a,b}, Soudeh Ghafouri-Fard^c, Azadeh Ebrahim-Habibi^{b,d}

^aGrowth and Development Research Center, Children Medical Hospital, Tehran University of Medical Sciences, Tehran, Iran; ^bEndocrinology and Metabolism Clinical Sciences Institute, Endocrinology and Metabolism Research Center, Tehran University of Medical Sciences, Tehran, Iran; ^cDepartment of Medical Genetics, Shahid Beheshti University of Medical sciences, Tehran, Iran;

^dBiosensor Research Center, Endocrinology and Metabolism Molecular-Cellular Science, Tehran, Iran

Background: Hyperostosis-hyperphosphataemia syndrome (HHS) is a rare autosomal recessive metabolic disorder, characterized by recurrent painful swelling of long bones, periosteal new bone formation and cortical hyperostosis or intramedullary sclerosis, hyperphosphatemia and low intact fibroblast growth factor 23 (FGF23) protein levels. It is caused by mutations in two genes, *N*-acetylgalactosaminyltransferase 3 (GalNAc-transferase; GALNT3) and FGF23. **Method:** Blood sample was collected from the patient. DNA was isolated using the standard salting out method. All exons and exon-intron boundaries of GALNT3 and FGF23 genes were amplified according to Ichikawa *et al.* and Garringer *et al.* respectively. PCR products were sequenced using the ABI Prism3130 Genetic Analyzer (Applied Biosystems). In order to analyze the effects of observed missense variant PolyPhen-2 was used. This software shows that the mutation leads to substitution of a highly conserved amino acid and is predicted to be probably damaging with a score of 1.000. With this software, values nearer 1 are more confidently predicted to be deleterious. **Results:** No nucleotide change was observed in GALNT3 exons and exon-intron boundaries. However, a homozygous mutation was detected in exon 3 of FGF23 gene (NM_020638.2: c.471C>A). The nucleotide change results in aminoacid change from phenylalanine 157 to leucine (p.F157L) in receptor interaction site. **Conclusion:** Previous researches have proposed that HFTC (hyperphosphatemic familial tumoral calcinosis) and HHS are clinical variants of the same disease. This study, in accordance with previous studies shows that FGF23 mutations can cause HHS.

P2-D1-289**Pseudohypoparathyroidism Type 1A Due to Novel GNAS Mutation**

Yael Levy-Shraga^{a,b}, Noah Gruber^{a,b}, Kineret Mazor-Aronovitch^{a,b}, Dalit Modan-Moses^{a,b}, Orit Pinhas-Hamiel^{a,b}

^aPediatric Endocrinology and Diabetes Unit, Sheba Medical Center, The Edmond and Lily Safra Children's Hospital, Tel Hashomer, Ramat Gan, Israel; ^bTel-Aviv University, Tel-Aviv, Israel

Background: Pseudohypoparathyroidism (PHP) encompasses a group of rare disorders defined by target organ unresponsiveness to parathyroid hormone (PTH). Patients with PHP type 1A carry heterozygous mutations of the maternal *GNAS* gene that encodes the α -subunit of the G protein. This protein is coupled to the PTH receptor as well as to other heptahelical receptors - TSH, GHRH and gonadotropins receptors. **Objective and hypotheses:** To describe a case of PHP type 1A due to a novel *de-novo* *GNAS* mutation. **Method:** The patient was born at 36 weeks gestation weighing 3535 g after an uncomplicated pregnancy. Physical examination at birth was unremarkable except for umbilical hernia. At the fifth day of life, he developed hypothermia. Blood tests revealed TSH 76 mIU/l (normal range: 0.7–9.8), FT₄ 9.9 pmol/l (7–16) and FT₃ 4 pmol/l (3.8–6). Thyroid scan showed a normally located thyroid gland. Levothyroxine treatment was initiated with normalization of TSH, FT₄ and FT₃ levels. However, excessive weight gain ensued and at 6 months he weighed 11.3 kg (+3.3 SDS for his age). Therefore, further workup was performed and revealed: PTH 91.8, 129 and 211 pg/ml in sequential blood tests (nl=16–87), calcium 9.7 mg/dl, phosphorus 6.7 mg/dl, 25-hydroxy vitamin D 21.9 ng/ml and calcium/creatinine ratio in the urine 0.02. Both parents had unremarkable physical examination and lab results. DNA was extracted from whole blood and full sequencing of the coding regions of the *GNAS* gene was performed. **Results:** Sequence analysis revealed a novel heterozygous frameshift mutation with a premature stop codon in exon 7 (c.518_521delACTG). This mutation has not been previously reported and is predicted to be deleterious. Neither parent carried the mutation. **Conclusion:** This case presents a novel *de-novo* *GNAS* mutation. Physicians should consider the rare diagnosis of PHP among neonates with congenital hypothyroidism with normally located gland and marked obesity in the newborn period.

P2-D1-290

Sleep-related Breathing Disorders in Pycnodysostosis

Serap Turan, Zeynep Atay, Yasemin Gokdemir, Nilay Bas, Belma Haliloglu, Saygin Abali, Serpil Bas, Refika Ersu, Abdullah Bereket

Marmara University, Istanbul, Turkey

Background: Pycnodysostosis is an autosomal recessive disease characterized by short stature, osteosclerosis, increased bone fragility. In these patients maxillary and mandibular hypoplasia, flattening of the mandibular angle, long soft palate, narrow palate structure can lead to pharyngeal narrowing and obstructive sleep apnea syndrome (OSAS). **Objective and hypotheses:** Our aim was to evaluate sleep disordered breathing in children with pycnodysostosis. **Method:** Demographic data, pediatric sleep questionnaire (PQ16) scores, polysomnography results and treatments of pycnodysostosis patients who were followed by Pediatric Endocrinology Department in Marmara University were evaluated. **Results:** Mean age of the eight patients (seven girls and one boy) in the study was 12.2 ± 4.2 years, mean

age at diagnosis was 6.5 ± 4 years. Habitual snoring was reported in 7 (87%) and apnea during sleep was reported in 3 (37.5%) patients. Two patients had adenoidectomy and one had tonsillectomy. Four patients (50%) received GH. Mean PQ16 score was 0.41 ± 0.19 (normal < 0.33). Polysomnography revealed OSAS in six patients (75%). Two (25%) had severe and 4 (50%) had mild OSAS. OSAS was detected in five of six patients with PQ16 score > 0.33 . One of the two patients with PQ16 score < 0.33 had mild OSAS. Obstructive apnea hypopnea index (OAHI) ranged between 0 and 15.1 (median 2.9) (1–5; mild, 5–10; moderate, > 10 ; severe), central apnea index ranged between 0–2.1 (median 0.4). Mean SpO₂ value was $94.5 \pm 1.6\%$ and lowest SpO₂ value was $90.5 \pm 3.5\%$. BPAP was started in three patients. Control PSG was planned for other patients during follow-up. **Conclusion:** Sleep related breathing disorders are frequent in pycnodysostosis and although PQ16 can be used to screen, polysomnography should be offered to all patients with pycnodysostosis.

P2-D1-291

Cystinosis as a Cause of Hypophosphatemic Rickets: a Single-Center Experience

Murat Dogan, Keziban Bulan, Sultan Kaba

Yuzuncu Yil University, Van, Turkey

Introduction: Cystinosis is an inherited (autosomal recessive) lysosomal storage disorder characterized by accumulation of cystine crystals in kidney, liver, eyes and brain. Patients can present to pediatric endocrinology clinics with growth retardation and vitamin D resistant rickets particularly in nephropathic infantile form. Here, we aimed to present genetic and clinical spectrum of ten patients who have been followed with the diagnosis of cystinosis, a rare cause of hypophosphatemic rickets, in our clinic. **Material and method:** The study included ten patients who have been followed with diagnoses of cystinosis in our outpatient clinic. Data regarding presenting complaint, history, physical examination findings, anthropometric measurements, age, and laboratory findings were extracted from electronic database. Blood samples were drawn into EDTA tubes from all patients and mutation analyses were performed. **Findings:** It was found that age range was 2 and 12 years in patients and age at diagnosis was ranging from 6 to 18 months. Overall ten patients (four girls and six boys) from nine families were identified. There was consanguinity between parents in seven families and there was an affected sibling in three families. Proteinuria of varying degrees and hypophosphatemic rickets were present in all patients at presentation. Renal failure of varying degrees developed in four patients during follow-up. In one patient, cystine crystals were detected in eyes at presentation. No cystine crystal was detected in patients underwent bone marrow aspiration. In CTNS gene, c18-21del14bp mutation was detected in four patients, whereas homozygote p.E227E(c.681G>A) mutation was detected in six patients. These mutations were among those recently identified

and should be considered as explanatory for the disease. **Conclusion:** In the present study, we aimed to emphasize that patients presented with hypophosphatemic rickets should be evaluated for proximal tubular dysfunction and cystinosis should be considered in such patients, as consanguinity between parents is relatively high in our province.

P2-D1-292

Pseudohypoparathyroidism Type Ib: Two Cases with Different Clinical Presentation

Claudia Balsamo^a, Federico Baronio^a, Angelica Marsigli^a,
Valentina Bonifacci^b, Giovanna Mantovani^d, Angelo Molinaro^c,
Harald Jüppner^c, Paola Visconti^e, Laura Mazzanti^a,
Antonio Balsamo^a

^aPediatric Unit, Department of Medical and Surgical Sciences, Program of Endocrinology, University of Bologna and S.Orsola-Malpighi Hospital, Bologna, Italy; ^bDepartment of Pediatrics, University of Ferrara, Ferrara, Italy; ^cEndocrine Unit, Harvard Medical School and Massachusetts General Hospital, Boston, Massachusetts, USA; ^dDepartment of Clinical and Community Sciences, University of Milan, Milano, Italy; ^eInfantile Neuropsychiatry Unit-Maggiore Hospital, Bologna, Italy

Background: Sporadic pseudohypoparathyroidism type Ib (spor-PHP-Ib) is caused by *GNAS* methylation alterations with loss of imprinting at the exon A/B differentially methylated region (DMR), without genetic deletions disrupting the STX16 ICR. These patients classically display hormone resistance limited to PTH and TSH with no Albright hereditary osteodystrophy (AHO). **Objective and hypotheses:** We describe two cases with the same imprinting methylation defect, but different clinical presentation. **Method:** Patient (pt) 1 was first evaluated for suspicious neurologic disease presenting with vertigo, eye lateral deviation and diplopia. He underwent brain computed tomography that did not show cerebral infarction or expansive lesion, but basal ganglia calcifications. He showed high PTH levels, severe hypocalcemia and hyperphosphatemia. TSH levels were slightly elevated. Pt 2 was firstly evaluated for slipped capital femoral epiphysis (SCFE) at 6 years of age and severe osteoporosis. She showed high PTH levels, normal calcium levels, but hyperphosphatemia. TSH was in normal range. Both cases did not show AHO. Therefore PHP-Ib was suspected and confirmed by molecular analysis. **Results:** Our patients share the same methylation abnormality on the *GNAS* gene locus, however they differ in phenotype expression. We hypothesized that our patients probably have different bone sensitivity to PTH, higher in case 2. According to this theory, prolonged (unrecognized) hypocalcemia led to basal ganglia calcification in case 1; higher bone PTH sensitivity led to normal calcium serum levels, with secondary osteoporosis and SCFE in case 2. Interestingly all cases with PHP Ib with SCFE reported by literature are females. **Conclusion:** Our two cases differed in clinical features, while showing comparable genotypes, and

confirming that the long-term effects of elevated PTH on bone are still controversial in these patients and they may be related to other factors.

P2-D1-293

A Very Rare Case of Rickets: Fanconi–Bickel Syndrome

Adel Djermane^a, Asmahane Ladjouze^b, Yasmine Ouarezki^c,
Sandrine Vuillaumier-Barrot^e, Benfetima Ali Khodja^d, Leila Kedji^b,
Abdeljalil Maoudj^b, Karima Berkouk^b, Menoubia Bensmina^b,
Tahar Anane^b, Abdennour Laraba^b

^aDepartment of Paediatrics, EPH Gouraya, Tipaza, Algeria; ^bDepartment of Paediatrics, CHU Bab El Oued, Algiers, Algeria; ^cDepartment of Neonatology, EPSP Baraki, Algiers, Algeria; ^dDepartment of Paediatrics, CHU Constantine, Constantine, Algeria; ^eUF Génétique, Hôpital Bichat Claude Bernard, Paris, France

Background: Fanconi–Bickel syndrome (FBS) is a rare glycogen storage disease characterized by hepato-renal glycogen accumulation, severe renal tubular dysfunction and impaired glucose and galactose metabolism. We present the case histories of two sisters who were diagnosed with FBS. **Case reports:** The proband, Lina, was referred to our clinic for growth retardation and abdominal distention aged 27 months. She is the 4th child of consanguineous parents and was born small-for-gestational age (BW 2700 g at 41 weeks gestation). She received oral vitamin D3 at 1 and 6 months according to our national rickets prevention program. At initial examination auxology showed: severe short stature height – 5.72 SDS; BMI – 0.98 SDS. There was hepatomegaly, gross motor delay but normal intelligence. She had clinical manifestations of severe rickets with odd-shaped skull, pigeon chest, swollen wrist and ankle joints and bowing of the legs. X-rays showed typical signs of rickets with multiple fractures. Laboratory investigations confirmed severe hypophosphatemic rickets with calcium 96 mg/l (90–110 mg/l), phosphate 12 mg/l (40–60 mg/l) and proximal renal tubular dysfunction with glycosuria. She also showed fasting hypoglycemia (glucose 0.4 g/l) and postprandial hyperglycemia (glucose 2.2 g/l). Molecular analysis of the *SLC2A2* (*GLUT2* gene) revealed a homozygous splicing mutation c.964-2A>C (intron 7). She was treated with oral phosphorus and 1- α -Vitamin D and the parents were encouraged to frequent meals with adequate caloric intake; and uncooked cornstarch. Amani, sister of the proband, was not small-for-gestational age (BW 3200 g at 38 weeks gestation). She was first evaluated at the age of 7 months when auxology showed: height: – 2.43 SDS, weight: – 2.24 SDS, BMI: -1.07 SDS. By this age she was already showing clinical and radiological signs of rickets. Laboratory investigations were consistent with the diagnosis of FBS. **Conclusion:** The association of short stature, hypophosphatemic rickets and impaired glucose homeostasis is very evocative of FBS. Our proband presented with a homozygous *SLC2A2* mutation which resulted in a severe phenotype.

P2-D1-294

Determinants of Vitamin D Levels in Children and Adolescents with Down Syndrome

Stefano Stagi, Elisabetta Lapi, Perla Scalini, Paolo Del Greco, Franco Ricci, Achille Marino, Maurizio de Martino, Salvatore Seminara

Health Science Department, Anna Meyer Children's University Hospital, University of Florence, Florence, Italy

Background: Down syndrome (DS) is the most common genetic (chromosomal) mental retardation syndrome. In these patients, several environmental and hormonal factors contribute to low bone mineral density (BMD), among these factors, vitamin D may play a significant role in the health of patients with DS. However, poor studies have evaluated 25-hydroxy cholecalciferol (25(OH)D) levels in DS. **Objective and hypotheses:** The purpose of this study was to assess serum 25(OH)D and to identify risk factors for vitamin D deficiency in this syndrome. **Methods:** We have longitudinally evaluated 31 DS children and adolescents (17 males, 14 females, aged 4.5–18.9 years). In all subjects we analysed serum calcium and phosphate, serum parathyroid hormone (PTH), 25(OH)D concentrations, dietary intakes of calcium and 25(OH)D, and we quantified outdoor exposure. After 8.5 ± 2.3 months of 400 UI 25(OH)D supplementation, we re-evaluated these patients. The results were compared to a control group included 99 healthy age- and sex-matched subjects (51 males, 48 females, range 4.8–19.8 years). **Results:** DS subjects showed very reduced 25(OH)D levels than controls ($P < 0.0001$), in particular DS with obesity ($P < 0.05$), and history of autoimmune diseases ($P < 0.005$). Moreover, PTH levels were significantly higher than controls ($P < 0.0001$). After 25(OH)D supplementation, 25(OH)D levels was significantly ameliorated ($P < 0.05$), even if significantly reduced than controls ($P < 0.0001$), in particular in DS with obesity ($P < 0.05$), and with autoimmune diseases ($P < 0.001$). **Conclusions:** Our results indicate that hypovitaminosis D is very frequent in DS, assessing the importance of vitamin D prophylaxis in these subjects, in particular in DS with obesity and autoimmune diseases. The reduced 25(OH)D levels seem to be also related to reduced outdoor activity levels. Accordingly, DS patients with obesity and autoimmune diseases may require higher 25(OH)D supplementation.

P2-D2-295

Determinants of Vitamin D Levels in Children, Adolescents, and Young Adults with Juvenile Idiopathic Arthritis

Stefano Stagi^a, Laura Capirchio^a, Achille Marino^a, Federico Bertini^b, Salvatore Seminara^a, Maurizio de Martino^a, Fernanda Falcini^b

^aHealth Science Department, University of Florence, Anna Meyer Children's University Hospital, Florence, Italy; ^bDepartment of Biomedicine, Section of Rheumatology, Transition Clinic, University of Florence, Florence, Italy

Background: 25-Hydroxyvitamin D (25(OH)D) deficiency is reported to be common in patients with rheumatoid arthritis and associated with disease activity, physical disability, and cardiometabolic intermediates; data in patients with juvenile idiopathic arthritis (JIA) are inconsistent. **Objective and hypotheses:** To assess serum 25(OH)D in children, adolescents, and young adults with JIA, and to identify the risk factors for vitamin D deficiency in JIA patients. **Method:** We evaluated 152 patients with JIA (115 female, 37 males, mean age 16.2 ± 7.4 years; 96 oligoarticular, 35 polyarticular, seven systemic and 14 enthesitis-arthritis onset). These patients were compared with a sex- and age-matched control group. All patients and controls performed laboratory evaluation of plasma 25(OH)D, parathyroid hormone (PTH), calcium, phosphorus, bone alkaline phosphatase levels, and dual energy X-ray absorptiometry of the lumbar spine examination to evaluate bone mineral density (BMD) expressed as estimation, bone mineral apparent density. **Results:** JIA patients showed significantly reduced 25(OH)D levels in comparison to controls ($P < 0.001$), even if divided into subtypes (oligoarticular $P < 0.05$; polyarticular $P < 0.005$; systemic $P < 0.001$; ERA $P < 0.005$). Patients with active disease and/or frequent relapses had significantly reduced 25(OH)D levels than patients with no active disease and no frequent flares ($P < 0.005$, respectively). Nevertheless, JIA patients had significantly higher PTH levels compared to controls ($P < 0.0001$). Finally, JIA patients with 25(OH)D deficiency showed a significant lower BMAD Z-score than those with normal 25(OH)D levels ($P < 0.001$). **Conclusion:** JIA patients have reduced 25(OH)D and higher PTH values. These data may explain, at least partially, why JIA patients do not reach bone normal condition over the time, despite more effective current drugs. JIA patients with more severe subtype, such as polyarticular and systemic onsets, may require higher supplementation of Vitamin D to maintain normal 25(OH)D serum levels. Future long-term studies are needed to explore the relationship between serum 25(OH)D levels and disease activity.

P2-D2-296

Determinants of Vitamin D Levels in Italian Children and Adolescents of Mugello, an Area of Tuscany: a Longitudinal Evaluation

Perla Scalini, Stefano Stagi, Chiara Iurato, Cristina Manoni, Paola Pelosi, Laura Capirchio, Maurizio de Martino, Salvatore Seminara

Health Science Department, University of Florence, Anna Meyer Children's University Hospital, Florence, Italy

Background: Few studies have assessed 25-hydroxy vitamin D [25(OH)D] status among Italian children. **Objective and hypotheses:** To assess 25(OH)D in children and adolescents living in Tuscany, Italy, identifying risk factors for vitamin D deficiency in different age groups. **Method:** We evaluated 446 children and adolescents (2.4–17.8 years), from Mugello (latitude 44° N), and we determined 25(OH)D, calcium, alkaline phosphatase and parathyroid hormone (PTH) levels. Of these, 275 subjects were selected randomly and followed-up. Subjects with

25(OH)D deficiency were treated with cholecalciferol 10 mcg/day, while those with insufficiency were followed-up improving diet, milk's intake, and hours spent outdoors. **Results:** Initially 11.4% of subjects had sufficient 25(OH)D, 33.2% insufficient and 55.4% deficient levels. Mean 25(OH)D was 19.08 ± 8.44 ng/ml, with a significant difference between children and adolescents ($P < 0.0005$). Significantly better 25(OH)D levels were observed in the group spending more outdoor hours day ($P < 0.005$), and in children with normal milk consumption ($P < 0.005$). At longitudinal evaluation, 26.9% of subjects had sufficient 25(OH)D, 38.9% insufficient, and 34.2% deficient levels. Mean 25(OH)D was 23.79 ± 6.89 ng/ml. For the subjects supplemented with cholecalciferol, 25(OH)D were significantly higher ($P < 0.0001$) in respect to those not supplemented. Significant differences remained regarding 25(OH)D in the group spending more time outdoors ($P < 0.005$), and in children with normal milk consumption per day ($P < 0.0001$). We found that 25(OH)D levels correlated significantly with age, BMI, cows' milk consumption, outdoor physical activity, the use of sunscreens, PTH, and calcium. **Conclusion:** The presence of inadequate 25(OH)D levels represents a complex problem involving dietary errors, use of sunscreens, increase in the obesity rate. Neither changes of lifestyle or supplementation with cholecalciferol alone appear to be sufficient to restore adequate levels of vitamin D.

P2-D2-297

Severe Heterotopic Ossifications in a 10-year-old Boy with PHP1a

Adalbert Raimann^a, Diana Alexandra Ertl^a, Stefan Riedl^{a,b}, Werner Schlegel^a, Gabriele Haeusler^a

^aMedical University of Vienna, Vienna, Austria; ^bSt Anna Children's Hospital, Vienna, Austria

Background: Progressive osseous heteroplasia (POH) is a rare condition characterized by extensive heterotopic ossification (HO) of connective tissues. Associations of HO and Albright hereditary dystrophy (AHO) lead to the identification of GNAS mutations to be causative for ectopic bone formations. The highly imprinted GNAS locus is known to cause a broad spectrum of pathologic conditions, including pseudohypoparathyroidism (PHP), pseudoPHP AHO. While PHP is caused by maternal inheritance, paternal inheritance leads to pseudoPHP and POH. Only a small subpopulation of patients with maternally inherited GNAS mutations has been reported to feature HO. **Objective and hypotheses:** Here, we report the case of a 10-year-old boy with PHP1a, featuring extensive dermal ossification at multiple locations. In contrast to reported mild ectopic ossification in PHP1a patients, this case shows the potentially progressive character of HO despite maternal inheritance of a GNAS mutation. **Method:** The patient's history including genetic analysis, lab and imaging findings as well as treatments are reported. **Results:** Genetic analysis of the GNAS locus has been performed in the patient and both parents, excluding a paternal inheritance. In the course of treatment, both extensions of existing lesions as well as occurrence of new lesions were observed despite

treatment and serum calcium levels within the target range. While being progressive in size and number of lesions, HO in our patient has been shown to be limited to the dermis which is in line with the small number of similar cases. **Conclusion:** We hereby report the occurrence of severe heterotopic ossification in a patient with a maternally inherited GNAS mutation and PHP1a. Despite serum calcium levels in the target range, bone formation remains progressive raising the need of specific treatments for this impairing symptom.

P2-D2-298

Zoledronic Acid for Management of Osteopenia of Prematurity and Associated Ventilator Dependency

Mary White^a, Anastasia Pellicano^b, Margaret Zacharin^a, Peter Simm^{a,c}

^aDepartment of Endocrinology & Diabetes, Murdoch Childrens Research Institute at The Royal Children's Hospital, Parkville, Melbourne, Australia; ^bDepartment of Neonatology, The Royal Children's Hospital, Parkville, Melbourne, Australia; ^cDepartment of Endocrinology & Diabetes, Monash Children's Hospital, Clayton, Melbourne, Australia

Background: The effect of bisphosphonates in patients with severe osteopenia of prematurity is unknown in terms of either fracture prevention or long-term safety. A 6-month-old male infant born at 24+2 weeks gestation was referred for consideration of bisphosphonate therapy in the management of severe osteopenia of prematurity. The neonatal course included chronic lung disease requiring four courses of corticosteroids. Despite optimal calcium, phosphate and vitamin D supplementation an atraumatic oblique femoral fracture was documented at 4 weeks corrected age. The infant remained mechanically ventilated after two failed attempts at extubation, despite minimal ventilator requirements. One further attempt at extubation was planned with palliation thereafter if unsuccessful. **Objective and hypothesis:** It was postulated that severe osteopenia of the ribs was contributing to inadequate chest wall movement and support. Given the end of life nature of the request, a decision was taken to trial bisphosphonates to improve chest wall function after counselling that this was in the absence of any published evidence of benefit in this scenario. **Methods:** A single dose of zoledronic acid 0.02 mg/kg (0.07 mg) was given which was well tolerated. **Results:** Successful extubation to CPAP occurred 1 week later; serum alkaline phosphatase had decreased from 2190 to 1094 IU/l (normal range 100–350) during this timeframe. At 8 months corrected, no further fractures have occurred and the infant remains on nasal oxygen at home. **Conclusion:** In this instance, the use of zoledronic acid was used to confer mechanical support to the chest wall of a ventilator-dependent infant with complex medical needs. Successful extubation was temporally related to the administration of a single dose of the bisphosphonate. Potential mechanisms include pain reduction or strengthening of the thoracic cage. Clinical trials are warranted prior to general consideration of change in management practice, but in extreme circumstances this stratagem may be considered.

P2-D2-299

Mutation in the TBCE Gene Associated with Kenny-Caffey Type 1 Syndrome: a Rare Cause of Hypocalcemia

Bensalah Meriem^a, Bouzidi Fatma Zohra^a, Véronique Beauloye^b, Hoyos Maria Garcia^c, Kemali Zahra^a

^aCentral Hospital of Army, Algiers, Algeria; ^bClinique Universitaire Saint-Luc, Bruxelles, Belgium; ^cMedical Genetic Department, Valencia, Spain

Background: Kenny-Caffey syndrome type 1 is a rare autosomal recessive syndrome caused by mutation in the TBCE gene (Tubulin specific chaperone E) located in the chromosome region 1q42-q43. Less than 60 cases have been reported in the literature especially in the Middle East and Arabic countries. This syndrome is characterized by growth retardation, dysmorphic features, with thickened bone cortex and medullary stenosis, hypoparathyroidism, teeth anomalies. Hypopituitarism with pituitary hypoplasia may be associated. **Case report:** A 3-year old Algerian girl was referred to pediatric endocrinology unit for etiological research of hypocalcemia. Her birth weight was 1370 g. At the 72 h of birth she has been admitted in intensive unit for hypocalcemia which has been related to prematurity. At 13 months, she developed seizures and hypocalcemia was detected with total calcium 6.8 mg/dl, serum parathormone (PTH) level was low: 2.8 ng/ml. She has been treated with calcium and vitamin D. On examination she has severe growth retardation weight was 6 kg (< -3DS), normal mentality height 65 cm (< -3DS), dysmorphic face with microcephaly, deep-set eyes with hypermetropia, peaked nose, thin lips, micrognathia, low set ears, microdontia, enamel defects and caries. She has normal total calcium: 2.38 mmol/l under calcium and vitamin D supplements, IGF1: 8.3 ng/ml, glucagon test showed low GH secretion with pic of 5.23 mUI/l. Radiological findings showed internal cortical thickening and medullary stenosis of the tubular bones. Pituitary MIR showed pituitary hypoplasia. Variant c.155_166del in the TCBE gene has been identified in homozygosity, which is predicted to cause at protein level, an in frame shift deletion of four aminoacids (p.ser52_gly55del) which is compatible with the clinical diagnosis of Kenny-Caffey syndrome. **Conclusion:** Kenny-Caffey syndrome is a rare cause of hypocalcemia. The association of severe short stature, dysmorphic face, teeth abnormalities and bone dysplasia must guide us to suggest the diagnosis especially in the Middle Eastern and Arabic countries and confirm them genetically.

P2-D2-300

Vitamin D Levels in Children, Adolescents, and Young Adults with Juvenile onset Systemic Lupus Erythematosus: a Cross-sectional Study

Stefano Stagi^a, Laura Capirchio^a, Federico Bertini^b, Camilla Menchini^a, Perla Scalini^a, Salvatore Seminara^a, Maurizio de Martino^a, Fernanda Falcini^b

^aHealth Science Department, University of Florence, Anna Meyer Children's University Hospital, Florence, Italy; ^bDepartment of Biomedicine, Section of Rheumatology, Transition Clinic, University of Florence, Florence, Italy

Background: Hypovitaminosis D is common in the general population. Although many studies on 25-hydroxyvitamin D (25(OH)D) are available on systemic lupus erythematosus (SLE), little data is present in juvenile onset SLE (JSLE) patients. **Objective and hypotheses:** This study aimed to assess serum 25(OH)D levels in JSLE patients and to identify risk factors for vitamin D deficiency in this population. **Method:** Forty-five consecutive Caucasian patients (36 females and nine males, mean age 18.9 ± 6.3 years) with JSLE that was consistent with the American College of Rheumatology criteria entered the study. **Results:** Levels below the recommended 25(OH)D values were found in the 84.4% of the JSLE patients, comparable to that of controls (80.2%). Nevertheless, JSLE patients exhibited lower 25(OH)D levels than controls ($P < 0.005$), with lower values observed in patients with active vs inactive disease ($P < 0.05$). JSLE patients exhibited reduced total calcium levels ($P < 0.001$) and higher phosphate levels ($P < 0.001$), BSAP ($P < 0.001$) and PTH ($P < 0.001$) than controls. In addition, JSLE patients exhibited lower spine bone mineral apparent density SDS values than controls ($P < 0.001$), with higher values in patients with 25(OH)D sufficiency and insufficiency than those with 25(OH)D deficiency ($P < 0.001$). **Conclusion:** Patients with JSLE have significantly lower 25(OH)D levels than controls. Therefore, supplementation with vitamin D may be a useful approach for promoting the normalization of bone mass and quality in subjects with JSLE.

P2-D2-301

Disproportionate Short Stature with Advanced Bone Age Due to PTHLH Mutation

Annemieke Boot, Irene Stolte-Dijkstra, Irma Veenstra-Knol

University Medical Center Groningen, Groningen, The Netherlands

Background: Skeletal dysplasia is the main cause of disproportionate short stature. The severity may vary. The present patient had disproportionate short stature with brachydactyly. **Patient and method:** A boy of 5 years old presented with height 108.9 cm (-1.8 s.d.), sitting height/height ratio was $+3.4$ s.d., short hands and feet with short metacarpal 4 and metatarsal 4 on both sides. He had increased lumbar lordosis and painful legs after walking of a long distance. The mother had a height of 150.6 cm (-3.0 s.d.) and father 179.9 cm (-0.4 s.d.). The mother had a

disproportionate short stature and brachydactyly. The boy was born from a twin pregnancy after an amenorrhea duration of 34 weeks, birth weight 1740 g (-1.4 s.d.) with a moderate start. His twin sister is healthy. His development was retarded. His bone age was 3 years advanced. Additional laboratory assessment showed normal serum calcium, phosphate, alkaline phosphatase, parathyroid hormone (PTH) and immeasurable PTH-related protein (PTH-rp). DNA analysis was performed. He had no mutation in the *FGFR3* gene, no mutation/deletion/duplication of the *SHOX* or *COL2A1* genes and a normal array CGH. **Results and discussion:** DNA analysis showed a mutation in exon 4 of the (PTH-like hormone) *PTH1LH* gene (c.25T>C, p.Trp9Arg). The mutation was also found in the mother, but not in her parents, the mutation had therefore occurred *de novo* in the mother. A *GNAS* gene mutation was excluded in the mother. Other *PTH1LH* mutations have been described in patients with short stature and brachydactyly type E. PTH-rp acts through the PTH-receptor and is essential for normal cartilage development. Failure of this activation leads to increased chondrocyte apoptosis and premature closure of the growth plates. **Conclusion:** Disproportionate short stature with advanced bone age may be caused by a *PTH1LH* mutation.

P2-D2-302

Plasma 25-OH Vitamin D and pth Concentrations in Cord Blood: relationship with Ethnic Groups, Nutritional Habits and Degree of Maternal Sun Exposure

Sandra Ortigosa Gómez^a, Oscar Garcia Algar^a, Antonio Mur Sierra^a, Roser Ferrer Costa^b, Antonio Carrascosa Lezcano^b, Diego Yeste Fernández^b

^aParc de Salut Mar, Barcelona, Spain; ^bHospital Vall d'Hebron, Barcelona, Spain

Introduction: Several studies showing a high prevalence of vitamin D deficiency in pregnant women have been published in recent years. Vitamin D deficiency during pregnancy has been related to adverse events both in mother and child. Plasma 25-OH vitamin D (25(OH)D) levels in the newborn are dependent on maternal deposits and show a close correlation with maternal levels; thus, neonates of vitamin D-deficient mothers present a greater risk of hypocalcaemia, rickets and a higher incidence of infections during the first year of life, particularly if exclusively breastfed without vitamin D supplementation. **Subjects and methods:** Between March and May 2013, 99 pregnant women in whom plasma 25(OH)D by chemoluminescence and PTH by (LIAISON[®] N-TACT[®] PTH II Assay) levels were measured in cord blood at birth. Clinical history data of the mothers and neonates were collected and a nutritional survey was made on maternal vitamin D and calcium intake and degree of sun exposure. **Results:** Race distribution was: 45% Caucasian, 24% IndoPakistani, 20% SouthAmerican, 11% others. Mean 25(OH)D value in cord blood was 10.4 ± 6.1 ng/ml. Vitamin D deficiency (25(OH)D < 20 ng/dl) was present in 94% of pregnant women. Mean PTH value in cord blood was 6.1 ± 2.5 pg/ml and did not

correlate with 25(OH)D. Vitamin D and calcium intake was considered adequate in the majority of mothers although sun exposure was deemed deficient in 47%. Vitamin D levels in cord blood were significantly related to race, skin type, degree of sun exposure, use of traditional dress and vitamin D and calcium intake. **Conclusions:** The prevalence of vitamin D deficiency in pregnant women was very high after the winter months and consequently in their offspring. Thus, the administration of vitamin D supplements should be indicated during pregnancy.

P2-D2-303

Cleidocranial Dysplasia Misdiagnosed as Rickets in Three Generations

Roberto Franceschi^a, Evelina Maines^a, Michela Fedrizzi^a, Maria Rosaria Piemontese^b, Maria Bellizzi^a, Vittoria Cauvin^a, Annunziata Di Palma^a

^aPediatrics Unit, S. Chiara General Hospital, Trento, Italy;

^bDepartment of Evolutive Age, Medical Genetics Unit,

IRCCS-Ospedale Casa Sollievo della Sofferenza, San Giovanni Rotondo, Foggia, Italy

Background: Cleidocranial dysplasia (CCD; MIM 119600) is a rare congenital autosomal dominant skeletal dysplasia characterized by hypoplastic or aplastic clavicles, late closure of the fontanelles, open skull sutures, dental anomalies, moderately short stature and a variety of other skeletal features. CCD is caused by mutations, deletions or duplications in the runt-related transcription factor 2 gene (*RUNX2*), which encodes for a protein essential for osteoblast differentiation and chondrocytes maturation. **Case report:** We report three familial cases of CCD, misdiagnosed as rickets in three generations. The proband was a 5-year-old girl, who at 3 years of age was diagnosed as having rickets and treated with vitamin D because of large anterior fontanelle and patent skull sutures. At 5 years of age, she was referred to our Pediatric Clinic because persistently open skull sutures and anterior fontanelle associated with frontal and parietal bossing. Physical examination revealed drooping and hypermobile shoulders, which were easily apposed at the midline. Chest X-ray displayed bilateral hypoplastic clavicles. Skull X-ray confirmed a wide open anterior fontanelle, separated sutures, multiple wormian bones, and supernumerary teeth. Family history revealed that her father and her paternal grandmother were treated with vitamin D during childhood, because rickets was diagnosed on the basis of delayed ossification of cranial sutures and fontanelles, as well as pectus excavatum. Chest X-ray of father confirmed bilateral hypoplastic clavicles. No mutations were detected by standard DNA sequencing analysis of *RUNX2* gene, but screening for intragenic deletions and duplications by quantitative PCR (qPCR) and multiple ligation-dependent probe amplification (MLPA) revealed a novel deletion of exons 1–3. **Conclusion:** Our cases indicate that the diagnosis of CCD could be missed at birth and misdiagnosed as rickets during childhood, leading to inappropriate treatment. Our cases confirm that standard DNA sequencing analysis could not identify mutations in *RUNX2* gene in all CCD patients; in these cases screening by qPCR and MLPA can turn out positive results.

P2-D2-304

Age- and Gender-Specific Reference Values of Bone Mineral Density in Korean Adolescents and Young Adults

Shin Hye Kim^a, Mi Jung Park^a, Duk Hee Kim^b

^aSanggye Paik Hospital, Inje University College of Medicine, Seoul, Republic of Korea; ^bSowha Children's Hospital, Seoul, Republic of Korea

Background: Low bone mass during growth may increase risk of fracture. Adequate reference data for bone mineral density (BMD) are needed to identify adolescents with bone deficit.

Objective and hypotheses: We aimed to provide normative values and reference curves for BMD in Korean adolescents and young adults. **Method:** Using the data from Korean Nutrition Health and Nutrition Examination Survey (KNHANES) in 2008–2011, a total of 3352 subjects (1635 males and 1717 females aged 10–25 years), were included for this study. BMD were measured using dual X-ray absorptiometry at lumbar spine (LS), total body (TB), TB less than head (TBLH), total hip (TH), and femoral neck (FN). Age-related reference curves for BMD were generated using the LMS statistical procedure. **Results:** The BMD increased with age in both genders ($P < 0.0001$), and reached a plateau at ages 16–17 in males and at age 15 in females. Peak BMD velocities occurred at ages 13–14 in males; at ages 11–12 in females. Peak bone mass (PBM) of all study regions was achieved by the age of 21 and 19 in males and females, respectively. BMD in LS, TB, and TBLH was maintained until the age of 25, whereas decrease in BMD was noted in TH and FN from the age of 23 and 22 in males and females, respectively (Table 1). **Conclusion:** This reference values for BMD can be used to assess and monitor the bone health in Korean adolescents and youth.

P2-D2-305

Status of Vitamin D in Pregnancy to Childhood in Northern Spain: Seasonality, Sun Exposure, and Intake

Ana Cristina Rodríguez-Dehli^a, Isolina Riaño-Galán^a, Inés Olaya Velázquez^a, Ana Fernández-Somoano^b, Ane Miren Castilla^c, Mercedes Espada^c, Eva M Navarrete-Muñoz^d, Adonina Tardon^b

^aSan Agustín Hospital, Avilés, Asturias, Spain; ^bCIBERESP and Oviedo University, Oviedo, Asturias, Spain; ^cCIBERESP and Public Health Laboratory, Bilbao, País Vasco, Spain; ^dCIBERESP and Miguel Hernández University, San Juan de Alicante, Comunidad Valenciana, Spain

Background: Vitamin D3 (25OHD) insufficiency is becoming a public health issue. Adequate 25OHD status during pregnancy may influence the health status of the offspring. **Objective and hypotheses:** To evaluate the levels of 25OHD during pregnancy (at 12 weeks) and at 4 years old, assessing seasonality, time of sun exposure, and intake. **Method:** Data were obtained from 485 pregnant mothers recruited in Asturias between 2004 and 2007 and their children from of the Environment and Childhood (Infancia y Medio Ambiente) (INMA) Project, a population-based birth cohort study. **Results:** The mean maternal age was 32 years (range 18–42). 94.1% were term infants and 47.6% female. 25OHD was analyzed in 453 gestations: mean 27.7 ng/ml (range 6.4–69.5). There was no association between 25OHD in pregnancy and birth somatometry. 25OHD was analyzed at 4 years in 260 children: mean 21.36 ng/ml (range 2.8–45) and parathyroid hormone 35.36 pg/ml (15.07–76.40), with normal calcium and phosphorus. Statistically significant relationship was found between 25OHD in pregnancy and at 4 years (Pearson's r 0.257) and each one with size at 4 years (Pearson's r 0.167 and 0.190). The 25OHD was lower in winter and spring in gestation and at 4 years. The average pregnant

Table 1. Lumbar spine BMD: LMS values and $-2s.d.$ (z -score) by age and gender (for abstract P2-D2-304).

Age year (n)	Male (n=1574)				Age year (n)	Female (n=1647)			
	LMS parameters and $-2s.d.$ (z -score)					LMS parameters and $-2s.d.$ (z -score)			
	L	M	S	$-2s.d.$		L	M	S	$-2s.d.$
10 (119)	0.068	0.577	0.133	0.441	10 (106)	0.560	0.643	0.150	0.463
11 (123)	0.226	0.630	0.135	0.477	11 (113)	0.588	0.710	0.144	0.518
12 (131)	0.380	0.687	0.136	0.515	12 (95)	0.616	0.774	0.139	0.571
13 (110)	0.516	0.749	0.137	0.557	13 (120)	0.640	0.828	0.134	0.617
14 (139)	0.624	0.810	0.137	0.600	14 (100)	0.656	0.869	0.129	0.655
15 (101)	0.701	0.861	0.136	0.638	15 (84)	0.661	0.899	0.125	0.684
16 (90)	0.743	0.901	0.133	0.669	16 (97)	0.659	0.920	0.121	0.706
17 (100)	0.754	0.929	0.131	0.695	17 (90)	0.648	0.934	0.119	0.722
18 (83)	0.746	0.951	0.128	0.716	18 (64)	0.625	0.942	0.116	0.733
19 (92)	0.731	0.968	0.125	0.735	19 (116)	0.587	0.948	0.115	0.741
20 (45)	0.719	0.984	0.122	0.752	20 (87)	0.531	0.952	0.113	0.747
21 (55)	0.712	0.997	0.120	0.767	21 (106)	0.451	0.955	0.113	0.753
22 (102)	0.712	1.005	0.117	0.778	22 (102)	0.352	0.957	0.112	0.758
23 (101)	0.721	1.007	0.115	0.784	23 (122)	0.241	0.957	0.111	0.762
24 (78)	0.735	1.006	0.113	0.786	24 (134)	0.123	0.957	0.110	0.766
25 (105)	0.754	1.003	0.111	0.787	25 (111)	0.001	0.957	0.109	0.770

outdoor time was 5 h 35 min (range 0000–1515 h) and at 4 years 0300 (0021–0655 h), without association with 25OHD levels. The median estimated VitD intake was 4.63 g/day (range 0.71–22.52) at pregnancy and 2.74 g/day (range 0.81–12.66) at 4 years. **Conclusion:** A high frequency of 25OHD insufficiency/deficiency in pregnancy and at 4 years was found, despite the time of sun exposure as recommended, perhaps due to the latitude of 43°. The estimated intake was lower than recommended in most of the cohort. There is a relationship between levels in pregnancy and at 4 years and both with size at age 4, although not with birth anthropometry.

P2-D2-306

Effects of Recombinant Human GH on Bone Mass and Body Composition in Paediatric Inflammatory Bowel Disease

M A Altowati^a, S Shepherd^a, P McGrogan^b, R K Russell^b, S F Ahmed^a, S C Wong^a

^aDevelopmental Endocrinology Research Group, Royal Hospital for Sick Children, University of Glasgow, Glasgow, UK; ^bDepartment of Gastroenterology, Royal Hospital for Sick Children, Glasgow, UK

Background: rhGH therapy may improve linear growth in children with inflammatory bowel disease (IBD). Poor bone health and abnormal body composition are recognised complications in paediatric IBD. **Objective and hypotheses:** To investigate the effects of rhGH on bone health and body composition. **Method:** Sub-analysis of 13 children with IBD (12CD; 1UC) in a randomized controlled trial. Either rhGH (0.067 mg/kg per day) as daily s.c. injections (rhGH group; *n*, 7CD) or no rhGH (Ctrl; *n*, 5CD 1UC) for 6 months. Results expressed in median (range). **Results:** In the rhGH group, BMC for bone area (BA) SDS was 0.0 (−0.5, 0.5) at the baseline and −0.2 (−0.7, 0.5) (*P*=0.5) at 6 months and in the Ctrl group it was 0.0 (−0.1, 1) and −0.05 (−0.3, 0.7) (*P*=0.3). Median P1NP increased from 169 µg/l (21 250) at baseline to 241 µg/l (238 250) at 6 months (*P*=0.06) in the rhGH group, whereas in the Ctrl group, it was 199.5 µg/l

(155 218) and 211.5 µg/l (162 231) respectively (*P*=0.30). There were no significant changes in urinary CTX after 6 months in the rhGH and Ctrl group. In the rhGH group, DXA lean mass for height centiles changed from 43 (0.0, 97) at base line to 47 (7, 56) at 6 months (*P*=0.9) and in the Ctrl group it was 13.5 (0.0, 26) and 10.5 (0.0, 29) (*P*=0.3) respectively. DXA percentage fat mass in rhGH group was 26.3% (15.1, 30.3) at baseline and 20.8% (8.6, 29.1) (*P*=0.2) at 6 months and in the Ctrl group it was 24.6% (16.7, 36.1) and 26.6% (16.8, 39.2) (*P*=0.1). Leptin was 3.7 ng/ml (0.4, 4.2) in the rhGH group at baseline and 1.7 ng/ml (0.4, 11.8) (*P*=0.8) at 6 months, whereas this was 3.3 ng/ml (0.8, 11.7) and 2.8 ng/ml (0.6, 116.6) (*P*=0.6) in the Ctrl group. Similarly, adiponectin was 15 712 ng/ml (10 675, 25 000) in the rhGH group at baseline and 19 072 ng/ml (6512, 25 000) (*P*=0.8) at 6 months, whereas this was 14 923 ng/ml (8778, 15 820) and 15 429 ng/ml (9151, 20 459) (*P*=0.5) in the Ctrl group. **Conclusion:** Over a 6-month period of high-dose rhGH, there are no significant changes in bone mass and body composition in paediatric IBD despite some evidence of an increase in a marker of bone formation.

P2-D3-307

Suppression of Bone Turnover and its Determinants in Children Receiving Bisphosphonate Therapy

Andreas Kyriakou^a, Jane D McNeilly^b, Martin McMillan^a, Guftar M Shaikh^a, Avril Mason^a, Syed Faisal Ahmed^a

^aDevelopmental Endocrine Research Group, University of Glasgow, Glasgow, UK; ^bDepartment of Biochemistry, RHSC, Glasgow, UK

Background: Bisphosphonate therapy (BPT) reduces osteoclast activity and may be associated with adynamic bone turnover. The extent of suppression of bone turnover and its determinants are unclear. **Method:** Markers of bone metabolism were evaluated in 15 children (9M/6F) undergoing BPT for osteoporosis. The median age at first biochemical assessment was 10.8 years (0.16, 16.3). Serum type I collagen cross-linked C-telopeptide (CTX), alkaline phosphatase (ALP), calcium(CA), phosphate(P),

Table 1. (for abstract P2-D3-307)

	Reference range	Time since start BPT (years)					
		0.5	1	1.5	2	3	>3
<i>n</i>		7	10	8	8	5	5
CTXcentile		2.8 (0.7, 4.1)	2.8 (0.6, 4.9)	2.7 (0.5, 3.8)	2.8 (0.5, 5.5)	2.1 (1.4, 7.1)	2.1 (1.0, 4.9)
ALP(U/l)	60–424	351 (62, 500)	261 (49, 421)	192 (36, 455)	141 (39, 396)	215 (136, 346)	145 (105, 274)
PTH(pmol/l)	1.6–7.5	2.9 (1.4, 4.5)	2.35 (1.0, 6.9)	3.35 (2.8, 6.0)	3.4 (2.1, 7.8)	2.95 (2.5, 5.1)	4.3 (2.8, 5.6)
VitD(nmol/l)	>40	47 (26, 78)	36 (19, 108)	15 (14, 44)	23 (14, 36)	31 (23, 38)	57 (34, 98)

Values: median (range)

parathyroid hormone (PTH) and 25 hydroxy vitamin D (VitD) were measured on day 1 of each BPT cycle. The CTX was expressed as a centile of the reference range in healthy children. **Results:** The median interval between the first BPT cycle and first biochemical assessment was 0.67 years (0.17, 4.8). The median duration of observation was 1.1 years (0.58, 3.3) and the median number of samples per patient was 5 (3, 9) (Table 1). The median CTX centile was 2.4 (0.5, 7.1), thus below 10th centile, throughout the duration of observation ($P < 0.0001$). ALP was negatively correlated with the duration of treatment ($r = -0.35$, $P < 0.05$) and positively correlated with CTX ($r = 0.72$, $P < 0.0001$). Median CTX in patients who had ($n = 4$) and did not have consistently low VitD was 26.1% (12.8, 51) and 19.6% (3.4, 35.7) ($P < 0.05$). PTH was positively correlated with CTX ($r = 0.51$, $P < 0.05$). **Conclusion:** Bone resorption is markedly suppressed compared to bone formation. Vitamin D and PTH status influence the extent of suppression of bone resorption. An assessment of bone turnover markers may allow improved titration of BPT.

P2-D3-308

A Case of Vitamin D Dependent Rickets Type 1 with a Novel Mutation in CYP27B1 (25-OH Vitamin D-1- α -Hydroxylase) Gene

Bahar Ozcabi, Olcay Evliyaoglu, Oya Ercan, Feride Tahmiscioglu, Sevinc Jaferova, Cigdem Oruc, Amra Adrovic

Cerrahpasa Medical School, Istanbul, Turkey

Background: Vitamin D dependent type 1 rickets is a rare, autosomal-dominantly inherited disorder due to an inactivating mutation in CYP27B1 (25-OH vitamin D-1- α -hydroxylase) gene. It is characterized by early onset of rickets with hypocalcemia. We report a boy admitted with symptoms of hypocalcemia and who carried a novel mutation in CYP27B1 gene. **Case:** The patient was admitted with tetany at the age of 12 months. When he had his first convulsion, he was 9 months old. He did not have prophylaxis of vitamin D and hypocalcemia was detected in his country. Vitamin D was administered orally. Carbamazepine was added for the treatment of seizures and pancrelipase for the treatment of repeated diarrhea episodes. He was born from a consanguineous marriage. He had one healthy sister and one brother died at the age of 12 months because of hypocalcemia and pneumonia. At physical examination, he had carpopedal spasm. Height, weight and head circumference SDS were -1.83 , -1.02 , 1.64 respectively. He had caput quadratum and enlargement of wrist. His serum calcium, phosphorus, alkaline phosphatase levels were 5.9 mg/dl, 3.5 mg/dl and 987 IU/l respectively. No abnormalities of acid-base metabolism or renal function were detected. Renal ultrasound revealed nephrocalcinosis (grade 1). Radiological findings included metaphyseal fraying and cupping in wrists. Serum levels of parathormone and 25-OH vitamin D levels were high; 1, 25 OH vitamin D level was low; urine calcium/creatinine ratio was 0.006 . Calcium carbonate and calcitriol were

administered orally. In follow-up, his liver enzyme levels increased, it was related to Cytomegalovirus infection. With normal electroencephalography findings and without diarrhea, treatments of carbamazepine and pancrelipase were withdrawn. Serum levels of calcium were normal under treatment of calcitriol and calcium-carbonate. DNA sequencing revealed a novel homozygous mutation of p.Q135X (c.403 C>T) in CYP27B1 gene. **Conclusion:** Vitamin D dependent rickets tip 1 is a rare disorder but must be considered even in countries where vitamin D deficiency is still common.

P2-D3-309

Risedronate Use in Duchenne Muscular Dystrophy: a Pilot Randomised Control Trial

Niamh Mc Sweeney^a, Malachi Mc Kennan^{b,c}, Susan van der Kamp^b, Mark Kilbane^c, Ciara Mc Donnell^d, Nuala Murphy^d, David Webb^e, Bryan Lynch^{a,f}

^aDepartment of Paediatric Neurology, The Central Remedial Clinic, Dublin, Ireland; ^bDXA Unit, St Vincent's University Hospital, Dublin, Ireland; ^cMetabolism Laboratory, St Vincent's University Hospital, Dublin, Ireland; ^dDepartment of Paediatric Endocrinology, The Children's University Hospital, Dublin, Ireland; ^eDepartment of Paediatric Neurology, Our Lady's Children's Hospital, Dublin, Ireland; ^fDepartment of Paediatric Neurology, The Children's University Hospital, Dublin, Ireland

Background: Boys affected with Duchenne Muscular Dystrophy (DMD) have lower bone mineral density compared with unaffected boys. **Objective and hypotheses:** We sought to determine the effects on bone mineral density (BMD) of 1 year treatment with Risedronate and calcium/vitamin D supplementation vs calcium/vitamin D supplementation alone. **Method:** BMD was measured at spine and whole body. We obtained early morning fasting blood samples for 25-hydroxyvitamin D (25OHD), calcium, parathyroid hormone (PTH), procollagen type I N-terminal propeptide (PINP), and timed-urine for N-terminal telopeptides of type I collagen (NTX). Eligible patients (spine Z-score < -1.0) were randomized to each treatment arm: Risedronate 1 mg/kg per week (max 35 μ g) and calcium (500 mg/day) and vitamin D (10 μ g/day), or calcium/vitamin D alone. Tests were repeated after 12 months. **Results:** Twenty-nine of 62 patients were eligible; 13 consented; six were in the Risedronate arm. Nine were ambulant and were on steroid therapy. Median (range) at entry for the entire group for age was 8.5 (5.4 – 15.5) years, for 25OHD was 41.3 (21.5 – 64.4) nmol/l, for PINP was 540 (149 – 788) μ g/l, and for NTX was 927 (361.8 – 2332.9) nMBCE/mMCr. In the Risedronate group: median (range) spine Z-score at baseline was -1.75 (-1.2 to -3.5), and at 12 months was -0.8 (-1.7 to 0); whole body Z-score was -1.95 (-0.5 to $+2.7$) and at 12 months was 1.3 (-1.0 to 2.5). In the control group: mean spine Z-score at baseline was -2.2 (-4.1 to -1.2) and at 12 months was -1.6 (-8.4 to -0.8), whole body

Z-score at baseline was -1.2 (-1.6 to $+4.7$) and at 12 months was -0.8 (-3.1 to 3). There was no significant change in PINP or NTX after 12 months in either group. **Conclusion:** We demonstrated a significant improvement in BMD at spine and whole body at 12 months in the Risedronate group. Bone resorption marker was increased with respect to bone formation marker. This pilot study suggests benefit of Risedronate therapy, but would need validation in a larger study.

Chirurgie infantile orthopédique, Hôpital Necker-Enfants Malades, 149 rue de Sèvres 75015, Paris, France

P2-D3-310

Outcomes of Vitamin D Analogues and Phosphate Supplements in Patients With Hereditary Hypophosphatemic Rickets, Comparison With Non-Treated Patients

Emese Boros^a, Anya Rothenbuhler^b, Claudine Heinrichs^a, Cécile Brachet^a, Laure Esterle^b, Peter Kamenicky^c, Pol Harvengt^d, Sylvie Brailly-Tabard^e, Hazar Haidar^e, Céline Gaucher^f, Caroline Silve^b, Charles Gossio^{me}, Philippe Wicart^g, Martin Biosse Duplan^f, Frederic Courson^f, Catherine Chaussain^f, Agnès Linglart^b

^aService d'endocrinologie pédiatrique- Hôpital Universitaire des Enfants Reine Fabiola, Avenue J J Crocq 15, Bruxelles, Belgium;

^bCentre de Référence des Maladies Rares du Métabolisme du Calcium et du Phosphore, Service d'Endocrinologie et Diabétologie de l'Enfant, Université Paris Sud, Hôpital Bicêtre, APHP, 78 rue du Général Le, Paris, France; ^cCentre de Référence des Maladies Rares du Métabolisme du Calcium et du Phosphore, Université Paris Sud, Service d'Endocrinologie et Diabétologie, Hôpital Bicêtre, APHP, 78 rue du Général Leclerc 9427, Paris, France; ^dRepresentant association pour les personnes atteintes de rachitisme vitamino-résistant hypophosphatémique, Paris, France; ^eService de Pharmacogénétique, Biochimie Moléculaire et Hormonologie, Service GMPH, Hôpital Bicêtre, APHP, Université Paris Sud, 78 rue du Général Leclerc 94270, Paris, France; ^fService d'odontologie Hôpital Bretonneau, HUPNVS, AP-HP, EA 2496, UFR d'Odontologie Paris Descartes Sorbonne Paris Cité, Paris, France; ^gService de

Background: Hereditary Hypophosphatemic Rickets (HHR) is caused by persistently elevated FGF23 resulting in renal phosphate wasting and decreased 25 vitamin D hydroxylation. Treatment with vitamin D analogues (VDA) has been added to phosphate supplements in the late seventies. **Objective and hypotheses:** Our objective was to evaluate the outcomes of VDA and phosphate supplements in adult patients with HHR in comparison with patients who did not receive VDA (i.e. non-treated patients). **Method:** We performed a retrospective study of patients diagnosed with HHR. Patients were divided in two groups: group 1: 50 patients (mean age 25.2 years) who received VDA and group 2: 58 patients (mean age 41.7 years), 27 received phosphate supplements, 31 never had any treatment. **Results:** Group 1 patients were taller than group two patients, had better correction of leg bowing, less leg corrective surgeries and better dental health. VDA treatment was associated with a higher femoral neck *T* score and lower fracture incidence in adulthood. Complications such as nephrocalcinosis and hyperparathyroidism were similar between groups (Table 1). **Conclusion:** The current conventional treatment improves height, leg bowing and cortical bone density. Our results in a large cohort of HHR patients confirm that the use of vitamin D analogues is safe and associated with better long-term outcomes. However several features of the disease are not cured and require new therapies.

P2-D3-311

Hyperostosis-Hyperphosphataemia Syndrome: Shortening a Diagnostic Odyssey

Jaya Sujatha Gopal Kothandapani^a, Amaka Offiah^c, Sally Hobson^d, Paul Arundel^b

^aDepartment of Human Metabolism, University of Sheffield, Sheffield, UK; ^bDepartment of Paediatric Endocrinology, Sheffield Children's NHS Foundation Trust, Sheffield, UK; ^cAcademic Unit of Child Health, University of Sheffield, Sheffield, UK; ^dDepartment of Orthopaedic Surgery, Hull Royal Infirmary, Hull, UK

Table 1. (for abstract P2-D3-310)

Adult outcomes	Group 1 (with VDA)	Group 2	P
Female height cm/DS	153.8/ -1.6	147.7/ -2.7	0.0039
Male height cm/DS	163.4/ -1.9	153.2/ -3.7	0.0038
Female BMI (kg/m ²)	23.4	25.5	0.3440
Male BMI (kg/m ²)	24.3	27.0	0.4029
Leg bowing	35.9%	89%	<0.0001
Corrective leg surgery	28.0%	69.0%	0.0001
Femoral neck Z score	1.8	-0.5	0.0005
Fractures	5.1%	58.6%	0.0019
Decayed Missing Filled Teeth index	3.4	19.3	<0.0001

Introduction: Hyperostosis-hyperphosphataemia syndrome (HHS) is a rare autosomal recessive condition caused by inactivating mutations in the *GALNT3* gene, characterised by elevated serum phosphate and 1,25(OH)₂ vitamin D, increased urinary tubular reabsorption of phosphate and hyperostosis of long bones. **Case report:** A 15-year-old boy (weight +1.05 SD; height -0.1 SD) with consanguineous parents of Palestinian descent, presented with a 6 year history of recurrent episodes of flitting pain in his forearms and lower legs. Episodes typically lasted 1–4 weeks were associated with erythema of the overlying skin, swelling of the underlying tissue with no obvious triggers. Previous investigations had included a biopsy of the ulna which revealed only non-specific findings (ossified material surrounding calcified cartilaginous tissue). Diagnoses of osteopetrosis and chronic recurrent multifocal osteomyelitis (CRMO) had been made in the past. Treatment with intermittent glucocorticoids and NSAIDs had produced symptomatic benefit. General examination was unremarkable apart from thickening and widening of the right ulnar border and anterior border of the right tibia. Biochemical investigations showed a persistent high fasting serum phosphate (2.29 mmol/l) with an inappropriately elevated TmP/GFR (3.11 mmol/l). Serum 25(OH) vitamin D concentration was low (13 nmol/l), 1,25(OH)₂ vitamin D was elevated (195 pmol/l) and PTH was previously normal (6 pmol/l). Radiographs showed mild periosteal reaction, cortical irregularity and poor cortico-medullary distinction throughout the shafts of the radius, ulna, tibia and fibula. MRI revealed high signal lesions within the medullary cavity of the diaphyses of the left fibula and right tibia on T2-weighted and STIR, corresponding to low signal on T1 sequences. Mutation analysis of the *GALNT3* gene revealed a homozygous *GALNT3* frame shift mutation (c.803dupC), confirming the clinical diagnosis of HHS. **Conclusion:** This case illustrates the value of both thorough clinical assessment and targeted genetic screening in the prompt diagnosis of rare disorders. This case illustrates the value of both thorough clinical assessment and targeted genetic screening in the prompt diagnosis of rare disorders.

P2-D3-312

Severe Osteogenesis Imperfecta and Epidermolysis Bullosa Simplex Caused by *FKBP10* Mutation: New Case

Ayla Güven^a, Mukaddes Kavalab, A Nurten Akarsu^c

^aGöztepe Education and Research Hospital, Pediatric Endocrinology Clinic, Istanbul, Turkey; ^bGöztepe Education and Research Hospital, Dermatology Clinic, Istanbul, Turkey; ^cGene Mapping Laboratory, Hacettepe University Medical Faculty, Ankara, Turkey

Background: Mutations in genes encoding type 1 procollagen (T1PC) and proteins responsible for posttranslational modifications of the T1PC heterodimer may result in brittle bone disorder osteogenesis imperfecta (OI). *FKBP65* is a known

chaperone for type I procollagen and encoded by *FKBP10*. Autosomal-recessively inherited epidermolysis bullosa simplex and moderately severe OI caused by *FKBP10* mutation reported in consanguineous Turkish and Mexican families. **Objective and hypotheses:** Our aim is to demonstrate new case with *FKBP10* mutation. **Methods:** 19^{5/12} years-old male admitted with multiple skin lesions and recurrent bone fractures since birth. His parents were first cousins. He was born with skin blisters on his body. His left arm was broken during delivery and until today he had recurrent long bone and vertebral fractures. At 10 years-old, he was diagnosed as OI and alendronat treatment started; however patient did not use the drug. He was untreated for a period of 9 years and had multiple fractures in long bones and vertebrae. **Results:** On the admission his weight was 15.9 kg, length was 87 cm. He had greyish-white sclera and normal teeth. Diffuse bullous erythematous lesion was determined on extensor surface of both extremities and thorax. Severe kyphoscoliosis and multiple deformities in both extremities due to recurrent fractures were determined. He was early-pubertal stage. Skin biopsy was consisting with bullous dermatitis. BMD-Z score was -6.7 (0.340 g/cm³) on lumbar vertebrae 1–4. Audiometric examination revealed mild mixed type sensorineural hearing loss. Pamidronat-sodium therapy was started as 1 mg/kg per day for 3-days (3-monthly). *FKBP10* gene mutation analysis was performed in all family members. Patient has homozygous p.Met107-Leu117del mutation in *FKBP10*. Parents has heterozygous this mutation. **Conclusion:** Homozygosity for a 33 bp deletion (c.321_353del) in *FKBP10* is resulted in deletion of 11 amino acids (p.Met107-Leu117del). Disrupted type 1 collagen was synthesized and caused severe skin and bone disorders in patients.

P2-D3-313

Osteogenesis Imperfecta Type I Caused by a Novel Mutation in the Start Codon of the *COL1A1* Gene in a Korean Family and the Course of Pamidronate Treatment for 1 Year

Sung Yoon Cho^b, Dong-Kyu Jin^c, Jae-Hong Yu^d, Heon-Seok Han^a

^aCollege of Medicine, Chungbuk National University, Cheongju, Chungbuk, Republic of Korea; ^bHanyang University Guri Hospital, Guri, Republic of Korea; ^cSchool of Medicine, Sungkyunkwan University, Seoul, Republic of Korea; ^dJoy Children's Hospital, Daejeon, Republic of Korea

Background: A 3-year-old boy appeared healthy at birth and did not experience any fractures until 12 months of age. Blue sclera, frequent fractures without adequate trauma, nearly normal stature, the absence of dentinogenesis imperfecta, no bony deformity, and no limitation of mobility were characteristics suggestive of OI type I that were observed in the patient. The patient's mother had blue sclera and a history of frequent fracture episodes until the age of 15 years. **Objective and hypotheses:**

These findings suggested OI type I. We performed genetic testing to identify type and mutation of OI, and pamidronate was tried to examine its effectiveness. **Method:** Genetic testing and cyclic treatment of pamidronate was performed. **Results:** A novel *COL1A1* missense mutation (c.2T>G) was found in the patient and his mother, and this is the first such case reported in the literature. After 1 year of treatment, the bone mineral density increased in lumbar spine and femur neck, and radiography showed laminar sclerosis at distal metaphysis of tibia, fibula and femur, so called zebra stripe sign from cyclic bisphosphonate treatment. There has been no fracture till 1.5 year after pamidronate treatment. **Conclusion:** This is a clinical and radiological findings of one Korean patient with OI type I with a novel mutation in the start codon of *COL1A1* (c.2T>G) disrupting the start codon of the gene (ATG to AGG (MetIArg)). Identification of this mutation expands the knowledge and significance of the start codon of the *COL1A1* gene in the pathogenesis of OI type I. The pamidronate was effective in preventing fracture in this patient.

P2-D3-314

Early Calcinosis Cutis, Short Stature and Brachydactyly: a Case Evolution

Isolina Riaño-Galan^a, Cristina Rodriguez-Dehli^a, Belen Huidobro-Fernandez^b, M Victoria Alvarez^c, Silvia Avila Flores^d, Joaquin Fernández Toral^e

^aHospital San Agustín Pediatría, Aviles, Spain; ^bHospital V Alvarez-Buylla. Pediatría, Mieres, Spain; ^cHUCA – Genética Molecular, Oviedo, Spain; ^dGENETADI, Bilbao, Spain; ^eHUCA – Genética and University of Oviedo, Oviedo, Spain

Background: Subcutaneous calcification is a rare clinical symptom in infancy. Progressive evolution and association with brachydactyly could be indicators of Albright hereditary osteodystrophy (AHO). In clinical practice, AHO is difficult to diagnose because of clinical heterogeneity. Typical features of AHO without any evidence of hormone resistance are termed pseudopseudohypoparathyroidism (PPHP; OMIM 612463). **Case report:** Male patient referred to study due to short stature. He was the third of unrelated parents (one miscarriage and a male apparently healthy). The pregnancy was complicated due to fetal growth retardation and oligohydramnios. He was delivered at term (birth weight 2170 g (−2.42 SDS), length 43 cm (−3.83 SDS), head circumference 33 cm (−1.38 SDS)). He had right phrenic nerve palsy, cortico-subcortical atrophy and hypotonia. He also was severely malnourished and needed gastrostomy feeding; although this problem was later overcome He has good psychomotor development. He presented an early onset of disseminated calcinosis cutis at the age of 3 months. On examination, at 54/12 years, he has short stature (height 94.8 cm (−4.12 SDS), weight 12.15 kg (−2.44 SDS), BMI 13.52 kg/m² (−1.23 SDS), subcutaneous diffuse (abdomen and feet) and intra-articular (right

shoulder) calcifications and middle phalanx hypoplasia of the 2nd and 5th fingers on both hands. Repeated endocrine investigations showed normal levels of serum calcium, phosphate, PTH, 25-hydroxy vitamin D, and other hormones, except a persistent low value of IGF1 and deficient answer to two provocative test for GH (peak of GH <7.5 ng/ml). On the genetic study, a heterozygous mutation in exon 7 of the *GNAS* gene (c.568_571del) (p.Asp190Metfs * 14) (*) was found (the novo mutation). **Comments:** PPHP is caused by heterozygous inactivating mutations in Gs alpha coding exons of *GNAS*. The identification of affected patients can raise awareness about this rare disease and reach their best clinical management and improve quality of life. In our patient, short stature most likely results from a combination of multiple factors that include GH deficiency.

P2-D3-315

Does Vitamin D Affect Mean Platelet Volume Values or Not

Keziban Bulan, Murat Dogan, Sultan Kaba, Oktay Aslan
Yuzuncu Yil University, Van, Turkey

Objective: Platelets play a key role in the development and progression of cardiovascular disease. The degree of platelet activation may be assessed by platelet indices such as platelet count, mean platelet volume (MPV) and platelet distribution width (PDW). In addition, both epidemiological and *in-vitro* studies have linked vitamin D deficiency to enigmatic disease including cardiovascular disease however a clear mechanistic link remains missing. In present study, we aimed to evaluate the relationship between mean platelet volume which sometimes has been suggested to be a biological marker of cardiovascular disease especially coronary arterial disease and vitamin D levels. **Methods:** In present study, a total of 484 children with vitamin D deficiency or insufficiency and 200 children as control were enrolled the study. The vitamin D deficiency and insufficiency group were divided in two groups (Group 1; children who had a vitamin D levels below 20 ng/ml; group 2; children who had a vitamin D levels between 20 and 30 ng/ml). All the children in control group had a vitamin D level above 30 ng/ml). The hemogram and MPV values were compared in these three group. **Results:** We did not find any statistically significant difference between group with regard to age and gender. The mean MPV values were found to be 7.95 ± 0.95 fL in group 1, 7.96 ± 1.03 fL in group 2, 7.89 ± 1.23 fL in control. No statistically significant difference was found with regard to MPV values and also no statistically significant correlation was found between vitamin D and MPV values ($r: -0.48, P > 0.05$). **Conclusion:** Due to observation of no changing in MPV values according to different vitamin D levels, we concluded that MPV might not play a role in vitamin D associated cardiovascular disease. But for certainly definition further large studies are needed.

P2-D3-316

Bone Size and Bone Mineral Content in Adolescents and Young Adults with Eating Disorders

Avril Mason^a, Sheila Shepherd^a, Charlotte Oakley^b,
Michelle Thrower^b, Andreas Kyriakou^a, Guftar Shaikh^a,
Syed Faisal Ahmed^c

^aRHSC, Glasgow, UK; ^bConnect Eating Disorders, Glasgow, UK;
^cUniversity of Glasgow, Glasgow, UK

Background: There is growing concern about the impact of eating disorders on the bone health during adolescence where peak bone mass acquisition is of paramount importance. **Method:** A total of 85 patients (77F/8M, 75% anorexia nervosa (AN) and 25% atypical eating disorder), median age 15.2 years (range, 10.9–19.8) and median BMI SDS -1.3 (-4.7 to 0.8) attended the bone densitometry service between Jan 2009 and Dec 2013 for total body (TB) and lumbar spine (LS) DXA scans. 13 patients (11F/2M, all AN) had a follow-up scan at an interval of 1.4 years (0.8 – 2.5). Bone size is reported as percent predicted bone area for age (ppBA-for-age), and for size adjustment, the extent of bone mineralisation within the bone is described as percent predicted bone mineral content for bone area (ppBMC-for-BA). **Results:** Median ppBA-for-age was 89% (66–124) at TB site, with 54% of patients presenting with ppBA-for-age $\leq 90\%$. Median ppBMC-for-BA was 99% (89–116) at TB site, with only 5% being $\leq 90\%$. At LS site, median ppBA-for-age was 96% (65–128), while median ppBMC-for-BA was 94% (73–131). TB ppBA-for-age and LS ppBA-for-age correlated positively with BMI SDS ($r=0.44$, $P<0.0001$ and $r=0.213$, $P=0.05$). Median DXA software derived paediatric analysis centiles were 38th (0–91) for height age (shorter bones = less linear growth), 21st (0–78) for bone area for height (thinner bones = less periosteal expansion), 20th (0–95th) for lean mass for height (reduced muscle mass), and 52nd (1–100th) for BMC for lean mass centile (adequate BMC for reduced lean mass). There was no significant difference between baseline and follow-up in ppBA-for-age or ppBMC-for-BA at TB or LS. **Conclusion:** In young adults with an eating disorder, bones are small compared to the normal healthy population, but do not show reduced bone mineralisation. Muscle mass is low, but BMC appears preserved at the expense of a combination of periosteal expansion and linear growth. Long-term follow-up in these patients is required.

P2-D3-317

Infantile Hypercalcemia: Still a Diagnostic and Therapeutic Enigma

Veselin Boyadzhiev^a, Dimitrichka Bliznakova^a, Violeta Iotova^a,
Karl Schlingmann^b

^aMedical University, Varna, Bulgaria; ^bUniversity Children's Hospital, Muenster, Germany

Background: Hypercalcemia requires new investigation pathways after publishing the mutations of the CYP24A1 gene.

Furthermore, diagnostic puzzles connected to it still remain. **Objective and hypotheses:** We present a 1.5-years-old girl with infantile hypercalciuria who has been followed-up since she was 4 months old. The child is born from uneventful pregnancy, normal delivery, on term with weight 3600 g and length 52 cm. Two months after birth she became irritable, with decreased appetite, several episodes of blood in the stools and slow weight gain. The urine analysis showed erythrocyturia and leucocyturia. **Method:** After admission in hospital a bilateral nephrocalcinosis was revealed accompanied by hypercalciuria (Ca/creatinine 1.37 (<0.20), hypercalcemia (total Ca 3.65 mmol/l (2.08–2.65), iCa 1.70 mmol/l (1.13–1.32), suppressed PTH (<3.00 pmol/l) and elevated 25-hydroxyvitamin D3 > 70 ng/ml. A PTH-independent hypercalcemia was diagnosed. There was no history of familial hypercalcemia, subcutaneous fat necrosis or vitamin D intoxication. No syndromic or dysmorphic features were found. Partial improvement was registered after conventional treatment. After introducing bisphosphonates (Pamidronate) infusions in 2 consecutive days the clinical symptoms gradually resolved and calcium levels became stable around the upper limit of the norm – total Ca 2.73 mmol/l, iCa 1.29 mmol/l. **Results:** In the context of the new etiological causes a defect in 24-hydroxylase activity was suspected. A molecular genetic testing for mutation in the CYP24A1 gene was done in a referent center but showed negative results. Looking back to our investigations lower phosphate serum levels of 1.0 mmol/l at presentation were noticed to be present too. During the follow-up the phosphate levels slowly increased up to the lower limits of 1.6 mmol/l with TmP/GFR of 1.32, calcium levels are still on the upper limits and there is no significant progression of the nephrocalcinosis and no impairment of the renal function. **Conclusion:** Infantile hypercalcemia still remains a diagnostic and therapeutic enigma.

P2-D1-318

Serum Level of Osteoprotegerin and Total sRANKL in Adolescents with Type 1 Diabetes Mellitus

Mieczyslaw Szalecki^{a,b}, Elzbieta Wierzbicka^c, Pawel Pludowski^d,
Maciej Jaworski^d

^aDepartment of Endocrinology and Diabetology, Children's Memorial Health Institute, Warsaw, Poland; ^bFaculty of Health Sciences UJK, Kielce, Poland; ^cFaculty of Human Nutrition and Consumer Sciences, Warsaw University of Life Sciences, Warsaw, Poland; ^dDepartment of Biochemistry and Experimental Medicine, Children's Memorial Health Institute, Warsaw, Poland

Background: There is still small clinical data regarding the influence of IDDM on bone structure, density and biochemical markers of bone turnover. **Objective and hypotheses:** To evaluate the potential role of OPG/sRANKL system in adolescents with IDDM and the influence of age, sex, metabolic control, diabetes duration and age of onset. **Method:** Serum concentration of OPG and total sRANKL in 60 children (25 boys and 33 girls) with IDDM since 5.09 years \pm 3.95 (1.0–11.8), aged 15.03 \pm 1.95

(11.4–17.8), age of diagnosis IDDM 9.98 ± 3.90 (2.5–17.0), HbA1c in last year 7.8 ± 1.7 (5.1–13.6). Control group consists of 17 age and sex matched healthy children. OPG and total sRANKL (free and bound) were measured by EIA and ELISA commercial kits respectively. **Results:** Both serum OPG, tsRANKL and OPG/tsRANKL ratio were insignificantly lower in diabetic children. OPG concentration in IDDM boys was significantly lower than in control group of boys. Negative correlation was observed between OPG concentration and the age of onset of diabetes and positive with diabetes duration. There was no influence of age and tendency to positive correlation with metabolic control. Statistical analysis across tertiles showed that higher levels of OPG (third and/or second vs first tertiles) was associated with the earlier age of diagnosis, longer diabetes duration and poor metabolic control. tsRANKL did not correlate with sex, metabolic control, diabetes duration and age of onset. However, a negative correlation between serum tsRANKL and age was observed. The OPG/tsRANKL ratio values depend only on the age of IDDM children (positive correlation). There were no correlations with sex, metabolic control, diabetes duration and age of onset. **Conclusion:** OPG/tsRANKL system may be use as prediction marker of bone and cardiovascular system status in children and adolescents with IDDM but precise reference data for children considering age, sex and puberty status should be determined first.

P2-D1-319

Simultaneous Changes in Trends in Incidence of Children Diabetes Type 1 in Distant Geographic Regions

Noemi Auxiliadora Fuentes-Bolaños^a, Francisco Javier Arroyo Díez^a, Violeta Delgado Carballar^b, Pilar Méndez Pérez^a, Manuela Núñez Estevez^a

^aHospital Materno Infantil, Badajoz, Spain; ^bHospital Juan Ramón Jiménez, Huelva, Spain

Introduction: The epidemiology of childhood type 1 diabetes (DM1) allows to understand the genetics and environmental factors involve in one of the most prevalent chronic disease in children. The unification of methodological recommendations has allowed to detect new research lines. **Method:** We present an observational study of population under 13 years old and DM1 in Extremadura (1996–2011). The aim was to examine secular trends in the incidence of DM1 in children, by annual percentage change (APC). **Results:** A total of 577 cases were diagnosed (case ascertainment: 98.9%). Age- and sex-adjusted incidence was 22.7 cases/100 000 (95% CI 13.5–31.9) and the peak of incidence was in 2005 (30.7). The incidence by periods (4 years) was not significantly different. The APC was analyzed by Jointpoint Regression highlighting one significant change in the term trend: the incidence increased annually by 6.6% until 2004, followed by a plateau until the end of 2011 ($P < 0.01$). The same pattern was presented in the male group ($P 0.012$) but not in women group, in which there was not change in the annual growing trend. Analysis

by age: the group of 10–14 years old presented an acceleration of 7% annually until 2005, and a deceleration period until 2011 ($P 0.025$). There were no changes in the trends in other groups of age. **Conclusions:** i) The analysis of annual percentage change should be included in the recommendations of the international epidemiological DM1 studies in order to avoid mistakes in the interpretation of the results. ii) We report the first evidence of the reversed trend in the incidence of DM1 in Southern Europe. Two other studies published similar findings, in Finland and Sweden, in 2005. iii) Even more, according these results, the environmental factors related could specifically affect the group of men aged 10–14 years.

P2-D1-320

Risk Factors for Type 2 Diabetes Mellitus in Secondary School Students in Port Harcourt Nigeria

Tamunopriye Jaja, Iroko Yarhere

University of Port Harcourt Teaching Hospital, Port Harcourt, Nigeria

Background: There is evidence to suggest an increase in type 2 diabetes mellitus worldwide even in children and adolescents. It is usually preceded by a period known as prediabetes and other risk factors such as elevated blood pressure, obesity, hypertriglyceridemia and family history of diabetes mellitus. **Objective and hypotheses:** To determine the number of risk factors for type 2 DM in each subject studied for selected risk factors. **Method:** A cross sectional study was carried out in six public secondary schools in Port Harcourt metropolis. Children whose parents gave informed written consents had their bio data, and risk factors for diabetes collected. Blood pressure, FBS, weight and height then BMI were also measured. Children with FBS > 5.5 mmol/l had an OGTT done. Data collected were analysed using medical 3000 to determine BMI and BP percentile, and SPSS 20 to calculate measures of central tendencies of FBS, BP, BMI. Students *t*-test was used to compare mean values of variables, and *P* values < 0.05 were considered significant. **Results:** Eight hundred and eighty children were screened during the study period for four risk factors. The mean FBS was 5.18 mmol/l (range 1.9–7.3). 17.4% had FBS > 5.5 mmol/l. Systolic BP was elevated in 130 (14.8%) subject, while 135 (15.3%) had elevated diastolic BP. 25 (2.6%) were obese, 101 (11.5%) were overweight. Only one female had all four risk factors while 24 (0.03%) subjects had three risk factors for type 2 DM. A total of 60 children had OGTT out of which 10 (6%) had impaired glucose tolerance. Of the 24 subjects with three risk factors, 2 (8.3%) females were in early adolescence, 12 (50%) (two males, ten females in mid adolescence, 10 (41.7%) (five males and females each) in late adolescence. **Conclusion:** The population studied showed a large percentage with risk factors for type 2 diabetes, and it is proposed that urgent and efficient measure are taken to reduce the prevalence of this preventable disease and also the long term effect it has on young children.

P2-D1-321

Interaction of Pubertal Development and Metabolic Control in 1303 Adolescents with Diabetes Mellitus Type 1

Michaela Hamm^a, Bettina Gohlke^a, Joachim Wölfle^a, Katharina Fink^b, Katja Konrad^c, Tilman Rohrer^d, Sabine Hofer^e, Reinhard Holl^b

^aPediatric Endocrinology and Diabetology, Children's Hospital, University Bonn, Bonn, Germany; ^bDepartment of Epidemiology, University Ulm, Ulm, Germany; ^cPediatric Endocrinology and Diabetology, Children's Hospital, University Essen, Essen, Germany; ^dPediatric Endocrinology and Diabetology, Children's Hospital, University Homburg, Homburg/Saar, Germany; ^ePediatric Endocrinology and Diabetology, Children's Hospital, University Innsbruck, Innsbruck, Austria

Background: T1DM may influence growth and pubertal development and *vice versa*. Delayed pubertal development and reduced final height are known to be associated with inadequate metabolic control. Many factors including insulin resistance during puberty and insufficient adherence may be responsible for increasing HbA1c. **Objective:** Is pubertal growth spurt associated with an increase of HbA1c? Are there gender differences in metabolic control during puberty? Is the pubertal growth spurt impaired in patients with T1DM compared to German reference data? **Methods:** 1303 complete longitudinal patient data out of a diabetes follow up program could be analysed over a period of 9 years. Inclusion criteria were continuous recording of height and HbA1c every 6 months from the age of 7–16 years in patients with T1DM. Exclusion criteria were celiac disease, eating disorders, steroid or GH therapy, <3 months duration of disease, BMI <3rd or >97th percentile at start of documentation. **Results:** HbA1c levels increased continuously from 7.3% at 7 years to 8.4% at 16 years of age. HbA1c levels of boys were lower except for 1.5 years between 13.5 to 15 years. Highest HbA1c increase in boys (Δ HbA1c 0.38 between 12 and 14 years) was associated with maximum growth spurt. In contrast, in girls main HbA1c increase was observed postpubertal (15–16 years). Growth velocity during puberty was impaired. In boys mean peak growth velocity was reduced by 1.1 cm. Growth velocity in girls declined rapidly after maximum growth spurt. **Conclusion:** HbA1c increase in puberty is caused by a complex interaction consisting of physiological and psychological reasons. Gender differences could be explained by higher BMI-SDS, greater insulin resistance, higher prevalence of eating disorders and insulin purging in females. In turn worsening of metabolic control reflected by HbA1c increase is associated with reduced growth velocity.

P2-D1-322

Quality of Life and Glycaemic Assessment Before and After Pump School

Patricia Leahy^a, Norma O'Toole^b, Susan O'Connell^{a,b}, Stephen O'Riordan^{a,b}

^aUniversity College Cork, Cork, Ireland; ^bCork University Hospital, Cork, Ireland

Background: Childhood type 1 diabetes (T1DM) is associated with poor quality of life and significant family burden. Children, parents, extended family members and teachers were invited to a novel 2 day structured educational programme, 'Pump School', delivered by a Consultant Led multidisciplinary team. Each Pump School included two age-matched children. **Objective and hypotheses:** To evaluate the effect of continuous s.c. insulin infusion (CSII) in a cohort of children and adolescents with T1DM through the assessment of glycaemic control, quality of life (QOL) and family burden. **Method:** A prospective study of suitable pump candidates (Kaufman Competency (5/8)) with T1DM was conducted over 12 months. Children ($n=22$; 11 female) ranging in age from 3 to 17 (mean=10.5) years who were previously treated with multiple daily injections (MDI), started CSII. HbA1c, QOL (Diabetes Quality of Life for Youths) and family burden (Hvidoere questionnaire) measurements were obtained at baseline, 3, 6 and 12 months following pump school. **Results:** Mean HbA1c reduction at 3/12 was 6.1 mmol/mol (0.6%; $P<0.01$). A non-statistically significant upward trend in HbA1c was evident at 12-month follow-up. Those with highest baseline HbA1c (>68.3 mmol/mol (8.4%)) had the largest HbA1c reduction at 3/12 (8.0 mmol/mol (0.7%); $P<0.01$). A significant increase on baseline QOL scores ($P<0.05$) and decrease on baseline family burden scores ($P<0.05$) was obtained at 6 and 12 months, indicating sustained improvement. Pump therapy was associated with a decline in the perceived impact of diabetes on activities ($P<0.05$). Children and their carer's expressed a high level of satisfaction with the Pump School training programme. **Conclusion:** Findings suggest a substantial improvement in biopsychosocial functioning. Glycaemic control improved at 3/12. QOL and family burden were improved 1 year after Pump School. Further research is warranted to ascertain whether these outcomes are maintained at 18 and 24 months.

P2-D1-323

Improving Paediatric Diabetes Care with the Use of an Electronic Diabetes Information Management System (Twinkle.Net) and Routine Uploading of Blood Glucose Meters and Insulin Pumps (Diasend) in Outpatient Clinic

Sze May Ng, Linda Connellan, Lynne Finnigan

Southport and Ormskirk NHS Trust, Lancashire, UK

Background: The UK has the highest number of children and young people with type 1 diabetes mellitus in Europe, but the lowest number of children and young people attaining good diabetes control. **Methods:** In December 2012, our diabetes service established the use of an electronic diabetes information management system that was web-based (Twinkle.Net) and routine uploading of glucose meters and pumps (Diasend).

The electronic management system Twinkle.Net allowed monthly audit by the diabetes team which identified specific patients who had poor metabolic control (HbA1c) and those who were recurrent non-attenders to clinic. These patients were identified for more intensive contact and education with the diabetes nurse specialists. The Diasend system allowed the diabetes team to upload and view patient's data within all outpatient clinics. Clinical outcomes were compared in the period before and the period after the implementation of the electronic diabetes information management system and use of a routine uploading of patient's blood glucose meters and insulin pumps. **Results:** In 2012 prior to implementing the technology, the average HbA1c was 8.6% and in 2013 the average HbA1c was 8.4%. Hospital admissions due to diabetes was 22% in 2012 and 16% in 2013 ($P < 0.05$). The median hospital length of stay for was 2.7 days in 2012 compared with 1.8 days in 2013 ($P < 0.05$). A patient satisfaction survey conducted within the outpatient setting had a 79% positive feedback pertaining to the use of this new technology. **Conclusions:** The use of an electronic diabetes data management system and routine downloading of all blood glucometers and insulin pumps in clinics can help provide a high quality service for children and young people who require treatment, education and advice for the management of type 1 diabetes. This initiative showed effective use of technology in achieving significant clinical improvements in glycaemic control and patient satisfaction.

P2-D1-324

Two Novel Homozygous Mutations in *WFS1* Gene in Two Turkish Families with Mild Phenotypic Expression of Wolfram Syndrome

Maha Sherif^a, Huseyin Demirbilek^{a,b}, Atilla Cayir^b, Mehmet Nuri Ozbek^c, Riza Taner Baran^c, Ayse Nurcan Cebeci^d, Sophia Tahira^a, Sofia Rahman^a, Mehul Dattani^a, Khalid Hussain^a

^aUCL Institute of Child Health, London, UK; ^bErzurum Research and Training Hospital, Erzurum, Turkey; ^cDiyarbakir Children State Hospital, Diyarbakir, Turkey; ^dDerince Research and Training Hospital, Kocaeli, Turkey

Background: Wolfram syndrome (WS or DIDMOAD) is a rare (prevalence of 1/770,000) autosomal recessive multi-systemic neurodegenerative disease, characterized by non-autoimmune diabetes mellitus (DM) and optic atrophy. Additional features include diabetes insipidus (DI), sensorineural deafness, urinary tract abnormalities, ataxia, psychiatric illness, and other endocrine disturbances leading to death in mid-adulthood. This syndrome is caused by recessive mutations in the wolframin gene (*WFS1*) on chromosome 4p16.1. *WFS1* encodes a trans-membrane protein localized to the endoplasmic reticulum (ER), suggesting that ER dysfunction is a major pathogenic component of WS. In WS, pancreatic β -cells and neuronal cells undergo apoptosis due to ER stress. **Objective and hypotheses:** To describe the molecular basis of syndromic DM in two Turkish families. **Method:** Two

unrelated consanguineous Turkish families, with two affected children in each family were evaluated. In family 1; the two affected have DM, deafness and optic atrophy. In family two; the two affected have DM and deafness. None of the affected members of both families had diabetes insipidus. Homozygosity mapping (HZM) was performed followed by whole exome sequencing in the families. **Results:** Two novel nonsense mutations were identified in *WFS1* in each of the affected patients in family 1 (p.Y405X) and family 2 (p.W185X), leading to premature stop codons in exons 8 and 5 respectively. These novel exonic mutations lead to a mild form of WS in both families. All patients were found to be homozygous for the change, whereas parents and other unaffected siblings were carriers. **Conclusion:** Our study expands the molecular spectrum of *WFS1* mutations with two novel nonsense mutations in two unrelated consanguineous Turkish families. Therefore, detailed phenotypic and genotypic information may help to discover yet undisclosed genotype-phenotype correlations in WS.

P2-D1-325

Imbalance Between Pro-Oxidative and Anti-Oxidative Mechanisms in Children and Adolescents with Type 1 Diabetes Mellitus

Maria Karampali^{a,b}, Ioannis Kyrgios^a, Stavros Kalogiannis^b, Efthimia Efstratiou^a, Assimina Galli-Tsinopoulou^a

^a4th Department of Pediatrics, Papageorgiou General Hospital, Faculty of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece; ^bDepartment of Human Nutrition and Dietetics, Alexander Technological Educational Institute of Thessaloniki, Thessaloniki, Greece

Background: Type 1 diabetes mellitus (T1DM) has been described to be associated with altered oxidative status. Combined analysis of pro-oxidative and anti-oxidative mechanisms in youngsters with T1DM has been less studied. **Objective and hypotheses:** To evaluate pro-oxidative/anti-oxidative status in T1DM youngsters and healthy controls and investigate their possible association with glycemic control. **Method:** Sixty-three children and adolescents with T1DM and 20 healthy controls of similar age (13.4 ± 2.5 vs 12.5 ± 2.3 years, $P = 0.169$) and gender (T1DM boys 37/63 (58.7%) vs healthy boys 13/20 (65.0%), $P = 0.813$) were included. Anthropometric measurements as well as an estimate of pro-oxidative/anti-oxidative balance (PAB), expressed as an hydrogen peroxide percentage and multiplied by 6, were determined. Questionnaires regarding dietetic habits and physical activity were also filled. **Results:** T1DM participants as compared with controls had higher PAB (213.1 ± 79.8 vs 155.0 ± 43.8 , $P < 0.001$) but similar BMI (20.6 ± 3.6 vs 21.7 ± 4.5 kg/m², $P = 0.281$) and physical activity score (PAS) (6.5 ± 1.5 vs 6.1 ± 1.9 , $P = 0.286$). No differences were detected in PAB levels between T1DM patients with HbA1c levels above 7.5 as compared with those of below 7.5 (224.0 ± 85.3 vs 202.5 ± 74.0 , $P = 0.29$). Serum PAB levels were significantly correlated (negatively) with

age ($r = -0.361, P = 0.001$) but not with HbA1c ($r = 0.108, P = 0.40$). A tendency towards higher levels of PAB was also observed with higher BMI levels or PAS ($r = -0.192, P = 0.083, r = -0.185, P = 0.094$ respectively). In a multivariate analysis (overall model: $r^2 = 0.227, P = 0.01$), only age and physical activity were found to be independently associated with PAB levels ($b = 0.358, P = 0.011, b = -0.271, P = 0.041$ respectively) in contrast to HbA1c and diabetes duration ($b = 0.158, P = 0.207, b = 0.873, P = 0.041$ respectively). **Conclusion:** Imbalanced pro-oxidative/anti-oxidative state exists in T1DM youngsters independent of diabetes control. This may predispose and contribute at least partially to the early development of long-term complications.

P2-D1-326

Trends in Incidence and Prevalence of DM Type 1 in Children in Ukraine During 2002–2012

Evgenia Globa, Nataliya Zelinska

Ukrainian Center of Endocrine Surgery, Endocrine Organs and Tissue Transplantation, MoH of Ukraine, Kiev, Ukraine

Background: The aim of the study was to describe the incidence and prevalence trends of diabetes mellitus (DM) type 1 in children of different age groups in Ukraine during 2002–2012.

Objective and hypotheses: Ukraine has a 25 districts, with a population of 45 553 000, including 7 971 638 children. **Method:** We analyzed data based on a clinical diagnosis in child population aged 0–17 years old centrally from all regions of Ukraine during 2002–2012. The prevalence and incidence of DM1 were studied in children aged 0–17 years old and in different age groups (0–6, 7–14, and 15–17 years old). **Results:** Based on the Ukrainian Pediatric Diabetes Register the number of children with DM1 0–17 years old in 2012 was 8178 (one in 975), with DM2 – 64 (one in 124 557), with neonatal diabetes – 32 reported cases (one in 249 113). Among DM1 group the number of children without chronic complication was 58.3%, HbA1c level was $8.72 \pm 1.3\%$ (vs $7.09 \pm 1.23\%$ in DM2 group, $P < 0.05$). During 2002–2012 the prevalence and incidence of DM1 in pediatric population 0–17 years old has greatly increased from 7.77 to 10.26 and from 1.0 to 1.42 (per 1000) accordingly, especially in the youngest age group

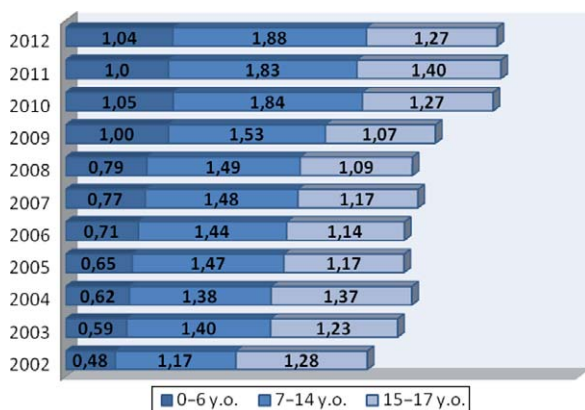


Figure 1 Incidence of DM1 in different age groups (per 1000 population).

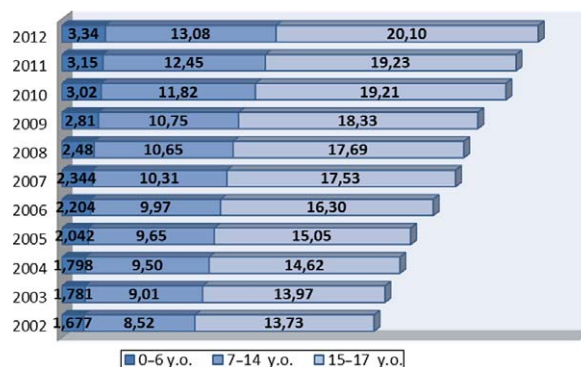


Figure 2 Prevalence of DM1 in different age groups (per 1000 population).

(0–6 years old) [Figs 1 and 2]. **Conclusion:** In recent years incidence rate of childhood DM1 continues to rise, especially in children aged 0–6 years old (vs 15–17 years old) on a background of decreasing of the total child population. The annual increase of incidence of DM1 in 2012 was 2.98%.

P2-D1-327

Effectiveness of Insulin Pump Therapy in Children and Adolescents with Type 1 Diabetes

Darya Osokina, Irina Osokina

State Research Institute for Medical Studies of the North, Krasnoyarsk, Russia

Background: Consistent use of insulin pump therapy and continuous glucose monitoring (CGM) has been shown to improve glycemic control and reduce hypoglycemia. **Objective and hypotheses:** The aim of this study compared multiple daily injection (MDI) therapy to pump insulin therapy (CSII) in children and adolescents. **Method:** A total of 28 children (aged 7–12) and 34 adolescents (aged 13–18) participated in this study. The participants were randomized to either CSII or MDI therapy. Quarterly A1C values were obtained from all participants. One week CGM studies were obtained at baseline, 6 months, and 12 months on all subjects. **Results:** Subjects with similar A1c values were randomly assigned to the CSII (8.1–0.55%) and MDI groups (8.30–0.53%). All subsequent A1c values showed a significant difference ($P < 0.05$), favoring CSII therapy. Compared to the MDI group, subjects in the CSII group were more likely to achieve their age-appropriate A1c goals and had lower values of hyperglycemia without an increased risk of hypoglycemia. Glucose variability improved in the CSII group compared to the MDI group. Children ages 7–12 years old were more likely to wear the CGM sensors and reach age-specific A1c goals than the adolescents (13–18 years old). **Conclusion:** Both children and adolescents with inadequately controlled type 1 diabetes can benefit from CSII therapy, allowing them to reduce A1c values, hyperglycemic excursions, and glycemic variability in a sustainable and safe way.

P2-D1-328**Functional Condition of the Kidneys (K/DOQI, 2002) By ACE Gene I/D Polymorphism in Children and Adolescents with Type 1 Diabetes Mellitus***Akidahon Sadykova, Gulnara Rakhimova*

Center for the Scientific and Clinical Study of Endocrinology, Tashkent, Uzbekistan

Objective and hypotheses: The work was initiated to assess functional condition of the kidneys and to study interrelation between ACE gene I/D polymorphism and stage of chronic kidney disease in children and adolescents with type 1 diabetes mellitus (DM) in compliance with K/DOQI recommendations (2002). **Method:** We examined 120 children and adolescents with type 1 DM, 53 (44.2%) males and 67 (55.8%) females among them (mean age 13.8 ± 0.24 years). GFR was used to classify stages of chronic kidney disease in compliance with K/DOQI recommendations. DNA was isolated by Higuchi H. Erlich method (1989) with dry kit of Diatom DNAprep 200. 49 (40.8%), 28 (23.4%), and 43 (35.8%) examinees with type 1 DM were carriers of II, I/D and DD genotype respectively. **Results:** Normal and high GFR (I stage) was found in 69 (57.5%) children and adolescents with type 1 DM, mean GFR being 168.9 ± 7.03 ml/min per 1.73 m^2 (95% CI 155.1–18.7). Insignificant GFR reduction (CKD II stage) was found in 21 (17.5%) examinees, mean GFR being 77.8 ± 2.05 ml/min per 1.73 m^2 . GFR reduction (III stage) was registered in 12 (10.0%) patients, mean value being 39.3 ± 2.05 ml/min per 1.73 m^2 . CKD IV stage was observed in 18 (15.0%) examinees, mean GFR being 23.9 ± 0.90 ml/min per 1.73 m^2 . No CKD V stage was registered. II genotype was found prevalent in the examinees with CKD I stage ($n=46$, 66.7%), ID genotype being found in 23 (33.3%) and no DD genotype being found. With progression of CKD stage frequency of persons with II genotype was found decreasing, DD genotype cases being increased. ID genotype was found at III and IV stages CKD ($n=4$, 19% and $n=1$, 8.3% respectively). No cases of II genotype was found at III and IV stages CKD, while DD genotype incidence was very high ($n=11$, 91.7% and $n=18$, 100% respectively). DD genotype correlated with CKD severity and presence of diabetic nephropathy. **Conclusion:** In most children and adolescents with type 1 DM (75.0%) CKD I and II stages were classified. With CKD progression upon DN in children and adolescents with type 1 DM DD genotype incidence was found increased, II genotype occurring more frequently with DN absent. DD genotype confers high risk of renal pathology in type 1 DM in children.

P2-D2-329**Lipid Profile is Related to Androgen Level in Adolescent Girls with Type 1 Diabetes Mellitus***Agnieszka Zachurzok^a, Grażyna Deja^a, Aneta Gawlik^a, Agnieszka Drosdzol-Cop^b, Ewa Malecka-Tendera^a*^aDepartment of Paediatrics, Paediatric Endocrinology and Diabetes, Medical University of Silesia, Katowice, Poland; ^bDepartment of Women's Health Medical University of Silesia, Katowice, Poland

Background: The mechanisms underlying dyslipidaemia in the context of polycystic ovary syndrome may include not only metabolic aberrations but also hormonal factors, in particular hyperandrogenaemia. **Objective and hypotheses:** The aim of the study was to establish whether dyslipidaemia and metabolic control disturbances are related to hyperandrogenaemia in adolescent girls with type 1 diabetes mellitus (T1DM). **Method:** We studied 54 girls with T1DM in the chronological age 15.9 ± 1.3 years and gynecological age 33.7 ± 16.7 months. 28 of them had normal androgen plasma levels and in 16 hyperandrogenaemia was found. Fourteen healthy, regularly menstruating girls without hyperandrogenaemia (chronological age 16.1 ± 1.2 years; gynecological age 48.9 ± 14.9 months) served as control group (CG). In all girls levels of lipids and hormones were measured. In each diabetic subject HbA1c records from the beginning of T1DM and daily insulin requirement (DIR) for last 3 days were obtained. **Results:** Total cholesterol was significantly higher in diabetic girls with hyperandrogenaemia than in CG (196.1 ± 41.2 vs 162.2 ± 32.8 mg/dl, $P=0.01$). Also LDL-cholesterol was the highest in girls with T1DM and elevated androgen level (117.3 ± 33.1 mg/dl) and significantly higher than in diabetic girls without hyperandrogenaemia (97.7 ± 26.7 mg/dl, $P=0.03$) and in CG (90.9 ± 28.8 mg/dl, $P=0.02$). There were no significant differences between the studied groups with respect to triglycerides. There was no significant relationship between BMI Z-score and lipids concentration in diabetic group. We did not find any significant differences in mean HbA1c from the beginning of T1DM and for the last year as well as in DIR and type of insulin therapy (intensive vs continuous) between the groups. In diabetic group significant correlations between LDL-cholesterol and hyperandrogenaemia ($r_{\text{gamma}}=0.4$, $P=0.01$) and free androgen index (FAI) ($r=0.4$, $P=0.01$) were found. In multivariate logistic regression analysis the association between LDL-cholesterol and FAI did not change significantly after adjusted for BMI Z-score. **Conclusion:** It is concluded that hyperandrogenaemia may contribute to dyslipidaemia in adolescent girls with T1DM.

P2-D2-330**A Multicentre Study Evaluating the Risk and Prevalence of Diabetic Retinopathy in Children and Young People with Type 1 Diabetes Mellitus***Sze May Ng^a, Omolola O Ayoola^b, Michael McGuigan^c, Surendran Chandrasekaran^d*^aSouthport and Ormskirk NHS Trust, Ormskirk, UK; ^bLancashire Teaching Hospitals NHS Foundation Trust, Preston, UK; ^cMid Cheshire Hospitals NHS Foundation Trust, Chester, UK; ^dMacclesfield District General Hospital, Macclesfield, UK

Background: There is currently limited data published on the prevalence of diabetic eye disease in children and young people (CYP) with type 1 diabetes mellitus (T1DM), yet diabetic retinopathy remains one of the commonest causes of blindness in young adults. **Objectives:** To determine the risk and prevalence

of diabetic retinopathy and to evaluate the risk factors associated with diabetic retinopathy in CYP with T1DM. **Methods:** All CYP with T1DM between 12 and 18 years registered with the regional diabetic retinopathy screening programme were evaluated between 2012 and 2013 in four paediatric diabetes centres in the Northwest of England. Patients who had evidence of diabetic retinopathy were reviewed to identify risk factors for presence or absence of diabetic retinopathy. Risk factors assessed were duration of diabetes (years), pubertal status, mean blood pressure, mean urine albumin creatinine ratio, and mean HbA1c during the preceding 12 months. All patients underwent mydriatic three-field 45 degree fundus photography. **Results:** 237 patients between the ages 12 and 18 years were included in the study from four paediatric diabetes centres. The prevalence of diabetic retinopathy was 11%. Out of 27 patients with evidence of diabetic retinopathy, 44% were reported as background changes, and 56% were stage 1 retinopathy. Significant risk factors for diabetic retinopathy disease in the population using univariate analyses were duration of diabetes, puberty, age at diagnosis, and mean HbA1c in the preceding 12 months. Multivariate logistic regression analysis found age of diagnosis ($P=0.04$) and mean HbA1c as significant independent risk factors for presence of diabetic retinopathy ($P=0.02$). **Conclusions:** The prevalence of diabetic retinopathy in this paediatric population in our study was 11%. Early age at diagnosis and poor metabolic control are independent risks factor for diabetic retinopathy. Implementation of national screening programmes should take account of early detection of retinopathy in CYP with T1DM.

P2-D2-331

ACE Gene Insertion/Deletion Polymorphism and ACE Enzymatic Activity in Egyptian Children with Type 1 Diabetes with and without Microalbuminuria

Ghada Anwar, Hafez Bazaraa, Olfat Shaker, Noha Arafa, Mona Hafez, Noha Mousa

Kasr Alainy School of Medicine, Cairo, Egypt

Background: Diabetic nephropathy is a major cause of morbidity and mortality among young adults with type 1 diabetes mellitus. Strong evidence exists in multiple studies for genetic predisposition of diabetic nephropathy. Genetic studies have revealed that the genes for the renin-angiotensin system (RAS) are highly polymorphic, one of such is insertion/deletion polymorphism in ACE gene. This polymorphism was associated with the circulating ACE level and increased plasma activity of this enzyme. **Objective and hypotheses:** The aim of the present study was to determine the relationship between ACE gene insertion/deletion polymorphisms, serum ACE activity and the risk of diabetic nephropathy in patients with type 1 diabetes mellitus. **Method:** The current study included thirty type 1 diabetic patients with diabetic nephropathy. Their mean age was 14.73 ± 4.17 years and their mean duration of diabetes was 8.47 ± 3.43 years. Also thirty type 1 diabetic patients with no evidence of nephropathy were included as a control group. Their mean age was 13.57 ± 3.72 years and their mean duration of diabetes was

8.80 ± 3.47 years. ACE DD/ID/II genotypes were determined by PCR, and the quantity of serum ACE was determined using ELISA. **Results:** The current study revealed that ACE enzyme activity was significantly higher in diabetic patients with nephropathy (mean 74.2 vs 53.3 ng/ml, $P=0.04$). Diabetics with microalbuminuria had higher frequency of DD and ID alleles (13 and 63 vs 10 and 46% respectively), also they had lower frequency of II allele (23.3 vs 43.3%) with a borderline statistical significance ($P=0.05$). The overall allelic occurrence of deletion (D) was insignificantly higher in those with nephropathy (45 vs 33%, $P=0.095$). **Conclusion:** ACE enzyme activity and ACE genotypes (DD and ID) are higher in type 1 diabetic children with microalbuminuria. Genetic susceptibility might have a role in diabetic nephropathy.

P2-D2-332

Game Interaction Between a Humanoid Robot and a Diabetic Teenager: Might This Improve Motivation to Fill in the Nutritional Diary?

Alberto Sanna^b, Ilaria Baroni^c, Elettra Oleari^b, Maria Iole Colombini^a, Clara Pozzi^a, Gianni Russo^a, Andrea Rigamonti^a, Giulio Frontino^a, Valeria Favalli^a, Roseila Battaglino^a, Clara Bonura^a, Riccardo Bonfanti^a, Giusy Ferro^a, Giuseppe Chiumello^a

^aPediatric Department, San Raffaele Hospital, Milan, Italy;

^bFondazione San Raffaele, Milano, Italy; ^cTelbios, Milano, Italy

Introduction: This study describes the experience of introducing Nao, a humanoid robot, into a Summer Camp for children with diabetes (August 2013, Misano Adriatico, Italy), with the aim to provide them a companion capable to support and motivate. Our goal was to investigate if, Nao's interactions with children could positively affect the adherence to specific medical recommendations during their stay. Namely children were asked to fill in a specific nutritional diary. This activity was carried out in the context of the ALIZ-E EU co-funded project, which develops the theory and the practice behind the development of embodied cognitive robots capable of long-term interaction with children. **Methods:** Among all the participants attending the Camp (age: 11-14), 58 were involved in the study: 20 volunteered to interact individually with Nao, the remaining 38 were the control group. During the interaction, the child and the robot played different activities related to nutrition and diabetes. Meanwhile Nao provided motivational hints about the diary, underlining its importance to fill it. Finally, adherence of diabetic children to this task was measured by checking whether the child, after the interaction, filled in the diary at least once during the following days. **Results:** All the 58 children showed a good glycometabolic control (HbA1c M 7.2% , ds 0.93). Eight of 20 children who met Nao filled in the diary whereas four of 38 in control group did it. A two-tailed t -test comparing the two means confirmed statistical significance ($t=2.39$ with $P=0.0103$). **Conclusions:** This study revealed a better adherence to fill the diary thanks to the individual child-robot interactions, compared to that of the control group.

The result shows the efficacy of this useful and enjoyable way to motivate diabetic children.

P2-D2-333

A Novel AVPR2 Mutation (L161P) Causing Partial Nephrogenic Diabetes Insipidus

Sumie Yamashita^a, Astuko Hata^a, Naoto Kaneko^a, Takeshi Usui^b, Daisuke Hata^a

^aPediatrics, Kitano Hospital Tazuke Kofukai Medical Research Institute, Osaka, Japan; ^bNational Hospital Organization Kyoto Medical Center, Kyoto, Japan

Background: Nephrogenic diabetes insipidus (NDI) is a disorder characterized by renal resistance to the antidiuretic effect of AVP. Affected patients are exhibiting symptoms as polyuria and polydipsia. Approximately 90% of congenital NDI are inherited in an X-linked recessive manner and caused by mutations of arginine vasopressin type 2 receptor (AVPR2) gene. **Objective and hypotheses:** An 8-year-old Japanese boy was referred to our hospital for nocturnal enuresis and polydipsia from infancy. He was habitually drinking 3.3–4.0 l liquids/day and urinating 2.8–3.0 l/day. His younger brother, his mother and his mother-side uncle also have polydipsia and polyuria. We suspect him as congenital NDI. **Method:** We performed the water deprivation test following DDAVP administration and the hypertonic saline test. We also analysed the genomic DNA for mutations in AVPR2. **Results:** On the water deprivation test following DDAVP administration, his peak urine osmolality increased to 546 mOsm/l, and it proved that his renal tubule had responded to AVP. However throughout the entire test, basal AVP level were high nevertheless his serum osmolality is within normal range. On the hypertonic saline test, his serum osmolality and ADH level raised to 292 mmHg and 16.4 pg/dl. These results strongly suggested that his partial renal AVP resistance. The genomic DNA was analysed for mutations in AVPR2 and we identified a novel missense mutation (L161P) in the patient and his mother was heterozygous for the mutation. **Conclusion:** In the clinical practice, it is not simple to diagnose the partial NDI. The DNA analysis was useful to diagnose partial NDI. Nocturnal enuresis is one of the most common diseases in children, and it is important to perceive the underlying disease.

P2-D2-334

New-Onset Type 2 Diabetes Presenting with Hyperglycaemic Hyperosmolar State in a Renal Transplant Patient on GH Treatment

Francesca Harrington, Taffy Makaya, Helen Wolfenden
Oxford University Hospitals NHS Trust, Oxford, UK

Background: Hyperglycaemic hyperosmolar state (HHS) is a life-threatening condition rarely seen in paediatrics. It is however becoming increasingly recognised with the growing incidence of childhood type 2 diabetes mellitus (T2DM). **Objective and hypotheses:** We present a child with Bardet–Biedel syndrome (BBS), with new-onset T2DM presenting in HHS, and discuss the dilemmas encountered in his management due to multiple co-morbidities, including renal replacement therapy, and GH deficiency. **Method:** A 16-year-old Asian boy with BBS presented with hyperglycaemia (45.7 mmol/l) on routine 6-weekly follow-up. Medical history included chronic renal impairment, requiring a renal transplant, isolated GH deficiency and obesity. GH treatment was suspended peri-transplant and restarted 4-month post-transplant. He was also on prednisolone and tacrolimus. His father and brother had T2DM. **Results:** Further investigations revealed HHS (ketones 0.1 mmol/l, pH 7.38, osmolality 311 mOsmol/kg). Acute management included fluid resuscitation and i.v. insulin. He is now stable on daily glargine. HbA1c is now 6.9%, he has lost weight, renal function is stable and he is off GH therapy. **Conclusion:** Our patient had multiple risk factors for T2DM: a predisposing syndrome, obesity, family history of T2DM, a high-risk ethnic background, steroid/tacrolimus treatment, on-going puberty, and GH therapy. There was significant family anxiety about the influence of GH in triggering the T2DM, and the impact of the high HbA1c on the transplanted kidney. While the influence of GH on the development of T2DM remains controversial, in this particular case, given the significant risk factors for T2DM, re-analysis of the risk-benefit analysis of continuing GH treatment post-transplant was warranted. Patients with syndromes predisposing to metabolic syndrome, like BBS, require cautious management. In complex cases with significant T2DM risk, including where diabetogenic medications are prescribed, screening for diabetes is essential, to ensure early treatment and preserve renal function in what is likely to be a precious kidney.

P2-D2-335

Insulin Therapy via Tubeless Patch Pump: Really an Alternative?

Claudia Boettcher, Maïke Schaefer, Lucia Weiss, Stefan A Wudy

Paediatric Endocrinology and Diabetology, Centre of Child and Adolescent Medicine, Justus Liebig University, Giessen, Germany

Background: For a few years now tubeless disposable patch pumps are available for insulin therapy. **Objective and hypotheses:** Alarmed by initially non explainable beginning metabolic decompensation of two children with type 1 diabetes during their hospital stay for the initial therapy adjustment with patch pumps and alarmed by patients' reports of frequent premature pump changes and alarms, we decided to scrutinize the patch pumps under laboratory conditions. **Method:** Ten patch pumps with different lot numbers were successively filled with insulin (2 ml) according to instructions, brought into the horizontal, fixed on a reagent vessel and hermetically sealed.

Subsequently the pumps were activated via control device and the cannulae 'inserted' into the reagent vessel. After the expiration of exactly 72 h under a constant basal rate (0.5 U/h) the volume of the collected insulin of each pump was pipetted. Additional patch pumps delivered boli à 0.5, 5.0, and 15.0 U respectively into reagent vessels and again the volume of the escaped insulin was measured. **Results:** One of the ten patch pumps under constant basal rate gave alarm ('blocked') before expiry of the 72 h and was taken out of analysis. The mean volume of the remaining nine pumps was 199.5 µl, the median 215.0 µl with a range of 35.0–284.0 µl. This corresponds to a mean deviation of 50.4% (range 21.1–90.3%) referred to the expected 360.0 µl. The boli à 0.5 E (5.0; 15.0 U) showed a mean volume of 3.6 µl (41.3; 138.2 µl), corresponding a deviation of 30.2% (17.4; 7.9%) of the expected volume. **Conclusion:** We conclude that the available tubeless patch pumps by far do not show the desired accuracy and reliability neither with respect to basal rate delivery nor to bolus delivery. A recommendation for usage in the paediatric field cannot be made until technical improvement.

P2-D2-336

GAD Antibody Positivity is Associated with Higher Prevalence of Autoimmune Thyroiditis in Children with Type 1 Diabetes Mellitus

Saygin Abali^a, Enes Celik^b, Belma Haliloglu^a, Serpil Bas^a, Zeynep Atay^a, Serap Turana^a, Abdullah Bereket^a

^aPediatric Endocrinology and Diabetes Unit, Marmara University, Istanbul, Turkey; ^bDepartment of Pediatrics, Marmara University, Istanbul, Turkey

Background: The prevalence of autoimmune thyroid disease is higher in children with type 1 diabetes mellitus (T1DM). **Objective and hypotheses:** The aim of this study is to compare the frequency of autoimmune thyroiditis in children with T1DM according to the presence of diabetes autoantibodies. **Method:** This study included 533 (49% female) children with T1DM based on hospital records from a single center. Frequency of glutamic acid decarboxylase antibodies (GADA) ($n=252$), insulin antibodies (IA) ($n=250$), and islet cell antibodies (ICA) ($n=264$) determined at T1DM onset were compared with the frequency of positivity of anti-thyroglobulin and/or thyroid peroxidase antibodies ($n=404$) determined in a follow-up duration of 0–16.5 years (median 3.2 years). **Results:** The mean age of diabetes onset is 8.53 ± 4.11 (range 0.59–17.7). GADA, IA, and ICA were positive in 60.3, 31.6, and 54.5% of patients at the onset of diabetes respectively. At least one thyroid autoantibody was positive in 22% ($n=89$) of the patients during follow-up. This was more frequent in girls (28.9 vs 15.5%, $P=0.001$) than boys. The percent of autoimmune thyroiditis was 28.0 ($n=37$) and 10.8 ($n=9$), in GADA positive and negative patients respectively

($\chi^2=8.950$, $P=0.003$). IA or ICA positivity did not show any significant association with prevalence of autoimmune thyroiditis (IA positive vs negative 26.9 vs 18.4%, $P=0.157$ and ICA positive vs negative 23.0 vs 20.2%, $P=0.612$). **Conclusion:** In children with T1DM, GADA positivity carries a higher risk for autoimmune thyroiditis.

P2-D2-337

The Length of the Deletion in the Region 17q Contributes to the Individual Variability of the Phenotype of Patients with Renal Cysts and Diabetes Syndrome (RCAD, HNF1B-MODY)

Stepanka Pruhova^a, Petra Dusatkova^a, Michal Malina^a, Zuzana Slamova^b, Kveta Blahova^a, Radana Kotalova^a, Jiri Dusek^a, Jan Lebl^a, Tomas Seeman^a, Ondrej Cinek^a

^aDepartment of Pediatrics, 2nd Faculty of Medicine, Charles University in Prague and University Hospital Motol, Prague, Czech Republic; ^bDepartment of Biology and Medical Genetics, 2nd Faculty of Medicine, Charles University in Prague and University Hospital Motol, Prague, Czech Republic

Background: The renal cysts and diabetes (RCAD) syndrome caused by defects in the *HNF1B* is characterized by a broad spectrum of clinical features. While heterozygous point mutations are relatively rare, we focused on gross deletions of the *HNF1B* that are determined by multiplex ligation probe-dependent amplification (MLPA). Rather importantly, the deletions most often extend beyond the single *HNF1B*, thus more deleted genes may participate in the clinical picture. **Method:** We compared the clinical phenotype of 13 patients (six males, median age 15.5 years) carrying the gross deletions whose extent was precisely determined by array comparative genomic hybridisation (aCGH) on CytoChip Oligo 8x60K with five patients (one male, median age 15.5 years) having point mutations in the *HNF1B*. **Results:** The average length of heterozygous deletion was 1.69 Mb. The longest deletion reached 2.5 Mb affecting 47 genes and the shortest deletion found in three patients was 1.4 Mb long and deleted 16 genes including *LHX1*. Patients having longest deletions (2.5 and 2.1 Mb) manifested renal dysfunction at older age (10 and 30 years) with milder changes of the kidney structure (isolated cysts and functional changes only) and both presented diabetes as a first clinical feature. Patients with shorter deletion manifested renal changes (cystic kidney disease) prenatally and are mostly without diabetes. Comparing deletion and point mutation carriers, prenatal ultrasound kidney changes were found in 10/13 and 4/5 patients respectively. Diabetes manifested at the median age of 17 years in 5/13 and 2/5 patients. Hypomagnesaemia was present in 11/13 and 2/5 patients. **Conclusion:** Although the dominating clinical phenotype of the patients with whole *HNF1B* deletion is similar with those having point mutations, the length of the deletion can contribute to the individual variability in the age of manifestation and other variability of the phenotype.

P2-D2-338

Urinary Vitamin E Metabolites as a Biomarker of Oxidative Stress in Type 1 Diabetes

Chloe Bulwer^{a,b}, Peter Hindmarsh^{a,b}, Simon Pope^a, Sally Tollerfield^c, Ernestas Sirka^a, Kevin Mills^a

^aInstitute of Child Health, London, UK; ^bUniversity College London Hospitals NHS Foundation Trust, London, UK; ^cGreat Ormond Street Hospital, London, UK

Background: Oxidative stress has been implicated in the development and progression of complications in type 1 diabetes (T1DM). Vitamin E (α -tocopherol) undergoes β -oxidation of its chomanol ring and the resulting metabolite α -TLHQ has been proposed as a potential biomarker of oxidative stress. HbA1c relates in T1DM to microvascular complications predominantly although the end-points are late in disease development. The oxidative stress process may act independently of HbA1c and oxidative stress markers may be useful predictors of early vascular damage. **Objective and hypotheses:** We aimed to measure the levels of vitamin E metabolites in T1DM and see whether they were elevated when compared with age-matched controls and to relate the measures to HbA1c, mode of insulin therapy, and duration of diabetes. **Method:** We developed a new assay using triple quadrupole tandem mass spectrometry to measure vitamin E metabolites α -TLHQ-SO3 and α -TLHQ-glucuronide. Urine samples were analysed from 133 children with T1DM and 88 age-matched controls. All subjects had normal renal function. **Results:** Both vitamin E metabolites were significantly higher in T1DM compared to controls: mean α -TLHQ-SO3 (nmol/mmol creatinine) 3.09 ± 0.39 T1DM vs 1.96 ± 0.33 controls ($P=0.04$); mean α -TLHQ-glucuronide (nmol/mmol creatinine) 76.63 ± 5.65 T1DM vs 47.87 ± 2.16 controls ($P<0.0001$). No statistically significant differences were seen with HbA1c level, mode of insulin therapy, duration of diabetes, or use of continuous glucose monitors. **Conclusion:** These results demonstrate that urinary α -TLHQ, a biomarker of oxidative stress, is elevated in T1DM. Further work is required to validate these results and analyse variation with other parameters of diabetic control.

P2-D2-339

Direct Costs of Diabetes Care in Pediatric Patients with Type 1 Diabetes in Greece

Feneli Karachaliou^a, Konstantinos Athanasakis^b, Charalabos Tsendidis^c, Maria Kitra^c, Stefanos Michalakos^a, Kyriaki Karavanaki^c

^aDepartment of Endocrinology – Growth and Development, ‘P & A Kyriakou’ Children’s Hospital, Athens, Greece; ^bDepartment of Health Economics, National School of Public Health, Athens, Greece; ^cDiabetic Clinic, Second Department of Pediatrics, ‘P & A Kyriakou’ Children’s Hospital, University of Athens, Athens, Greece

Background: Type 1 diabetes (T1DM) is a chronic disease with increasing incidence and major impact on the health care

costs. **Objective and hypotheses:** To estimate the direct cost of pediatric T1DM in the Greek National Health System (NHS) and its distribution by service category. **Method:** This is a retrospective cost-of-illness study, focusing on the direct costs from the healthcare system’s point of view. All patients aged 0–18 years, diagnosed with T1DM, who were followed in the Diabetes Outpatients’ Clinic of the University Pediatric Department of one of the two main pediatric hospitals in Athens, for a 2-year period (1st January 2011–31st December 2012) were included. **Results:** Total diabetes-related direct costs per person-year were estimated at €2712 (95% CI 2468–2956). Diabetes healthcare provider and education visits including laboratory tests, accounted for only 7.6% of total costs. Cost for hospitalizations were only 1.7%. Medication costs were 17% of total costs and were the highest for multi-injection therapy. Supply costs accounted for 73.7% of the total costs and were the highest for insulin pump therapy ($P=0.000$). 12.4% of patients were admitted yearly for diabetes related cause and the mean length of hospitalization was 0.18 days/person-year (95% CI 0.05–0.3). **Conclusion:** This is a preliminary study based on a single institution’s data, which however constitutes a major referral center, thus dealing with a balanced sample of the Greek pediatric diabetic population. Considering that standards of diabetes care are common throughout the NHS, the management of patients in our hospital represents the common practice for pediatric diabetes in Greece. Data are suggesting that cost for hospitalization and outpatients’ care for T1DM patients followed in the public sector was rather low compared to other countries, the medication cost was at similar or lower levels and the cost of supplies was generally higher.

P2-D3-340

Coated Pellets With Controlled Glucose Release in Treatment of Children with Diabetes

David Neumann^a, Ales Franc^b, Jan Muselik^b

^aDepartment of Pediatrics, University Hospital Hradec Kralove, Hradec Kralove, Czech Republic; ^bUniversity of Veterinary and Pharmaceutical Sciences Brno, Brno, Czech Republic

Background: Usually a diet plan includes meals with suitable glycaemic index together with sophisticated insulin delivery for balanced sacharides-insulin intake. Nevertheless, the need of controlled sugar release is urged in specific day-to-day life situations, especially for young children with diabetes. Nocturnal hypoglycaemia, parental fear of insufficient snack intake in nursery, sports with prolonged race periods and others are amongst these life situations. **Objective and hypotheses:** To achieve a controlled glucose release formulation with a 4, 6, and 8 h lag time offering a chance to substitute snacks or other meals in advance. Aiming to decrease inconvenience in lifestyle and improve the therapy and adherence of children with diabetes and their parents. **Method:** A dosage form with a controlled glucose release was successfully prepared, which included a lag time of 4, 6, and 8 h and a release period of 2–4 h. The variables of the dosage form included an optimal diameter of the pellet, resistance of the coat, volume, taste and acceptable form for swallow. These variables were refined via pharmaceutical methods

for optimal efficiency in patient use. **Results:** Two exchange units or more in the form of pellets are easily added to standard meals, e.g. yoghurt. Pellets (clinically powder) don't cause abdominal discomfort. In CGM studies, formulation prevents nocturnal hypoglycaemia. **Conclusion:** A successful formulation of dose was achieved with a controlled glucose release, it also expressed a specific easy-to-explain lag time. This can be an acceptable alternative means for diabetes treatment.

P2-D3-341

A Rare Cause of Obesity and Type 2 Diabetes: a Novel *Alms1* Mutation in Two Siblings with Alstrom Syndrome

Suna Hancili^a, Ayla Güven^a, Süheyla Apaydin^b, Aylin Ardagil^c, Diana Valverde Perez^d

^aGöztepe Education and Research Hospital, Pediatric Endocrinology Clinic, Istanbul, Turkey; ^bHaydarpaşa Numune Education and Research Hospital, Nephrology Clinic, Istanbul, Turkey;

^cDepartment of Ophthalmology, Göztepe Education and Research Hospital, Istanbul, Turkey; ^dDepartamento de Bioquímica, Genética e Inmunología, Facultad de Biología, Universidad de Vigo, Spain

Introduction: Alström syndrome is a rare autosomal recessive disorder characterized by type 2 diabetes, early-onset obesity, hypogonadism, dyslipidemia, progressive retinal degeneration, sensorineural hearing loss, cardiomyopathy and renal failure. **Case Report 1:** A 13 years-old girl consulted because of high blood glucose (442 mg/dl). HbA1c was 8.9%, C-peptide was 4.5 g/dl, insulin was 17.5 µU/ml, insulin antibodies were negative. The parents were consanguineous. She was overweight from infancy. One year ago acute rheumatic fever prophylaxis has been started due to cardiomyopathy. She had truncal obesity, acanthosis nigricans, photophobia, horizontal nystagmus and enophthalmia. Her weight was 69.2 kg (90–97p), height was 153 cm (10–25p), BMI was 29.5 kg/m² (>95p), blood pressure was 120/70 mmHg. Puberty was Tanner stage 5. Subclinical hypothyroidism and hyperlipidemia were identified. Echocardiographic examination revealed cardiomyopathy. Rod-con dystrophy and bilateral sensorineural hearing loss were determined. In follow up, with menstrual irregularity clinical and laboratory investigation were consistent with polycystic ovary syndrome. Alström syndrome were considered with all these findings and learned that there were no obesity or diabetes in her family except her sister. **Case Report 2:** Twenty-four year old female, whose sister was followed-up with the preliminary diagnosis of Alström syndrome was invited to our clinic. She had been followed with the diagnosis of obesity and type 2 diabetes for 4 years. She had hearing loss and visual impairment since the age of 12 and 1 years-old respectively. Genetic analysis proved a novel homozygous frameshift mutation p.(E754fs*755) in the eighth exon of the *ALMS1* gene in both cases. **Conclusion:** Alström syndrome is a rare cause of early-onset obesity, type 2 diabetes and accompanying various endocrine abnormalities. For this reason, Alström syndrome should be kept on mind in the differential diagnosis of the patients with obesity associated with cardiomyopathy, hearing loss and visual impairment.

P2-D3-342

Prolonged Treatment with Vitamin D Supplementation and High Dose is Necessary to Treat Vitamin D Deficiency/Insufficiency (VDD/I) in Children and Adolescents with Type 1 Diabetes

Maria Xatzipsalti^a, Maria Dolianiti^a, Konstantina Papadopoulou^a, Penelope Kouloufakou^a, Vasiliki-Ioanna Mitravela^a, Maria Dracopoulou^b, Lela Stamogiannou^a, Andriani Vazeou^a

^aP&A Kyriakou Children's Hospital, Diabetes Center, A Dept of Pediatrics, Athens, Greece; ^bAghia Sophia Children's Hospital, Unit of Endocrinology, Metabolism & Diabetes, Athens, Greece

Background: Increased frequency of VDD/I has been found in warmer countries over the last years. **Objective and hypotheses:** To evaluate the response to vitamin D treatment in VDD/I among children and adolescents with type 1 diabetes. **Method:** Total 25OHvitamin D levels (VDL) were measured in 76 consecutive children and adolescents with type 1 diabetes (36 males, mean age (s.d.) 13.6 (5.09) years, median disease duration 5.38 (range 0.1 to 25.3 years)) who were attending the diabetes center. Children who were found to have VDD/I were treated with either high (2000–2400 units) or low dose (1000–1200) vitamin D, with/without calcium supplementation according to the dairy product consumption. VDL and PTH levels were frequently monitored during treatment. **Results:** Out of 76 patients only 21 (27.6%) were found to have normal VDL, 32 (42.1%) had vitamin D insufficiency and 23 (30.3%) deficiency. PTH levels were significantly lower in patients with normal VDL compared to those with VDD/I (26.1 ± 8.11 vs 31.9 ± 12.9 $P=0.28$). Patients with VDD/I were consuming significantly less dairy products daily vs those with normal levels (2.09 ± 1.098 vs 3.19 ± 0.96 $P=0.011$). Out of 55 patients with VDD/I, 47 were treated with vitamin D. VDL increased significantly in those treated vs untreated (78 vs 28% $P=0.002$). High vs low dose of vitamin D did not succeed in raising significantly its levels to normal within a 3 month period. VDL returned to normal in 42% of patients treated with high dose supplementation after 6.8 ± 5.6 months of treatment and remained in the range of vitamin D insufficiency in 45%. Reduced exposure to sunlight (<30 min/day) prolonged duration of treatment. **Conclusion:** VDD/I is found in increased frequency among children and adolescents with type 1 diabetes. Prolonged treatment is necessary even with high dose supplementation to reach normal vitamin D levels.

P2-D3-343

No Association Between Serum Vitamin D and Left Ventricular Mass Index in Children and Adolescent with Type 1 Diabetes Mellitus

Angeliki Klissarhaki, Kyriaki Papadopoulou-Legbelou, Ioannis Kyrgios, Maria Eboriadou-Petikopoulou, Assimina Galli-Tsinopoulou

Background: Vitamin D deficiency has been associated with left ventricular geometry and hypertrophy and larger end-systolic diameters and worse left ventricular function in animals and humans. **Objective and hypotheses:** The aim of this study was to investigate any possible association between vitamin D levels and geometry of left ventricle (LV) in youngsters with type 1 diabetes mellitus (T1DM). **Method:** 58 youngsters with T1DM with mean age 14.0 ± 2.5 (range 7–19 years) were included in the study. Left ventricular mass index (LVMI) was calculated by an echocardiographic study. Left ventricular hypertrophy (LVH) was defined as the $LVMI > 39.36 \text{ g/m}^2.7$ in boys and $> 36.88 \text{ g/m}^2.7$ in girls according to recommendations of the European Society of Hypertension and the patients were divided in two groups accordingly. Anthropometric measurements including BMI as well as arterial blood pressure (BP). HbA1c was used to evaluate glycemic control. Serum vitamin D levels were measured in all patients and values $> 30 \text{ ng/ml}$ were considered as normal. **Results:** Patients with LVH presented lower levels of vitamin D (20 ± 8.0 vs 23.7 ± 8.4) in comparison with those without LVH, however this difference did not reach the level of statistical significance ($P=0.463$). No difference in age (13 ± 3.5 vs 14.1 ± 2.3 , $P=0.418$), HbA1c (8.3 ± 0.7 vs 8.2 ± 1.5 , $P=0.929$), systolic (115.2 ± 10.8 vs 115.3 ± 10.5 , $P=0.965$) and diastolic (66 ± 10.8 vs 65 ± 8.9 , $P=0.758$) BP was also observed between the two studied groups. Higher values of BMI tended to be associated with increased LVMI and LVH (23.1 ± 3.2 vs 20.9 ± 3.8 , $P=0.083$). **Conclusion:** LVH is already present in young patients with T1DM regardless of serum vitamin D levels. Although T1DM patients are not obese, increased BMI remains in association with LVH.

P2-D3-344

Lifestyle and Health Related Quality of Life in Adolescents with Diabetes Mellitus Type 1

Enza Mozzillo^{a,b}, Eugenio Zito^a, Elena De Nitto^a, Carla Cerrato^a, Rosa Nugnes^a, Valentina Fattorusso^a, Adriana Franzese^a, Giuliana Valerio^b

^aSection of Pediatrics, Department of Translational Medical Science, University of Naples Federico II, Naples, Italy; ^bDepartment of Movement Sciences, Parthenope University of Naples, Naples, Italy

Background: Adolescence is a critical period of life, and even more if a chronic illness is present like type 1 diabetes mellitus (T1DM). The healthy lifestyle practice is one of the pillars of the T1DM treatment. **Objective and hypotheses:** To evaluate the association between lifestyle and health related quality of life (HRQoL) in adolescents with T1DM. **Method:** Lifestyle and HRQoL were evaluated in 69 T1DM adolescents (34 male, mean age 15.8 ± 1.7 years, with diagnosed with T1DM more than 2 years, without other diseases) attended to the Pediatric Diabetology Regional Center of our Department. Lifestyle was evaluated through the following behaviours: healthy nutrition (KIDMED

questionary), moderate/intensive physical activity (questionary), hours/day of television, consumption of tobacco, consumption of alcohol. Health Style (HS⁺) was defined by concurrence of at least four of the following behaviours: KIDMED ≥ 8 , physical activity for 7 days/week, television $< 2 \text{ h/day}$, no consumption of tobacco, no consumption of alcohol. HRQoL has been evaluated with PedsQL 3.0 Diabetes Module, composed by five scales: (1) diabetes symptoms, (2) management difficulties, (3) adherence to therapy, (4) worry and (5) communication. **Results:** Only 18 T1DM adolescents showed HS⁺ (26%) and higher scores ($P < 0.05$) than those with no health style (HS⁻) in scales 1, 3 e 4 of PedsQL, without difference in scale 2. Even higher levels ($P < 0.05$) were found in adolescents less sedentary (scale 1) and in those who practiced sport (scale 5). Diabetic adolescents with HS⁺ perceived the illness less problematically and showed increased adherence to treatment, they were less concerned about the disease and communicated more with doctors and sanitary team. **Conclusion:** This is the first study that investigates the association between HRQoL and a cluster of healthy behaviors, these singularly examined in other papers of literature.

P2-D3-345

Improvement in Type 1 Diabetes Mellitus Metabolic Control: From Conventional to Functional Insulin Therapy

Joana Serra-Caetano, Sara Ferreira, Helena Lourenço, Lina Aveiro, Nanci Batista, Filomena Freitas, Luísa Simão, Rita Cardoso, Isabel Dinis, Alice Mirante

Pediatric Endocrinology and Diabetology Unit, Coimbra Pediatric Hospital, Centro Hospitalar Universitário de Coimbra, Coimbra, Portugal

Background: Type 1 diabetes mellitus (1DM) is a common chronic disease of childhood. Treatment targets the best metabolic control in order to prevent long-term complications. **Objective:** To evaluate metabolic control in children and adolescents with 1DM along the years. **Methods:** Retrospective study including 1DM children and adolescents with more than 2 years of disease. Data were collected at 2005 and at 2012: sex, age at diagnosis, therapy in the last year, number of group educational sessions, insulin daily dosis (IDD) and mean A1c along last year, BMI and lipid profile. **Statistic analysis** performed with SPSS 21. **Results:** We included 243 children with 1DM: 107 in 2005, all in conventional therapy (CT) and 136 in 2012, all in functional therapy (FT) (75% MDII, 25% CSII). There were no differences in sex, age at diagnosis (6.0 ± 3.3 vs 6.6 ± 3.6 years), duration of illness (6.8 ± 3.3 vs 6.2 ± 3.6 years). Comparing data from 2005-CT to 2012-FT, we found statistical difference in number educational sessions (1.6 ± 0.9 vs 4.8 ± 2.5 ; $P < 0.001$), IDD (1.04 ± 0.27 vs $0.91 \pm 0.22 \text{ IU/kg per day}$; $P < 0.001$), mean HbA1c in the last year (8.7 ± 1.3 vs $7.7 \pm 1.0\%$; $P < 0.001$), total cholesterol (4.1 ± 0.82 vs $4.4 \pm 0.86 \text{ mmol/l}$; $P = 0.01$) and HDL-cholesterol (1.3 ± 0.45 vs $1.6 \pm 0.35 \text{ mmol/l}$; $P < 0.001$) and BMI sds (0.95 ± 0.84

vs 0.43 ± 1.1 , $P < 0.001$). In 2005 and 2012 A1c had a positive correlation with: age date of study ($r = 0.28$; $P = 0.004$ and $r = 0.18$; $P = 0.04$); diabetes duration ($r = 0.25$; $P = 0.008$ and $r = 0.24$; $P = 0.005$); IDD ($r = 0.41$; $P < 0.0001$ and $r = 0.3$; $P = 0.002$); total cholesterol ($r = 0.43$; $P < 0.0001$ and $r = 0.32$; $P < 0.0001$) and LDL-cholesterol ($r = 0.27$; $P = 0.006$ and $r = 0.24$; $P = 0.005$). In 2012 we found a negative correlation between A1c and relative duration of FT ($r = -0.28$; $P = 0.001$). **Conclusion:** The relevant changes were FT implementation and educational reinforcement. With FT there was better metabolic control with lower insulin dosis and lower BMI. Longest FT was associated with better metabolic control, reinsuring the advantage of intensive insulin therapy since diagnosis.

P2-D3-346

Two Cases of 'Unknown' Lipoprotein Lipase Deficiency and Diabetes Mellitus

Carla Bizzarri^a, Sara Ciccone^{a,b}, Stefania Pedicelli^c, Danila Benevento^a, Francesca Baldari^c, Ippolita Patrizia Patera^a, Maria Cristina Matteoli^a, Marco Cappa^a

^aBambino Gesù Children's Hospital, IRCCS, Rome, Italy;

^bFerrara University, Ferrara, Italy; ^cTor Vergata University, Rome, Italy

Background: Lipoprotein lipase (LPL) deficiency is an autosomal recessive disease with deficient extrahepatic removal of blood lipoproteins. **Objective and hypotheses:** Primary LPL deficiency can be exacerbated by coexistent conditions such as diabetes, where relative or absolute insulin deficiency leads to an additional secondary LPL deficiency. **Method:** We describe two cases in which primary LPL deficiency overlapped with previously diagnosed T2DM and with T1DM at onset, respectively. **Results:** Case 1: a 17-year-old T2DM girl with positive family history for T2DM, obesity, mixed dyslipidemia and early cardiovascular diseases presented with central obesity (BMI 30.7 kg/m², WC 99 cm), acanthosis nigricans, limb xanthomas. Laboratory showed HbA1c 123 mmol/mol, total cholesterol 562 mg/dl, triglycerides 2400 mg/dl, normal ApoA1 and ApoB, high levels of ApoB/A1 (1.94). An enlarged, steatotic liver with focal nodular hyperplasia and an ovarian cyst were evident at abdominal ultrasound. Case 2: a 7-year-old male presented with rapidly progressive polyuria, polydipsia, weight loss and impaired consciousness. A diagnosis of T1DM was reached (HbA1c 66 mmol/mol, C-peptide 0.12 ng/ml, positive β -cell antibodies). Concurrent severe hypertriglyceridemia (11 628 mg/dl) and hypercholesterolemia (1128 mg/dl) were evident. Despite the early diagnosis, the intensive intravenous rehydration and insulin therapy, clinical recovery from ketoacidosis was very slow. After stabilization of vital status, plasmapheresis was performed in order to decrease serum triglycerides (from 7430 to 2510 mg/dl) and cholesterol (from 940 to 380 mg/dl). Because of increased indexes of myocardial cytolysis, ST depression with T-wave at ECG and hypokinetic interventricular septum at echocardiogram, a non-ST segment elevation myocardial infarction was suspected. Abdominal ultrasound showed thickening of

the gallbladder wall, with thick bile and hyperechogenic thinned pancreas. **Conclusion:** Molecular analysis showed three heterozygous variants of the LPL gene in the first case. In the second case, a heterozygous mutation of LPL gene and a polymorphism of APOA5 gene were found.

P2-D3-347

Predictors of Direct Costs of Pediatric Diabetes in Greece

Feneli Karachaliou^a, Konstantinos Athanasakis^b, Charalabos Tsendidis^c, Maria Kitra^c, Stefanos Michalacos^a, Kyriaki Karavanaki^c

^aDepartment of Endocrinology-Growth and Development, 'P & A Kyriakou' Children's Hospital, Athens, Greece; ^bDepartment of Health Economics National School of Public Health, Athens, Greece; ^cDiabetic Clinic, 2nd Department of Pediatrics, University of Athens, 'P & A Kyriakou' Children's Hospital, Athens, Greece

Background: There is a dearth of data examining the direct costs of diabetes type 1 (T1DM) in Greece and their predictors. **Objective and hypotheses:** To examine the predictors of elevated direct costs of T1DM in the National Health System in Greece. **Method:** All patients diagnosed with T1DM, who were followed in the Diabetic Clinic of the University Pediatric Department of one of the two major Children's hospitals in Athens, from 1st January 2011 to 31st December 2012 were included. Data on age, gender, ethnicity, insulin dosage and type of insulin regimen, outpatient visits and hospital diabetes-related admissions, laboratory tests and supplies costs were collected. Metabolic control was estimated as the mean of all HbA1c measurements obtained for each patient over the 2-years study period. **Results:** Total diabetes-related direct costs per person-year (pppy) were estimated at €2 712 (95% CI 2468–2956). The mean number of hospitalization days pppy was 0.067 (95% CI: 0.03–0.1) and the mean length of hospitalization 0.18 days pppy (95% CI: 0.05–0.3) The mean number of outpatient visits pppy was 2.88 (95% CI: 2.5–3.2). Multivariate linear regression analysis showed that total costs were significantly higher for i) pump therapy ($P < 0.0001$), ii) older age ($P < 0.001$) and iii) daily insulin dose ($P < 0.001$). Patients on pump therapy had significantly higher cost €5538.2 (1377.0) compared to patients on multi-injection €2446.8 (537.0) and conventional regimen €1978.5 (386.1) ($P = 0.000$). Patients on pump therapy had better glycaemic control compared to the rest of patients ($t = -2.101$, $P = 0.039$). **Conclusion:** The main factor that predicted direct cost of diabetes care in our study was the type of insulin regimen and especially the use of pump. Supply costs accounted for the majority of annual direct costs. However, it is noteworthy that the use of pump was associated with better glycaemic control, which has to be co-estimated, since long-term microvascular complications constitute the major component of the total long-term diabetes care cost.

P2-D3-348**Early Detection and Treatment of Cystic Fibrosis Related Diabetes Mellitus in a Tertiary Paediatric Centre: a Case Series**

Eirin Carolan^a, Claire Murphy^a, Caoimhe Howard^a,
Dubhfeasa Slattery^b, Fiona Healy^b, Ciara Mc Donnell^a,
Nuala Murphy^a

^aDepartment of Diabetes and Endocrinology, Children's University Hospital, Temple Street, Dublin 1, Ireland; ^bDepartment of Respiratory Medicine, Children's University Hospital, Temple Street, Dublin 1, Ireland

Background: Early recognition and treatment of cystic fibrosis related diabetes (CFRD) significantly improves respiratory and nutritional status of patients with cystic fibrosis (CF). American Diabetes Association (ADA) guidelines recommend annual screening with oral glucose tolerance test (OGTT) for all affected children from age 10 years. **Objective and hypothesis:** We sought to determine if screening for CFRD was optimal and to determine if early treatment of CFRD improved respiratory and nutritional outcomes. **Methods:** We retrospectively reviewed laboratory data for all CF patients > 10 years and medical records of patients where OGTT was abnormal. **Results:** Ninety-six CF patients aged 8.53 ± 4.7 years attend our centre. All 47 patients (49% of total CF population) aged > 10 years had annual OGTT. CFRD was diagnosed in 6 (6.3%) patients, two following lung transplantation. Four (4.1%) patients had impaired glucose tolerance and 1 (1%) had indeterminate glycaemia. Mean age at diagnosis of CFRD was 12.7 ± 2.8 years. Mean HbA1c at diagnosis of CFRD was 55.5 ± 22.2 mmol/mol, however two patients had normal HbA1c values. All patients were managed with subcutaneous insulin analogues. Predicted FEV1 values increased by $6 \pm 4.3\%$ and BMI by 1.85 ± 0.35 kg/m² in CFRD patients 1 year post commencement of insulin therapy. **Conclusion:** Early detection of CFRD allows prompt treatment and is associated with improved respiratory and nutritional outcomes.

P2-D3-349**Retinol Binding Protein 4 and Adiponectin Levels During Oral Glucose Tolerance Test in Obese Children Newly Diagnosed of Type 2 Diabetes**

So Hyun Park^a, Jae Hong Kim^a, Kyung Soon Cho^b, Min Sun Cho^b,
In A Jung^b, Sin Hee Kim^b, Min Ho Jung^b, Byung Kyu Suh^b

^aSt Vincent's Hospital, Suwon-si, Gyeonggi-do, Republic of Korea;
^bThe Catholic University of Korea, Seoul, Republic of Korea

Background: Retinol binding protein 4 (RBP4) and adiponectin are known to be related with insulin resistance and type 2 diabetes. **Objective and hypotheses:** This study was aimed at investigating (RBP4) and adiponectin secretion in obese Korean children and adolescents with newly diagnosed type 2 diabetes (T2DM). **Method:** Nine obese children and adolescents with

newly diagnosed T2DM (DM group) and ten obese age-matched subjects without T2DM (NDM group) were included. An oral glucose tolerance test (OGTT) was conducted for all patients, and insulin, C-peptide, glucagon, RBP4, and adiponectin were measured. **Results:** The mean age of the patients was 13.8 ± 2.0 years, and the mean BMI Z-score was 2.1 ± 0.5 . Both groups were comparable in age, sex, pubertal state, BMI Z-score, and waist:hip ratio. The DM group had significantly lower homeostasis model assessment of β and insulinogenic index values ($P < 0.001$). The homeostasis model assessment of insulin resistance was not different between the two groups. Insulin and C-peptide total area under the curve (TAUC) and incremental AUC (iAUC) values were significantly lower in the DM group than in the NDM group ($P < 0.001$). RBP4 levels were higher in NDM group than in the DM group during OGTT ($P = 0.021$). However, there were not significantly different in RBP4 and adiponectin concentration according to time difference in both groups. RBP4 TAUC was significantly higher in the NDM group than in the DM group ($P = 0.046$), while adiponectin TAUC was not different in the two groups. RBP4 iAUC was negatively correlated with BMI ($r = -0.46$, $P = 0.49$), and adiponectin iAUC was positively correlated with HDL and negatively correlated with total cholesterol ($r = 0.62$, $P = 0.005$; $r = -0.5$, $P = 0.03$). **Conclusion:** Obese Korean children and adolescents with newly diagnosed T2DM had lower insulin levels than those without T2DM. RBP4 levels might be related with serum insulin levels rather than the degree of hyperglycemia.

P2-D3-350**Wellbeing of Adolescents with Type 1 Diabetes: Influence of Metabolic Control and Family Factors**

Jesse Vanbesien^a, Laurence Berlangier^a, Susanne Böhler^a,
Jolien Laridaen^b, Inge Gies^a, Sara Van Aken^b, Kathleen De Waele^b,
Martine Cools^b, Ellen Maris^b, Johan Vanderfaillie^c,
Jean De Schepper^{a,b}

^aUniversity Hospital, Brussels, Belgium; ^bUniversity Hospital, Ghent, Belgium; ^cDepartment of Psychology, Free University, Brussels, Belgium

Background: Adolescence is often a period of worse metabolic control and less wellbeing in diabetic children. We studied global (GW) and diabetic-related (DRW) wellbeing in diabetic adolescents and the influence of sex, age, ethnic origin, family composition (single- or two-parent family), family income and metabolic control. **Method:** 133 (71 girls, 120 autochthonous, 20 treated with CSII, 107 from a two-parent family, 68 from families with a monthly income above 3 000 euro) of 310 diabetic adolescents (12–18 years) from two University hospitals completed the Pediatric Quality of Life Inventory PedsQL and a demographic questionnaire. **Results:** Median (range) age and diabetes duration was 15.2 years (12.4–18.8) and 5 years (1–16) respectively. Mean (s.d.) HbA1c was 7.9% (1.0), comparable between the two hospitals, but significantly ($P < 0.001$) lower than in the non-responding adolescents (8.4(1.2)%). The mean (s.d.) GW and DRW total scores were 82 (12) and 74 (14), comparable

between sexes and hospitals and strongly correlated ($r=0.676$, $P<0.001$). An abnormal score for physical, psychosocial, emotional, social and school performance was found in 9.0, 14.3, 15.0, 9.8 and 20.3% respectively. HbA1c ($r=-0.230$, $P<0.01$) and age ($r=-0.180$, $P<0.05$) correlated negatively with DRW, however not with GW. Autochthonous diabetics had, compared with immigrants, a significantly ($P<0.005$) higher DRW score, but a comparable GW score. The GW and DRW scores of patients living in a single-parent family were significantly lower compared with two-parent families ($P<0.005$). Each subscore of GW varied significantly with family income ($P<0.005$). Using multiple regression analysis, only family income as a strong predictor of GW ($P<0.05$) and only ethnicity of DRW ($P<0.05$). **Conclusion:** The global wellbeing of diabetic adolescents in Flanders is comparable with that in other countries. Metabolic control, family income and ethnic origin has to be taken into account in the comparison of wellbeing of diabetic patients between centers.

P2-D3-351

Wolcott-Rallison Syndrome: New Mutations and Report of Two Cases

Erdal Eren^a, Esra Deniz Papatya Cakir^a, Sefika Elmas Bozdemir^b, Solmaz Celebi^b, Cécile Julier^c, Halil Saglam^a, Omer Tarim^a

^aDepartment of Pediatric Endocrinology, Medical Faculty, Uludag University, Bursa, Turkey; ^bDepartment of Pediatric Infection Diseases, Medical Faculty, Uludag University, Bursa, Turkey; ^cUMR-S958 Inserm Faculte de Medicine Villemin 10 avenue de Verdun, Paris, France

Background: Wolcott-Rallison syndrome (WRS) is a rare, autosomal recessive disease and characterized by early-onset diabetes, spondyloepiphyseal dysplasia, short stature, osteopenia, acute liver failure, and neurological deficit. It results from mutation in a gene of the eukaryotic translation initiation factor 2- α kinase 3 (EIF2AK3). **Objective and hypotheses:** We report two WRS patients diagnosed in infantile period. **Method:** PCR techniques were used to amplify the 17 exons of the EIF2AK3 gene and DNA direct assay techniques were used for gene mutation analysis. Patient 1: a boy was admitted to our clinic for diabetic ketoacidosis at the age of 15 months. Liver biopsies were performed due to elevated transaminases were consistent with chronic hepatitis. At the age of 8.5 years, height 109 cm (-3.82 SDS), weight 21.6 kg (-1.6 SDS), genu valgum deformity, difficulty in walking and running were remarkable on physical examination. Patient 2, a boy was diagnosed diabetes at the age of 17 months. At 7 years of age, intracranial abscess developed which was successfully treated with posaconazole and hyperbaric oxygen. At the age of 9.5 years, physical examination showed height of 103 cm (-5.2 SDS), weight of 16.1 kg (-5.6 SDS), genu valgum deformity, difficulty in walking and running. **Results:** Two new homozygous mutations (E926K and K939R) in patient 1, and internal deletion in the EIF2AK3 gene which has never been reported in patient 2 were identified. **Conclusion:** Major skeletal

abnormalities of WRS are osteoporosis/osteopenia, thoracolumbar kyphosis, and bowing of the femur. In addition, pancreas exocrine insufficiency, hypothyroidism, and various central nervous system anomalies have been reported. WRS should be suspected in any child who presents with permanent, nonimmune neonatal/infantile diabetes associated with skeletal dysplasia, short stature, episodes of acute liver failure, or pancytopenia, diabetes associated with skeletal dysplasia, short stature, episodes of acute liver failure, or pancytopenia.

P2-D3-352

Socioeconomic Deprivation is Associated with Increased Hospital Admissions in Children with Type 1 Diabetes Mellitus

Louise Apperley, Sze May Ng

Paediatrics, Southport, UK

Background: Socioeconomic deprivation is an important determinant of health. **Objectives:** This study examined the relationship between incidence of hospital admissions for patients with Type 1 diabetes mellitus (T1DM) and their socioeconomic deprivation. **Methods:** All hospital admissions of patients with T1DM from 0 to 16 years were identified during a 5-year period between 2007 and 2012 using the hospital episodes statistics database (HES). Each hospital admission was classified as either an accident and emergency (A&E) admission or inpatient ward admissions. Causes of admissions were evaluated from individual hospital medical records. Socioeconomic status of individual patients with T1DM was measured using the deprivation data obtained by cross-referencing postcodes with indices of multiple deprivation (IMD) 2010 for overall deprivation scores. The IMD for 32 484 small geographic areas (lower super output areas) in England are ranked from 1 (most deprived) to 32 482 (least deprived). The Spearman rank correlation coefficient looked at associations between IMD indices and admissions rate. **Results:** Records from the 135 (65 F: 69 M) patients showed a significant correlation was found between hospital admission rates and overall deprivation score ($r=-0.18$, $P=0.04$). Patients living in deprived areas were more likely to self-present to A&E ($r=-0.24$, $P=0.02$) but there were no significant associations between inpatient ward admissions and overall deprivation scores ($r=-0.14$, $P=0.17$). Analysis of individual medical records show that patients with T1DM living in deprived areas were more likely to have a hospital admission for diabetes related problems ($r=-0.50$, $P=0.003$). There was no association between non-diabetes related hospital admissions with overall deprivation scores ($r=-0.01$, $P=0.27$). **Conclusions:** Early intervention from primary care and specialist diabetes nurses within the community in deprived areas may be effective in reducing hospital admissions for diabetes-related problems. We believe this has significance for planning health care resources for children and young people with T1DM in the future.

P2-D3-353**Household Unemployment and Low Levels of Education are Associated with Poor Glycaemic Control in Children and Young People with Type 1 Diabetes Mellitus**

Louise Apperley, Sze May Ng

Paediatrics, Southport, UK

Background: Socioeconomic deprivation, obesity and emotional well-being are important determinants of health inequalities and poor glycaemic control in adults with type 1 diabetes mellitus (T1DM). **Objectives:** This study aims to look at the effect of social deprivation, BMI and patient reported emotional well-being on glycaemic control in children and young adults with T1DM. **Methods:** Socioeconomic status was measured by cross-referencing postcodes with indices of multiple deprivation (IMD) 2010 from records of 124 T1DM patients aged 1–16 years. 32 484 small geographic areas (lower super output areas) in England are ranked from 1 (most deprived) to 32 482 (least deprived). The mean BMI standard deviation scores (SDS) were determined and adjusted for age and sex. The World Health Organization-5 Well-Being Index (WHO-5) were used as a measure of psychological emotional well-being obtained for each patient. Data was analysed using statistical software Statistical Package for the Social Sciences (SPSS 20.0). The Spearman rank correlation coefficient looked at associations between HbA1c (mmol/mol), IMD indices, BMI SDS and WHO-5 well-being index scores. **Results:** Records from the 124 (63F:61M) patients with T1DM showed that the mean age of diagnosis was 8.2 years (s.d. 4.1), range 1–16 years. Average HbA1c was 68.1 mmol/mol (s.d. 15.1). Poor glycaemic control were significantly associated with lower levels of education ($r = -0.22$, $P = 0.02$) and unemployment ($r = -0.19$, $P = 0.04$). Significance was not reached for level of income ($r = -0.16$, $P = 0.07$) and overall deprivation ($r = -0.17$, $P = 0.06$). There were no associations between HbA1c and BMI SDS or emotional well-being. **Conclusions:** This study shows that household level of education and employment were important factors to achieving good glycaemic control in children and young adults with T1DM. It will be important to health policy makers to give focus to those of lower socioeconomic backgrounds in planning potential interventions for better diabetes control in children and young people.

P2-D3-354**An Infant with a Novel Kir6.2 Mutation Causing Neonatal Diabetes and Unexplained Lack of Response to Sulphonylurea**Susan M O'Connell^a, Aoife Mc Donald^a, Norma O'Toole^a, Anne Bradfield^a, Maura Bradley^a, Andrew Hattersley^b, Sian Ellard^b, Peter Proks^c, Katia K Mattis^c, Frances Ashcroft^c, Stephen M P O'Riordan^a^aDepartment of Paediatrics and Child Health, Cork University Hospital, Cork, Ireland; ^bRoyal Devon and Exeter Foundation Trust,Exeter, UK; ^cDepartment of Physiology Anatomy and Genetics Parks Road, Oxford, UK

Background: Neonatal diabetes (NDM) is defined as diabetes developing before 6 months of age, affecting one in 100 000 live births. Permanent NDM is diagnosed in the first 6 months of life with no remission. The majority have a mutation in the ATP-sensitive potassium (K_{ATP}) channel (KCNJ11 in 31%, ABCC8 in 13%). Autosomal dominant and recessive forms are described. The majority of patients with NDM caused by K_{ATP} mutations respond to sulphonylureas. **Objective and hypotheses:** To describe response to sulphonylurea in an infant with NDM, heterozygous for a novel Kir6.2 subunit KCNJ11 missense *de novo* mutation (W68G). **Method:** A female born at 37 weeks by Caesarean section for intrauterine growth retardation (birth weight 1.95 kg < 0.4th centile) was hyperglycaemic from day one of life. Initial encouraging C-peptide response was seen (post feed glucose 21.5 mmol/l with C-peptide 223 pmol/l). Initially stabilised with intravenous insulin she was treated with subcutaneous basal insulin with erratic glucose control. Glibenclamide was commenced slowly (0.05 mg/kg per day) from day 20 of life up to a maximum dose of 1 mg/kg per day over 2 months according to the Exeter transfer protocol. At age 2 months insulin pump therapy was commenced resulting in tighter glycaemic control and weight gain. **Results:** Transfer off insulin was unsuccessful. Subsequent C-peptide levels have been low (< 94 pmol/l). *In vitro* testing of the mutant channels indicates she should respond to glibenclamide. Further investigations are continuing. She doing well on insulin pump (total daily dose 0.7 units/kg per day) – HbA1c 55 mmol/mol (20–42). **Conclusion:** This infant with a novel Kir6.2 mutation failed to respond to glibenclamide despite a sustained period on a recognised effective dose and clear *in vitro* response. Investigations are progressing to explain the unexpected failed response. If an unusually rapid rate of sulphonylurea metabolism can be demonstrated by ongoing pharmacokinetic studies, a higher dose of glibenclamide will be warranted in this patient.

P2-D3-355**Glycaemic Control and Microvascular Complications in Adolescents and Young Adults with Type 1 Diabetes: Outcome Following Transfer of Care to Adult Services**Suma Uday^a, Fiona Campbell^a, James Yong^a, Ramzi Ajjan^b^aDepartment of Paediatric Diabetes, Leeds Children's Hospital, Leeds, UK; ^bDivision of Cardiovascular and Diabetes Research, University of Leeds, Leeds, UK

Introduction: Transition of young adults with diabetes has received much attention in recent years. Despite concerns regarding deterioration in glycaemic control and lack of engagement in services following transfer of care from paediatric

to adult services, very few studies have looked at the effect of transfer on glycaemic control and clinic attendance as the primary outcome. **Objectives:** To establish the glycaemic control and rate of microvascular complications in adolescents and young adults with childhood onset type 1 diabetes mellitus (T1DM) before and after transfer from paediatric to adult care at a single centre. **Methods:** Data was collected from our electronic database on patients with T1DM currently attending transition clinic and those transferred to adult services between August 2009 and 2012. **Results:** Hundred and four (55 males) patients with a median age of 19.2 years were identified. Mean (\pm s.d.) age at diagnosis and duration of diabetes were $9.2(\pm 3.8)$ and $9.4(\pm 3.9)$ years respectively. Mean HbA1c was 77 ± 18 mmol/mol. Microalbuminuria was noted in 8.6% and retinopathy in 43.2%, with the majority (41.3%) having only background changes. Fifty four patients were in transition and 50 post transfer to adult care. In the latter group, mean age of transfer was $18.5(\pm 1.2)$ years. Mean HbA1c 1 year pre and post transfer was similar (78 ± 20 and 78 ± 22 mmol/mol, respectively; $P=0.22$). Mean HbA1c 2 and 3 years post transfer were also similar. Although clinic appointments became less frequent following transfer, failure to attend rate did not change. A small subset of patients ($n=7$) who opted for e-mail support demonstrated improved mean HbA1c over 1 year from 68 ± 8 to 63 ± 10 mmol/mol, $P=0.051$. **Conclusions:** Glycaemic control and clinic attendance is stable following transfer of care of young diabetes patients. Background retinopathy is present in a large percentage of patients. Email support may represent one strategy to improve engagement and diabetes control in this population and warrants further investigation.

P2-D3-356

Diabetic Ketoacidosis at the Onset of Type I Diabetes: a Retrospective Study in a Paediatric Population

Gerdi Tuli, Giovanna Maria Ignaccolo, Davide Tinti, Elisa Gioia, Sabrina Sicignano, Franco Cerutti, Ivana Rabbone

Department of Pediatric Diabetology and Endocrinology, University of Turin, Turin, Italy

Background: There is wide geographic variation in the frequency of diabetic ketoacidosis (DKA) at onset of diabetes from ~15–70% in Europe and North America. **Objective and hypotheses:** To evaluate the frequency of DKA at the onset of type 1 diabetes (T1D) in the paediatric population seen in the Department of Pediatric Diabetology of Turin (Italy) from 1/1/2008 to 31/12/2013. **Method:** Data (venous pH and HCO₃, season at the onset) of 305 children (mean age 8 ± 6 years; M/F 1.16/1) at T1D onset were retrospectively analyzed. DKA was defined according to the ISPAD criteria. **Results:** 117 of 305 children (38.4%) had DKA and 36 of 117 had a severe DKA (pH < 7.1 , HCO₃ < 5 mmol/l) (11.8%). M/F ratio was 1/1.2 (OR 0.613, IC 0.385–0.976), revealing higher prevalence among females. Season onset evaluation showed a higher DKA frequency in summer (35%) than spring and autumn (respectively OR 0.477 IC 0.223–0.896 and OR 0.4 IC 0.198–0.804). Stratifying patients by

age (0–4, 5–10 and > 10 years), we observed a higher DKA prevalence in the 0–4 year age group (82 patients: 47.6% of all DKA cases and 15.8% of all severe DKA) which was greater than in the other age groups (respectively OR 0.738 IC 0.335–1.628 and OR 0.458 IC 0.245–0.855). **Conclusion:** DKA at the onset of T1D still represents a frequent event, more so in children aged < 5 years old, in which severe DKA prevalence is still too high with an increased risk of complications.

P2-D3-357

Early-Onset Autoinflammatory Partial Lipodystrophy Characterized by Recurrent Fever and Rash: Candle Syndrome

Korcan Demir^a, Melek Yildiz^a, Balahan Makay^b, Hüseyin Anil Korkmaz^a, Özlem Nalbantoglu Elmas^a, Behzat Özkan^a

^aDivision of Pediatric Endocrinology, Dr Behçet Uz Children's Hospital, Izmir, Turkey; ^bDepartment of Pediatric Rheumatology, Dokuz Eylül University, Izmir, Turkey

Background: CANDLE (chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature) syndrome is a recently described autoinflammatory disease that manifests in early infancy with recurrent fever, violaceous swelling of the eyelids, purpuric skin lesions, hypochromic anemia and elevated acute phase reactants. It is autosomal recessively inherited and associated with partial lipodystrophy, growth retardation and hepatomegaly. *PSMB8* (proteasome subunit β type 8) mutation was identified in majority of the cases. **Objective and hypotheses:** To define clinical and laboratory characteristics of CANDLE syndrome. **Method:** A 14-year-old girl was admitted due to short stature with a history of growth hormone therapy for 2 years without sufficient response. She was suffering from rash, recurrent fever and finger swelling, hepatosplenomegaly and cytopenia since 2–3 months of age without any drug treatment. Her mental motor development was normal. She was born to non-consanguineous parents from the same village after an uneventful term pregnancy. Physical examination revealed severe growth retardation (weight, 27.4 kg, SDS -4.24 ; height, 136.5 cm, SDS -3.57), lipodystrophy of face and limbs, hepatosplenomegaly, minimal joint contractures in the fingers, pubic hair and breast development consistent with Tanner stage II. Laboratory findings disclosed hypochromic microcytic anemia, hypertriglyceridemia, elevated ferritin levels, asymmetric thinning and signal changes of fat tissue with whole body MRI, and no insulin resistance. **Results:** The presumed diagnosis of CANDLE syndrome was confirmed with demonstration of mainly neutrophilic inflammation of the fat tissue in skin biopsy. Methylprednisolone treatment resulted in cessation of episodes of fever and rash. *PSMB8* mutation and whole exome sequencing was negative. Whole genome sequencing analysis is planned. **Conclusion:** Lipodystrophy syndromes are a group of heterogeneous diseases. Patients with growth retardation, skin rashes and signs of inflammation should be searched for lipodystrophy and CANDLE syndrome should be kept in mind.

P2-D3-358**Is There a Change in the Presentation of Childhood Type-1 Diabetes Mellitus in the Last 15 Years? Data from a Tertiary Care Center in Turkey**

Saygin Abali^a, Enes Celik^b, Belma Haliloglu^a, Serpil Bas^a, Zeynep Atay^a, Serap Turan^a, Abdullah Bereket^a

^aPediatric Endocrinology and Diabetes Unit, Marmara University, Istanbul, Turkey; ^bDepartment of Pediatrics, Marmara University, Istanbul, Turkey

Objective and hypotheses: To answer the question of whether the age of diabetes onset is shifting to younger ages and whether the rate of DKA at presentation has changed over the 15 years in children with T1DM. **Method:** Patients with T1DM from a single center for Pediatric Endocrinology and Diabetes in Turkey since 1999 were included. In a period of 15 years, 517 patients (249 females) were divided into three groups due to the year of diabetes diagnosed (group 1=1999–2003, $n=75$; group 2=2004–2008, $n=190$; and group 3=2009–2013, $n=252$). **Results:** The mean age of diabetes onset was 8.4 ± 4.1 years in the total cohort (0.6–17.7). In three groups, the mean ages of diabetes onset were 7.2 ± 4.2 , 8.0 ± 3.7 and 9.0 ± 4.3 , respectively ($P=0.002$). Mean age of diabetes onset was significantly higher in the 2009–2013 group. The percentage of patients diagnosed under 4 years of age were 28.0, 16.3 and 13.9%, respectively ($P=0.016$). Diabetic diabetic ketoacidosis (DKA) and severe DKA rates at onset of diabetes ($n=329$) were 52.3 and 10.6%, respectively in the total cohort. There was no significant difference in DKA and severe DKA rates between three groups. The mean age of patients with DKA was younger than the patients without DKA (8.0 ± 4.0 vs 9.3 ± 4.2 , $P=0.04$). The mean age of the patients with severe DKA was 6.7 ± 3.5 years. There was a positive correlation between the age of diabetes onset and HCO_3 level ($r: 0.222$, $P < 0.001$). Diabetes onset < 4 years of age patients had HCO_3 level significantly lower than that of > 4 years of age (11.7 ± 6.8 vs 15.1 ± 7.4 , respectively, $P=0.002$). **Conclusion:** In this cohort there is no evidence for shifting the age of onset in T1DM getting younger in the last 15 years. Younger age at presentation with T1DM is associated with more severe acidosis.

P2-D3-359**The Sugarsquare Study: a Multicenter Randomized Controlled Trial Concerning a Web-based Patient Portal for Parents of a Child with Type 1 Diabetes**

Emiel Boogerd^{a,b}, Christianne Verhaak^a, Jan Kremer^a, Judith Prins^a, Kees Noordam^{a,b}

^aRadboud University Medical Center, Nijmegen, The Netherlands;

^bChildren's Diabetes Center Nijmegen, Nijmegen, The Netherlands

Background: Raising a child diagnosed with type 1 diabetes can have a profound impact on parents. Having to combine the

demands of the disease and treatment with every day parenting tasks can be overwhelming. Easy accessible communication with healthcare professionals was found to support parents in adequately coping with the disease and the disease self-management in everyday life, as well as peer support and tailored disease information. The Internet is regarded to be a suitable mode for delivery of these aspects of care. **Objective and hypotheses:** This study describes the assessment of feasibility and efficacy of a web-based patient portal, called Sugarsquare, which delivers online parent-professional communication, online peer support and online disease information. **Method:** The hypotheses were tested by means of a multicenter randomized controlled trial. The 189 participants were all parents of a child with type 1 diabetes under the age of 13. Participants were recruited offline from one of seven participating clinics in the Netherlands. User statistics were gathered throughout the 12-month study-period for feasibility, which was assessed in terms of acceptability (did recipients use Sugarsquare?), demand (did recipients continue to use Sugarsquare?), practicability (can recipients access Sugarsquare?) and integration (does using Sugarsquare fit with international guidelines for pediatric diabetes care?). For efficacy (what is the effect of using Sugarsquare on recipients?), self-reported parenting stress (PSI-SF) was assessed at baseline (T0) and at 6 (T1) and 12 (T2) months following baseline. **Results:** Data on T2 are currently gathered and analyzed. In the presentation, results and conclusion will be presented along with overview of the intervention and best practice of usage of a web-based patient portal in usual pediatric diabetes care.

P2-D3-360**'My Diabetes' Application for Android Devices as a Diabetes Management Tool**

María José Ballester^a, Luis Alberto Santillana^a, Rossen Varvanov^b, Katarzyna Buch-Gasz^c, Adam Gasz^d, María José Sanchez^a, Carmen María Lopez^a, Elena Martín^a, Enrique Palomo^a

^aHospital General Universitario Ciudad Real, Ciudad Real, Spain;

^bFreelance IT Specialist, Sofia, Bulgaria; ^cFreelance Language Teacher, Puertollano, Spain; ^dD-Brother, Puertollano, Spain

Introduction: A fundamental element in the successful diabetes management is the education of patients. Modern technology opens new horizons and provides new tools in empowering patients in their learning process. **Objectives:** Presentation, evaluation and critical medical review of 'My Diabetes' application whose Spanish version has been studied, reviewed and analysed in detail by our endocrinology unit and D-parents. Provide insight into its potential for young D-patients, parents and their medical teams. **Material and methods:** This non-commercial, free application is unique in many aspects. It has been carefully designed with sound medical knowledge incorporated in the form of scientific algorithms and thorough understanding of the daily diabetes management requirements which result in extensive compilation, graphic visualization and history

analysis of data. 'My Diabetes' puts in the hands of the patient/parent a highly sophisticated system of analysis of trends in glycemia and insulin needs assisted by a calculator of bolus in the form of separate bolus estimate for carbohydrates and protein/fat (Dual Wave, Square, Normal) with extensive country-specific food list to rely on. There is a full insulin action tracking with allowance for corrections and exercise. The insulin sensitivity and carbohydrate ratio can be adjusted to different parts of the day. Apart from standard tracking of medicine, blood pressure, weight, HbA1c, food intake and exercise, the application generates all statistics including hypoglycemia/hyperglycemia risk factor and variability. The information input is manual or by data transfer (CSV, CareLink, On Track), data can be sent to the medical staff by e-mail. Available in ten languages. **Conclusion:** This free Android application with its sound medical background, is a powerful diabetes management tool for young diabetic patients and parents enabling them to learn, keep close monitoring on daily basis, facilitating information exchange and medical feedback.

P2-D3-361

Comparison of HbA1c and OGTT to Diagnose Diabetes in Korean Children

Min Sun Kim, Dae-Yeol Lee

Department of Pediatrics, Chonbuk National University Medical School, Jeonju-si, Republic of Korea

Background: Recently, the American Diabetes Association introduced HbA1c test for diagnosing diabetes with a cut point of $\geq 6.5\%$ in addition to criteria based on glucose levels. **Objective and hypotheses:** The aim of this study was to evaluate the correlation between plasma glucose (fasting plasma glucose (FPG) and 2-h plasma glucose after an OGTT (2-h OGTT)) and HbA1c for diagnosing diabetes in Korean children. **Method:** A total of 110 children without known diabetes completed an OGTT and HbA1c sampling. Diabetes was defined as a 2-h OGTT ≥ 200 mg/dl, FPG ≥ 126 mg/dl or HbA1c $\geq 6.5\%$. **Results:** Of 45 children with diabetes, 41 (91.1%) were diagnosis by HbA1c, 40 (88.9%) by 2-h OGTT, and 31 (68.9%) by FPG. Diagnostic sensitivity and specificity of diabetic criteria was higher in HbA1c than 2-h OGTT and FPG. Moderate agreement existed for HbA1c and FPG criteria (κ coefficient=0.714), and almost perfect agreement existed for HbA1c and 2-h OGTT criteria (κ coefficient=0.824) and HbA1c and FPG and/or 2-h OGTT criteria (κ coefficient=0.824) for diagnosing diabetes. FPG had the highest estimated area under the curve (AUC) among them. The AUC of HbA1c for identifying diabetic subjects according to FPG or 2-h OGTT criteria was 0.836 and 0.910. And, we found that an HbA1c level of 6.35% and FPG of 113 mg/dl have higher sensitivity and specificity, and an improved positive predictive value and negative predictive value than 6.5% and 126 mg/dl. **Conclusion:** As a screening test for diagnosing diabetes, HbA1c is useful better than FPG and 2-h OGTT in children. But sensitivity and specificity of HbA1c $\geq 6.5\%$ for diagnosis of diabetes is low. So, children with HbA1c of 6.35 to 6.5% or FPG of 113 to 125 mg/dl should be tested OGTT to confirm diagnosis of diabetes.

P2-D1-362

Age at Onset of Weight Gain in Prader-Willi Syndrome is Often Between 1 and 2 Years, Preceding the Hyperphagic Phase; Implications for Management

Malcolm Donaldson^a, Noran Abu-Of Hammed^b, M Guftar Shaikh^c

^aSection of Child Health, Glasgow University School of Medicine, Glasgow, UK; ^bKing Abdul Aziz University Hospital, Jeddah, Saudi Arabia; ^cRoyal Hospital for Sick Children, Glasgow, UK

Background: Prader-Willi syndrome (PWS) results from loss of paternally imprinted genes from the 15q11-13 region and causes hypotonia with weight faltering in infancy, followed later by obesity which is classically attributed to hyperphagia. **Objective and hypotheses:** To determine, where possible, the age at onset of unwanted weight gain (as opposed to actual obesity) in children with PWS attending a specialist clinic. **Methods:** BMI was calculated for each clinic visit in patients with PWS (M=24; F=16) from a single centre over a 20-year period. Two researchers independently scrutinised the BMI chart for each patient to identify the age at which an inappropriate rise in BMI began. **Results:** Seventy-six patients were identified of which 36 had insufficient data for analysis, leaving 40 for study. No inappropriate increase in BMI trend occurred in ten patients at the last data point of 5.3 (1.5-15.2) years. Age at BMI increase was not ascertainable in nine patients, all of whom became obese (BMI SDS > 2) by 3.2 (2-5) years. Of 21 subjects in whom age at BMI increase could be either estimated (eight patients) or precisely identified (13 patients) the median age at the time of increase was 2 (0.5-3.8) years, with 18/21 patients showing onset of increase between 1 and 2 years. **Conclusion:** The critical age of inappropriate BMI increase in PWS is frequently between 1 and 2 years. This is attributable to physical inactivity related to the hypotonia rather than to hyperphagia, the onset of which is > 2 years of age. Efforts to increase physical activity in young children with PWS, including encouraging regular swimming, should be promoted in parallel with healthy eating habits and appropriate portion sizes.

P2-D1-363

Novel Uncoupling Protein 1 Expression in White Adipocytes of Subcutaneous Abdominal Adipose Tissue in Children and Adolescents: A Protective Mechanism for Metabolic Equilibrium?

Alexia Karvela^a, Aikaterini Avgeri^a, Eleni D Vlotinou^b, George Georgiou^c, Dionysios J Papachristou^b, Bessie E Spiliotis^a

^aResearch Laboratory of the Division of Pediatric Endocrinology and Diabetes, Department of Pediatrics, University of Patras School of Medicine, Patras, Greece; ^bDepartment of Anatomy-Histology-Embryology, Faculty of Medicine, University of Patras, Patras, Greece; ^cDepartment of Pediatric Surgery, Karamandaneio Childrens Hospital, Patras, Greece

Background: Morbid childhood obesity predisposes to metabolic disorders such as diabetes type 2. In mice, heat-producing 'brown-like' (beige) adipocytes can suppress weight gain and metabolic disease through the action of uncoupling protein 1 (UCP1) localized in the mitochondria. **Objective and hypotheses:** To study the expression of UCP1 in the adipose tissue of lean and obese children and adolescents. **Method:** Paraffin embedded subcutaneous abdominal adipose tissue microarrays were developed from surgical biopsies of 33 lean (BMI <85%) and 29 obese (BMI ≥95%) prepubertal children (groups A: 2 months–7 years and B: 8–12 years) and adolescents (10–15 years of age). Staining intensity and distribution of UCP1 were studied with immunohistochemistry and mean adipocyte size and total number were estimated by image analysis (adiposoft). **Results:** UCP1 was expressed in the mitochondria of morphologically white adipocytes in all groups without typical beige multilocular lipid droplet morphology. The lean and obese prepubertal children expressed UCP1 with a higher distribution (>50% of tissue) compared to the lean and obese adolescents ($P=0.01$). UCP1 intensity was high in: i) 100% of group A lean and 50% of group A obese, ii) 100% of group B lean and obese, and iii) 67% of lean and 54% of obese adolescents, ($P=0.022$). Adipocyte size and number did not differ between lean and obese of each group, although size tended to increase with age. The children with high UCP1 intensity though, exhibited a higher adipocyte number (107.33 ± 35.02 vs 83.0 ± 17.93 , $P=0.011$). **Conclusion:** The expression of UCP1 in typical white adipocytes in the children and adolescents may reflect a transitional stage of browning recently observed in young sheep studies. UCP1 expression during childhood may contribute towards increased metabolic rate and decreased adipocyte size in an attempt to protect against the development of metabolic disorders. The decreased distribution of UCP1 positive adipocytes in the adolescents may reflect the loss of browning with age and puberty that may impair further the metabolism of obese adolescents.

P2-D1-364

The Association Between Self-Reported Sleep Quality, Ghrelin Hormone and Obese Children and Adolescents

Abeer El-Ashmawy, Iman Eyada, Nahed Mohamed, Mona Attya, Shereen Abdel-Ghaffar, Marwa Farouk

Kasr Elaini, Cairo, Egypt

Background: Sleep quality, ghrelin hormone and obesity are associated with metabolic syndrome. **Objective and hypotheses:** To study associations between sleep duration, level of ghrelin and obesity in children and adolescents. **Method:** A prospective study was conducted on 50 children (their mean age: 8.7 ± 3.2 years) with simple exogenous obesity (BMI SDS >2) recruited from Diabetes Endocrine and Metabolism Pediatric Unit, Children Hospital, Cairo University, Egypt and 70 children

age and sex matched as control. Both patients and control groups were subjected to history taking including sleep history, clinical, Anthropometric assessment and laboratory investigations including (serum ghrelin, lipid profile, fasting blood glucose, and serum insulin). **Results:** According to sleep history; 58 of cases showed interrupted sleep, According to mean number of sleep hours 36% of cases sleep < 6 h, 60% sleep 6–8 h, and 4% sleep more than 8 h. Mean number of sleep hours were significant less compared to the control group (P value =0.001). Mean serum ghrelin were significantly higher in cases than control (2.63 ± 1.798 and 1.11 ± 0.412 pg/ml; respectively, P value =0.004). Mean HOMA-IR level highly significant more in cases compared to control group (5.05 ± 2.47 and 2.47 ± 0.56 , P value =0.001). Serum triglycerides was significant higher in cases than control group (P value=0.008). There was significant correlation between serum ghrelin level and insulin resistance (P value=0.001 and $r=-0.133$). There were non-significant correlation between serum ghrelin level and weight SDS (P value=0.18, $r=0.03$), height SDS (P value=0.6 and $r=-0.107$), waist to hip ratio circumference (P value=0.8 and $r=0.04$), BMI SDS (P value=0.3 and $r=0.004$) and serum triglycerides (P value=0.6 and $r=-0.0758$). **Conclusion:** Obese children has short interrupted sleep which leads to increase level of ghrelin hormone and subsequently increase appetite leading to obesity, insulin resistance, and hypertriglyceridemia.

P2-D1-365

Large-Born Infants Switch from an Adipose to a Lean and Insulin-Sensitive State with Low Concentrations of Circulating Myostatin and Follistatin

Giorgia Sebastiani^a, Miriam Perez Cruz^a, Marta Díaz Silva^a, María Dolores Gomez Roiga^a, Abel Lopez Bermejo^b, Lourdes Ibañez Toda^a, Francis De Zegher^c

^aSant Joan de Déu Hospital, Barcelona, Spain; ^bJosep Trueta Hospital, Girona, Spain; ^cDepartment of Development & Regeneration, University of Leuven, Lauven, Belgium

Background: Muscle is key to glucose metabolism. Myogenesis is completed in early infancy, partly under the inhibitory control of myostatin, a myokine whose actions can be influenced by follistatin. Early lowering of myostatin actions is thus a potential strategy to reduce the risk for later diabetes. **Objective and hypotheses:** We performed a first screening of whether such lowering is among the natural mechanisms whereby some human infants augment their lean mass. **Method:** Body composition (by DXA) and pre-feeding concentrations of circulating glucose, insulin, IGF-I, high-molecular-weight adiponectin (HMW-adip), myostatin and follistatin were assessed longitudinally (at 0 and 4 months) in large-for-gestational-age (LGA, $n=30$) newborns born from non-diabetic mothers; results were compared to those of infants born appropriate for gestational age (AGA, $n=95$); all infants were breastfed for >4 mo. In addition, circulating

myostatin and follistatin were measured cross-sectionally in ten AGA newborns (mean postnatal age, 35 h) and in 14 pregnant women (mean gestational age, 35 wk) who delivered healthy AGA infants. **Results:** LGA, breast-fed infants from non-diabetic mothers were found to switch from an adipose to a lean body composition (with a surplus of lean mass and a normal fat mass) and to an insulin-sensitive state, while having the lowest myostatinemia and follistatinemia so far reported in the human. In the cross-sectional study, myostatinemia and follistatinemia in late-gestational women were the highest so far reported, perhaps contributing to late-gestational adipogenesis. Myostatinemia and follistatinemia in first-week newborns were higher than at birth, suggesting that myostatin and follistatin in the fetal circulation are not of (trans-) placental origin. **Conclusions:** Myostatinemia and follistatinemia are extreme in early life and late gestation, and their fetal-neonatal lowering may be among the natural mechanisms whereby some infants augment their myogenesis, potentially for life.

P2-D1-366

Uric Acid and Risk for Atherosclerotic Disease Early in Life

Judit Bassols^{a,b}, Jose-Maria Martínez-Calcerrada^c, Anna Prats-Puig^{a,b}, Gemma Carreras-Badosa^{a,b}, Ferran Díaz-Roldán^{a,b}, Inés Osiniri^d, Elena Riera-Pérez^d, Francis de Zegher^e, Lourdes Ibáñez^f, Abel López-Bermejo^{a,b}

^aDr. Josep Trueta Hospital, Girona, Spain; ^bGirona Institute for Biomedical Research, Girona, Spain; ^cInstitute of Legal Medicine of Catalonia, Girona, Spain; ^dSalut Emporda Foundation, Figueres, Spain; ^eUniversity of Leuven, Leuven, Belgium; ^fHospital Sant Joan de Déu, Barcelona, Spain

Background: Increased uric acid is an independent risk factor for cardiovascular disease in obese adults and adolescents. The relationship between uric acid and atherosclerotic risk early in life is unknown. **Objective and hypotheses:** We investigated whether uric acid relates to carotid intima-media thickness (cIMT), a marker of preclinical atherosclerosis, in a rather large sample of school-age children and investigated the interaction of obesity status and fat distribution. **Method:** Subjects were 635 asymptomatic Caucasian children (330 boys and 305 girls; mean age 8.3 years), of whom, 405 were lean, 125 were overweight and 105 were obese. Serum uric acid levels, insulin (and HOMA index of insulin resistance (HOMA-IR)), C-reactive protein (CRP) and fasting lipids (triacylglycerol and HDL-cholesterol) were quantified in fasting serum samples. BMI, waist circumference, systolic blood pressure (SBP), and both abdominal fat, and cIMT (by ultrasound) were also assessed. **Results:** Overweight and obese children had higher uric acid levels and higher cIMT than lean children ($P < 0.0001$). Uric acid was associated with several cardiovascular risk factors, namely, lower HDL-cholesterol and higher HOMA-IR, C-reactive protein, triacylglycerol, BMI, waist, SBP, abdominal fat and cIMT (all $P < 0.0001$). Both obesity and

abdominal fat showed interactions in the association with cIMT, as uric acid was preferentially related to cIMT in obese children ($n = 105$; $\beta = 0.396$, $P < 0.0001$, $r^2 = 15.7\%$) and in children with higher abdominal fat ($n = 221$; $\beta = 0.287$, $P < 0.0001$, $r^2 = 13.9\%$). **Conclusion:** Increased serum uric acid is associated with cIMT in school-age children. Both obesity and increased abdominal fat aggravate the risk of atherosclerotic disease imposed by higher uric acid.

P2-D1-367

Prevalence of Idiopathic Intracranial Hypertension and Related Factors in Obese Children and Adolescents

Derya Tepe, Fatma Demirel, Esra Dag Seker, Meltem Tayfun, Ihsan Esen, Ozlem Kara, Ebru Petek Arhan

Ankara Children's Hematology and Oncology Training Hospital, Ankara, Turkey

Background: Idiopathic intracranial hypertension (IIH) is a disorder of elevated intracranial pressure without any evidence of intracranial pathology or underlying systemic disease. Obesity was reported as a significant cause of IIH in childhood especially in adolescents. **Objective and hypotheses:** IIH is a disorder of elevated intracranial pressure without any evidence of intracranial pathology or underlying systemic disease. Obesity was reported as a significant cause of IIH in childhood especially in adolescents. **Method:** 1058 obese children and adolescents were enrolled into the study between January 2011 and January 2013. They were evaluated for IIH by pediatric endocrinologists, neurologists, and ophthalmologist. **Results:** Mean age was 10.8 ± 3.1 years, female/male ratio was 1.31. The prevalence of IIH was found as 1.32%. The mean age of cases with IIH was 11.1 ± 2.7 years, female/male ratio was 2.5%. In the cases with IIH; headache rate was 78.6% and frequency of hypertension were significantly higher than in the others ($P < 0.05$). Mild and medium papilledema were found 78.6 and 21.4% respectively. Fasting insulin, HOMA-IR, cortisol levels were found significantly higher than in the obese individuals without IIH ($P < 0.05$). Medical treatment performed in all patients with IIH. Lumboperitoneal shunt was required in only one patient (7.1%). After treatment, 50% of fundoscopic examinations were normal and the others had mild papilledema. None of the patient developed optic atrophy during follow-up period. Recurrence occurred only in one patient (7.1%). **Conclusion:** IIH is one of the most serious complication of obesity in childhood. Most of the patients with IIH had intractable headache which impacts life quality and risk of permanent visual loss. Complete resolution of clinical symptoms of IIH is observed by prompt diagnosis and treatment, and serious complications can be prevented. For this reason, obese children and adolescents who have complaint of intractable headache should be evaluated for IIH. Weight losing is one of the most effective ways for regression of IIH alongside other treatments.

P2-D1-368**MAINTAIN: an Intervention Study of Weight Regain After Weight Loss in Adolescents and Children Reveals an Only Minor Role of Leptin in Weight Regain**

Susanna Wiegand, Anne-Madeleine Bau, Andrea Ernert, Heiko Krude

Institut Exp.Päd, Endocrinology, Charite-Universitymedicine-Berlin, Berlin, Germany

Background: Lifestyle interventions show a long lasting weight reduction in only 10–20% of obese children and adolescents. Leptin as one major player within the central regulation of food intake and energy expenditure is most likely to mediate the endogenous drive for weight regain. **Objective and hypotheses:** To estimate weight regain after weight loss and the role of leptin in regain. **Method:** We included 153 obese children/adolescents (14 ± 1.9 years; 53% female; BMI 31 ± 4.0 kg/m²) into a multiprofessional lifestyle intervention program. After 3 months weight loss (timepoint T3 to T0) 137 children who lost at least -0.2 BMI-SDS were randomized (T0) into a 'control group' ($n=71$) without further intervention and into a life style 'intervention group' ($n=64$). After 12 months (T12; $n=126$) and 18 months (T18; $n=109$) the study cohort was re-evaluated. **Results:** At T12 and T18, the BMI-SDS is significantly higher in the control group in relation to the intervention group (T12: 2.40 vs 2.20, $P=0.003$; and T18: 2.46 vs 2.30, $P=0.045$), demonstrating the positive effect of further intervention on weight maintenance. Leptin is significantly correlated to BMI-SDS ($r>0.45$; $P<0.001$) and even stronger to % body fat ($r>0.59$; $P<0.001$) at all study dates and furthermore Leptin at T0 to BMI-SDS ($r=0.43$; $P<0.001$) and % body fat ($r=0.63$; $P<0.001$) at T18. **Conclusion:** Although weight regain in obese children and adolescents is partly preventable with further lifestyle intervention the majority of patients show significant weight regain within 18 months. Leptin levels were shown to play an only marginal role in the endogenous regulation of weight regain. Therefore the molecular basis of weight regain still need to be determined.

P2-D1-369**The Expression of IGF Type 1 Receptor is Increased in Obese Children**

Rafaela Ricco, Rodrigo Custódio, Patricia Atique, Raphael Liberatore, Rubens Ricco, Carlos Martinelli

Department of Paediatrics, Ribeirão Preto Medical School-USP, Ribeirão Preto Medical School-USP, Brazil

Background: Obese children are often taller than non-obese ones before puberty. Reports on the GH/IGF system in obese children are not consistent and do not explain the increased height observed. Changes in IGF1 bioavailability/bioactivity have been claimed as a possible explanation, however, no data is available regarding the expression of the IGF type 1 receptor (IGF1R) gene. **Objective and hypotheses:** To study the expression of IGF1R gene in obese children. **Method:** Twenty-nine obese children

(BMI >2 SDS) with height $>+1$ SDS (15 males) and 18 non-obese ($-2<BMI<+2$ SDS) age-matched controls with height between -2 and $+2$ SDS were studied (nine males). All were prepubertal and none had any metabolic, endocrine, or genetic disease. Fasting blood samples were collected to analyze IGF1R gene expression in peripheral lymphocytes and determine the serum concentrations of IGF1 and IGFBP3. Lymphocytes were isolated from other blood cells using Fycoll-Hypaque and the RNA extracted. The IGF1R mRNA expression was analyzed by quantitative real-time PCR. IGF1 and IGFBP3 were determined by Immulite 2000 Kits. Data were compared by Mann-Whitney and Fisher tests. **Results:** The expression of IGF1R mRNA, expressed as $2^{-\Delta\Delta CT}$, was higher in obese children than in non-obese controls (1.9 vs 1.15) ($P=0.02$). IGF1 levels were also higher in obese children (237 vs 143 ng/ml) ($P=0.02$). However, no difference was found on IGFBP3 levels. **Conclusion:** Obese children showed higher IGF1R mRNA expression and higher serum IGF1 levels than non-obese children. This higher expression of IGF1R and the higher IGF1 levels may contribute to the increased height observed in many obese children. Differently from obese adults, in which GH secretion is decreased, the role of GH in the growth promotion of obese children is still unclear as IGFBP3 levels do not follow the increase in IGF1 levels.

P2-D1-370**Childhood Obesity, Renal Injury, and Future Disease Risk**

Mina Lateva^{a,b}, Dimitrichka Bliznakova^{a,b}, Sonya Galcheva^{a,b}, Maria Neshkanska^a, Vilhelm Mladenov^b, Veselin Boyadzhiev^{a,b}, Irina Halvadžhiyan^a, Galina Yordanova^a, Violeta Iotova^{a,b}

^aMedical University Varna, Varna, Bulgaria; ^bUMHAT 'Sv. Marina', Varna, Bulgaria

Background: Evidence associates obesity with glomerular hyperperfusion. Concurrent inflammation, hypertension, dyslipidemia, and insulin resistance represent further established risks to renal health in both children and adults. **Objective and hypotheses:** To investigate the relationship between childhood obesity and risk of renal impairment. **Method:** A total of 114 (38.6% boys) obese according to the IOTF reference but otherwise healthy children, who were investigated in 2013, were included in the study (mean age 11.5 ± 3.6). Body weight, height, waist circumference (WC), and blood pressure (BP) were measured using standard procedures. The pubertal status was defined applying Tanner scale. Blood and urine samples were collected after overnight fast. Kidney size was measured by standard abdominal echography; kidney volume and glomerular filtration rate (Schwartz formula, adjusted to ml/min per 1.73 m²) were calculated. **Results:** Microalbuminuria (MA) was detected in 8.5% of the children, and 40.2% of all were with high systolic BP. Close to half of the children (43.4%) showed insulin resistance (assessed by HOMA-IR) and 95.4% displayed hyperinsulinism. High hsCRP was present in 32.5%. Elevated LDL-cholesterol was found in 42.1% of the children, with high total cholesterol in 6.2% of all. Kidney volume correlated with WC (left $r=0.488$, $P<0.001$; right $r=0.292$, $P=0.021$), as well as with weight and elevated systolic

BP. Children with hyperfiltration (9.6% of all) are booked for poor metabolic health as at this stage they all had elevated total cholesterol and triglycerides. In further 14.3% of the children (all pubertal) glomerular filtration rate was low, and they had significantly larger kidney volume (left $P < 0.001$; right $P = 0.004$), HOMA-IR ($P = 0.001$), WC and BMI ($P < 0.001$) compared to those with normal and hyperfiltration rate. **Conclusion:** To summarize, childhood obesity showed association with established risk factors for renal toxicity. Whether kidney volume in obese children has an independent predictive value of future chronic kidney disease remains to be investigated.

P2-D1-371

Replacement of the Neonatal Leptin Surge During Maternal Deprivation Normalizes Some Endocrine Parameters but Exacerbates Others

Virginia Mela^a, Alvaro Lopez-Rodriguez^a, Sara Peñasco^b, Vicente Barrios^c, Jesús Argente^c, María-Paz Viveros^a, Julie A Chowen^c

^aDepartment of Physiology (Anim Physiol II), Faculty of Biology, Complutense University, Madrid, Spain; ^bDepartment of Neuroscience, Faculty of Medicine and Odontology, UPV, Bilbao, Spain; ^cDepartment of Endocrinology, Hospital Infantil Universitario Niño Jesús, Universidad Autónoma de Madrid, CIBERobn, Madrid, Spain

Introduction: Maternal deprivation (MD) during neonatal life has diverse long-term effects, including modification of metabolism. Some of these effects are sexually dimorphic. We have previously reported that MD in rats blocks the physiological neonatal leptin surge, which could underlie the long-term metabolic changes. **Hypothesis:** We hypothesized that replacement of leptin during MD would normalize long-term endocrine changes. **Methods:** MD was carried-out in Wistar rats for 24 h on postnatal day (PND)9. Female and male MD and control rats were treated from PND 9 to 13 with rat leptin (3 mg/kg per day s.c.) or vehicle. After weaning weight gain, food intake and pubertal onset were monitored and an oral glucose tolerance test (OGTT) performed at PND60. Rats were sacrificed at PND90. Serum insulin, leptin, interleukin 6 (IL6), and tumor necrosis factor (TNF) α levels were measured by multiplex assay. **Results:** MD reduced weight gain ($P < 0.001$) and food intake ($P < 0.005$) and leptin treatment further decreased both parameters in males, with no effect in females. Leptin treatment delayed vaginal opening (pubertal onset) in females ($P < 0.05$). In males MD ($P < 0.01$) advanced pubertal onset. Leptin also advanced puberty in controls, but normalized it in MD males ($P < 0.005$). The OGTT area under the curve was lower in females ($P < 0.001$) compared to males and MD reduced it in both sexes ($P < 0.05$), with no effect of leptin treatment. There was no effect of MD or leptin treatment on serum leptin, IL6, or TNF α levels. In males MD increased insulin levels, with neonatal leptin treatment normalizing it in MD rats, but increasing it in controls ($P < 0.05$). No effect was found in females. **Conclusion:** Neonatal leptin treatment of MD rats normalizes some of the endocrine parameters disrupted by the manipulation, but exacerbates other changes. Hence, the factors inducing long-term changes are most likely multiple with diverse interactions.

P2-D1-372

Longitudinal Development of Adiponectin in Early Childhood and the Influence of Breastfeeding and Essential Fatty Acid Status

Josefine Roswall^a, Emma Kjellberg^a, Birgitta Strandvik^b, Jovanna Dahlgren^a

^aDepartment of Pediatrics, Institute of Clinical Sciences, University of Gothenburg, Gothenburg, Sweden; ^bDepartment of Biosciences and Nutrition, Karolinska Institute, Stockholm, Sweden

Background: Adiponectin is an adipokine related to insulin sensitivity. In adults and older children adiponectin correlates inversely to BMI, insulin resistance, and cardiovascular risk. Less is known about these relationships in early childhood. **Objective and hypotheses:** To explore the longitudinal development of adiponectin and correlations to early feeding patterns and serum essential fatty acids. **Method:** 324 term infants were followed from birth to 3 years of age. Adiponectin was measured in cord, at 4, 12, and 36 months of age. Feeding practices were collected through questionnaires. In a subgroup of 92 infants essential fatty acid status in cord, serum at 2 days, 4, 12 and 36 months and breast-milk at 4 months were determined. Length and weight were measured. **Results:** Mean (S.D.) adiponectin levels were significantly higher in cord blood and at 4 months (33 (12.8) vs 36 (12.5)) compared with a significant lowering thereafter (18 (7.3) and 14 (5.3), $P < 0.001$). No significant gender difference was found except for significant lower adiponectin levels in females at 12 months of age. Feeding patterns at 4 months of age did not influence adiponectin levels. A significant negative correlation was found between omega-6/omega-3 ($n-6/n-3$)-ratio in cord blood and serum adiponectin levels at 36 months ($r = -0.36$ $P < 0.05$). Eicosapentaenoic acid plus docosahexaenoic acid (EPA + DHA) in serum at two days correlated with adiponectin levels at 12 and 36 months ($r = 0.31$ $P < 0.05$). There was a strong correlation between the serum LC-PUFAs at 4 months and in breast-milk ($r = 0.68$, $P < 0.001$). Serum $n-6/n-3$ -ratio differed between exclusive breast-fed infants and mixed/formula-fed infants 5.6 (1.2) vs 6.9 (2.5), $P < 0.001$. **Conclusion:** Term infants present with high adiponectin levels at birth, lowering after 4 months of age. Essential fatty acid status at birth predict adiponectin levels at 36 months of age and may suggest early programming of later insulin sensitivity.

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Expression Levels of the Growth-Arrest-Specific Transcript 5 in Overweight and Obese Children and Adolescents

Terpsihori Fragouli^a, Amalia Sertedaki^a, Ioanna Farakla^a, Nicolas C Nicolaidis^a, Maria Dracopoulou^a, Ioannis Papassotiriou^b, George P Chrousos^a, Evangelia Charmandari^a

^aDivision of Endocrinology, Metabolism and Diabetes, First Department of Pediatrics, University of Athens Medical School, Athens, Greece; ^bDepartment of Clinical Biochemistry, 'Aghia Sophia' Children's Hospital, Athens, Greece

Background: The noncoding RNA growth-arrest-specific transcript 5 (Gas5) is abundant in cells whose growth has been arrested owing to lack of nutrients or growth factors. Gas5 is a riborepressor of the glucocorticoid receptor, influencing cell survival and metabolic activities during starvation by inhibiting the latter's transcriptional activity. **Aim:** To determine the expression levels of Gas5 in blood samples of obese, overweight and lean children and adolescents. **Patients and Methods:** One hundred ($n=100$) children and adolescents (males: 55, females: 45) were recruited to participate in the study. Of these, 35 were obese (age: 10.92 ± 3.43 years; BMI: 27.44 ± 3.98 kg/m²), 35 overweight (age: 10.85 ± 1.58 years; BMI: 21.97 ± 2.26 kg/m²), and 30 of normal BMI (age: 10.56 ± 2.55 years; BMI: 19.36 ± 1.95 kg/m²). Total RNA was isolated from peripheral blood samples and cDNA was prepared. RT-PCR was performed using the Light Cycler 480 Probes Master Kit, employing primers and TaqMan probes specifically designed for Gas5 and RPLP0 (used as control gene), on a Light Cycler 480 System (Roche). The Cp values obtained for Gas5 expression were normalized for those of RPLP0. **Results:** The expression levels of Gas5 did not differ among obese (1.1637 ± 0.1661), overweight (0.9304 ± 0.1340), and normal-BMI (1.0352 ± 0.1612) children. **Conclusion:** This study did not reveal a difference in the expression levels of Gas5 in overweight and obese children compared with those of normal BMI. This is probably due to the stability of the *milieu interieur*. Further studies are necessary to determine whether the expression levels of Gas5 differ between patients with severe anorexia nervosa and their normal counterparts.

Table 1. (for abstract P2-D2-374).

	Leptin (ng/ml)	HbA1c (%)	LDL-cholesterol (mmol/l)	HDL/TC (%)
T1DM	2.2 ± 3.3	7.7 ± 1.6	2.4 ± 0.7	36 ± 7.8
Obese	8.1 ± 5.9	5.2 ± 0.2	3 ± 0.8	26 ± 7.2
Control	2.4 ± 0.9	5.4 ± 0.1	2 ± 0.6	37 ± 10

activator of nuclear factor NF- κ B ligand (RANKL), fat tissue-derived leptin and adiponectin, as well as vitamin D, lipid profile, glucose, HbA1c concentrations were taken at 0800 h. Hormones were measured by immunochemistry, vitamin D by HPLC and other parameters by routine chemistry methods. Statistical analysis was performed in all groups using ANOVA with *post-hoc* Turkey test and multiple regression analysis. **Results:** There were significant differences regarding leptin, HbA1c, LDL-cholesterol, HDL-cholesterol/total cholesterol levels among groups $P < 0.001$ (Table 1). In T1DM, multiple regression analysis adjusted for age and BMI showed negative correlation between OC and leptin ($r = -0.37$, $P = 0.02$) and HbA1c ($r = -0.4$, $P = 0.01$), and positive correlation between OC and HDL/TC ($r = 0.3$, $P = 0.02$). In contrary, serum RANKL correlated positively with adiponectin ($r = 0.3$, $P = 0.04$). Moreover, vitamin D correlated negatively with HbA1c ($r = -0.3$, $P = 0.03$). In obese patients strong correlation between adiponectin and HbA1c ($r = -0.8$, $P = 0.02$) has been found. In control group only positive correlation between OC and vitamin D ($r = 0.7$, $P = 0.03$) was noted. **Conclusion:** It is suggested that cross-talk between bone and fat tissue in pediatric patients depends on insulin action.

P2-D2-374

The Role of Bone and Fat Tissue in Glucose Metabolism in Two Different Metabolic Conditions: Obesity and Diabetes Mellitus Type 1: Pilot Study

Anna Wedrychowicz^a, Krystyna Sztętko^b, Jerzy Starzyk^a

^aDepartment of Pediatric and Adolescent Endocrinology, Medical College, Polish-American Pediatric Institute, Jagiellonian University, Krakow, Poland; ^bDepartment of Clinical Biochemistry, Polish-American Pediatric Institute, Jagiellonian University, Kraków, Poland

Background: Recent studies have shown a new link between skeleton, fat tissue, and insulin action. However, clinical data are still limited, especially in children. **Objective:** The aim of the presented study was to investigate the relationship between bone and fat hormones and glucose metabolism in children with type 1 diabetes mellitus (T1DM) and obesity. **Methods:** Forty-six T1DM children, mean age 12.2 ± 4.6 years, mean BMI 20.0 ± 4.7 kg/m², 16 obese children, (age 11.3 ± 3.8 years and BMI 27.2 ± 7.3 kg/m²), and 11 control, healthy children, (11.5 ± 5.0 years), BMI 19.0 ± 2.8 kg/m² were included into the study. Fasting blood samples for measurement of bone derived osteocalcin (OC) and receptor

P2-D2-375

Family and Genetic Factors Influence the Metabolic Changes in Children

Anzhalka Solntsava^a, Liudmila Viazava^a, Alexander Sukalo^a, Elena Aksionava^b, Nina Danilenko^b

^aBelarusian State Medical University, Minsk, Belarus; ^bInstitute of Genetics and Cytology, National Academy of Science, Minsk, Belarus

Background: Primary and secondary prevention of childhood obesity is an essential public health priority. **Objective and hypotheses:** To determine relationships between families, genetic and metabolic obesity risk factors in children. **Method:** 782 children (204 lean/578 obese; m/f = 414/368) aged from 2 to 17.9 years were examined and classified in line with the pubertal stage: 392 prepubertal, 141 early, and 249 late puberty. Family history (FH) of impaired glucose tolerance/diabetes mellitus (IGT/DM), cardiovascular disease (CVD), and obesity (O) was obtained from questionnaires. BMI was calculated and standardized referring to national reference data. 243 obese and 112 lean children were

genotyped in INS gene (A-23HphIT polymorphism). In order to assess metabolic changes, serum insulin (INS), cholesterol (Ch), triglycerides (TG), HDL and LDL, glucose levels were detected, and HOMA-IR index was calculated. Statistical analysis was performed using SPSS 16.0 ($P=0.05$). **Results:** INS level was significantly higher in children with FH of CVD ($P1=0.001$) and O ($P2=0.014$) than in ones without; *vice versa* to children with FH of IGT/DM ($P>0.05$). These patterns of relationships were similar regardless of sex and pubertal stage. In multivariate analysis with INS indexes as dependent variables, parameters independently associated to INS was FH of CVD ($\beta=0.203$ $P=0.006$ in girls and $\beta=0.149$ $P=0.028$ in boys). Family history of IGT/DM and O were not influenced INS levels. There were correlations between LDL and INS ($r=0.3$, $P=0.05$) and HOMA-IR index ($r=0.3$, $P=0.05$) levels in late pubertal obese children. HDL concentrations correlated with INS ($r=-0.5$, $P=0.003$) and HOMA-IR ($r=-0.5$, $P=0.004$) in late pubertal overweight girls. INS and HOMA-IR were higher in AA homozygous O children respecting to TT-genotype of INS gene ($P=0.003$ and 0.006 in order). **Conclusion:** FH of CVD and O, AA homozygous genotype of A-23HphIT polymorphism influenced INS level in children. Lipid spectrum in obese children associates with INS and HOMA-IR.

P2-D2-376

Non-Alcoholic Fatty Liver Disease in Children/ Adolescent Affected by Prader-Willi Syndrome

Danilo Fintini^a, Elena Inzaghi^b, Sarah Bocchini^a, Graziano Grugni^d, Mauro Colajacomo^e, Claudia Brufani^a, Marco Cappab^b, Valerio Nobili^c, Stefano Cianfarani^b, Antonino Crinò^a

^aAutoimmune Disease Unit, Bambino Gesù Children's Hospital, Rome, Italy; ^bEndocrinology Unit, Bambino Gesù Children's Hospital, Rome, Italy; ^cHepatometabolic Unit, Bambino Gesù Children's Hospital, Rome, Italy; ^dItalian Auxological Institute Foundation, Piancavallo, Verbania, Italy; ^eRadiology Unit, Bambino Gesù Children's Hospital, Rome, Italy

Background: Prader-Willi syndrome (PWS) has a relative hypoinsulinemia and a lower insulin resistance than non-PWS subjects. Mostly on the basis of such higher insulin sensitivity, PWS subjects have been hypothesized to be at lower risk of non-alcoholic fatty liver disease (NAFLD). **Objective and hypotheses:** In this cross-sectional study, we analyzed the presence and the severity of NAFLD in a group of PWS children compared to matched pairs. **Method:** Twenty-two PWS patients (eight males, mean age 12.4 ± 2.4 years, Tanner 2.2 ± 1.3 ; BMI-SDS 3.7 ± 2.2) were compared to a control group (CNT) of a one to one age (12.0 ± 2.5 years), sex (eight males), pubertal status (Tanner 2.4 ± 1.7), and BMI-SDS (3.1 ± 1.5) matched pairs. All patients underwent standard oral glucose tolerance test, liver ultrasonography (US) and body composition by DEXA scan (free fat mass (FFM); total fat mass (FM); trunk fat mass (TFM) as percentage of body weight). NAFLD was established by a validated

method of US grading (ranged G0=no NAFLD-G3=moderate NAFLD) **Results:** A not significant lower HOMA-IR and insulin were found in PWS compared to CNT (3.1 ± 2.0 vs 6.4 ± 8.4 and 17.4 ± 9.6 vs 32.1 ± 44.8 respectively). No difference of insulin sensitivity index and body composition were detected between the two groups. The grading of NAFLD showed a higher percentage of PWS at G0 (28.3 vs 6.3% of CNT; $P>0.05$) and lower at G1 and G2 (47.6 vs 56.3 and 19.1 vs 31.3% respectively; $P<0.05$). Univariate analysis showed a positive correlation in PWS between NAFLD grading and BMI-SDS ($r=0.644$), FM ($r=0.667$), and negative with FFM ($r=-0.673$), FFM/FM ($r=-0.655$) while in CNT no correlation were found. When inserted in a regression model, adjusted also for GH therapy we did not find any correlation. **Conclusion:** Our data seems to support the hypothesis that PWS children were protected by NAFLD compared to CNT. BMI and metabolic parameters, and GH therapy, did not seem to have influence on NAFLD developing.

P2-D2-377

Short-Term Results of Single-Port Sleeve Gastrectomy in Adolescents with Severe Obesity

Gianpaolo De Filippo^a, Guillaume Pourcher^b, Catherine Piquard^a, Stefano Ferretti^b, Ibrahim Dagher^b, Pierre Bougnères^a

^aAssistance Publique – Hôpitaux de Paris, Hôpitaux Universitaires Paris Sud, Hôpital Bicêtre, Service d'Endocrinologie et Diabétologie Pédiatrique, Le Kremlin-Bicêtre, France; ^bAssistance Publique – Hôpitaux de Paris, Hôpitaux Universitaires Paris Sud, Hôpital Bécélère, Service de Chirurgie Viscérale Mini-Invasive, Clamart, France

Background: Dietary and lifestyle modifications commonly proposed to overweight or obese youth lack efficacy in those with severe obesity. Early results with bariatric procedures in obese adolescents suggest that weight loss and safety are comparable or better than those seen in adults. One of these procedures, laparoscopic sleeve gastrectomy, is commonly performed using multiple ports. We selected single port sleeve gastrectomy (SPSG) as a minimally invasive surgery to be tested in severely obese adolescents. **Methods:** Prospective clinical and biochemical data were collected from 16 young severely obese patients who underwent SPSG (mean age 17.5 years, 12 girls, four boys). **Results:** Weight averaged 119.2 kg and BMI 43.9 kg/m². All patients were insulin-resistant, including hypertriglyceridemia in six. Median operating time was 66 min. There were no intraoperative complications. No conversion to open surgery was required. No patient required additional trocars. No patient had postoperative complications. The median hospital stay was 3 days. During a median follow-up of 12.4 months, weight decreased by 41.7 kg, resulting in a decrease of excess weight loss by 59.9%. Insulin-resistance decreased in 16/16 patients and hypertriglyceridemia in 5/6. **Conclusion:** SPSG seems safe and effective in the short term in severely obese adolescents.

P2-D2-378**Circulating Concentrations of Fibroblast Growth Factor 21 are Undetectable in Human Infants at Term Birth and Surge within Hours After Birth**

David Sánchez-Infantes^{a,c}, José Miguel Gallego-Escudero^b, Rubén Cereijo^b, Marta Díaz^{a,c}, Gemma Aragonés^a, Abel López-Bermejo^d, Francis de Zegher^e, Francesc Villarroya^b, Lourdes Ibáñez^{a,c}

^aSant Joan de Deu Hospital, Barcelona, Spain; ^bUniversity of Barcelona, Barcelona, Spain; ^cCIBERDEM-ISCIII, Madrid, Spain; ^dDr Josep Trueta Hospital, Girona, Spain; ^eUniversity of Leuven, Leuven, Belgium

Background: In rodents, fibroblast growth factor 21 (*FGF21*), an endocrine member of the FGF family, is mainly produced in the liver and promotes glucose oxidation in several tissues; the circulating concentrations of *FGF21* rise shortly after birth. In the human, the ontogeny of circulating *FGF21* is essentially unknown. **Objective and hypotheses:** To assess whether there is also a neonatal surge of circulating *FGF21* concentrations in human infants and, if any, whether *FGF21* concentrations in human infants relate to their prenatal growth (as judged by birthweight for gestational age), to body composition (as judged by neonatal absorptiometry) and to insulin resistance (as judged by HOMA-IR calculated from prefeeding glycaemia and insulinaemia). **Method:** Concentrations of circulating *FGF21* were measured longitudinally (birth, 4 and 12 months) in 66 term infants (22 born small-, 22 appropriate-, and 22 large-for-gestational-age; SGA, AGA, and LGA) and cross-sectionally in first-week newborns ($n=10$; 1–4 days). **Results:** Circulating *FGF21* was not detectable in human infants at term birth but was readily detectable in first-week newborns. *FGF21* concentrations in infants aged 4 or 12 months compared to those in first-week newborns, were similar in girls and boys, similar in SGA, AGA, and LGA infants, and were ~1.4-fold higher than those previously described in adults ($P<0.0001$). In SGA infants aged 4 months, circulating *FGF21* associated negatively to HOMA-IR ($P=0.001$), but not to birthweight or body composition variables. **Conclusion:** Pilot evidence suggests that there is a neonatal surge of circulating *FGF21* in human infants. The mechanisms underpinning this neonatal surge remain to be disclosed but may involve the neonatal initiation of enteral nutrition as well as neonatal changes in hepatic perfusion and/or metabolism.

P2-D2-379**Severe Childhood-Onset Obesity and Testicular Function After Puberty**

Saila Laakso^a, Heli Viljakainen^a, Marita Lipsanen-Nyman^a, Ursula Turpeinen^b, Tero Saukkonen^{a,c}, Outi Mäkitie^{a,d}

^aChildren's Hospital, Helsinki University Central Hospital, Helsinki, Finland; ^bLaboratory of Women's Clinic, HUSLAB, Helsinki, Finland; ^cNovo Nordisk Farma Oy, Espoo, Finland; ^dDepartment of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden

Background: Obesity has in males been associated with reduced testosterone levels during and after puberty. However, the onset and progress of puberty into fertility in obese boys remain inadequately evaluated. **Objective and hypotheses:** We aimed to study testicular function at the end of pubertal development (15–24 years) in males with severe childhood-onset obesity (height-adjusted relative weight exceeding 160% before the age of 7 years). **Method:** Fasting blood samples were analyzed for testosterone and several parameters characterizing pituitary function, adipose tissue, skeleton, and insulin resistance. Findings were compared with results in normal-weight age-matched control males. Results are expressed as median (range) and statistical analyses were performed with Mann-Whitney *U*-test and Kendall's rank correlation test. **Results:** BMI was 36.7 (26.3–62.1) kg/m² in obese subjects ($n=20$) in comparison to 22.1 (16.6–24.95) kg/m² in control subjects ($n=17$, $P<0.001$). Obese subjects had lower serum free testosterone levels than control subjects (pmol/l; 232 (111–505) vs 418 (118–720), $P=0.002$). Levels of serum LH, FSH, and estradiol did not differ between the groups. In the obese subjects, serum free testosterone level correlated positively with serum luteinizing hormone ($\tau=0.52$, $P=0.003$), and negatively with BMI ($\tau=-0.42$, $P=0.009$), serum leptin ($\tau=-0.51$, $P=0.002$), and fasting plasma insulin ($\tau=-0.49$, $P=0.007$). In the control group, testosterone level correlated positively with serum estradiol level ($\tau=0.42$, $P=0.02$). Serum free testosterone did not correlate with age, serum FSH level, serum anti-Müllerian hormone level or serum hydroxyvitamin D level in either group. **Conclusion:** Young men with childhood-onset obesity have lower testosterone levels than their normal-weight peers. The degree of testosterone reduction increased with increasing severity of obesity. Our findings indicate that severe childhood-onset obesity significantly impacts testicular function.

P2-D2-380**A New Case of Proopiomelanocortin Deficiency**

Noemi Auxiliadora Fuentes-Bolaños^a, Francisco Jose Tinahones Madueño^c, Luis Castaño González^d, Isabel Leiva Gea^b, Maria Jose Martínez-Aedo Ollero^b, Juan Pedro Lopez-Siguero^b

^aHospital Materno Infantil, Badajoz, Spain; ^bHospital Regional Universitario de Málaga, Malaga, Spain; ^cHospital Universitario Virgen de la Victoria, Malaga, Spain; ^dHospital de Cruces, Vizcaya, Spain

Introduction: The proopiomelanocortin is a polypeptide of many biologically active peptides involved in many key functions which have not yet been clarified. The mutation in the gene encoding this polypeptide is associated with a clinical trials characterized by early-onset obesity, tertiary adrenal insufficiency, and alteration of pigmentation. Eight cases with known genetic mutation have been published. **Case report:** Newborn male 27 days old from North African, was admitted because hypoglycemia since the fifth day of life. The red hair and pale skin was noted on physical examination. The results of the

biochemical analysis: TSH and free T_4 and electrolytes were normal. In the other hand: ACTH <5 pg/ml, 0.4 µg/dl cortisol, DHEAS <1 ng/ml, and plasma renin activity (PRA) 3.40 ng/ml per h (n : 0.2–3.3 ng/ml per h). Imaging MRI was normal. The glycemic profile was normalized after starting treatment with hydrocortisone and fludrocortisone. Genetics analysis revealed a novel homozygous mutation in the POMC gene, in exon 3. In the evolution presented increased appetite with significant weight gain at 2 years (BMI +6.66DS). Psychomotor development was accorded to the age. **Conclusions:** We describe a new case of complete loss-of-function mutations of the POMC gene, manifested by the triad features of early obesity, hypocortisolism and pigmentation problems, despite not belonging to Caucasian ethnicity. A new mutation of the POMC gene is described. The analysis of the clinical characteristics of the patient can help the better understanding of the functions of these peptides, such as the leptin-melanocortin system, which could help in the understanding of obesity and possible therapeutic avenues.

P2-D2-381

Neuroendocrine and Psychological Status in Obese Children

Anzhalka Solntsava^a, Olga Zagrebaeva^a, Tatsiana Yemelyantsava^b, Hanna Mikhno^a, Helena Dashkevich^c, Yuliya Tkachova^d

^aBelarusian State Medical University, Minsk, Belarus; ^bRepublican Research and Practice Center for Mental Health, Minsk, Belarus; ^c10th State Clinic, Minsk, Belarus; ^d8th State Paediatric Outpatient Clinic, Minsk, Belarus

Background: Emotional disorders are serious complications in obese children. Dopamine is known to be one of the neurotransmitters, which is in charge of such conditions. **Aim:** To determine neuroendocrine and psychological status in obese children. **Methods:** We examined 296 children in the Endocrinological Department of University Hospital (Minsk); group 1 – 206 obese children (simple obesity: 14.35 ± 2 years; BMI 30.8 ± 2.5 kg/m², morbid: 15.6 ± 1.6 years; and BMI 39.7 ± 4.3 kg/m²), group 2 – 90 normal-weight controls (BMI 20.5 ± 1.47 kg/m² ($P=0.0001$), 14.5 ± 1.5 years ($P=0.6$)). We examined patient's levels of plasma dopamine (D); all children and parents underwent psychological testing: Children Eating Disorder Examination Questionnaire (ChEDE-Q), Depression Self-Rating Scale (DSRS), and Child Behavior checklist (CBCL). **Results:** The reliable increasing of D levels were noted in all children with obesity in comparison with normal-weight controls (median (Me) D in simple obesity 12.1 ng/ml; morbid 61.1 ng/ml; and control 5.96 ng/ml) (($ps-c=0.012$), ($pm-c=0.0001$), and ($pm-s=0.009$)). The reliable differences on CBCL testing were in obese children vs controls – anxious and depressive scale ($P=0.002$), impulsiveness scale ($P=0.009$), estrangement scale ($P=0.0001$), and attention deficiency scale ($P=0.001$). The frequency of depressive disorders were in 18.1% obese children. The severity of depressive symptoms didn't correlate with BMI. Clinical depression correlated with

compulsive symptoms severity ($P=0.02$). Binge eating (BE) disorders were diagnosed in 20% obese ($P=0.016$). The reliable difference between BE and age, gender, and BMI didn't noted ($P=0.3-0.06$). We can say with the probability of 99% ($P=0.002$ and 0.004) that compulsive mechanisms of BE in obese children are determined with the presence of emotional disorders (anxious and depressive symptoms and estrangement). **Conclusions:** The increase in the frequency of psychological and behavioral disorders were noted in all obese children comparison with normal-weight control. The reliable excess of D levels in obese children can show violations in binding to the dopamine receptors and impaired utilization.

P2-D2-382

Is 24-h Blood Pressure Monitoring Necessary in Obese Children and Adolescents?

Malgorzata Wojcik, Jadwiga Malek, Dominika Janus, Anna Kalicka-Kasperczyk, Katarzyna Tyrawa, Jerzy B Starzyk

Department of Pediatric and Adolescent Endocrinology, Medical College, Jagiellonian University, Krakow, Poland

Background: Arterial hypertension (AH) is one of the most common and the earliest complications of childhood obesity. It is diagnosed on the basis of at least three results of the standard setting measurements of systolic (SBP) and diastolic (DBP) blood pressure. Nevertheless, some data suggest, that this diagnostic standard may be not sufficient for obese children, because some BP abnormalities, unique for these patients, (decrease of night dip, elevated SBP/DBP load) cannot be recognized on the basis of the standard AH definition. Therefore an alternative, supplementary diagnostic method is needed. **Objective and hypotheses:** Assessment of the usefulness of ABPM in the diagnosis of BP disorders in obese children and adolescents with (47) or without (83) previously diagnosed AH. **Method:** In 130 (58 boys) obese (mean BMI SDS 4.54, 95% CI 4.2–4.8) patients at the mean age of 13.3 years (95% CI 12.8–13.7), standard blood pressure measurements and ABPM (BP Monitor Spacelabs 90217, USA) were performed. **Results:** Out of 47 patients (36%) diagnosed with AH 29 (22%) and 5 (3.6%) presented with isolated SBP and DBP AH respectively. In 92 (70.8%) patients the results of ABPM were abnormal, however only 35 (26.9%) were previously diagnosed with HA. Elevated (>2.0 s.d.) 24-h mean arterial BP was diagnosed in 7 (5.4%) patients, and only in three with AH. An elevated SBP and DBP load were observed in 39 (16%) and 19 (14.6%) patients respectively; only 20 and ten respectively met criteria for AH. The decrease (<10%) of the night time dip was present in 69 (53%) of the patients, and only 20 of them were diagnosed with AH. **Conclusion:** The majority of obese children and adolescents have an abnormal BP profile, that can be not recognized on the basis of the standard setting BP measurements. Therefore ABPM should be considered as a supplementary method in the diagnosis AH in obese pediatric patients.

P2-D2-383**Fetuin A Serum Levels in Children with Nonalcoholic Fatty Liver Disease**

Valentina Pampanini^a, Elena Inzaghi^a, Valerio Nobili^b, Daniela Germani^a, Antonella Puglianiello^a, Stefano Cianfarani^{c,d}

^aTor Vergata' University, Rome, Italy; ^bHepato-Metabolic Disease Unit 'Bambino Gesù' Children's Hospital, Rome, Italy; ^cD.P.U.O. 'Bambino Gesù' Children's Hospital, 'Tor Vergata' University, Rome, Italy; ^dDepartment of Women's and Children's Health, Karolinska Institute, Stockholm, Sweden

Background: Fetuin A is a hepatokine known as a natural inhibitor of the insulin receptor tyrosine kinase and is associated with insulin resistance and nonalcoholic fatty liver disease (NAFLD). Studies on adults provided conflicting results regarding the link between fetuin A and the severity of liver damage in NAFLD. Data on children are limited. **Objective:** To investigate the relationship between fetuin A, metabolic parameters, and NAFLD in obese children. **Methods:** 118 obese subjects (48F/70M), aged 9.3 ± 2.4 years, were studied. Anthropometry, OGTT, biochemical measurements, and fetuin A serum levels were assessed. In 19 children the presence of NAFLD was investigated by ultrasonography (US). 7/19 children had a normal liver US (group 1), whereas 12/19 were diagnosed as NAFLD (group 2). Ninety-nine children underwent liver biopsy to assess the presence of NASH: 14 were diagnosed as 'NASH' (group 3) and 85 as 'not NASH' (group 4). Differences between groups were assessed by Mann-Whitney *U*-test. **Results:** Fetuin A levels were related to age ($r=0.25$, $P<0.01$), waist circumference (WC) ($r=0.2$, $P<0.05$) systolic blood pressure ($r=0.2$, $P<0.05$), apolipoprotein B ($r=0.275$, $P<0.01$), fasting plasma glucose ($r=0.2$, $P<0.05$) and insulin levels ($r=0.3$, $P<0.005$), OGTT mean insulin ($r=0.26$, $P<0.05$), 2 h postload insulin ($r=0.26$, $P<0.01$), HOMA-IR ($r=0.3$, $P<0.01$), and ISI ($r=-0.3$, $P<0.01$). Stepwise regression analysis revealed that among age, BMI SDS and WC, fetuin A was the major predictors of 2 h postload insulin levels (adj R^2 0.105). Group 2 tended to have significantly higher levels of fetuin A (723.2 ± 102.6 $\mu\text{g/ml}$) than group 1 (641.1 ± 81.4 $\mu\text{g/ml}$) ($P=0.056$). No significant differences between groups were found in age and BMI. Among children who underwent liver biopsy no significant difference between groups 3 and 4 was found in fetuin A serum levels. **Conclusion:** Fetuin A may represent a biomarker of NAFLD in obese children, though not related to the severity of the disease.

P2-D2-384**Ambulatory Arterial Stiffness Index in Obese Children**

Christoph Saner^a, Primus Mullis^a, Giacomo Simonetti^b, Marco Janner^a

^aDepartment of Pediatric Endocrinology, University Hospital, Bern, Switzerland; ^bDepartment of Pediatric Nephrology, University Hospital, Bern, Switzerland

Background: Altered arterial stiffness is a recognized risk factor of poor cardiovascular health. Ambulatory arterial stiffness index (AASI, defined as one minus the regression slope of diastolic on systolic blood pressure values derived from a 24 h arterial blood pressure monitoring (ABPM)) is an upcoming and readily available marker of arterial stiffness. We tested the hypothesis that AASI is increased in obese children compared to healthy subjects. **Method:** AASI was calculated from ABPM in 101 obese children, 45% girls (BMI-SDS median 2.9 (interquartile range (IQR) 2.4 to 3.8), median age 11.5 years (IQR 9.0 to 13.4) and compared with an age- and gender-matched healthy control group of 71 subjects (49% girls) with BMI-SDS median 0.0 (IQR -0.75 to 0.5), and median age 12 years (IQR 10.0 to 14.0). Multivariate regression analysis was applied to identify significant independent factors explaining AASI variability in this population. **Results:** AASI was significantly higher in obese children compared to the controls (0.388 (IQR 0.253 to 0.499) vs 0.190 (0.070 to 0.320), $P<0.0001$), whereas blood pressure values were similar ($P=0.18$). In a multivariate analysis including obese children only, AASI was independently predicted by BMI and daytime systolic blood pressure ($P=0.04$); and in a multivariate analysis including obese children and controls BMI and pulse pressure independently influenced AASI ($P<0.001$). **Conclusion:** This study demonstrated increased AASI, a surrogate marker of arterial stiffness, in obese children. AASI seems to be influenced by BMI independently to blood pressure values, suggesting that other factors are involved in increased arterial stiffness in obese children.

P2-D2-385**Evaluation of the Risk of Dyslipidemia in Adolescents with Obesity**

Jurgita Gailite^{a,b}, Urzula Nora Urbane^{a,b}, Ieva Strele^a, Renars Erts^a, Una Lauga-Tunina^b, Inara Kirillova^b, Dace Gardovska^{a,b}, Iveta Dzivite-Krisane^{a,b}

^aRiga Stradin's University, Riga, Latvia; ^bChildren's Clinical University Hospital, Riga, Latvia

Introduction: Abnormal levels of lipids and lipoproteins are recognized as a prominent cardiovascular risk factor associated with increased morbidity and mortality. In many studies childhood obesity has been shown to be associated with increased levels of total cholesterol (TH), triglycerides (TG), LDL-cholesterol, and decreased levels of HDL-cholesterol. **Objective:** The aim of this study was to evaluate the risk of dyslipidemia (abnormal levels of all of TH, TG, LDL, and HDL-cholesterol) in adolescents with obesity. **Material and methods:** The study included 272 adolescents aged 11-18 who visited a pediatric endocrinologist as outpatients. All participants filled out a survey, underwent physical examination and had their blood lipid profile taken. The probability of dyslipidemia (abnormal levels of all components of lipid profile) was determined by using logistic regression. **Results:** The study included 148 (54.4%) girls and 124 boys (45.6%).

The average age of adolescents was 15.6 ± 1.2 years, the average weight was 102.9 ± 16.3 kg, and the average waist circumference was 110.0 ± 14.2 cm. All four lipid components were abnormal in 35 adolescents (12.9%). The results showed that adolescents with weight 100 kg or more had increased risk of dyslipidemia (ExpB (95% CI)=5.74 (2.01–16.4); $P=0.001$), other factors used in the study (waist circumference 110 cm or more, smoking, family history of myocardial infarction or diabetes mellitus) did not show a statistically significant impact on the risk of dyslipidemia ($P>0.05$). **Conclusion:** The study showed that the risk of dyslipidemia was 5.74 times higher in adolescents with weight 100 kg or more. Other factors had no significant impact on the risk of dyslipidemia.

P2-D3-386

Miglitol Upregulates Uncoupling Protein 1 (ucp1) by Enhancing β 3-Adrenergic Signaling in Mature Brown Adipocytes of Rat

Satoru Sugimoto, Hisakazu Nakajima, Taichiro Nishikawa Nishikawa, Kazuki Kodo, Ikuyo Itoh, Kitaro Kosaka, Hajime Hosoi

Department of Pediatrics, Kyoto Prefectural University of Medicine Graduate School of Medical Science, Kyoto, Japan

Introduction: We previously reported that miglitol, an alpha-glucosidase inhibitor (α -GI), increases energy expenditure by enhancing β 3-adrenergic signaling of brown adipose tissue (BAT) and reduces obesity in dietary-induced obese mice (S Sugimoto *et al*, at the 9th joint meeting of Pediatric Endocrinology, 2013) (*Nutrition & Metabolism*). However, this report did not describe the mechanism by which miglitol enhances β 3-adrenergic signaling. Miglitol, unlike other α -GIs, enters the circulation. We hypothesized that miglitol acts in the blood where it directly enhances β 3-adrenergic signaling. **Objective:** The purpose of this study was to determine whether miglitol has a direct effect on β 3-adrenergic signaling in mature brown adipocytes. **Methods:** We used a rat brown adipocyte culture kit (Takara, Japan). After the cells finished maturing, we added medium containing miglitol with or without β 3-adrenergic agonist CL316,243. After 24 h, the cells were harvested. The gene expressions of uncoupling of protein 1 (UCP1) and peroxisome proliferator-activated receptor gamma coactivator 1 α (PGC1 α) were analyzed by quantitative real-time PCR. **Results:** Miglitol at concentrations of 5–50 μ M had no effect on the gene expression of PGC1 α and UCP1 in the absence of CL316,243, but in the presence of CL316,243, it significantly increased the expression of both genes. **Conclusion:** Miglitol increased the sensitivity of β 3-adrenergic receptor in mature brown adipocytes. This suggests that, in our experiment, miglitol entered the circulation where it directly enhanced β 3-adrenergic signaling of BAT in mice.

P2-D3-387

Enhanced Liver Fibrosis Test in Obese Children with Ultrasound-Proven Steatosis

Krystyna Sztefko^b, Patrycja Szybowska^b, Malgorzata Wojcik^a, Jerzy B Starzyka

^aDepartment of Pediatric and Adolescent Endocrinology, Medical College, Jagiellonian University, Krakow, Poland; ^bDepartment of Clinical Biochemistry, Medical College, Jagiellonian University, PAIP, Krakow, Poland

Background: Non-alcoholic fatty liver disease (NAFLD) in obese children is a diagnostic challenge. Presently recommended markers of liver steatosis and risk of progression to fibrosis are: ultrasound imaging (US) and liver aminotransferases (ALT and AST). Owing to the poor sensitivity of these tests, there is a need to search for biomarkers which could indicate early stages of NAFLD. The enhanced liver fibrosis test (ELF) based on the combination of serum concentration of hyaluronic acid (HA), aminoterminal propeptide of type III procollagen (PIIINP), tissue inhibitor of matrix metalloproteinase type 1 (TIMP-1) was developed as a noninvasive diagnostic tool for estimation of degree of liver fibrosis. **Objective and hypotheses:** The aim of our study was to investigate the performance of ELF in obese children. **Method:** Based on the abdominal US results two groups of obese children were studied: GI ($n=22$, 8/13 M/F, mean age 14.4 ± 0.41 years) with steatosis and GII ($n=40$, 20/20 M/F, mean age 13.7 ± 0.46 years) with normal US. HA, PIIINP, and TIMP-1 levels were measured and ELF results were calculated. FIB4 score was calculated based on platelets counts, age, AST and ALT according to formula: $\text{age} \times \text{AST} / \text{PLT} \times (\text{ALT})^{1/2}$. Standard oral glucose tolerance test with the assessment of glucose and insulin level was performed. **Results:** The ELF were higher in GI (9.0 ± 0.15 vs 8.48 ± 0.09 , $P<0.005$). The mean values of HA, PIIINP, TIMP1, and FIB4 score were also higher in GI, significantly for HA (19.6 ± 2.73 vs 12.0 ± 0.95) and TIMP-1 (251.1 ± 8.44 vs 220.0 ± 6.15 , $P<0.005$). There was a correlation between ELF and insulin level 120' after glucose load ($R=0.4$, $P<0.05$), but no correlation with fasting insulin or glucose level, HOMA nor Matsuda indices, aminotransferases, FIB4, age, and BMI. **Conclusion:** ELF test cannot be used as a single biochemical component for assessing of NAFLD, but can be useful as its predictor. To assess its relationship with insulin resistance parameters further investigations are needed.

P2-D3-388

Metformin Treatment in Obese Children Enhances Weight Loss Related Improvement in Impaired Glucose Tolerance

Andrea Bartucci^c, Gabriel Á. Martos-Moreno^{a,b}, Vicente Barrios^{c,b}, Jesús Argente^{a,b}

^aHospital Infantil Universitario Niño Jesús, Endocrinology Dept. IIS La Princesa, Universidad Autónoma de Madrid; Pediatrics Dept., Madrid, Spain; ^bInstituto de Salud Carlos III, CIBER Fisiopatología

Background: Impaired glucose tolerance ((IGT), glucose ≥ 140 mg/dl at 120' in the oral-glucose-tolerance-test (OGTT)) is prevalent in childhood obesity. It is frequently reversed after weight loss, although an eventual role for metformin treatment has been postulated. **Objective:** To evaluate the benefits of metformin addition to conservative treatment on weight loss and IGT in obese children. **Patients and methods:** We studied 87 obese (BMI $> +2$ SDS) children (mean 11.20 ± 2.63 years; 46% females/54% males) with IGT, at diagnosis and after 1 year follow-up with (MET, $n=40$) or without (No-MET, $n=47$) metformin added to conservative treatment. Anthropometric and biochemical features including fasting and post-OGTT surrogate indexes of insulin resistance (IR): HOMA; insulinogenic-index and the area under the curve (AUC) for glucose and insulin were analyzed. **Results:** At baseline MET group showed higher age (12.16 ± 1.81 vs 10.37 ± 2.93 years, $P < 0.001$), raw, but not standardized, BMI (31.00 ± 5.25 vs 27.36 ± 3.20 kg/m², $P < 0.05$) and both fasting (HOMA: 5.81 ± 5.58 vs 3.67 ± 1.98 ; $P < 0.05$) and post-OGTT IR (insulin-AUC: 309.46 ± 200.78 vs 214.01 ± 110.06 mcU/ml, $P < 0.01$). At 1-Year, the drop-out rate was 15% in MET (34/40 patients remaining, 6 (15%) still with IGT) and 42.6% (27/47 remaining, 3 (15%) still with IGT) in No-MET ($P < 0.01$). Both groups reduced their BMI-SDS significantly ($P < 0.001$) in a similar fashion (BMI-SDS reduction: MET: -1.11 ± 0.86 vs No-MET: -0.85 ± 1.00 SDS) although a higher rate of 'intense weight losers' (> 1 BMI-SDS from baseline) was observed in the MET group (21/34 vs 9/27; $P < 0.05$). Both groups significantly reduced their post-OGTT insulin secretion at 1-Year ($P < 0.001$), with a more intense decrease in the insulin-AUC and insulinogenic-index (both $P < 0.05$) in MET. However, only MET group improved fasting IR after 1 year (HOMA 1-Year: 3.30 ± 1.21 vs 5.09 ± 3.42 at baseline, $P < 0.01$). **Conclusion:** Weight loss is effective in resolving obesity-associated IGT and can be enhanced by the addition of metformin treatment, with further improvement of fasting IR.

P2-D3-389

Type and Time of Feeding in the First Year of Life are Not Associated to Circulating Multimeric Adiponectin Levels in Obese Children

Simonetta Bellone^a, Flavia Prodam^{a,b}, Letizia Trovato^a, Marta Roccio^a, Agostina Marolda^a, Cristina Fiorito^a, Enza Giglione^a, Gianni Bona^a

^aDivision of Pediatrics, University of Piemonte Orientale, Novara, Italy; ^bEndocrinology, University of Piemonte Orientale, Novara, Italy

Background: Nutrition and growth in the postnatal phase seems to have an important role for the future risk of obesity,

type 2 diabetes, and cardiovascular diseases. It has been suggested that circulating levels of adiponectin in the first 2 years of life are influenced by type of feeding in small for gestational age. **Objective and hypotheses:** Aim of our study was to evaluate if total and multimeric adiponectin levels in obese adequate for gestational age (AGA) children could be influenced by type and time of feeding in the first year of life. **Method:** 112 obese children and adolescent (BMI classification by IOFT), born AGA, underwent a clinical and metabolic evaluation, included OGTT. They have been divided in three groups based on type of feeding in the first year of life: group 1 (prolonged breastfeeding, > 6 months; 41 subjects); group 2 short breastfeeding, 2–6 months; 37 subjects); group 3 (formula feeding since the first 15 days of life; 35 subjects). Total, high (HMV) and medium (MMV) molecular weight adiponectin levels have been measured. **Results:** Auxological parameters were similar among the three groups. Nor metabolic differences nor differences in circulating levels of different adiponectin isoforms have been found, not even when data are corrected by sex and pubertal stage. Instead, HMV adiponectin levels were differently distributed by sex and pubertal stage, being lower in males compared to females starting from puberty, independently by BMI-SDS ($P < 0.02$). Total, HMV and MMV adiponectin levels did not correlate to clinical parameters at birth, time of feeding or weaning. **Conclusion:** In pediatric obesity adiponectin secretion seems not to be influenced by type of feeding in the first year of life, while demonstrate a different regulation by sex and puberty. Other nutritional factors in the short period could have a role in adiponectin regulation and should be investigated.

P2-D3-390

POMC Deficiency Mimicking Neurometabolic Disease

Samim Ozen^a, Nurhan Ozcan^a, Sema Kalkan Ucar^b, Damla Goksen^a, Sukran Darcan^a

^aDepartment of Pediatric Endocrinology, School of Medicine, Ege University, Izmir, Turkey; ^bDepartment of Pediatric Metabolism, School of Medicine, Ege University, Izmir, Turkey

Background: Proopiomelanocortin (POMC) deficiency is characterized by severe, early-onset hyperphagic obesity and congenital adrenal insufficiency, the latter secondary to ACTH deficiency. **Case:** 3.5 years old female patient whose initial diagnosis was neurometabolic disease because of motor mental retardation, ataxia, and bilateral hyperintense lesions in the basal ganglia in magnetic resonance imaging, increased lactate-lipid peak in proton magnetic resonance spectroscopy was consulted due to rapid weight gain, obesity, and episodes of hypoglycemia at the time of infection. Birth weight: 3100 g, her parents are first degree cousins. She has gained weight since she was 5.5 months. She had been treated because of neonatal cholestasis and hypoglycemic seizures in the neonatal period and gastroenteritis when she was 2.5 years old. Physical examination; weight, height, BMI were: 26 kg (SDS: 5.6), 110 cm (SDS: 2.6), and 21.5 kg/m² (SDS: 3.1) respectively. Her hair color was red. Serum electrolyte,

glucose, insulin, lipid, fT_4 , and TSH levels were normal. Metabolic tests (aminoacids, carnitine profiles, lactate, ammonia levels, and urinary organic acids analysis) were normal. Morning ACTH levels were <10 pg/ml (n : 10–60), cortisol levels were 0.01 μ g/dl (n : 7–29). Maximum serum ACTH level was 15 pg/ml during the CRH test. Bilateral hyperintense lesions in the basal ganglia were detected in cranial MRI and an increased lactate-lipid peak was revealed by Proton magnetic resonance spectroscopy. Early-onset severe obesity, red hair and adrenal failure due to ACTH deficiency is observed in POMC deficiency, and molecular analysis was performed. A homozygous mutation (c.64delA/pMet22TrpfsX49) in POMC gene in the patient and heterozygous mutation in her parents were found. **Conclusion:** Severe motor mental retardation and cranial MRI pathology in patients with POMC deficiency haven't been reported previously in the literature. Bilateral hyperintense lesions in the basal ganglia and the increased lactate-lipid peak was thought to be the result of recurrent hypoglycemia.

P2-D3-391

The Relationship Between Weight-Related Anthropometric Parameters and Menarche in Norwegian Girls

Heiko Bratke^a, Bente Ellingsen Brannsether^d, Jörg Ålbmus^e, Robert Bjercknes^{b,c}, Pétur B Júlíusson^{b,c}

^aSection of Paediatrics, Department of Internal Medicine, Haugesund District Hospital, Haugesund, Norway; ^bSection of Paediatrics, Department of Clinical Medicine, University of Bergen, Bergen, Norway; ^cDepartment of Paediatrics, Haukeland University Hospital, Bergen, Norway; ^dDepartment of Paediatrics, Stavanger University Hospital, Stavanger, Norway; ^eCentre for Clinical Research, Haukeland University Hospital, Bergen, Norway

Aim: A decline in the age at menarche has been reported in recent years in several well-off populations. The prevalence of childhood overweight and obesity has increased during the last decades with some levelling off during the last years. The aim of the present study was to study the association between parameters of overweight and menarche in Norway. **Material:** Cross-sectional data from The Bergen Growth Study, collected in 2003–2006 from 4016 girls aged 0–19 years, were analysed. **Results:** The mean age at menarche in the study population was 13.2 years. Girls with overweight (International Obesity Task Force definitions) had menarche at a mean age of 12.7 years, those with obesity at a mean age of 11.5 years. Analysis of subscapular skinfold thickness (SSF), triceps skinfold thickness (TSF), and waist circumference (WC) did show similar negative correlation, with SSF showing the strongest correlation (-0.38). The relatively low number of individuals with overweight or obesity did not influence the mean age at menarche in the whole group compared to non-overweight, non-obese girls. **Conclusions:** Different overweight-related anthropometric traits showed a strong negative correlation with

age at menarche. Mean age at menarche might be affected in populations with high prevalence of overweight and obesity.

P2-D3-392

HbA1c and Metabolic Parameters in a Pediatric Overweight/Obese Population

Maria Chiara Pellegrin^a, Andrea Grillo^a, Elena Faleschini^b, Gianluca Tornese^b, Alessandro Ventura^{a,b}

^aUniversity of Trieste, Trieste, Italy; ^bInstitute for Maternal and Child Health – IRCCS 'Burlo Garofolo', Trieste, Italy

Background: HbA1c was recommended as diagnostic tool in adults at risk for diabetes. In obese patients, HbA1c shows an association even with other features of metabolic syndrome. However, its value in pediatric population for this purpose has yet to be established. **Material and methods:** We determined HbA1c (IFCC method) in 307 overweight/obese children and adolescents (age 11.4 ± 3.2 ; range 3.0–17.9 and BMI 27.9 ± 4.7 ; range 20.4–47.6) evaluated in our Pediatric Endocrinology Unit from July 2011 to March 2013. Considering ADA guidelines, HbA1c between 39–47 mmol/mol would indicate the presence of impaired hyperglycaemia, responsible for an increased risk of diabetes, while levels above 47 mmol/mol would indicate diabetes. The aim of this study is to analyze the diagnostic power of HbA1c in detecting prediabetes and to establish the relationship between HbA1c and other features or co-morbidity of metabolic syndrome (BMI, lipid values, hypertension, insulinemia, liver steatosis). **Results:** Sensibility and specificity in detecting prediabetes for HbA1c cutoff of 39 mmol/mol were respectively 52.6 and 67.0%. In multivariate analysis, HbA1c showed a significant relationship with BMI ($r=0.173$, $P=0.002$), triglycerides ($r=0.133$, $P=0.02$), glycemia after OGTT ($r=0.111$, $P=0.05$), insulin levels after OGTT ($r=0.157$, $P=0.007$). No relationship was found regarding hypertension and steatosis. **Conclusion:** Using 39 mmol/mol as cutoff value, HbA1c showed a poor diagnostic power for prediabetes in a pediatric overweight and obese population. Given its continuous association with glycemic values after OGTT and with metabolic syndrome features (triglycerides, BMI, insulinemia), HbA1c could be a useful and rapid tool in layering risk for metabolic syndrome in overweight/obese children, although the threshold levels and the prognostic value for HbA1c in this population have yet to be confirmed.

P2-D3-393

Comparison of FM_{DXA} and FM_{BIA} in Obese Adolescents

Julian Ziegler, Roland Schweizer, Gerhard Binder

Paediatric Endocrinology, University Children's Hospital, Tübingen, Germany

Background: Determining fat mass (FM) using methods of body composition analysis is useful in diagnosis and treatment of obese adolescents who undergo life style intervention. The use of dual-energy X-ray absorption (DXA) is time-consuming, potentially harmful and expensive. Alternative methods for accurately estimating FM are needed. **Objective and hypotheses:** We evaluated single-frequency arm-to-leg bioelectrical impedance analysis at 50 kHz (sf-BIA) in combination with anthropometry for estimating FM in obese adolescents. **Method:** 251 obese adolescents (102 males, aged 11.1–19.9 years and 142 females aged, 9.0–25.8 years) were recruited. Height, weight, sf-BIA resistance (R) and reactance (Xc) were measured. FM was measured by DXA. Using linear regression analysis equations for FM were separately determined for both sexes. **Results:** Using BIA and anthropometry for estimation of FM we found an acceptable correlation to FM measured by DXA. Linear regression analysis provides the following equations:

$FM (kg) = -347.7 \times ht (cm) + 712.1 \times wt (kg) - 63.20 \times R (\Omega) - 196.1 \times Xc (\Omega) + 11\,127$ (male; $r^2 = 0.87$) and $FM (kg) = -158.2 \times ht (cm) + 695.1 \times wt (kg) + 27.86 \times R (\Omega) - 7745$ (female; $r^2 = 0.96$).

The differences between individual estimated and measured FM ranged from -7.7 to $+7.9$ kg in male adolescents and from -4.8 to $+4.8$ kg in female adolescents. The influence of R and Xc in both equations was low. **Conclusion:** Single-frequency BIA analysis is not adequate to accurately estimate FM in obese adolescents. It may have a value for longitudinal monitoring.

healthcare centres of two districts in the area of Barcelona. The score was calculated adding the punctuation obtained in three sections: i) family background (4–27 points) (social, job state, career education, toxic habits, and obesity in parents), ii) prenatal (1–7 points) (ponderal gain and complications during pregnancy), and iii) neonatal (1–4) determinants (birthweight adjusted for sex and gestational age). The highest score possible is 38 points, meaning higher risk of obesity in the future and the lowest six points. The patients are planned to be followed in clinics ten times over the 4 years of life and will be divided at random into two groups: one receiving usual care advices and the other receiving gradually additional information about a healthy lifestyle to prevent obesity. **Preliminary results:** A total of 96 healthy newborns have been already recruited (59.8% male) during a period of 6 months with a birthweight mean of 3323 gr (± 0.416). The total mean score was 11.4 (± 3.4) and if we consider the different sections of the score the results expressed by mean \pm S.E.M. are: family background 8.7 (± 3.1), prenatal factors 2.2 (± 0.08) and, neonatal factors 0.6 (± 0.1). In this sample there was no association found between the total score either the Family Background section and birthweight. **Conclusion:** This study is the first relating a new score with birthweight, pointing that infantile obesity is not programmed at birth, but is built during the firsts years of life. So on, following up these children and offering some interventions will help us to better understand the origins of this new pandemic.

P2-D3-394

From the Need of Preventing Infantile Obesity as soon as Possible: a New Score at Birth

Nuria Sanz^a, M Jesus Asencio^c, Angeles Buj^c, Corpus Marzo^d, Juan Manuel Rodriguez^d, Consol Sanchez^b, Lourdes Ibañez^a, Maria Victoria Marcos^b

^aHospital Sant Joan de Deu, Barcelona, Spain; ^bHospital de Terrassa, Terrassa, Spain; ^cCAP Sant Llatzer, Terrassa, Spain; ^dCAP Creu Alta, Sabadell, Spain

Background: Infantile obesity is nowadays a pandemic disease and needs a paediatrician interventional attitude. Since 1990 until 2010 it has trebled and the World Health Organization recommends prevention 'as soon as possible' even during the first year of life. A Spanish study (Aladino 2011) stimated the prevalence of overweight in boys as a 26.3% and in girls a 25.9% and the prevalence of obesity as a 22% and a 16.2% respectively. Our aim was to set up a new score to be applied to the newborn at birth, calculating risk of obesity, and to be correlated with the obesity/overweight future outcomes. There is not a precedent of using this kind of tool in the Spanish population. Our hypothesis is that the child's background can predict obesity during infancy and consequently adulthood. **Patients and methods:** The study population consisted of healthy newborns recruited at two

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Body Composition in 10–15 Years Old Children Exposed to Pesticides Prenatally

Jeanette Tinggaard^a, Christine Wohlfahrt-Veje^a, Ida M Schmidt^a, Malene Boas^a, Steffen Husby^b, Katharina M Main^a, Niels E Skakkebaek^a, Tina K Jensen^{a,c}, Helle R Andersen^c

^aDepartment of Growth and Reproduction, University Hospital of Copenhagen, Rigshospitalet, Copenhagen, Denmark;

^bHans Christian Andersen Children's Hospital, University of Southern Denmark, Odense, Denmark; ^cInstitute of Public Health, University of Southern Denmark, Odense, Denmark

Background: Exposure to non-persistent pesticides may have an effect on prenatal growth and later risk of adiposity. Prenatal pesticide exposure has been found to be associated with lower birth weight and higher body fat percentage calculated from skinfolds at age 6–11 years. Body composition measured by using DXA in children prenatally exposed to pesticides has not previously been reported. **Objective and hypotheses:** To study the effects of prenatal pesticide exposure on body composition measured by DXA in children. We hypothesize that prenatal exposure to pesticides predispose to childhood adiposity. **Method:** A prospective study including 247 children born by female greenhouse workers. The children were examined at 3 months ($N=203$), 6–11 years ($N=177$), and 10–15 years of age ($N=163$).

The examination included anthropometry, skinfold measurements, pubertal staging, urine, and blood sampling. Whole body DXA scan was performed in 160 of 163 children at age 10–15 years. **Results:** Children exposed to pesticides had significantly lower birth weight and weight for gestational age ($P=0.032$ and $P=0.038$ respectively). At age 10–15 years the following parameters were significantly higher in exposed children compared to unexposed children, irrespective of gender: BMI SDS, increase in BMI SDS from birth, waist circumference, skinfold measurements, total body fat percentage (calculated from skinfold measurements using Slaughter equation and by DXA), and android and gynoid fat percentages (DXA). Total body fat SDS (DXA) was 0.46 s.d. higher in exposed than unexposed children when adjusting for maternal smoking during pregnancy, puberty and socioeconomic status. **Conclusion:** Prenatal pesticide exposure was associated with reduced prenatal growth followed by increased childhood adiposity measured by skinfolds and DXA.

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D2 Dopamine Receptor Agonists Influence in the Animal Model of Dietary Obesity

Liudmila Viazava^a, Anzhaliika Solntsava^a, Alexander Sukalo^a, Elena Dashkevich^b, Yuliya Stukach^c

^aBelarusian State Medical University, Minsk, Belarus; ^bMinsk Clinical Hospital Number 10, Minsk, Belarus; ^cInstitute of Physiology, National Academy of Sciences, Minsk, Belarus

Background: Increased caloric intake in dietary obesity (DO) can be driven by central mechanisms regulating reward-seeking behavior. Leptin modulates the mesolimbic dopamine system and *vice versa*. **Objective and hypotheses:** We supposed D2 dopamine receptor agonists to influence weight gain and leptin level in genetically unmodified rats (GUR) with high caloric diet (HCD) as dietary obesity. **Method:** Male rats ($n=48$, 183.0 ± 14.0 g) were divided into HCD group ($n=24$) and control (C) ($n=24$, standard diet). HCD rats received daily i.p. injections of bromocriptine (Br) (1 mg/kg), dimethyl sulfoxide (vehicle, 1 ml/kg), and both ($n=8$, respectively) during 3 months. Length, weight, and caloric intake were registered twice a week. Both leptin levels (immunoenzyme analysis with standardization relatively to length/weight coefficient (LWC) and rodents' total mobility (TM, plus maze test) were detected at the first and third months. Nonparametric analysis was performed (SPSS 16.0, $P<0.05$). **Results:** HCD rats showed weight gain in first and third months irrespective to injected agent ($P<0.05$). Weight gain was similar in Br injected HCD rats and HCD group ($P>0.05$). TM had no changes in HCD group after 1 month whereas open arm visits significantly decreased in HCD one ($P<0.05$). TM diminished after 3 months compared to C rodents and to the same group after 1 month ($P>0.05$). Br injected HCD rats showed TM decrease

and closed arm time increase in 1 month relative to HDC group. These changes were leveled in 3 months. Leptin trended to decrease after 3 month of Br injections in HCD rats ($P>0.05$), but LWC reduced significantly ($P=0.028$) related to the HCD rodents. Leptin and LWC levels were extensively lower in Br injected HCD group at third month in regard to first month. **Conclusion:** We supposed long term bromocriptine injections to prevent obesity in HCD GUR.

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Combined Evaluation of Glucose Levels at Fasting State and 1-H After Glucose Load Can Safely Predict Prediabetes in Obese Youth

Eleni P Kotanidou, Ioannis Kyrgios, Assimina Galli-Tsinopoulou

4th Department of Pediatrics, Faculty of Medicine, Papageorgiou General Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece

Background: According to current literature 1-h glucose ≥ 155 mg/dl during an oral glucose tolerance test (OGTT) is considered an independent predictor of β -cell deterioration and future progression to prediabetes in obese individuals. **Objective and hypotheses:** To investigate whether determination of glucose level obtained 1-h after glucose load can improve predictive ability of prediabetes. **Method:** Ninety-eight overweight/obese youngsters aged 2.6–16.5 years were included for analysis. History taking, physical examination and an OGTT were performed. In order to predict prediabetes, defined as impaired fasting glucose and/or impaired glucose tolerance, four models were evaluated: i) a basic model including demographics (gender, pubertal stage, BMI percentile, ethnic origin, hypertension, hypercholesterolemia, acanthosis nigricans, history of gestational diabetes, parental family history of diabetes type 2 or obesity and birth weight below 5th percentile-for-gestational-age), ii) a second one combining the basic model plus measurement of fasting glucose, iii) a third one that compiled the basic model and the 1-h glucose level obtained during the OGTT, and iv) a fourth model that incorporated both fasting and 1-h glucose level into the basic model. **Results:** Prediabetes was diagnosed in 67/98 participants (69.4%). The basic model significantly contributed to prediction of prediabetes (area under the curve (AUC): 0.74, 95% CI: 0.636–0.851). The additional determination of fasting glucose or 1-h glucose level obtained during the OGTT also increased the predictive ability (AUC: 0.84, 95% CI: 0.75–0.92 and AUC: 0.80, 95% CI: 0.70–0.89 respectively). The fourth model, comprised of all previous parameters (basic model+fasting+1-h glucose), predicted prediabetes to even a further degree (AUC: 0.87, 95% CI: 0.8–0.94). **Conclusion:** The 1-h glucose appears to be a reliable parameter to detect prediabetes, especially in combination with demographic and clinical characteristics as well as fasting glucose levels.

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Association Between Calcium Deficiency and Obesity in Children

Hanna Mikhno^a, Anzhalka Solntsava^b, Olga Zagrebaeva^b, Katsiaryna Konchyts^b

^a2nd City Children Clinical Hospital, Minsk, Belarus; ^bThe 1st Children's Disease Department, Belorussian State Medical University, Minsk, Belarus

Background: Obesity is a worldwide pathological epidemic. Children and adolescents are a major concern in this trend. **Objective and hypotheses:** To identify the dynamics of body composition in children with alimentary obesity in puberty. **Methods:** 105 children with alimentary obesity with BMI over 30 kg/m² were examined. Anthropometric parameters (height, weight, waist, and hip circumference (WC, CH)), BMI, biochemical parameters (Ca²⁺, Mg²⁺, and P) were analyzed. Bone mineral density (BMD) were measured by dual X-ray absorptiometry (DXA). Depending on the stage of puberty two groups were identified: first group – with early puberty (2–3 Tanner stage) (boys/girls=28/36, age 13.4±0.9, and 12.6±0.4 years); and second group – with late puberty (4–5 Tanner stage) (boys/girls=21/15, age 16.4±0.5, and 14.2±0.8 years). **Results:** An increase of BMI in puberty: in first group was 33.3±0.8 kg/m² in boys and 32.7±0.9 kg/m² in girls; 36.5±0.9 and 35.3±0.5 kg/m² respectively, in second group ($P<0.05$). Body weight was 89.5±3.9 kg for boys and 73.3±2.5 kg for girls in first group, 110.9±2.1 kg and 88.4±3.5 kg respectively, in second group ($P<0.05$). Levels of ionized calcium, 1.04±0.03 mmol/l and ionized magnesium 0.41±0.01 mmol/l in first group in boys were decreased, levels of phosphorus were within normal range 1.4±0.07 mmol/l. Indicators of BMD in first group were 1.22±0.03² in boys and 1.03±0.04 g/cm² in girls, 1.44±0.02 g/cm² and 0.86±0.15 g/cm² respectively, in second group ($P<0.05$). Age and sex differences in Z-scores were not observed ($P<0.05$). In the second group the percentage of fat decreased with increasing lean mass in boys; total fat mass, free fat increased in girls ($P>0.05$). **Conclusion:** Calcium deficiency is common among obese children and adolescents. Low calcium levels in obese individuals may accelerate the development of metabolic syndrome.

P2-D3-399

Is Small for Gestational Age Status Associated with an Increase Risk of Atherogenesis?

Ramona Stroescu^{a,b}, Ioana Micle^b, Monica Marazan^b, Otilia Marginean^{a,b}, Teofana Bizerea^{a,b}, Gabriela Doros^{a,b}

^aVictor Babes' University of Medicine and Pharmacy, Timisoara, Romania; ^bLouis Turcanu' Emergency Hospital for Children, Timisoara, Romania

Background: The 'catch-up growth' phenomenon in children born small for gestational age (SGA) has been linked to early onset obesity with the subsequent emergence of metabolic syndrome

(MetS). The intima media thickness of the common carotid artery (CIMT) is a well-known marker of subclinical atherosclerosis. **Objective and hypotheses:** To determine the association between being born SGA and CIMT, a measure of atherogenesis and to investigate metabolic risk factors which impact on CIMT in obese children. **Method:** A prospective study was carried out over a 1-year period (March 2012–March 2014). We analyzed 122 obese patients, 96 patients appropriate for gestational age (AGA) and 26 patients SGA. Both groups were matched for age, sex, and BMI. Blood pressure, lipids and glucose were determined. Oral glucose tolerance tests (OGTT) were performed. Insulin resistance (IR) was assessed by homeostasis model assessment (HOMA). CIMT was measured in all the patients. **Results:** CIMT in obese children born SGA was significantly increased as compared with obese children born AGA similar age, sex, and BMI ($P=0.0035$). We demonstrated a strong correlation between CIMT and all other metabolic factors ($r=0.98$). In both groups, mean CIMT of was significantly related to diastolic blood pressure, triglycerides and HOMA. CIMT was not significantly related to systolic blood pressure and baseline glucose. **Conclusion:** High triglycerides levels and low HDL-cholesterol levels, IR and diastolic blood pressure, which are all components of MetS are strong predictors of increased CIMT in obese children. Being born SGA increases the atherogenic risk.

P2-D3-400

Association between Lipid Profile, BMI, and Insulin Resistance Markers in Obese Prepubertal Children

Ramon Cañete^a, Miguel Valle^b, Rosario Martos^c, Maria Dolores Cañete^d, Rosario Valle-Martos^e

^aUnidad de Endocrinología Pediátrica, Hospital Universitario Reina Sofía, IMIBIC, Córdoba, Spain; ^bServicio de Análisis Clínicos, Hospital Valle de los Pedroches, IMIBIC, Córdoba, Spain; ^cCentro de Salud de Pozoblanco, IMIBIC, Córdoba, Spain; ^dGrupo PAIDI CTS-329, Universidad de Córdoba, IMIBIC, Córdoba, Spain; ^eFacultad de Medicina, Córdoba, Spain

Introduction and aims: Obesity is often associated with elevated insulin levels and resistance to insulin action (IR). Insulin regulates the lipid metabolism. In overweight children, IR may well play a greater role than obesity in the development of lipid alterations. This study sought to ascertain whether there was any difference in lipid levels between obese and non-obese children, and to test for correlations between IR markers and BMI. **Patients and methods:** This transversal study in obese prepubertal children (6–9 years old) included 58 obese children and 61 non-obese controls. Lipid profiles, baseline insulin levels, and insulin resistance index (HOMA-IR) were measured in all subjects. **Results:** The composition of the two groups was similar, with no significant difference in age or gender. Mean insulin levels ($P=0.038$), HOMA-IR values ($P=0.009$), and triglyceride levels ($P<0.001$) were significantly higher in the obese group than in controls, while HDL-C ($P=0.004$) and Apo-A1 levels ($P<0.001$) were significantly lower. Simple linear correlation analysis in obese children revealed a positive correlation between BMI and

triglyceride levels, and a negative correlation between BMI and HDL-C and Apo-A1 levels. A significant association was observed between triglyceride, HDL- and Apo-A1 levels and both baseline insulin levels and HOMA-IR values. Total cholesterol and LDL-C displayed no correlation with either insulin levels or the IR index. Multiple regression analysis showed that the three variables tested (BMI, insulin, and HOMA) were independent prediction factors for triglyceride levels, while insulin was an independent prediction factor for HDL-C and Apo-A1. **Conclusions:** The lipid profile in obese children is similar to that of obese adults. Changes in lipid-related variables appear to depend more on insulin levels than on the degree of obesity.

P2-D3-401

Mannose Binding Lectin and Carotid Intima-Media Thickness in Chinese Obese Children

Wei Wu, Liqing Cheng, Junfen Fu

Zhejiang University, Hangzhou, China

Background: Mannose binding lectin (MBL) is an important innate immune molecule and is previously found to be related to artery damage in some diseases as SLE rheumatoid arthritis and severe atherosclerosis. However, its role in artery change is still contradictory according to different studies. We found the carotid intima-media thickness (CIMT) increased in obese children which indicated an early change of atherosclerosis. **Objective and hypotheses:** To investigate association of CIMT with serum MBL and cell adhesion molecule levels in obese Chinese children and test the hypotheses that MBL play a role in early artery change of obese children. **Method:** It is an observational and descriptive study which included 126 obese children age 10.5+2.8 years, ranged from 3.3 to 17.7 year, BMI >95th percentile for their age and sex, 41 females and 85 males), and 105 age- and sex-matched controls. CIMT was determined by means of ultrasonography as MBL, sICAM and sVCAM levels were assessed by ELISA Kit. **Results:** MBL levels in obese children are significantly lower than that in controls and correlated negatively with right internal carotid artery intima-media thickness ($R = -0.24, P = 0.019$), which also correlated positively with blood sICAM, and sVCAM levels. **Conclusion:** MBL may play a protective role in early change of artery in obese children and cell adhesion molecule may be involved in the process.

P2-D3-402

Usefulness of Hypertriglyceridemic Waist Phenotype in Obese Indian Children

Janani Ravi, Hemchand Krishna Prasad, Lakshmi Venugopalan, Gowrishankar Chokanathan, Nedunchelian Krishnamoorthy, Kannan Narayanaswamy

Mehta Children's Hospital, Chennai, India

Background: BMI to screen children for cardiometabolic risk has numerous drawbacks. Hypertriglyceridemic-waist (HW) phenotype is recognized as an effective screening tool to identify adults but role in children is not known. **Objective and hypotheses:** To evaluate HW-phenotype as an alternative for BMI in recognizing children (5–18 years) at risk for cardiometabolic risk factors. **Method:** Retrospective review of case records of children evaluated for cardiometabolic risks in the Paediatric Endocrine Clinic of a developing country. Children with waist circumference ≥ 90 th percentile and serum triglyceride levels > 100 mg/dl considered to have abnormal HW-phenotype. **Results:** Records of 40 children (mean age 10.0 ± 3.3 years; 27 males; mean BMI-SDS 2.8 ± 0.6) reviewed. 87.5, 50, and 40% subjects had abnormal waist, elevated triglycerides, and abnormal HW-phenotype respectively. Children with abnormal HW-phenotype had higher total cholesterol (166.7 ± 38.1 vs 161.2 ± 33.4 mg/dl; $P < 0.05$), higher LDL levels (105.7 ± 38.1 vs 102.9 ± 30.4 mg/dl; $P < 0.05$), and lower HDL levels (41.3 ± 17.1 vs 45.0 ± 14.1 mg/dl; $P > 0.05$). Low HDL was more frequently observed in children with abnormal HW-phenotype (46.7 vs 30.8%; $P < 0.05$). Comparison of BMI, waist circumference alone, and HW-phenotype revealed that BMI has highest sensitivity and HW phenotype has highest specificity to recognize cardiometabolic risk factors (Table 1). **Conclusion:** Though HW phenotype is more specific, BMI remains the gold standard to screen children for metabolic risk factors.

P2-D3-403

Concomitant Changes in Full Body DXA Values and BMI-SDS During Multidisciplinary Treatment of Childhood Obesity

Tenna R H Nielsen^{a,b}, Cilius E Fonvig^{a,b}, Thomas A Gerds^c, Ulrik Lausten-Thomsen^a, Jens-Christian Holm^a

Table 1. (for abstract P2-D3-402)

	BMI-SDS > +2		HW phenotype		WC >90th percentile	
	Sen (%)	Sp (%)	Sen (%)	Sp (%)	Sen (%)	Sp (%)
TC ^a > 170 mg/dl	92.3	13.4	37.5	58.3	75	4.1
LDL ^b > 110 mg/dl	91.6	13.0	40	62.5	73.3	4.1
HDL ^c < 35 mg/dl	80	8	58.3	70.3	83.3	11.1
Insulin > 15 mIU/ml	100	5	50	64	88.8	25
Blood sugar > 110 mg/dl	83.3	9.5	42.8	68.1	79	12.3

^aDepartment of Pediatrics, The Children's Obesity Clinic, Copenhagen University Hospital Holbæk, Holbæk, Denmark;

^bThe Novo Nordisk foundation Center for Basic Metabolic Research, Section of Metabolic Genetics, University of Copenhagen, Copenhagen, Denmark; ^cDepartment of Public Health, Core Biostatistics, University of Copenhagen, Copenhagen, Denmark

Background: Childhood obesity and related co-morbidities are increasing world wide and consequently effective treatment interventions are much needed. **Objective and hypotheses:** The aim was to investigate concomitant changes in body composition in relation to changes in BMI-SDS during The Children's Obesity Clinics Treatment (TCOCT) program. Hypothesis: reductions in body fat percentage may not be revealed by reductions in BMI-SDS. **Method:** One-hundred-ninety- three (108 girls) children and youths with a median age of 12.4 years (range 6.2–22.7) were examined by height, weight, and dual-energy X-ray absorptiometry (DXA scan) at baseline and after 1 year of multidisciplinary childhood obesity treatment. **Results:** At the baseline the participants had a median BMI-SDS of 2.8 (range 1.5–4.9) and a median percent body fat (%BF) of 43.6% (range 28.9–57.1). Of the 193 children and youths, 57% reduced their BMI-SDS, 30% had a stable BMI-SDS (Δ BMI-SDS \pm 0.15), and 13% increased their BMI-SDS during treatment. The group reducing their BMI-SDS ($n=110$) decreased their %BF by -4.0% (95% CI: $(-4.8; -3.3)$, $P<0.0001$). The group with a stable BMI-SDS ($n=58$) tended to decrease their %BF by -0.5% (95% CI: $(-1.1; 0.2)$, $P=0.15$), and the group increasing their BMI-SDS ($n=25$) increased their %BF by 1.6% (95% CI: $(0.1; 3.1)$, $P=0.04$). Reductions in BMI-SDS were positively correlated to reductions in %BF ($P<0.0001$). **Conclusion:** During multidisciplinary treatment of childhood obesity, a reduction in %BF may be possible even in children exhibiting a stable BMI-SDS indicating a favorable treatment response in a larger percentage of children treated.

P2-D3-404

Cystic Fibrosis: Dyslipidemia in Brazilian Children

Ana Catarina Araujo^{a,b}, Ana Cristina Bezerra^{a,b}, Luciana Monte^{a,b}, Cristina Moreira^{a,b}, Andrea Abdalla^c

^aHospital da Criança de Brasília, Brasília, Federal District, Brazil;

^bHospital de Base do Distrito Federal, Brasília, Federal District, Brazil; ^cUniversidade Católica de Brasília, Brasília, Federal District, Brazil

Background: Cystic fibrosis is associated with abnormal lipid metabolism and this abnormality is commonly characterized by low cholesterol and hypertriglyceridemia. The increasing in life expectancy of cystic fibrosis patients has enhancing the interest for prevent the risk factors for cardiovascular diseases like dyslipidemias. **Objective and hypotheses:** Determine whether concentrations of cholesterol and triacylglycerol are related to nutritional status and fasting glucose in pediatric patients with cystic fibrosis. **Method:** Fasting lipid profiles and fasting glucose were measured in 52 pediatric patients with cystic fibrosis

(10.5 ± 5.0 years – 23F/29M). **Results:** Twenty patients (38.4%) had hypertriglyceridemia (143.4 ± 37.8 mg/dl), and nine patients (17.3%) had elevated cholesterol (162 ± 15 mg/dl). In most cases, hypertriglyceridemia was isolated; only three subjects had elevation of both cholesterol and hypertriglyceridemia. Twenty-eight patients (53.8%) had low HDL-cholesterol (34.8 ± 6.5 mg/dl). Lipid concentrations were not related to BMI, gender or age or fasting glucose. These results have showed a group with higher triacylglycerol, lower cholesterol, and lower HDL-cholesterol concentrations than the general Brazilian pediatric population and also in comparison with some other studies in cystic fibrosis group. **Conclusion:** Isolated hypertriglyceridemia appears to be common in cystic fibrosis, whereas cholesterol concentrations are generally low. Whether abnormal lipid metabolism is associated with a high risk of cardiovascular disease in general population, like elevation in cholesterol and triacylglycerol and low HDL-cholesterol, these findings arouse an importance to understand the abnormalities in lipid metabolism in this special group of children with cystic fibrosis in order to prevent the factors of risk of cardiovascular diseases and to improve the survival.

P2-D3-405

Do Children with Down Syndrome Show Lipid Profile Disorders?

Dominika Zimny, Marta Szatkowska, Julian Maciaszek, Mikolaj Machaj, Ewa Barg

Wroclaw Medical University, Wroclaw, Poland

Background: People with Down syndrome (DS) are considered to be atherosclerosis-free. However, obesity predispositions and thyroid gland dysfunction that accompanies this syndrome can influence on the heart ischemic risk. The aim of the study was the evaluation of lipid profile of children with DS and estimation of omega-3 supplementation effect on serum lipid profile. **Materials and methods:** The group constituted 69 children with DS (41 boys), average age $4.1 (\pm 3.5)$ years. 102 tests of lipid profiles were obtained – total cholesterol, LDL, HDL, and triglycerides (TG). The children were divided into two groups A – (36.4%) supplemented, B – (63.6%) not supplemented. Statistica 10 was used to perform the statistical analysis. **Results:** Concentration of lipids was evaluated basing on sex and age centile charts. It was stated: Total cholesterol – 22.8% above 75 percentile (pc.) and 11.4% above 95 pc.; LDL – 25% above 75 pc. and 8.3% above 95 pc.; TG – 25.7% above 75 pc. and 17.6% above 95 pc.; and HDL – 24.7% under 25 pc. and 11.7% under 5 pc. Negative correlation between the level of TG and the age of children ($P<0.05$; $R=-0.297$) was found. Average value of the total cholesterol/HDL ratio (chol/HDL) was $3.52 (\pm 1.09)$, that is increased in 42.5% children. Children with DS had pharmacologically aligned thyroid function. Group A in comparison to group B was characterized with a significantly lower level of TG, a significantly higher level of HDL and lower chol/HDL ratio of 3.48 (vs 3.99 in group B). **Conclusion:** Performed study confirmed the presence of serum lipid profile disorders in children with DS. Taking all this into account, some recommendations should be done in order to enable monitoring and treatment of lipid

disorders in this group of patients. In the context of this research, supplementation of children with DS using preparations containing polyunsaturated fatty acids omega-3 is justified, due to its beneficial effects on lipid disorders.

P2-D3-406

Relationship Between Obesity and Platelet Indices in Children

Elif Özsu^a, Bahadır Yazicioglu^b

^aDepartment of Pediatric Endocrinology, Samsun Gynecologic and Children Hospital, Samsun, Turkey; ^bDepartment of Family Medicine, Ondokuz Mayıs University School of Medicine, Samsun, Turkey

Background: Platelet levels plays a key role for determining insulin resistance by a simple test. The degree of platelet activation may be assessed by platelet indices such as platelet count, mean platelet volume (MPV), and platelet distribution width (PDW). **Objective and hypothesis:** The aim of this study is to assess platelet count, MPV, and PDW as metabolic indicator in obese children with or without insulin resistant. **Methods:** Two hundred sixty seven obese patients (girl 160) and 50 (girl 25) controls were enrolled. Anthropometric measurements, triglyceride, total cholesterol, HDL cholesterol, LDL cholesterol, alanine aminotransferase, aspartate aminotransferase, uric acid, hemoglobin, platelet count, MPV, PDW, and insulin resistance by homeostasis model of assessment of insulin resistance and oral glucose tolerant test were investigated. Obese patients were grouped according to the insulin resistance. **Results:** In obese group mean age was 11.5 ± 3.2 years, BMI: 28.6 ± 4.8 , mean hemoglobin level: 13 ± 0.98 g/dl, mean platelet count: $328\ 500 \pm 155\ 191$ mm³, PDW: 11.5 ± 2.0 , MPV: 9.8 ± 0.98 , LDL: 98 ± 26 mg/dl and uric acid: 4.9 ± 1.0 mg/dl. Uric acid is significantly higher in obese group ($P < 0.05$) and there was no statistically significant differences in platelet indices in two groups. Only uric acid and ALT levels were significantly different between obese and control group/and obese with insulin resistance (IR) and control group. Platelet counts, MPV, and PDW levels were not significant different in obese, obese with IR and control groups. But MPV inversely correlated with HOMA-IR, platelet counts, ALT, and LDL levels. MPV is positive correlated with PDW. **Conclusion:** The relationship between platelet, MPV, PDW, and obesity have been shown previously demonstrated. But platelet indices may not to be related to the degree of obesity as we think.

P2-D3-407

Examining β -Cell Reserve in Extremely Obese Children

Maria Neshkinska^a, Sonya Galcheva^{a,b}, Mina Lateva^{a,b}, Violeta Iotova^{a,b}

^aMedical University Varna, Varna, Bulgaria; ^bUMHAT 'Sv. Marina', Varna, Bulgaria

Background: Obesity is a major risk factor for developing type 2 diabetes mellitus (T2DM). Despite the obesity epidemics, the incidence of childhood T2DM is not increased. **Objective and hypotheses:** To assess the β -cell reserve expressed as an oral glucose disposition index (GDIo), an independent predictor of developing T2DM. **Method:** A total of 80 adolescents (61.3% girls), aged from 10.0 to 17.6 years (mean age 13.59 ± 2.34 years), with age- and gender-specific BMI over 95th percentile and waist circumference (WC) over 90th percentile, were included. The participants underwent anthropometry, fasting blood analyses, oral glucose tolerance test (OGTT), and abdominal ultrasonography. Insulin sensitivity was estimated as $1/\text{fasting insulin}$; insulin response – as the change in insulin divided by the change in blood glucose (BG) from 0 to 30 min and GDIo – as a relation between insulin sensitivity and β -cell function. **Results:** At fasting, a total of 50 adolescents (62.5%) were normoglycemic and 30 (37.5%) were with impaired fasting glucose (IFG). After OGTT subjects were divided into three categories depending on 2 h postload glucose levels: normal glucose tolerance – 63 (78.8%); impaired glucose tolerance (IGT) – 16 (20.0%); and T2DM – 1 (1.3%). The mean GDIo was 2.2450 ± 2.30 mM⁻¹ (boys 2.8057 ± 1.93 , girls 1.8991 ± 2.46 , $P = 0.096$). The group with the lowest GDIo consisted of 31.9% of all girls vs 13.8% of all boys. The GDIo decreased significantly with increasing of 2 h postload BG levels ($P = 0.042$). The former also had a strong relationship with the family history of obesity ($P = 0.005$) and showed no associations with T2DM family history. **Conclusion:** The current study confirmed the low frequency of T2DM in paediatric population and suggested a stronger correlation with obesity and future disease risk. The results in females deserve further exploration.

P2-D3-408

SHBG Integrates the Cardiovascular Risk and Metabolic Dysfunction of Gestational Obesity

Judit Bassols^{a,b}, Pilar Soriano-Rodríguez^c, Anna Prats-Puig^{a,b}, Gemma Carreras-Badosa^{a,b}, Miguel-Angel Miranda-Arce^c, Elena Álvarez-Castaño^a, Francis de Zegher^d, Lourdes Ibáñez^e, Abel López-Bermejo^{a,b}

^aDr Josep Trueta Hospital, Girona, Spain; ^bGirona Institute for Biomedical Research, Girona, Spain; ^cSalut Emporda Foundation, Figueres, Spain; ^dUniversity of Leuven, Leuven, Belgium, ^eHospital Sant Joan de Déu, Barcelona, Spain

Background: Sex hormone-binding globulin (SHBG) is the major sex steroid carrier protein. Its production is negatively regulated by insulin and monosaccharides. The concentration of SHBG increases between 16 and 27 weeks gestation and is negatively associated with pre-gestational BMI and weight gain during pregnancy. The link of SHBG with cardiovascular risk is poorly understood. **Objective and hypotheses:** In obese pregnant women, we aimed to study the association of circulating SHBG with cardiovascular risk factors independently of

endocrine-metabolic parameters. **Method:** Fasting serum SHBG levels were quantified between 24 and 28 weeks of gestation in 160 healthy pregnant women (87 with normal weight and 73 with pre-pregnancy obesity and/or gestational obesity, as defined by international references). Cardiovascular risk parameters (C-reactive protein (CRP) and blood pressure (BP)), metabolic parameters (HbA1c), pre- and post-load glucose, C-peptide, insulin (and insulin resistance index (HOMA-IR)), triglycerides, and high molecular weight adiponectin (HMW)), and endocrine parameters (total testosterone and estradiol) were also assessed. **Results:** As expected, lower concentrations of SHBG were associated with increased BMI, HbA1c, pre- and post-load glucose, C-peptide, HOMA-IR, triglycerides and less HMW adiponectin; lower SHBG was also associated with more CRP and BP ($P < 0.01$ – $P < 0.0001$ for all comparisons). These associations were more robust in women with obesity, who had lower SHBG concentrations compared to normal-weight women ($P < 0.0001$). In multivariate analysis in obese women, SHBG showed independent associations with CRP ($\beta = -0.377$, $P < 0.001$, $R^2 = 16.7$) and BP ($\beta = -0.255$, $P = 0.030$, $R^2 = 6.4$) independently of metabolic (HOMA-IR and HbA1c) and endocrine (testosterone and estradiol) parameters. **Conclusion:** SHBG is decreased in obese pregnant women in association with a less favorable cardiovascular profile. We suggest that SHBG can integrate the cardiovascular risk and metabolic dysfunction of gestational obesity.

P2-D1-409

Ternary Complex Formation and IGFBP3 Proteolytic Activity During Childhood: Age-Dependent Changes

Judith S Renes^a, Jaap van Doorn^c, Anita C S Hokken-Koelega^{a,b}

^aErasmus MC – Sophia Children's Hospital, Rotterdam, The Netherlands; ^bDutch Growth Research Foundation, Rotterdam, The Netherlands; ^cUniversity Medical Center Utrecht, Utrecht, The Netherlands

Background: IGF1 is mainly sequestered in a 150 kDa ternary complex with IGFBP3 and the acid-labile subunit (ALS). Dissociation of IGF1 from the ternary complex is in part regulated by proteolysis of IGFBP3, which reduces its affinity for IGF1. Short children born SGA have lower IGF1 and IGFBP3 levels compared to healthy peers. **Objective and hypotheses:** To determine complex formation in healthy normal statured children, and assess variables influencing complex formation. Secondly, we determined complex formation in short SGA children. We hypothesized that complex formation is less adequate in these children thus contributing to their short stature. **Method:** Complex formation was assessed using ¹²⁵I-hIGF1 column chromatography in 70 controls (40 boys), median age 10.6 years, and 40 short SGA children (25 boys), median age 8.6 years. IGFBP3 was determined by western immunoblotting. **Results:** In controls, ¹²⁵I-hIGF1 ternary complex formation was strongly positively correlated with age ($P < 0.001$). Variables positively influencing ternary complex formation were higher serum IGF1 levels compared to IGFBP3 levels ($P < 0.001$), and lower serum IGF2 ($P < 0.001$) and IGFBP1 levels ($P < 0.001$). In addition, a higher presence of proteolyzed

IGFBP3 negatively influenced ternary complex formation ($P = 0.006$). At a young age, healthy children showed considerable IGFBP3 proteolytic activity which declined with aging ($P < 0.001$). IGFBP3 proteolytic activity was negatively correlated with IGF1 levels ($P < 0.001$). In short SGA children, formation of the ternary complex was positively correlated with height SDS ($P = 0.01$). Compared to healthy controls, short SGA children showed reduced IGF1 levels (-1.3 vs 0.1 SDS) and increased proteolyzed IGFBP3 (35.1 vs 12.2%). **Conclusion:** ¹²⁵I-hIGF1 ternary complex formation is age-dependent. A decrease in IGF1, and an increase in IGF2, IGFBP1 and IGFBP3 proteolytic activity results in reduced ¹²⁵I-hIGF1 ternary complex formation. In conditions where serum IGF1 levels are low, such as young age and in short SGA children, IGFBP3 proteolytic activity is increased to ensure IGF1 bioavailability.

P2-D1-410

GHR Gene Variants within Coding and Intronic Regions in Children with Idiopathic Short Stature

María Gabriela Ballerini, Paula Scaglia, Alicia Martínez, Ana Keselman, Débora Braslavsky, Ignacio Bergadá, Héctor Guillermo Jasper, María Gabriela Ropelato, Horacio Domené

Centro de Investigaciones Endocrinológicas 'Dr César Bergadá' (CEDIE) CONICET – FEI – División de Endocrinología, Hospital de Niños Ricardo Gutiérrez, Buenos Aires, Argentina

Background: Heterozygous *GHR* gene variants were found in 5–8% of idiopathic short stature (ISS) children. Frequent polymorphisms within *GHR* coding regions, but not intronic SNPs, have been investigated in ISS. **Objectives:** To characterize *GHR* gene variants in ISS children, and to test their influence on height and the peripheral GH/IGF1/IGFBPs system. **Methods:** *GHR* gene (coding/intronic flanking regions) were PCR-amplified and sequenced in 64 unrelated ISS children (median height, range: -2.88 , -4.79 to -2.00). The genotype influence on height and GH/IGF1/IGFBPs system was investigated for SNPs with a minor allele frequency (MAF) $> 10\%$ (HapMap-Project). ISS children were grouped as: homozygous carriers for the major allele and carriers of one or two copies of the minor allele. IGF1 and IGFBP3 (ICMA), ALS (RIA), and GHBP (in house functional immunofluorometric-assay) were measured¹. Hardy-Weinberg equilibrium was verified. Fisher's exact test and Mann-Whitney analysis were used as appropriate. **Results:** Eight common polymorphisms were identified: exon-3 deletion (MAF: 26%), rs6179 (exon-6, 23%), rs6180 (exon-10, 42%), rs12521020 (intron-1, 32%), rs10941579 (intron-2, 32%), rs33972388 and rs34223737 (intron-7, 37 and 2%, respectively), rs6880730 (intron-8, 3%). MAF in ISS were not different to the HapMap frequencies. SNPs genotypes were not associated to height, GHBP-SDS, IGF1-SDS, IGFBP3-SDS, or ALS-SDS ($P > 0.10$ for all analysis). Three heterozygous uncommon variants (exon-7: p.R229H, exon-10: p.R386C and p.C440F) were also identified in 3/64 children (4.7%) with normal IGF1-SDS, IGFBP3-SDS, and ALS-SDS levels, two of them with low GHBP (< -1.8 SDS). These variants were not found in 41 control children. **Conclusions:** The prevalence of heterozygous uncommon *GHR* variants was in accordance with

previous studies. These variants could be present even in children with normal GHBP and GH-dependent factors. Common SNPs genotypes are distributed as reported in the general population and do not seem to have an impact on height or components of the GH/IGF1/IGFBPs system in ISS.

P2-D1-411

Spontaneous Baseline GH Secretion Signalling as a Regulator of Bone Metabolism in Children

Ralph Decker, Björn Andersson, Anders Nygren, Kerstin Albertsson-Wikland

Gothenburg Pediatric Growth Research Center (GP-GRC),
University of Gothenburg, Göteborg, Sweden

Background: GH is secreted in a pulsatile manner. The resulting GH peaks are known to be associated with growth, whereas the trough levels between the peaks are thought to be associated with metabolism in different tissues. GH trough levels were identified as a metabolically active signal in rats in the 1980th leading to differences in fat patterning with central obesity. Obese children are known to have low bone mass and bone mass is reduced in short children. **Objective and hypotheses:** To evaluate the impact of GH trough levels and waist circumference on bone metabolism in short prepubertal children. Our hypothesis was that the trough levels are associated with bone metabolism. **Method:** The study population consisted of 137 short prepubertal children (age range, 3–11 years; 91 boys, 46 girls) who participated in a longitudinal, prospective, multicenter study. Children had either normal or reduced levels of GH secretion. Data from baseline examinations were analyzed. **Results:** The GH baseline/GHmax ratio (correlation loading in PCA, $r=0.724$), lipotrotein(a) ($r=0.383$) and waist/hip ratio ($r=0.705$) formed a cluster and correlated inversely with bone mineral content (BMC-SDS) ($r=-0.732$). This indicates a negative influence of high GH baseline levels on bone metabolism and thus bone metabolic GH resistance. **Conclusion:** This is the first time that trough levels of GH have been identified as a potentially metabolically active signal in man. The association of the ratio of minimum to maximum GH secretion with bone mass indicates a partial metabolic GH resistance in bone tissue. We suggest GH trough levels being a metabolically active signal on bone tissue in man.

P2-D1-412

ALS Deficiency due to a Novel and Two Already Described IGFALS Gene Mutations in an Unusual Non Consanguineous Family: Two Compound Heterozygous (Father and Son) and Two Heterozygous Carriers (Brother and Mother)

Paula Scaglia, Ana Keselman, Lucía Martucci, Liliana Karabatas, María Gabriela Ballerini, Sabina Domené, Acosta Johanna, Héctor Jasper, Horacio Domené

Centro de Investigaciones Endocrinológicas 'Dr César Bergadá' (CEDIE), CONICET – FEI – División de Endocrinología, Hospital de Niños Ricardo Gutiérrez, Buenos Aires, Argentina

Introduction: Complete ALS deficiency (ALS-D), caused by inactivating mutations in both *IGFALS* gene alleles, presents severe IGF1 and IGFBP3 deficiencies associated to moderate growth retardation. **Aim:** To characterize the molecular defect in a family where the index case and his father presented short stature and IGF1 and IGFBP3 deficiencies. **Methods:** IGF1, IGFBP3, and GH serum levels were determined by CLIA, ALS by ELISA and western immunoblot (WIB). *IGFALS* gene was PCR amplified and automatically sequenced. **Results:** We studied a short boy (CA 2.4 years, 81.5 cm, -2.9 SDS). He presented normal GH secretion (GHmax: 15.3 ng/ml), undetectable IGF1 (<25 ng/ml), IGFBP3 (<0.5 μ g/ml), and ALS (<100 mU/ml) serum levels. *IGFALS* sequencing revealed he was compound heterozygous for a frameshift mutation (c.103dupG, p.E35Gfs*17) and a novel missense variant (c.1469C>G, p.S490W). His father (156.5 cm, -2.4 SDS) presented IGF1, IGFBP3, and ALS deficiencies (29 ng/ml, <0.5 μ g/ml, and <100 mU/ml respectively) and was compound heterozygous for the p.S490W variant and p.L409F.A475V, previously described in an ALS-D family. Patient's mother (162.3 cm, 0.26 SDS) and his brother (CA 6.0 years, 116.5 cm, 0.41 SDS) were heterozygous for p.E35Gfs*17 and p.S490W variants respectively, with normal levels of IGF1 (128 and 126 ng/ml) and IGFBP3 (2.64 and 2.00 μ g/ml). His paternal aunt (153 cm, -1.26 SDS) presented the same genotype as the father and had low IGF1 with undetectable IGFBP3, while the paternal grandmother (156.4 cm, -0.70 SDS) was heterozygous for p.L409F.A475V with normal IGF1 and IGFBP3. **Conclusions:** The finding of undiagnosed ALS-D adult subjects, compound heterozygous for *IGFALS* gene mutations and the appearance of heterozygous carriers in a non consanguineous family, support that these genetic variants are present in the population and are not under a strong negative selection pressure. Remarkably, this is the first report showing fertility is preserved in an ALS-D patient.

P2-D1-413

A Re-Evaluation of GH Secretion with Combined Test (GHRH + ARG/PD) in Children with Prader-Willi Syndrome

Danilo Fintini^a, Sarah Bocchini^a, Graziano Grugni^c, Claudia Brufani^a, Armando Grossi^b, Marco Cappab, Antonino Crinò^a

^aAutoimmune Endocrine Disease Unit, Bambino Gesù Children's Hospital, Rome, Italy; ^bEndocrinology Unit, Bambino Gesù Children's Hospital, Rome, Italy; ^cItalian Auxological Institute Foundation, Piancavallo, Verbania, Italy

Background: A reduced GH response to different stimulation tests have been documented in both children and adults with Prader-Willi syndrome (PWS), independently from obesity.

Previous reports suggested the hypothesis of an age dependent derangement of the hypothalamus-pituitary axis occurring in PWS subjects. **Objective and hypotheses:** In this longitudinal study we re-evaluated the GH responsiveness to a combined test after long-term GH therapy in children with PWS, analyzing the possible impact of sex, BMI and genetic subtypes. **Method:** GH peak (GHP) after GHRH + arginine or GHRH + pyridostigmine and IGF1 levels in 28 genetically confirmed PWS children were evaluated at baseline (16 males; age 4.7 ± 2.7 years; height-SDS -1.0 ± 1.1 ; BMI-SDS 2.9 ± 3.2 ; 16 obese, 16 with del15) and after a median period of 9.4 years (age 14.3 ± 2.4 years; height-SDS -1.1 ± 1.2 ; BMI-SDS 3.0 ± 2.0 ; 20 obese). All subjects underwent GH treatment after the first evaluation, withdrawn in all cases at least 6 months before the retesting. **Results:** A decrease in GHP at retesting was observed (baseline: 20.5 ± 12.3 ; at retesting: 13.5 ± 11.1 ; $P=0.031$), while IGF1 levels were similar. PWS with del15 showed a higher IGF1 at baseline compared to UPD15 subjects (119.3 ± 63.2 vs 63.9 ± 47.7 ng/ml respectively; $P=0.023$) but not at retesting. Obese subjects compared to non obese patients showed lower GHP either at baseline (15.8 ± 10.6 vs 26.8 ± 11.9 ng/ml; $P=0.016$) and at retesting (10.2 ± 7.7 vs 22.8 ± 14.4 ng/ml; $P=0.007$). At baseline we did not find any correlation between GHP, IGF1 and other parameters considered, while at retesting we found a negative correlation between GHP ($r = -0.531$) and IGF1 ($r = -0.422$) and BMI-SDS. These negative correlations were confirmed in the multivariate model when age, sex, genetic subtypes and pubertal stage were considered ($\beta = -0.531$ and -0.422 respectively). **Conclusion:** Our data suggest that PWS children have a normal GH pituitary reserve that gradually declines with age. Obesity seems to be the only factor influencing this impairment over time.

P2-D1-414

Final Height SDS Gain of GH Treated Children with SHOX Deficiency Describing Observational and Clinical Trial Data

Imane Benabbad^a, Christopher Child^b, Jean-Claude Carek,
Myriam Rosilio^a

^aMedical Department Lilly Diabetes, Neuilly-sur-Seine, France;
^bLilly Research Laboratories, Windlesham, UK; ^cUniversité Paris Diderot, Sorbonne Paris Cité, Service d'Endocrinologie Diabétologie Pédiatrique and INSERM U1141 – Président CMEL AP-HP Hôpital Universitaire Robert-Debré, Centre de Référence Maladies E, Paris, France

Background: Patients with mutations of the short-stature-homeobox-containing (SHOX) gene likely have impaired growth, with or without a spectrum of skeletal anomalies consistent with mesomelic skeletal dysplasia. In a multinational clinical trial, GH has been shown to increase growth rate and final height (FH). **Objective and hypotheses:** The aim of this analysis was to describe FH outcome after GH treatment in an observational

setting (Genetics and Neuroendocrinology of Short Stature International Study (GeNeSIS)) and in a monitored randomized clinical trial (B9R-MC-GDFN). **Method:** Twenty-eight prepubertal children (54% girls) with SHOX deficiency from the clinical trial and 85 children (72% girls) from GeNeSIS who had attained FH during observation were included in both analyses. Last observed height was considered FH (SDS/chronological ages) if any of the following criteria applied: closed epiphyses, height velocity < 2 cm/year, last bone age > 14 years in girls/ > 16 years in boys. **Results:** Due to inclusion criteria, patients were younger at start of GH treatment (mean \pm sd; 9.2 ± 2.4 and 11.1 ± 2.3 years) and treatment duration was longer (6.0 ± 2.0 and 4.2 ± 2.3 years) in the clinical trial than in GeNeSIS respectively. Other relevant variables were similar between the two cohorts: baseline height SDS (-3.2 ± 0.8 and -3.0 ± 0.9), GH dose (0.36 ± 0.02 and 0.32 ± 0.11 mg/kg per week) at GH start, age at FH (15.5 ± 1.3 and 15.5 ± 1.5 years) and FH SDS (-2.0 ± 1.3 and -2.2 ± 1.2) each respectively. FH Height SDS gain from baseline (1.3 ± 0.9 and 0.9 ± 1.2) was notable for both cohorts. FH in the normal range (> -2 SDS) was achieved by 57 and 49% of the patients respectively. **Conclusion:** In conclusion, GH treatment results in gain in height SDS at FH in SHOX deficient patients, both in a regulated clinical trial and in a real life observational study setting. In real life, GH treatment was initiated at an older age, probably a more advanced tanner stage and administered for a shorter duration.

P2-D1-415

IGF1 is Associated with a More Favourable Pattern of Body Composition in Obese Children

Elena Inzaghi^a, Valentina Pampanini^a, Paola Alessio^a, Rossana Fiori^a,
Barbara Baldini Ferrolli^a, Stefano Cianfarani^{a,b}

^aD.P.U.O. 'Bambino Gesù' Children's Hospital – 'Tor Vergata' University, Rome, Italy; ^bDepartment of Women's and Children's Health, Karolinska Institute, Stockholm, Sweden

Background: Recent studies have suggested a role of IGF1 as a candidate prognostic marker for cardiometabolic complications of obesity. **Objective:** To investigate the relationship between IGF1 serum levels and both biochemical and metabolic parameters as well as body composition in a cohort of obese children. **Methods:** obese subjects (130F/157M), aged 11.2 ± 2.7 years, were studied. Anthropometry, biochemical and metabolic parameters, and IGF1 serum levels (expressed as SDS) were assessed. Body composition was evaluated by dual X-ray absorptiometry (DXA) in 201 children. IGF1 levels were subdivided in ascending tertiles. Differences between tertile groups were assessed by Mann-Whitney *U*-test. **Results:** IGF1 levels were inversely related to waist circumference (WC)/height ratio ($r = -0.35$, $P < 0.001$), BMI SDS ($r = -1.31$, $P = 0.03$), aspartate aminotransferase (AST) levels ($r = -0.231$, $P = 0.001$), alanine aminotransferase (ALT) levels ($r = -0.257$, $P < 0.001$), fat mass percentage ($r = -0.281$,

$P < 0.001$), and C-reactive protein (CRP) levels ($r = -0.222$, $P = 0.009$) and directly related with height SDS ($r = 0.125$, $P = 0.035$), lean mass percentage ($r = 0.273$, $P = 0.041$), total lean mass ($r = 0.145$, $P = 0.041$), and trunk lean mass ($r = 0.159$, $P = 0.024$). Stepwise regression analysis revealed that IGF1 was the major predictor of both fat mass percentage ($\beta = -0.3$, $P < 0.001$) and lean mass percentage ($\beta = 0.28$, $P < 0.001$). Compared to subjects with IGF1 levels in the highest tertile, patients with in the lowest tertile showed higher WC/height ratio (0.6 ± 0.051 vs 0.65 ± 0.058 , $P = 0.012$), fat mass percentage (38.98 ± 4.93 vs 42.81 ± 4.03 , $P = 0.001$), CRP levels (0.3 ± 0.29 vs 0.55 ± 0.43 , $P = 0.033$), LDL cholesterol levels (88.06 ± 19.57 vs 96.93 ± 23.88 , $P = 0.042$), AST levels (23 ± 7.15 vs 33.63 ± 19.67 , $P = 0.002$), and ALT levels (25.14 ± 17.83 vs 33.02 ± 20.67 , $P = 0.037$) while lean mass percentage resulted lower (55.01 ± 3.9 vs 58.58 ± 4.85 , $P = 0.002$). **Conclusions:** Our findings suggest that IGF1 may play a role in the pathogenesis of obesity related cardiometabolic alterations and could represent a biomarker of risk in obese children.

Table 1. Levels of cytokines (pg/mg protein) in the hypothalamus.

	WTND	WTHF	KOND	KOHF
TNF α	7.76 \pm 0.21	7.84 \pm 0.39	9.75 \pm 0.45*	7.16 \pm 0.41 [†]
IL1 β	31.97 \pm 1.82	32.52 \pm 1.51	36.91 \pm 1.29*	26.43 \pm 1.47* ^{†,‡}
IL6	3.47 \pm 0.23	3.24 \pm 0.19	4.01 \pm 0.22	2.62 \pm 0.06* ^{†,‡}
MCP1	6.86 \pm 0.25	6.75 \pm 0.33	8.07 \pm 0.36*	6.05 \pm 0.34 [†]
IL10	7.22 \pm 0.29	7.61 \pm 0.32	9.07 \pm 0.70*	6.70 \pm 0.21 ^{†,‡}
IFN γ	0.21 \pm 0.01	0.24 \pm 0.02	0.27 \pm 0.01*	0.19 \pm 0.01 ^{†,‡}

ANOVA: * $P < 0.01$; vs WT ND; [†] $P < 0.01$ vs KO ND; [‡] $P < 0.01$ vs WT HFD. $n = 5-6$ /group.

KOHF: 1.3 ± 0.01 . $P < 0.01$) that could induce hypothalamic inflammation. While HFD had no effect in WT mice, it decreased serum NEFA levels and hypothalamic cytokines in GHRKO mice (Table 1). **Conclusion:** As increased NEFA levels have been associated with hypothalamic inflammation, the decreased hypothalamic cytokine levels could be due to the decline in NEFA induced by HFD in GHRKO mice.

P2-D1-416

Absence of GH Signaling Induces Hypothalamic Inflammation that is Reversed in Response to a High Fat Diet

Eva Baquedano^a, Ana Ruiz-López^a, Elena Pardo-Barquín^a, Elahu S Gosney^b, James Herpy^b, Julie A Chowen^a, Jesús Argente^a, John J Kopchick^b, Laura M Frago^a

^aDepartment of Endocrinology and Pediatrics, Instituto de Investigación Sanitaria Princesa (IP), Centro de Investi, Hospital Infantil Universitario Niño Jesús, Universidad Autónoma de Madrid, Madrid, Spain; ^bThe Edison Biotechnology Institute, Biomedical Sciences, Heritage College of Osteopathic Medicine, Ohio University, Biomedical Sciences, Athens, Ohio, USA

Background: The GH/IGF1 axis has important roles in growth, metabolism, lipid profile and body composition. GH receptor disrupted mice (GHRKO mice) are resistant to the action of GH, thereby, GHRKO mice are dwarf, hypoinsulinemic, hypoglycemic and obese. Consumption of a high fat diet (HFD) induces inflammatory processes in a multitude of peripheral tissues, including hypothalamus. **Objective and hypotheses:** Our aim was to evaluate the effect of HFD intake on hypothalamic inflammation in the absence of GH signalling. **Method:** Male C57BL/6J WT and GHRKO mice, 30 days of age were feed with standard chow (normal diet; ND) or HFD (60% fat) during 50 days and were then sacrificed. Levels of cytokines were measured in the hypothalamus by multiplex assay. **Results:** The absence of GH signalling in young mice has an impact on lipid metabolism that leads to an increase in circulating NEFA levels (WTND: 1.1 ± 0.08 ; WTHF: 0.9 ± 0.05 ; KOND: 1.8 ± 0.16 ;

P2-D1-417

GH Stimulated Levels in Prader-Willi Syndrome During the Transition Period between Childhood and Adulthood

Graziano Grugni^a, Andrea Corrias^b, Stefania Di Candia^c, Danilo Fintini^d, Luigi Gargantini^e, Lorenzo Iughetti^f, Letizia Ragusa^g, Alessandro Salvatori^h, Alessandro Sartorio^a, Sarah Bocchini^d, Maurizio Delvecchioⁱ, Giuseppe Chiumello^c, Antonino Crinò^d

^aItalian Auxological Institute, Verbania, Italy; ^bRegina Margherita Hospital, Turin, Italy; ^cS. Raffaele Hospital, Milan, Italy; ^dBambino Gesù Hospital, Palidoro-Rome, Italy; ^eCivic Hospital of Treviglio, Treviglio (BG), Italy; ^fUniversity of Modena and Reggio Emilia, Modena, Italy; ^gOasi Maria SS, Troina (EN), Italy; ^hUniversity of Insubria, Varese, Italy; ⁱCasa Sollievo della Sofferenza, S. Giovanni Rotondo (FG), Italy

Introduction: Previous reports support the hypothesis of an age dependent derangement of the hypothalamus-pituitary axis occurring in PWS subjects. In this context, transition years represent an important phase of growth process when somatic development reaches its completion. In the general population, GH deficiency (GHD) during the transition phase is associated with deterioration of body composition, metabolic alterations and reduced bone mineral density. PWS subjects have reduced muscle mass, increased risk of cardiovascular disease and osteoporosis, similarly to what observed in patients with non-syndromal GHD. Consequently, assessment of the GH status from late teenage years

until 6–7 years after achievement of final height may be particularly helpful in the management of PWS in this particular period. The objective of this study was to investigate the GH response to combined GHRH + arginine administration in a large group of PWS patients during the transition period. **Patients and methods:** Sixty-six patients with genetically-confirmed PWS, 29 males, aged 20.0 ± 2.6 years (mean \pm s.d.), were studied. Forty-seven subjects were obese, 11 overweight and 8 normal weight. Pituitary GH secretion was evaluated by dynamic testing with GHRH + arginine. In order to define GHD, we have adopted the cut-off limit specific for transition phase (GH peak (GHp) $< 19 \mu\text{g/l}$) (Corneli *et al.*, *Eur J Endocrinol* 2007). In addition, the appropriate BMI-related diagnostic cut-off limits of GHp have been used (Corneli *et al.*, *Eur J Endocrinol* 2005). **Results:** Fifty-two patients had GHp $< 19 \mu\text{g/l}$ (78.7%). Accordingly to the cut-off limits related to BMI, 13 obese PWS subjects (27.6%) could be defined as severe GHD (GHp $< 4.2 \mu\text{g/l}$) as well as three overweight patients (27.3%) (GHp $< 8 \mu\text{g/l}$), whereas none of normal weight individuals had GHp $< 11.5 \mu\text{g/l}$. **Conclusion:** Our findings showed that an impairment of GH response occurred in a significant percentage of PWS during transition phase, with an evident impact of their weight status.

P2-D1-418

Response to GH Treatment in Patients with Silver Russell Syndrome

C C J Smeets, J S Renes, M van der Steen, A C S Hokken-Koelega
Erasmus University Medical Centre, Rotterdam, The Netherlands

Background: Silver Russell syndrome (SRS) is characterized by low birth weight, severe postnatal short stature and distinctive facies. In $\sim 50\%$ of patients, (epi)genetic alterations can be detected ($\sim 40\%$ hypomethylation of H19 on chromosome 11, $\sim 10\%$ maternal uniparental disomy (UPD) 7). As SRS patients are usually born small for gestational age (SGA), they are treated with GH to improve height. However, data on long-term effects of GH treatment in SRS patients are very limited. **Objective and hypotheses:** To investigate the response to GH treatment in SRS vs non-SRS patients born SGA. **Method:** The study population consisted of 38 GH-treated SRS patients (SRS) ($n=8$ H19 hypomethylation, $n=5$ UPD7, $n=25$ clinical diagnosis (Netchine *et al.*, 2006)) and 301 non-SRS patients born SGA (non-SRS). Height and weight gain after 1 year of GH and adult height were compared between SRS and non-SRS. All subjects were treated with GH 1 mg/m^2 per day. **Results:** Mean (s.d.) age at start of GH was 5.2 (2.17) years in SRS and 6.45 (2.13) in non-SRS ($P=0.56$). Mean height SDS increased in first year of GH with 1.0 SDS from -3.41 to -2.42 SDS vs 0.8 SDS from -2.99 to -2.17 SDS in

non-SRS ($P=0.006$). Height gain was similar in genetically confirmed and clinical SRS. Weight for height SDS increased in first year of GH from -2.70 to -2.24 SDS in SRS vs -1.07 to -0.77 SDS in non-SRS ($P=0.002$). Mean adult height was -2.07 SDS in SRS vs -1.77 SDS in non-SRS ($P=0.51$). Distance to target height was 1.78 SDS in SRS vs 1.05 SDS in non-SRS ($P=0.05$). **Conclusion:** SRS patients showed a better weight- and height gain in first year of GH than non-SRS patients and attained a similar adult height. Distance to target height was larger in SRS patients.

P2-D1-419

Pubertal Development During GH Treatment with or without Additional GnRH Analogue Treatment in Short Children Born Small for Gestational Age

M van der Steen^{a,b}, A J Lem^b, A C S Hokken-Koelega^{a,b}

^aDivision of Endocrinology, Department of Pediatrics, Erasmus MC Sophia, Rotterdam, The Netherlands; ^bDutch Growth Research Foundation, Rotterdam, The Netherlands

Background: GH treatment is effective in improving adult height (AH) in short children born Small for Gestational Age. If SGA children are short at the start of puberty, they could benefit from combined GH/GnRH Analogue (GnRHa) treatment. **Objective and hypotheses:** To determine the timing and progression of pubertal development in short SGA children, comparing GH treatment with combined GH/GnRHa treatment. **Method:** For the present study, 61 GH-treated SGA children were included. At the onset of puberty, 42 continued GH treatment (group A), while 19 started GnRHa treatment in addition to GH for 2 years (group B). Fifty-three children reached AH during follow-up. Pubertal onset was defined in girls as breast stage 2, in boys as a testicular volume $\geq 4 \text{ ml}$. **Results:** Age at pubertal onset was similar for girls in groups A and B ($P=0.42$). Boys in group B started puberty at a significantly younger age than boys in group A ($P=0.01$). For girls in group B, the time between restart of puberty, after discontinuation of GnRHa treatment, and menarche was 1.2 years. This was significantly shorter than the time between pubertal onset and menarche in girls in group A (1.9 years; $P=0.02$). In addition, time between pubertal restart and AH for girls and boys in group B was shorter than the time between pubertal onset and AH for children in group A ($P=0.004$ and $P=0.044$ respectively). **Conclusion:** The pace of pubertal progression in SGA children is different after treatment with combined GH/GnRHa treatment compared with GH treatment only. This may be explained by the fact that in children receiving combined treatment, puberty was already present before start of GnRHa treatment.

P2-D1-420

S.c. Injections of a Reversible Albumin-Binding GH Derivative (NNC0195-0092) in Adult Subjects with GH Deficiency is Well Tolerated

Michael Højby Rasmussen^a, Jurgita Janukonytė^b, Marianne Klose^c, Djordje Marina^c, Mette Tanvig^d, Lene Nielsen^a, Charlotte Höybye^e, Marianne Andersen^d, Ulla Feldt-Rasmussen^c, Jens Christiansen^b

¹Global Development, Novo Nordisk, Soeborg, Denmark; ²Aarhus University Hospital, Aarhus, Denmark; ³Rigshospitalet University of Copenhagen, Copenhagen, Denmark; ⁴Odense University Hospital, Odense, Denmark; ⁵Karolinska University Hospital, Stockholm, Sweden

Background: Recombinant human GH (rhGH) is normally administered as a daily s.c. injection. NNC0195-0092 is a reversible albumin-binding GH derivative developed with the aim of reducing clearance and thereby extending the exposure. It has previously been demonstrated that NNC0195-0092 is well tolerated in healthy subjects with the potential for once weekly administration. **Objective and hypotheses:** In this trial NNC0195-0092 was administered subcutaneously once weekly for 4 weeks to adult subjects with GH deficiency (AGHD). The subjects enrolled into the trial were on GH replacement therapy, either male or female with a BMI between 18.0 and 35.0 kg/m², age 20–70 years, HbA1c ≤8.0% and not on insulin treatment. **Method:** Fourteen days before being randomized the AGHD subjects discontinued their GH replacement therapy. Four escalating doses of NNC0195-0092 were tested; 0.02, 0.04, 0.08, and 0.12 mg/kg per week and in each dose-group 8 AGHD subjects were dosed with a s.c. administration of NNC0195-0092 (*n*=6) or Norditropin (*n*=2). At each dose level the safety and tolerability of NNC0195-0092 were evaluated. In addition, after first and fourth dosing at each dose level the pharmacokinetics and pharmacodynamics (IGFI and IGFBP3) was evaluated as well. **Results:** Multiple doses of NNC0195-0092 administered s.c. to AGHD subjects were well tolerated at all doses investigated, with no serious safety issues, or clinically significant local tolerability issues identified. No positive test results for anti NNC0195-0092 antibodies or anti hGH antibodies were reported. The reported adverse events (AE's) were overall similar to AE's observed in trials with daily hGH treatment and were thus well-known GH AE's (peripheral oedema, headache, myalgia, and arthralgia). **Conclusion:** In conclusion, multiple doses of NNC0195-0092 administered to AGHD patients are well tolerated and NNC0195-0092 may have the potential to serve as an efficacious and safe once-weekly treatment of GHD in children and adults.

P2-D1-421

The Effects of Delaying Puberty with GnRH Agonists in Patients with Idiopathic GH Deficiency

David B Dunger^a, Anders Lindberg^e, Helmut G Dörr^c, Cecilia Camacho-Hübner^d, Mitchell E Geffner^b

^aUniversity of Cambridge, Cambridge, UK; ^bThe Saban Research Institute of Children's Hospital, Los Angeles, USA; ^cPediatric Endocrinology Division, Children's Hospital, University of Erlangen, Erlangen, Germany; ^dPfizer Inc., Endocrine Care, New York, New York, USA; ^ePfizer Inc., Endocrine Care, Sollentuna, Sweden

Background: Treating central precocious puberty with GnRH agonist (GnRHa) to increase height gain is well-established. Although not recommended, GnRHa have also been used in patients with IGHD at onset of puberty yet there are few data on its efficacy. **Objective and hypotheses:** Growth prediction models derived from KIGS (Pfizer International Growth Database) may provide an opportunity to estimate additional height gain produced by pubertal blockade. **Method:** Growth data from all idiopathic GH deficiency (IGHD) patients in KIGS treated with GH and GnRHa (with start and end dates) were analyzed. From total pubertal growth (TPG) prediction models, we know the estimates for the effect of age at start of puberty, boys = -3.97 cm/year and girls = -3.68 cm/year (1). Therefore, we can estimate the effect of GnRHa by adjusting the model effect accordingly. By replacing the model effect with the actual cm in height, while on GnRHa, an estimated height gain can be calculated. **Results:** All results are summarized in the Tabl: Pubertal growth in a cohort of IGHD patients treated with GH and GnRHa. **Conclusion:** With addition of GnRHa to treat relatively early puberty in GH-treated children with IGHD, the estimated additional median gain in adult height is 2 cm/year on GnRHa (boys = 1.8 cm/year and girls = 2.2 cm/year). Our data show that this therapeutic concept may not achieve the expected benefit in height according to the TPG model.

	Boys ^a (<i>n</i> = 84)	Girls ^a (<i>n</i> = 113)
Start of GH		
Age (years)	9.7	9.5
Ht-SDS	-2.9	-3.3
Age at start of puberty (girls B2, boys testicular volume > 3 ml)	11.4	10.3
Start of GnRHa		
Age (years)	12.3	11.2
Ht-SDS	-1.8	-2.1
End of GnRHa		
Delta Ht (cm)	9.3	9.3
Delta Ht (cm) adjusted per KIGS model	2.7	3.0
Estimated cm/year	1.8	2.2
Duration of GnRHa (years)	1.6	1.7

^aAll are median values.

P2-D2-422

Perceptions and Expectations of Patients and their Families for the Effects of GH Treatment

Chrysoula Drosatou, Elpis-Athina Vlachopapadopoulou, Feneli Karachaliou, Vassileios Petrou, Eirini Kaloumenou, Stefanos Michalakos

Department of Endocrinology-Growth and Development, 'P & A Kyriakou' Children's Hospital, Athens, Greece

Background: Children's and parents' expectations regarding GH therapy results have been previously assessed. However, there are limited data on children's and adolescents perceptions of their own body size as compared with that of their age-related peers, as well as their expectations of their final stature. **Objective and hypotheses:** To evaluate the perceptions of GH treated children and their families for the child's stature and to assess the expectations and the degree of their satisfaction from it. **Method:** It is a prospective study using validated questionnaires (SAT). The patient cohort included 66 children (43 boys) with mean-age 13.2 years (s.d.=2.5 years) and it was conducted in the Endocrinology Department of one of the two main Pediatric Hospitals in Athens. For the comparisons of proportions χ^2 tests were used. **Results:** Results from the current study suggest that the majority of children have an inaccurate picture of their actual height as well as their predicted height, overestimating it in 80.3 and 89.4% respectively. Parents' perceptions of their child's height was somehow more realistic, with 65% holding an overestimated picture. Only 20.7% of parents were found to have realistic expectations for the growth promoting effects of GH treatment. There was a high level of agreement between parents' and children's perceptions (70.7%) and expectations (81%) for the child's present and future height. Moreover, a high percentage 86.3% of the children were convinced on the benefits of the treatment and 82.8% of them would continue it if they had the choice. **Conclusion:** The majority of children treated with GH and their families have overestimated both the child's present and predicted height. The high degree of agreement between them is probably due to failure of effective communication between the physician and the family or reflects misinterpretation of the given information within the family.

P2-D2-423

Normal Onset of Clinical Puberty for Age in GH-Treated Children with Noonan Syndrome or Turner Syndrome: Data from the NordiNet[®] IOS and ANSWER[®] Program

Judith Ross^a, Henrik Christesen^b, Peter Lee^c, John Germak^d, Birgitte Tønnes Pedersen^e, Primoz Kotnik^f

^aThomas Jefferson University, Philadelphia, Pennsylvania, USA;

^bHans Christian Andersen Children's Hospital, Odense University

Hospital, Odense, Denmark; ^cPenn State College of Medicine, The Milton S. Hershey Medical Center, Hershey, Pennsylvania, USA;

^dNovo Nordisk, Inc., Princeton, New Jersey, USA;

^eGlobal Development, Novo Nordisk A/S, Søborg, Denmark;

^fDepartment of Pediatric Endocrinology, UMC University Children's Hospital, Ljubljana, Slovenia

Introduction: Noonan syndrome (NS) and Turner syndrome (TS) are distinct genetic disorders with similarities in phenotype, including short stature. The NordiNet[®] IOS and the ANSWER Program[®] are observational studies evaluating effectiveness and safety of GH treatment in real-world practice. **Methods:** The study population included children with NS or TS with puberty recordings, enrolled in NordiNet[®] IOS or ANSWER[®] Program. Start of puberty was defined as the midpoint between last prepubertal and first pubertal records. Physical evidence of puberty was defined clinically by Tanner breast stage \geq II or testicular volume \geq 4 ml (or Tanner stage \geq GII). **Results:** Mean age for puberty start in female NS patients ($n=15$) was 11.61 ± 1.38 years; in male NS ($n=37$), 12.46 ± 1.51 years; in TS ($n=489$), 12.91 ± 1.87 years. Mean age at start of GH therapy in female NS was 9.21 ± 3.18 years; in male NS, 10.34 ± 2.67 years; in TS, 9.73 ± 3.28 years. In 100 TS patients with documented sex hormone therapy, 45% received sex hormones before (mean time 0.49 years) and 55% (mean time 1.09 years) after start of clinical puberty. Mean age at start of GH therapy in TS patients given sex hormones before puberty was 9.51 ± 3.58 years (puberty start 13.93 ± 1.69 years) and 10.07 ± 3.19 years in patients given sex hormones after start of puberty (puberty start 13.14 ± 1.57 years). TS patients starting sex hormones after spontaneous puberty tended to be shorter (height SDS at baseline -2.78 ± 0.99 vs -2.43 ± 1.06) compared with those receiving sex hormones before puberty start, and age for sex hormone initiation was 14.23 ± 1.52 vs 13.44 ± 1.83 years. **Conclusions:** This analysis suggests that clinical puberty onset in GH-treated NS and TS patients occurred within the normal population range. Some clinicians are confident to induce puberty in TS girls on GH therapy with exogenous sex hormone while a tendency to postpone sex hormone treatment in shorter TS patients has also been observed.

P2-D2-424

What Dose of hGH is Adequate as a Substitution Therapy in GH Deficient Children?

Antonis Voutetakis, Maria-Alexandra Magiakou, Catherine Dacou-Voutetakis, George Chrousos, Christina Kanaka-Gantenbein

Division of Endocrinology, Metabolism and Diabetes, 1st Department of Pediatrics, Medical School, National and Kapodistrian University of Athens, Athens, Greece

Background: After 50 years of hGH use for GH deficient (GHD) children the definition of the adequate hGH substitution

dose and response remain uncertain. **Objective and hypotheses:** We hypothesized that subjects with GHD caused by congenital pituitary defects constitute an ideal model for defining substitution dose of hGH. Consequently, an appropriate study group was formed and pertinent long-term data were retrospectively analyzed. **Method:** A total of 18 patients (12 boys and six girls) were included in the study: 12 with pituitary stalk interruption syndrome (PSIS), five with Prop1 and one with SHH gene mutations. **Results:** In boys, age at GHRx initiation was 5.3 ± 1.9 years, first year growth velocity (GV) 11.6 ± 2.2 cm, final height (FH) 175.3 ± 3.6 cm with a target height (TH) 169.9 ± 4.2 cm. In girls, age at GHRx initiation was 9.8 ± 2.6 years, first year GV 9.4 ± 2.2 cm, FH 160 ± 4.2 cm with a TH 160.4 ± 4.1 . First year GV in all patients fell within limits suggested as adequate first year response (Bakker *et al.*, 2008). The mean GH dose throughout the treatment period was 0.140 mg/kg per week. **Conclusion:** A GHRx dose of 0.140 mg/kg per week appears to be an adequate substitution therapy in GHD children offering a good first year GV and a FH well within or above the TH range. The better outcome in boys must be attributed to earlier therapy initiation rather than gender difference in responsiveness. It seems that currently recommended GHRx doses are supra-substituting doses apparently needed to overcome obstacles such as deficient hGH responsiveness and growth failure from other factors. In such cases, a search for other causes of deficient response or the use of prediction models may offer an improved outcome.

P2-D2-425

Electronic Devices and Single-Dose Dispensing Systems GH are the Most Efficient and Less Loss of Drug

Ignacio Diez-Lopez^a, Ainhua Sarasua-Miranda^a, Miriam Miriam Elizalde^a, Isabel Lorente-Blazquez^a, Cristina Minguez^b, Carlos Martínez-Martínez^b

^aChildren's Endocrinology Section, Pediatric Service, Vitoria/Basque Country, Spain; ^bPharmacy Service, University Hospital of Alava, Itoia/Basque Country, Spain

Background: Several pharmaceutical formulations marketed GHRH, were being restricted in their choice occasions. Three display groups: single-dose, pre-filled pens/vials and electronic devices, self-injection systems. The choice may contribute to a greater or lesser adherence and a difference in the final cost of treatment (drug loss), attributable to the device itself or presentation. Presentations that require reconstitution device load, partial doses or stop in Pen contribute to overall loss of mg. **Objective:** Comparison of costs and product loss between presentations of GH. **Method:** Retrospective observational study of comparative costs from the record regarding prescribed

dispensed mg: single dose syringes (JM) vs multidose vials (VM) vs electronic devices (DE). Variables: lost mg (and cost) annual/patient environment, noncompliant patients and patients with good fit. Studio 2012 (full 12 months). **Results:** 86 cases (100%) valid for loss analysis. Distribution: JM 38/86 (44%), VM 22/86 (26%) of 26/86 (30%). 12 patients collected less medication (14%) and of these three were noncompliant (3.5%). The number patients collected less medication is homogeneous in each subgroup. Globally more drug is collected: total dose prescribed mg 27 553 28 181 doses dispensed mg (628 mg difference (+2.2%)) in total additional cost of € 6 999.55 (+1.7%)/year. Total expenditure computed in pharmacy. 436 929 75€. Lost annually mg were significantly lower in the JM where even less hormone prescribed collected: -1.60 mg/patient per year (-4.50 to $+3.8$) with the DE: 3.65 mg/patient per year ($1.5-5.8$) vs the VM 19.08 mg/patient per year ($15.40-30.2$), $P < 0.001$, for the annual JM dispensation regarding prescribed is $< 0.45\%$ for most of $+1.32\%$ and for VM $+5.85\%$ more (depending on device $4.5-10.5\%$). A real purchase price 2012, for global spending requirements (mgr prescribed/€) (€ 429 929.75) could be a cost computed if everything was JM/DE 2.9% lower, compared to 9.8% higher if everything was VM. **Conclusion:** The use of JM and DE, could help prevent the annual loss of drug and thus improve the cost-related treatment, unless that improves the efficiency of VM.

P2-D2-426

The Level and Conformation of Blood Plasma Carotenoids in GH Deficient Children After 1 Year of GH Therapy

Maria Faassen^a, Maria Pankratova^a, Tatyana Shiryayeva^a, Elena Nagaeva^a, Valentina Peterkova^a, Svetlana Kovalenko^b, Adil Baizhumanov^b, Evgenia Parshina^b, Alexander Yusipovich^b, Georgy Maksimov^b

^aEndocrinology Research Centre, Moscow, Russia; ^bMoscow State University, Moscow, Russia

Background: Epidemiologic studies have shown strong associations between high carotenoids levels and reduced risk of developing various forms of cancer, cardiovascular system diseases, etc. **Objective and hypotheses:** Carotenoids are hydrophobic substances and are contained in blood in lipoprotein particles. Their conformation depends on their molecular environment. By evaluating the conformation of carotenoids we can obtain various information about the lipoprotein structure. The aim was to examine the total level of carotenoids and their conformation during GH treatment in prepubertal children with GHD and to elucidate their relationship to oxidative stress development. **Method:** 11 treatment-naïve prepubertal children with GHD were included in the study. The conformation

and total concentration of carotenoids were examined using Raman spectroscopy, their concentration – by calculating the area of Raman spectrum peak, the conformation was assessed as Raman spectrum select band ratios. The blood antioxidant system was examined using the activity of superoxide dismutase and catalase, thiobarbituric acid reactive substances and ceruloplasmin levels and the total antioxidant capacity of plasma. **Results:** The concentration of plasma carotenoids before treatment did not differ from data after treatment. The mean values of band ratios I_{1525}/I_{1160} and I_{1160}/I_{1008} before and after treatment did not differ. However, the mean value of ratio I_{1525}/I_{1008} after treatment decreased by 60%. The plasma carotenoid concentration didn't change significantly. **Conclusion:** The lack of change in total carotenoids levels, the same as a antioxidant parameters, during treatment in children with GHD probably indicates the absence of oxidative stress development and the lack of deterioration during treatment correspondingly. The decreasing of the band ratio at I_{1525}/I_{1008} was probably caused by changing of characteristics of the C-CH₃ bonds in carotenoids as a result of alterations in lipoproteins structure.

P2-D2-427

Effects and Safety of Recombinant Human GH in GH Deficient Children with Rathke Cyst

Liyang Liang, Lina Zhang, Zhe Meng, Hui Ou, Zhanwen He, Lele Hou, Dongfang Li, Pinggan Li, Xiangyang Luo

Department of Pediatrics, Sun Yat-sen Memorial Hospital, Guangzhou, China

Objective: To assess the effects and safety of recombinant human GH (rhGH) in GH deficient (GHD) children with Rathke cyst. **Methods:** The clinical data of 12 GHD children aged from 5–12 years old, whose radiologic diagnosis showed Rathke cyst during Jan 2010–Dec 2012 in our hospital, were analyzed retrospectively. rhGH was given subcutaneously to each enrolled child with a night dose of 0.1 IU/kg six to seven 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 SDs, IGF1, 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 -2.83 ± 1.36 ($P < 0.01$). In addition, IGF1 rose from (186.73 ± 73.32) $\mu\text{g/l}$ to (436.78 ± 208.60) $\mu\text{g/l}$ ($P < 0.01$), with IGFBP3 from (4.32 ± 0.96) mg/l to (5.63 ± 1.45) mg/l. The peak values of both IGF1 and

IGFBP3 were within normal limits. During the treatment and the follow-up period, the biochemical indices were normal and the volumes of the Rathke cysts didn't increase. **Conclusion:** The treatment of low level rhGH in GHD children with Rathke cyst was demonstrated effective in this study. Moreover, GH treatment is safe when fully evaluated and closely monitored.

P2-D2-428

The Interconnectivity Between GH Replacement Therapy and Subclinical Hypothyroidism on Growth Response in Children with Pituitary Dwarfism

Ioana Bodescu, Jeanina Idriceanu, Ioana Vasiliu, Adina Manolachie, Irina Oana Chifu, Iulia Crumpei, Cristina Cristea, Cristina Preda, Voichita Mogos, Carmen Vulpoi

University of Medicine and Pharmacy 'Gr.T. Popa', Iasi, Romania

Background: Administration of recombinant GH (rhGH) to GH-deficient children has yielded conflicting results concerning its impact on thyroid function. Data about patients developing subclinical hypothyroidism are scanty, but it is thought to be associated with impairment of metabolic profile and lower growth response. **Objective:** To investigate the frequency of SH in children with pituitary dwarfism treated with rhGH, as well as its influence on rhGH therapy effectiveness. **Method:** We reviewed the cases of 42 children (29 boys, 13 girls, aged between 4 and 14) with GH deficiency, who were qualified to rhGH therapy and treated for at least 1 year. Clinical and hormonal data (IGF1, TSH, and fT_4), as well as radiographic bone assessments were documented at the beginning and after first year of rhGH treatment. **Results:** At therapy onset, all patients had the height below the -2.5 s.d. (mean s.d. of -3.2), bone age was delayed, IGF1 concentration was either decreased or close to lower limit of normal range and there was no impairment in thyroid function. After one year of rhGH therapy, SH was the only impairment in thyroid function and it was diagnosed in 6 patients (16.6% of cases). Despite similar IGF1 secretion increase, the improvement of height velocity was significantly lower in children with SH (0.65 cm/month) than in those who remained euthyroid (0.88 cm/month, $P < 0.05$). Furthermore, an increase in IGF1 levels was associated with increasing levels of TSH in SH patients and led in two cases to administration of L-T₄ substitution. **Conclusion:** The incidence of subclinical hypothyroidism during the initial phase of rhGH treatment in children with pituitary dwarfism and on the growth rate should be taken into account, as it may worsen the growth response and may be worsened by the rhGH therapy.

P2-D2-429

What Should be the Diagnosis and Management of Short Children with IGF1 Deficiency, Responding to GH Administration Despite Normal GH Secretion?

Joanna Smyczynska^a, Renata Stawerska^a, Andrzej Lewinski^{a,b}, Maciej Hilczer^{a,c}

^aDepartment of Endocrinology and Metabolic Diseases, Polish Mother's Memorial Hospital, Research Institute, Lodz, Poland;

^bDepartment of Endocrinology and Metabolic Diseases, Medical University of Lodz, Lodz, Poland; ^cDepartment of Pediatric Endocrinology, Medical University of Lodz, Lodz, Poland

Background: GH deficiency (GHD) is currently defined as secondary IGF1 deficiency (IGFD). In the patients with normal GH secretion and IGFD, significant increase of IGF1 during generation test excludes primary IGFD, however is not an approved indication for GH therapy. **Objective and hypotheses:** The aim of the study was to assess GH therapy effectiveness in children with IGFD, responding to short-term GH administration despite normal GH peak after falling asleep and in stimulating tests. **Method:** Analysis comprised 42 patients with spontaneous (after falling asleep) and stimulated GH peak >10.0 ng/ml, and IGFD (IGF1 SDS for age and sex <-1.0), in whom IGF1 concentrations at least doubled and normalised during generation test, subjected to GH therapy. First-year response to treatment: height velocity (HV) increase and IGF1 SDS increase was assessed in all of them, final height FH - in 28 patients. The therapy effectiveness was compared with 110 children with partial GHD (pGHD), including 42 treated up to FH. **Results:** In IGFD group, height SDS before treatment (hSDS-0) was -2.87 ± 0.72 , in first year of treatment HV increased from 3.8 ± 0.9 to 9.4 ± 1.9 cm/year, IGF1 SDS increased from -2.19 ± 0.78 to 0.34 ± 1.07 , FH SDS was -1.14 ± 0.82 and increased by 1.61 ± 1.08 SDS with respect to hSDS-0. In pGHD group, hSDS-0 was -2.79 ± 0.59 , HV increased from 3.8 ± 1.4 to 9.8 ± 2.1 cm/year, IGF1 SDS increased from -1.76 ± 0.88 to 0.52 ± 0.87 , and FH SDS was -1.20 ± 0.80 and increased by 1.48 ± 0.83 vs. hSDS-0. The differences in age, GH dose, therapy duration and all the analysed indices of GH therapy effectiveness between the groups were insignificant. **Conclusion:** Children with short stature, normal spontaneous and stimulated GH secretion and decreased IGF1 concentrations which increase significantly in generation test, may benefit during GH therapy similarly to children with pGHD. It seems worth considering not diagnose idiopathic short stature in such patients.

P2-D2-430

A Reappraisal of the Cut-Off Limits of the Peak GH Response to Stimulation Tests for the Diagnosis of GH Deficiency in Children and Adolescents

Chiara Guzzetti^a, Anastasia Ibba^a, Sabrina Pilia^a, Nadia Beltrami^b, Natascia Di Iorgi^c, Alessandra Rollo^d, Giorgio Radetti^b,

Stefano Zucchini^d, Mohamed Maghnie^c, Marco Cappa^e, Sandro Loche^a

^aServizio di Endocrinologia Pediatrica, Ospedale Microcitamico, Cagliari, Italy; ^bOspedale Generale Regionale, Bolzano, Italy;

^cUniversità di Genova/IRCCS Giannina, Genova, Italy; ^dUniversità di Bologna, Ospedale S. Orsola-Malpighi, Bologna, Italy; ^eUnità Operativa di Endocrinologia, Ospedale Pediatrico Bambin Gesù, Roma, Italy

Background: The diagnosis of GH deficiency (GHD) in children and adolescents is classically established when GH concentrations fail to reach an arbitrary cut-off level (usually 7–10 µg/l) after at least two provocative tests (PT). **Objective and hypotheses:** Aim of the study was to define optimal GH cut-offs to different PT in children and adolescent with short stature. **Method:** This was a retrospective study in 437 subjects who underwent GH secretion studies for short stature, after exclusion of other causes for their shortness. GH and IGF1 were measured by the same chemiluminescence assay in all samples (Immulite, Siemens). Patient group (P) consisted of 126 patients (66 boys, 60 girls, aged 11.4 ± 3.7): 121 organic or genetic GHD and five subjects with peak GH <8.5 µg/l in two PT, H-SDS <-3 SDS and IGF1 SDS <-2 SDS. Control group (C) consisted of 311 subjects (196 boys, 115 girls, aged 9.8 ± 4.5) with normal GH response to at least one PT. The PT used were Arginine (154 C, 90 P), insulin tolerance test (ITT; 74 C, 86 P) and Clonidine (173 C, 26 P). All PT were performed between 08.00 and 09.00 h after fasting overnight. Receiver operating characteristic (ROC) analysis and likelihood ratio (LR) were used to evaluate the optimal GH cut-offs and the diagnostic accuracy of the PT. **Results:** ROC analysis showed that optimal GH cut-off for Arginine test is 8.2 µg/l (Sens=83.3%, Spec=81.2%, LR=4.43), for ITT is 5.3 µg/l (Sens=79.1%, Spec=87.8%, LR=6.5) and for Clonidine test is 8.6 µg/l (Sens=88.5%, Spec=90.2%, LR=9). ROC analysis showed that IGF1 SDS has low accuracy in diagnosing GHD (AUC=0.69). **Conclusion:** The results of ROC analysis showed that the cut-off limits which discriminate between normal and GHD are lower than those commonly employed, and differ according to the stimulation test. IGF1 is characterized by low diagnostic accuracy.

P2-D2-431

Vitamin D Concentrations in Children with GH Deficiency During First Year of GH Treatment

Beata Pyrzak, Ewelina Witkowska-Sedek, Anna Kucharska, Magdalena Sagala, Anna Majcher

Medical University of Warsaw, Warsaw, Poland

Introduction: The start of GH (rhGH) treatment in children with GH deficiency (GHD) causes a significant increase in bone

turnover and increases height velocity. The increase in IGF1 concentrations during rhGH treatment is a marker of the efficiency of treatment. A significant increase in bone turnover during rhGH treatment results in an increased demand for vitamin D. It is important to determine proper supplementation doses of vitamin D in patients during catch-up growth. **Aim of study:** The aim of the study was to evaluate the correlation changes of 25-hydroxyvitamin D concentrations during the first year of GH treatment. **Material and methods:** The study group consisted of 76 children aged 3–16 years with GHD. IGF1, 25-hydroxyvitamin D concentrations and anthropometric parameters were measured at baseline and after 6 and 12 months of treatment. Bone age was evaluated at baseline and after 12 months of treatment. **Results:** Vitamin D status at baseline correlated with height velocity before rhGH treatment ($P < 0.05$, $r = 0.49$). The mean 25-hydroxyvitamin D concentration at baseline was 19.57 ng/ml (± 6.19 s.d.) and after 12 months of rhGH treatment with vitamin D supplementation it increased to 24.1 ng/ml (± 6.88 s.d.). A negative correlation between $\Delta 25$ -hydroxyvitamin D and Δ IGF1 ($P < 0.05$, $r = -0.38$) was found. **Conclusions:** Vitamin D status is related to height velocity and adequate vitamin D supplementation is important in patients with GHD during catch-up growth, when their bone turnover is increased as a result of rhGH treatment. Determining proper supplementation doses of vitamin D in such cases requires further research.

Table 1.

Visit	HOMA-IR		HOMA-IR by PS	
	All children	<i>n</i>	Tanner I	Tanner \geq II
Basal	1.2	294	1.2	2
1	2	292	1.8	3.6
2	2.3	231	1.9	3.4
3	2.6	170	2.4	3.1
4	2.5	120	2.2	2.8
5	2.8	63	2.2	3.3

1.0–1.5 and Tanner \geq II: 2.0–2.8)) (Cuartero 2007). HOMA-IR increased to 2.8 (2.8) in the fifth year, above normality in both PS groups (2.2 (1.0) vs. 3.3 (3.7)). GV and height difference (HSDS) were the highest during the first year of treatment tending to approach the reference value. Four adverse events were detected, including one event of type 2 diabetes mellitus in patient without medical history of glucose intolerance. No events were associated with insulin insensitivity. **Conclusion:** Treatment with GH during 5 years increased GV, reducing the height differences presented by SGA children, regardless PS. HOMA-IR showed an increase during the 5 years, with slightly higher values than in normal population. This study demonstrated efficacy of GH treatment in children SGA. Insulin sensitivity should be monitored as per SmPC.

P2-D2-432

Growth Hormone Treatment in Children with SGA During a 5-Year Period, Assessment of Auxological Development and Insulin Resistance

J P López-Siguero^a, M J Martínez-Aedo^a, J A Bermúdez^b, N Cabrinety^c, J Bosch^d, J L Lechuga^e, R Torralba^f

^aHospital Materno-Infantil de Málaga, Málaga, Spain; ^bHospital Virgen de la Macarena, Sevilla, Spain; ^cHospital Sagrado Corazón, Barcelona, Spain; ^dHospital Arnau de Vilanova, Lleida, Spain; ^eHospital Virgen del Mar, Cádiz, Spain; ^fMerck S.L., Madrid, Spain

Background: Treatment with GH of children born SGA allows an increase in growth velocity (GV) and improves adult height. Increased insulin resistance has been described in these patients, which reverts after interrupting GH administration. However, long-term metabolic consequences are not clearly established. **Objective and hypotheses:** Describe insulin resistance (HOMA-IR index) and auxological development (GV and height) in SGA children treated with GH for 5 years, and analyse the influence of the pubertal status (PS). **Method:** Prospective observational study of 407 SGA subjects treated with GH (Saizen[®]) for up to 5 years, determining the HOMA-IR index, GV, height, and PS annually. **Results:** Baseline HOMA-IR was 1.2 (1.5), where Tanner I children had lower values than Tanner \geq II (1.2 (1.6) vs. 2.0 (0.7)), as reported in normal population (Tanner I:

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Comparison of Measured Lean Body Mass (LBM_{DXA}) and Estimated LBM_{BIA} in Children with GH Deficiency

Roland Schweizer, Julian Ziegler, Laura Frank, Gerhard Binder
University Children's Hospital, Tübingen, Germany

Background: Long standing GH deficiency (GHD) causes loss of muscle mass. DXA enables the measurement of LBM_{DXA} but is accompanied with a potentially harmful X-ray exposition. BIA measures the electric resistance of the body which correlates with LBM. A comparison of both methods in children with GHD has not been performed yet. **Aim:** Calculation of a regression formula for LBM using resistance and anthropometry based on LBM_{DXA} in children with GHD. **Method:** We recruited 120 prepubertal children (31 females) with GHD defined as growth failure, bone age retardation, low IGF1 and two GH test peaks < 10 μ g/l (mean \pm s.d.; age 7.68 ± 2.96 years, peak GH 5.72 ± 1.76 ng/ml). Height (ht), weight (wt), LBM by DXA (Lunar, DPXL/PED), resistance (R) and reactance (Xc) by BIA (BIA 2000-M) were measured before the start of GH therapy. Using multiple stepwise regression analysis we established a formula to calculate LBM based on age, height, weight, R and Xc. **Results:** The best equation formula calculated was $LBM_{BIA} \text{ (kg)} = 233.64$

$\times \text{ht (cm)} + 181.41 \times \text{wt (kg)} - 6.89 \times R (\Omega) - 9421.74$ ($R = +0.98$). Comparison of LBM_{BIA} and LBM_{DXA} by Bland-Altman plot gave a mean difference of -0.075 ± 0.923 kg within an LBM_{DXA} range of 7–30 kg. In an individual patient the delta between LBM_{BIA} and LBM_{DXA} were up to 3 kg at an LBM_{DXA} of 30 kg. **Conclusion:** Calculation of LBM with help of anthropometry and BIA shows a good correlation with measured LBM in the total group of GHD patients, but in individual patients there is a broad variation between measured and calculated LBM.

P2-D2-434

Metabolic Assessment in Children with GH Deficiency Before, During, and After Human GH Replacement Therapy

Barbara Predieri, Silvia Mazzoni, Valentina Paraluppi, Viviana Patianna, Laura Lucaccioni, Simona Madeo, Patrizia Bruzzi, Lorenzo Iughetti

Department of Medical and Surgical Sciences of the Mother, Children and Adults, University of Modena and Reggio Emilia, Modena, Italy

Background: GH has several effects on lipid and glucose homeostasis. In adults GH deficiency (GHD) has been associated to increased mortality for cardiovascular disease (CVD). In childhood few studies have investigated the effect of GHD and recombinant human GH (rhGH) therapy on metabolic parameters that may increase the risk of CVD. **Objective and hypotheses:** To assess changes of lipid profile, insulin-resistance indexes, and CVD risk in children and adolescents with GHD before, during, and after rhGH therapy. **Method:** Forty-six subjects (11.3 ± 2.28 years old; 25 boys) with GHD were studied. All patients underwent to fasting blood samples in order to assess glycemia (G), insulin (I), total cholesterol, LDL, HDL, triglycerides, and IGF1. Moreover, G/I ratio, HOMA-IR, and atherogenic index (AI) were calculated. All data were collected at diagnosis (T_0), during rhGH therapy (T_1 1-year, rhGH dose 0.034 ± 0.003 mg/kg per day; T_2 2-year, rhGH 0.030 ± 0.003 mg/kg per day; T_3 stop-therapy, and rhGH 0.028 ± 0.004 mg/kg per day), and at 1-year off-therapy (T_4). Longitudinal data were analyzed using Friedman ANOVA and are reported as mean \pm s.d. **Results:** We demonstrated a significant increased of insulin levels (T_0 6.65 ± 4.17 , T_1 13.4 ± 5.19 , T_2 10.2 ± 2.55 , T_3 16.1 ± 6.76 , T_4 9.07 ± 4.05 $\mu\text{IU/ml}$; $\chi^2 = 36.8$, $P < 0.0001$) and HOMA-IR (1.41 ± 0.88 , 2.91 ± 1.27 , 2.20 ± 0.61 , 3.65 ± 1.88 , and 1.91 ± 0.91 ; $\chi^2 = 34.0$, $P < 0.0001$). A significant decreased of G/I ratio (18.1 ± 10.7 , 7.27 ± 2.44 , 9.40 ± 3.88 , 6.50 ± 2.92 , and 11.9 ± 7.31 ; $\chi^2 = 34.4$, $P < 0.0001$) and HDL levels (61.6 ± 15.3 , 62.1 ± 15.2 , 65.2 ± 10.1 , 56.0 ± 17.7 , and 52.8 ± 16.6 mg/dl; $\chi^2 = 13.3$, $P = 0.0100$) was also found. AI was not significantly changed (2.77 ± 0.52 , 2.73 ± 0.48 , 2.69 ± 0.43 , 3.00 ± 0.78 , and 3.12 ± 0.74 ; $\chi^2 = 4.69$, $P = 0.3208$) **Conclusion:** GHD was not associated with impaired lipidic and glycemic metabolism. During rhGH

treatment we demonstrated a significant worsening of insulin-resistance indexes and HDL values despite they were always in the normal range. No change of AI was found. GHD and rhGH therapy seem not to impair CVD metabolic risk factors.

P2-D3-435

First-year Growth Response to GH in Relation to Final Height Outcome in Prepubertal Children with Idiopathic GH Deficiency

Saartje Straetmans^{a,b}, Muriel Thomas^c, Sylvie Tenoutasse^{c,d}, Jean De Schepper^{e,f}, Raoul Rooman^{b,c}

^aDepartment of Pediatric Endocrinology, University Hospital Maastricht, Maastricht, The Netherlands; ^bDepartment of Pediatric Endocrinology, University Hospital Antwerp, Antwerp, Belgium; ^cThe Belgian Study Group for Pediatric Endocrinology, Brussels, Belgium; ^dDepartment of Pediatric Endocrinology, University Children's Hospital HUDE, Brussels, Belgium; ^eDepartment of Pediatric Endocrinology, University Hospital Brussels, Brussels, Belgium; ^fDepartment of Pediatric Endocrinology, University Hospital Ghent, Ghent, Belgium

Background: Several definitions of poor growth response to first-year GH treatment, have been proposed based on the observed response of a large group of patients. **Objective and hypotheses:** Since a complete compensation of the height deficit is expected in children with GH deficiency (GHD) treated with GH, we have studied the different parameters for the first-year growth response in relation to the adult height gain in prepubertal children with iGHD. **Method:** Height data at start, after 1 year of GH treatment, and at near final adult height (nFAH) of 142 prepubertal children (93 boys) with GHD, were retrieved from the National Database of the Belgian Study Group for Pediatric Endocrinology. These patients had been treated with GH for at least 4 consecutive years with at least 1 year before pubertal onset. First-year change in height SDS (ΔHtSDS), first-year height velocity (HV) and total height SDS gain from start up to nFAH (total $\Delta\text{Ht SDS}$) were calculated. A poor final growth outcome was defined as total $\Delta\text{Ht} < 1$ SDS. **Results:** Mean (s.d.) nFAH SDS was -1.69 ± 3.26 , nFAH – midparental height SDS was -0.03 ± 1.79 , and total $\Delta\text{Ht SDS}$ was 1.73 ± 0.66 . By ROC analysis first-year HV SD < 0.70 , and $\Delta\text{HtSDS} < 0.3$ are very sensitive criteria (96.8 and 96.6% sensitivity respectively) to predict a total gain in height SDS < 1 . The corresponding specificities are 20 and 23.1%. The areas under the curve are respectively 77.1 and 79%. The accuracies of the tests are respectively 79.8 and 81.7%. **Conclusion:** Our results confirm that a first-year change in height SDS < 0.3 will detect almost all poor final height responders, but due to its low specificity it is not always associated with a poor final height outcome. Depending on the chosen sensitivity or specificity, different cut-offs for poor first-year response can be determined by ROC analysis.

P2-D3-436**Reevaluation of GH Secretion During Puberty in Children Diagnosed as GH-deficient During Childhood**

Diego Ramaroli, Evelina Maines, Claudia Anita Piona, Grazia Morandi, Rossella Gaudino, Franco Antoniazzi

Department of Life Sciences and Reproduction Sciences, Pediatric Clinic, 'Giambattista Rossi' Hospital, University of Verona, Verona, Italy

Background: GH secretion increases physiologically during puberty and GH levels correlate with pubertal stage. Therefore, puberty is the most likely time for normalization of GH secretion in children with GHD. No studies have so far evaluated in children diagnosed as GH-deficient during childhood potential predictors of response to the reevaluation of GH secretion during puberty. **Objective and hypotheses:** The aim of our study is to establish and compare the characteristics of children with isolated GHD who normalized GH secretion during puberty (group A) compared with those who showed a persistently deficient secretion (group B). **Method:** Auxological data and GH peak level at initial diagnosis and at reevaluation of GH secretion during puberty were evaluated in 58 children (35 boys and 23 girls) diagnosed with GHD by means of arginine and insulin or glucagon tests (peak <7 µg/l) during childhood. All children underwent reevaluation of GH secretion by mean of arginine test during puberty. **Results:** Thirty-nine subjects (67.2%) normalized GH secretion and 19 subjects (32.7%) confirmed GHD. No significant differences were observed at diagnosis between the two groups in the mean height s.d. (-2.47 ± 0.53 s.d. in group A and -2.43 ± 0.38 s.d. in group B) and in the mean difference between chronological age and bone age (1.62 ± 1.25 years in group A and 1.64 ± 1.17 years in group B). GH peak level by mean of arginine test in patients classified as having persistent GHD was significantly lower than patients with normalized GH secretion (3.81 ± 2.72 µg/l in group B and 5.24 ± 2.34 µg/l in group A; $P=0.028$). **Conclusion:** As regard of the results, in children diagnosed as affected by GHD during childhood seems convenient to reevaluate GHD during puberty. Children with lower levels of GH peak value by mean of arginine test at diagnosis seem to have more probabilities to keep GHD during puberty.

P2-D3-437**Long-Term Effects of GH Replacement Therapy on Thyroid Function in GH Deficiency Children**

Andrea Esposito, Iolanda Di Donato, Martina Rezzuto, Sara Alfano, Cristina Moracas, Donatella Capalbo, Mariacarolina Salerno

Pediatric Endocrinology Unit, Department of Translational Medical Sciences, University 'Federico II' of Naples, Naples, Italy

Background: Several studies have investigated the effects of GH replacement therapy (GHRT) on thyroid function in children with GH deficiency (GHD) leading to contrasting results. Indeed, GHRT has been reported to affect the peripheral metabolism of thyroid hormones, to alter TSH secretion by pituitary and to unmask secondary hypothyroidism. **Objective and hypotheses:** To evaluate long-term effects of GHRT on thyroid function in a large cohort of GHD children. **Method:** Sixty-five children (40M) aged 9.47 ± 3.73 years with isolated GHD were studied before and during the first 3 years of GHRT. Clinical parameters (height, weight, BMI, and growth velocity) and serum TSH, FT₄, FT₃, and IGF1 levels were evaluated at baseline, after 6 months of GHRT and then annually. **Results:** At study entry, all GHD children were euthyroid and none became hypothyroid during the follow-up. Six months of GHRT were associated with reduction in FT₄ levels and increase in FT₃ levels even though they were still normal associated with no differences in TSH concentrations. No further modifications were observed in the following years of therapy. **Conclusion:** In GHD children GHRT was associated with a persistent decrease of FT₄ concentrations which however remained within reference ranges. Whether these mild changes may have a clinical impact should be further investigated.

P2-D3-438**Does Priming with Sex Steroids Before GH Stimulation Test Increase the Diagnosis of Normal GH Secretion in Short Children?**

Ashraf Soliman^a, Vincenzo De sanctis^b, Elkhansa Elgaali^a, Hannah Ahmed^a, Aml Sabt^a, Randa Nassar^a

Table 1. (for abstract P2-D3-437)

	Baseline	6 months	1 year	2 years	3 years
Height (SDS)	-2.73 ± 0.82	-2.42 ± 0.73^a	-2.18 ± 0.72	-1.77 ± 0.78	-1.52 ± 0.85
BMI (SDS)	-0.35 ± 1.21	-0.51 ± 1.20^a	-0.44 ± 1.13	-0.45 ± 1.16	-0.32 ± 1.20
Growth velocity (SDS)	-2.57 ± 1.45	3.30 ± 2.63^a	3.09 ± 3.16	2.65 ± 3.21	1.62 ± 2.81
FT ₄ (ng/dl)	1.20 ± 0.22	1.14 ± 0.20^a	1.13 ± 0.22	1.14 ± 0.21	1.14 ± 0.21
FT ₃ (pg/ml)	3.79 ± 0.72	4.01 ± 0.69^a	4.03 ± 0.71	3.97 ± 0.66	3.99 ± 0.69
FT ₄ /FT ₃	0.32 ± 0.06	0.28 ± 0.04^a	0.28 ± 0.04	0.29 ± 0.04	0.28 ± 0.04
TSH (µU/ml)	2.67 ± 1.28	2.63 ± 1.48	2.71 ± 1.45	2.48 ± 1.15	2.55 ± 1.28
IGF-1 (SDS)	-0.99 ± 1.06	0.22 ± 1.45^a	0.81 ± 1.69	0.93 ± 1.72	0.58 ± 1.34

Table 1. (for abstract P2-D3-438)

		Age	HtSDS	Basal GH	Peak GH	IGF1	Free T ₄
Primed >9 years n=50	Mean s.d.	12.0 1.5	-2.1 0.3	1.5 3.1	11.4 6.4	164.1 77.6	15.0 2.0
Non primed >9 years n=42	Mean s.d.	12.5 1.4	-2.2 -0.3	3.0 4.4	10.5 7.5	160.7 57.9	15.3 2.4
Non primed <9 years n=32	Mean s.d.	7.2 1.6	-2.2 -0.4	3.0 4.4	10.5 7.5	160.7 57.9	15.3 2.4

^aHamad General Hospital, Doha, Qatar; ^bQuisisana Hospital, Ferrara, Italy

Introduction: There is still controversy for priming with sex steroid before GH testing. **Objective and hypotheses:** We studied GH response to stimulation in 92 children >9 years with idiopathic short stature (HtSDS -2). They were divided randomly into two groups. Children in group 1 (n=50) were primed with premarin in girls and testosterone in boys and those in group 2 were not primed (n=42). All children were tested using standard clonidine test and their serum IGF1 factor-I concentration measured. Additionally the growth and GH-IGF1 data of group 2 children were compared with those for 32 short children (HtSDS <-2) < age 9 years who were also non-primed before GH testing (group 3). **Results:** Neither GH peak response to provocation nor IGF1 concentrations differed between the two groups with and without priming. **Discussion:** Taking a cut-level of 10 µg/l for normal GH response to clonidine, priming with sex steroids did not significantly increase the percentage of patients with normal GH response (52%) vs non-priming (47%). IGF1 level did not show any significant difference among the two studied groups >9 years. The peak GH response to clonidine provocation did not differ before (n=42) vs after 9 years (n=32) of age. **Conclusion:** In this randomized study priming with sex steroids before GH testing did not significantly increase the yield of diagnosing short patients with normal GH secretion. In addition, GH response to provocation did not vary significantly between young (<9 years) and old (>9 years) short children.

^aHôpital des Enfants, Toulouse, France; ^bInstitute for Experimental Paediatric Endocrinology, Charité – Universitätsmedizin Berlin, Berlin, Germany; ^cSchool of Medicine, Belgrade University, Belgrade, Serbia; ^dInstitute for Mother and Child Health Care of Serbia, Belgrade, Serbia; ^eNovo Nordisk A/S, Søborg, Denmark; ^fNovo Nordisk Health Care AG, Zurich, Switzerland

Introduction: In Europe, GH is approved for short (height SDS <-2.5) children born small for gestational age (SGA) who fail to show catch-up growth by 4 years of age. **Methods:** This report analysed the patterns of GH dose used in everyday clinical practice based on short children born SGA enrolled in NordiNet[®] IOS, an observational study evaluating the long-term effectiveness and safety of Norditropin[®]. Average GH dose, exposure time, age and height SDS at baseline and after initiation of GH treatment were calculated. The proportions of patients with low (<30 µg/kg per day), medium (30-50 µg/kg per day), and high (≥50) GH dose were analysed as were the proportions with a decrease or an increase of >10%, or no change from baseline dose within the first year of treatment. **Results:** Overall, 2652 children born SGA were analysed (mean ± s.d.) (exposure, 3.4 ± 2.4 years; age at GH start, 7.8 ± 3.3; and baseline height SDS, -2.9 ± 0.8). The mean ± s.d. GH dose for the full treatment period was 38.6 ± 10.0 µg/kg per day. Mean GH dose was similar between genders and unchanged through 4 years of treatment (Table). Baseline height SDS significantly correlated with GH dose (P<0.0001): mean height SDS was -2.8 in the low (n=296; GH, 25.8 ± 5.1 µg/kg per day), -2.9 in the medium (n=2044; GH, 37.3 ± 4.8 µg/kg per day), and -3.1 in the high (n=312; GH, 59 ± 9.4 µg/kg per day) dose groups. Within the first year of treatment, dose increased for 1.7% and decreased for 14.8% of patients. Baseline height SDS was lower in patients with increasing GH dose (-3.1 ± 1.1) than for those with no change (-2.8 ± 0.8) (P=0.003) or decreased (-2.3 ± 0.7) dose (P=0.005). **Conclusions:** In clinical practice, a very narrow range of GH doses is used for short children born SGA and doses tend to remain unchanged

P2-D3-439

GH Dosing Patterns in Short Children Born Small for Gestational Age

Isabelle Oliver Petit^a, Oliver Blankenstein^b, Dragan Zdravkovic^{c,d}, Birgitte Tønnes Pedersen^e, Effie Pournara^f

Table 1. (for abstract P2-D3-439)

	GH dose (mean ± s.d.)				
	Baseline	Year 1	Year 2	Year 3	Year 4
All	37.6 ± 12.3	38.8 ± 11.7	40.1 ± 11.8	40.4 ± 11.8	39.8 ± 11.8
Girls	37.6 ± 12.0	38.9 ± 11.3	40.5 ± 11.3	40.8 ± 11.4	40.3 ± 11.8
Boys	37.7 ± 12.7	38.7 ± 12.0	39.7 ± 12.2	40.1 ± 12.1	39.4 ± 11.9

over time. Children with the lowest height SDS are more likely to receive GH in the higher dose range.

P2-D3-440

Two-Year Data from a Long-Term, Phase IV Study of Omnitrope[®], a Recombinant Human GH, in Short Children Born Small for Gestational Age

Hans-Peter Schwarz^a, Dorota Birkholz-Walerzak^b, Mieczyslaw Szalecki^c, Mieczyslaw Walczak^d, Corina Galesanu^e, David Metrevelif, Jasmin Khan-Bolukij^g, Ellen Schuck^g

^aUniversity Children's Hospital Munich, Munich, Germany; ^bMedical University, Gdansk, Poland; ^cChildren's Health Research Institute, Warsaw, Poland; ^dPomeranian Medical University, Szczecin, Poland; ^eUniversity of Medicine and Pharmacy 'Gr.T.Popa', Iasi, Romania; ^fTbilisi State Medical University, Tbilisi, Georgia; ^gSandoz Biopharmaceuticals, Holzkirchen, Germany

Background: Children born small for gestational age (SGA) are predisposed to metabolic abnormalities. While the therapeutic benefit of recombinant human growth hormone (rhGH) therapy in improving height is widely recognised, it can affect carbohydrate metabolism, potentially inducing diabetes. **Objective and hypotheses:** This ongoing, prospective study aims to evaluate the long-term safety and efficacy of Omnitrope[®] (somatotropin) in children born SGA. Here, interim data from patients who completed 2 years of treatment are provided. **Method:** Prepubertal children born SGA were recruited according to standard criteria and will be treated with Omnitrope[®] and followed at predetermined time intervals until final height is reached. **Results:** Of 278 children enrolled, 249 completed their 2-year assessment. Mean oral glucose tolerance (2 h), HbA1c, and fasting glucose levels did not change significantly from baseline to year 2; however, fasting insulin levels increased from baseline to year 1 ($\Delta +18.03$ pmol/l) and from years 1 to 2 ($\Delta +6.59$). Auxological measurements indicated improvements in height parameters from baseline to year 2, including mean height SDS (HSDS; net gain $\Delta +1.25$), height velocity (HV; $\Delta +3.04$ cm/year), and peak-centred HVSDS (baseline: -2.13 ; year 1: $+4.16$; year 2: $+2.23$). Similarly, mean IGF1 SDS and IGFBP3 SDS also increased markedly throughout the study; the mean difference (baseline to Year 2) in molar IGF1/IGFBP3 SDS ratios was: $\Delta +2.14$. Reasons for treatment discontinuation comprised non-response ($n=13$), withdrawal of consent ($n=11$), loss to follow-up ($n=3$), adverse event ($n=1$), and other ($n=1$). There was one treatment-related serious adverse event (severe headache); the patient recovered and continued treatment. The incidence of anti-rhGH antibodies remained low

and transient during the study (1.2% at year 2) and did not lead to discontinuation. **Conclusion:** At this 2-year follow-up, no patient developed diabetes during rhGH treatment and there were no concerning or clinically relevant safety findings. In addition, Omnitrope treatment was effective, as documented by all height parameters.

P2-D3-441

Effects of Gender and Gestational Age on GH Treatment in Very Young Children Born Small for Gestational Age

Margaret Boguszewski^a, Anders Lindberg^b, Hartmut A Wollmann^c

^aFederal University of Parana, Curitiba, Brazil; ^bPfizer, Inc., Endocrine Care, Sollentuna, Sweden; ^cPfizer, Inc., Endocrine Care, Berlin, Germany

Background: Children born small for gestational age (SGA) with poor growth during the first years of life often remain with short stature during childhood and as adults. **Objective and hypotheses:** To evaluate the effects of gender and gestational age (GA) on outcomes of GH treatment in very young children born SGA. **Method:** 620 short SGA children on GH treatment enrolled in KIGS (The Pfizer International Growth Database) were analysed: 2–4 years age group ($n=156$; 100 boys; median age 3.3 years; 50% with GA ≤ 37 weeks) and 4–6 years group ($n=464$; 284 boys; median age 4.9 years; 42.2% with GA ≤ 37 weeks). **Results:** In the 2–4 years group, girls presented lower height SDS (HSDS) at start of treatment (-4.18 vs -3.80 ; $P<0.01$), presented a higher increase in height during the first year (Δ HSDS 1.02 vs 0.87; $P<0.05$), with consequent disappearance of the difference in height at 3 years of treatment. In the 4–6 years group, girls were also shorter (HSDS -3.57 vs -3.33 ; $P<0.01$), but their height velocity (HV) during the first year of treatment was lower (2.74 vs 3.36 SDS; $P<0.01$); HSDS was still different at 3 years of therapy (-2.15 vs -1.93 SDS; $P<0.05$). Preterm children in the 4–6 years group were younger than the term ones at GH start (4.8 vs 5.0 years, $P<0.01$), leaner (weight SDS -3.41 vs -2.95 , $P<0.001$) and had a lower adjusted parental height (-2.44 vs -2.14 , $P<0.01$). In the 2–4 years group, compared to term ones, preterm children received higher GH dose (0.38 vs 0.32 mg/kg per week, $P<0.05$) and presented higher HV SDS only during the first year of therapy (2.49 vs 1.87, $P<0.05$). **Conclusion:** Among very young SGA children, girls and those born preterm were reported to be shorter at start of GH treatment but presented a significant improvement in height during GH therapy.

P2-D3-442**Two-Year Results from Patro Children, a Multi-Centre, Non-Interventional Study of the Long-Term Efficacy and Safety of Omnitrope® in Children Requiring GH Treatment**

Roland Pfaffle^a, Shankar Kanumakala^b, Charlotte Höybye^c, Berit Krström^d, Ellen Schucke^e, Markus Zabransky^e, Tadej Battelino^f, Michel Colle^g

^aDepartment of Paediatric Endocrinology, University of Leipzig Medical School, Leipzig, Germany; ^bDepartment of Paediatrics, Royal Alexandra Children's Hospital, Brighton, UK;

^cDepartment of Endocrinology, Metabolism and Diabetology, Karolinska University Hospital, Stockholm, Sweden;

^dDepartment of Clinical Science/Paediatrics, Umeå University, Umeå, Sweden; ^eSandoz International GmbH, Holzkirchen, Germany; ^fDepartment of Endocrinology, Diabetes and Metabolic Diseases, University Children's Hospital, Ljubljana, Slovenia; ^g25 Rue Boudet, Bordeaux, France

Background: PATRO children is an international, open, longitudinal, noninterventional study of the long-term safety and efficacy of Omnitrope®, a biosimilar recombinant human GH (rhGH). **Objective and hypotheses:** The primary objective is to assess the long-term safety of Omnitrope®, particularly the diabetogenic potential of GH in short children born small for gestational age, the risk of malignancies, and potential risks of GH therapy in Prader-Willi syndrome. The long-term efficacy of Omnitrope® is a secondary objective. **Method:** PATRO children includes infants, children, and adolescents who are receiving treatment with Omnitrope® according to country-specific 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 SDS (HSDS), height velocity (HV), and HVSDS are derived from height measurements and country-specific reference tables. **Results:** To date, 2816 patients have been recruited from 250 sites across 14 countries. The mean (s.d.) treatment duration is 22.5 (18.6) months. There has been one case of new-onset diabetes. No patients have tested positive for anti-hGH antibodies so far (83 tests in 43 patients). In total, 119 patients (4.3%) have experienced treatment-related adverse events (AEs) and 77 (2.8%) have experienced a serious AE (SAE). SAEs were treatment-related in 4 (0.1%) patients. There have been no reports of GH-related malignancies and no additional safety concerns. Efficacy data at 2 years indicate a positive effect of Omnitrope® on growth parameters in prepubertal children across all indications, irrespective of gender and pre-treatment status. **Conclusion:** This 2-year analysis shows that Omnitrope® was safe and well tolerated in a wide range of paediatric indications. Omnitrope® was effective in the majority of children. This ongoing study will extend the evidence base for Omnitrope®, and GH in general, in paediatric indications.

P2-D3-443**The Effect of Two Different GH Dosages on Final Height and Bone Geometry**

Fiorenzo Lupi^a, Mauro Bozzola^b, Fabio Buzi^c, Silvia Longhi^a, Amelia Mascolo^b, Alba Pilotta^d, Rossella Porto^b, Giulia Ruffinazzi^b, Valentina Zattoni^d, Giorgio Radetti^a

^aOspedale Regionale, Bolzano, Italy; ^bUniversità di Pavia, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; ^cOspedale Carlo Poma, Mantova, Italy; ^dSpedali Civili, Brescia, Italy

Background: GH has a strong positive influence on bone stimulating both bone elongation and increase in size by enhancing the accrual of trabecular and cortical bone up to the attainment of peak bone mass in young adult. **Aim of the study:** We compared the effect of two different GH dosages on statural growth and bone geometry in two groups of GH-deficient children at final height. Data has been collected retrospectively from 1994 to 2013. **Patients and methods:** We evaluated 121 (86 males and 35 females) children of two different cohorts. group 1 (44 patients) had been treated with GH at a mean dose of 0.3 mg/kg per week and group 2 (77 patients) at 0.2 mg/kg per week. The auxological data were collected at the beginning and at the end of treatment. A digitalized X-ray obtained at final height for the determination of bone age was used to study bone geometry. **Results:** Height was corrected for mid-parental height (parentally adjusted height SDS), while the following parameters were employed to assess bone geometry: metacarpal index (MI), cross-sectional area (CSA), cortical area (CA), and medullary area (MA). **Height:** At the beginning of treatment was significantly shorter in group 1 than in group 2 (-0.18 vs -0.63 ; $P < 0.002$), while at the end of treatment there was no difference between the two groups (0.15 vs 0.11). Height gain was significantly higher in group 1 than in group 2 (0.33 vs -0.52 ; $P < 0.001$). Bone geometry: MI was significantly greater in group 1 (0.62 vs 0.55 ; $P < 0.001$) as well as CA (-46.87 vs 42.69 ; $P < 0.005$), while MA was significantly lower in group 1 (8.48 vs 11.65 ; $P < 0.002$). There was no difference in total cross sectional area. **Conclusions:** Higher GH doses elicit a significantly greater statural gain and an improvement of the bone geometry by stimulating the growth of the cortical area.

P2-D3-444**Baseline Body Composition of Children with Short Stature Diagnosed for GH Deficiency**

Pawel Matusik^a, Aleksandra Barylak^b, Patrycja Cholewka^b, Marta Klesiewicz^b, Karolina Klos^b, Martyna Stasiulewicz^b, Maria Cetera^b, Ewa Malecka-Tendera^a

^aDepartment of Pediatrics, Pediatric Endocrinology and Diabetes, Medical University of Silesia, Katowice, Poland; ^bScientific Society of Medical Students, Medical University of Silesia, Katowice, Poland

Background: Severe GH deficiency (GHD) is associated with significant body composition abnormalities. However there is no data assessing initial body composition parameters in the children with partial GHD. **Objective and hypotheses:** Study objective was initial body composition assessment in the short stature children diagnosed for GHD. **Method:** 54 consecutively diagnosed for GHD short statured children (40 boys) in the mean age 10.83 ± 2.6 years, were included into the study. The auxological data (height SDS, BMI SDS, and waist/height ratio (WHtR)) laboratory test (GH and IGF1 levels) and body composition (fat tissue (FAT%) and fat-free mass (FFM%)) based on bioelectrical impedance analysis (BIA) were evaluated. **Results:** Finally in 22 children partial GHD (peak GH > 3 and < 10 ng/ml in the night profile and two stimulation tests) was diagnosed. Children with partial GHD had significantly higher ($P < 0.05$) WHtR than normal GH group (0.47 vs 0.44 respectively). BMI SDS and FAT% were insignificantly higher in partial GHD group and FFM% insignificantly lower vs normal GH children. WHtR was significantly related to the body composition ($r = -0.667$; $P < 0.01$ vs FAT% and $r = 0.658$; $P < 0.01$ vs FFM%) in the whole short statured children. Moreover, peak GH level assessed in the night profile, correlated significantly with body composition parameters in all studied children ($r = -0.317$; $P < 0.01$ vs FAT% and $r = 0.319$; $P < 0.01$ vs FFM%) even after the adjustment to age. **Conclusion:** i) Body composition assessed by BIA was no significantly impaired in children with partial GHD. ii) However significant difference in the central adiposity (assessed by WHtR) was revealed in the partial GHD children. iii) Body composition in short statured children was significantly related to the GH releasing in the night profile.

P2-D3-445

GH Treatment to Final Height in Children with Idiopathic Short Stature: Evidence for an Early Therapy Initiation Effect

Kiriaki Hatzigapiou, Paraskevi Zosi, Dionisis Karakaidos, Eleftheria Kaiafa, Thomais Vlahou, Likourgos Kanaris, Georgios Kafalidis

Pediatric Department of Nikaia, Piraeus General Hospital 'Agios Panteleimon', Athens, Greece

Background: GH treatment aims to normalise growth, increasing growth velocity, thus helping patients achieve an adult height in the normal range for the general population and for their familial genetic potential. **Objectives:** To evaluate the efficacy of early replacement therapy with recombinant GH (rGH) in Caucasian pre-pubertal children treated for GH deficiency. **Methods:** Our study included 64 boys and 49 girls, diagnosed with partial or total GH deficiency that attained their final height. None of them suffered from organic hypopituitarism. At least two standard GH stimulation assays were performed in each patient.

All children had received rGH 0.15 mg/kg per week. Boys and girls were assigned to one of four categories according to the age of rGH initiation. Target height was predicted according to the Tanner *et al.* equation. **Results and conclusions:** The mean adult height in boys aged < 10 years at treatment initiation was 1.83 ± 1.028 SDS (average height 160.08 ± 5.226 cm) and compared favourably to the Tanner target height, as the mean difference between final and target height was -3.22 ± 6.63 cm. Younger patients with marked bone age delay had better outcomes. On the contrary, for boys that aged $12-14$ and > 14 years at treatment initiation, the mean final height was significantly lower than target height (mean difference -13 ± 4 and -8.625 ± 7.360 cm respectively). In the girl group, although final height measurements were within the normal adult height range, the results concerning the effect of early treatment were inconclusive. Thus, early rGH initiation appears to have a favourable effect on target height in boys, whereas in girls other factors, e.g. estrogens may affect the results.

P2-D3-446

Evaluation of the Safety and Usability of FlexPro[®] 30 mg/3 ml, for the Delivery of Norditropin[®] in Patients Requiring GH Therapy

Gitte Schønning Fuchs^a, Yanhong Wen^b, Rasmus Klinck^b, Marianne Qvist^a, Anne-Marie Kappelgaard^a

^aNovo Nordisk A/S, Søborg, Denmark; ^bNovo Nordisk A/S, Hillerød, Denmark

Introduction: This test assessed the safety and usability of FlexPro[®] 30 mg/3 ml (Novo Nordisk A/S, Denmark), a pen-injector for injection of human GH in patients with GH deficiency (GHD), Turner syndrome (TS), Noonan syndrome (NS) and children born small for gestational age (SGA), and validated the instructions for use (IFU) and instructional video. **Methods:** Children with GHD/SGA or TS/NS, adult patients, caregivers of patients with GHD/SGA/TS/NS and specialist/inpatient nurses were enrolled in accordance with FDA Human Factors Engineering (HFE) guidelines. Except for inpatient nurses, participants received training in using FlexPro[®] 30 mg/3 ml. All enrolled participants were tested on normal use (of new pen-injector), end-of-content use (almost depleted pen-injector), and IFU comprehension. Use errors, close calls and operational difficulties observed were recorded and evaluated based on participants' subjective feedback. All participants completed a post-test questionnaire (21-item; 7-point scale: 1, strongly disagree, and 7, strongly agree). **Results:** Ninety-four participants underwent evaluation (male/female (mean age years)): children with GHD/SGA (11/5 (13)) or TS/NS (1/15 (12)), adult patient/s/caregivers (10/22 (42)); nurses (2/28 (42)). No task failures, potential serious use errors or non-serious use errors were reported. 81% of participants recorded no use errors; 23 use

errors (no potential for harm) were committed by 18 participants (>50% use errors were committed by untrained participants). Three close calls and four operational difficulties were reported by three and four participants respectively. All participants correctly interpreted three out of four IFU excerpts, and provided positive responses for their experience with FlexPro[®] 30 mg/3 ml and evaluation of the IFU and instructional video (mean ratings, 6–7). **Conclusions:** Overall, participants reported positive experiences with FlexPro[®] 30 mg/3 ml, the IFU and instructional video. No task failures, potentially serious or non-serious use errors were observed. Use errors (no potential for harm) were committed more often by untrained, than trained, participants.

P2-D3-447

Efficacy, Adherence, and Cost Study According to Pathology and Treatment Devices in Children Treated with GHRH

Ignacio Diez-Lopez^a, Ainhoa Sarasua-Miranda^a, Miriam Miriam Elizalde^a, Isabel Lorente-Blazquez^a, Cristina Minguez^b, Carlos Martínez-Martínez^b

^aChildren's Endocrinology Section, Pediatric Service, Vitoria/Basque Country, Spain; ^bPharmacy Service, University Hospital of Alava, Vitoria/Basque Country, Spain

Background: Currently there are three distinct groups of GH devices: single dose (JM), preloaded pen/vial (VM) systems and electronic devices (DE) autoinjector systems. The choice could determine a greater or lesser adherence and thus influence the final treatment efficacy. **Objective:** Comparison of the therapeutic efficacy as measured by growth rate (VC), IGF1 as a function of various clinical variables, indicating GH and device used. **Method:** Observational study retrospective from comparative clinical registry, analytical control, and pharmaceutical data base regarding prescribed dispensed mg: single dose (JM) vs multidose vials (VM) vs electronic devices (DE). One year study 2012 (full 12 months). **Results:** 86 patients enrolled, of which 86 (100%) were valid. 46/86 (50%) girls. Mean age 9.97 years (4–16). Pubescent 56/86 (65%). Deficit partial/total 50/86 (58%), PEG 17/86 (19%) Turner 4/86 (5%), dysfunction/inactive GH 13/86 (15%) and other 2/65 (3%) (JM Global distribution: 38/86 (44%), VM: 22/86 (26%) OF: 26/86 (30%) of 12 patients collected less medication (14%) and of these three were noncompliant (3.5%). Although the final expenditure is lower in mg JM, the distribution of collecting less medication and defaulting is similar in each device group, slightly higher in the group of partial/total deficit (16 vs 5%) and pubertal (15 vs 4%), and equal in both sexes. The VC and IGF1 was significantly lower in the non-adherent. The number of patients collected less medication is distributed evenly across each of the subgroups. **Conclusion:** The use of different devices does not seem to influence compliance, time with treatment (pubescent and deficit), and patient autonomy (puberty).

P2-D1-448

Isolated GH Deficiency (IGHD) may be due to Several Different Causes: mutations in the GHRH Receptor Gene Are a Relatively Rare Cause of IGHD

Huseyin Demirbilek^{a,b}, Sophia Tahir^b, Riza Taner Baran^c, Maha Sherif^b, Mehmet Nuri Ozbek^c, Khalid Hussain^{a,b}

^aDepartments of Paediatric Endocrinology, Great Ormond Street Hospital for Children NHS Trust, London, UK; ^bClinical Molecular Genetic Unit, Institute of Child Health, University College London, London, UK; ^cDepartment of Paediatric Endocrinology, Diyarbakir Children State Hospital, Diyarbakir, Turkey

Background: Isolated GH deficiency (IGHD) may be due to several different causes. Mutations in the GHRH receptor (*GHRHR*) gene are a relatively rare cause of IGHD. **Objective and hypotheses:** To understand the molecular cause of severe short stature in a large highly consanguineous family with IGHD. **Method:** Affected patients were evaluated for GH secretion and other anterior pituitary function. Anterior pituitary size was measured using magnetic resonance imaging (MRI). Homozygosity mapping was performed on two affected and one unaffected member from subfamily-1 and subfamily-2. A shared homozygous region overlapping between affected members from both subfamilies and absent in the unaffected individuals was found on chromosome 7. This region contained the *GHRHR* gene which was subsequently sequenced. Sequence analysis of the whole *GHRHR* coding regions and the intron–exon boundaries from peripheral DNA showed a novel homozygous missense mutation in exon-4 of *GHRHR* gene in two affected patients from each subfamily. **Results:** The maximum stimulated serum GH peak was 1.01 µg/l with serum IGF1 and IGFBP3 levels <2 SDS in all affected members. Eight subjects (five from subfamily-1 and three from subfamily-2) were homozygous for a novel missense mutation in the coding sequence of exon-4 (p.C64G). The parents and two unaffected from each subfamily were heterozygous. Evaluation of anterior pituitary with MRI showed marked anterior pituitary hypoplasia in affected subjects from subfamily-1 whereas normal anterior pituitary size in the subfamily-2. In addition basal IGF1 levels of subjects from subfamily-1 with AHP were lower than those of the subfamily-2. **Conclusion:** We describe a novel mutation in the *GHRHR* in a large consanguineous family with IGHD. The variability between the AP sizes showed that phenotypic expression of *GHRHR* gene mutations can be quite different even in same family members carrying the identical mutation.

P2-D1-449

Fibroblast Growth Factor 21 is Inversely Associated with Growth Rates in Infancy

Veronica Mericq^a, Francesco De Luca^b, Maria Isabel Hernandez^a, Veronica Peña^a, Katherine Rossel^a, Gabriel Cavada^c, Alejandra Avila^a, German Iñiguez^a

^aFaculty of Medicine, Institute of Maternal and Child Research, University of Chile, Santiago, Chile; ^bSection of Endocrinology and Diabetes, St Christopher's Hospital for Children, Drexel University College of Medicine, Philadelphia, Pennsylvania, USA; ^cPublic Health Department, University of Chile, Santiago, Chile

Background: FGF21 is a metabolic and growth regulator. **Aim:** To investigate the role of FGF21 during growth in infancy. **Methods:** Cohort of 40 term (T) and 40 preterm (PT) newborns whose length and weight were evaluated prospectively at birth, 6 months, and 12 months. Blood samples for FGF21, IGF1, leptin, insulin and glucose were collected at 6 and 12 months. In addition, FGF21, IGF-I, leptin, and insulin were measured in cord blood in a group of 55 T and 40 PT newborns. **Results:** From birth through 12 months of age, PT infants' linear growth and weight gain were larger than those of T infants, irrespective of birth weight (BW) SDS. At birth and at 12 months, there was no difference in FGF21 levels among infants; in contrast, at 6 months serum FGF21 in T infants was significantly higher than that of PT infants. Length CUG was inversely associated with FGF21 concentrations determined at 6 or 12 months ($r = -0.22$, $P < 0.05$) and weight ($r = 0.28$, $P < 0.05$) and length change in first year ($r = 0.65$, $P < 0.05$) positively associated with the change (decrease) in FGF21 concentrations. FGF21 level in cord blood was significantly associated with leptin and IGF1 levels, independent of or gestational age or BW SDS. **Conclusions:** Our results support the notion that FGF21 in infancy is correlated with weight gain and linear growth rate.

characterized by disproportionate short stature and Madelung deformity. The molecular defect is unknown in the remaining ~30%. **Objective:** To determine if *NPR2* mutations are present in LWD patients with no known *SHOX* defect. **Method:** 87 Spanish patients with suspected LWD and no known *SHOX* defect. Mutation screening was carried out using a Skeletal Next-generation sequencing panel (Haloplex/SeqCap) on a MiSeqDefault (Illumina), or by High Resolution Melting and sequencing. Pathogenicity was assessed using Alamut V2.3-6. **Results:** Five heterozygous *NPR2* mutations were identified: c.1262C>T (p.Thr421Met), c.1641_1643del (p.Val548del); c.2759G>A (p.Gly920Asp), c.2972A>G (p.Glu991Gly) and c.3058C>T (p.Arg1020Trp). All mutations were absent or very infrequent in 1000 genomes and Exome Variant Server databases. *In silico* analysis indicated that the affected amino acids are highly conserved and suggested that the missense mutations are likely to be pathogenic, whilst the pathogenicity of the in frame deletion is unknown. Where possible, the mutations were shown to cosegregate, with the phenotype. Functional analysis is ongoing. **Conclusions:** i) *NPR2* heterozygous mutations were identified in 4.6% of patients with LWD without known *SHOX* defects; ii) it is plausible that *NPR2* mutations may cause disproportionate short stature as homozygous defects result in severe disproportionate short stature; iii) Two of the patients with *NPR2* mutations showed a good response to rhGH treatment (height increase by 1SD); iv) *NPR2* mutation screening should be indicated in patients with disproportionate short stature who tested negative for *SHOX* defects; v) Further data are required to evaluate whether rhGH treatment is appropriate for these patients.

P2-D1-450

Identification of *NPR2* Mutations in Disproportionate Short Stature

Alfonso Hisado-Oliva^{a,b}, Sara Benito-Sanz^{a,b}, Alberta Belinchón^{a,b}, Elena Vallespin^{a,b}, Angela del Pozo^{a,b}, Ana C. Barreda-Bonis^c, Joaquin Ramirez^d, Cristina Luzuriaga^e, Isabel González-Casado^c, Ángel Campos-Barros^{a,b}, Karen E. Heath^{a,b}

^aInstitute of Medical and Molecular Genetics (INGEMM), Hospital Universitario La Paz, Madrid, Spain; ^bCIBERER, ISCIII, Madrid, Spain; ^cDepartment of Pediatric Endocrinology, Hospital Universitario La Paz, Madrid, Spain; ^dDepartment of Pediatric Endocrinology, Hospital Universitario Príncipe de Asturias, Alcalá de Henares, Madrid, Spain; ^eDepartment of Pediatric Endocrinology, Hospital Universitario Marqués de Valdecilla, Santander, Spain

Background: Homozygous natriuretic peptide receptor-2 (*NPR2*) mutations cause acromesomic dysplasia, type Maroteaux, a skeletal dysplasia with extreme disproportionate short stature and recently, heterozygous *NPR2* mutations have been identified also in patients with idiopathic short stature (ISS, 2–6%). *SHOX* mutations are found in ~2–5% of ISS cases and ~70% of Léri-Weill dyschondrosteosis (LWD) cases,

P2-D1-451

Eleven Years of Letrozole Treatment in a Child with 11-β Hydroxylase Deficiency: Effect on Bone Age and Height Prognosis

Abdullah Bereket, Zeynep Atay, Tulay Guran, Belma Haliloglu, Saygin Abali, Serpil Bas, Serap Turan

Department of Pediatric Endocrinology, Marmara University, Istanbul/Pendik, Turkey

Background: Aromatase inhibitors (AI) are being used in clinical trials in children related to peripheral precocious puberty, and idiopathic short stature to improve height prognosis. **Case report:** A 2^{11/12} year-old boy was referred to our center for evaluation of penile enlargement and pubic hair development. Physical examination revealed a well-developed muscular boy with a body weight of 22 kg (>97p), height of 110.1 cm (>97p), with oily skin and acne on his face. His blood pressure was 140/90 mmHg. Testicular volumes were 6 cc, stretched penile length was 9 cm and he had Tanner stage II pubic hair. His bone age was 13 years with predicted adult height of 129.5 cm. Laboratory results with total testosterone: 10.01 nmol/l, ACTH: 1250 mmol/l, 17-OH progesteron: 5.75 nmol/l, Plasma renin

activity: 0.1 µg/l per hour, 11-desoxycortisol: 140 ng/ml were consistent with 11-β hydroxylase deficiency. Genetic analysis demonstrated a previously described g.4643_4644insGA mutation in CYP11β1. After 9 months of initiation of hydrocortisone treatment, his bone age became 13 6/12 years, which gave him an adult height prediction of 130 cm. Because of this poor height prognosis, patient was started on letrozole 2.5 mg/day. After 11 years of letrozole therapy, at the age of 15 y 5/12 mo his near-final height is 157.7 cm, bone age is 14 y 9/12 mo and predicted adult height is 164.4 cm. The expense to this dramatic increase in height prognosis is a decrease in bone mineral density (DEXA) Z-score from -0.3 to -0.9 during treatment with some morphologic changes in vertebral bodies noted on MRI. **Conclusion:** As far as we know, this is the longest duration of letrozole use to improve height potential and is highly encouraging regarding the use of aromatase inhibitors early in the disease course in selected patients with advanced bone-age and severely impaired height prognosis.

P2-D1-452

Rasopathies: Assessment of Growth, Genetic Study, Genotype-Phenotype Correlation and Therapeutic Response to GH in Noonan Syndrome

Claudia Heredia^{a,b}, Francisco Barros^c, Lidia Castro-Feijóo^a, Jesús Barreiro Conde^a, Paloma Cabanas Rodríguez^a, Manuel Pombo Arias^a

^aUnidad de Endocrinología Pediátrica, Crecimiento y Adolescencia, Hospital de Santiago de Compostela, Universidad de Santiago de Compostela, España, Santiago de Compostela, A Coruña, Spain;

^bHospital Militar Central, Bogotá, Colombia; ^cUnidad de Medicina Molecular, Fundación Pública Galega de Medicina Xenómica, Santiago de Compostela, Spain

Background: Rasopathies are a heterogeneous group of diseases that share phenotypic characteristics such as facial dysmorphism, congenital heart disease and short stature. **Objective and hypotheses:** Evaluation of growth and study of the GH-IGF1 axis. Molecular Study of the PTPN11, SOS1, RAF, KRAS, NRAS, MAP2K1 and MAP2K2 genes. Evaluation of growth and study of the GH-IGF1 axis. **Method:** Descriptive retrospective study in patients with suspected Rasopathies in the period 1993–2013 that have been studied in the Hospital Clínico Universitario de Santiago de Compostela. **Results:** 25 patients with high suspicion of Rasopathies: 19 with Noonan syndrome (NS), three with Leopard syndrome, two with Cardio-facio-cutaneous syndrome and one with Neurofibromatosis-Noonan syndrome, distributed as follows: 56% girls ($n=14$) and 44% male ($n=11$). Gestational age mean was 39-week, average length -0.45 SDS. Target height: male -1.28 SDS and girls -0.85 SDS. During the first 2 years there was a decrease in the growth channels, predominantly in girls. The growth velocity of the group showed a delayed growth spurt, with later and less intense than in the

Spanish population. 33% had values below the normal range for IGF1 and IGFBP3. Six patients (24%) were diagnosed with GHD and SN, the pretreatment height was -3.1SDS. After a year of treatment with GH we found an increased growth velocity to 8.14 cm/año in average and height variation was observed at -2.43 SDS. Molecular study demonstrated a genetic disorder, like this: PTPN11 ($n=8$), SOS1 ($n=2$), RAF1 ($n=1$), NF1 ($n=1$) and MAP2K1 ($n=1$). Patients with mutations in PTPN11 had alterations in the EKG, associating with GH deficiency. The patient has RAF1 mutation had hypertrophic cardiomyopathy. **Conclusion:** 59, 1% have a genetic mutation in any of the genes studied. 24% have associated GH deficiency. Treatment with GH in these patients appears to be effective.

P2-D1-453

New Reference for Height in Swedish Boys and Girls

Kerstin Albertsson-Wikland^a, Aimon Niklasson^a, Lars Gellander^a, Anton Holmgren^{a,b}, Andreas F M Nierop^c

^aGP-GRC Department of Pediatrics, Institute of Clinical Sciences, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden; ^bDepartment of Pediatrics, Halmstad Hospital, Halmstad, Sweden; ^cMuvara bv, Multivariate Analysis of Research Data,

Leiderdorp, The Netherlands

Background: The actual Swedish growth references are based on a cohort born 1974. **Objective and hypotheses:** Due to secular changes there is need for new height references. **Method:** *Material:* Height measurements from birth to adult height (AH) in a cohort of healthy, Nordic and born full term 1990, 20,796 from 1647 boys, 19,202 from 1501 girls were used (ALL) and compared to both a subgroup with puberty close to mean (PHV ± 0.25 years) of 3,726 heights from 259 boys; 3,759 from 271 girls, and a subgroup (AM) with >10 height measurements evenly distributed (15,324 in 989 boys; 14,381 in 919 girls), and of high data quality. The 1974 cohort, with similar subgrouping, were used for comparison. *Methods:* For construction of height curves the LMS method was applied with LMS parameters based directly on the data: the power in the Box-Cox transformation (L), the median (M), and the generalized coefficient of variation (S). The GAMLSS R-package with a special LMS program was used, giving L, M, S and optional kurtosis as functions of age. **Results:** Height reference curves, with mean, ± 1 , ± 2 SDS were obtained for 1990 of the ALL vs the AM material with similar results whereas the close puberty material showed the same mean but more narrow ± 1 , ± 2 SDS during adolescence. When the different 1990 references were compared to 1974 references, the corresponding 1974 differences were found. The new references takes into account that the 1990 cohort had a more rapid infancy growth, increased prepubertal growth, especially in boys, increased pubertal gain, only in girls, and increased AH in both genders.

Conclusion: There were no or only small differences between the ALL and AM material for both boys and girls, except when using close puberty as inclusion criteria, where an expected reduced variation in total growth during adolescence was found. Thus, the entire 1990 ALL material will be used for developing new height references, taking the gender specific secular changes in height into account.

P2-D1-454

Endocrine characteristics of patients with anorexia nervosa in a large paediatric study cohort

Moritz Toenne^a, Nicolin Datz^a, Sabine Heger^a, Rainhard Hartmann^a, Thomas Danne^a, Gerd Kuznik^b, Burkhard Neuhaus^b, Olga Kordonouri^a

^aDepartment of General Paediatrics, Diabetology, Endocrinology and Clinical Research, Children's and Youth's Hospital AUF DER BULT, Hannover, Germany; ^bDepartment of Child and Adolescent Psychiatry and Psychosomatics, Children's and Youth's Hospital AUF DER BULT, Hannover, Germany

Aim: To examine the prevalence of endocrine abnormalities and outcome in children and adolescents with Anorexia nervosa (AN). **Methods:** The study cohort consisted of 181 patients (age 14.6 ± 1.9 years; 160 girls, 21 boys) with AN ($n=137$), atypical AN ($n=6$) and other eating disorders except of Bulimia ($n=38$) who were hospitalized between Jan 2010 and Feb 2013. Somatometric [body-mass-index (BMI), BMI-SDS] and endocrine parameters were analysed retrospectively. **Results:** Serum concentrations (mean, range) were determined for leptin (1.60, 0.4-22.0 ng/ml), 8h-cortisol (18.2, 0.9-39.1 g/dl), basal LH (0.11, 0.1-8.19 mU/ml), basal FSH (2.94, 0.1-13.1 mU/ml), TSH (1.97, 0.01-6.37 μ U/ml) and free-T4 (1.06, 0.6-4.19 ng/dl). 57.9% of patients had leptin levels below 2.0 ng/ml (31.4% below 1.0 ng/ml). 1.8% of patients had suppressed TSH ($<0.6 \mu$ U/ml) and 9.8% elevated TSH ($>4.0 \mu$ U/ml) along with normal free-T4 (>0.9 ng/dl). Hypercortisolaemia (>25.0 g/dl) was detected in 7.7% of patients. BMI-SDS at admission (-2.26 ± 1.02 , -6.0 to 0.2) was significantly correlated with leptin ($R=0.25$, $P=0.002$) and LH ($R=0.24$, $P=0.004$). Leptin was correlated with LH ($R=0.30$, $P=0.001$) and FSH ($R=0.23$, $P=0.012$). No correlation with patient's age was found. During hospitalization (duration 16.4 ± 10.3 days), BMI-SDS increased by 0.46 ± 0.57 . BMI-SDS gain was negatively correlated with leptin ($R=-0.25$, $P=0.002$), but not with other baseline parameters. Multiple regression analysis revealed length of stay ($\beta=0.227$, $P=0.020$), BMI-SDS at admission ($\beta=-0.274$, $P=0.005$) and leptin ($\beta=-0.205$, $P=0.024$) as independent covariates of BMI-SDS gain. **Conclusion:** Data of this large study population indicate that the positive effect of hospitalization on weight gain is influenced by prolonged stay as well as low weight and low leptin levels at admission. Thus, decreased leptin levels at admission could not be confirmed to be a negative predictor of short-term treatment success.

P2-D1-455

The Effect of Long Term GH Therapy in Discordant Twins Where One Twin is Born Small for Gestational Age: A Case Control Study

Johannes Letshwiti^a, Elaine O'Mullane^{a,b}, Hilary Hoey^b, Edna Roche^{a,b}

^aThe National Children's Hospital, Tallaght Hospital, Dublin 24, Ireland; ^bUniversity of Dublin, Trinity College, Dublin 2, Ireland

Background: The positive effect of GH therapy in small for gestational age (SGA) singletons has been shown in previous studies. Little is known about twin growth and GH treatment where only one twin is born SGA. **Objective and hypotheses:** We present data from two set of twins where one was appropriate for gestational age (control) and the other twin was SGA (treatment). **Method:** Twin pair 1: male monochorionic diamniotic (MCDA) twins born at 33 weeks gestation. Twin 1 (control) birth weight (BW) 1.5 kg (-1.15 s.d.). Twin 2 (GH treated) BW 1 kg (-2.93 s.d.). Pre-GH treatment Twin 2 had peak GH of 15.3 mU/l, normal IGF1, height velocity 6.0 cm/years and height of 100.8 cm (-2.55 s.d.). The control twin's corresponding height was 103.7 cm (-0.8 s.d.). GH therapy was commenced at 6 years. Twin pair 2: male dichorionic diamniotic (DCDA) twins born at 35 weeks gestation. Birth weight of control and SGA twin (Twin 2) were 2.3 kg (-0.89 s.d.) and 1.62 kg (-2.96 s.d.) respectively. Pre-GH treatment Twin 2 had peak GH level of 17.9 (μ g/l), normal IGF1, height velocity 5.8 cm/years and height 98.8 cm (-2.94 s.d.). The corresponding height of the control twin was 106.3 cm (-1.36 s.d.). GH treatment was commenced at 5.5 years. **Results:** Twin pair 1: at age 13.5 years, height was 157.4 cm (-0.04 s.d.) and 151.1 cm (-0.8 s.d.) for the SGA and control twin respectively. Twin pair 2: at 10 years of age Twin 2 measured 131.4 cm (-1.11 s.d.) and the control twin 130.3 cm (-1.29 s.d.). **Conclusion:** These cases demonstrate the value of GH therapy on catch up and maintenance of growth over time. Further research on the varying growth between twins including genetic factors is required.

P2-D1-456

How Early is the Rise in Leptin Levels in Small for Gestational Age Children With Catch Up Growth

Ainam Gupta, Sangita Yadav, Siddharth Ramji, T K Mishra

Department of Pediatrics and Biochemistry Maulana Azad Medical College University of Delhi, New Delhi, India

Background: Strong association of early postnatal catchup growth in SGA with higher leptin levels and increased risk of insulin resistance has been described. **Objective:** To determine

leptin levels in term small for gestational age (SGA) children at 15–18 months age and assess their relationship with postnatal catchup growth (CUG). **Methods:** Birth and current weight and length of 60 term SGA (<10th percentile) children at 15–18 months was recorded and data analyzed for CUG (gain in weight/length SDS or both >0.67). Fasting leptin and insulin levels measured using ELISA kit and Electro-chemiluminescence, respectively. Insulin sensitivity evaluated using homeostatic model assessment index (HOMA-IR). **Results:** Average birth weight, length, gestational age was 2.08 ± 0.2 kg (-2.89 ± 0.59 SD), 45.1 ± 2.5 cm (-2.37 ± 1.36 SD), 38.4 ± 1.2 weeks respectively. At enrolment mean age, weight and length was 16.9 ± 1.2 months, 8.2 ± 0.8 kg (-2.00 ± 0.98 SD), 73.0 ± 3.0 cm (-2.36 ± 1.11 SD). 39 (65%) of 60 SGA infants showed CUG and 21 did not have catchup growth (NCUG). Mean leptin levels were 2.3 ± 1.8 ng/dl and higher in CUG (2.6 ± 1.98 ng/dl) as compared to NCUG (1.8 ± 1.20 ng/dl) but not statistically significant ($P=0.09$), however positively correlated with insulin levels, $P=0.004$ and HOMA-IR value, $P=0.002$. Insulin and HOMA-IR value significantly higher in CUG vs NCUG; 4.29 ± 5.0 vs 2.15 ± 1.9 μ IU/ml, $P=0.031$ and 0.87 vs 0.43 , $P=0.039$ respectively. Four children in CUG had HOMA-IR in insulin resistance range (HOMA-IR>2.0) with average leptin and insulin levels of 3.9 ng/ml and 17.6 μ IU/ml respectively. **Conclusion:** The rise in leptin levels was evident as early as 15 months in SGA children showing early postnatal catchup. Further, hyperinsulinemia and increased HOMA-IR value as marker of insulin resistance and adult metabolic syndrome were also observed. Therefore, high leptin levels strongly correlated with fasting insulin and HOMA-IR value in SGA with catchup growth indicating early onset of insulin resistance in these children.

P2-D1-457

Relation Between CNP and the Effect of Combined Treatment With GnRHa and GH on the Linear Growth in Mid/Late Pubertal Girls with Central Precocious Puberty or Early and Fast Puberty at Great Bone Ages

M A Hua-me^a, S U Zhe^a, L I Yin-ya^b

^aThe First Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, China; ^bThe Third Affiliated Hospital the Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, China

Background: It's well known that GnRH analogue (GnRHa) could not improve the final height of mid/late pubertal girls with central precocious puberty (CPP) or early and fast puberty (EFP) for their low growth potential. **Objectives:** To evaluate the effect of combined treatment with GnRHa and GH on the linear growth in mid/late pubertal girls with CPP/EFP at great bone ages. To investigate the relation between C-type natriuretic peptide (CNP) and GH's effect on their linear growth. **Methods:** Twenty-two girls with CPP/EFP, whose bone ages were older than 11.5 years,

received treatment of combined GnRHa with GH (GH-combined group) and GnRHa alone (control group) ($n=11$, respectively). Serum amino-terminal proC-type natriuretic peptide (NTproCNP), IGF1 and procollagen type 1 amino-terminal propeptide (P1NP) concentrations were measured at the beginning and end of 6 months' treatment. Comparisons were made among the height velocity, increment of predicted adult height (Δ PAH) and changes of serum NTproCNP, IGF1, P1NP concentrations between the two groups. **Results:** During the 6-months treatment, the height velocity (6.7 ± 1.4 cm/year) and Δ PAH (2.4 ± 0.8 cm) of GH-combined group were higher compared with those of control group (4.5 ± 0.7) cm/year, (1.0 ± 1.1) cm, respectively, $P<0.01$). After 6-months treatment, serum NTproCNP, IGF1 and P1NP remained at the same level as those of beginning in GH-combined group ($P>0.05$). In contrast, girls in control group showed a significant decrease of serum NTproCNP (6.9 ± 1.5 post vs 10.5 ± 3.6 pmol/l, pre) and P1NP, (394.7 ± 114.6 post vs 877.5 ± 132.2 ng/ml pre) ($P<0.05$), with no significant change of IGF1. **Conclusions:** Combined treatment with GnRHa and GH may accelerate linear growth and improve predicted adult height. In mid/late pubertal girls with CPP or EFP at great bone ages. This growth-accelerating effect of GH could in part be induced by increasing of CNP production.

P2-D1-458

Two Duplications Within PAR1 in a Family With Idiopathic Short Stature

Barbora Obermannova^a, Jana Drabova^b, Petra Dusatkova^a, Jan Lebl^a

^aDepartment of Paediatrics, 2nd Faculty of Medicine, Charles University in Prague and University Hospital Motol, Prague, Czech Republic; ^bDepartment of Biology and Medical Genetics, 2nd Faculty of Medicine, Charles University in Prague and University Hospital Motol, Prague, Czech Republic

Background: Short stature homeobox-containing gene (SHOX) is located within the pseudoautosomal region 1 (PAR1) of the sex chromosomes. SHOX mutations and PAR1 deletions encompassing SHOX or its upstream/downstream enhancers have been identified in ~60% of Léri-Weill dyschondrosteosis (LWD) and ~5–15% of idiopathic short stature (ISS) patients. Recently SHOX duplications have been described in LWD/ISS individuals.

Case presentation: The boy was born full-term, BW 3200 g, BL 47 cm. At the first endocrine investigation for short stature at 11 years, his height was 128.5 cm (-2.9 SD), P2, testes 5/5 ml, bone age slightly advanced up to 12.6 years (TW3-RUS). His father and paternal mother have short stature (final height -3.2 SD; -4.6 SD respectively). Neither proband nor family members have Madelung deformity, other skeletal deformities or mesomelic disproportion of the extremities. The basic laboratory work up was normal: chronic inflammation, thyroid disease, celiac disease was excluded, IGF1 was normal (241 μ g/l; -0.57 SD). **Method:** We performed FISH; MLPA and array-CGH in proband and his father. **Results:** Both of them carry two duplications within the

PAR1 region. First large duplication of 267 kbp reaches the Y subtelomere; the second duplication consisting of 58 kbp is located upstream from SHOX gene in the region of gene transcription regulatory elements. Following these findings, we started GH administration in dose 50 µg/kg per day at age 11.5 years. The growth velocity accelerated up to 10 cm/year. **Conclusion:** In conclusion, we have identified the first PAR1 duplication encompassing the upstream SHOX transcription regulatory elements in a family with ISS. The loss of these elements may result in SHOX haploinsufficiency because of decreased SHOX transcription.

methodology and population allows a consistent interpretation of the results.

P2-D1-459

Comparison Between GH assay: serum GH Cut-off Levels by ECLIA Performed in Pharmacological Estimulation Tests in Children With Short Stature

Cecilia Aguirre^a, Gabriela Sobrero^a, Giselle Schvab^b, Liliana Silvano^a, Julia Alvarez^b, Mariana Ochetti^a, Maria Lescurat^a, Alejandra Paez^b, Liliana Muñoz^a, Silvia Martin^a, Mirta Miras^{a,b}

^aHospital de Niños Santísima Trinidad, Córdoba, Argentina;

^bCentro de Endocrinología Pediátrica, Córdoba, Argentina

Background: The diagnosis of GH deficiency in children is based on clinical, auxological, radiographic and biochemical criteria which include response to Pharmacological Estimulation Tests (PhT). It is well known that GH concentrations vary according to the assay method used. Currently in our population, the proposed cut-off value of serum GH PhT is 4.7 ng/ml measured by ICMA using the IRP 98/574. **Objective and hypotheses:** The aims of this study were to define GH cut-off level by ECLIA in our population and to compare the concentrations measured by ECLIA and ICMA. **Method:** We analyzed 245 PhT performed with arginine n: 175 and clonidine n: 70 (71 F, and 174 M) from 190 children with short stature aged 0.8–16 years. GH concentrations was determined by ICMA (Immulite 2000) and ECLIA (Cobas e 601) using the IRP 98/574. **Results:** Linear regression analysis was performed on the 1120 samples measured by ICMA vs ECLIA showing highly significant linearity ($y=0.28+0.98x$; $R^2=0.95$). The ECLIA cut-off of 4.65 ± 0.22 ng/ml is the best match with the proposed by ICMA (association coefficient $\phi=0.88$). **Conclusion:** Using uniform standardization and the establishment of the cut lines for each

P2-D1-460

Skeletal Disproportion and Final Adult Height in Childhood-Onset Crohn's Disease

Avril Mason^a, Jelena Iljuhhina^b, Susan Laird^c, David Ross^c, Syed Faisal Ahmed^{a,b}, Dan R Gaya^c, Konstantinos Gerasamidis^b

^aRHSC, Glasgow, UK; ^bUniversity of Glasgow, Glasgow, UK;

^cGlasgow Royal Infirmary, Glasgow, UK

Background: Short stature is a recognized complication of Crohn's disease (CD) in children. Less is known on the impact of disease on final adult height and body proportions. **Objective and hypotheses:** To assess height and body proportions in 48 adults (F: 30; M: 18) with childhood (ACO) or adult (AAO) onset CD and 44 children (C) (F:22; M:22) with CD. **Method:** Standing, sitting height (SH) and leg length (SILL) were measured and parental heights were measured (C) or self-reported (A) to calculate mid-parental Ht (MPH). **Results:** Although there was no significant difference between the female and male child group of CD, both groups had significantly low SHSDS (Table). In females there was no significant difference in height, SH or SILLSDS between participants with ACO and AAO. However, men with ACO were significantly shorter, below their MPH and had a lower SHSDS than participants with AAO. BMI SDS at recruitment was positively associated with Δ MPHSDS in C group ($r, 0.4$; $P=0.015$). **Conclusion:** In children with CD, short stature and skeletal disproportion are present in childhood and persist into adulthood.

P2-D2-461

Anophthalmia, Abnormal Pituitary Development, and Suboptimal Response to GH Therapy in Two Children With Microdeletions of 14q22q23

Petra Dusatkova^a, Zuzana Slamova^b, Zdenek Sumnik^a, Martina Simandlova^b, Elsa Zemankova^c, Zdenek Sedlacek^b, Jan Lebl^a

Table 1. (abstract for P2-D1-460)

	Female		Male		Female				Male			
	C		C		ACO		AAO		ACO		AAO	
	Med	Range	Med	Range	Med	Range	Med	Range	Med	Range	Med	Range
Age (years)	13.9	10:17	13.4	10:17.3	23.0	18:30	32 ⁺	22:40	20.0	18:32	30 ⁺	24:39
HtSDS	-0.1	-2.5:2.0	-0.2	-2.6:1.5	-0.4	-1.7:2.1	-0.1	-1.3:1.8	-0.9 [#]	-2.3:0	0.6 ⁺	-0.9:1.0
Δ MPHSDS	-0.2	-2.5:1.3	-0.2	-2.4:2.4	0.1	-1.5:1	-0.2	-1.1:1.6	0.3	-0.5:1.5	-0.5 ⁺	-1.5:1.0
SHSDS	-0.4 [*]	-3.0:1.8	-0.5 [*]	-2.2:1.0	-0.6	-2.8:1.8	-0.7 [*]	-1.6:0.6	-1.1 [#]	-2.5:-0.5	0.2 ⁺	-0.7:0.8
SILLSDS	0.0	-2.7:1.6	-0.3 [*]	-3.0:1.7	-0.1	-1.5:1.6	0.3	-1.6:1.8	-0.3	-3.1:1.4	0.4	-0.8:0.9

* $P<0.05$ compared with UK1990; ⁺ $P<0.05$ CO vs AO same gender; [#] $P<0.05$ between genders of same type of CD; Δ MPH: Target minus actual height SDS.

^aDepartment of Pediatrics, 2nd Faculty of Medicine, Charles University in Prague and University Hospital Motol, Prague, Czech Republic; ^bDepartment of Biology and Medical Genetics, 2nd Faculty of Medicine, Charles University in Prague and University Hospital Motol, Prague, Czech Republic; ^cGenetic and Pediatric Out-Patient Clinic, Benesov, Czech Republic

Background: Microdeletions of 14q22q23 have been associated with eye abnormalities. Other symptoms in deletion carriers are less well recognized. **Objective and hypotheses:** We focused on growth characteristics and response to GH treatment in two unrelated children with 14q22q23 deletions. **Method:** Array comparative genomic hybridisation (aCGH). **Results:** Both patients displayed bilateral anophthalmia. Their brain MRI revealed absence of optic nerves and chiasm; the pituitary stalk and posterior pituitary were normally located, but the anterior pituitary was undetectable. Both children suffered from GH deficiency. The initially normal growth of patient 1 started to decelerate at 10 months and reached -1.8 s.d. at 1.8 years. At this time GH therapy (25 μ g/kg per day) was initiated. It improved the growth rate and the serum IGF1 level but did not lead to full catch-up growth (-1.9 s.d. at 3.1 years). In contrast to patient 1, patient 2 was born with IUGR that was followed by severe postnatal growth failure (-3.7 s.d. at 1.5 years). GH therapy (25 μ g/kg per day) initiated at the age of 2.3 years led to an improved height velocity in the first year of GH administration but without full catch-up (-4.0 s.d. at 3.2 years). Also the serum IGF1 level remained low. Other pituitary functions were normal in both patients. aCGH revealed heterozygous *de novo* deletions of 8.9 and 5.8 Mb in patients 1 and 2, respectively. Both deletions removed the *OTX2* gene, critical for eye and pituitary development. No other gene related to growth has been detected in the deleted region. **Conclusion:** Genotype–phenotype description of two patients with deletions of 14q22q23 demonstrated that *OTX2* gene defects alone could explain most of the reported clinical features, although their expressivities are very variable. GH deficiency is remarkable in these patients and may be difficult to correct with GH therapy.

P2-D2-462

Adiponectin Levels as Early Marker of Insulin Resistance in Children Born Small for Gestational Age in Our Cohort

Sangita Yadav, Ainam Gupta, Siddharth Ramji, T K Mishra

Department of Pediatrics and Biochemistry, Maulana Azad Medical University of Delhi, New Delhi, India

Background: Small for gestational age (SGA) children, especially those with postnatal catchup growth, have increased risk of insulin resistance and adult metabolic diseases. Adipokines produced by adipose tissue play crucial role in fetal growth and early postnatal life. Low adiponectin (adipokine) is marker of

insulin resistance. **Objective:** To evaluate adiponectin levels in term SGA at 15–18 months age and its relationship with postnatal catchup growth (CUG). **Methods:** Sixty term SGA children (birth weight <10th percentile) were enrolled at 15–18 months age. Birth weight and length recorded from discharge document and current weight and length measured at inclusion. Data analyzed for CUG as gain in weight or length SDS or both >0.67 (percentile band). Adiponectin levels were measured using ELISA Kit. **Results:** Average birth weight, length, and gestational age was 2.08 ± 0.2 kg (-2.9 ± 0.6 s.d.), 45.1 ± 2.5 cm (-2.4 ± 1.4 s.d.), 38.4 ± 1.2 weeks respectively. At enrolment mean age, weight, and length was 16.9 ± 1.2 months, 8.2 ± 0.8 kg (-2 ± 0.9 s.d.), 73.0 ± 3.0 cm (-2.3 ± 1.1 s.d.). 65% (39) out of 60 SGA infants showed CUG and 21 did not have catchup growth (NCUG). Adiponectin levels in the cohort were 8.6 ± 4.0 μ g/ml and were similar in CUG (8.7 ± 4.36 μ g/ml) and NCUG (8.5 ± 3.41 μ g/ml). **Conclusion:** 65% infants born SGA showed CUG by 18 months. The study cohort had lower mean adiponectin levels when compared with western studies; 21.6 ± 0.6 μ g/ml at 1 year and 15.7 ± 0.4 μ g/ml at 2 years (Iniguez *et al*) and 35.51 ± 8.76 μ g/ml at 1 year (Bozzola *et al.*). Thus lower adiponectin levels might suggest that our SGA cohort is more prone to develop adiposity and insulin resistance. This further reinforces inherent susceptibility of Indian population to develop adult metabolic syndrome. May also reflect ethnic variations of mean adiponectin levels as there are no normograms available for our Indian population. This warrants further research.

P2-D2-463

Recombinant Human GH Effects on Growth and Clinical Status in Cystic Fibrosis

Robabeh Ghergherehchi, Mandana Rafeey, Afshin Habibzadeh, Masoud Zamani, Khalil Ansarin, Mahnaz Sadeghi Shabestari

Tabriz University of Medical Sciences, Tabriz, Iran

Background: Growth retardation is a common finding in cystic fibrosis (CF) patients. Recombinant human GH (rhGH) has shown promising results in improving weight, height and clinical status of CF patients. **Objective and hypotheses:** In this study we aim to evaluate efficacy of rhGH on growth and clinical status in CF patients. **Method:** In this prospective clinical trial we recruited 34 CF patients (58.8% male with mean age of 62.05 ± 31.11 months). Patients were followed for 6 months without treatment and then were treated with rhGH 0.35 mg/kg per week for the next 6 months. Measurements included height, weight, growth velocity, pulmonary function, hospitalizations, and out-patient antibiotic use. **Results:** Growth velocity, IGF1 levels, hospitalization, and antibiotic therapy were significantly improved after rhGH treatment. 18 patients underwent pulmonary function evaluations including forced vital capacity and forced expiratory volume in 1 min which showed no significant difference with baseline findings. **Conclusion:** In conclusion, these results show significant effects of rhGH treatment on growth and clinical status of CF patients.

P2-D2-464

Interrelationships Between BMI and Other Overweight Related Anthropometric Variables in Childhood

Bente Brannsether^{a,c}, Geir Egil Eide^a, Mathieu Roelants^c, Robert Bjercknes^a, Pètur Benedikt Jùliusson^a

^aUniversity of Bergen, Bergen, Norway; ^bKatholieke Universiteit Leuven, Leuven, Belgium; ^cStavanger University Hospital, Stavanger, Norway

Background: Anthropometry is the general tool for defining overweight and obesity, with BMI cut-offs adjusted for sex and age, as the most commonly used variable in childhood. **Objective and hypotheses:** Based on the interrelationships between BMI and different overweight-related anthropometric variables we wanted to find out which anthropometric variables contribute most to the variation in BMI, and how age affect this picture? **Method:** Data on BMI, height (H), sitting height (SH), waist circumference (WC), waist to height ratio (WHtR), waist to sitting height ratio (WSHtR), subscapular skinfold (SSF), and triceps skinfold (TSF), from 4576 Norwegian children 4.00–15.99 years of age, were transformed to standardized scores (SDS) and studied by means of correlation and regression analyses. **Results:** The correlations between BMI SDS and the standardized anthropometric variables were in general strong and positive. WC SDS and WHtR SDS were strongest correlated to BMI SDS through all ages and in both sexes. A model with seven anthropometric variables adjusted for sex and age group explained 81.4% of the variation in BMI SDS. When adjusted for all other variables, WC SDS explained most of the variation in BMI SDS ($b=0.467$). Age group but not sex, contributed significantly to variation in BMI SDS. The correlations between all variables were weakest in the youngest age-group. **Conclusion:** Independent of sex and age, WC SDS was superior to other anthropometric variables in this study in explaining variations in BMI SDS. The interrelationships between BMI and all variables studied were weakest in the youngest age group.

P2-D2-465

Assessment of Omentin-1, Vaspin, and Visfatin Levels in Pediatric Patients with GH Deficiency

Beata Sawicka, Hanna Borysewicz-Sanczyk, Aneta Zasił, Ewa Jakubowska, Artur Bossowski

Department of Pediatrics, Endocrinology and Diabetology with the Cardiology Division, Medical University in Białystok, Białystok, Poland

Introduction: GH deficiency (GHD) is a disease, in which the pituitary gland does not produce enough GH. GHD has a variety of different negative effects at different ages; e.g. it can result short stature and increased adiposity. Excessive intra-abdominal fat is

associated with an increased risk of cardiovascular disease. In recent years new adipokines such as omentin-1, vaspin, and visfatin have been described. Omentin-1 is decreased in obesity in contrast to increased vaspin and visfatin. **Aim:** The aim of the study was to estimate the concentration of omentin-1, vaspin, and visfatin in serum in patients with GH deficiency and in control subjects with idiopathic short stature. **Materials and methods:** The research was performed on the group of 30 patients with GHD (average age 10.6 ± 0.7 years old) and 21 children with short stature with normal serum level of GH (9.4 ± 0.6 years old). Laboratory analysis included the assessment of cytokines serum concentration, levels of lipid parameters and glucose and IGF1 values. The expression of omentin-1, vaspin, and visfatin were analyzed by BioVendor ELISA reader. To analyze statistically significant differences occurring among the groups we used ANOVA and Mann-Whitney *U* nonparametric tests and Pearson's correlation coefficient. **Results:** In patients with GHD we observed a significant elevation of vaspin and visfatin concentration in comparison to control group (vaspin – 6.4 ± 2.6 vs 0.67 ± 0.43 ; $P < 0.046$; visfatin – 4.91 ± 0.62 vs 2.97 ± 0.4 ; $P < 0.05$). However, serum level of visfatin was major in female group with GHD in opposite to female control group. The analysis of omentin-1 showed increased levels of that cytokine in group with GHD in comparison to the control, but it was not statistic value (561.46 ± 54.85 vs 530.96 ± 59.81 ; NS). Levels of lipids and glucose were similar in both groups. We observed lower level of IGF1 in patients with GHD (119.37 ± 18.76 vs 151.33 ± 36.2 ; NS). BMI (s.d.) was higher in children with GHD, but it was not statistic value. **Conclusion:** In conclusion, both vaspin and visfatin cytokines may connect with developing of adiposity in children with GHD. These adipokines may seem be more sensitive in progress excessive intra-fat tissue in patients with GHD.

P2-D2-466

Normal Growth in Aromatase Excess Syndrome by Pharmacological Inhibition of Aromatase Activity

Beate Deubzer, Gerhard Binder

University Children's Hospital, Pediatric Endocrinology, Tübingen, Germany

Introduction: In the rare aromatase excess syndrome aromatase turnover from androgens to estrogens is constitutively increased. Affected males show signs of hyperestrogenism such as feminization (particularly gynecomastia), hypogonadism, and short adult height due to early epiphyseal closure. **Case report:** Here, we report the different statural growth of two first degree cousins affected by aromatase excess syndrome. Both carried the same heterozygote deletion of the regulatory part of the aromatase gene explaining the phenotype. Only one cousin was treated with an aromatase inhibitor before puberty started. Cousin 1 was the index patient of the family and presented at an age of 13 years because of bilateral gynecomastia (Tanner stage B4). Bone age was advanced by 2 years. He went for surgical mastectomy and was

only seen aged 18 years due to incomplete virilisation. His adult height was 162 cm (-2.15 SDS) and his target height was 165 cm (mother's height 145.7 cm due to aromatase excess syndrome). At that time the diagnosis was made based on a pathologically low testosterone to estradiol ratio, and low-normal LH and FSH levels. Treatment with an aromatase inhibitor (testolacton 5 mg/kg per day for 1 year, then anastrozole 1 mg/day for 1 year) improved virilisation, but no further gain in height could be reached. Cousin 2 presented at the age of 9 years with unilateral breast development (Tanner B2) and accelerated bone age. He showed elevated estrone levels and was immediately diagnosed with aromatase excess syndrome because of his relationship to cousin 1. Treatment with anastrozole 1 mg orally was given and he already reached a normal adult height of 175 cm at the age of 15 years (0.75 SDS). His target height was 171 cm. **Conclusion:** These two cases illustrate the potential of aromatase inhibitors to effectively prevent short stature in aromatase excess syndrome.

P2-D2-467

The Effect of the Environmental Factors on Growth Pattern of Turkish Children Having the Same Genetic Origin

Sevil Ari Yuca^a, Yasar Cesur^b, Selim Kurtoglu^c, Mumtaz Mustafa Mazicioglu^c, Emine Ayca Cimbeke^a

^aSelcuk University Medical School, Konya, Turkey; ^bBezmi Alem Foundation University Medical School, Istanbul, Turkey; ^cErciyes University Medical School, Kayseri, Turkey

Background: Childhood is a dynamic process with continuous growth and development. Growth charts are essential for the assessment of children's health status. Standards previously established in children aged 6–18 years, according to percentile curves are used in Turkey. **Objective and hypotheses:** To determine the effect of different environmental factors on growth of children with the same genetic origin. We investigated the parameters of growth in the east of Turkey and compared them with those of Turkish children living in other regions and countries. **Method:** The growth data in the east of Turkey were obtained from the primary and secondary schools in 6 months period. A total of 6917 primary and secondary school students whose height and weight were between the 3rd and 97th percentiles were enrolled. The smoothed percentile curves of weight and height were constructed by the LMS method. The median curves obtained from the east of Turkey were compared with the west of Turkey and Europe (among Turks). **Results:** Boys and girls in eastern Turkey were shorter, lighter and had a lower BMI value from Western peers of all ages. All children living in Turkey were lighter and had a lower BMI than European peers at early age. The weight and BMI curves living in the west of Turkey reached to European peers after 11 years old in boys and after 12 years old in girls. The median height in the west of Turkey and Europe were similar between 7 and 11 years of age, later it was higher in west Turkey. The girls in the east of Turkey were shorter than peers until 16 years of age. **Conclusion:** Weight and BMI may interact with environmental factors but the final height

doesn't change. The most important factor determining final height is genetic origin. Nevertheless more efforts are needed.

P2-D2-468

Successful GH Treatment for Severe Growth Failure in Paediatric Patients with Anorexia Nervosa

Anne Fjellestad-Paulsen^{a,c}, Anne Bargiacchi^b, Catherine Doyen^b, Cecile Raverdy^a, Jean-Claude Carel^{a,c}, Marie-France Leheuzey^b, Juliane Leger^{a,c}

^aPaediatric Endocrinology–Diabetology Department, Robert Debre Hospital, Assistance Publique–Hopitaux de Paris, Universite Paris-Diderot, Paris, France; ^bPedopsychiatric Department, Robert Debre Hospital, Assistance Publique–Hopitaux de Paris, Universite Paris-Diderot, Paris, France; ^cReference Center for Rare Endocrine Growth Diseases, Paris, France

Background: Anorexia nervosa (AN), a state of chronic nutritional deprivation prevalent in children and young adolescents, is associated with major changes to the hypothalamic–pituitary axis including the GH–IGF1 axis, thyroid function, hypercortisolemia, and hypogonadotropic–hypogonadism, with delayed puberty and a low growth velocity (GV) at a time critical for the pubertal growth spurt, potentially affecting adult height. The effects of supraphysiological human GH on GV are currently unknown. **Aim:** To investigate the effect of hGH on GV in children with AN and profound growth impairment. **Method:** Ten girls diagnosed with AN (DSM IV) at a median chronological age of 10.0 (8.5–11.1) years were treated for severe prolonged growth failure (GV < 2 cm/year for at least 18 months) at a median age of 13.3 (12.5–14.1) years and a bone age of 11.5 (10.0–12.0) years, Tanner stage I (n=7), II (n=1) or III (n=2), and 2.0 (1.0–2.3) years after the lowest SDS for BMI, with open-label GH (0.050 mg/kg per day), until adult height was achieved. **Results:** A significant increase in GV directly attributed to GH therapy was observed in all children, resulting in adult height potential being reached, with no side effects. IGF1 concentration normalized without exceeding the reference ranges (166 ± 71 vs 429 ± 134 ng/ml, before and after 1 year of treatment) (Table 1). **Conclusions:** We report the first study on the efficacy of GH therapy in children with AN and a very low GV. A randomized controlled trial in a large cohort of children is now required to determine the ultimate impact of GH treatment.

Table 1

	Baseline	+ 1 year	+ 2 years	Adult height
GV (cm)/year	1.5 ± 1.2	7.8 ± 2.4*	5.8 ± 3.3*	
Height (cm)	141.7 ± 8.9	149.3 ± 8.1	153.2 ± 7.5	161.8 ± 4.4
Height SDS	-2.2 ± 1.3	-1.6 ± 1.3	-1.3 ± 1.4	-0.3 ± 0.8*
Height - target height SDS	-2.6 ± 1.3	-2.0 ± 1.2	-1.7 ± 1.4	-0.7 ± 1.0*

*P < 0.0001 vs baseline.

P2-D2-469**The Analysis of Limb Segments Length and Body Proportion of Children and Adolescents Aged 6–17 Years in the Main Urban Area of Chongqing**

Yanhua Jiao, Min Zhu, Feng Xiong

The Children's Hospital of Chongqing Medical University, Chongqing, China

Objective: To accumulate the information in the long-term studies of the variation of the limb segments length and proportion in the process of growth and development of children, we have measured and summarized the average level of limb segments length for the children and adolescents in the main urban area of Chongqing, calculated the ratios of limb segments length to height and extremities-trunk ratio, body proportions, and analyze their age trends. **Methods:** Using cluster sampling, sampling 4715 students of five schools aged 6–17 years in the main urban area of Chongqing, we measured their standing height, sitting height, arm span, forearm length, upper arm length and lower leg length, calculated their average level and ratios, and observed their age trends. **Results:** The study obtained the average levels of limb segments lengths, they show similar growth trend to height, and no significantly gender differences were found before the age of 13. The correlation analysis showed that sitting height, forearm length, upper arm length, arm span and lower leg length are highly correlated with standing height, the correlation coefficient r is all above 0.9 ($P < 0.05$). With the growth of age, the ratios of forearm length, upper arm length, arm span, lower leg length to standing height increased, while the forearm length/upper arm length showed a downward trend ($P < 0.05$). Sitting height/leg length rebounded slightly after the first gradual decline trend with age, gender difference was not obvious before the age of 11, while males smaller than females after 11-year-old ($P < 0.05$), extremities-trunk ratio showed opposite trend. **Conclusions:** Sitting height, arm span, forearm length, upper arm length, lower leg length and their ratio to standing height present regular changes with the growth of age, and limb segments length is highly correlated with height.

P2-D2-470**Severe Short Stature due to a Heterozygous *igf1r* Mutation With a Good Response to rhgh Therapy: a Family Study**Victoria Borrás-Pérez^a, Monica Fernández-Cancio^{b,c}, Ana Gómez-Núñez^{d,e}, M Catalá-Puigbó^a, Laura Audí^{b,c}, Angel Campos-Barros^{d,e}

^aPediatric Endocrinology, Hospital General de Granollers, Barcelona, Spain; ^bPediatric Endocrinology, Hospital Vall d'Hebron, Barcelona, Spain; ^cVHIR; CIBERER (U712), Autonomous University, Barcelona, Spain; ^dHospital Universitario La Paz; INGEMM, IdiPAZ, UAM, Madrid, Spain; ^eCIBERER (U753), ISCIII, Madrid, Spain

Background: IGF1 resistance syndrome (IGF1RS) is characterized by intrauterine and postnatal growth deficit with normal or supranormal IGF1 levels. Additional features may include intellectual deficit, microcephaly, and dysmorphisms. IGF1RS may be caused by genomic or genetic defects affecting the *IGF1R* locus (15q26.3). **Objective and hypotheses:** Case report: a girl born at 36.5 weeks, BW 1.935 g (−3.2 SDS), length 41 cm (−4.4 SDS) and cephalic perimeter (CP) 29 cm (−5.2 SDS), was examined at 3.5 years for developmental delay, BA: 2.5 years, BW 10.5 kg (−2.4 SDS), height 87.4 cm (−3.0 SDS), CP 46.5 cm (−2.5 SDS), and mild psychomotor retardation. Maternal grandparents were consanguineous. Hormonal tests: IGF1 95.4 ng/ml (−0.8 SDS), IGFBP3 3 μg/ml (0.51 SDS), and GH test peak: 2.9 ng/ml (glucagon). **Method:** Molecular studies: Mutation screening of *GHR*, *IGF1R*, and *IGFALS* by HRM and DNA sequencing in the proband and relatives. **Results:** A heterozygous point mutation in *IGF1R* exon 10, c.2155C>T, was detected in the proband. The mutation causes the substitution of a highly conserved residue, p.Arg719Cys, located in the IGF1R fibronectin type III and tyrosine-protein kinase intracellular domains. The mutation was maternally transmitted. Evolution: rhGH treatment (0.04 mg/kg per day) was initiated at age 4.7 years. A good clinical response was observed after 1.5 years (growth velocity 10 cm/year; +4.7 SDS), with no BA progression and IGF1 254 ng/ml (+1.6 SDS). **Conclusion:** We present a family case of partial IGF1 resistance due to a novel heterozygous *IGF1R* mutation with good response to rhGH treatment. Mutation analysis of *IGF1R* is recommended if proportional short stature coexists with IUGR, microcephaly, and intellectual delay, especially if there is evidence of familial clustering. Evaluation of the response to rhGH therapy seems an adequate option to improve growth rate.

P2-D2-471**When and Why Should We Investigate the SRCAP Gene in Cases of Short Stature?**Luiza Silveira Lucas^a, Kym M Boycott^b, Sarah M Nikke^b, Elizabeth Lemos Silveira Lucas^c

^aFaculdade de Medicina – Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre, Rio Grande do Sul, Brazil; ^bChildren's Hospital of Eastern Ontario Research Institute, University of Ottawa, Ottawa, Ontario, Canada; ^cAmbulatório de Genética Médica da Secretaria Municipal de Saúde de Porto Alegre, Porto Alegre, Rio Grande do Sul, Brazil

Background: The heterozygous mutation in the SRCAP gene (611421) on chromosome 16p11.2 causes a rare genetic disorder named Floating-Harbor syndrome (FHS). The clinical diagnosis of FHS is characterized by a triad of short stature with significantly delayed bone age; expressive language delay, usually in the

presence of normal motor development; and a triangular face with prominent nose and deep-set eyes. **Objective:** To investigate the presence of SRCAP gene mutation in a girl with 6 years old and clinical diagnosis of FHS. **Methods:** Blood sample to DNA extraction was sent to FORGE (Finding of Rare Disease Genes in Canada) and Sanger sequencing of exons 31–34 of SRCAP was performed. **Results:** A novel heterozygous SRCAP mutation was identified in codon 2407 (Gln2407*). **Conclusions:** From the clinical point of view, molecular testing allowed us to establish a treatment plan based on scientific evidence. The main recommendations were: complete assessment of auditory and visual systems; renal and urinary tract ultrasound; neurological assessment if there is a suspicion of seizures; dental hygiene to prevent cavities and monitoring for malocclusion; and evaluation for GH deficiency at baseline, to be repeated if loss of growth velocity. Furthermore, the molecular study establishes that the mechanism of inheritance is autosomal dominant with a recurrence risk of 50% for offspring of affected person.

P2-D2-472

Body Proportions Estimated by Photometry

Willem Jan Gerver, Ralph Brecheisen, Bas Penders, Saartje Straetemans

Maastricht University, Maastricht, The Netherlands

Background: The growth process that transforms a newborn into an adult implies that there is not only an increase in height but above all a constant change in body proportions. Knowledge of the body proportions gives insight into the natural process of maturation and any disturbance can be used as a diagnostic tool. **Objective and hypotheses:** Manual measurement of body dimensions is a highly time-consuming procedure requiring a variety of measurement tools. Therefore, photometry as an alternative method is developed that allow a much faster measurement of body dimensions. **Method:** The main procedure involves taking both frontal and lateral digital pictures of the subject, transferring the pictures to the photometry software and using a mouse device to select up to ten anatomical points in the images. A reference object on the photograph is used in order to determine the correspondence between pixels in the image and real centimetres. **Results:** Comparison of the manual taken measurements and the results of photometry shows a good correlation between both methods provided standardized photography setup is used. All measurements are expressed in centimetres and SDS based on the reference of the atlas 'Paediatric Morphometrics'. **Conclusion:** The main advantages of the photometry method are speed and ease of use. Taking pictures using a digital camera and transferring them to a computer running the photometry software can be done relatively fast. Within a few minutes one is informed about ten measurements, which will take about 15 min otherwise.

P2-D2-473

GH Deficiency in a Child With *De Novo* 2q31.1 Microdeletion

Irene Kaloumenou^a, Feneli Karachaliou^a,
Elpis-Athina Vlachopapadopoulou^a, Aspasia Fotinou^b,
Stefanos Michalacos^a

^aEndocrinology Department, 'P & A Kyriakou' Children's Hospital, Athens, Greece; ^bMicrobiology, 'P & A Kyriakou' Children's Hospital, Athens, Greece

Background: The clinical phenotype of the chromosome 2q31 deletion syndrome consists of a variety of limb abnormalities and other skeletal defects, craniofacial dysmorphic features, developmental delay, and other not specific congenital anomalies. **Objective and hypotheses:** To describe a patient with 2q31.1 microdeletion syndrome and short stature, diagnosed with GH deficiency. **Method:** We describe a 5 years and 4 months girl with developmental delay, growth retardation, motility disorders, mild tremor upper limb, craniofacial dysmorphic features (microcephaly, high arched palate, downslanting palpebral fissures, and micrognathia), camptodactyly, clinodactyly, and bilateral hypoplastic middle phalanges particularly of the fifth fingers of the upper and lower extremities and low degree of syndactyly. She had moderate intellectual disability with slow developmental milestones. She was unable to concentrate and therefore attended special education. **Results:** No chromosomal abnormalities were detected by conventional karyotyping. Array CGH revealed a *de novo* 2q31.1 microdeletion. Endocrinological evaluation revealed GH deficiency. She was started on recombinant GH (160 µg/kg per week) and during the first 8 months of treatment she showed an increase in height velocity from a pretreatment value of 3.5–9 cm/year. **Conclusion:** In recent years, the spectrum of available methods for the characterization of chromosomal aberrations has significantly increased. Micro-array technologies now allow the rapid fine mapping of small genomic imbalances, as it was in our case. We describe this case because of the rarity of this syndrome and its association with GH deficiency, which to the best of our knowledge has not been reported before.

P2-D3-474

Plasma Glucagon and Somatostatin Levels in Children with Congenital Hyperinsulinism During Hypoglycaemia

Pratik Shah^{a,b}, Gregg Mamikunian^c, Clare Gilbert^a, Kate Morgan^a,
Louise Hinchey^a, Ved Arya^{a,b}, Huseyin Demirbilek^{a,b},
Khalid Hussain^{a,b}

^aGreat Ormond Street Hospital for Children NHS Trust, London, UK; ^bUniversity College London and Institute of Child Health, London, UK; ^cInter Science Institute, Inc., Inglewood, California, USA

Background: Congenital hyperinsulinism (CHI) causes severe hypoglycaemia in children, due to dysregulated insulin secretion from pancreatic β -cells. Glucagon, secreted from the pancreatic α -cells, is critical for blood glucose homeostasis. Somatostatin is secreted by Δ -cells of the islets and by extraislet neuroendocrine cells. Exogenous somatostatin potentially inhibits insulin and glucagon release from pancreatic islets. Under normal physiological conditions, low blood glucose levels reduce insulin release and promote glucagon and somatostatin secretion. **Objective and hypotheses:** To determine the changes in the plasma levels of glucagon and somatostatin in children with CHI at normoglycaemia and during hypoglycaemia. **Method:** All children admitted at our tertiary centre with a diagnosis of CHI were included in the study. Blood samples for glucose, insulin, glucagon, and somatostatin were collected at the time of normoglycaemia and then at the time of hypoglycaemia screen. The children did not receive glucagon or octreotide infusions at the time of hypoglycaemia screen. **Results:** Nine children (five males and four females) were included in the on-going study. Six children had *ABCC8/KCNJ11* mutations. Three children had focal lesions in the pancreas and underwent partial pancreatectomy. The median value (25th–75th interquartile range) for insulin, glucagon, and somatostatin at normoglycaemia was 12.3 mU/l (7.3–29.8); 52.0 pg/ml (33.5–72.0); and 8.0 pg/ml (3.0–10.0) and during hypoglycaemia was 9.3 mU/l (6.8–14.9); 58.0 pg/ml (40.5–68.5); and 7.0 pg/ml (3.0–11.0) respectively. There is a positive correlation between the somatostatin and insulin level ($r=0.68$; $P=0.003$) and somatostatin and glucagon level ($r=0.48$; $P=0.045$). But no correlation either between glucagon and insulin level ($r=0.246$; $P=0.342$) or glucose level ($r=-0.066$; $P=0.800$). **Conclusion:** There was no statistically significant difference (P value >0.05) between insulin, glucagon, and somatostatin levels during normoglycaemia and hypoglycaemia in children with CHI. Our preliminary data highlights that the children with CHI have inadequate response of glucagon and somatostatin secretion during hypoglycaemia.

P2-D3-475

Long-Term Follow Up of Children with Congenital Hyperinsulinism on Octreotide Therapy

Huseyin Demirbilek^{a,b}, Pratik Shah^{a,b}, Ved Bhushan Arya^{a,b}, Khalid Hussain^{a,b}

^aDepartment of Paediatric Endocrinology, Great Ormond Street Hospital for Children NHS Trust, London, UK; ^bClinical and Molecular Genetics Unit, Institute of Child Health, University College London, London, UK

Background: Octreotide, a long-acting somatostatin analogue, is commonly used in diazoxide unresponsive congenital hyperinsulinism (CHI) patients as a second line medication. However, there are no large studies evaluating long-term follow-up CHI patients on octreotide therapy. **Objective and hypotheses:** To evaluate the dose range, side effects and long-term follow-up in

CHI patients on daily octreotide injections. **Method:** Twenty-eight (17 males and 11 females) diazoxide unresponsive CHI patients managed with daily multidose octreotide therapy between 2001 and 2013 at Great Ormond Street Hospital for Children NHS Trust were evaluated. Regular follow up of auxology, hormonal, liver function tests, and hepatobiliary ultrasonography results were reviewed from hospital notes. **Results:** The median age of diagnosis was 1 week (range: 1–80 weeks) and the mean dose of octreotide commenced was 17.8 ± 7.5 $\mu\text{g}/\text{kg}$ per day (range: 7.5–33.7 $\mu\text{g}/\text{kg}$ per day). The mean duration of follow-up on octreotide therapy was 52.4 ± 33.8 months (range: 6 months–9.5 years). Elevation of liver enzymes was the most prevalent side effect of octreotide therapy ($n=13$, 46.4%) which resolved spontaneously. Gallstone ($n=6$, 21.2%) and gall bladder sludge ($n=3$, 10.7%) were detected in nine out of 28 (32%) patients. There was no relation between the dose and duration of octreotide therapy with either elevation of liver enzyme or development of gall bladder pathology. However, the younger age for commencement of octreotide was found to be related with the higher rate of elevation in liver enzymes. GH deficiency and hypothyroidism were not detected during long-term follow-up on octreotide therapy. **Conclusion:** Transient elevation of liver enzymes and asymptomatic gallbladder pathology are the most prevalent long-term side effect of octreotide therapy in children with CHI. There is no correlation between dose or duration of octreotide therapy and development of liver dysfunction and gallbladder pathology.

P2-D3-476

Glucagon Secretion in Response to Hypoglycemia in Patients with Congenital Hyperinsulinism

Yi Wang, Chunxiu Gong, Chang Su

Beijing Children's Hospital, The Capital Medical University, Beijing, China

Background: Hypoglycemia triggers the secretion of counter-regulatory hormones such as cortisol, GH, and glucagon, all of which are protective mechanisms to restore euglycemia. It has been suggested that CHI patients have abnormal glucagon secretion during hypoglycemia, but the data is limited. **Objective and hypotheses:** To investigate the secretion of counter-regulatory hormones including glucagon during hypoglycemia. It is supposed that these hormones are not low. **Method:** Three groups of patients with CHI ($n=41$), ketosis hypoglycemia (KH, $n=19$), and type 1 diabetes at the first onset of ketoacidosis (DKA, $n=19$) were reviewed retrospectively. All patients were admitted to the Department of Endocrinology at our hospital. Blood was collected during hypoglycaemia. **Results:** The median glucose levels in CHI patients were 1.34 (range: 0.1–2.5) mmol/l, and the levels were 2.26 (0.71–3.88) mmol/l, ($P<0.01$) in KH patients. The median glucagon value in CHI patients was 280 (range: 4.8–800) pg/ml compared to 142 (64–535) pg/ml in KH patients ($P<0.01$). Furthermore, glucagon secretion in DKA patients was not low: glucagon levels were 124 (85–299) pg/ml.

The glucagon/glucose ratio showed similar results. CHI was 253 (2.8–6580) vs KH: 69 (16–328), $P < 0.01$. Compared to diazoxide-sensitive CHI patients ($n = 18$), Diazoxide-unresponsive CHI patients ($n = 23$) had a higher insulin/glucose ratio, 8.4 (2.9–382) vs 7.1 (2.3–40), $P < 0.05$. However, the glucagon/glucose ratio in these two groups of CHI patients was similar: diazoxide sensitive: 202 (87–815) vs insensitive: 253 (3–6580). There were 20 cases of CHI carry mutations at KATP channel gene (ABCC8 or KCNJ11). Glucagon secretion in response to hypoglycemia in patients with KATP channel mutations was similar to the patients with negative mutations for known CHI genes. **Conclusion:** Glucagon secretion in the CHI patients of the Chinese population is not impaired. Glucagon secretion had reverse correlation with glucose levels. These data also indicate that hypoglycemia is mainly the driving force for glucagon secretion, despite its causes.

P2-D3-477

Opioid-Induced Endocrinopathy in a Toddler with Chronic Codeine Intoxication

Sara Van Aken, Saskia Van Der Straaten, Kathleen De Waele, Martine Cools, Margarita Craen, Jean De Schepper

University Hospital Ghent, Ghent, Belgium

Background: Several studies in adults have provided evidence for opioid-induced hypofunction of the hypothalamo-pituitary-adrenal and GH-IGF1 axis after chronic (oral and intrathecal) administration. This so-called opioid endocrinopathy has not been reported in children. **Objective and hypotheses:** We report the occurrence of delayed growth with low serum IGF1 levels and recurrent hypoglycemia due to central hypocorticism in a toddler after a presumably intentional chronic codeine administration by her parents. **Method:** In a healthy 12 months old girl, admitted for coma related to a benzodiazepine and codeine intoxication, a symptomatic hypoglycemia (glucose < 45 mg/dl), responding to glucose administration, was documented when excessive sleepiness reoccurred at the third day of hospitalization. Subsequent glucose monitoring showed several asymptomatic hypoglycemic episodes during the next day. Poor growth and previous episodes of excessive sleepiness were evidenced during the 4 months preceding the hospitalization. **Results:** A critical sample analysis documented a ACTH level of 10 pg/ml and a cortisol of 1.7 μ g/dl, which increased up to 13.9 μ g/dl after a low dose ACTH test. Basal serum PRL and TSH were normal, but IGF1 was low (25 μ g/l) and DHEAS not measurable. A normal pituitary and hypothalamus were seen on MR imaging of the brain. After the instauration of hydrocortisone therapy, glucose levels remained normal and hydrocortisone was stopped after 6 weeks. Four weeks after stopping therapy, a normal basal cortisol, but a weak response to ACTH was documented. A normal GH and cortisol response at glucagon testing was found after 6 weeks. **Conclusion:** In contrast with hyperglycemia seen in toddlers with acute codeine intoxication, recurrent hypoglycemia due to a transient central hypocorticism can be observed in chronic codeine ingestion. Genetic differences in opioid receptor binding and metabolizing properties might be responsible for the induction and recovery of the endocrine dysfunction after opioid administration in children.

P2-D3-478

Case Report: a Rare Cause of Hypoglycemia in a Neonate

Parissa Salemi, Jessica Strohm Farber

University of Maryland Medical Center, Baltimore, Maryland, USA

Background: Hypoglycemia in the neonate occurs in approximately one to five per 1000 live births. Common causes may be due to sepsis, IUGR or LGA. Rarer causes are congenital hyperinsulinism, panhypopituitarism, GHD, cortisol deficiency, insulinoma, insulin-receptor stimulating antibodies, BWS, and congenital disorders of glycosylation. We present a case of hypoglycemia in a neonate secondary to intraductal papillary mucinous neoplasm of the pancreas (IPMN). IPMN was first reported by Ohashi *et al.* (1982). The majority of IMPNs occur in the sixth to seventh decade of life with rare reports in children. **Objective and hypotheses:** Patient presented to the ER following a seizure with bg of 55. UA revealed many WBCs resulting in US evaluation of kidneys with abdominal mass identified. Our hypothesis was that the seizure may have been due an insulin secreting mass resulting in hypoglycemia. To further confirm this, we evaluated the patient biochemically and obtained more accurate imaging. **Method:** A critical sample was obtained when bg < 40 followed by administration of glucagon. A dedicated abdominal US followed by an MRI of the abdomen was obtained. **Results:** Insulin level at the time of hypoglycemia was with bg rise to within half an hour of glucagon, consistent with hyperinsulinism. Abdominal US identified mass as a mixed solid/cystic structure, medial to the right kidney. MRI further delineated a retroperitoneal, multiloculated cystic mass, located in the RUQ of the abdomen appearing to arise from the pancreas. Dimensions were 2.2 \times 3.7 \times 3.9 cm. The mass was resected with pathological analysis revealing multiple cystic lesions described as multifocal intraductal papillary mucinous neoplasm (IPMNs) with high-grade dysplasia. Insulin immunostain of the tumor was positive. **Conclusion:** The final diagnosis was an isolated IPMN with high-grade dysplasia. This is the first known reported case of this diagnosis in a neonate.

P2-D3-479

The Majority of Late Presenting Congenital Hypoglycaemia Disorders are Really Missed Diagnosis: What Can we do to Improve Diagnosis in the New-Born Period?

Lisa Troung, Paul Thornton

Department of Endocrinology and Diabetes, Congenital Hyperinsulinism Center, Cook Children's Medical Center, Fort Worth, Texas, USA

Background: Patients with hyperinsulinism (HI) and anterior hypopituitarism often present in the new-born period (NBP). However up to 30% patients with HI and an unknown number with hypo-pit will present in the first year of life. Despite advances

in care the long-term neurological outcome for patients with HI is poor in 20-40% cases. **Aim:** To retrospectively evaluate the care given during the NBP in a series of patients diagnosed with late presenting potential congenital hypoglycaemia conditions to see if there was evidence of the disease in the NBP and whether they could have been identified during that time. **Methods:** We reviewed the new-born records of children identified outside of the NBP with hypoglycaemic disorders that would usually present during the NBP to determine if they had evidence of significant hypoglycaemia requiring i.v. glucose treatment at that time. **Results:** Thirteen patients (four males) had either HI (7) or hypopituitarism (6) with pituitary malformation. Five (71%) of the seven HI patients had hypoglycaemia requiring treatment with i.v. glucose during the NBP. One had no risk factors to enable a diagnosis to be made and one had a strong family history of autosomal dominant diazoxide treated HI. Thus 6 or 86% of late presenting HI patients were simply missed congenital patients. Of the six hypopituitarism children all 6 (100%) had hypoglycaemia requiring treatment with i.v. glucose in the NBP. Thus 92% patients either had evidence of hypoglycaemia requiring i.v. glucose treatment in the NBP or a history that should have triggered glucose screening. **Conclusion:** New-born infants requiring i.v. glucose to treat hypoglycaemia should have an investigation performed to determine the aetiology of hypoglycaemia prior to discharge from the neonatal unit. This could simply be done with a 6 h fasting study. Early identification of patients with serious hypoglycaemia disorders may lower the incidence of poor neurological outcome.

P2-D3-480

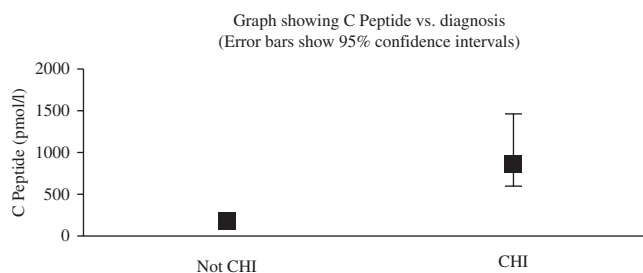
The Role of Plasma C-Peptide Concentration in the Diagnosis of Congenital Hyperinsulinism

Julie Green, Dinesh Giri, Arundoss Gangadharan, Jo Blair, Poonam Dharmaraj, Urmi Das, Senthil Senniappan, Mohammed Didi

Alder Hey Children's Hospital, Merseyside, UK

Background: The hallmark of congenital hyperinsulinism (CHI) is the demonstration of detectable plasma insulin during hypoglycaemia. Insulin can be undetectable in a significant proportion of patients with CHI. Plasma samples for insulin requires rapid and careful handling for reliable results. There is little published data on the value of C-peptide in the diagnosis of CHI. **Objective and hypotheses:** To assess the usefulness of C-peptide in the diagnosis of CHI. **Method:** All completed hypoglycaemia (laboratory glucose <2.6 mmol/l) screening tests undertaken at a tertiary referral centre over a 4-year period were assessed retrospectively. The diagnosis of CHI was made on a combination of glucose requirement >8 mg/kg/min, detectable insulin during hypoglycaemia, suppressed ketones and a glycaemic response to glucagon. The plasma C-peptide concentration during hypoglycaemia in patients with CHI was compared with that of the patients with other diagnoses. **Results:** 60 results were available from 41 patients. Median age was 16 months (1 day–20.5 years). Diagnoses included 23 CHI, one GH deficiency, one peroxisomal disorder, one respiratory chain disorder, and 15 ketotic

hypoglycaemia. The concentration of plasma C-peptide in patients with CHI was significantly higher than that for patients with a diagnosis other than CHI as shown in Fig. 1 ($P < 0.001$). The positive predictive value for a diagnosis of CHI with C-peptide concentration of 350 pmol/l is 96.7% and the negative predictive value is 80%. **Conclusion:** A plasma C-peptide concentration of >350 pmol/l during hypoglycaemia could be used to differentiate CHI from other causes of hypoglycaemia especially when plasma insulin level is low or could not be obtained.



P2-D3-481

Presentation, Clinical and Genetic Outcomes in a Series of Infants With Congenital Hyperinsulinism

Aoife Carroll^a, Brian Gibney^a, Ciara McDonnell^a, Sinead Moloney^a, Ardeshir Monavari^b, Nuala Murphy^a

^aDepartment of Endocrinology, Children's University Hospital, Temple St, Dublin, Ireland; ^bNational Centre for Inherited Metabolic Disorders, Children's University Hospital, Temple St, Dublin, Ireland

Background: Congenital hyperinsulinism (CHI) is a rare condition but a significant cause of recurrent hypoglycaemia in infancy and childhood. Prompt recognition and appropriate management is important to avoid long-term neurological sequelae. **Objective and hypotheses:** To describe the presentation, clinical and genetic outcomes in a series of infants with CHI. **Method:** Retrospective case series of 35 patients diagnosed with CHI between 1992 and 2014 at The Children's University Hospital, Temple Street, Dublin. **Results:** Twenty of 35 patients were male. Median age at presentation was day 2 of life (range: day 1–21 months) with 19 patients (54%) presenting in the first 48 h of life. Seizure was the most common presentation, occurring in 13 patients (37%). Mean glucose requirements to maintain euglycaemia were 14.5 mg/kg per min (range: 7.5–23 mg/kg per min). First line treatment with diazoxide was commenced in all patients of whom 22 (63%) responded. Of those who did not respond to diazoxide, three were stabilized on octreotide and ten required surgery. Genetic testing was performed on 31 patients (89%). A genetic diagnosis was possible in 18 patients (58%); 13 had a mutation(s) in the *ABCC8*, three had mutations in the *HNF4A* gene, one mutation in *KCNJ11* gene, and one had a novel mutation in the *HADH* gene. Twenty-seven patients (77%) had a normal

neurological outcome. Of the remaining eight patients, four have severe developmental delay, one of whom died of respiratory complications, one has moderate impairment, and the remaining three patients have mild dyspraxia and speech delay. Oral aversion occurred in 14/35 (40%) of children but resolved by age 3 years in 11 of 14 (78%). **Conclusion:** No clinical parameter significantly predicted developmental outcome. Advances in both molecular genetics and ^{18}F -L-DOPA PET scanning have revolutionised management of children diagnosed with CHI but early recognition and prompt appropriate treatment for hypoglycaemia are critical to reducing morbidity and mortality.

P2-D3-482

Feeding Issues in Children With Congenital Hyperinsulinism

Clare Gilbert^a, Kate Morgan^a, Louise Hinchey^a, Rebecca Margets^a, Alex Forsyth^a, Martina Ryan^a, Pratik Shah^{a,b}, Khalid Hussain^{a,b}

^aGreat Ormond Street Hospital for Children NHS Trust, London, UK; ^bInstitute of Child Health, University College London, London, UK

Background: Congenital hyperinsulinism (CHI) is the most common cause of persistent hypoglycaemia in the neonatal period, characterized by unregulated insulin secretion by pancreatic β -cells. In addition to medical therapy, frequent feeding to prevent hypoglycaemia is one of the most important aspects in the management of CHI. **Objective and hypotheses:** To identify the number of patients with CHI who have associated feeding difficulties and determine the level of parental concern around feeding issues and improve the outcomes. **Method:** 15 consecutive patients with confirmed diagnosis of CHI who were admitted in our tertiary referral centre between 24th January 2012 and 16th August 2012 were included in the study. Information was collected from medical/nursing notes and also parents were asked to fill out feeding questionnaire. **Results:** 87% (13/15) of parents had concerns about feeding at some point between admission and discharge. 73% (11/15) parents had concerns about feeding on admission whilst 60% (9/15) parents had concerns about feeding on discharge. The concerns raised were like unsafe swallow, vomiting, gastroesophageal reflux, not completing oral feeds and needing top up via gastrostomy. 92% (12/13) parents, who were concerned about their child's feeding, were referred to the speech and language therapy and/or dietetics services. 33% (5/15) patients had a delay in discharge, out of which four had feeding issues causing delay in discharge. 60% (9/15) patients had a positive and 40% (6/15) patients had no change to their feeding method by the point of discharge respectively. No patient had a negative change to their feeding method. **Conclusion:** Feeding difficulties are common in this group of complex patients. The cause of feeding difficulties in CHI patients is not clear and may be related to the disease pathophysiology or iatrogenic. This study highlights the need for dedicated feeding services to support the patient and their families. A follow-up study is in progress to evaluate feeding outcomes since we have now changed our practice.

P2-D3-483

Neurodevelopmental Outcomes in Early and Late Presenting Congenital Hyperinsulinism

Zainaba Mohamed^{a,b}, Jacqueline Nicholson^a, Imran Zamir^a, Thomas Butler^a, Lindsey Rigby^a, Louise Bowden^a, Philip Murray^{a,c}, Caroline Steele^a, Raja Narender Rao Padidela^a, Leena Patel^a, Karen Cosgrove^b, Peter Clayton^{a,c}, Mark Dunne^b, Indraneel Banerjee^{a,b}

^aDepartment of Paediatric Endocrinology, Royal Manchester Children's Hospital, Manchester, UK; ^bFaculty of Life Sciences, University of Manchester, Manchester, UK; ^cFaculty of Human Sciences, University of Manchester, Manchester, UK

Background: Hypoglycaemia due to congenital hyperinsulinism (CHI) usually presents early (E-CHI) in the neonatal period, but late presentation (age >1 month) (L-CHI) also occurs. Adverse neurodevelopment is well recognised in both early and late CHI, but differences between both groups are not known. **Objective and hypotheses:** We examined a cohort of children with E-CHI and L-CHI to test neurodevelopmental outcomes in mid-childhood. **Method:** A cohort of children with E-CHI ($n=24$) and another with L-CHI ($n=13$), who underwent psychometric testing using the parent reported Vineland Adaptive Behaviour Scales II (VABS-II) 2 years after diagnosis of CHI, were assessed for performance in the domains of communication, daily living skills, socialisation, motor skills, and behaviour. VABS-II scores were categorised as low (< -2 SDS) or acceptable (> -2 SDS), using normative data. **Results:** Children with E-CHI and L-CHI presented at median (range) 1 (1:6) and 270 (72; 1260) days respectively. Mutations in *ABCC8/KCNJ11* were identified in 12 (50%) E-CHI children, compared to 3 (23%) in L-CHI children. In E-CHI, low VABS-II was observed in the following domains in decreasing order of frequency: behaviour (56%), motor (25%), daily living skills (16%), social (16%), and communication (8%). In contrast, in L-CHI, the order of frequency of low VABS-II was: behaviour (30%), communication (30%), daily living skills (30%), motor (18%), and social (16%). These domain frequencies were not significantly different between E-CHI and L-CHI. However, within E-CHI, mean (s.d.) VABS-II scores were lower for motor than for communication (80.3 (23.2) vs 92.1 (19.6), $P=0.02$) while in L-CHI, VABS-II was similar among all domains. **Conclusion:** Adverse neurodevelopmental outcomes occur in several domains in both early and late presenting CHI. In early presenters, motor ability is reduced more than communication, while in late presenters all domains are equally affected. Prompt recognition and treatment of hypoglycaemia, particularly in older children, may prevent neurodevelopmental morbidity in CHI.

P2-D3-484

Abstract withdrawn.

P2-D3-485**Nocturnal Hypoglycaemia in Diabetic Children: Continuous Glucose Monitoring Reveals More of the Iceberg**

Sara Bachmann^a, Eva Martin^b, Vreni Ritschard^a, Melanie Hess^a, Katharina Jockers^a, Jean-Marc Vuissoz^a, Urs Zumsteg^a

^aPediatric Endocrinology and Diabetology, University Children's Hospital, Basel, Switzerland; ^bInstitute for Social and Preventive Medicine, Zurich, Switzerland

Background: Hypoglycaemia is the most common and threatening complication in diabetic children. Nocturnal hypoglycaemia is mostly unrecognised and asymptomatic, but recurrent mild hypoglycaemia at night can lead to hypoglycaemia unawareness and reduced performance at daytime. **Aims:** To evaluate frequency and duration of nocturnal hypoglycaemia in type 1 diabetic children and to identify risk factors for such events. **Patients/methods:** 60 children with type 1 diabetes for >6 months were included. The data of 51 patients (29 m, 22 f, age 12.1 years, 2.4–17.6 years) were complete (> five nights recorded). For a 6-day period glucose was measured by continuous glucose monitoring (iPro, Medtronic) and physical activity was measured by accelerometry. Patients were asked to perform four capillary blood glucose measurements per day and to keep notes about bed time and wake-up time, carbohydrates and insulin. HbA1c was determined at the routine visit preceding the study. Nocturnal hypoglycaemia was defined as any glucose excursion <3.7 mmol/l during night time. **Results:** 128 nocturnal hypoglycaemia were found, only eight of them being symptomatic. In 97 out of 297 nights one or more hypoglycaemia occurred. Duration of hypoglycaemia ranged from 5 to 665 min, 36% of the episodes lasted <1 h, 34% 1–3 h, 24% 3–6 h, and 6%, >6 h. Hypoglycaemia frequency was negatively correlated to HbA1c (-0.32^* , also hypoglycaemia duration, -0.293^*) and to physical activity (mean time in moderate to vigorous physical activity, 0.305^*). Furthermore, low bedtime glucose was associated with higher risk of nocturnal hypoglycaemia. No association was found with insulin dosage, age, and diabetes duration. **Conclusion:** Nocturnal hypoglycaemia is a relevant issue in diabetic children: it is frequent, mostly asymptomatic and often prolonged. Tight metabolic control, high activity and low bedtime glucose could be identified as possible risk factors. Cgms represents a helpful tool in detecting nocturnal hypoglycaemia and therefore optimising patient instruction and treatment.

P2-D3-486**Fasting Hypoglycemia Associated With Hyperinsulinemia in a Child With Acute Lymphoblastic Leukemia and 6-Mercaptopurine Therapy**

Jadranka Popovic

Children's Hospital of Pittsburgh, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA

Background: Symptomatic fasting hypoglycemia has been reported as an uncommon side effect in patients with acute lymphoblastic leukemia (ALL) on maintenance therapy with purine analogs. The exact mechanism of the hypoglycemic effect of the antimetabolic therapy remains unclear. The association of 6-mercaptopurine (6-MP) therapy with hypoglycemia and hyperinsulinemia has not been described previously. **Case:** A 6 9/12 years old girl with pre-B ALL and 6-MP therapy presented with fasting hypoglycemia. She was also having symptoms of reactive hypoglycemia post breakfast. Paradoxically, she was having hyperglycemia during dexamethasone pulses. Her height was 120.5 cm (53%); weight 33.3 kg (98%), and BMI 22.9 kg/m² (99%)

It was assumed that hypoglycemia was related to 6-MP, and dosing was changed from evening to morning. Unfortunately, hypoglycemia persisted. She was admitted for a fasting study, few days before scheduled dexamethasone pulse, to rule out other etiologies. She developed hypoglycemia with lab glucose of 45 mg/dl. Critical sample was obtained. Insulin level was inappropriately elevated for the degree of hypoglycemia; β -hydroxybutyrate was not completely suppressed but was not elevated as seen in ketotic hypoglycemia. Subsequently it was recommended to continue 6-MP in the morning and to increase protein with meals, avoid concentrated sweets, and add cornstarch to bedtime snack. Unfortunately, hypoglycemia was occurring more frequently. Furthermore, she was symptomatic during hypoglycemia, and it was impeding quality of life. 6-MP therapy was discontinued for 7 days to evaluate if hypoglycemia would resolve. Within 3 days, hypoglycemia resolved, with no hypoglycemic symptoms. Subsequently, split dosing of 6-MP was recommended and she experienced relief from hypoglycemia. **Conclusion:** Association of 6-MP therapy with severe hypoglycemia and hyperinsulinemia has not been described previously. Although the exact mechanism of hypoglycemia remains unclear and is likely multifactorial, our findings indicate the possibility of associated hyperinsulinemia. Further, large scale studies are needed to further delineate exact etiology.

P2-D3-487**The Cytotoxic Ability of NK Cells in Children with Autoimmune Thyroiditis**

Anna Kucharska^a, Katarzyna Popko^b, Iwona Osinska^b, Urszula Demkow^b

^aDepartment of Paediatrics and Endocrinology, Medical University of Warsaw, Warsaw, Poland; ^bDepartment of Laboratory Diagnostics and Clinical Immunology of the Developmental Age, Medical University of Warsaw, Warsaw, Poland

Background: In autoimmune thyroiditis type Hashimoto the key role in thyrocytes destruction plays the spontaneous cytotoxic activity of T cells, and antibodies dependent mechanisms are of

a less value. A spontaneous cytotoxicity is associated with the number and degree of activity of NK cells. An important role in this process plays perforin contributed in permabilization of target cells. **Objective and hypotheses:** The aim of the study was to evaluate the number of NK cells, their cytotoxic ability and the perforin expression in peripheral CD56 cells in children with Hashimoto's thyroiditis. **Method:** Ten children at the age 10–17 years diagnosed with Hashimoto's thyroiditis were enrolled and nine healthy children as the control group. In every child were evaluated: the number of NK cells (CD56+), cytometric test of cytotoxic ability of NK cells and perforin expression in CD56+ cells. **Results:** In cytometric test of cytolysis with K 562 cells the values of spontaneous cytotoxicity of NK cells were significantly higher in children with Hashimoto's thyroiditis in comparison to healthy children ($P=0.04$), whereas the percentage of circulating NK cells in both groups was comparable. Simultaneously in children with Hashimoto's thyroiditis the expression of perforin in CD56+ cells was significantly lower than that observed in healthy children ($P=0.04$). **Conclusion:** In children with Hashimoto's thyroiditis in comparison to healthy children a higher cytotoxic activity of T cells is observed with simultaneously decreased perforin expression in NK cells. Probably this apparently paradoxical effect might be a consequence of hyperactivity of NK cells.

P2-D3-488

High Prevalence of Diabetes Mellitus Among Patients with APS Type 1 in Russia

Elizaveta Orlova^a, Leila Sozaeva^a, Lubov Zilberman^a, Galina Svetlova^a, Maria Kareva^a, Olga Ivanova^b, Valentina Peterkova^a

^aInstitute of Paediatric Endocrinology, Endocrinological Research Centre, Moscow, Russia; ^bLaboratory of Genetics and Immunology, Endocrinological Research Center, Moscow, Russia

Background: Diabetes mellitus (DM) is one of 'minor' components of autoimmune polyglandular syndrome type 1 (APS1). The prevalence of DM in APS1 varies from 2.5 to 18% in different populations. **Objective and hypotheses:** To study disease phenotype and genotype of APS1 patients with DM. **Method:** All patients diagnosed with DM were selected from the Russian registry of APS1 patients. Clinical data, AIRE-gene mutations and immunological studies were retrospectively assessed in this group. APS1 was confirmed by clinical criteria and/or AIRE mutations in all 87 patients. **Results:** Ten of 87 patients with APS1 were found to have DM (nine patients) or glucose intolerance (one patient). Islet autoantibodies were investigated in eight of ten patients (100% were positive for IA2, 60% were positive for GAD65, 30% were positive for IAA and none were positive for ICA). Frequent R257X AIRE mutation was

Table 1. Oral glucose tolerance test in APS1 patient with DM

Time	0 min		120 min	
Months after diagnosis with DM	0	30	0	30
Insulin (mU/ml)	7.44	3.3	35.0	15.6
Glucose (mmol/l)	5.9	5.6	14.9	16.5

found in 14 of 20 alleles (70%). The mean age of DM manifestation was 13.0 (1.5–20.1). The mean level of HbA1c was 8.0% (5.4–9.6). Seven patients require insulin therapy with average dose 0.7 U/kg per day (0.5–1.3). Three patients remain insulin-independent and have normal HbA1c (5.1%, 5.3%, 5.4%) during 12, 22 and 30 months of follow-up, respectively. Very slow decrease of insulin secretion has been observed (Table 1). **Conclusion:** Prevalence of DM in APS1 in Russia is very high (11.4%) compared to other populations except Finnish. One-third (30%) of patients with APS1 show slowly progressive insulin deficiency. Autoantibodies to IA2 were positive in all investigated patients which corresponds to other studies.

P2-D3-489

Immunogenetics and Clinical Characteristics of Patients with the Most Common Organ-Specific Autoimmune Diseases: Evaluation in Respect of Gender and Autoimmunity

Murat Karaoglan, Mehmet Keskin, Ozlem Keskin, Sibel Öztürk
Gaziantep Medical Faculty, Gaziantep, Turkey

Background: Most of autoimmune disease such as type 1 diabetes (T1DM), autoimmune thyroiditis (AIT) and coeliac disease (CD) often coexist in the same patient. Although there are a lot of number of studies on autoimmunity against the thyroid glands and small bowel in patients with type 1 diabetes, little is known about pancreatic β -cell immunity in patients with AIT and CD. **Objective and hypotheses:** We studied autoimmune markers in children patients with AIT, CD and T1DM and investigated interactions between three autoimmune diseases in the terms of sex based clinical and immunogenetic characteristics. **Method:** Children ($n=227$) diagnosed with T1DM were screened for thyroid peroxidase autoantibodies (TPOAb) and thyroglobulin autoantibodies (TgAb), tissue transglutaminase autoantibodies (TTGAb) HLA DQ, HLADR alleles and children ($n=148$) diagnosed with autoimmune thyroiditis and patients with coeliac ($n=112$) were screened for glutamic acid decarboxylase antibodies (GADAb), islet cell antibodies (ICA), insulin antibodies (IA), TTGAb and HLA DQ, HLADR alleles. **Results:** Of the 227 children (115 boys and 112 girls) with diabetes had at least one-islet cell antibodies, 55 had at least one-thyroid autoantibodies

(TPOAb and TgAb). There were 52 who were positive for TTGAb, of whom had T1DM. There were thyroid antibodies in 21 of children with diabetes at onset of diabetes. HLA DRB1*03 allele was significantly higher than the others. In GAD Ab positive patients, the average of TPOAb level was higher than negative patients group's. Of the 148 children (110 girls and 38 boys) with autoimmune thyroiditis, 52 associated with diabetes, 14 had at TTGAb positive. Six patients with autoimmune thyroiditis had at least one-islet cell antibodies. Of the all girl with autoimmune thyroid disease ($n=110$), 28(25%) had patients with autoimmune thyroiditis associated diabetes. Of the 38 boys with autoimmune thyroiditis, 27(69.2%) had diabetes. HLA DQB1*03 and HLA DRB1*11 were higher than the others. There were three organ specific autoimmune antibodies positivity in 11 patients at the same time. **Conclusion:** Most of autoimmune antibody positive patients coexist with additional autoimmune diseases. Children with autoimmune thyroid disease in particular male gender are prone to T1DM. We recommend to screen islet cell antibody in particularly GAD Ab in autoimmune thyroid disease and celiac disease.

P2-D3-490

Genetic Susceptibility in Autoimmune Polyglandular Syndrome Type 3 Variant

Amir Babiker^a, Iman Al Gadi^a, Nasir Al Jurayyan^a, Sarar Mohamed^a, Hessah Al Otaibi^a, Khalid Hussain^{b,c}

^aPaediatric Endocrine Division, College of Medicine (39), King Khalid University Hospital, King Saud University, PO Box 2925, 11461 Riyadh, Saudi Arabia; ^bDepartment of Paediatric Endocrinology, Great Ormond Street Hospital for Children NHS Trust, London, UK; ^cThe Institute of Child Health, University College London, WC1N 1EH London, UK

Background: Autoimmune polyglandular syndrome type 3 (APS3) comprises a wide spectrum of autoimmune endocrine disorders other than adrenal insufficiency. It includes the association of autoimmune thyroid disease (ATD) with type 1 diabetes (T1D) which is known as APS3 variant (APSA3v). Genes linked to possible joint susceptibility for APS3v have been reported in few cases. We report a 10-year-old girl with Graves' disease (GD) who developed T1D after 6 years of the diagnosis. **Case report:** A 10-year-old girl was diagnosed with GD at 3-years of age and treated with carbimazole but had frequent relapse when medication was stopped. She was admitted for surgery as definitive treatment rather than radioactive iodine because of an active thyroid eye disease. On admission, she reported classic symptoms of T1D. Investigations revealed a normal cortisol level, HbA1c of 10% and a persistent hyperglycaemia which was well controlled by insulin treatment. Her mother has T1D, and two of her aunts were diagnosed with ATD. **Discussion:** In a cross sectional study,

60% of APS3v patients developed GD before the onset of T1D, and 30% developed GD after the onset of T1D; while only 10% of patients developed both simultaneously. Insidious onset of diabetes was more common in APS3v patients who developed GD first, suggesting an influence of GD on the speed of B-cell destruction. A number of genes were reported in association with APS3v, including: HLA class II, CTLA-4, FOXP3, Insulin VNTR, PTPN22 and IL2R α /CD25 genes. **Conclusion:** The reported cases of APS3v with genetic association provide potential illustration of genes linked to joint susceptibility of APS3v, and if these genes could be clustered in certain families or ethnic groups. Our patient has a strong first-degree family history of autoimmune endocrine disorders; therefore, genetic testing was planned for the family.

P2-D3-491

Autoimmune Thyroiditis in Type 1 Diabetes Mellitus Pediatric Population

Clara Gomes, Joana Andrade, Assunção Luís, Gabriela Laranjo, Joana Campos

Tondela-Viseu Central Hospital, Viseu, Portugal

Background: Increased prevalence of autoimmune thyroid disease (ATD) in patients with type 1 diabetes mellitus (T1DM) has been extensively described. Since 1996, screening for thyroid disease has been implemented in children and adolescents with T1DM and is performed at least annually. **Objective and hypotheses:** The aim of this study is to determine the natural history and incidence of ATD in T1DM pediatric patients and the relationship between positive anti-thyroid antibodies and potential risk factors, including age, gender and duration of diabetes. **Method:** We designed an observational, transversal and analytic study, based on patient data from the Pediatric Diabetes Consultation in a Tertiary Hospital in Portugal. We studied a total of 104 patients (49 females and 55 males) aged 3.3–17.9 years (mean 12.5 ± 4.4) with T1DM. TSH, free thyroxine (FT₄), anti-peroxidase (anti-TPO) and anti-thyroglobulin (anti-TG) antibodies were measured. **Results:** ATD was diagnosed in 17 patients (16.3%). The prevalence rates of anti-thyroid antibodies were: anti-TPO 16.3% ($n=17$), anti-TG 12.5% ($n=13$). The presence of serum anti-thyroid antibodies was significantly higher in females (76.5%). In the age group <10 years, 5.9% ($n=1$) had thyroid antibodies and in the age group ≥ 10 years, 94.1% ($n=16$). 35.3% ($n=6$) of ATD patients had hypothyroidism and were medicated with levothyroxine. 64.7% ($n=11$) of the 17 patients had T1DM for at least 5 years. **Conclusion:** Thyroid autoimmunity was related with increasing age, female gender and longer diabetes duration. Our results confirmed the high prevalence of ATD in patients with T1DM. The screening of autoantibodies in type 1 diabetic patient, regardless of symptoms, could reveal cases of ATD.

P2-D3-492**Autoimmune Polyglandular Syndrome in a Patient with Tuberous Sclerosis**

Sophie Stoppa-Vaucher^a, Eglantine Elowe-Gruau^a,
Franziska Phan-Hug^a, Nelly Pitteloud^{a,b}, Michael Hauschild^a

^aDivision of Pediatric Endocrinology, Diabetology and Obesity, Department of Pediatric Medicine and Surgery, Centre Hospitalier Universitaire Vaudois (CHUV), Rue du Bugnon 46, 1011 Lausanne, Switzerland; ^bEndocrinology, Diabetes and Metabolism Service, Centre Hospitalier Universitaire Vaudois (CHUV), Rue du Bugnon 46, 1011 Lausanne, Switzerland

Background: Tuberous sclerosis (TS) is an autosomal dominant neurocutaneous disorder involving many organ systems. The frequency of TS is around one per 5000 to 10 000 live births and is caused by mutation in the *TSC1* or *TSC2* genes. Autoimmune polyglandular syndrome type 2 (APS2) is an endocrinopathy characterized by two or more autoimmune diseases. Several susceptibility genes are known. The prevalence of APS2 is around 1:20 000. **Objective and hypotheses:** To provide the first description of concomitant TS and APS2. **Method:** Clinical and laboratory work up were done. **Results:** The proband was born at term after IVF to a healthy mother and an unrelated father. Family history revealed that maternal grandmother had vitiligo and vitamin B12 deficiency. Pregnancy and neonatal period were uneventful. She had a slightly delay of language development. Due to family history and suspected lesions of vitiligo, her dermatologist had undergone workup revealing increased antithyroglobulin and antimicrosomal auto-antibodies and normal thyroid function tests. Our patient suddenly presented at 4 years of age partial complex epilepsy. On physical examination, she was well proportioned, with weight, height and head circumference in the normal range (90–97thP). No goiter was found. She showed depigmented macula 1–2 mm on back and 5 cm on the leg (right thigh, buttock and calf) compatible with achromic hamartomas. MRI of the brain confirmed pathognomonic lesion of TS. Further work-up revealed increased anti-transglutaminase auto-antibodies and biopsy by gastroduodenoscopy confirmed celiac disease. She had no sign suggesting other autoimmune disease at this time. Genetic testing is in progress. **Conclusion:** To our knowledge, this is the first report describing the association of TS and APS2 in a patient. Due to the relatively high frequency of TS, this finding could be incidental. Long-term follow up is needed for both chronic diseases.

P2-D3-493**Role of Metformin in the Treatment of Hypothalamic Obesity**

Arundoss Gangadharan^a, Mohammed Didi^a, Barry Pizer^b,
Lisa Howell^b, James Hayden^b, Conor Mallucci^c, Benedetta Pettorini^c,
Joanne C Blair^a

^aDepartment of Paediatric Endocrinology, Alder Hey Children's Hospital, Liverpool, UK; ^bDepartment of Paediatric Oncology, Alder Hey Children's Hospital, Liverpool, UK; ^cDepartment of Paediatric Neurosurgery, Alder Hey Children's Hospital, Liverpool, UK

Background: Disruption of homeostatic functioning of the hypothalamic centres results in hyperphagia, autonomic imbalance, reduction of energy expenditure, and hyperinsulinemia. A syndrome of rapid, unrelenting weight gain is often observed in patients with structural lesions of the hypothalamus. Hypothalamic obesity syndrome (HOS) is often refractory to standard dietary and lifestyle interventions. It has been reported that metformin induces anorectic effects via an increase in the central sensitivity to leptin. This provides a rationale for novel therapeutic approaches associating leptin and metformin in the treatment of HOS. **Objective:** To describe rate of increase in BMI SDS before and during treatment with metformin. **Method:** A retrospective study of the rate of BMI gain in patients before and during metformin therapy was undertaken. **Results:** Data from five patients (5F) mean age 10.2 years (5.7–13.6) at diagnosis of hypothalamic lesions (hypothalamic hamartoma ($n=2$), craniopharyngioma ($n=2$), hypothalamic pilomyxoid astrocytoma + NF1 ($n=1$)) are reported. Patients were treated with surgery ($n=4$), adjuvant proton radiotherapy ($n=1$) and primary fractionated radiotherapy ($n=1$). Metformin was introduced at a mean age of 13.1 (10.8–15.8) years when mean gain in BMI SDS was 1.3/year (0.1–3.48). After 22 (4–56) months of treatment, mean gain in BMI SDS was 0.0/year (–0.12 to +0.27). Treatment with metformin was well tolerated. **Conclusion:** Although metformin is only licensed for treatment of type-2 diabetes, there has been a steady increase of its use in the management of obesity, as an adjuvant to diet and lifestyle measures. We believe metformin had a positive effect on the management of HOS in these five patients and that a randomised control trial should now be considered to rigorously examine its role in the management of HOS.

P2-D3-494**Three Year Experience of a National Interdisciplinary Initiative to Improve Outcomes for Children with Hypothalamic Pituitary Axis Tumours (HPATs) Using Multi-site Videoconferencing for Decision Making on Behalf of the UK HPAT Interest Group**

Daniel Perelberg^a, Paul Morillon^a, Ash Ederies^b, Kristan Aquilina^b,
Neil Dorward^c, Anton Michalski^b, Darren Hargrave^b,
Yen-Ching Chang^c, Nillofar Bozorgi^b, Samantha James^b,
Marta Korbonits^d, William Drake^d, Scott Akker^d, Connor Mallucci^e,
Barry Pizer^e, Jo Blair^e, Ian Kamaly^f, Peter Clayton^f, Helen Spoudeas^b

^aUniversity College London, London, UK; ^bGreat Ormond Street Hospital, London, UK; ^cUniversity College London Hospitals, London, UK; ^dSt Bartholomew's Hospital, London, UK; ^eAlder Hey Children's Hospital, Liverpool, UK; ^fRoyal Manchester Children's Hospital, Manchester, UK

Background: Childhood tumours of the hypothalamic pituitary axis (HPATs) are very rare and hence any single centre experience is limited. Without evidence-based guidance, treatment is individualised on a case basis. Survival rates are high, but at the expense of significant morbidity. Centralised care or wider multi-professional consultation may improve neuroendocrine and visual outcomes. **Objective and hypotheses:** i) To facilitate multi-professional dialogue across centres nationally (including adult pituitary specialists) in a videoconference format. ii) To enhance diagnostic and treatment decision making through education and sharing audits, knowledge and experience. **Method:** From April to October 2010, a live, monthly videoconference was piloted across three sites. Pituitary physicians and surgeons, paediatric neurooncologists, neuroradiologists, neurosurgeons, neuropathologists and clinical oncologists all contributed. Having overcome initial technical limitations, monthly meetings continued over the next 2 years. **Results:** In 27 meetings spanning 2.5 years, the clinical cases (including quality imaging) of 67 HPAT patients were discussed in relation to formulating management plans. Of these, 16 were discussed on multiple occasions. Of the 67 cases, craniopharyngiomas (17) were the most common tumour type. In addition, three guest lectures and five new audits of centre experience in craniopharyngiomas (3), prolactinomas (1) and suprasellar gliomas (1) were presented. To date, there are seven participating centres, increased attendees and 3–4 case discussions per month, even attracting international participation from centres in Ireland and Australia. **Conclusion:** A national, regular, multidisciplinary consultation for discussing rare HPATs is feasible and welcomed, facilitating dialogue amongst a wide specialist professional grouping and influencing management. With appropriate funding, such collaborative experience with outcome monitoring, regular on-going audits and an educational programme should enhance the management of this rare group of patients, resulting in better outcomes and shaping the national standard of care.

P2-D3-495

Early Occurrence of Graves' Disease After Severe Hypothyroidism in Boy Irradiated for Hodgkin's Disease

Grazia Cantelmi, Anna Grandone, Caterina Luongo, Maria Carmela Affinita, Flora Micillo, Carmine Ficociello, Paolo Indolfi, Fiorina Casale, Emanuele Miraglia del Giudice, Laura Perrone

Department of Woman, Child and General and Specialized Surgery, Seconda Università degli Studi di Napoli, Naples, Italy

Background: Thyroid dysfunction is a well-known endocrine complication after cervical irradiation for Hodgkin's lymphoma (HL). The most common are primary hypothyroidism (20–30%), central hypothyroidism, transient thyroiditis and thyroid cancer. Graves' disease (GD) is less frequent (5%). **Objective and hypotheses:** We describe a boy, already diagnosed with thyroiditis, who developed GD during follow-up for severe

hypothyroidism following radiotherapy for HL. **Method:** A 16-year-old boy, with a previous diagnosis of euthyroid autoimmune thyroiditis, was diagnosed with a Stage III A Nodular Sclerosing HL. He was treated with six cycles of COPP/ABV and 14.4 Gy total dose of mantle radiation. Thyroid function follow-up was performed. **Results:** Thirty-one months after diagnosis, he showed severe hypothyroidism (TSH > 100 mUI/l), hence he started therapy. During the following 30 months, he presented anxiety and palpitations, low levels of TSH and consequently therapy was lowered and then stopped. Eight months later he presented again tachycardia and restlessness. His TSH was frankly suppressed with elevated fT_3 and fT_4 and raised TSH receptor stimulating autoantibodies (TSAb). We diagnosed GD and started metimazole treatment. **Conclusion:** Our case has several points of interest: history of thyroiditis before diagnosis of HL, occurrence of GD after severe hypothyroidism, its early onset (3.4 years) after a low total dose of radiotherapy (14.4 Gy). In fact GD average onset period after HL neck irradiation is 8 years. Moreover the risk for radiation doses < 30 Gy is very low, (1%). In literature we found only five patients with overt hypothyroidism and five with subclinical hypothyroidism before diagnosis of hyperthyroidism after irradiation for HL. None of these cases showed autoimmune thyroiditis before LH. Hyperthyroidism is a possible complication even in hypothyroid patients after neck irradiation. Even if no consensus exists yet, we stress the importance of an accurate follow-up of thyroid function in HL irradiated subjects.

P2-D3-496

Endocrine Dysfunction Following Treatment of Medulloblastoma: a Single Centre Experience

Suma Uday^a, Midhu Raju^b, Sabah Alvi^a

^aDepartment of Paediatric Endocrinology, Leeds Children's Hospital, Leeds, UK; ^bDepartment of Paediatric Oncology, Leeds Children's Hospital, Leeds, UK

Introduction: Medulloblastoma is the commonest paediatric brain tumour and accounts for 20–30% of all brain tumours in the first decade of life. Improvements in treatment strategies have enhanced long-term survival resulting in an increased risk of late sequelae. **Aim:** Review the prevalence of endocrine dysfunction in survivors of medulloblastoma at a single centre. **Methods:** Case note review of patients treated for medulloblastoma between 1982 and 2002. **Results:** Twenty-nine patients (22 males) were identified. Mean (\pm s.d.) age at diagnosis was 7.7 (\pm 4.1) years. All patients received radiotherapy and 76% also received chemotherapy. All except one patient had surgery. Mean dose of craniospinal irradiation and posterior fossa boost were 33.5 (\pm 3.6) and 24 (\pm 10) gray respectively. All except one patient received posterior fossa boost. All patients developed pituitary hormone insufficiency. The median duration from end of treatment to loss of GH was 1.65 years, loss of ACTH was 3.0 years and thyroid hormone deficiency was 3.75 years. All except one patient developed GH deficiency (96.5%) both clinically

(growth failure, fatigue) and biochemically. Primary hypothyroidism was detected in 44.8% ($n=13$). Similar to previous reports, secondary hypothyroidism was rare. ACTH deficiency was detected in 31% ($n=9$). All patients with ACTH deficiency also had GH and thyroid hormone deficiency except one patient, who had received the lowest posterior fossa boost of 18 gray and had no surgical intervention. Forty-one percent (67% male) received GnRH analogues to optimize growth, but no patients developed gonadotrophin deficiency. **Conclusion:** There is a high prevalence of endocrine dysfunction in medulloblastoma survivors. Figures from our unit for GH and ACTH insufficiency are higher than those published in the literature despite comparable radiation doses. Effective multidisciplinary management in a joint clinic ensures that all patients are closely monitored and hormone deficiencies detected and treated early to maximize growth and wellbeing.

P2-D3-497

Gonadal Tumor in 46,XY and 45,X/46,XY Female Patients: One Clinical Center Experience

Aneta Gawlik^a, Aleksandra Antosza^a, Grzegorz Kudela^b, Agnieszka Drosdzol-Cop^c, Agnieszka Zachurzok^a, Pawel Matusika^a, Halla Kaminska^a, Tomasz Koszutski^b, Ewa Malecka-Tendera^a

^aDepartment of Pediatrics, Pediatric Endocrinology and Diabetes, Medical University of Silesia, Katowice, Poland; ^bDivision of Pediatric Urology, Department of Pediatric Surgery, Medical University of Silesia, Katowice, Poland; ^cWoman's Health Institute, Medical University of Silesia, Katowice, Poland

Background: The incidence of gonadal tumor development varies significantly between subsets of patients with disorder of sex development (DSD). In some female patients with Y chromosome too early gonadectomy is perceived as overtreatment. **Objective and hypotheses:** The aim of the study was to analyze the gonadal tumor incidence in DSD female patients with 45,X/46,XY or 46,XY. **Method:** 15 patients, managed at single institution between Oct 1997 and Feb 2014: seven with 45,X/46,XY diagnosed as Turner syndrome (TS), eight with 45,XY DSD caused by androgen insensitivity syndrome (AIS) or gonadal dysgenesis (GD). **Results:** The mean age of diagnosis in 45,X/46,XY TS and for the patients with 46,XY DSD were 6.63 ± 6.0 and 13.56 ± 5.73 years, respectively ($P < 0.05$). Gonadectomy was performed in 14 of 15 patients: in 7/7 TS patients (mean age 7.65 years, before GH treatment), in 3/4 with AIS and in 4/4 with GD (in 6/7 within 1 year after diagnosis). 27 gonads were evaluated by histopathology. The risk of gonadal tumor was estimated at 22.2%. Gonadoblastoma was found in 2/13 gonads of TS (in two patients). Gonadoblastoma with dysgerminoma was detected in 2/8 gonads of GD patients (in two patients). Leydig-Sertoli cell tumor was described in 2/6 AIS gonads (in one patient). There were no evident clinical indicators of gonadal tumor risk in 45,X/46,XY and 46,XY female patients. **Conclusion:** In 1/3 of our patients gonadal tumor was diagnosed. Further search for useful clinical/lab markers of individual tumor risk is urgently needed.

P2-D3-498

A Rare Brain Tumor in Noonan Syndrome: Report of Two Cases

Maria Chiara Pellegrin^a, Gianluca Tornese^b, Elisabetta Cattaruzzi^b, Eva Blank^c, Matthias Kieslich^c, Alessandro Ventura^{a,b}

^aUniversity of Trieste, Trieste, Italy; ^bInstitute for Maternal and Child Health – IRCCS ‘Burlo Garofolo’, Trieste, Italy; ^cZentrum für Kinder-und Jugendheilkunde, Klinik I, Abteilung Neuropädiatrie Universitätsklinikum, Frankfurt/M, Germany

Background: Noonan syndrome (NS) is a congenital polymalformative disorder caused by aberrant up-regulated signalling through RAS GTPase. Although NS is associated with hematologic malignancies, no predisposition for neuronal tumors was reported so far. **Objective and hypotheses:** We describe two cases of young patients with NS and dysembryoplastic neuroepithelial tumor (DNET). This is the first case series reporting a rare type of intracranial tumor in NS. **Results:** First case is a boy introduced to the Neuropediatric Department at 13 years of age because of recurrent paroxysmal paresthesia, lasting for about 15 s. He was diagnosed with NS at the age of 6 years, after workup for delayed growth, with genetic confirm of heterozygous mutation of PTPN11 gene exon 3. Clinical examination was unremarkable. The cranial MRI showed an $\sim 3 \times 3 \times 2$ cm lesion in the left parietal lobe, without sign of compression. The morphology corresponded to a DNET. The diagnosis was biopsy-proven afterward and anticonvulsive therapy was initiated. After repeated consideration of possible risks, GH therapy was started 1 year after the initial diagnosis and suspended after 6 months because of tumor growth.

Second case is a 13 years old asymptomatic boy who presented to Endocrinology Clinic with delayed growth. He received a diagnosis of NS because of typical phenotype and cardiac malformations (genetic diagnosis confirmed PTPN11 mutation). A MRI, performed after starting GH therapy, reported an oval lesion in the right parietal-occipital cortex, with greater diameter of 3 cm, consistent with DNET. GH therapy was cautiously stopped. **Conclusion:** DNET is a rare intracranial tumor, diagnosed in young patients with seizures or more rarely in asymptomatic patients, characterized by good prognosis. Because of the possibility intracranial tumors, a brain MRI is mandatory in NS patients before starting GH therapy.

P2-D3-499

GH-Secreting Pituitary Adenoma with Gigantism: a Challenging Case

Amish Chinoy^a, Dunia Ismail^a, Jennifer Kalits^b, Nadia Gordon^b, Peter Bullock^b, Ritika Kapoor^b, Simon Aylwin^b, Charles Buchanan^b

^aRoyal Alexandra Children's Hospital, Brighton, UK; ^bKing's College Hospital, London, UK

Background: Pituitary gigantism is a rare condition that occurs due to excessive GH secretion during childhood, usually

associated with a pituitary adenoma. We describe a case that required the full spectrum of standard therapeutic options available. **Case report:** A 15-year-old boy presented with a 3-year history of intractable occipital headaches and being psychologically distressed by his tall stature (203 cm). He had mild clinical features of GH excess. Investigations: IGF1 markedly elevated (103 nmol/l); basal GH 28 µg/l failed to suppress by oral glucose; testosterone low for pubertal status; impaired cortisol response to Synacthen. MRI scan revealed a sellar/parasellar macroadenoma (17×13 mm), impinging on the posterior optic chiasm, with lateral invasion of the cavernous sinus. **Results:** Hydrocortisone replacement was started, together with testosterone (1000 mg/3 monthly i.m.) to accelerate epiphyseal fusion. Octreotide was commenced to control GH excess and promote tumour shrinkage. After 2 months, the headaches persisted and a unilateral upper quadrant visual field defect was apparent. Trans-sphenoidal debulking of the tumour was performed, leaving left parasellar and posterior tumour mass; histology confirmed GH-immunopositive pituitary adenoma. Headaches improved, but GH and IGF1 levels remained elevated, in keeping with residual disease. Pegvisomant treatment was initiated to block GH effect, achieving normalisation of IGF1, and his height stabilised at 205 cm (epiphyses fused). Interval MRI showed residual tumour growth, therefore treatment with Pasireotide was started (a test dose pre-operatively had shown greater suppression of GH than octreotide). The patient is now undergoing radiotherapy, which had initially been deferred at patient's request to avoid disruption of his academic studies. **Conclusion:** Treatment goals for a GH-secreting adenoma with gigantism include limiting final height attainment, normalising GH, replacement of pituitary hormone deficiencies, and definitive tumour control. With unresectable residual tumour, this patient has required multiple therapeutic strategies.

resulted in smaller babies with lower BP at birth, but a greater change (Δ) in BP to 12 months of age. **Objective and hypotheses:** To now present BP measurements out to 3 years of age. **Method:** Height, weight, and blood pressure (BP) were measured on 164 babies (75 males and 89 females) at birth, 12, 24, and 36 months. Blood samples collected at 12 months were analysed for IGFI, lipids (triglyceride, HDLc, and LDLc), insulin, adiponectin, and leptin. The effect of malaria on BP and Δ BP (0–12 and 0–36 months) was compared by *T*-tests. Backward regression analysis was used to assess the association of malarial exposure, sex and biochemical markers on changes in BP over time ($P > 0.1$ to exclude variables). **Results:** Δ sBP over 0–12 months was higher in babies exposed to maternal malaria (no malaria 14 ± 17 vs malaria 19 ± 14 mmHg; $P = 0.03$) and this effect persisted to 36 months (18 ± 15 vs 25 ± 13 mmHg; $P = 0.002$). Δ sBP over 0–36 months was lower in females ($\Delta 20$ mmHg) than males ($\Delta 23$ mmHg) but the impact of malaria was more pronounced in females ($+8.7$ mmHg with malaria; $P = 0.003$) than males ($+5.0$ mmHg; $P = 0.15$). Δ sBP over 0–12 months was associated positively with malarial exposure ($\beta = +5.3$; $P = 0.05$) and HDLc ($+7.9$; 0.08) and negatively with leptin (-0.09 ; 0.008) and LDLc (-0.45 ; 0.009) ($r^2 = 16\%$). Δ sBP over 0–36 months was associated positively with malarial exposure ($\beta = +8.1$; $P = 0.001$) and IGFI ($+0.1$; 0.029) and negatively with leptin (-0.1 ; 0.003), LDLc (-2.9 ; 0.06) and being female (-5.4 (m:f); 0.038) ($r^2 = 20\%$). **Conclusion:** Changes in systolic BP over time are greater in children exposed to maternal malaria than those who are not, an effect that is more pronounced in females than males. This increased change in sBP is also independently associated with lower leptin and LDLc levels.

P2-D3-500

The Contribution of Maternal Malaria Exposure and Metabolic Markers to Change in Blood Pressure in Nigerian Children over the First 3 Years of Life

Jasmin Farikullah-Mirza^a, Andrew Whatmore^a, Omolola Ayoola^a, Olayemi Omotade^b, Imogen Butcher^a, Handrean Soran^c, Kennedy Cruickshank^d, Peter Clayton^a

^aCentre for Paediatrics and Child Health, Royal Manchester Children's Hospital, University of Manchester, Manchester, UK; ^bCollege of Medicine, University of Ibadan, Ibadan, Nigeria; ^cCardiovascular Research Group, University of Manchester, Manchester, UK; ^dCardiovascular Medicine Group, Diabetes and Nutrition Division, King's College, London, UK

Background: In Nigeria, where malaria is endemic, hypertension is common. We reported that exposure to maternal malaria

P2-D3-501

Kabuki 47,XXY Syndrome: a Case Report

Stefania Pedicelli^a, Romana Marini^b, Sara Ciccone^c, Paola Cambiaso^b, Maria Cristina Digilio^b, Carla Bizzarri^b, Marco Cappa^b

^a'Tor Vergata' University, Rome, Italy; ^bBambino Gesù' Children's Hospital, Rome, Italy; ^cFerrara University, Rome, Italy

Background: Klinefelter syndrome is the most common sex chromosome disorder (prevalence: 1/600 newborn males), characterized by at least one extra X chromosome. If the diagnosis is not made prenatally, the disorder can remain unknown until pubertal or adult age. Kabuki syndrome, instead, is a rare, dysmorphic syndrome (1:32 000 newborn) characterized by distinctive facial features, multiple anomalies, and mental retardation. About 50–80% of cases are due to *de novo* or autosomal dominant *MLL2* or *KMT2B* gene mutation (point mutation, deletion, duplication) located on 12q13.12; less frequently, and deletions or point mutations involving the *KDM6A* gene, located on Xp11.3, are implicated. **Objective and hypotheses:** We report the case of a boy affected by both Klinefelter and Kabuki syndromes. **Method:** Our patient was born

at 38 weeks of gestational age by cesarean section; he underwent neonatal resuscitation with O₂-administration. Weight and length at birth were at the 50th percentile, head circumference at the 35th Progressive postnatal weight growth retardation (associated with normal height velocity) and recurrent aspiration pneumonia needed enteral nutrition by percutaneous gastrostomy. Microcephaly, distinctive facial appearance (big eyes with long palpebral fissures, long cilia, anteverted nostrils, extroverted lower lip with pits, cupped ears, and operated cleft palate), persistence of fetal fingertip pads, eczema, hypotonia in infancy, congenital heart disease (atrial septal defect), joint and cutaneous laxity, and mild development delay became evident. Genitalia were normal at clinical examination; abdominal ultrasound showed normal kidneys and liver. **Results:** Karyotype was 47,XXY, while sequence analysis of the Kabuki genes showed a heterozygous c.721delC *de novo* mutation (L241CfsX260) of the *MLL2* gene. **Conclusion:** An association between Klinefelter and Kabuki syndromes has not been described yet. Probably these two genetic conditions casually coexist in our patient, due to the relatively high prevalence of the first.

P2-D3-502

Retrospective Analysis of Cortisol Measurement in Neonates

Geetika Kumar, Jane McNeilly, Helen McDevitt, Faisal Ahmed, Avril Mason, Guftar Shaikh

Royal Hospital for Sick Children, Glasgow, UK

Background: The predictive value of a random cortisol measurement in the neonatal population with suspected adrenal insufficiency is unknown. **Objective and hypotheses:** i) determine the indications for measuring cortisol; ii) review subsequent management; and iii) establish predictors for adrenal insufficiency. **Method:** A laboratory database search identified cortisol results in babies <1 year from three neonatal units between September 2010 and May 2013. Gender, gestational age, birthweight, time of test, CRIB II score, and sodium level were investigated as potential predictive factors. A random cortisol >100 nmol/l was accepted as normal. A short Synacthen test (SST) peak cortisol >450 nmol/l indicated an adequate response.

Table 1. (abstract for P2-D3-502)

	All-SST Median (Interquartile Range (IQR))	Passed-SST Median (IQR)	Failed-SST Median (IQR)
Gestation (weeks)	36.1 (28.6–39.0)	38.2 (33.5–40.9)	31.9 (27.9–36.1)
Birthweight (g)	1960 (790–3215)	2520 (1687–3373)	1220 (520–1960)
Age (weeks)	42.5 (40–44.3)	44.0 (42.5–45.5)	40.0 (35.8–40.3)
Weight at test (g)	3080 (2120–3455)	3340 (2715–3850)	2175 (181–2800)
Random cortisol (nmol/l)	49.0 (33.0–79.0)	45.5 (32.0–67.8)	43.5 (32.5–50.6)
Peak cortisol (nmol/l)	574 (340.3–848.3)	825 (622.5–858.5)	301.5 (183.5–354.3)

Results: 60 infants (M40:F20) had cortisols analysed, 58 had random cortisol and two a SST directly. Indications included: prolonged postnatal steroid use (*n*=4), conjugated hyperbilirubinaemia (*n*=22), hypoglycaemia (*n*=24), midline defect (*n*=6), hyponatraemia (*n*=4), and 'other' (*n*=2); two patients had two risk factors. In total 86 random cortisol levels were analysed; 46 were normal (209.0 nmol/l (138.3-340.8)) and 40 were low (50.5 nmol/l (30.0–71.5)). Twenty-four SST were carried out in 20 infants; ten infants (41.7%) had suboptimal cortisol peaks. In 8/10 cases, hydrocortisone was commenced, 1/10 hydrocortisone when unwell and 1/10 no plan for unclear reasons (Table 1). **Conclusion:** No statistically significant predictive factors for adrenal insufficiency were found from this study. There was a trend for lower gestational age, weight at birth and at time of test, and male sex (9/10 infants), suggesting potential predictive factors. There is a need for clear guidelines for the management of sub-optimal cortisol levels in neonates.

P2-D3-503

Survey of Opinion on the Antenatal and Surgical Management of Disorders of Sex Development and Congenital Adrenal Hyperplasia

Mary White^a, Jacqueline Hewitt^{a,b}

^aMurdoch Children's Research Institute at The Royal Children's Hospital, Melbourne, Victoria, Australia; ^bUniversity of Melbourne, Melbourne, Victoria, Australia

Background: Congenital adrenal hyperplasia (CAH) is characterised by elevated adrenal androgens which can lead to virilisation of affected females. **Objective and hypotheses:** To outline clinical opinion on two controversial aspects of CAH management (antenatal dexamethasone and genital surgery of affected females) which was hypothesised would differ between regional centres. **Methods:** A survey was conducted via the Australian Paediatric Endocrine Group (APEG). **Results:** There were 52 participants comprising consultant endocrinologists (75%), endocrinology trainees (11.5%), nurse specialists (1.9%), and others (11.5%) including geneticists, surgeons, and gynaecologists. Respondents were practicing in all regions of Australia

(86.5%), New Zealand (7.7%), and a small group in international locations (5.8%). A multidisciplinary group for the management of disorders of sex development (DSD) was in practice for 75% of the participants; however only 14% experienced a specialised clinic for DSD. Forty per cent had personal experience of prescribing antenatal dexamethasone, 33% were confident that the risks of this treatment were adequately conveyed to the parents, 90% had concerns with the prescription of antenatal dexamethasone, and 4% thought the standard dosing is appropriate. Most respondents thought that antenatal dexamethasone should be provided only as part of prospective research trial (59.6%) or long-term follow-up registry (11.5%). Regarding genital surgery, most respondents thought that surgery at any age is only indicated in Prader stages III–V virilisation (69.2%), with 17.3% recommending surgery only at Prader stage IV or V. When early surgery was considered, the most popular recommendation was for surgery to occur at 6–12 months (46%), followed by 12–18 months (22%). The majority of respondents supported universal neonatal screening for CAH (88.5%). **Conclusion:** These results show that although opinions were broadly within the scope of international consensus, significant differences remain regarding critical aspects of care. A comparison with international opinion will follow.

P2-D3-504

Vitamin D Deficiency as the Primary Cause of Neonatal Hypocalcemia in a Tertiary Hospital

Ariadna Campos-Martorell, Karla Narvaez, Maria Clemente, Diego Yeste, Eduard Mogas, Laura Gerones, Antonio Carrascosa
Hospital Vall Hebron, Barcelona, Spain

Background: Hypocalcemia is a common metabolic disorder in the neonatal period and may involve life-threatening situations. The aim is to analyze the main causes of hypocalcemia and its management. **Objective and hypotheses:** The aim is to analyze the main causes of hypocalcemia and its management. **Method:** Retrospective descriptive study by reviewing reports of 75 patients diagnosed of neonatal hypocalcemia (total Ca <7.6 mg/dl and/or ionic fraction <1 mmol/l) in the last 5 years (2009–2013) in a tertiary hospital. It was considered deficiency <20 and severe <10 ng/ml. **Results:** 70% of the babies were born at term. There was no mother with phosphocalcic alterations. 18% of the mothers had gestational diabetes. Mean plasma calcium levels at diagnosis 6.2 mg/dl, and ionic fraction 0.7 mmol/l. Calcemia recovered after 9 days on average. Etiology by order of frequency: vitamin D deficiency (31 cases, 41%, six of them were also premature, 11 (33%) associated transient hypoparathyroidism), prematurity (13, 17%), idiopathic transient hypocalcemia (17, 22%), transient hypoparathyroidism (4, 5%), infant of diabetic mother (5, 6%), primary hypoparathyroidism (2, 2.6%), suffocation (2, 2.6%), and renal failure (1, 1.3%). Regarding the clinic, 93% were asymptomatic, two had tremors, and four generalized seizures. Those four neonates had vitamin D deficiency (<4 ng/ml). There were five patients with radiological signs of rickets. 40% of

deficient patients received vitamin D at prophylactic doses (400 IU/day) and 60% at treatment doses (1000–2000 IU/day). 20% received oral calcium when they were discharged. We did maternal study in 7 (20%) of the deficient patients. All the mothers had severe vitamin D deficiency and none had received supplements during pregnancy. Most of them were dark skinned. **Conclusions:** Vitamin D deficiency is the most common etiology of hypocalcemia in our sample. Transient hypoparathyroidism may aggravate the clinical manifestations of vitamin D deficiency and makes the diagnosis more difficult. The determination of vitamin D levels in risky pregnancies is essential to prevent perinatal complications.

P2-D3-505

Random Serial Cortisol Levels in Neonates: Does it Reduce Synacthen Testing?

Susannah Pye^a, Zoe Smith^a, Rakesh Amin^b

^aHomerton University Hospital, London, UK; ^bGreat Ormond Street Hospital, London, UK

Background: Diagnosis of adrenal insufficiency in the neonatal period is most accurately diagnosed with a short Synacthen test. Some tertiary endocrinology centres advocate random serial cortisol measurements over a 3-h period; a normal cortisol reading during such a test would negate the need for a Synacthen test. **Objective and hypotheses:** Our aim is to assess whether serial cortisol level readings accurately identifies neonates with normal adrenal function, therefore avoiding a Synacthen test. We hypothesise that serial cortisol readings in a neonate generates inconclusive results. In such cases Synacthen testing is the most accurate and reliable way of formally assessing adrenal function. **Method:** This retrospective study identified all abnormal cortisol results on neonates at a tertiary centre NICU between June 2012 and December 2013. The notes and lab results of eligible neonates were reviewed to determine how many patients were advised on having serial cortisol level readings, and of those, how many went on to have a short Synacthen test following inconclusive results. **Results:** 38 neonates had a random cortisol level requested during the 18-month period. Of those, 18 had an abnormal result. 13 had a further abnormal repeat cortisol level. Four patients had serial cortisol level readings: the results were inconclusive in 3 (75%), and therefore had a formal Synacthen test. None of the patients requiring a Synacthen test had a diagnosis of adrenal insufficiency during the admission. **Conclusion:** Although adrenal assessment is relatively rare in the neonatal unit, our results indicate that there was no obvious gain in performing serial cortisol level testing in neonates with abnormal cortisol readings. 75% of neonates who underwent serial cortisol level testing had inconclusive results and required a formal Synacthen test. We conclude that the most accurate and efficient way of assessing adrenal function in neonates continues to be a Synacthen test.

P2-D3-506

Metabolic Profile of Neonates With Different Duration of Gestation and Different Size at Birth

Mirjana Kocova^a, Snezana Palcevska-Kocevska^a, Marija Krstevska^b, Elena Sukarova-Angelovska^a, Elizabeta Zisovska^c

^aUniversity Pediatric Clinic, Medical Faculty, Skopje, Macedonia;

^bMedical Faculty, Institute of Medical and Experimental Biochemistry, Skopje, Macedonia; ^cUniversity Clinic of Gynecology and Obstetrics, Skopje, Macedonia

Background: Controversial findings about the metabolic profile in newborns depending on the length of gestation and size at birth have been reported. **Objective and hypotheses:** Insulinemia, adiponectin, and leptin levels are different in children born prematurely and SGA neonates compared to term normal newborns. **Method:** 196 healthy newborns were studied at the age 3-4 days. Birth weight (BW), birth length (BL), BMI, ponderal index (PI), and BW/BL ratio were recorded at birth. Neonates were divided according to the length of gestation to term and preterm, and according to the size to: appropriate for gestational age (AGA), SGA, and large for gestational age (LGA). Samples of blood were taken on the third day after delivery. Glycemia, insulinemia, cortisol, leptin, and adiponectin were measured. **Results:** Insulinemia and C-peptide were highest in the group of term female newborns. However, HOMA index was highest in the SGA group. Leptin levels in term neonates were 2.12 ± 1.02 ng/ml vs 1.24 ± 0.35 in preterm, and 1.71 ± 0.53 in SGA neonates ($P < 0.001$). Levels of adiponectin were significantly higher in the term group; 30.77 ± 22.64 ng/ml vs 13.40 ± 1.70 in SGA ($P < 0.05$) and 9.43 ± 4.82 in preterm neonates ($P < 0.001$). Cortisol levels were also significantly different 167.55 ± 75.56 nmol/l in terms versus 135.54 ± 61.12 in preterm (0.01), and 189.5 ± 64.7 ($P < 0.05$) in SGA neonates. SGA babies had higher leptin level ($P < 0.0002$) and adiponectin level ($P < 0.001$) compared to premature neonates. **Conclusion:** The positive correlation between BW, BMI and PI and concentration of leptin and adiponectin is probably a result of increased production from the growing adipose tissue during the last trimester of pregnancy. Adipocytokines level depends on gestational age and ponderal index. Leptin and adiponectin levels are more likely to correlate with birth weight than with gestational age. Careful planning of nutrition of both premature and SGA neonates based on their metabolic profile might prevent obesity later in life.

P2-D3-507

A Couple of Naturally Conceived Twins Affected by Prader-Willi Syndrome

Stefania Di Candia, Marta Massimello, Bruna Cammarata, Paola Sgaramella, Giuseppe Chiumello

Department of Pediatrics, San Raffaele Scientific Institute, Milan, Italy

Background: Prader-Willi syndrome (PWS) is a relatively common multisystem disorder with a prevalence estimated in several studies to be in a range of one in 10 000–30 000 individuals. **Objective and hypotheses:** For the first time to our knowledge, we describe the case of a couple of twin, naturally conceived, monozygotic diamniotic, both affected by PWS. **Method:** The gravida 3 para 1 mother was 43, and the father 40, at the time of birth. The mother is affected by Addison's disease and Hashimoto's thyroiditis. At 25th week of gestation, 1st foetus displayed a neck mass detected by ultrasound. Karyotyping by G-banding of amniocentesis specimens in both fetuses showed 46XX. They were born via emergency cesarean section at 34th week. The newborns, small for gestational age, presented marked neonatal axial hypotonia, weak crying, and poor reflexes, including poor sucking, resulting in failure to thrive. They underwent genetic test which demonstrated a *de novo* deletion in the paternally inherited chromosome 15q11–q13 region, confirming diagnosis of PWS. **Results:** The 1st twin was further evaluated with head/neck/thorax MR imaging which demonstrated a multiloculated, multicystic lesion, measuring ($44 \times 42 \times 53$ mm) with well-defined contours. The mass occupied left side of the neck, extended to the head and involved part of the posterior occipital area, parapharyngeal area, the vital blood vessel of the neck. Histologic and immunohistochemical examination demonstrated that the definite diagnosis was cystic lymphangioma. In 32nd day of life a dissection of the lymphoangioma was performed, respecting anatomical structures. Three days after the surgery, the patient showed a recurrence under the previous site of the excision. Therapeutic approach with sildenafil was tested and demonstrated no results. During the first month of life both twin presented hypothyroidism, even if they were negative at neonatal screening. Ultrasound scan detected eutopic and normal thyroid and the autoimmune screening was negative. They needed L-thyroxine treatment. **Conclusion:** Well established approach in treatment of PWS is the use of the GH, on the other hand, such treatment can severe interfere with of development of lymphangioma, making the follow up a challenging task.

P2-D3-508

Various Presentations of X-linked Adrenoleukodystrophy: Case Reports

Alina Daniela Fădur^a, Aurora Constantinescu^b, Cristina Rusu^c, Adina Manolachie^a, Ioana Bodescu^a, Dumitru D Brănișteanu^a, Cristina Preda^a, Voichița Mogoș^a, Carmen Vulpoi^a

^aDepartment of Endocrinology, University of Medicine and Pharmacy 'Gr.T.Popa' Iași, IASI, Romania; ^bDepartment of Neurology, University of Medicine and Pharmacy 'Gr.T.Popa' Iași, IASI, Romania; ^cDepartment of Genetics, University of Medicine and Pharmacy 'Gr.T.Popa' Iași, IASI, Romania

Background: Adrenoleukodystrophy (ALD) is an X-linked disease characterized by impaired β -oxidation of very long-chain fatty acids (VLCFA) and in the most severe cases by inflammatory demyelination in the brain, adrenocortical insufficiency (AI),

and death. Seven phenotypes were described, with a higher prevalence of the cerebral forms. **Case report:** We report two cases of ALD with different evolution, in February 2014. First case, an 11 years old boy with normal early development and a history of head trauma at the age of 8, presented progressive cognitive (declining school performance, and behavioral changes) and neurological (visual disturbances, seizures, and slowly progressive tetraparesis) perturbations, slightly ameliorated with ASEA (redox molecules). After ruling out other neurological disorders and infections, the supposition of ALD was confirmed by brain MRI (specific white matter lesions) and increased VLCFA. No family history could be found. In the absence of clinical signs, the laboratory testing (normal cortisol and high ACTH > 1250 pg/ml) diagnosed subclinical AI. Second case, 27 years old man, with family history of ALD (one sister with genetic confirmation, and two deceased male nephews at the age of 8) and onset of progressive neurological (spastic paraparesis) and cognitive (behavioral changes) perturbations at the age of 18. The clinical findings of AI (hyperpigmentation of the skin, low blood pressure, and asthenia) were biologically confirmed (ACTH > 1250 pg/ml, cortisol = 7.36 ng/dl) and treated with substitutive doses of glucocorticoids. **Conclusion:** The clinical presentation of ALD is highly variable and without accurate diagnosis, ALD will continue to spread and mystify the medical professionals. Early diagnosis has important implications for genetic counseling and management. The eventual phenotype in an individual will be determined by the combination of several epigenetic and environmental modifiers. More research and new treatments strategies are desperately needed and prenatal testing, biochemical diagnosis to prevent unnecessary new cases of this devastating disease should become available in more countries.

P2-D3-509

Neonatal Pituitary–Thyroid Axis Dysregulation with Combined Thyroid Hormone and TSH Resistance in Infant with Trisomy 21 and Maternal Subclinical Hypothyroidism

Astha Soni^a, Shivaram Avula^b, Mohammed Didi^b, Sze May Ng^a

^aSouthport and Ormskirk Foundation Hospitals NHS Trust, Ormskirk, UK; ^bAlder Hey Children's NHS Foundation Trust, Liverpool, UK

Background: Trisomy 21 is associated with dysregulated pituitary thyroid axis with higher TSH and lower FT₄ than controls. This may be due to genomic imbalance from trisomy of chromosome 21. Transient congenital hypothyroidism (CH) in newborns is recognised in association with maternal thyroperoxidase (TPO) antibody positivity. 'Thyroid hormone resistance' in infancy in CH is also been described. **Objective and hypotheses:** We report an interesting case of pituitary thyroid dysregulation with elevated plasma TSH and FT₄ in an infant with Trisomy 21. **Method:** A term infant with Trisomy 21 was born to a mother with plasma TSH of 7 mU/l, FT₄ of 11 pmol/l and TPO

Table 1

Age (days)	T4 (11–22 pmol/l)	TSH (0.3–5.0 mU/l)	FT3 (3.9–6.8 pmol/l)	Thyroxine replacement
16	28.3	22.9		Started on thyroxine 37.5 µg
24	31.2	6.0		Thyroxine reduced to 25 µg
40	27.9	6.5	7.5	Further reduction to 12.5 µg
50	22.2	9.4	7.2	Thyroxine 12.5 µg
60	21.1	10.9	7.4	Same dose as above

positivity during the third trimester. He had FT₄ of 23.8 pmol/l and TSH 30.9 mU/l on day 10. TPO antibodies were absent. 99mTc-Perchnetate scan showed uptake within a bilobed structure in the lower neck. Ultrasound scan showed normal appearance of the thyroid gland. Thyroxine replacement was started at 37.5 µg daily because of high TSH, persistent jaundice and widely open posterior fontanelle consistent with CH. TFT results are shown in Table below. The elevated plasma thyroid hormones failed to normalise plasma TSH. **Results:** (Table 1). **Conclusion:** The unusual thyroid function and its subsequent behaviour is consistent with combined thyroid hormone and TSH resistance in an infant with Down syndrome and CH.

P2-D3-510

Neonates with Acute Kidney Injury Continue to be at Risk of Iatrogenic Iodine Toxicity and Hypothyroidism with Attendant Risk to the Developing Brain

Carley Frerichs, Richard Holt, Henry Morgan, Caroline Jones, Mohammed Didi

Alder Hey Children's NHS Foundation Trust, Liverpool, UK

Background: There are published recommendations for neonates to avoid exposure to iodine. Iodine is trapped by the thyroid gland from the blood stream and used for the synthesis of thyroid hormones. Any excess is excreted almost entirely in the urine. Acute kidney injury, especially anuria places infants at risk of toxicity when exposed to iodine and paradoxical hypothyroidism can occur (Wolff–Chaikoff effect). Hypothyroidism of sufficient severity to seriously put the brain at risk has been reported. The paediatric nephrology community have taken appropriate precautions and this problem stimulated an alert by Medicines and Healthcare products Regulatory Agency in the UK. However, we describe a case where this has occurred again. **Objective and hypotheses:** To describe a case of severe hypothyroidism secondary to iodine toxicity. **Method:** A male infant born at 38 weeks with autosomal recessive polycystic kidney disease requiring bilateral nephrectomies and continuous peritoneal dialysis on day 7 of life was studied. **Results:** Newborn

screening result for hypothyroidism revealed a blood spot TSH of 7.5 mu/l, that would have been accepted by many screening programs as normal. This was repeated, as our centre has a cut-off point of 5 mu/l for further attention. Peritoneal dialysis had been established for 24 days when hypothyroidism was confirmed with plasma free T₄, 6.0 pmol/l (ref 10–25) and TSH 312 mU/l (ref 0.3–3.8). Ultrasound demonstrated a normally sited thyroid. The dialysis catheter cap used for long-term dialysis contains iodine as an antimicrobial. The peritoneal dialysate fluid iodine concentration, 13.3 μmol/l, was significantly higher than a paired plasma iodine concentration of 3.1 μmol/l (NR 0.32–0.62). 50 μg thyroxine daily normalised thyroid function. Dialysis was adjusted to reduce to infusion of iodine contaminated dialysis fluid. **Conclusion:** Peritoneal dialysis, using iodine impregnated dialysis caps, places a neonate at risk of serious hypothyroidism and thyroid function must be checked.

P2-D1-511

Relationship Between Adenoid Vegetation and Neurosecretory Dysfunction (Pituitary Dysfunction)

Murat Dogan^a, Keziban Bulan^a, Sultan Kaba^a, Fatih Garca^b

^aDivision of Pediatric Endocrinology, Yuzuncu Yil University, Van, Turkey; ^bDepartments of ETN, Yuzuncu Yil University, Van, Turkey

Introduction: The role of enlarged adenoid tissue has been long discussed in terms of causes leading obstructive sleep apnea. Sleep disorders in children with adenoid vegetation impair quality and duration of REM sleep where GH secretion is higher. We also thought that cortisol that displays a circadian rhythm might be also affected by sleep disorders. For this purpose, we planned to determine presence of neurosecretory dysfunction (NSD), time and level of cortisol peak in the morning in children with adenoid vegetation. **Material and method:** Patients with indication for surgery were identified by measuring grade of adenoid vegetation via flexible fiberoptic endoscope among patients who presented to ETN outpatient clinic. Blood samples were drawn by 20-min intervals after onset of deep sleep for GH measurements. In addition, blood samples were drawn for measurements of ACTH and cortisol, and thyroid function tests at 0700–0900 h. **Results:** There were 29 boys (52.7%) and 26 girls (47.3%) with an age range of 5–12.5 years. Mean GH level was below 3 ng/ml in 32 (58%) of the patients, being consistent with neurosecretory dysfunction. Thyroid function tests were found to be within normal range in all patients, while peak cortisol levels were found to be below 18 μg/dl occurring at 0700 h. When 77.5% degree adenoid obstruction was used as cut-off value for prediction of NSD, sensitivity, specificity, positive predictive value and negative predictive value were calculated as 77, 74, 77, 27%, respectively. Accuracy rate was found as 56%. **Conclusion:** We concluded that likelihood of NSD and related growth retardation can be higher in cases with adenoid vegetation grade of 77.5%. We think that early surgical treatment should be come order in cases with adenoid vegetation and that this can be further clarified by larger studies.

P2-D1-512

Clinical Phenotype and Complications, Endocrinopathies and Neuroimaging Findings in a Case Series of SOD

I Maris^a, C Howard^a, C Bogue^a, R Morrissey^a, L C Gregory^b, S M O'Connell^b, M T Dattani^b, S M P O'Riordan^a

^aUniversity Hospital, Cork, Cork, Ireland; ^bThe Institute of Child Health, University College London, London, UK

Background: Septo-optic dysplasia (SOD) is a highly heterogeneous condition with a variable phenotype, defined as two or more features of the classical triad: i) optic nerve hypoplasia, ii) midline brain defects, and iii) pituitary hormone abnormalities. **Objective and hypotheses:** To describe the clinical, endocrine, and neuroimaging features in eight children with SOD. **Method:** Eight (six males) consecutive patients, diagnosed with SOD in a Regional Paediatric Endocrinology Service, underwent a retrospective review of all clinical, biochemical, neuroimaging, and genetic characteristics. **Results:** All children met the SOD diagnostic criteria: 50% had all three features and 50% two out of three. SOD was diagnosed in the neonatal period in 5/8 (62.5%) patients. Maternal age was <25 years in 4/8 (50%) cases. Midline brain defects were identified in 7/8 (87.5%) patients, with schizencephaly in 57%. Hypoplastic optic nerves and chiasm was described in 6/8 (75%) patients. Pituitary MRI scanning revealed abnormal gland in 50% of the cases. Clinically the most prevalent features were moderate/severe visual impairment and developmental delay (62.5%), endocrine disorders (62.5%), and seizures (62.5%). Three cases (37.5%) developed hydrocephalus, with acute onset in 2/3, requiring urgent VP shunt insertion and resulting in a fatal outcome in one child. All five patients with endocrinopathies had GH deficiency (one with panhypopituitarism). Growth was normal in the absence of endocrine dysfunction (3/7), and with GH therapy 2/5 patients experienced normal height velocity (−0.97 to 1.14 SDS) and normal BMI. Karyotype was normal in all cases and screening for *HESX1*, *PROKR2*, *FGFR1*, *FGF8*, *LHX4*, and *SOX2* mutations was negative. **Conclusion:** This case series confirms that the phenotypic heterogeneity in SOD is high. Genetic screening was negative, in keeping with previous data. The acute complication of sudden onset hydrocephalus is novel and has not been described to date. These complex patients with a life threatening condition require careful clinical management.

P2-D1-513

Polyuria and Polydipsia: The Deep Waters of Diagnosis

Gabriella Pozzobon, Maria Piera Ferrarello, Chiara Maria Damia, Gisella Garbetta, Sara Osimani, Andrea Voto, Cristina Partenope, Giulia Pruccoli, Giuseppe Chiumello

Department of Pediatrics, San Raffaele Scientific Institute, Vita-Salute University, Milan, Italy

Background: Polyuria and polydipsia must never be underestimated. **Objective and hypotheses:** A 7-year-old girl presented with polyuria, polydipsia and nocturia of 1 year duration, during which she underwent outpatient follow up with her general practitioner and urologist. No weight loss or other endocrine signs. **Method:** Polyuria was confirmed by water balance (120 ml/kg per 24 h), urinary osmolality (222 mmol/kg), plasma osmolality (296 mmol/kg), and U-Osm/S-Osm (0.75). During water deprivation test (WDT) urine osmolality partially increased without desmopressin, plasma osmolality, and sodium were stable. WDT revealed a partial DI, no other hormone deficits were diagnosed. For a second opinion, she was admitted in our center. An MRI was performed which showed thickening of the pituitary stalk and the lack of posterior pituitary hyperintensity. Diffuse pathological enhancement of the optic chiasm and optic nerves was shown. Hypothesis: chronic inflammatory granulomatous disease suspect for Langherans-cell histiocytosis (LCH). No other organs were involved. Cerebrospinal fluid: negative for β -HCG and α -fetoprotein. **Results:** The patient was discharged with sublingual desmopressin acetate treatment and the water balance progressively improved. At 1 month of follow-up, the patient presented neurological deterioration (decline in school performance, difficulty in concentration, and memory). Brain MRI showed worsening of the neuroradiological features with a neurodegenerative pattern of the white matter. There was no apparent involvement of the cerebellum, which instead is a typical complication of LCH. Bioptic evaluation of the pituitary stalk was compatible with a germinoma. **Conclusion:** This case shows the importance of performing brain MRI and to successively evaluate the need for bioptic examination. If the cause should remain unclear, tumors should always be excluded. Furthermore, the thickening of the stalk and the inflammatory aspect initially led to hypothesize LCH, but may also have been suggestive of germinoma. Therefore, this neuroradiological aspect should be monitored in time. Finally, the neurodegenerative component (paraneoplastic or dysimmune) is an atypical presentation of germinoma and may be misleading.

P2-D1-514

Urinary Gonadotrophins for Assessment and Management of Pubertal Disorders

Laura Lucaccioni^{a,b}, Jane McNeilly^c, Avril Mason^a,
Claudio Giacomozzi^a, M Guftar Shaikh^a, Lorenzo Iughetti^b,
S Faisal Ahmed^a

^aDevelopmental Endocrinology Research Group, Royal Hospital for Sick Children, University of Glasgow, Glasgow, UK; ^bPaediatric Unit, Department of Medical and Surgical Sciences for the Children and Adults, University of Modena and Reggio Emilia, Modena, Italy; ^cDepartment of Biochemistry, Royal Hospital for Sick Children, Glasgow, UK

Background: With improvements in assays and an increasing need for non-invasive out-patient based investigations, there is a

renewed interest in the use of urinary gonadotrophins (uGn) for assessing pubertal progress. **Objective and hypotheses:** This study aims to establish the correlation between serum and urinary LH and FSH in patients with pubertal concerns. **Method:** 36 boys and girls aged 14.9 years (range 7.8–17.3) and 9.5 years (4.3–18.4) respectively, who were undergoing an assessment of puberty had a non-timed spot urine sample on one occasion (n , 24) or consecutively (n , 12) for measurement of LH and FSH by chemiluminescent microparticle immunoassay. 13 of them (5M, 8F) were receiving GnRH-agonist (GnRH-a) treatment. In 24 cases (12M, 12F), matched serum gonadotrophins were also available. Urinary LH (uLH) and urinary FSH (uFSH) were corrected for creatinine excretion and compared to previously published reference data. **Results:** A significant correlation was found between serum LH and uLH:uCr (ρ , 0.87; $P < 0.001$) and serum FSH and uFSH:uCr (ρ , 0.91; $P < 0.001$). In pubertal boys (n , 10) and girls (n , 8) with raised serum gonadotrophins, median uLH:uCr was 0.17 (0.1, 1.3) and uFSH:uCr 0.55 (0.1, 16.1), higher compared to pre-pubertal reference ranges ($P = 0.000$, both for uLH and uFSH). In 13 boys and girls on GnRH-a, median uLH:uCr was 0.02 (0.01–0.08) and uFSH:uCr was 0.16 (0.04–0.32), similar to the pre-pubertal reference range (p uLH:uCr = 0.39 and p uFSH:uCr = 0.31). uGn of patients on GnRH-a showed a rapid decrease after treatment onset, while maintained pre-pubertal values when evaluated after the second injection, and consistent with clinical evidence of pubertal suppression. **Conclusion:** uGn reflect serum gonadotrophin concentrations and may represent a useful non-invasive method of assessing puberty and monitoring effectiveness of puberty suppressive therapy.

P2-D1-515

High Prevalence of *PROPI* Gene Defects Among Patients with Multiple Pituitary Hormone Deficiency in Lithuania

Ruta Navardauskaite^a, Petra Dusatkova^b, Barbora Obermannova^b,
Roland W Pfaeffle^c, Werner F Blum^c, Dalia Adukauskiene^d,
Natalija Smetanina^a, Ondrej Cinek^b, Rasa Verkauskiene^a, Jan Lebl^b

^aMedical Academy, Institute of Endocrinology, Lithuanian University of Health Sciences, Kaunas, Lithuania; ^b2nd Faculty of Medicine, Charles University in Prague and University Hospital Motol, Department of Pediatrics, Prague, Czech Republic; ^cDivision of Pediatric Endocrinology, Department of Pediatrics, University of Leipzig, Leipzig, Germany; ^dMedical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania

Background: Mutations in *PROPI* are the most common known genetic cause of congenital multiple pituitary hormone deficiency (MPHD). **Objective and hypotheses:** Aim of our study was to clinically and genetically characterize a cohort of Lithuanian patients with MPHD. **Method:** Seventy-six Lithuanian MPHD patients were tested for *PROPI* gene by Sanger sequencing. Hormonal investigations, pituitary imaging and GH therapy were

performed at a single centre in Kaunas. Ancestral origin of mutation was assessed by haplotype analysis of 21 single nucleotide polymorphisms flanking the *PROPI* gene. **Results:** Fifty-two subjects (28 males) including ten sibling pairs and two sibling triples from 38 unrelated families were found to carry a biallelic *PROPI* gene mutation. Fifty of these were homozygous for c.296delGA and two patients were compound heterozygotes for c.296delGA/R71H and c.296delGA/c.150delA, respectively. Birth lengths/weights of *PROPI* mutation carriers were normal. Height declined to SDS -1.56 , -2.34 , -3.43 , -3.52 ; and -3.70 (medians) at years 1–5. Deficiencies of GH, TSH, ACTH, and FSH/LH were diagnosed in 50/52, 52/52, 21/52; and 25/52 subjects at median age of 5.5; 5.6; 13.1; and 15.0 years, respectively. Pituitary height ranged from 16.6 mm ($+20.2$ s.d.) to 1.4 mm (-15.5 s.d.) and declined with age ($r^2=0.27$, $P=0.001$). GH therapy increased growth rates to 12.2; 9.1; 6.9; 6.8; 6.7; 5.6; and 5.7 cm/year (medians) at 1–7 years. Perinatal events attributable to hypopituitarism were not frequent, except testicular retention recorded in 28% of boys. The c.296delGA mutation carriers shared a common haplotype spanning ~ 1 Mb around the *PROPI* gene. **Conclusion:** We found the highest rate of *PROPI* mutations among MPHD patients from populations studied so far (17.5 per million). High prevalence of *PROPI* defects in Lithuania is caused by a presence of ancestral mutation c.296delGA.

P2-D1-516

Neuroendocrine Dysfunctions Following Traumatic Brain Injury in Children: a 12-Month Prospective Study

Pilar Rojo, Atilano Carcavilla, Irene Ortiz, David Arjona, Raúl Borrego, Ángel Aragonés

Hospital Virgen de la Salud, Toledo, Spain

Background: Traumatic brain injury (TBI) is a frequent cause of endocrine dysfunctions. However, studies in children are scarce. **Objective and hypotheses:** To determine pituitary function in children after TBI. To analyze risk factors related with endocrine dysfunctions after 12 months follow up. **Method:** A prospective study of endocrine function in children after head injury was performed. Data was collected for baseline Glasgow coma score (3–15) and Marshall Classification (LEDI–VI). Patients were evaluated within 72 h of head injury, and 6 and 12 months thereafter. Physical exam, bone age and basal hormone levels (TSH, fT_4 , ACTH, cortisol, prolactin, IGF1, and IGFBP3) were assessed at each visit. When necessary, dynamic tests were performed to confirm endocrine dysfunctions. **Results:** Of 52 patients initially enrolled, the study was completed by 36 (mean age 5.9 years). TBIs were classified as moderate or severe in 16.7% of cases, 44% presented intracranial injury, and 5.6% required surgery. Baseline hormonal assessment was abnormal in 12 patients (33.4%), diminishing to 19.5 and 16.7 at 6 and 12 months respectively. One patient with severe TBI initially developed multiple endocrine dysfunction requiring treatment for diabetes

insipidus at 12 month follow-up. Our data show that intracranial injury (LEDII–VI) is associated to a three fold risk of endocrine dysfunction at baseline assessment ($P 0.038$). Furthermore, hormone dysfunction at 6 months of follow-up may predict the risk of developing dysfunctions at 12 months ($P 0.052$). **Conclusion:** In our study, intracranial injury is related to higher risk of endocrine dysfunctions at admission time. During follow-up, most hormone dysfunctions were transitory and of uncertain clinical importance. However, one patient still required treatment after 12 months of TBI. Risk factors predicting the development of long-term endocrine dysfunctions could not be assigned. Further studies are in progress.

P2-D1-517

Could Brain MRI Replace GH Stimulation Tests in the Work-Up of GH Deficiency in the First Years of Life?

Stefania Pedicelli^a, Giuseppe Scirè^{a,b}, Valentina Pampanini^a, Jessica Gubinelli^a, Gian Luigi Spadoni^{a,b}, Maria Luisa Manca Bitti^a, Marco Cappa^b, Brunetto Boscherini^a, Stefano Cianfarani^{b,c}

^a‘Tor Vergata’ University, Rome, Italy; ^bD.P.U.O. ‘Bambino Gesù’ Children’s Hospital, Rome, Italy; ^cDepartment of Women’s and Children’s Health, Karolinska Institute, Stockholm, Sweden

Background: Currently, the diagnosis of GH deficiency (GHD) in infants and young children is based on the assessment of GH serum levels either during hypoglycaemia or after pharmacological stimulation tests. However, GH cut-off values have not been standardized and provocative tests may be unsafe in this age range. **Objective and hypotheses:** Brain MRI may replace GH measurements in diagnosing GHD in infancy and young childhood. **Method:** 68 children diagnosed with GHD before 4 years of age were retrospectively studied to evaluate the prevalence of hypothalamic–pituitary defects and analyze the associations of brain abnormalities with age and presence of isolated GHD (iGHD) vs multiple hormone pituitary deficiency (MPHD). **Results:** The prevalence of MPHD was 45.6% and of iGHD 54.4%. In patients with iGHD, brain MRI showed abnormalities in 83.8% of cases: 18 isolated pituitary hypoplasia and 13 complex defects (ectopic posterior pituitary with or without pituitary hypoplasia, pituitary stalk agenesis, or midline defects). In patients with MPHD, MRI showed complex brain alterations in 100% of cases. The cohort was subdivided into 3 groups, according to the age at diagnosis: <12 ($n=17$), 13–24 ($n=16$), or 25–48 ($n=24$) months. In the first 2 years of life MRI showed hypothalamic–pituitary abnormalities in all cases, regardless the diagnosis. Complex defects were found in 94.1% of patient <12 months and in 75% of patient between 13 and 24 months. **Conclusion:** Our data suggest that brain MRI may represent the first and, in most cases, only investigation to be performed for diagnosing GHD in infants and young children.

P2-D1-518

Goliath, a Variant of DAVID Syndrome?

Caroline Hasselmann^a, Mark E Samuels^{b,c}, Guy Van Vliet^{b,d}

^aTours University Hospital, Tours, France; ^bEndocrinology Service and Research Center, CHU Ste-Justine, Montreal, Quebec, Canada;

^cDepartments of Medicine, Université de Montréal, Montreal,

Quebec, Canada; ^dDepartments Pediatrics, Université de Montréal, Montreal, Quebec, Canada

Background: DAVID syndrome (deficit in anterior pituitary function and variable immune deficiency) (*J Clin Endocrinol Metab* **97** E121, 2012) can be caused by *NFKB2* mutations (*Am J Hum Genet* **93** 13, 2013). All patients have an orthotopic posterior pituitary (PP) and most only ACTH deficiency. **Objective and Hypothesis:** To describe a girl with common variable immunodeficiency (CVID), ectopic PP (EPP) and multiple pituitary hormone deficiencies, and to demonstrate genetic heterogeneity of DAVID syndrome. **Case presentation:** A 17-year-old girl with unexplained intellectual disability was admitted for glomerulonephritis and found to have CVID (*Pediatr Nephrol* **24** 601, 2009). In addition, she had height at target, primary amenorrhea and Tanner B2P1. On ultrasound, the uterus was small but the ovaries were normal. The epiphyses were fused. MRI showed an EPP, a thin stalk and a small anterior pituitary. Cortisol was <11.1 nmol/l, DHEAS <0.5 µmol/l, and ACTH 0.8 pmol/l. Cortisol replacement was given. fT₄ and total T₃ were normal. IGF-I was 3.9 pmol/l and peak GH after arginine 0.02 µg/l. On LHRH testing, LH rose from 3.2 to 28.8 mIU/l and FSH from 5.3 to 13.5 mIU/l; on TRH testing, TSH rose from 7.2 to 31.2 mIU/l at 30 min and remained high at 90 min (15.5 mIU/l) while prolactin rose from 10.4 to 45.2 µg/l at 10 min. Pubertal induction was started. Between 17 and 20 years, BMI increased from 24 to 31 kg/m². *NFKB2* was normal. **Discussion:** This patient has CVID and severe cortisol deficiency, as is the rule in DAVID syndrome, but also severe GHD and hypothalamic hypogonadism. The EPP suggests that the endocrinopathies are developmental rather than autoimmune. **Conclusion:** DAVID syndrome is clinically and genetically heterogeneous. While a search for an alternative genetic etiology is underway, we suggest describing our patient's condition as GOLIATH syndrome: GHD, obesity, low IQ, IgG, and ACTH deficiency, Triad and Hypogonadism.

P2-D1-519

Hyperthyroidism Due to TSH Secreting Pituitary Adenoma in a 7-Year-Old Boy

Saygin Abali, Zeynep Atay, Belma Haliloglu, Tulay Guran, Abdullah Bereket, Serap Turan

Pediatric Endocrinology, Marmara University, Istanbul, Turkey

Background: Pituitary adenomas in childhood are 2–6% of all surgically treated pituitary adenomas at all ages. It has been estimated that TSH secretion is rare (<1% of all pituitary adenomas). Therefore, TSH secreting adenoma is very rare

in childhood. Here we present the youngest patient with TSH secreting adenoma. **Case:** A 7-year-old boy was referred to our clinic with thyroid dysfunction by the psychiatry clinic, during his evaluation of hyperactivity and nervousness. He had mild headache for 2 years. On presentation to our clinic, his BMI was >95p, blood pressure and heart rate were 130/80 mmHg and 110 beats/m respectively. There was no thyroid enlargement, tremor or ophthalmopathy. His serum TSH level was 11 mIU/ml with a fT₄: 2.1 ng/dl (0.93–1.7) and a fT₃: 7.5 pg/ml (1.8–4.6). Thyroid functions of the parents were normal. On TRH test, fairly normal response with a TSH peak of 47.9 µIU/ml was observed. The α-glycoprotein hormone subunit level was 8.8 IU/l (0–0.8) and suggestive for TSH secreting adenoma, and, pituitary MRI revealed a 17 mm adenoma infiltrating right cavernous sinus. His prolactin level was 25 ng/ml. There were no other pituitary hormone deficiencies or hypersecretions including GH and ACTH. Transsphenoidal adenoma resection was performed and histopathology showed pituitary adenoma with prolactin, GH, and TSH staining. **Conclusion:** Although it is a rare condition for pediatric age, TSH secreting adenoma should be excluded in children having high or normal TSH level with high serum T₄ and T₃ levels.

P2-D1-520

Hypothalamic Obesity in Children with Craniopharyngioma: Prevalence and Risk Factors of Obesity and Longitudinal Trends of BMI

Ja Hyang Cho, Ja Hye Kim, Yoo-Mi Kim, Jin-Ho Choi, Han-Wook Yoo

Department of Pediatrics, Asan Medical Center Children's Hospital, University of Ulsan College of Medicine, Seoul, Republic of Korea

Background: Craniopharyngioma is the most common parasellar tumor in childhood arising from remnants of Rathke's pouch. As the hypothalamus plays a vital role in regulation of body weight by balancing energy intake and expenditure, hypothalamic damage by structural lesions is one of the most common causes of hypothalamic obesity. This study investigated prevalence, risk factors for the development of hypothalamic obesity, and consequent morbidities in children following treatment of craniopharyngioma. **Methods:** Thirty-two patients treated for craniopharyngioma were included. Mean age at diagnosis was 9.6 ± 4.3 years (range, 1–18 years). Mean follow-up duration after surgery was 14.2 ± 4.1 years. Following clinical parameters were analyzed: treatment modalities, tumor locations, presence of pituitary hormone deficiency, and morbidities such as dyslipidemia, non-alcoholic fatty liver disease (NAFLD), and type 2 diabetes. **Results:** Twenty-six patients (81.3%) underwent gross total resection and the remaining six patients received subtotal resection. At diagnosis, four patients (12.5%) were overweight and three patients had hypothalamic lesions. At last follow-up (age range, 17.5–36 years; mean, 23.9 ± 4.6 years), 18 patients (54.5%) were obese, six patients (18.2%) were overweight, and eight patients (24.2%) had normal BMI. There was significant increase in BMI at last follow-up ($P < 0.001$). Patients with hypothalamic involvement ($n = 19$) presented higher BMI than those without hypothalamic lesions at diagnosis and last follow-up, but it was not

statistically significant. Dyslipidemia was detected in 62.5%, type 2 diabetes in 6.3%, and NAFLD in 12.5%. Unusually, one patient received liver transplantation due to hepatopulmonary syndrome caused by NAFLD. **Conclusion:** Most patients underwent gross total resection or adjuvant treatment after subtotal resection, resulting in high prevalence of subsequent obesity, panhypopituitarism, and co-morbidities related to obesity. Obesity and consequent morbidities are more prevalent in patients who underwent gross total resection.

P2-D2-521

Association of Pituicytoma and Cushing's Disease: a Rare Pediatric Case

Sara Ciccone^{a,c}, Paola Cambiaso^a, Daniela Longo^a, Romana Marini^a, Stefania Pedicelli^b, Annalisa Deodati^b, Stefania Galassi^a, Marco Cappa^a

^aBambino Gesù Children's Hospital IRCCS, Rome, Italy; ^bTor Vergata University, Rome, Italy; ^cFerrara University, Ferrara, Italy

Background: Pituicytoma is a very low-grade glioma that originate in the neurohypophysis and infundibulum. **Objective and hypotheses:** Describe diagnosis and treatment of associated pituicytoma and ACTH-secreting adenoma in a 6-year-old girl. **Method:** Case report and literature review. **Results:** We report the case of a 6-year-old presented with growth failure and associated weight gain, premature pubarche, and hypertrichosis. Cushing's syndrome was biochemically diagnosed on the basis of loss of serum cortisol circadian rhythm, i.e. an elevated sleeping midnight cortisol level of >50 mmol/l and failure of serum cortisol suppression to <50 mmol/l during an overnight 1 mg dexamethasone and successive high-dose suppression test. MRI scanning displayed a focal area of altered signal (bright on T2-sequence) in the middle and superior portion of pituitary gland, suggestive for an ACTH-secreting adenoma. Bilateral simultaneous inferior petrosal sinus sampling was performed. A central to peripheral ACTH ratio was not indicative of central ACTH secretion and an inter-petrosal sinus gradient <1.4 was suggestive of a midline lesion. The patient underwent excision of a small, soft mass by endoscopic transsphenoidal approach. Unexpectedly, the definite postoperative histopathological diagnosis of the removed tumor was pituicytoma and not pituitary adenoma. Hence, the microadenoma responsible for Cushing's disease was not yet removed. For persistent hypercortisolism, the patient underwent a second MRI that confirmed the presence of an intraglandular small area of altered signal in the same region. A second transsphenoidal operation was performed; histological examination of the removed lesion revealed a pituitary adenoma ACTH-secreting. **Conclusion:** Pituicytoma is a very rare tumor: 65 cases are described in literature, with only three children affected. Coincidence of pituicytoma and pituitary-dependent Cushing's disease was only reported in an adult man. It is difficult to explain this extremely rare association, that represented a diagnostic and therapeutic challenge.

P2-D2-522

Treatment Options in a 14-Year-Old Boy with an Atypic Cabergolin-Resistant Macroprolactinoma with Somatostatin Receptor 2 Expression and an Increased Proliferation Rate

Angela Huebner^a, Felix Reschke^a, Gabriele Hahn^b, Thomas Pinzer^c, Matthias Meinhardt^d, Anke Pyper^a, Salvatore Cannavò^e, Gunter Stalla^f, Lorenz C. Hofbauer^g

^aDepartment of Paediatrics, Universitätsklinikum Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany;

^bDivision of Paediatric Radiology, Universitätsklinikum Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany;

^cDepartment of Neurosurgery, Universitätsklinikum Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany;

^dDepartment of Neuropathology, Institute for Pathology, Universitätsklinikum Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany;

^eSection of Endocrinology, Department of Medicine and Pharmacology, University of Messina, Messina, Italy;

^fDepartment of Internal Medicine, Endocrinology and Clinical Chemistry, Max Planck Institute for Psychiatry, Munich, Germany;

^gDivision of Endocrinology, Diabetes and Bone Diseases, Universitätsklinikum Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany

Background: Macroprolactinomas in children below 10 years of age are rare. Usually prolactinomas respond well to dopamine agonists so that neurosurgical resection is rarely necessary. For non-responders to dopamine agonist therapy other extended treatment options have to be considered. **Clinical case:** We report a 14-year-old boy who presented at the age of 11 years with headaches for 5 years and progressive bilateral vision problems. The diagnosis of a macroprolactinoma was made on the basis of elevated prolactin levels of 6727 mU/l (NR 86–324) and on typical MRI features with a large intra- and suprasellar mass infiltrating the clivus and both sinus cavernosus and displacing the chiasm. Cabergoline treatment was started immediately with increasing doses of 0.5–7 mg/week resulting in a transient fall of prolactin levels to 2000 mU/l with no reduction of tumour mass after 10 weeks of treatment. In order to prevent bilateral blindness, partial resection of the tumour was performed. **Results:** Histopathology confirmed a prolactinoma with an increased proliferation rate (Ki 67) of 5% (focally up to 10%) as well as p53 (10%), and a strong somatostatin receptor 2 expression. Metastases were not found and MEN1 and AIP gene sequencing was normal. Postoperatively, cabergoline and quinagolide treatment were ineffective. The tumour partially responded to octreotide up to 30 mg/month, however prolactin levels are rising and tumour size increased again after 13 months. Repeated transsphenoidal surgery will be performed followed by either temozolamide treatment or radiotherapy. **Conclusion:** Atypic macroprolactinomas with a high proliferation index starting at an age of about 6 years as in our case are extremely rare. If dopamine agonist therapy fails and the tumour cells express somatostatin receptor 2 octreotide could be one treatment option although there is little experience for this age group. Final treatment strategies may include stereotactic radiation and temozolamide.

P2-D2-523

Long-Term Data Including Fertility in Two Females with Hypothalamic Hamartoma Associated with Central Precocious Puberty

Antonis Voutetakis, Christina Kanaka-Gantenbein, Maria-Alexandra Magiakou, George Chrousos, Catherine Dacou-Voutetakis

Division of Endocrinology, Metabolism and Diabetes, 1st Department of Pediatrics, Medical School, National and Kapodistrian University of Athens, Athens, Greece

Background: Hypothalamic hamartomas (HH) are congenital morphogenetic defects frequently associated with central precocious puberty (CPP). **Objective and hypotheses:** Data on the outcome of girls with CPP due to HH are limited. **Method:** We report two patients with CPP caused by HH, one with normal fertility. **Results:** Patient 1, now aged 33 years, was examined at age 15 months (vaginal bleeding, breast and pubic hair development since age 4 months). Pertinent studies disclosed CPP. MRI showed a lesion hanging in the interpeduncular cistern (diameter: 8 mm). Cyproterone acetate was initially used, changed to GnRHa at age 4 years. Following GnRHa discontinuation (at 8.25 years), menses occurred regularly. She has normal mental development and no seizures. Her final height (FH) was 155 cm (TH 151 ± 4.5 cm). Subsequent MRIs showed no changes until age 30 years when HH reduction was observed (diameter: 5 mm). She had three spontaneous pregnancies, the first and third one resulted in the birth of two normal children. Patient 2, now a 20-year-old college student, was examined at age 2.5 years (breast and pubic hair development and vaginal bleeding). Pertinent studies disclosed CPP. MRI showed HH in the tuber cinereum (15×10 mm). GnRHa was administered until age 9.75 years. Upon discontinuation, puberty progressed normally (menses at 11.5 years, occurring regularly within a year). Her FH was 157 cm (TH 163 ± 4.5 cm). No seizures of any kind were observed. Her last MRI revealed HH size reduction. **Conclusion:** Patients with HH not associated with seizures develop normally with appropriate GnRHa therapy (surgical therapy is not indicated). It seems that after discontinuation of GnRHa therapy, the hypothalamic-pituitary-gonadal axis recovers its normal tempo permitting regular menses and fertility. Diminution in the size of the hamartoma might be expected with age.

P2-D2-524

Pituitary Stalk Interruption Syndrome: a Sequential Manner to Gain Pituitary Hormone Deficiencies with Still Unknown Molecular Basis

Elena Jerez, Gabriela Echeverría, Teresa Muñoz-Calvo, Jesús Pozo-Román, Gabriel Martos-Moreno, Jesús Argente

Hospital Infantil Universitario Niño Jesús. Universidad Autónoma de Madrid, Pediatrics and Pediatric Endocrinology, Instituto de Investigación La Princesa, Centro de Investigación Biomédica en Red de fi, Madrid, Spain

Background: Pituitary stalk interruption syndrome (PSIS) is characterized by the absence of the pituitary stalk, pituitary hypoplasia and an ectopic posterior pituitary. **Objective:** We aimed to retrospectively analyze the clinical, auxological, biochemical, and radiological findings in Spanish patients with PSIS. **Patients and results:** Of 27 patients, 25% were female and 75% male. Perinatal features, auxological and endocrine study at diagnosis and during the first 3 years of follow-up were analyzed; 23% exhibited intrauterine growth restriction (most symmetric), 38.5% were delivered by Cesarean section and 46.2% suffered dystocia. GH deficiency occurred in 100% of patients, TSH deficiency in 65.4%, ACTH deficiency in 38.5%, FSH/LH deficiency in 26.9%, hyperprolactinemia in 19.2%, and ADH deficiency in 3.8%. Among these, 18.5% had isolated GH deficiency, 51.9% had combined pituitary hormone deficiencies, 25.9% had three, and 4.9% had four. Age at diagnosis for GH, TSH, ACTH, FSH/LH, and hyperprolactinemia was 3.9 years ± 3.5 SDS (range: 0.05–11.64), 3.7 ± 4.6 , 4.1 ± 5.4 , 12.3 ± 5.1 , and 3.4 ± 4.8 respectively. Adult height was available for eleven patients (42.3%), 7 (63.6%) reaching or surpassing target height. rGH treatment was started at 4.1 ± 3.6 years. Mean height before rGH therapy was -3.2 ± 1.4 SDS. Mean IGF1 and IGFBP3 levels before treatment were -4.4 ± 1.8 and -1.8 ± 1.6 SDS respectively. Growth velocity before therapy was -2.2 ± 1.3 SDS, increased to $+2.9 \pm 3$ SDS during the first year, and $+2.6 \pm 2.1$ SDS during the second year, reaching $+1 \pm 1.2$ SDS in the third year. No molecular abnormalities were found in the genes analyzed. **Conclusions:** Children with PSIS develop pituitary hormone deficiencies in a sequential manner, starting with GH deficiency. Good response to rGH therapy is seen with the highest growth velocity observed during the first year of treatment.

P2-D2-525

Challenging Treatment of Gigantism in a Boy with McCune-Albright Syndrome

Melanie Hess, Sara Bachmann, Gabor Szinnai, Urs Zumsteg
Pediatric Endocrinology/Diabetology, Basel, Switzerland

Background: McCune-Albright syndrome (MAS) is a complex disorder characterized by the triad of fibrous dysplasia of multiple bones, café-au-lait skin macules and endocrinopathies. **Objective and hypotheses:** Long-term treatment of a boy with gigantism due to MAS. **Method:** Case report. **Results:** We present the clinical course of a now 14 years old boy with MAS and GH excess, clinical signs of precocious puberty and hyperprolactinemia. He presented at the age of 5 years with a complicated bone fracture of the femur. Histological bone examination revealed

fibrous dysplasia. On clinical examination, large café-au-lait macules were found, leading to the diagnosis of MAS. Cerebral MRI displayed generalized fibrous dysplasia of his skull base surrounding the pituitary gland and his facial bones. Ultrasound of his testes showed bilateral microlithiasis. At that time, clinical and biochemical evaluation showed no abnormalities besides a height of +2.2 SDS, in particular no precocious puberty or GH excess. At the age of 8.5 years, he was readmitted to due to increased growth velocity and signs of precocious puberty. Clinically, he presented with pubic hair Tanner III, testicular volume of 4 and 5 ml, and height of +2.9 6SDS. Bone age was advanced by 18 months, now. Further, IGF1, IGFBP3, and prolactin (PRL) were also markedly increased whereas hormones of thyroid and adrenal gland were normal. Therefore, a GH- and PRL-suppression therapy with somatostatine and cabergoline was started. After initiation of this therapy, his growth velocity markedly decreased, with suppression of GH and PRL. After about 4 years of successful therapy, GH and PRL increased again and stayed high during the last 12 months despite repetitive dose adjustments. Now, introduction of pegvisomant, a GH receptor antagonist, is planned to optimize pharmacological treatment. **Conclusion:** Pharmacological treatment of MAS remains challenging during adolescence, especially in regard of adequate growth and increased risk of complications in future.

P2-D2-526

Child with GH Deficiency due to Remnant Craniopharyngeal Duct

Elpis Vlachopapadopoulou^a, Evgenia Maniatakou^a, Spyros Sgouros^b, Georgia Papaioannou^b, Irene Dikaiakou^a, Stefanos Michalacos^a

^aChildren's Hospital P& A, Athens, Greece; ^bMitera Hospital, Athens, Greece

Background: A child with slow growth rate (< -2 SDS) polyuria and polydipsia warrants urgent investigation for hypothalamic-pituitary tumors. **Objective and hypothesis:** To present the case of a boy with slow growth rate, polyuria NAD polydipsia due to remnant craniopharyngeal duct. **Method:** Boy 11 years old, was evaluated because of short stature and slow growth rate documented for 2 years. He reported no headaches but he reported polyuria, polydipsia, fatigue and earache. Target height was on the 75th percentile. He had no dysmorphic features, height was on the 3rd percentile and weight on the 50th percentile. His physical exam was unremarkable, with normal proportions, unpalpable thyroid, and prepubertal external genitalia. MRI of the hypothalamus-pituitary area as well as hormonal investigations were scheduled. IGF1: 115 ng/ml, TSH: 4.28 μ IU/ml and fT4:0.72 ng/dl. GH response to stimulation was low, as well as cortisol response to glucagon. Morning cortisol was within normal range. Bone age was 2.5 years delayed. MRI revealed a bony defect of the sphenoid bone, 2.8 mm large and 4 mm long, at the level of

sella turcica. There was apparent prolapse of the anterior pituitary lobe through the duct, reaching to the upper part of the rhinopharynx. The intense signal of the posterior pituitary lobe was not recognized. The patient is under replacement therapy with GH and thyroxine. **Conclusion:** Remnant craniopharyngeal duct is a rare congenital disorder. To our knowledge there are no previous report of a child with a large craniopharyngeal duct and hormonal deficiencies.

P2-D2-527

Adolescents with Chronic Endocrine Diseases: a Multidisciplinary Approach: the Experience of the Paediatric Clinic of Palermo

Maria Cristina Maggio^a, Rita Riticella^a, Giuseppe Salvo^b, Giuseppe Santangelo^b, Giovanni Corsello^a

^aUniversity Department Pro.Sa.M.I. 'G. D'Alessandro', University of Palermo, Palermo, Italy; ^bIOU of Paediatric Neuropsychiatry, Children Hospital 'G. Di Cristina', ARNAS, Palermo, Italy

Background: Adolescents affected by chronic diseases need a specific support and care, in a contest dedicated to them and not integrated with children. They often ask a specific attention to their asks, only partially secondary to their primary disease. **Objective and hypotheses:** The need of a support in communication of the diagnosis, in the adherence to a long-life or to a prolonged treatment and a long follow-up, with repeated blood samples, strumental examinations induced us to create a multidisciplinary day service exclusively dedicated to adolescents. **Method:** In a 3 years experience we selected 30 adolescents (14 males and 16 females) with chronic endocrinological diseases (GHD, panhypopituitarism), between all the patients who followed the Unit of Paediatric Endocrinology, and proposed them specific tests, addressed to the evaluation of the Anxiety Scale, the Eating Attitude Test (Eat 26), the CBCL (evaluating comportamental attitudes and social relations), the CRS-L (evaluating psychosomatic problems, inattention, and emotional instability). **Results:** The Anxiety Scale was pathological in 12/30 patients (40%; seven males and five females). The Eat 26 was borderline only in two patients (7%; two females). The Conners' Rating Scales-Revised (CRS-R) was pathological in ten patients (33%; three males and seven females, with a significant prevalence in females). The CBCL was pathological in six (four males and two females). The psychological support was integrated with the evaluation of the whole family, and personalized with the objective to remove the problems linked to the chronic disease. **Conclusion:** Eating disorders were described in females, as reported in literature, with a significant incidence (7%) in adolescents with chronic endocrine diseases as GHD. Chronic endocrine diseases, especially if they need a long-life treatment, favourite psychological disabilities and relational consequences. The multispecialistic assistance assured to those patients with pathological skills to the tests a follow-up twice/month, with a significant reduction of the pathological items, especially for the CBCL and the CRS-R.

P2-D2-528**Atypical Presentation of Hypothermia Induced Diabetes Insipidus: a Case Report***Ellen Klocker, Himala Kashmiri*

Loyola University Medical Center, Maywood, Illinois, USA

Background: Central diabetes insipidus (DI) is a well-known complication of CNS trauma or tumors, but is a rare complication of hypothermia. Review of the literature reveals scant case reports of DI as a complication of therapeutic hypothermia after cardiopulmonary resuscitation or head injury, but to date there has been no mention of DI resulting from hypothermia alone. **Objective and hypotheses:** Severe hypothermia alone may constrict CNS blood flow, mimicking the effects of circulatory cessation leading to DI. **Method:** Case report. **Results:** We present a perplexing case of central DI in a previously neurologically intact 13-year-old Caucasian male who developed severe spontaneous hypothermia during treatment for antipsychotic induced toxic epidermal necrolysis. Despite aggressive internal and external warming, his core temperature reached a nadir of 85.1 F (29.5 °C) while his sodium concentration simultaneously increased. He required ECMO for temperature regulation and while his hypothermia improved his hypernatremia worsened to 164 mEq/l despite fluid resuscitation. Initial septic work-up for hypothermia was negative. Interesting within 48 h of starting vasopressin for mild hypotension, he became eunatremic. However, when vasopressin was discontinued, his hypernatremia returned to 152 mEq/l with a serum osmolality of 332 mOsm/kg, an inappropriate urine osmolality of 400 mOsm/kg, and an inappropriately normal antidiuretic hormone level of 8.8 pg/ml (1.0–13.3). He did experience intermittent polyuria while off vasopressin. Additional pituitary workup revealed a normal cortrosyn stimulation test and thyroid function tests. **Conclusion:** Given these findings, he was diagnosed with partial DI and his sodium only began to normalize after oral desmopressin was initiated. Unlike previous case reports citing hypothermia related DI, our case is not confounded by an inciting anoxic event. This unusual case encourages investigation into the role hypothermia may play in disrupting neuroendocrine functioning in pediatric patients.

P2-D1-529**Is There Any Influence of TSH Serum Levels on Insulin Resistance in Euthyroid Adolescents with Polycystic Ovary Syndrome?***Alice Albu^{a,b}, Serban Radiana, Suzana Florea^b, Simona Fica^{a,b}*^aUMF Carol Davila, Bucharest, Romania; ^bElias Hospital, Bucharest, Romania.

Background: Few previous studies suggested an association between insulin resistance (IR) and TSH serum levels in euthyroid

patients. This relation could have some particularities in populations characterized by intrinsic insulin resistance like polycystic ovary syndrome (PCOS) patients. **Objective and hypotheses:** The aim of our study was to study the relationship between IR and TSH serum levels in adolescent euthyroid PCOS patients. **Method:** We performed a cross-sectional study on 85 adolescent PCOS patients with normal thyroid function (mean age 18.05 ± 1.65 years, range 13–20 years, mean BMI 25.5 ± 6.9 kg/m²) diagnosed based on Rotterdam Consensus criteria. All the patients were evaluated by clinical and hormonal exam. HOMA-IR was calculated as an index of IR and free androgen index (FAI) was calculated as an index of bioavailable testosterone. Variables with non-Gaussian distribution were log-transformed. **Results:** Linear regression analysis showed that HOMA-IR was positively associated with BMI ($P < 0.0001$), serum TSH level ($P < 0.05$), and FAI ($P < 0.005$). Multivariate linear regression with HOMA-IR as dependent parameter and BMI, TSH and FAI as independent variables showed that only BMI was independently associated with HOMA-IR after adjustment for TSH and FAI. **Conclusion:** Although TSH serum levels are positively associated with HOMA-IR in adolescent euthyroid PCOS patients, this relationship seems to be dependent of adiposity.

P2-D1-530**The Vaginal Maturation Index as a Marker of Local Sensitivity to Estrogens in Girls with Congenital Adrenal Hyperplasia During Puberty***Irina Kopylova, Sofya Blokh, Elizaveta Orlova, Irina Yarovaya, Maria Kareva*

Endocrinology Research Centre, Department of Pediatric Endocrinology, Moscow, Russia

Background: Introital stenosis is the main complication of vaginoplasty in females with Congenital Adrenal Hyperplasia (CAH) which could result from poor estrogenization of vaginal tissue during puberty. **Objective and hypotheses:** To evaluate the maturation of vaginal mucosa depending on the degree of compensation. **Method:** 19 adolescent girls with CAH (salt-wasting (SW) – 9, simple virilizing (SV) – 10; 15.9 years (14.4, 16.9), Tanner 4 (3, 5)) were divided into two groups according to the mean serum 17-hydroxyprogesterone (17-OHP), testosterone (Ts) levels and regularity of menstrual cycle during last year: group 1 – satisfactory compensation ($n=10$, regular/irregular cycle – 6/4); group 2 – inadequate compensation ($n=9$, regular cycle/primary amenorrhea/secondary amenorrhea = 2/3/4). The control group 3 included 12 age-matched healthy adolescent girls with regular menstrual cycle. Cytological examination of vaginal smears with the determination of vaginal maturation index ($VMI = (\% \text{ intermediate cells} \times 0.5) + \% \text{ superficial cells}$) and atrophic index (AI, % parabasal cells) has been performed. **Results:** Serum Ts level negatively correlated with VMI ($r_s = -0.58$, $P = 0.008$) and positively correlated with AI ($r_s = 0.51$,

$P=0.024$) in total CAH group. No significant correlations were observed between indices and serum estradiol and 17-OHP levels. In group 1 VMI was significantly higher than in group 2 (62.5% (56, 64.5) vs 48.3% (43.2, 53.75), $P=0.002$). No significant difference of VMI was revealed between group 1 and group 3. Parabasal cells were found in five girls from group 2 (AI = 3.5% (0.0, 20.0) vs 0.0% (0.0, 0.0) in group 1). The significant difference of AI was observed in group 2 between SW and SV form (20.25% (10.0, 33.75) vs 0.0% (0.0, 3.5), $P=0.04$). **Conclusion:** The estrogenization of vaginal tissue mainly depends on the compensation of CAH. Epithelium maturation is reduced more in SW in comparison to the SV form.

P2-D1-531

Very Low Estradiol Levels are Independent From Duration of Amenorrhea in Girls with Severe Anorexia Nervosa

Christèle Kyheng^a, Gianpaolo De Filippo^{a,b}, Anne-Laure Castell^{a,b}, Jennifer Flandrin^a, Julie Durin^a, Manon Delafoya^a, Lise Duranteau^{a,b}

^aAssistance Publique – Hôpitaux de Paris, Hôpitaux Universitaires Paris Sud, Hôpital Bicêtre, Service de Médecine des Adolescents, Le Kremlin-Bicêtre, France; ^bAssistance Publique – Hôpitaux de Paris, Hôpitaux Universitaires Paris Sud, Hôpital Bicêtre, Service d'Endocrinologie et Diabétologie de l'Enfant, Le Kremlin-Bicêtre, France

Background: Anorexia nervosa (AN) is a primary psychiatric disease, complicated by serious endocrine disturbances. Hypogonadotropic hypogonadism with primary or secondary amenorrhea is the most common endocrine repercussion of AN, with consequent estrogen deficiency and concerns about bone mineral density. Furthermore, establishing regular menstrual cycles is considered as one of the important milestones in girls treated for AN. **Aim:** To quantify the estrogen deficiency through plasmatic estradiol (E_2) measurements in girls with severe AN and secondary amenorrhea. **Patients and methods:** E_2 measurements were performed in 17 post-pubertal girls (mean age 15 ± 1.6 years, 12–18.31) with severe AN and secondary amenorrhea (mean duration of 8.6 ± 5.53 months, 3–24) hospitalized for re-nutrition. Results were analyzed to data from ten age-matched girls with diagnosis of hypothalamic amenorrhea (HA) not related to a low nutritional status and from ten age-matched healthy controls. A complete anthropometric and biochemical evaluation was also carried out. Body composition and bone mineral density (BMD) were evaluated by dual energy X-ray absorptiometry. **Results:** Mean E_2 levels in AN patients were severely reduced: 25.44 ± 20.30 vs 90.3 ± 83 and 160 ± 92 pmol/l in HA and controls respectively ($P < 0.05$ and $P < 0.001$ respectively). E_2 levels were significantly correlated with % of fat mass ($P < 0.001$). No correlation was found between E_2 levels and duration of amenorrhea or E_2 levels and bone mineral density.

Conclusion: Analysis of plasmatic E_2 levels show that girls with severe AN and secondary amenorrhea present very low levels, independently from the duration of amenorrhea. No correlation was found with low BMD. Further studies are needed to evaluate the impact of such severe estrogen deficiency on physical and psychological health status and the efficacy of estrogen replacement in these patients.

P2-D1-532

Evaluation of the Free Androgen Index in Adolescent Females Diagnosed with Obesity, Hirsutism, and PCOS

Elif Sagsak^a, Zehra Aycan^a, Meliksah Keskin^a, Senay Savas Erdeve^a, Funda Cenesiz^a, Fatma Doga Ocal^b, Semra Cetinkaya^a

^aDr Sami Ulus Obstetrics and Gynecology, Pediatric Health and Disease Training and Research Hospital, Pediatric Endocrinology Clinic, Ankara, Turkey; ^bDr Sami Ulus Obstetrics and Gynecology, Pediatric Health and Disease Training and Research Hospital, Clinic of Gynecological Diseases and Obstetrics, Ankara, Turkey.

Background: It is difficult to define the laboratory finding of hyperandrogenism and associate it with clinical findings in children and adolescents. Androgen levels can be high in obesity, hirsutism, and PCOS. The free androgen index (FAI) is a simple ratio used to evaluate the biologically active testosterone. **Objective and hypotheses:** Our aim was to determine the FAI in adolescent females and to evaluate how this index is influenced in adolescents diagnosed with obesity, hirsutism, and PCOS. **Methods:** A total of 75 female patients aged 12–22 years, consisting of 25 patients each followed-up with diagnoses of obesity, hirsutism, and PCOS were included in the study. The control group consisted of healthy adolescents. The obesity group consisted of patients whose BMI was over SDS 2 and the hirsutismus group consisted of cases with a Ferriman–Gallwey score of 8 or over. The PCOS patient group consisted of patients who met all the PCOS Amsterdam 2013 diagnostic criteria for adolescents. Morning total testosterone and SHBG were measured in all patients. The FAI was calculated with the following formula: $FAI = (\text{total testosterone in nmol/l} / \text{SHBG in nmol/l}) \times 100$. **Results:** FAI values were 2.3 ± 1.3 (range, 0.2–6.4) in healthy adolescent females, 10.1 ± 6.1 (range, 1.7–27.3) in obese patients and 14.9 ± 9.3 (range, 2.7–4.3) in PCOS cases. There was a statistically significant difference between healthy adolescents and the patients. The difference between the obese and hirsutism groups was not significant while that between the other groups was. The ROC analysis performed to differentiate the FAI in healthy adolescents from the values in the patient group showed a sensitivity of 80.6% and specificity of 97.8% when the cut off value was accepted as 4.85. **Conclusion:** An FAI value over 4.85 can be used as a simple ratio that is inexpensive to measure with high sensitivity and specificity in defining hyperandrogenism.

P2-D1-533**Polycystic Ovarian Syndrome in Adolescents: Metabolic Profile at Diagnosis, During and After Treatment with Oral Contraceptive**

Andrea Arcari, Mirta Gryngarten, María Gabriela Ballerini, Analia Freire, María Eugenia Rodríguez, María Gabriela Ropelato, Ignacio Bergadá, María Eugenia Escobar

Centro de Investigaciones Endocrinológicas 'Dr César Bergadá' (CEDIE) CONICET – FEI – División de Endocrinología, Hospital de Niños Ricardo Gutiérrez, Buenos Aires, Argentina

Background: Obesity and unfavorable metabolic profile (insulin resistance and/or dyslipidemia) are frequently observed in Polycystic Ovarian Syndrome in Adolescents (PCOS) girls regardless of weight. **Objective and hypotheses:** To evaluate clinical features and metabolic profile in PCOS adolescents, before, during and after Oral Contraceptive (OC) treatment. **Method:** We performed a retrospective study on 51 girls with PCOS diagnosed according to the Androgen Excess Society criteria. Menstrual history, BMI (BMI-SDS), clinical and biochemical hyperandrogenism and metabolic profile were analyzed at diagnosis (age 16 ± 1.8 years). A group of 26 patients was assessed during OC treatment (etinilestradiol-drospirenone) for at least 2 years and after treatment withdrawal. **Results:** At diagnosis, all patients had menstrual disturbances (gynecological age: 4.0 ± 2.0 years; 30 oligo-amenorrhea, 11 poly-oligomenorrhea, five primary amenorrhea, and five secondary amenorrhea). BMI-SDS 0.67 ± 1.10 (40% overweight or obese). Hirsutism was present in 98% (Ferriman-Gallwey score 13 ± 4), 67% had acne and 21% acanthosis nigricans. Forty-nine percent of patients had elevated serum testosterone and androstenedione (0.76 ± 0.33 and 3.73 ± 1.42 ng/ml respectively). BMI-SDS and HOMA-IR were positively associated to free androgen index ($r=0.48$ and $r=0.53$, $P<0.001$ respectively). Elevated HOMA-IR and dyslipidemia (low HDL and high triglyceride levels) were present in 31 and 12% respectively. BMI and HOMA-IR remained unchanged throughout and after treatment, whereas total cholesterol, LDL cholesterol and triglyceride levels increased during OC treatment ($P<0.0001$) and decreased ($P<0.0001$) upon OC withdrawal. HDL cholesterol increased during treatment ($P<0.0001$) and remained elevated after treatment. **Conclusion:** Adolescent girls with PCOS may have overweight, insulin resistance and/or dyslipidemia at diagnosis. We strongly recommend the evaluation of metabolic profile in PCOS adolescents at diagnosis to further prevent future consequences. OC treatment in our cohort did not show a long term impact on BMI, insulin resistance or dyslipidemia.

P2-D1-534**Endocrine Disruptors and Polycystic Ovary Syndrome: Phthalates**

Leyla Akin^a, Mustafa Kendirci^a, Figen Narin^b, Selim Kurtoglu^a, Meda Kondolot^c, Recep Saraymen^b, Selda Ozkan Kocak^a, Nihal Hatipoglu^a, Ferhan Elmali^d

^aDepartment of Pediatric Endocrinology, Faculty of Medicine, Erciyes University, Kayseri, Turkey; ^bDepartment Biochemistry, Faculty of Medicine, Erciyes University, Kayseri, Turkey; ^cDepartment of Pediatrics, Faculty of Medicine, Erciyes University, Kayseri, Turkey; ^dDepartment of Biostatistics, Faculty of Medicine, Erciyes University, Kayseri, Turkey.

Background: Polycystic ovary syndrome (PCOS), characterized by hyperandrogenemia, anovulatory periods and polycystic ovaries, is a disorder in which metabolic and reproductive abnormalities overlap. The etiopathogenesis is currently unclarified. Besides the evidence of genetic causes, environmental factors are considered to be involved in development of phenotype. Phthalates are widely used industrial chemicals and have several known untoward effects on human reproductive health. **Objective and hypotheses:** In this study, we aimed to investigate a possible role of phthalates (MEHP and DEHP) in PCOS etiopathogenesis. We also wished to evaluate the relationship between phthalates and metabolic disturbances in adolescents with PCOS. **Method:** A total of 173 adolescents (112 PCOS, 61 controls, mean age: 15.2 ± 1.4 age range: 13–19 years) were included in the study. Physical examination and anthropometric measurements were performed in all participants. Hormonal and metabolic parameters and serum MEHP and DEHP levels measured by HPLC method were determined. OGTT was performed in PCOS and obese control groups. Insulin resistance was evaluated using HOMA-IR, QUICK-I, fasting glucose/insulin ratio, Matsuda index and total insulin levels during OGTT. Participants were further subdivided into lean and obese subgroups according to BMI. **Results:** Serum MEHP and DEHP levels were not significantly different between PCOS and control groups (mean MEHP levels: 0.29 ± 0.2 vs 0.36 ± 0.3 $\mu\text{g/ml}$; mean DEHP levels: 2.6 ± 0.3 vs 2.7 ± 0.4 $\mu\text{g/ml}$ in PCOS and control groups respectively, $P>0.05$). Serum MEHP levels were positively correlated with waist circumference, glucose, total cholesterol, insulin, and HOMA-IR. Serum DEHP levels were positively correlated with insulin, HOMA-IR, triglyceride, total cholesterol and negatively correlated with QUICK-I and Matsuda index. **Conclusion:** Serum MEHP and DEHP concentrations were not different between adolescent girls with or without PCOS. However, these phthalates are associated with metabolic disturbances such as dyslipidemia and insulin resistance in this population.

P2-D1-535**Correlation Research of Bisphenol A and Premature Thelarche in 6 Months to 2 Years Old Infant Girls**

Haiying Wu^a, Linqi Chen^a, Guangzhao He^b, Weipeng Wang^b

^aChildren's Hospital Affiliated to Soochow University, Suzhou, Jiangsu, China; ^bCollege of Pharmaceutical Science, Suzhou University, Suzhou, Jiangsu, China

Background: Now in many causes of precocious puberty, thinking of environmental endocrine disruptors (EDCs) is one of the causes. Bisphenol A (BPA), as a kind of environmental

endocrine disruptors, can interfere with normal endocrine activities. But up to now, there is few reports of the influence of BPA in premature thelarche (PT) of below 2 years girls. **Objective and hypotheses:** To investigate the association between BPA and premature thelarche in 6 months to 2 years old infant girls. **Method:** Forty infants aged 6 months to 2 years old with breast development and 32 female infants with no breast development as control group in our clinic from March to May 2014 were assigned in this study. Height and weight were measured and feeding condition was inquired. Serum BPA concentration was determined by HPLC-MS-MS. Sex hormones (FSH, LH, E₂, and PRL) were detected by chemiluminescence method. The difference between the two groups and the correlation between BPA and sex hormones were analysed. **Results:** For PT group, the BPA relevance ratio is 67.5%, and the concentration is 13.95 ± 1.187 ng/ml, which are higher than the control group with relevance ratio 30.9%, and the concentration 8.036 ± 0.548 ng/ml ($P < 0.05$). The FSH and PRL concentrations have no statistical significance ($P > 0.05$) between the two groups. The relevance ratio of E₂ of PT group (50%) is higher than the control group (18.75%) ($P < 0.05$). The relevance ratio of LH of PT group (47.5%) is higher than the control group (0.00%) ($P < 0.001$). There are no correlations between BPA and FSH ($r = 0.179$) and PRL ($r = 0.279$). There are correlations between BPA and LH and E₂ ($P < 0.05$). **Conclusion:** Six months to 2 years old infant girls under the existence of BPA exposure. BPA exposure is likely one of the causes of PT for 6 months to 2 years old infant girls. BPA exposure may affect the secretions of LH and E₂.

P2-D1-536

Monitoring GnRH Analog Treatment in Girls with Central Precocious Puberty: a Comparison of Four Methods

Amnon Zung^a, Ella Burundukov^a, Mira Ulman^b, Tamar Glaser^a, Malka Chen^b, Zvi Zadik^a

^aPediatric Endocrinology Unit, Kaplan Medical Center, Rehovot, Israel; ^bEndocrine Laboratory, Kaplan Medical Center, Rehovot, Israel

Background: The gold standard for adequate hormonal suppression during GnRHa treatment for precocious puberty (PP) is attenuated serum LH levels in response to LHRH stimulation. **Objective and hypotheses:** We aimed to compare basal and post-GnRHa levels of LH to LHRH stimulation test, and to evaluate first-voided urinary LH (ULH) as a non-invasive alternative method for monitoring treatment. **Method:** Seventeen girls with PP were followed over 12–36 months during GnRHa (Decapeptyl) treatment. ULH and serum LH levels were obtained every 4 months before and 24 h after GnRHa administration respectively, along with clinical evaluation of pubertal staging, growth velocity (GV) and bone age (BA) advancement. LHRH stimulation test was performed annually. ULH cutoff was 1.62 IU/l based on 2 s.d. above the mean in 29 pre-pubertal girls. **Results:** A total of 36 LHRH stimulation tests demonstrated adequate suppression of gonadotropins with peak LH of 0.57 ± 0.33

(0.1–1.4 IU/l). Corresponding mean post-GnRHa LH levels was 0.59 ± 0.33 (0.1–1.6) and mean basal LH levels was 0.27 ± 0.16 (0.1–0.7 IU/l). Both tests were correlated with LHRH-stimulated LH: $R = 0.807$ and $R = 0.696$ respectively ($P < 0.001$). Corresponding mean ULH levels was 1.12 ± 0.38 IU/l. Among 90 pair-tests of ULH and post-GnRHa LH measurements obtained over 380 patient-months, six ULH measurements levels were above the pre-pubertal cutoff (range 1.66–2.21) but none of post-GnRHa LH levels. In spite of adequate hormonal suppression, 21 episodes of clinical breakthrough were recorded: 13 episodes of GV-SDS > 2 and 11 episodes of BA advancement. ULH and post GnRH LH levels measured during these episodes were similar to levels obtained during clinical suppression. **Conclusion:** Decapeptyl Depot treatment provides adequate suppression of the hypothalamic – pituitary – gonadal axis during PP. When in doubt, both pre-GnRHa and post-GnRHa LH levels can provide reliable data on hormonal suppression. Clinical breakthroughs during treatment do not reflect unsuppressed gonadotropins and therefore therapy intensification is not necessarily indicated.

P2-D1-537

The Evaluation of Possible Role of Endocrine Disrupters in Precocious Puberty

Derya Bulus^a, Ali Ascı^b, Nesibe Andıran^c, Belma Kocer-Gumusel^d, Elif Yağlı Çolakoglu^a

^aDivision of Pediatric Endocrinology, Keçiören Research and Educational Hospital, Ankara, Turkey; ^bDepartment of Toxicology, Faculty of Pharmacy, Atatürk University, Erzurum, Turkey; ^cDivision of Pediatric Endocrinology, Keçiören Research and Educational Hospital, Yıldırım Beyazıt University, Ankara, Turkey; ^dDepartment of Toxicology, Faculty of Pharmacy, Hacettepe University, Ankara, Turkey.

Background: Human health might be negatively affected by chemicals named as endocrine disruptors. Researchers showed that phthalates (*bis*-(2-ethylhexyl) phthalate (DEHP), mono-(2-ethylhexyl) phthalate (MEHP)) and bisphenol A (BPA) have an anti-androgenic and/or estrogenic effects. These endocrine disruptors are accused in occurrence and/or possible increase in unusual early puberty in girls in recent years. **Objective and hypotheses:** The aim of this study is to measure urine BPA and plasma phthalate (MEHP and DEHP) levels in girls with idiopathic central puberty precocious (SPP) and peripheral puberty precocious (PPP) and compare them with healthy controls, in order to investigate possible role of them in occurrence of early puberty. **Method:** This study was performed in Keçiören Training and Research Hospital, Clinic of Pediatric Endocrinology between August 2012 and July 2013, newly diagnosed SPP and PPP patients and non-obese healthy girls as control group. **Results:** SPP, PPP and control group's mean ages were similar, as 7.4 ± 0.61 (6.05–8.26); 7.4 ± 0.68 (6.09–8.28), and 7.4 ± 0.68 (6.01–8.33) years respectively. Basal FSH levels were similar in the SPP and PPP groups and significantly higher than the control group ($P < 0.0001$). Basal LH levels had no significant difference between PPP and control groups ($P > 0.05$). Basal estradiol levels

were similar PPP and SPP groups and significantly higher than control group ($P < 0.0001$). SEP group had higher LH levels at 20 and 40 min in LHRH test than PEP group ($P < 0.0001$). At suprapubic pelvic ultrasonography; mean ovarian volume and uterine length of SPP were significantly higher than PPP group (respectively; $P = 0.007$, and 0.0001). Urine BPA levels was measured similarly in SPP, PPP and control groups, within median levels of 10.15 (2.08–50.22); 10.60 (2.46–55.58), and 10.91 (2.93–53.43) $\mu\text{g/g}$ creatinine respectively ($P > 0.05$). Mean plasma DEHP levels in SPP, PPP and control groups were 0.141 ± 0.106 (0.052–0.568); 0.110 ± 0.027 (0.059–0.188), and 0.095 ± 0.036 (0.055–0.166) $\mu\text{g/ml}$ respectively; plasma MEHP levels were 0.207 ± 0.089 (0.056–0.397); 0.147 ± 0.088 (0.061–0.470), and 0.172 ± 0.147 (0.050–0.670) $\mu\text{g/ml}$ respectively. Plasma DEHP and MEHP levels did not differ significantly between PPP and control groups ($P > 0.05$), however in SPP group levels were significantly higher than PPP and control groups (respectively $P = 0.022$ and $P = 0.018$). **Conclusion:** Our study showed that phthalates might be possible risk factor in etiology of precocious puberty while BPA effect might be limited impact. But more studies are necessary to confirm this theory.

P2-D1-538

Acute Exposure of Endocrine Disruptor does not Induce Oxidative Stress in the Rat's Brain

Neeraj Kumar^a, Varsha Sharma^b

^aShri Ramswaroop Memorial University, Barabanki, UP, India;

^bCSIR-Indian Institute of Toxicology Research, Lucknow, UP, India

Background: The ever increasing uses of electronic gadgets are becoming a widespread source of Bisphenol-A accumulation. As studies have been reported that low level BPA accumulation may produce neurological effects but still limited studies have re-examined for its adverse effects in terms of acute exposure from electronic devices. **Objective and hypotheses:** To investigate the effects of BPA on oxidative damage in terms of activity level of antioxidant enzymes in different regions of the rat brain. **Method:** In this study, BPA migration was estimated through physico-chemical parameters and leachate (equivalent to 4 mg/kg body weight) was used for animal dosing. Three groups of Albino Wistar rats (190 ± 20 g) were used for control, sham, and treated. The antioxidant enzymes including superoxide dismutase (Mn-SOD), catalase (CAT), glutathione peroxidase (GPx), and reduced glutathione level (GSH) were measured in different brain regions, i.e. corpus striatum, frontal cortex, thalamus, and midbrain. **Results:** No significant changes were observed in most of the brain regions yet the level of GPx activity in corpus striatum (29.65 ± 0.98 nmol/min per mg protein) and level of GSH activity in frontal cortex (2.33 ± 0.12 $\mu\text{mol/g}$ protein) was found to decrease significantly ($P < 0.05$) when compared to controls. In addition, no significant effects were observed for the oxidative damage in brain regions of sham group when compared to control group. **Conclusion:** Thus study suggests that acute exposure (4 mg/kg body weight per day up to 28 days) of BPA does not induce significant oxidative damage in the rat's brain.

Furthermore, study might re-examine before affirm the final remark for subscribers and regulatory bodies at similar doses.

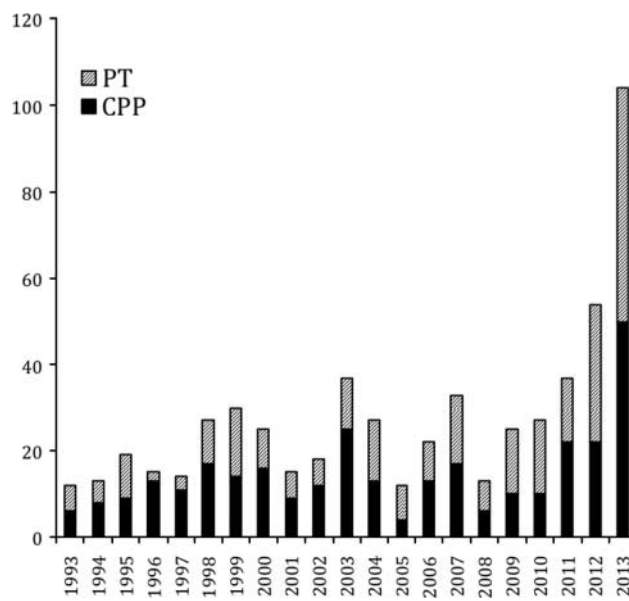
P2-D1-539

Dramatic Rise in the Prevalence of Precocious Puberty in Girls Over the Past 20 Years in the South of France

Laura Gaspari^{a,b}, Emilie Morcrette^a, Claire Jeandel^a, Fabienne Dalla Valé^a, Françoise Paris^{a,c}, Charles Sultan^{a,c}

^aDepartment of Pediatric Endocrinology, CHU Montpellier, Montpellier, France; ^bDepartment of Pediatrics, CHU Nîmes, Nîmes, France; ^cDepartment of Hormonology, CHU Montpellier, Montpellier, France

Background: Epidemiological evidence in Europe indicates the increasing prevalence of premature puberty, especially in girls. This may be attributed to *in utero* and early-life exposure to environmental estrogen-like compounds present in pesticides, plastics (bisphenol A, phthalates ...) and beauty products. **Objective and hypotheses:** The aim of this study was to assess the prevalence of premature thelarche (PT) and central precocious puberty (CPP) in girls up to 8 years followed in the Pediatric Endocrine Clinic over the last 20 years. **Method:** We conducted a retrospective and current chart review (1993–2013) of girls ≤ 8 years referred for premature puberty. Four doctors contributed their patient data and the yearly number of referred patients was relatively stable (3843 ± 323). **Results:** The figure shows the number of girls with PT+CPP for every year. From 1993 to 2007, the average number of cases per year was 21.1. From 2008, the average rose to 43.5 cases per year, to reach a peak of over 100 cases in 2013. Moreover, in the first 2 months of 2014, 51 cases have already been recorded. It is deeply worrisome that in 2 months we have reached nearly the same number of PT+CPP as recorded in the middle of 2013. **Conclusion:** Although we have



not yet questioned the families about their occupational and/or residential risks of exposure to endocrine disruptors, our area is well known to be highly contaminated. It is likely that environmental pollution accounts for the dramatic rise in the prevalence of precocious puberty in girls.

P2-D1-540

A Novel Mutation at a Splice Acceptor Site of *WDR11* in a Patient with Combined Pituitary Hormone Deficiency

Yoko Izumi^{a,b}, Erina Suzuki^a, Shuichi Yatsuga^c, Shinichiro Sano^a, Kazuhiko Nakabayashi^d, Akihiro Umezawa^e, Kenichiro Hata^d, Tsutomu Ogata^f, Maki Fukami^a, Yasunori Yoshimura^b

^aDepartment of Molecular Endocrinology, National Research Institute for Child Health and Development, Setagaya-ku, Tokyo, Japan; ^bDepartment of Obstetrics and Gynecology, Keio University School of Medicine, Shinjuku-ku, Tokyo, Japan; ^cDepartment of Pediatrics and Child Health, Kurume University School of Medicine, Kurume, Fukuoka, Japan; ^dDepartment of Maternal-Fetal Biology, National Research Institute for Child Health and Development, Setagaya-ku, Tokyo, Japan; ^eDepartment of Reproductive Biology, National Research Institute for Child Health and Development, Setagaya-ku, Tokyo, Japan; ^fDepartment of Pediatrics, Hamamatsu University School of Medicine, Hamamatsu, Shizuoka, Japan

Background: *WDR11* has recently been reported as one of the causative genes of hypogonadotropic hypogonadism (HH). To date, five missense mutations in *WDR11* have been identified in six patients with normosmic isolated HH (nIHH) or Kallmann syndrome (KS). **Methods:** We performed mutation screening of *WDR11* for 46 cases with various types of HH. RT-PCR was carried out for a patient with a mutation. The protein structure of the mutant *WDR11* was predicted by *in silico* analysis. **Results:** A heterozygous mutation at a splice acceptor site of *WDR11* (g.IVS3-2A>G) was identified in a male patient. RT-PCR revealed that the mutation led to an in-frame deletion of the entire exon 4 of *WDR11*. The mutant allele was predicted to encode an aberrant protein (p.D118_L175delinsV) that disrupts the functionally-important WD40 domain. **Phenotype of the mutation-positive patient:** The male patient was born at 37 weeks of gestation with 3460 g (+1.9 s.d.) and 51.0 cm (+1.8 s.d.). The pregnancy was complicated by pregnancy-induced diabetes mellitus and hypertension. He showed apparent growth failure from 1.5 years of age. Endocrine evaluation revealed impaired GH secretion and normal thyroid and adrenal function. Brain MRI showed stalk interruption and ectopic posterior lobe of the pituitary. His sense of smell was normal. GH supplementation therapy from 1.11 years of age significantly improved his growth. At 7 years of age, he presented with micropenis, descended normal sized testes, obesity (height 111.1 cm, -1.7 s.d.; weight 30.4 kg, +1.8 s.d.) and mental retardation. Blood levels of testosterone and LH were low. His mother carrying the same heterozygous mutation manifested irregular menses without delayed puberty. **Conclusion:** The results indicate that *WDR11* mutations can underlie not only nIHH and KS but also CPHD.

P2-D2-541

Normal Minipuberty in a Patient with *DAX1* Mutation: a Reliable Marker of the Function of the Hypothalamic–Pituitary–Gonadal Axis?

Julie Fudvoye, Marie Christine Lebrethon, Jean Pierre Bourguignon, Anne Simone Parent

University Hospital of Liege, Liege, Belgium

Background: We report here the case of a 5-week-old male patient, referred to the hospital because of failure to thrive. An adrenal insufficiency was diagnosed and the genetic testing showed a mutation in the *DAX1* gene leading to a premature stop codon. In addition to adrenal hypoplasia congenita, *DAX1* mutation is known to be classically associated with hypogonadotropic hypogonadism which is mostly characterized by absence of onset of puberty and infertility. **Objective and hypotheses:** Our aim was to evaluate minipuberty onset in a patient with *DAX1* mutation to determine if the hypothalamic–pituitary–gonadal axis is already impaired during its early life activation. **Methods:** LH, FSH, and testosterone were measured by electrochemiluminescence. **Results:** Physical examination of our patient showed normal male sexual differentiation (normal penile length and descended testes bilaterally). The laboratory evaluation revealed a normal minipuberty onset: serum testosterone: 0.35 µg/l at 6 weeks of age and serum testosterone: 1.9 µg/l; LH: 1.3 UI/l and FSH: 6.3 UI/l at 10 weeks of age. **Conclusion:** The normal male sexual differentiation and the normal minipuberty in our patients as well as in a few patients with *DAX1* mutation reported in the literature suggest that the function of the hypothalamic–pituitary–gonadal axis is normal during the perinatal period. However, absent or delayed puberty in those patients highlights the involvement of *DAX1* in the central control of reproduction later in life. Based on these observations, one can hypothesize that *DAX1* might not play a crucial role during the early life activation of the hypothalamic–pituitary–gonadal axis. Another explanation could be that *DAX1* alteration of function at the hypothalamic–pituitary level is progressive or is partially compensated initially. This further highlights the difficulty for clinicians to predict pubertal timing and reproductive functions in patients with *DAX1* mutation.

P2-D2-542

GH Excess and Pseudoprecocious Puberty in a 8-Year-Old Boy with McCune–Albright Syndrome

Diana-Alexandra Ertl, Johannes Gojo, Daniela Aubrunner, Gabriele Haeusler

Medical University of Vienna, Vienna, Austria

Background: McCune–Albright syndrome (MAS) is defined by skin, bone and glands disorders, due to activating mutations in the *GNAS1*. Clinical presentation is heterogeneous. Reports about GH excess in MAS patients are scarce. **Case report:** We present the case of an 8-year-old male, previously diagnosed with mono-

ostotic fibrous dysplasia of the skull, referred due to signs of pubertal development since the age of 6. The patient presented only 1 café-au-lait spot in the right subscapular area, puberty stage Tanner IV with asymmetric testicular development, growth above 97th percentile and accelerated bone age. Testosterone levels were elevated for age (0.65 ng/ml), but low for Tanner stage and testicular volume (8 and 10 ml). Basal gonadotrophins were measurable, with some stimulation after LHRH (maximal LH 2.1 mU/ml and FSH 0.8 mU/ml). IGF1 levels were +4 SDS and GH excess was proven after oral glucose load (minimal GH level 7.7 ng/dl). Hyperprolactinemia (224.8 ng/ml) was present, with normal serum cortisol and thyroid hormones. Genetic analysis of the *GNAS* in peripheral lymphocytes was normal, suggesting somatic mosaicism. Therapy with the GH-receptor blocker Pegvisomant has recently been started. ALS values dropped dramatically from +3.2 to +0.2 SDS after only one month of therapy, faster than IGF1 serum concentrations. **Discussion:** There is little literature data regarding therapy with Pegvisomant in the paediatric population with GH excess. The main therapy target in this patient is lowering IGF1, as high levels represent a risk for compression of the optic nerve by the fibrotic bone tissue. Boys with MAS and signs of secondary sex characteristics are also rarely found in published reports, although testicular enlargement is more common. The inconsistent result of LHRH testing with a rather low testosterone level in this case speaks for an intermittent testicular activation, like is has been described in girls with MAS and pseudoprecocious puberty.

At the initiation of treatment, the median chronological (CA) and bone age (BA) were 8.7 years (IQR, 8.2–9.3) and 12 years (IQR, 11.5–12) respectively. The median treatment duration for whole cohort was 2.9 years (IQR, 2.3–3.5). Of the 98 girls, 57 (58%) reported menarche after completing GnRH treatment. Among these 57 girls, median interval between end of treatment and onset of the menarche was 13.4 months (IQR, 9.4–18.5). Cumulative incidence rate of onset of menarche was 31% at 12 months, 51% at 15 months, 61% at 18 months, and 82% at 24 months after completing treatment. In univariate analysis, factors associated with the time to menarche included BMI SDS at start of treatment (hazard ratio (HR), 1.33; 95% CI, 1.003–1.77), LH/FSH ratio at start of treatment (HR, 1.34; 95% CI, 1.04–1.72) and BMI SDS at end of treatment (HR, 1.88; 95% CI, 1.34–2.64). Multivariate analysis indicated only one risk factor was BMI SDS at end of treatment (HR, 1.02; 95% CI, 0.99–1.04). **Conclusion:** These results suggest that hormonal and auxological parameters at start as well as at end of treatment are related to time of menarche.

P2-D2-544

Impact of Being Born Small or Large for Gestational Age on Pubertal Onset and Progression

M Loredana Marcovecchio, Ilaria Di Giovanni, Tommaso de Giorgis, Nella Polidori, Valentina Chiavaroli, Angelika Mohn

University of Chieti, Chieti, Italy

Background: Perinatal factors seem to influence the onset of puberty. There is some evidence suggesting that being born small for gestational age (SGA) is associated with early puberty, whereas the effect of large size at birth on timing of puberty is not clear.

Objective and hypotheses: To evaluate the timing of puberty in children born SGA and large for gestational age (LGA) compared to children born appropriate for gestational age (AGA). **Method:** Longitudinal growth data collected from 40 AGA (20 boys), 20 SGA (ten boys), and 20 LGA (ten boys) subjects were analysed, using the Preece–Baines model, to calculate age at take-off (ATO), age at peak height velocity (APHV), age at attaining final height (AFH), peak height velocity (PHV), and final height. Duration of pubertal growth spurt (PGSd) was calculated as the difference between APHV and ATO. Analyses were adjusted for sex and prepubertal BMI. **Results:** SGA and LGA children showed an earlier ATO compared to AGA children. In contrast, APHV and AFH were not statistically different between the three groups ($P > 0.05$). PGSd was longer in SGA and LGA children compared to AGA. PHV was similar between the three groups, whereas final height SDS was significant lower in SGA children (-1.18 ± 1.19) compared to AGA (-0.41 ± 0.95) and LGA (-0.67 ± 1.08)

P2-D2-543

Time to Menarche After Completing GnRH Agonist in Girls with Central Precocious or Early Puberty

Shin-Hee Kim, In-Ah Jung, Won Kyoung Cho, Kyoung Soon Cho, So Hyun Park, Min Ho Jung, Byoung Kyu Suh

Department of Pediatrics, School of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

Background: Treatment goals for central precocious puberty (CPP) in girls include preventing short final height due to early epiphyseal closure, and avoiding premature onset of menarche.

Objective and hypotheses: Our aim was to evaluate the timing of menarche and the associated factors among patients with idiopathic CPP or early-onset puberty (EP) who were treated with GnRH agonists (GnRH). **Method:** We analyzed clinical and laboratory data of 98 girls (78 CPP and 20 EP) who were treated with GnRH. Cumulative incidence of menarche was calculated by Kaplan–Meier method. **Results:** A total of 98 girls were followed for median 24.2 months (interquartile ranges (IQR), 14.3–32.2).

Table 1. (for abstract P2-D2-544)

	AGA (1)	SGA (2)	LGA (3)	<i>P</i> for trend	<i>P</i> 1 vs 2	<i>P</i> 1 vs 3	<i>P</i> 2 vs 3
ATO (years)	11.3 ± 1.3	10.2 ± 1.0	10.2 ± 1.5	<0.01	<0.01	<0.01	0.59
APHV (years)	12.5 ± 1.2	12.3 ± 1.6	12.4 ± 1.4	0.43	0.19	0.76	0.39
PHV (cm/year)	8.3 ± 1.8	9.35 ± 1.7	8.5 ± 2.2	0.22	0.08	0.61	0.29
PGSd (years)	1.2 ± 1.1	2.2 ± 1.4	2.2 ± 1.2	<0.01	<0.01	<0.01	0.84

($P=0.04$). **Conclusion:** Being born SGA or LGA is associated with an earlier onset of puberty and a longer PGSd. These data confirm previous associations between SGA and early puberty and support a similar trend associated with being born LGA.

P2-D2-545

Diagnostic Spectrum of Female Pubertal Delay

Suma Uday, Sabah Alvi

Department of Paediatric Endocrinology, Leeds Children's Hospital, Leeds, UK

Introduction: Delayed onset of puberty is quite a common presentation in adolescent endocrine clinics, and the most common cause, particularly in boys is considered to be constitutional delay of growth and maturation. In girls, however, it is more likely that there is a significant underlying problem. **Objectives:** To review the aetiology of pubertal delay in female patients referred to a single tertiary centre. **Methods:** All female patients referred to the Endocrinology Clinic with delayed puberty, arrested puberty and primary amenorrhoea between January 2007 and December 2012 were identified using our clinic patient database. A review of medical case notes was carried out to identify the aetiology of pubertal delay, and information was also obtained on investigations, treatment, and outcome. Patients with known conditions associated with pubertal delay, pituitary/gonadotoxic therapy, or secondary amenorrhoea were excluded. **Results:** Thirty-three patients were identified with a median age of presentation of 15.5 years. A total of 15 different reasons for pubertal delay were found in our population. The three most common causes were low BMI, constitutional delay (no

abnormality found and no therapeutic intervention required for onset of menses) and idiopathic primary ovarian failure, but intracranial lesions (craniopharyngioma and prolactinoma), structural abnormalities of the genital tract (Mayer-Rokitansky syndrome), and genetic/chromosomal anomalies (androgen insensitivity syndrome and Turner Mosaic) were all identified. **Conclusion:** Although simple maturational delay can be a common cause of delayed puberty, in our study we found a large number (88%) of our patients had a significant underlying aetiology. Seven girls (21%) had a marked eating disorder or other reason for a very low BMI. These results confirm the importance of thorough evaluation of all girls presenting with delayed puberty.

P2-D2-546

Kallmann Syndrome: Diagnosis in Paediatric Age

Ângela Machado^a, Maria João Oliveira^a, Teresa Borges^a, Helena Cardoso^a, Paula Fonseca^b, Luis Ribeiro^a, Catarina Gonçalves^c, Manuel Lemos^c

^aDepartment of Paediatric Endocrinology, Centro Hospitalar do Porto, Oporto, Portugal; ^bDepartment of Paediatric, Centro Hospitalar do Médio Ave, Famalicão, Portugal; ^cCICS-UBI, Health Sciences Research Centre, University of Beira Interior, Covilhã, Portugal

Background: Kallmann syndrome (KS) is a rare clinical entity, characterized by the association of hypogonadotropic hypogonadism and hypo/anosmia, with an estimated prevalence of 1:8000 in males and 1:40 000 in females. **Method:** Retrospective study

Table 1. (for abstract P2-D2-546)

Case	1	2	3	4	5	6	7
Sex	Female	Male	Male	Male	Male	Male	Female
Decimal age at diagnosis	16.15	17.9	15.77	16.52	17.09	10.83	13.6
Presentation	Primary amenorrhoea	Pubertal delay	Pubertal delay	Pubertal delay	Pubertal delay	Screening	Pubertal delay short stature
Family history	Constitutional delay of puberty	None	None	None	None	Brother: KS	None
Basal LH and FSH	Low	Low	Low	Low	Low		Low
Hypo/anosmia	Present	Present	Present	Present	Present		Present
MRI olfactory bulbs	Absent	Absent	Hypoplasia	Absent	Absent		Absent
Genetic analysis	Without mutation	KAL1 – deletion of exon 1, c.67_92del26, p.Leu23fsX54	FGFR1 missense mutation (p.S96C)	Without mutation	KAL1 – whole gene deletion	KAL1 – whole gene deletion	FGFR1 frame-shift mutation (p.V460SfsX3)
Other malformations	Bilateral deafness	Bilateral cryptorchidism, renal agenesis	Bilateral cryptorchidism, right deafness	Cleft lip	Renal agenesis	Bilateral cryptorchidism	None

of cases of KS diagnosed in paediatric age. Genetic analysis was performed by PCR and DNA sequencing of KAL1, FGFR1, GNRHR, GNRH1, PROK2, PROKR2, KISS1R, TAC3, TACR3, and FGF8 genes. **Results:** Total of seven cases, 6 (85%) males. Median age at diagnosis was 16.15 years. All were referred to a tertiary Paediatric Endocrinology Outpatient Hospital due to pubertal delay, except case 6 (diagnosis made by genetic study after his brother's diagnosis). Results are summarized in Table 1. All patients, except case 6, are treated with sex hormones. **Conclusion:** The diagnosis of KS is mainly done during adolescence or adulthood because of incomplete or absent pubertal development. The sensitivity of molecular testing is only about 30%, however we identified mutations in 71% of our patients. Despite the availability of genetic testing the diagnosis is still mainly based on clinical findings. So the authors emphasize that it is essential take into account the associated malformations that may coexist in KS as well as assessment of the olfaction, often undervalued by patients.

P2-D2-547

The Triptorelin Test Compares Favourably with the GnRH Test in the Diagnosis of Central Precocious Puberty

Asmahane Ladjouze^a, Adel Djermane^b, Yasmine Ouarezki^c, Leila Kedji^a, Karima Berkouk^a, Maoudj Abdeljalil^a, Rawda Aboura^a, Minoubia Bensmina^a, Tahar Anane^a, Salah Eddine Bouyoucef^d, Abdenour Laraba^a

^aDepartment of Pediatrics, CHU Bab El Oued, Algiers, Algeria;

^bEPH Gouraya, Gouraya, Algeria; ^cEPH Gué de constantine, Algiers, Algeria; ^dDepartment of Nuclear Medicine, CHU Bab El Oued, Algiers, Algeria

Background: The i.v. GnRH test remains the gold standard for the diagnosis of central precocious puberty (CPP). Unfortunately however, GnRH is expensive and is not available worldwide. GnRH analogues have been used as an alternative, but their place is not established, while very few studies have compared between the two tests. **Objective:** To compare the effects of GnRH and Triptorelin on gonadotrophin secretion in patients with sexual precocity and hence evaluate the diagnostic accuracy of the Triptorelin test for the diagnosis of CPP compared with GnRH test. **Patients and methods:** In this prospective study the GnRH test was carried out using 100 µg LHRH intravenously. Triptorelin test was performed at least 2 weeks after the GnRH test, using 0.1 mg of s.c. Triptorelin. LH, FSH, and E₂ were determined at baseline, 30, 45, and 60 min during both tests. CPP was defined by clinical and radiological signs of precocious puberty associated with an LH peak > 5 UI/l on GnRH and/or Triptorelin testing. **Results:** We studied 26 patients (one boy) of whom ten (nine girls and one boy) had CPP, mean ± s.d. age at diagnosis 5.08 ± 2.61 years; four had precocious pseudopuberty (PPP); and 12 had premature thelarche (PT), age at diagnosis 6.03 ± 1.86 years. CPP patients showed mean ± s.d. (range) peak LH 13.35 ± 14.4

(3.19–42.62) mUI/ml after GnRH and 20.18 ± 23.44 (5.15–79) mUI/ml after Triptorelin. There was no difference between the two tests, 95% CI (–25.4141; 11.7141). In patients with PT or PPP, peak LH was 1.85 ± 1.49 (0.14–4.74) mUI/ml after GnRH and 2.24 ± 1.7 (0.2–4.95) mUI/ml after Triptorelin. There was no difference between the two tests, 95% CI (–1.5681; 0.7931). For the Triptorelin test both the sensitivity and specificity for the diagnosis of CPP were 100% for a LH peak of 5.15 UI/l. **Conclusion:** Our study confirms that the LH profiles after s.c. Triptorelin and i.v. GnRH are similar. Triptorelin can be used as an alternative to GnRH for the diagnosis of CPP when the latter is unavailable, or too costly.

P2-D2-548

Puberty in Children with Shunted Congenital Hydrocephalus with and without Myelomeningocele

Lemm Proos, Kai Arnell, Jan Gustafsson, Margareta Dahl

Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden

Background: Children with myelomeningocele (MMC) run an increased risk of developing early or precocious puberty (E/PP). In previous studies of such children we found that the incidence of E/PP was 52% in girls and 21% in boys and that E/PP was strongly associated with increased intracranial pressure perinatally. It is also known that the occurrence of hydrocephalus without MMC is associated with risk of E/PP. **Objective and hypotheses:** The aim was to study the influence of MMC and gender on timing of puberty in children with increased intracranial pressure perinatally. **Method:** All children with congenital hydrocephalus, born between 1980 and 2002, treated with shunt and living in the county of Uppsala, were identified. The study cohort included 35 children (16 girls) with congenital hydrocephalus. Eighteen children (eight girls) had MMC whereas 17 children (eight girls) had not. Health records were examined retrospectively. E/PP was defined as pubertal signs appearing before 10:2 years for boys and 9:2 years for girls. **Results:** (Table 1). **Conclusion:** All children with congenital shunted hydrocephalus are at high risk of developing E/PP. In the children without MMC the risk is comparable in the genders while in those with MMC it is most marked in girls. The mechanism behind the later onset of puberty in boys with MMC should be further investigated.

Table 1. (for abstract P2-D2-548)

	Girls		P	Boys		P
	Without MMC	With MMC		Without MMC	With MMC	
Age start puberty (years)	8.4 ± 2.0	8.3 ± 1.4	NS	8.5 ± 1.9	10.0 ± 0.9	0.044
E/PP	6/8 (75%)	7/8 (88%)		6/9 (67%)	3/10 (30%)	

P2-D2-549**Evaluation of Age at GnRH Analogue Treatment Discontinuation, Age at Menarche and Adult Height in Girls with Central Precocious Puberty from the Spanish Registry**

Raquel Corripio^a, Leandro Soriano-Guillén^b, Ramón Cañete^c, Lidia Castro-Feijóo^d, Arancha Escribano^e, Rafael Espino^f, Javier Herrero-Espinet^g, José-Ignacio Labarta^h, Jesús Argenteⁱ

^aHospital Sabadell, Corporació Parc Taulí, UAB, Sabadell, Barcelona, Spain; ^bHospital Fundación Jiménez Díaz, Madrid, Spain; ^cHospital Universitario Reina Sofía, Córdoba, Spain; ^dHospital Clínico Universitario de Santiago de Compostela, La Coruña, Spain; ^eHospital Universitario Virgen de la Arrixaca, Murcia, Spain; ^fH. Universitario Virgen de Valme, Sevilla, Spain; ^gHospital St. Jaume de Calella, Barcelona, Spain; ^hHospital Miguel Servet, Zaragoza, Spain; ⁱHospital Universitario Niño Jesús, Madrid, Spain

Background: The Spanish Registry PUBERE was created (2007) with 53 hospitals. **Objective and hypotheses:** i) To determine the chronological age (CA) and bone (BA) at GnRH analogue withdrawal; ii) to analyze the age at menarche and time elapsed after stopping treatment; and iii) to know adult height data. **Method:** Patients with central precocious puberty (CPP) born after 1992, diagnosed before 8 years in girls, with BA/CA > 1 year and LH peak after LHRH > 7 IU/l, were included. At diagnosis we calculated the adult height (AH) prediction (Bayley and Pineau method) in cm and SDS according to the reference population. We also collected data of GnRH analogue withdrawal (BA and CA), age at menarche and AH data (cm and SDS). **Results:** 386 patients (19.9% adopted and 87.4% idiopathic) were included. The CA at treatment onset was 7.26 ± 1.31 years and the BA 9.10 ± 1.51 years. The average CA at treatment discontinuation was 10.15 ± 1.01 years ($n=186$), coinciding with a BA of 11.6 ± 0.67 years. The age at menarche was 11.04 ± 1.14 years ($n=106$), occurring 13.52 ± 7.14 months after stopping treatment. The mean increase in height after treatment discontinuation was 13.1 ± 4.3 cm. Mean AH ($n=30$) was 157.5 ± 11.03 cm (SDS: -0.66 ± 1.98). The mean PAH at diagnosis was 161.5 ± 10.9 cm, so the mean difference between AH and PAH at diagnosis was -3.76 ± 8.61 cm (95% CI: -6.98 to -0.55 cm; $P=0.023$). **Conclusion:** i) The AH of PPC patients was significantly lower than their PAH, but within the margin of error of this method (95% CI: ± 6 cm). ii) Treatment withdrawal was done before the age of pubertal onset average in our population. iii) Menarche occurred about 13 months after stopping treatment.

P2-D2-550**Final Height in a Boy with McCune–Albright Syndrome and Precocious Puberty Treated with Ketoconazole, Cyproterone Acetate, and Leuprolide Acetate Depot for More than 5 Years**

Maria Francesca Messina, Tommaso Aversa, Mariella Valenzise, Filippo De Luca

Department of Pediatrics, University of Messina, Messina, Italy

Background: McCune–Albright syndrome (MAS) is a sporadic and rare disorder, clinically defined by the classic triad of café-au-lait skin lesions, polyostotic fibrous dysplasia, and peripheral precocious puberty. Precocious puberty is common in girls, but has been reported in only 15% of affected boys. Clinical trials on therapeutic management of precocious puberty in MAS boys are limited to case reports or small patient cohorts and no data are reported about final height. **Objective:** To describe the results in term of final height of a therapeutic combination ketoconazole–cyproterone acetate–leuprolide depot, a regimen that has never been experienced so far. **Case report:** A 4.6-year-old boy presented to our clinic owing to a painless enlargement of right testis (10 ml). On physical examination no other signs of precocious puberty were noticed and left testis volume was 3 ml and penis size was infantile (4.5×1.2 cm). Patient's height was 119.2 cm (+2.6 SDS) vs a target height of 181.2 cm (+1.2 SDS), weight was 19.2 kg (+0.8 SDS) and bone age 5.5 years. Endocrinological assessment excluded a central precocious puberty and an adrenal disorders. An atypical form of MAS was suspected and confirmed by molecular analysis (classic mutation R201C of GNAS1 gene). During the subsequent 2 years right testis volume, testosterone and free testosterone serum levels, growth velocity, and bone maturation progressively increased. At the age of 6.6 years, a combined treatment with both ketoconazole (400 mg/daily in two divided doses) and cyproterone acetate (50 mg/daily), aiming at both suppressing testicular steroidogenesis and inhibiting the peripheral effects of testosterone was started and at 8.8 years an LHRH analogue was added to prevent central precocious puberty. The complex pharmacological scheme was definitely stopped at a chronological age of 13.6 and resulted in a final height of 188.5 cm (+1.6 SDS). **Conclusion:** To the best of our knowledge, this is the first report in the literature in which a MAS boy with both peripheral and central PP has been treated with a complex pharmacological regimen up to final height. His excellent auxological outcome suggests that a combination of cyproterone acetate, ketoconazole and LHRH analogue may be effective in controlling both the peripheral and the central PP in MAS male patients, allowing the attainment of a final height in the normal range and very close to target height.

P2-D2-551**The Effect of Combined GH and GnRH Agonist Treatment for Near-Final Height Improvement in True Precocious Puberty and Early Puberty**

Se Young Kim^a, Eun Young Kim^b, Kyung Hee Yi^c

^aBundang Jesaeng General Hospital, Kwandong University College of Medicine, Seongnam Kyunggi-do, Republic of Korea; ^bChosun University Hospital College of Medicine, Gwangju Chollanam-do, Republic of Korea; ^cDepartment of Paediatrics, Wonkwang University Hospital, Gunpo, Republic of Korea

Purpose: The goal of treatment for true precocious puberty (TPP) and early puberty with GnRH agonist (GnRH_a) is to prevent loss of genetic potential of target height (TH). And to

regress secondary sex characteristics appropriate for patient's age. But some patient's growth velocity (GV) after treatment would decline and suggest that final height (FH) was not improved. So, we investigated the effect of combined GH and GnRHa treatment for near-FH (NFH) improvement. **Methods:** In this retrospective study, we collected data on the 167 girls with TPP (139 treated with only GnRHa (Group 1) and 28 treated with GnRHa and combined GH over 1 year (Group 2)) who diagnosed with LH level over 5 IU/ml and two- to threefold increment compared basal level after GnRH stimulation test. NFH was investigated after menarche at least 1 year has elapsed from 32 patients. 22 patents with NFH treated with only GnRHa are included Group 3. And eight patients with NFH treated with combined GnRHa and GH over 1 year are included Group 4. **Results:** The chronological age at diagnosis were 8.25 ± 1.10 years in Group 1 and 9.02 ± 1.45 years in Group 2. The height SDS at diagnosis were -1.76 ± 1.26 in Group 1, -0.59 ± 0.97 in Group 2, showed significant difference ($P < 0.05$). The predicted adult height (PAH) SDS at diagnosis were -1.76 ± 1.26 in Group 1, -2.82 ± 1.53 in Group 2 with significant difference ($P < 0.05$). After 1-year treatment, PAH SDS were -1.14 ± 1.17 in Group 1, -1.71 ± 1.29 in Group 2. After 2-year treatment, PAH SDS were -0.73 ± 1.01 in Group 1, -0.50 ± 1.40 in Group 2. After 3-year treatment, PAH SDS were -0.40 ± 1.13 in Group 1, -0.50 ± 1.05 in Group 2, appeared decreasing intergroup PAH difference. TH SDS at diagnosis were -0.50 ± 0.504 in Group 3, -0.97 ± 0.514 in Group 4, showed significant difference ($P < 0.05$). After over 1 year treatment, NFH SDS of Groups 3 and 4 were not statistically different. **Conclusion:** The combined GH and GnRHa therapy in TPP and early puberty, whose PAH SDS or TH SDS were shorter than 5%, could effective improving NFH in proportion to treatment duration.

P2-D2-552

Pubertal Development in a Cohort of Romanian School-Aged Children

Ionela Pascanu, Oana Capraru, Ancuta Cota, Raluca Pop

Endocrinology Department, University of Medicine and Pharmacy, Tirgu Mures, Romania

Background: The average age of onset of puberty development has lowered in last decades due to multiple confounding factors. No recent populational studies are available in our country regarding pubertal development. **Objective and hypotheses:** The aim of our study was to identify the timing of pubertal characteristics in our region in children of school age. Our hypothesis was that the age of pubertal onset has diminished. **Method:** Type of study: cross-sectional; target population: school-aged children 6–15 years of age; sample: composed of 1168 children randomly selected from four rural to four urban areas of Mures county. Variables: age, environment, sex, birth weight,

breast, and pubic hair Tanner stage, age of menarche. The pubertal evaluation was performed by two trained endocrinologists. The study was approved by the Local Ethics Committee and a written consent was obtained for every child. Statistical analysis used Microsoft Office Excel. The results are expressed as means and s.d.s. **Results:** Sex ratio boys:girls was 1.01; environment ratio urban:rural was 1.07. From the total sample, 107 children refused the evaluation and were excluded. The mean age of onset of pubertal development was 10.1 ± 1.5 years in girls and 10.4 ± 1.5 years in boys. Children from rural areas reached onset of puberty sooner both in girls and boys (by 0.19 respectively 0.07 years). The average age of menarche was 11.87 ± 0.96 years with only 0.06 years difference in rural and urban areas. The mean age of puberty stage 5 was 13.1 ± 1.21 years in girls and 13.33 ± 1.52 years in boys. **Conclusion:** This study shows that age of onset of normal pubertal development is not lower in our country, but the time frame of puberty has narrowed.

P2-D3-553

Inhibin B in the Diagnosis of Delayed Puberty

Camelia Procopiuc, Iuliana Gherlan, Cristina Dumitrescu, Andreea Brehar, Suzana Vladoiu, Livia Procopiuc, Andra Caragheorgheopol

C.I. Parhon National Institute of Endocrinology, Bucharest, Romania

Background: Existing tests are not 100% accurate in differentiating between isolated hypogonadotropic hypogonadism (HH) and constitutional delay of puberty (CDP) in boys. Inhibin B is a glycoprotein produced by the Sertoli cells and is measurable even before puberty. Its level increases at the beginning of puberty under the influence of FSH. **Objective and hypotheses:** The levels of inhibin B (InhB) could differentiate between HH and CDP. We aimed to establish a cut-off value for InhB which can distinguish between CDP and HH in boys. **Method:** We analyzed 18 boys with delayed puberty: ten with CDP-genital stage1 (CDP-G1) and eight with HH. We studied: auxometrical parameters, testicular volume, basal InhB, AMH, FSH, LH, testosterone and stimulated values of FSH, LH and testosterone after the soluble sc Triptorelin test. **Results:** The comparison between the CDP and the HH groups revealed that basal InhB, and LH levels at 4 h after the Triptorelin test were significantly lower for the HH group. The ROC curve for the CDP and HH groups shows that an InhB level < 29.2 pg/ml has 100% specificity and 60% sensibility for diagnosing HH, and InhB level > 78.1 pg/ml indicate CDP with 100% specificity. **Conclusion:** Basal Inhb concentrations are the most reliable in identifying the patients that suffer from hypogonadotropic hypogonadism. Moreover, it aids in cost reduction, since Triptorelin sc testing will only need to be performed for patients with InhB values in the grey zone (29.2–78.1 pg/ml).

P2-D3-554**Predominantly Matrilineal Inheritance of Familial Precocious Puberty Suggests an Underlying Imprint Anomaly**

Adelaide Durand^a, Raja Brauner^a, Anu Bashamboo^b, Ken McElreavey^b

^aUniversité Paris Descartes and Fondation Ophthalmologique Adolphe de Rothschild, Paris, France; ^bInstitut Pasteur, Paris, France

Background: The age of onset of puberty is known to be influenced by poorly understood genetic and environmental factors. Familial forms of precocious puberty suggest the involvement of autosomal genetic factors. **Objective and hypotheses:** We evaluated the mode of inheritance of precocious puberty in a large series of familial cases of both central precocious puberty (CPP) and advanced puberty. **Method:** A retrospective, single-centre study was carried out on 154 children, of whom 93 had CPP and 61 had advanced puberty, and all had an affected 1st, 2nd and/or 3rd degree relative. **Results:** 125 cases (81%, 91 girls and 34 boys) had at least one affected 1st degree relative. 29 cases (19%, 25 girls and four boys) had only 2nd ($n=18$) or 3rd ($n=3$) or both ($n=6$) degree relatives affected. The analysis of informative pedigrees showed a penetrance of 33%. Interestingly, 88 cases exhibited unilineal inheritance of which 86 cases were matrilineal. **Conclusion:** The data confirm the high incidence of affected girls with precocious puberty compared with boys. The mode of inheritance of the phenotype is predominantly matrilineal suggesting a possible imprinting anomaly as the underlying aetiology of the phenotype.

P2-D3-555**Tamoxifen-Induced Hirsutism: an Unusual Side Effect in a 5 Years Old Girl with McCune–Albright Syndrome**

Heves Kirmizibekmez^a, Rahime Gül Yesiltepe Mutlu^a, Fatma Dursun^b, Sükriye Pinar Isgüven^c

^aZeynep Kamil Obstetrics and Pediatrics Education and Research Hospital, Pediatric Endocrinology, Istanbul, Turkey; ^bÜmraniye Education and Research Hospital, Pediatric Endocrinology, Istanbul, Turkey; ^cSakarya University Faculty of Medicine, Pediatric Endocrinology, Sakarya, Turkey

Background: McCune–Albright syndrome is a rare disorder defined as the triad of peripheral precocious puberty, café-au-lait skin pigmentation and fibrous dysplasia of bone, caused by mutation of the gene GNAS1, resulting in autonomous endocrine hormone excess. **Objective and hypotheses:** This is the first pediatric case of hirsutism due to tamoxifen, a selective estrogen receptor modulator. **Case report:** A 5^{3/12} years old girl, diagnosed as McCune–Albright syndrome at 8th month, appealed for the

further follow up. She had peripheral precocious puberty, café-au-lait skin pigmentation, fibrous dysplasia and hyperthyroidism, and was receiving methimazole and cyproterone acetate. Thyroid hormones were in normal range, bone age was 11 years old, LHRH test revealed peripheral precocious puberty. There was no complain of vaginal bleeding or progression in breast tissue, but bone maturation was exceedingly accelerated. Rearranging the treatment with an estrogen receptor modulator, rather than cyproterone, was decided. Tamoxifen was prescribed as 5 mg/dose, twice a day. Approximately 2 months after, patient was brought with abnormal hair growth on the skin of abdomen and back. Excessive terminal hair was observed around linea alba and lower back, while a mild hypertrichosis on extensor surfaces of limbs was present. Serum androgen levels were in normal ranges for age, ultrasound imaging for any tumoral lesion was negative and there was not an evidence of exposure to any other substance, except tamoxifen. **Conclusion:** Recently a 77 years old patient with breast carcinoma was reported to have hirsutism 8 weeks after the initiation of tamoxifen and was reported to the manufacturer as ‘tamoxifen-induced hirsutism’. Similarly, unexpected onset of hirsutism and the exclusion of other possible causes suggested a relationship with the drug. According to a medical analysis website 8223 people, reported to have side effects when taking tamoxifen citrate, among them 5 (0.06%) of had hirsutism.

P2-D3-556**Long Term Outcomes of Precocious Puberty due to Hypothalamic Hamartomas**

Danielle Rodrigue^a, Cécile Thomas-Teinturier^a, Emmanuelle Motte-Signoret^{a,c}, Pierre Bougnères^{a,c}, Agnès Lingart^{b,c}

^aAssistance Publique des Hôpitaux de Paris – Hôpital Bicêtre-Service d’Endocrinologie et Diabétologie Pédiatrique, Le Kremlin-Bicêtre, France; ^bAssistance Publique des Hôpitaux de Paris – Hôpital Bicêtre-Service d’Endocrinologie et Diabétologie Pédiatrique Centre de Référence des Maladies Rares du Métabolisme du calcium et du Phosphore, Le Kremlin-Bicêtre, France; ^cUniversité Paris Sud – Faculté de Médecine Paris Sud, Le Kremlin-Bicêtre, France

Background: Hypothalamic hamartomas (HH) are rare benign tumours of the tuber cinereum revealed by central precocious puberty (CPP) and, in some cases, gelastic seizures and cognitive impairment. **Objective and hypotheses:** Evaluation of the treatment by GnRH analogues on control of puberty and final height in patients with HH. **Method:** We report a series of five cases of CPP secondary to HH (four girls and one boy). Early in infancy (9 months to 5 years), children presented with symptoms of PP, i.e. bilateral breast enlargement (Tanner B2 and B3), vaginal bleeding in one case, and increase in penis and testis size for the boy, accelerated growth velocity and advanced bone age. Estradiol, in girls, and testosterone, in the boy, were

significantly elevated (20–86 pg/ml and 7 ng/ml). After GnRH infusion, LH secretion rose up to 6–22 IU/l. Magnetic resonance imaging of the brain revealed a peduncular hamartoma in four cases, and a sessile hamartoma in the fifth case. Hamartomas did not change in size or shape throughout evolution. **Results:** In all cases, CPP was treated with GnRH analogues using the monthly or tri-monthly formula. During the 7 years (6–10 years) of therapy, no side effects were observed. Height velocity was steadied at 6 vs 9 cm/year before treatment. Final height was 162 cm (160–165) for girls ($n=3$) and 180 cm for the boy. Mean time of menarche was 15 months after the termination of treatment, and menses were regular in all cases. LH peak after GnRH infusion test was 10.9, 14.5 and 12.7 IU/l. Spine bone density was measured in one patient at the age of 18 years and was normal (Z -score: -0.8). **Conclusion:** CPP due to HH are extremely rare and always aggregated with CPP of other causes in the literature. Our series suggest that the height potential is conserved in this condition, even after years of treatment by GnRH analogues, and that occurrence of regular menstrual cycles is common after discontinuation of aGnRH.

P2-D3-557

Mutational Analysis of TAC and TACR3 in Idiopathic Central Precocious Puberty

Marina Krstevska-Konstantinova^a, Jana Jovanovska^a, Nevenka Slaveska^a, Velibor Tasik^a, Luciana Ribeiro Montenegro^b, Daiane Beneduzzi^b, Leticia Gontijo Silveira^b, Zoran Gucev^a

^aPediatric Clinic, Skopje, Macedonia; ^bUnidade de Endocrinologia do Desenvolvimento, Laboratorio de Hormonios e Genetica Molecular, Sao Paulo, Brazil

Background: The genetic background of idiopathic central precocious puberty (ICPP) is not well understood. The genetic activation of pubertal onset is thought to arise from the effect of multiple genes. Familial ICPP have been reported suggesting the existence of monogenic causes of ICPP. The neurokinin B (NKB) system has recently been implicated in the regulation of the human reproductive axis, but how NKB system exerts its effects on the central neuroendocrine control of human reproduction remains unknown. In humans, NKB and its receptor are encoded by the TAC3 and TACR3 genes, respectively. Mutations in these genes have been suggested to be causative for ICPP. **Method:** ICPP was defined by pubertal onset before 8 years of age in girls, and a pubertal LH response to GnRH testing. Twenty-eight girls with ICPP were included in the study (age at diagnosis was 5.72 ± 2.59 ; bone age, 6.12 ± 2.81 , height at the start of treatment, 0.90 ± 1.48 s.d.). LHRH test was performed and was pubertal in all subjects (LH 20.35 ± 32.37 mIU/ml; FSH 23.32 ± 15.72 mIU/ml). The coding regions of TAC and TACR3 were sequenced. **Results:** No rare variants were detected in TAC and TACR3 in the 28 subjects with ICPP. **Conclusion:** We confirmed that mutations in TAC and TACR3 are not a common cause for ICPP.

P2-D3-558

Pituitary–Ovarian Axis in Patients with Isolated Premature Thelarche

Beata Wikiera, Julita Nocon-Bohusz, Aleksander Basiak, Jolanta Bieniasz, Ewa Glab, Anna Noczynska

Medical University, Wroclaw, Poland

Background: Isolated premature thelarche (IPT) is characterised by precocious breast development without any other signs of puberty. **Objective and hypotheses:** The aim of the study was to analyze hormonal activity of the pituitary – ovarian axis in girls with IPT. **Method:** 102 girls with IPT (Tanner stage 2–3), mean age 2 ± 1.4 years (0.04–7 years), mean weight 12.3 ± 4.3 kg, mean height 85.0 ± 13.6 cm (45 ± 31 percentile), mean BMI 16.4 ± 1.7 (46.38 ± 27.5 percentile). The concentration of inhibin B, estradiol, FSH, LH, prolactine, TSH, FT₄, lipids and liver enzymes was estimated. Inhibin B was measured by ELISA (DSL, USA), the other hormones by LIA (DPC, USA). The patients were divided into two groups depending on the time of stating the enlargement of mammal glands: group 1 before finishing 1 year of age, group 2 after finishing 1 year of age. **Results:** All of the patients had normal thyroid hormones levels. Oestradiol concentration was below estimation threshold in 88% of them. Mean inhibin B level was 6.3 ± 10.6 pg/ml, LH 0.15 ± 0.07 IU/l, FSH 4.2 ± 2.7 IU/l, prolactine 15.1 ± 12 ng/ml. No significant differences were observed in both groups of patients. There was a negative correlation between FSH and the age of patients, positive correlation between FSH and inhibin levels. There was also a positive correlation between estradiol and insulin but not inhibin B and insulin levels. **Conclusion:** Inhibin B is produced by granulosa cells under the influence of FSH. The activity of this axis decelerates during first months of age. The synthesis of oestradiol and insulin in patients with IPT is mutually dependent.

P2-D3-559

The Buserelin Stimulation Test Given as an Intranasal Spray in Diagnosing Gonadotropin Deficiency in Males with Delayed Puberty

Gulnara Rakhimova, Kamil Gilyazetdinov

The Center for the Scientific and Clinical Study of Endocrinology, Tashkent, Uzbekistan

Background: Because of episodic secretion of gonadotropins (LH, and FSH), basal levels of these hormones can not objectively be assessed to differentiate delayed puberty in males. **Objective and hypotheses:** To assess the efficacy of the GnRH agonist (as spray) in diagnosing of delayed puberty in males. **Method:** Prepubertal males ($n=18$; age range 13.3–18.5 years) were studied; buserelin 0.15 (spray) μ g was administered intranasally, with blood sampling at 0; 1 and 4 h for serum LH and FSH. In 7/19 males had testicular volume (more than 8 ml) consistent with a

normal hypothalamic–pituitary–gonadal axis. In 12/19 males testicular volume were <4 ml suggesting hypogonadotropic hypogonadism (HH) or constitutional delay of growth and puberty (CDGP). **Results:** Stimulated serum LH response to busserelin was lower in males with HH (mean \pm under the mean for HH, at 1 h 3.6 ± 1.2 U/l; 4 h 3.0 ± 1.8 U/l compared with a normal HPG axis 9.4 ± 1.8 U/l at 1 h; 4 h 15.9 ± 0.9 U/l; $P < 0.0001$). Stimulated serum FSH response was 10.0 ± 2.2 U/l at 1 h and 16.1 ± 2.3 U/l. at 4 h in males with normal HPG axis and 4.4 ± 0.8 at 1 h and 3.9 ± 0.6 at 4 h in males with HH. There are no significant difference in basal levels of LH, FSH in both groups (2.6 ± 0.22 , 3.6 ± 0.9 for healthy males compared with HH $1.3 \pm 0.1/3.2 \pm 0.33$). **Conclusion:** The busserelin (in a spray form) stimulation test may be helpful in patients with delayed puberty to assess HPG axis.

months, was performed. Data on chronological age (CA), height (H), bone age (BA), BMI, predicted AH (PAH), target height (TH) were collected. In relation to BMI SDS at the begin and at the end of GnRHa treatment, patients were categorized in four groups: persistent normal weight (Group 1), normal weight who became overweight or obese (Group 2), overweight or obese who became normal weight (Group 3), persistent overweight or obese (Group 4). **Results:** (Table 1) **Conclusion:** A moderate increment in BMI was on overall observed in our cohort. However, BMI modifications during GnRHa treatment do not seem to influence adult height outcome in our population.

P2-D3-560

Adult Height Outcome of Girls with Idiopathic Central Precocious Puberty Treated with GnRH Analogs is Irrespective of BMI

Tommaso Aversa, Mariella Valenzise, Malgorzata Wasniewska, Maria Francesca Messina, Alessandra Santisi, Filippo De Luca

Department of Pediatrics, University of Messina, Messina, Italy

Background: GnRH analogs (GnRHa) have been used in treatment of idiopathic central precocious puberty (ICPP) for several decades. Their effectiveness on adult height (AH) improvement has been widely studied and is still debated. **Objective and hypotheses:** To assess whether BMI changes in ICPP girls during GnRHa treatment can influence AH. **Method:** A retrospective study of 131 ICPP girls (mean age at diagnosis: 7.6 ± 0.7 , range 4.3–9.0 years), treated for a period of 29.3 ± 7.6

P2-D3-561

Delayed Puberty: Between Chronopathology and Subclinical Pathology

Camelia Procopiuc^a, Cristina Dumitrescu^a, Iuliana Gherlan^a, Andreea Brehar^a, Mariana Costache^b, Livia Procopiuc^a, Andra Caragheorghieopol^a

^aC.I. Parhon National Institute of Endocrinology, Bucharest, Romania; ^bColtea Clinical Hospital, Bucharest, Romania

Background: At 14 years of age for boys and 13 years for girls, delayed puberty with low gonadotropic hormones can either be a chronopathologic feature (constitutional delay of puberty – CDP) or the subclinical unmasking of a future isolated hypogonadotropic hypogonadism (IHH). The two conditions are difficult to differentiate at these specific ages. **Objective and hypotheses:** We aimed to identify clinical and paraclinical features which correlate with either CDP or IHH in order to help in making an early diagnosis. **Method:** 82 boys with delayed puberty were followed between 2008 and 2013. The following clinical parameters were registered: significant family history, presence

Table 1. (for abstract P2-D3-560)

	Group 1 (n.64)	Group 2 (n.20)	Group 3 (n.16)	Group 4 (n.30)	P
Onset of therapy					
CA (years)	7.7 ± 0.6	7.6 ± 0.6	7.6 ± 0.6	7.6 ± 0.8	0.925
BA minus CA (years)	2.0 ± 0.8	2.4 ± 0.8	2.5 ± 0.6	2.5 ± 0.8	0.003
H (SDS)	0.2 ± 1.1	0.9 ± 1.3	0.3 ± 1.0	0.9 ± 1.2	0.018
BMI (SDS)	-0.2 ± 0.8	0.7 ± 0.3	1.3 ± 0.2	1.6 ± 0.4	0.001
PAH (SDS)	-1.5 ± 1.1	-1.1 ± 1.0	-2.0 ± 0.9	-1.4 ± 1.4	0.138
Treatment stop					
CA (years)	10.3 ± 0.7	10.0 ± 0.5	10.1 ± 0.6	10.0 ± 0.7	0.125
BA minus CA change (years)	-0.6 ± 0.6	-0.4 ± 0.6	-0.7 ± 0.4	-0.5 ± 0.6	0.460
H (SDS)	-0.1 ± 0.9	0.6 ± 1.2	-0.01 ± 0.9	0.5 ± 1.1	0.007
BMI (SDS)	0.2 ± 0.6	1.3 ± 0.2	0.7 ± 0.3	1.7 ± 0.4	0.001
Duration of treatment (months)	30.1 ± 8.3	28.8 ± 6.9	29.3 ± 5.7	27.9 ± 7.4	0.582
Menarche (years)	11.7 ± 0.7	11.5 ± 0.7	11.8 ± 0.7	11.5 ± 0.7	0.438
AH minus TH (SDS)	0.2 ± 1.1	0.4 ± 0.8	0.03 ± 1.0	0.3 ± 1.2	0.817
AH minus PAH (SDS)	0.4 ± 0.8	0.7 ± 0.8	0.8 ± 1.0	0.6 ± 1.0	0.443

of micropenis and/or cryptorchidia at birth, gonadal volume, pubic and axillary hair (Tanner stages), need for pubertal priming during follow-up. Paraclinically: at the beginning of follow-up soluble Triptorelin sc test (100 µg/m²) was performed with determination of basal FSH, LH, testosterone and 4 h FSH, LH and 24 h testosterone. Bone age was also analyzed. The data were analyzed using binary logistic regression and ROC curve. **Results:** At the end of follow-up 73 patients proved to be CDP, while nine patients had HH. A strong clinical prognostic factor for CDP was a family history of CDP ($P=0.039$). 4 h LH ≥ 5 mIU/ml after soluble Triptorelin sc test has a 91% accuracy in diagnosing CDP. Lack of the need for priming or a positive response to priming had the highest prognostic value for CDP. **Conclusion:** There is no hormonal test that can certainly distinguish between CDP and HH. If there is no pubertal onset up to the age of 18 years in boys, HH is certain. CDP is an exclusion diagnosis.

P2-D3-562

Central Precocious Puberty as the Initial Manifestation of a Pilocytic Astrocytoma with Leptomeningeal Dissemination Simulating a Hypothalamic Dysgerminoma

Blanca Lidia Galo, Diego Yeste Fernandez, Ariadna Campos, Maria Clemente, Antonio Carrascosa, Anna Llorc

Vall d'Hebron University Hospital, Barcelona, Spain

Introduction: Pilocytic astrocytoma is the most common type of CNS astrocytoma in children. Clinical manifestations depend on its location and size and initial symptoms are usually related to neurological deficits or signs and symptoms of intracranial hypertension. Involvement of the hypothalamic area, pituitary infundibulum and leptomeningeal spread are exceptional. The case of a patient with central precocious puberty in whom the initial neuroimaging study oriented the diagnosis of a dysgerminoma with meningeal metastases is presented. Arachnoid biopsy of the nodular lesion was diagnostic of leptomeningeal dissemination of a pilocytic astrocytoma. **Case report:** A 4-year-old boy was referred for study of pubic hair of 3 months' evolution with no other accompanying symptoms. Family and personal history normal. Physical examination: weight: 17.5 kg (-0.7 s.d.), height: 116.8 cm ($+2.4$ s.d.), Tanner: G1P2, testicular volume: 4–5 cc, bone age: 4 years, 6 months. Basal hormonal study: adrenal androgens and thyroid hormones: normal. LHRH test: basal LH: 1.4 IU/l; peak LH: 23.0 IU/l and basal FSH: 2.3 IU/l, peak: 4.4 IU/l, testosterone: 65.9 ng/dl, prolactin: 6.0 ng/ml, IGF –1: 139.2 ng/ml, ACTH: 52.4 pg/ml, basal cortisol: 15.0 µg/dl and urine osmolality after a dry dinner: 875 mOsm/kg. Study of serum tumour markers (α -fetoprotein and hCG β subunit): negative. Brain MRI: hypothalamic thickening with left predominance, consistent with germ cell tumour. Nodular images of supra- and infratentorial leptomeningeal dissemination. Lumbar puncture: cytochemical study normal, acellular cytology: and CSF tumour markers: negative. Arachnoid biopsy: leptomeningeal tissue

containing a nodule with tumour cells expressing GFAP and p16. Ki67 below 3%. Epithelial markers: negative. Diagnosis: pilocytic astrocytoma with leptomeningeal dissemination. **Conclusions:** Hypothalamic and infundibular involvement of pilocytic astrocytoma and its association with central precocious puberty are exceptional. This entity should be considered in the differential diagnosis of infiltrative processes of the hypothalamus and pituitary infundibulum.

P2-D3-563

Endocrine Abnormalities in Phosphoglucomutase 1 Deficiency

Barbara Mueksch^a, Eva Morava^b, Dirk Lefeber^b, Hedi Claahsen-van der Grinten^c, Eckhard Korsch^a

^aDepartment of Pediatrics, Children's Hospital, City of Cologne, Cologne, Germany; ^bLaboratory of Genetic, Department of Neurology, Endocrine and Metabolic Diseases, Radboud University Medical Center, Nijmegen, The Netherlands; ^cDepartment of Paediatric Endocrinology, Radboud University Medical Center, Nijmegen, The Netherlands

Introduction: Phosphoglucomutase 1 catalyzes the inter-conversion of glucose-6-phosphate and glucose-1-phosphate. Phosphoglucomutase 1 deficiency (PGM1-CDG), previously termed glycogenosis type XIV (OMIM 612934), is a rare variant of the congenital disorders of glycolysis (CDG), resulting in abnormal attachment and processing of protein linked *N*-glycans. We present a girl with PGM1-CDG and delayed pubertal development and review the endocrine findings of the few patients notified in the literature. **Case report:** We report on a girl with PGM1D who was presented first at the age of 13;7 years with growth retardation and absence of pubertal development. She had a medical history of a cleft soft palate, malignant hyperthermia, hepatopathy, fasting hypoglycemia, myopathy and dilated cardiomyopathy. Chromosomal analysis was 46,XX, the uterus and ovaries were prepubertal on sonography, and the MRI of the brain was normal. We found the following endocrine abnormalities: hypogonadotrophic hypogonadism, low blood IGF1, cortisol, TBG, and transcortin levels, fasting hypoglycaemia and hyperinsulinism at normoglycaemia. **Review of the literature:** There are only few patient with PGM1-CDG reported in the literature. As our patient, several case reports described abnormal endocrine features such as growth retardation with IGF1 and IGFBP3 around the lower range of normal, low cortisol concentrations and hypoglycaemia. Furthermore, low binding proteins like TBG and transcortin were reported. In difference to other forms of CDG, where hypergonadotrophic hypogonadism is featured, hypogonadotrophic hypogonadism seems to be unique for this disease. **Conclusion:** Endocrine abnormalities appear to be a consistent feature of PGM1-CDG substantially resulting in growth retardation and hypogonadotrophic hypogonadism.

P2-D1-564

46,XY Neonates and Infants with Ambiguous Genitalia: Who to Investigate?

Dorien Baetens^a, Wilhelm Mladenov^{b,c}, Barbara Delle Chiaie^a, An Desloovere^b, Violeta Iotova^c, Bjorn Menten^a, Eric Van Laecke^d, Piet Hoebeke^d, Elfride De Baere^a, Martine Cools^b

^aCenter for Medical Genetics, Ghent University Hospital and Ghent University, Ghent, Belgium; ^bDepartment of Pediatric Endocrinology, Ghent University Hospital and Ghent University, Ghent, Belgium; ^cDepartment of Pediatrics and Medical Genetics, University Hospital 'Sveta Marina', Varna, Bulgaria; ^dDepartment of Pediatric Urology, Ghent University Hospital and Ghent University, Ghent, Belgium

Background: Extensive and time-consuming hormonal and genetic work-up provides a genetic diagnosis in around 20% of 46,XY cases with ambiguous genitalia. It is currently unclear if such extensive screening might also be indicated in 46,XY newborns with milder undervirilization. **Method:** All 46,XY neonates and infants ($n=32$, EMS 2–12) referred to our pediatric endocrine service for atypical male genitalia in the period 2007–2013 were investigated according to a standardized hormonal and genetic protocol after clinical evaluation. This included *AR*, *NR5A1*, and *WT1* sequencing and multiplex ligation-dependent probe amplification (MLPA), array comparative genomic hybridization (array-CGH) in all patients; *HSD17B3* and *SRD5A2* sequencing in cases with suggestive hormonal results and *SRY* sequencing in cases with gonadal dysgenesis. **Results:** In 3/32 patients Kallmann syndrome was diagnosed based on clinical and hormonal data; for two of them the diagnosis was confirmed genetically (*KAL1* deletion, and *FGFR1* mutation). In 4/32 patients endocrine work-up suggested a testosterone biosynthesis disorder, however no mutations were identified in *HSD17B3* or *SRD5A2*. Three novel *NR5A1* mutations were found in non-syndromic patients (3/26, 11%), with EMS scores 2.5, 3, and 9. No *AR* or *WT1* changes were identified. Array-CGH revealed an underlying copy number variation in 2/6 syndromic patients, leading to a diagnostic yield of 33% in this subgroup. **Conclusion:** Overall, a genetic diagnosis was established in 5/26 (19%) non-syndromic and 2/6 (33%) syndromic cases. Our study did not yield a higher diagnostic success rate in patients with low EMS scores compared to higher EMS scores. Our systematic approach could not increase the diagnostic success rate. In view of the time investment, high costs and low success rate of gene by gene screening, whole exome sequencing might be considered instead of serial gene screening, except in syndromic cases, where array-CGH proved to reveal a genetic cause in over one third of cases.

P2-D1-565

Novel NR5A1 Gene Mutations Associated with 46,XY Disorders of Sex Development

Helena Fabbri^{a,b}, Juliana Gabriel Ribeiro de Andrade^{a,c}, Andrea Trevas Maciel-Guerra^{a,c}, Gil Guerra-Junior^{a,c}, Maricilda Palandi de Mello^{a,b}

^aState University of Campinas, Campinas, Brazil; ^bCenter of Molecular Biology and Genetic Engineering (CBMEG), Campinas, Brazil; ^cFaculty of Medical Sciences, Campinas, Brazil

Background: Disorders of sex development (DSD) characterize incomplete or disorganized genital or gonadal development. One in 4500 births requires genetic and endocrine studies due to abnormal external genitalia or gonadal dysgenesis and only 50% of the cases receive a definitive diagnosis. There are several genes that participate in both sex determination and differentiation processes. Mutations in *NR5A1* gene, which encoding SF1, a transcription factor, are responsible for different phenotypes of DSD and can be also associated with hypospadias, anorchia, male infertility, female primary ovarian insufficiency and, in some cases, with adrenal tumors and endometriosis. **Objective and hypotheses:** Evaluate *NR5A1* gene in 66 patients with 46,XY DSD. **Method:** Direct sequencing of the seven exons of *NR5A1* gene, including the promoter region and intron/exon boundaries and 3'UTR was performed. **Results:** The study revealed three novel *NR5A1* gene mutations. Two of them had been identified in patients with 46,XY partial gonadal dysgenesis: p.Lys38* within DNA-binding domain and p.Lys1187Argfs*34 within ligand-binding domain. The third is the p.Leu80Trpfs*8 within DNA-binding domain that was identified in an idiopathic 46,XY DSD case. Both p.Lys38* and p.Leu80Trpfs*8 located in the DNA binding domain of SF1 create a stop codon in the beginning of the protein. Assuming that the mRNA will be degraded by nonsense mRNA decay even before the translation, those mutations certainly are associated with DSD phenotypes. The p.Lys1187Argfs*34, localized within the ligand binding domain of SF1, is a frameshift mutation leading also to a stop codon, however in this case it is located at the end of the protein; for this reason, functional studies will be done to investigate how it influences SF1 transactivation activities. **Conclusion:** Those finds highlights the important role of SF1 in sexual development and demonstrate the significance of *NR5A1* molecular analyzes in cases of patients with disorders of sex development.

P2-D1-566

The Research About sf1 Gene Abnormality in 45 Children with Micropenis

Pin Li^{a,b}, Yan Gong^{a,b}, Ying Zhuzhi^{a,b}

^aShanghai Children's Hospital, Shanghai, China; ^bShanghai Jiaotong University, Shanghai, China

Background: Micropenis are the most common signs of incomplete masculinisation, but do not receive enough attention. The etiology is very complex, including endocrine factors, genetic factors and environmental endocrine disruptors. **Objective and hypotheses:** To explore 45 cases of micropenis children steroidogenesis factor 1 genetic abnormalities and to research the influence of the mutation on sex gland function.

Method: 45 micropenis boys were collected from Endocrinology Department in October 2011 to February 2013 and 50 healthy children as control, and blood DNA was extracted, then PCR amplification products and SF1 gene sequencing were analysed. Sequencing results using sequencer software for sequence alignment. **Results:** That in 45 cases detected 14 cases of mutation, a total of four kinds, including ten cases of mutation for c.437 G>C (p.G146A), the rs code rs1110061. And the H-W population genetic balance test, for *P* values > 0.05, which each genotype between the groups (GG, GC, and CC) and the frequency of allele (G/C) in the distribution between the two groups had no significant statistical difference. The rest mutations were two missense mutation and one synonymous mutation, respectively two cases of c.565C>T (p.P189S) mutation, one case of c.1056G>T (p.Q352H) mutation; one case of is 1062 (G>A). That applied Polyhen and Mutation-Tastor Software to predict c.565C>T (p.P189S) had no obvious effect on protein function, and c.1056G>T (p.Q352H) caused disease and amino acid change. **Conclusion:** SF1 genetic abnormality is an infrequent cause in children with micropenis, only one sample of c.1056G>T (p.Q352H) may be one of the pathogenic mutations in children with micropenis.

P2-D1-567

A New Mutation of MAMLD1 (CXorf6) Associated with NR5A1 (SF1) Variant in a Patient with 46,XY DSD

Asmahane Ladjouze^a, Pascal Philibert^b, Yasmine Ouarezki^c, Adel Djermane^d, Leila Kedji^a, Abdeljalil Maoudja^a, Karima Berkouk^a, Charles Sultan^b, Abdenour Laraba^a

^aDepartment of Pediatrics, CHU Bab El Oued, Algiers, Algeria;

^bDepartment of Hormonology, CHRU Montpellier, Montpellier, France; ^cEPH Gué de constantine, Algiers, Algeria; ^dEPH Gouraya, Gouraya, Algeria

Background: The investigation of patients with 46,XY DSD is often difficult, with no definitive diagnosis in more than 50% of cases investigated. We describe a new mutation of MAMLD1 in a patient with 46,XY DSD who also showed an alteration in the NR5A1 gene. **Case report:** A 5-year-old boy was referred to our clinic for DSD. He was born to non-consanguineous parents and was diagnosed with ambiguous genitalia at birth but had not been previously investigated. Examination showed undescended testes, peno-scrotal hypospadias and microphallus (3 cm). Investigations showed 46,XY karyotype; basal testosterone 0.11 nmol/l with an impaired response to hCG stimulation (peak: 0.5 nmol/l after 1500 UI×6 (every 2 days); basal FSH and LH 1.76 and <0.001 mUI/ml respectively; AMH low at 85.8 pmol/l. No testes could be seen on pelvic ultrasound but genitogram showed the presence of a Mullerian duct remnant connected to the bulbar urethra. At laparoscopic surgery two small testes were found. After three i.m. injections of Testosterone Enanthate 50 mg penile length increased from 3 to 5 cm. Orchidopexy and surgical correction of the hypospadias have

been performed. **Molecular studies:** Analysis of the NR5A1 (SF1) gene revealed the presence the variant p.Gly146A1a. Mutation analysis of MAMLD1 (CXorf6) showed a heterozygous mutation of MAMLD1 (c.1868G>A/p.Arg623His). **Discussion:** Mutations of MAMLD1 have been recently described in patients with complex 46,XY DSD including micropenis, cryptorchidism and peno-scrotal hypospadias. We describe a new heterozygous MAMLD1 (CXorf6) mutation causing 46, XY DSD with partial gonadal dysgenesis. Moreover, our patient presented a variant in the SF1 gene which has been reported more frequently in patients with cryptorchidism and microphallus. It is possible that the two gene alterations have had a digenic effect, with the MAMLD1 having a predominant effect on Leydig cell function while the SF1 variant has contributed to impaired Sertoli cell function.

P2-D1-568

46XY, DSD due to 5 α -Reductase Type 2 Deficiency in 19 Chinese Patients

Yan-Hong Li, Min-Lian Du, Hua-Mei Ma, Hong-Shan Chen, Qiu-Li Chen

Pediatric Department, The First Affiliated Hospital of Sun Yat-Sen University, GuangZhou, China

Background: Patients with 46,XY, DSD are characterized by ambiguous or female external genitalia, caused by incomplete intrauterine masculinization. 5 α -reductase type 2 deficiency due to SRD5A2 gene mutations result in inadequate conversion from testosterone to dihydrotestosterone (DHT), and is responsible for incomplete virilization in male patients. Up to date, more than 50 mutations have been reported, however, clinical features are variable and heterogeneous. **Objective and hypotheses:** The study was performed to report the clinical and genetic analysis of SRD5A2 deficiency, in order to help to build up the clinical management of these patients. **Methods:** From 2008 to 2013, 19 cases from 18 irrelevant families who had variable degree of incomplete virilization but normal male karyotype were confirmed as SRD5A2 deficiency according to the gene analysis. Phenotype and genotype, as well as the response to DHT gel management were studied. **Results:** i) 4 (21%) had ambiguous external genitalia, pseudovagina, bilateral testes palpable in inguinal canal. 2 (10%) had micropenis and severe hypospadias, bifid scrotum. 7 (37%) micropenis and mild to moderate hypospadias. 6 (32%) had isolated microphallus. ii) T/DHT ratio at basal line and after human chorionic gonadotropin (HCG) stimulation test was 22.79 (17.08, 28.27), and 67.23 (27.56, 128.56) respectively. iii) Direct sequencing analysis revealed five types of mutations in these patients. One was novel heterozygous mutation and the others were previous reported. 27% mutations were in exon 1, 73% mutations were in exon 4. iv) Almost all patients were raised as males, except one. v) Penis length, as well as penis diameter increased after 2.5% DHT gel (Andractin) transdermal management (12 mg (0.3 mg)/kg per day), except one case. **Conclusion:** Clinical presentation of SRD5A2 deficiency is extremely variable. No relationships are found between the degree of incomplete virilization, T/DHT ratio and genotypes. DHT gel can improve penile size and can be preparation before surgery.

P2-D1-569

Experience of Feminizing Operations in Cases of Incomplete Sexual Development of Girls

Alena Shybeka, Hanna Milkhno, Herman Druzhyenin, Vitali Dubrov, Anzhalka Solntsava, Izaokas Skobejus

2nd City Children's clinical Hospital, Minsk, Belarus

Background: Surgical correction of the external genitalia of girls with incomplete sexual development remains an urgent problem reconstructive urology. It is connected with a relative rare pathology, the need to achieve a good cosmetic and functional result. **Objective and hypotheses:** In this paper, we present our approach and experience in the surgical treatment of girls born with congenital malformations of sexual organs. **Method:** Between 2005 and 2013, we operated on 41 patients (4.8 ± 0.5 years). Diagnoses included 33 cases of congenital adrenal hyperplasia; six cases of gonadal dysgenesis; one true hermaphroditism; one anogenital cleft. We determined the genetic, gonadal, phenotypic, and hormonal status of these patients. Treatment was carried out in conjunction with a pediatric endocrinologist and, if necessary, hormonal therapy. To determine the level of interconnection of urinary and reproductive tract, cystoscopy was performed before each operation. When connecting the urinary and genital tract above the urogenital diaphragm (high urogenital sinus) only clitoroplasty was performed (29 patients, 5.5 ± 0.8 years), with a low urogenital sinus – single-step clitorovaginoplasty (12 patients, 3.3 ± 0.4 years). **Results:** The observation of patients ranged from 1 to 8 years. All the girls are satisfied with the result of the external genitalia. But children who underwent only clitoroplasty be the second phase of the operation to form the entrance to the vagina. Among patients who underwent one-stage clitorovaginoplasty positive result was achieved in ten cases (83.3%). In two cases (16.7%) diagnosed with stenosis of the vagina. In 2012 two patients postoperatively used Estriol (in candlelight or ointments) within a week after surgery. These patients were observed for a year, during which a narrowing of the vestibule was not observed. **Conclusion:** Differentiated approach to feminizing operations in young children, depending on the level of merger urethra and vagina what improves the cosmetic result, and facilitates a normal mental status and early social adaptation.

P2-D1-570

Four Cases of Isolated Partial Gonadal Dysgenesis due to NR0B1 (DAX1) Locus Duplication Inherited in a Large Family

Kathy Wagner Mahler, Caroline Devos, Jean Yves Kurzenne, Frédérique Gastaud, Marie Hoflack, Delphine Mallet, Houda Karmous Benailly, Fabienne Giuliano, Gilbert Simonin, Damien Sanlaville, Yves Morel

HPN CHU Lenval, Nice, France

Background: Isolated gonadal dysgenesis due to NR0B1 locus duplication is a rare cause of 46,XY DSD. Almost reported cases were a total gonadal dysgenesis with complete female phenotype and streak gonad diagnosed late because of absent of pubertal development and primary amenorrhea. Only two unrelated cases of isolated partial gonadal dysgenesis with molecular characterization have been reported. The risk of gonadoblastoma is high. **Family case reports:** All four cases (II.4, V.1, V.8, and V.I2) have a 46,XY DSD with external ambiguous genital (variable partial labial fusion, one urogenital orifice, and undervirilized tubercle). The age of diagnosis were 14 years (II.4), 11 years (V1), and antenatal (V.8, and VI.2) period. The absence of uterus and Mullerian structure was observed and suggest functional Sertoli cells in antenatal sex differentiation period. The sex rearing differs: II.4 was reared as girl but changed as boy at puberty (14 years old) and deceased at 70 years old; V.1 and V.8 reared as girl; VI.2 reared as boy after a collegiate decision (parents, medical, surgical, and psychologist professionals). Biological data in neonatal period of V.8 and VI.2 cases have confirmed the diagnosis of partial gonadal dysgenesis with low but detectable AMH, normal testosterone response to hCG test. Bilateral gonadectomy has been done in patients V.1 and V.8. At 13 months, gonads (V.8) were hypoplastic and showed subnormal testicular structure with abundant seminiferous tubules but few germinal cells. AMH was highly positive in Sertoli cells, at 11 years the gonads (V.1) were more dysplastic. **Molecular studies:** No mutation has been found in AR gene and several other genes (SF1, ...). This duplication of the NR0B1 gene detected by MLPA and bordered by CGH array was about of 452 kb including NR0B1 and four MAGEB genes, but not CXorf21 and GK genes. **Conclusion:** The explanation of the isolated partial gonadal dysgenesis vs. pure gonadal dysgenesis with high risk of gonadoblastoma could be the location and the extend of this NR0B1 duplication. These data suggest the screening of this duplication in all cases of partial 46,XY gonadal dysgenesis.

P2-D1-571

Identification of a Missense MAP3K1 Mutation in a Patient with Hypospadias

Maki Igarashi^a, Reiko Horikawa^b, Kazuhiko Nakabayashi^c, Kenichirou Hata^c, Tsutomu Ogata^{a,d}, Maki Fukami^a

^aDepartment of Molecular Endocrinology, National Research Institute for Child Health and Development, Tokyo, Japan;

^bDivision of Endocrinology and Metabolism, National Center for

Child Health and Development, Tokyo, Japan; ^cDepartment of

Maternal-Fetal Biology, National Research Institute for Child Health

and Development, Tokyo, Japan; ^dDepartment of Pediatrics,

Hamamatsu University School of Medicine, Hamamatsu, Japan

Background: Recently, eight MAP3K1 mutations have been identified in patients with 46,XY disorder of sex development (DSD), although detailed clinical findings of the mutation-positive

patients remain to be investigated. **Objective and hypotheses:** To clarify the frequency and clinical consequences of *MAP3K1* mutations. **Method:** Mutation screening of *MAP3K1* were performed for 37 patients with 46,XY DSD. Phenotypic analysis was performed for a patient with a *MAP3K1* variant. **Results:** We identified a heterozygous nucleotide change (c.745C>T, p.R249C) in a patient. He had no mutations in other 46,XY DSD-causative genes including *AR*, *DMRT1*, *NR5A1*, *SOX9*, *SRD5A2*, and *SRY*. Sequence analysis of the parental samples indicated maternal origin of the *MAP3K1* variant. The p.R249C variant has previously been submitted to the 1000 genome database as a rare polymorphism (rs200234617, allele frequency: 0.001, detected only in a female). The arginine residue at the 249th codon is conserved among species. *In silico* analysis using PolyPhen-2 and SIFT revealed that p.R249C is a probably damaging mutation. Salient clinical features of the patient were hypospadias and bifid scrotum. He had normal penile length (2.5 cm) and testicular volumes (1 ml). Abdominal ultrasound analysis detected no abnormalities. GnRH stimulation test revealed slightly elevated gonadotropin levels, and hCG stimulation test showed normal levels of testosterone. **Conclusion:** The results indicate a possible association between the p.R249C variant and hypospadias, together with the rarity of *MAP3K1* mutations in patients with 46,XY DSD. Endocrine data of the patient suggest that *MAP3K1* mutations permit apparently normal testicular function after birth.

P2-D1-572

Anogenital Distance, Penis Growth, and Masculine Behaviour Evidence for Independent Neurobehavioral Effects of Foetal Versus Postnatal Androgen Exposure in Boys

Vickie Pasterski^a, Carlo Acerini^a, David Dunger^a, Ken Ong^b, Ieuan Hughes^a, Ajay Thankamony^a, Melissa Hines^a

^aUniversity of Cambridge, Cambridge, UK; ^bAddenbrooke's Hospital & NHS Trust, Cambridge, UK

Background: Associations between foetal androgen deficiency and variations in anogenital distance (AGD) suggest that AGD is a reliable indicator of foetal androgen exposure. Similarly, variation in postnatal penis growth associated with variations in testosterone show penis growth to be a potential biomarker of early postnatal androgen exposure. Though variation in early androgen exposure is also hypothesized to underlie neurobehavioral masculinisation, until now, no reports have linked either biomarker to human sex-related behaviour. **Objective and hypotheses:** To investigate the potential utility of employing biomarkers of foetal and neonatal testosterone exposure as predictors of neurobehavioral masculinisation. We hypothesized that birth AGD and early neonatal penis growth would each contribute unique variance in explaining male-typical behaviour in boys. **Method:** As part of a large birth cohort study, measurements of AGD, penis length, and body length were taken in typically-developing boys at birth and at 3, 12, 18, and 24 months postnatally. Behaviour was measured in 81 boys (mean age 3.88 years, s.d. 0.55) using the Preschool

Activities Inventory (PSAI), a reliable and validated measure of sex-typed behaviour in children. Multiple regression was used for analysis. **Results:** Measurements suggested typical childhood development. Also, as predicted, the overall model was significant ($R^2=0.23$, $P\leq 0.01$) and birth AGD ($\beta=0.240$, $P<0.05$) and penis growth from birth to 3 months ($\beta=0.481$, $P\leq 0.001$) accounted for significant unique variance in PSAI scores, when controlling for penis length at birth, subsequent penis growth to 24 months, and body growth to 12 months. **Conclusion:** AGD and penis growth may provide a readily available methodology for assessing independent exposures to foetal and neonatal testosterone in boys. Findings also provide the first evidence of the importance of the postnatal testicular surge, independent of androgen exposure prenatally, in human neurobehavioral masculinisation.

P2-D1-573

Mutation Analysis of *kdm3a* (Lysine-Specific Demethylase 3a) in Patients with Hypospadias

Masafumi Kon^{a,d}, Maki Igarashi^a, Yoko Izumi^a, Yuko Kato-Fukui^a, Kentaro Mizuno^b, Yutaro Hayashi^b, Kenjiro Kohri^b, Yoshiyuki Kojima^c, Katsuya Nonomura^d, Tsutomu Ogata^{a,e}, Maki Fukami^a

^aDepartment of Molecular Endocrinology, National Research Institute for Child Health and Development, Tokyo, Japan;

^bDepartment of Nephro-Urology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan; ^cDepartment of Urology, Fukushima Medical University School of Medicine, Fukushima, Japan; ^dDepartment of Renal and Genitourinary Surgery, Hokkaido University Graduate School of Medicine, Sapporo, Japan;

^eDepartment of Pediatrics, Hamamatsu University School of Medicine, Hamamatsu, Japan

Background: Hypospadias is a relatively common form of 46,XY disorders of sex development. Although several genes have been implicated in the development of hypospadias, molecular basis of the majority of cases remain unknown. Recently, targeted disruption of lysine-specific demethylase 3A (KDM3A) were shown to cause defective sex development in male mice. **Objective and hypotheses:** The aim of this study was to clarify whether KDM3A mutations underlie hypospadias in human. **Method:** We performed mutation screening of KDM3A in 66 patients with hypospadias. The functional consequences of nucleotide changes were assessed by *in silico* assays. **Results:** We identified a heterozygous nucleotide change in KDM3A (p.D201H, c.601G>C) in a patient. The nucleotide change was assessed as 'probably damaging' by PolyPhen2 and 'damaging' by SIFT. The p.D201H variant was hitherto unreported. The patient manifested penoscrotal hypospadias and right vesicourethral reflux without micropenis or undescended testis. Endocrine evaluation at one year of age showed normal levels of testosterone, LH, and FSH. **Conclusion:** The results indicate that sequence alterations in KDM3A may constitute a rare etiology of hypospadias in human

P2-D2-574

Analysis of Steroid 5-Alpha Reductase 2 (SRD5A2) Gene in Patients with 46,XY Disorder of Sex Development

Giselle Neres de Souza, Aline Zamboni Machado, Ivo Jorge Prado Arnhold, Berenice Mendonca, Maria Helena Palma Sircili, Mirian Yumie Nishi, Rosana Barbosa Silva, Elaine Maria Frade Costa, Sorahia Domenice

Unidade de endocrinologia do desenvolvimento, LIM/42, FMUSP, Sao Paulo, Brazil

Background: The diagnosis of 46,XY disorder of sex development (DSD) due to 5-alpha reductase 2 (5α -RD2) deficiency has been based on testosterone: dihydrotestosterone (T:DHT) ratio, urinary steroid profiling and mutational analysis of SRD5A2 gene. The biochemical hallmarks of 5α -RD2 deficiency include increased T:DHT ratio. However, several difficulties are observed in the DHT measurement leading to misdiagnosis. The mutational analysis of the SRD5A2 has been proposed as the first line test in the investigation of 5α -RD2 deficiency. **Objective:** To screen SRD5A2 for mutation in 21 patients divided in two groups: group 1: six patients with known T:DHT ratio (range from 11 to 129) and group 2: 15 referred patients without T:DHT ratio, 13 of them previously orchiectomized. **Methodology:** PCR was used to amplify the SRD5A2 followed by sequencing. The variants were analyzed by PolyPhen and SIFT prediction websites. SRD5A2 CNVs was evaluated by MLPA technique. **Results:** In group I, four allelic variants were identified in homozygous state, two novel variants, p.Trp140Glnfs*19 and p.Gly123Val, both predict as potentially damage. The variant p.Trp140Glnfs*19 was found in two unrelated patients with T:DHT ratio of 11 and 43. The patient homozygous for p.Gly123Val mutation had T:DHT ratio of 24. The p.Arg227* and p.Gln126Arg mutations were found in two patients with T/DHT ratio of 46 and 129. In another patient with T:DHT ratio of 39, the heterozygous variants, p.Val89Leu (damage) and p.Asp164Val (benign) were identified. SRD5A2 CNV was not identified in this patient. From group 2, one patient, previously gonadectomized, is homozygous for p.Gly183Ser mutation. **Conclusion:** SRD5A2 sequencing identified mutations or potential deleterious allelic variants in 100% of patients with hormonal profile of 5α -RD2 deficiency and in two patients with normal or unavailable T:DHT ratio. Sequencing of SRD5A2 is a fast and effortless technique and should be used as the preferable approach for the diagnosis of 46,XY DSD due to 5α -RD2 deficiency.

P2-D2-575

AMH Levels in Pediatric Girls with Chronic Disease

Chelsey Grimby^a, Connie Prosser^b

^aDepartment of Pediatrics, University of Alberta, Edmonton, Alberta, Canada; ^bDepartment of Laboratory Medicine, University of Alberta, Edmonton, Alberta, Canada

Background: Anti-Mullerian Hormone (AMH) is becoming a useful marker for ovarian function and prospective fertility. It is known to reflect ovarian reserve and response to ovarian stimulation in aided reproductive protocols. Levels are decreased in adults with chronic medical conditions such as Crohn's disease and Turner's Syndrome and in survivors of childhood cancers. AMH levels are increased in polycystic ovarian syndrome as a reflection of increased numbers of antral follicles and may be a more sensitive diagnostic marker than ultrasound. **Objective and hypothesis:** This study investigates the effect of chronic illness on the reproductive development of pediatric girls. AMH levels are compared to those observed in healthy girls where there is an increase in serum AMH associated with puberty. **Methods:** A convenience sample of pediatric female patients was used. This included healthy subjects who had screening bloodwork, and subjects from various medical clinics. A biotinylated sandwich ELISA method was used (Beckman & Coulter Gen II) which has previously been validated in the pediatric population by multiple sources. **Results:** AMH levels remained low in all groups of chronic medical conditions including gastroenterology, cardiac, metabolic, oncologic, and solid organ transplant patients. The control patients demonstrated the expected rise in AMH at 6-8 years of age. **Conclusion:** Pediatric females with chronic medical conditions had a trend towards lower AMH levels. This may reflect impaired pubertal progression or reproductive potential. A larger sample size and sequential sampling is needed to determine if development is delayed or permanently impaired and if there is a correlation to severity of disease.

P2-D2-576

The Utility of AMH for Predicting Testosterone Response to hCG Stimulation in Children with Suspected DSD

Andreas Kyriakou^a, Jane D McNeilly^b, Guftar M Shaikh^a, Avril Mason^a, David Shapiro^c, Syed Faisal Ahmed^a

^aDevelopmental Endocrine Research Group, University of Glasgow, Glasgow, UK; ^bDepartment of Biochemistry, RHSC, Glasgow, UK; ^cDepartment of Biochemistry, Glasgow Royal Infirmary, Glasgow, UK

Background: In children undergoing investigation of testicular function the relationship between serum anti-Mullerian hormone (AMH) and the testosterone response to hCG stimulation test (HST) is unclear. **Method:** 75 children (3F, 72M) with a median age of 1.08 years (range, 0.003, 14.3) were investigated for suspected DSD by AMH on D1 and testosterone on D1 and D4, before and after 3-day HST. Of these children, 27 had an additional prolonged HST. Normal testosterone response to HST was defined as a T > upper prepubertal limit or a testosterone increment (Δ T) > twice the baseline value. A low AMH was defined as below the 5th centile for age. **Results:** The D4 testosterone response was normal in 63 with a median testosterone of 9.4 nmol/l (1.0, 40.7) and a median Δ T of 10.0 (0.8, 59.2) and abnormal in 12 with a median testosterone of 0.55 nmol/l (0.5, 3.0) and a median Δ T of 1.0 (0.7, 1.8). AMH was

low in 16/75 children and in 8 (50%) of these cases a low D4T was observed. An AMH > 5th centile was associated with a low D4T in only 4/59 cases (7%; $P < 0.0001$, ppv 93%). Median AMH in the two groups of patients who responded and did not respond by D4 was 734 pmol/l (97, 1926) and 93.6 pmol/l (0.4, 256; $P < 0.0001$). The testosterone response after prolonged HST was normal in 23/27 children with a median testosterone of 1.3.5 nmol/l (0.8, 43.4) and a median ΔT of 18.2 (0.57, 62.0) and abnormal in 4 with a median testosterone of 0.55 nmol/l (0.5, 1.0) and a median ΔT of 1.0 (0.6, 1.2). AMH was low in seven children and in 3 (37.5%) of these cases a low D22 testosterone was observed. An AMH > 5th centile was associated with a normal D22 testosterone in 19/20 cases (95%) ($P < 0.0001$, ppv 95%). Median AMH in children who responded and did not respond at D4 and D22 was 420 pmol/l (100, 1664) and 2.8 pmol/l (1.5, 214; $P < 0.0001$). **Conclusion:** A normal AMH may provide valuable information on overall testicular function. However, a low AMH does not necessarily predict a sub-optimal testosterone response to hCG stimulation.

P2-D2-577

A Novel Cyp19a1 Gene Mutation Identified in Three Turkish Families

Sema Akcurin^a, Erdem Durmaz^b, Woo-Young Kim^c, Doga Turkkahraman^d, Joe-Gook Shin^c, Su-Jun Lee^c

^aDepartment of Pediatric Endocrinology, Akdeniz University, Antalya, Turkey; ^bDepartment of Pediatric Endocrinology, Mersin State Hospital, Mersin, Turkey; ^cDepartment of Pharmacology, Inje University College of Medicine, Busan, Republic of Korea; ^dDepartment of Pediatric Endocrinology, Antalya Education and Research Hospital, Antalya, Turkey

The CYP19A1 gene product cP450aromatase enzyme is responsible for estrogen synthesis and androgen/estrogen equilibrium in many tissues; placenta and gonads are being the leading tissues. cP450aromatase deficiency has important effects on clinical phenotype due to excessive amount of androgen accumulation and insufficient estrogen synthesis in the pre- and postnatal periods. We identified a new point mutation in the CYP19A1 gene causing aromatase deficiency in three Turkish families. Here, we report three cousins carrying this mutation. Three cases with the current chronological ages of 12.3 (case I), 5 (case II) and 2 (case III) years applied to Pediatric Endocrinology Department because of ambiguous genital structures in the newborn period. Virilizing signs such as severe acne formation, voice deepening and clitoral enlargement during pregnancy were defined in the maternal history and physical examination. CYP19A1 gene analysis was performed with the preliminary diagnosis of cP450arom deficiency in three cases, and five parents, who were cousins. It was observed that 568insC mutation detected at the fifth exon, caused 'codon stop', so a nonfunctional product with 200 amino acids without the 'heme region', which was the requirement for the enzymatic activity, was formed, and the cases

were homozygote for this newly defined mutation whereas parents were heterozygote. During their follow ups, ovarian dimensions and LH, FSH, testosterone, and estradiol measurements of cases I and II were detected at the prepubertal levels. In the case III, ovaries could not be shown by neither ultrasonography nor MRI, and hormonal data were consistent with the age. Aromatase deficiency is a very rare autosomal recessive disorder there are only a limited number of case reports in the literature. The mutation detected in three Turkish families was a novel mutation. Concomitance of maternal virilization is the most important striking signal for aromatase deficiency in a virilized female baby.

P2-D2-578

46,XX Ovotesticular DSD: Is it Lawful to Wait for Gonadal Surgery?

Claire Bouvattier^{a,b}, Ariane Cuny^a, Sylvie Beaudoin^{c,d}, Frédéric Bargy^{c,d}

^aAssistance Publique des Hôpitaux de Paris – Hôpital Bicêtre-Service d'Endocrinologie et Diabétologie Pédiatrique Centre de Référence des Anomalies du Développement Sexuel, Le Kremlin-Bicêtre, France; ^bUniversity Paris Sud – faculté de Médecine Paris Sud, Le Kremlin-Bicêtre, France; ^cAssistance Publique des Hôpitaux de Paris – Hôpital Necker-Enfants Malades- Service de Chirurgie Viscérale Pédiatrique Centre de Référence des Anomalies du Développement Sexuel, Le Kremlin-Bicêtre, France; ^dUniversité Paris Descartes, Paris, France

Background: Ovotesticular disorder of sex development (DSD) is characterized by the presence of both testicular and ovarian tissue in the gonads of an individual. Selective gonadal surgery is usually performed in infancy. **Objective and hypotheses:** Little is known about the long-term outcome of conservative gonadal surgery in ovotesticular DSD. We present our experience in a 46,XX girl diagnosed in the neonatal period. **Method:** The patient was evaluated at 2 months of life with for a 2 cm clitoris above a single opening. Blood karyotype was 46,XX. Serum anti-Mullerian hormone (AMH) concentration was 150 pmol/l (normal range 2–40) and serum testosterone concentration was 0.7 ng/ml (normal range 0.04–0.4). At 20 months, on laparoscopy, a small uterus was noticed with, on the right a fallopian tube adjacent to an oblong gonad 'ovarian like' and, on the left, a fallopian tube adjacent to a second gonadal structure. Right biopsy revealed ovarian tissue, with normal ovarian stroma and oocytes. Two left biopsies revealed coexistence of testicular tissue with normal-appearing seminiferous tubules and ovarian tissue with oocytes. The girl underwent vaginoplasty, but no gonadal surgery. **Results:** Serum AMH and testosterone concentrations were followed. The girl had a spontaneous puberty with breast development at 11 and menarche at 13 years old with regular menstruations. At 14 years, her clitoris measured 1 × 0.8 cm. Pelvic MRI shown a 55 mm pubertal uterus. The right ovary measured 35 × 16 mm with multiple follicles. The left gonad is heterogeneous, measured 19 × 16 mm, and showed multiple

follicles below a parenchymal structure measuring 15×8 mm. Serum AMH concentration is 18 pmol/l (normal range 5–60) and serum testosterone is 0.18 ng/ml (normal <0.8). **Conclusion:** Conservative gonadal surgery could be proposed in 46,XX ovotesticular DSD, while serum AMH allows the monitoring of the testicular tissue. In our patient, it seems that the ovarian tissue remained functional and that testicular tissue regressed, allowing spontaneous puberty. Long-term follow-up remains essential regarding the gonadal tumoral risk.

P2-D2-579

Mosaicism: Study of Nine Patients

Laura Mazzanti^a, Federico Baronio^a, Rita Ortolano^b, Emanuela Scarano^a, Federica Tamburrino^a, Angela Colangiulo^a, Ilaria Bettocchi^a, Alessandra Cassio^a, Antonio Balsamo^a

^aDepartment of Medical and Surgical Sciences, Pediatric Unit, Program of Endocrinology, University of Bologna and S.Orsola-Malpighi Hospital, Bologna, Italy; ^bDepartment of Sciences for health promotion, mother and child care “Giuseppe D’Alessandro”, University of Palermo, Palermo, Italy

Background: The isodicentric Y (idic Y) is one of the most common aberrations of the Y chromosome. Most patients (pts) are chromosomal mosaics, including 45,X cell line. **Objective and hypotheses:** Our aim is to describe clinical and molecular features of our 45,X/46,Xidic(Y) cases. **Method:** We retrospectively evaluate the clinical description of nine cases (six females, one male, two with ambiguous genitalia) with mosaic karyotype 45,X/46,Xidic(Y) referred to our Centre in the last 23 years. **Results:** Main clinical features were: Turner stigmata (eight pts), delayed or incomplete pubertal development in six females (F), short stature (eight pts), malformations in 7/9 (congenital heart disease, horseshoe kidney). The two pts with ambiguous genitalia (AG) both have hypospadias, unilateral cryptorchidism and undervirilization; 2/6 F showed clitoral hypertrophy. Seven pts showed Mullerian remnants (6 F and 1 AG), wolffian structures (2 F) and urogenital sinus (1 AG). 6/9 pts (4 F, 2 AG) underwent gonadectomy to reduce the risk of gonadoblastoma. Gonads' histology: streaks in 3/4 F, dysgenetic testis in the M, mixed gonadal dysgenesis (1 AG, 1 F), atrophic testis (other AG). In 3/6 subjects, we obtained karyotype from gonads. The pts with Turner stigmata, short stature and the other malformations showed a predominance of peripheral 45,X cell line, that also predominates on the streak gonads. On dysgenetic testis we found higher % of 46,Xidic(Y) cell line. In 1/4 F, we found difference between blood and gonads percentage of 45,X: >93% 45,X cells in gonads vs 40% in blood. **Conclusion:** Our data seems to confirm that phenotypic variability and sexual differentiation of these cases are explained by the degree of mosaicism, particularly in gonads. To improve the genotype/phenotype correlation is useful to analyze more than one tissue and to perform histological and karyotype studies of the gonads when it is possible.

P2-D2-580

The V89L Polymorphism in the SRD5A2 Gene in Cases with Undescended Testis

Elif Yesilada, Aysehan Akinci, Gonca Gulbay, Sengul Yuksel, Serap Savaci

Inonu University, Malatya, Turkey

Background: Steroid 5 α -reductase catalyzes the conversion of testosterone into the more active androgen, dihydrotestosterone (DHT). In 46, XY patients with recessive mutations in steroid 5 α -reductase type 2 enzyme (SRD5A2) gene, the degree of ambiguity ranges from isolated hypospadias to severe undermasculinization. SRD5A2 gene is located on chromosome 2 (p23 region) and is comprised of five exons and four introns. **Objective and hypotheses:** Multiple mutations distributed throughout the coding region of the SRD5A2 gene have been identified in patients with steroid 5 α -reductase type 2 enzyme deficiency. We studied the SRD5A2 gene mutation in 23 patients with undescended testis. **Method:** Patients were evaluated by HCG stimulated T:DHT ratio (>10). Peripheral blood samples were collected from the subjects and genomic DNA was isolated. SRD5A2 gene was amplified by polymerase chain reaction using different sets of primers and reaction conditions specific for the 5 exon of SRD5A2 gene. DNA sequencing was carried out using a ABI-Prism automated DNA sequencer. DNA sequencing of the SRD5A2 gene reautomated DNA sequencer. **Results:** Exons 2–5 of the SRD5A2 gene were normal in 23 cases. DNA sequencing of the SRD5A2 gene revealed that the rare allele (leucine) of the V89L polymorphism in exon 1 was over represented in seven patients. **Conclusion:** We detected three boys being homozygous for the leucine allele, four were heterozygous. This corresponds to an allele frequency of 0.78 for the valine allele and 0.22 for the leucine allele.

P2-D2-581

Rare Disease Registries: Perception of Parents and Young People

Arundathi Jayasena, Miriam Muscarella, Faisal Ahmed

Developmental Endocrinology Research Group, School of Medicine, University of Glasgow, Yorkhill, Glasgow G3 8SJ, UK

Background: Rare-disease registries are considered to be the key for improving patient care through research and audit. In the field of paediatric endocrinology, the views of parents and affected young people about such registries are unclear. **Objective:** To conduct a survey to understand the views of parents and young people with rare conditions. **Method:** A structured questionnaire was completed by two groups of clinic attendees, those who were participating in the I-DSD Registry (www.i-dsd.org) and those who had a rare condition other than DSD. I-DSD participants were also asked about their recollection of the information sheet

received and non-IDSD participants were provided with generic rare disease registry information. **Results:** Of 28 people approached, 25(89%) completed the questionnaire. The DSD and non-DSD groups comprised of 11 and 14 participants respectively. Each group included one young person. 7/11(64%) participants had already joined the I-DSD registry, all had received the information sheet and found it informative. None of the non-DSD group had joined a registry, but 9/14(64%) found the information sheet informative. There were no differences between the responses from the DSD and the non-DSD participants. All agreed that the registry's goal was to improve care and that the Internet was the best medium to access information. More than 90% of the respondents wanted to use the registry to access information regarding diagnosis, surgery, investigations, genetics and medication. 23/25(92%) respondents agreed that accessing information regarding the tools for talking about the condition with others and the child, parenting strategies, connecting with support organizations would be useful. Of 25 respondents, one stated concerns of security. **Conclusion:** Parents of children with rare conditions generally have a positive outlook on Internet-based rare-disease registries and are keen to use such resources for more information.

P2-D2-582

Down Syndrome and Disorders of Sex Development: Only Coincidence or More?

Joyce Pupo, Tiago Jeronimo dos Santos, Leandra Steinmetz, Louise Cominato, Thais Della Manna, Hamilton Menezes Filho, Hilton Kuperman, Vaê Dichtchekenian, Nuvarte Setian, Durval Damiani

Instituto da Criança, HCFMUSP, São Paulo, SP, Brazil

Introduction: Down syndrome (DS) is a common condition and its association with disorders of sex development (DSD) is quite rare. **Case report:** We report four DS patients with DSD. Patient 1: 22 days old, undefined sex. 2.5 cm phallus, non-palpable gonads, and perineal urethra. Testosterone = 332 ng/dl (at 1 mo), uterus on ultrasound, 47,XY + 21 karyotype. A gonadoblastoma on the left gonad and a streak on the right. Dx - DSD Mixed Gonadal Dysgenesis. Patient 2: 7.1 year-old, male. 3 cm phallus, non-palpable gonads, proximal hypospadias. No response of testosterone under hCG. 46,XY + t(21q 21q) karyotype. Dx - DSD dysgenetic. Patient 3: 1.1 year-old, male. 47,XX + 21 karyotype. Testosterone = 250.5 ng/dl under hCG, no müllerian remnants, SRY +. Histology - bilateral testes. Dx - DSD testicular. Patient 4: 5.1 year-old, male. 1 cm phallus, palpable gonads, topic urethra. No T response to hCG. 47,XY qh + 21 karyotype. Dx - DSD disgenetic. **Conclusion:** Although uncommon, DS patients may present DSD and it is important not to miss these cases, since it will change the future approach with regard of rearing sex.

P2-D2-583

Novel Mutation in a Newborn with a Rare Cause of 46,XY Sex Reversal: 17 β - Hydroxysteroid Dehydrogenase Type 3 Deficiency

Korcan Demir, Melek Yildiz, Özlem Nalbantoglu Elmas, Hüseyin Anil Korkmaz, Behzat Özkan

Division of Pediatric Endocrinology, Dr. Behçet Uz Children's Hospital, Izmir, Turkey

Background: 17 β -Hydroxysteroid dehydrogenase type 3 (17 β -HSD3) deficiency is a rare cause of 46,XY sex reversal due to a defect in conversion of androstenedione to testosterone. It is autosomal recessively inherited and caused by mutations in 17HSD3. **Objective and hypotheses:** To define clinical and laboratory characteristics of 17 β -HSD3 deficiency during neonatal period. **Method:** An 8-day-old newborn with female external genitalia was admitted to hospital due to bilateral inguinal swelling. She was born to first degree consanguineous parents with a birth weight of 3300 g after an uneventful term pregnancy. Physical examination revealed a weight of 3.48 kg (SDs +0.17), height 47 cm (SDs -0.98), head circumference 35 cm (SDs +0.18), normal vital signs and blood pressure. Genital examination disclosed female phenotype with normal clitoral size, vaginal and urethral openings, and palpable gonads in the inguinal region. Laboratory studies showed normal biochemistry, normal adrenal steroids, low gonadotropin levels, no uterus and ovary in abdomen but testis and epididymis tissue at inguinal area on ultrasound imaging and a 46,XY karyotype. At first month gonadotropin and testosterone levels were still low. **Results:** Genetic analyses of 5 α -reductase and androgen receptor genes were negative. After hCG stimulation, total testosterone raised to 26.7 ng/dl with a 10-fold increase, normal testosterone:dihydrotestosterone ratio (2), and low testosterone:androstenedione ratio (0.22), leading to the diagnosis of 17 β -HSD3 deficiency. Mutation analysis of 17HSD3 gene revealed a novel and possibly pathogenic mutation: c.464A>C. **Conclusion:** 17 β -HSD3 deficiency should be kept in mind particularly in differential diagnosis of androgen insensitivity syndrome, therefore virilization during adolescence can be avoided. Determination of mutation in 17HSD3 is beneficial for future pregnancies as well.

P2-D1-584

Treatment of Pediatric Graves' Disease: Results of a Multicenter Survey in Portugal

Olinda Marques^a, Maria João Oliveira^b, Ana Antunes Antunes^c, Filipa Espada^d, Joana Guimarães^e

^aHospital de Braga, Braga, Portugal; ^bCHVNGE, Vila Nova Gaia, Portugal; ^cHospital de Braga, Braga, Portugal; ^dULSM, Matosinhos, Portugal; ^eCHBV, Aveiro, Portugal

Background: In 2011, ATA and AACE published Guidelines on pediatric Graves' disease (GD) treatment. Nevertheless it is still

a controversy. **Objective and hypotheses:** SPEDP conducted the first nationwide questionnaire survey among all the Endocrinologists and Pediatricians in the Portuguese Public Health System Hospitals about pediatric GD treatment in order to know the reality in our country. **Method:** SPEDP designed and distributed a questionnaire to all hospitals with pediatric endocrinology, to include all GD patients under 18 at diagnosis, and a minimum of 6 months follow-up, and a retrospective assessment of patients' records was performed from May to August 2013. **Results:** 67 out of 87 hospitals answered, only 25 had pediatric GD patients: 152 patients were identified, median age at diagnosis was 11.7 years (3–18), 76% females. All were initially treated with antithyroid drug (ATD) (median treatment duration 32.3 months): 69.1% tiamazol (TMZ) and 30.9% propylthiouracil (PTU), median initial dose 0.38 and 3.74 mg/kg respectively. After 2011, TMZ was used in 95% patients. Only minor side effects were found. Evolution: 39.4% (60) patients keep on ATD and 60.6% (92) finished first course treatment; 25.6% (39) remitted and remain euthyroid; 17.1% (26) relapsed after remission – second therapy: surgery = two patients, 131-iodine = 14, ATD = 10; in 17.7% (27) the disease persisted and undergone definitive therapy – surgery (13), 131-I (5) No significant predictors of remission like age, duration of initial treatment, ATS, initial TRABs levels were identified but patients with persistent disease had higher TRABs. **Conclusion:** ATD therapy was the first choice for our pediatric GD population; despite a long treatment duration only 25% patients achieved long term remission; definitive therapy was a second choice in few patients (22.4%) and more frequent in recent years. According to the recent literature this results reflect a tendency for changing pediatric GD therapy.

P2-D1-585

Subclinical Hypothyroidism is Associated with Low IGF1 Levels and Decreased Growth Velocity

Helena Bellini^a, Lea Maciel^b, Rodrigo Custodio^a, Soraia Milani^a, Mariana Paula^a, Sonir Antonini^a, Raphael Liberatore^a, Carlos Martinelli^a

^aDepartment of Paediatrics, Ribeirão Preto Medical School–USP, Ribeirão Preto, SP, Brazil, ^bDepartment of Medicine, Ribeirão Preto Medical School–USP, Ribeirão Preto, SP, Brazil

Background: Subclinical hypothyroidism (SH) is defined as normal tyrosine levels in the presence of TSH concentrations between 5 and 10 mU/ml. The impact of SH on IGF system and growth of infants remains unknown. **Objective and hypotheses:** To evaluate IGF1, IGFBP3 levels and growth velocity (GV) of infants with SH. **Method:** 98 children up to 36 months of age, recalled due to a TSH > 5 mU/ml in the neonatal screening test, were divided in two age-groups: I (0–4 months) and II (4.1–36 months). They were further split into subgroups according to the TSH level observed during follow-up: IA ($n = 14$) and IIA ($n = 49$),

TSH ≤ 5 mU/ml, IB ($n = 5$) and IIB ($n = 16$), $5 < \text{TSH} \leq 10$ mU/ml and IC ($n = 4$) and IIC ($n = 10$), TSH > 10 mU/ml. GV-SDS was calculated based on the previous 3 months of follow-up. IGF1 and IGFBP3 were determined by Immulite 2000 Kits in the same blood sample as TSH. **Results:** No difference was observed between group IA, IB, and IC regarding IGF1, IGFBP3 levels or GV, even when group IA was compared to combined IB + IC. However, IGF1 levels were higher in IIA than in IIB and IIC (median: 66, 36, and 30 ng/ml, respectively, $P = 0.005$). Similar results were observed for GV-SDS (mean \pm S.E.M.) with higher values in IIA (0.74 ± 0.3) than in IIB (-0.78 ± 0.4) and IIC (-0.5 ± 0.5) ($P = 0.03$). These findings were even more significant when IIA was compared to IIB + IIC (IGF1: 38 ng/ml, $P = 0.001$; GV: -0.67 ± 0.3 , $P = 0.004$). No difference was found on IGFBP3 levels. Negative correlation was observed between TSH and IGF1 levels ($r = 0.32$, $P = 0.005$). **Conclusion:** Reduced serum IGF1 levels and GV were observed in children aged 4–36 months with SH. This was not found earlier in life. These findings may reflect a direct action of thyroid hormones on IGF1 secretion rather than a modulation of GH action, as no changes were found on IGFBP3 levels. The real impact on height would demand a longer period of observation.

P2-D1-586

Thyroid Function and Autoimmunity and Their Relation to Weight Status in Healthy Children and Adolescents

Emilio García-García^a, Rafael Galera-Martínez^b, Iciar García-Escobar^c, Patricia Oliva-Pérez^b, José L. Gómez-Llorente^b, Jerónimo Momblán^b, María A. Vázquez-López^b, Antonio Bonillo Perales^b

^aVirgen del Rocío Hospital, Sevilla, Spain; ^bTorrecedenas Hospital, Almería, Spain; ^cPunta de Europa Hospital, Algeciras, Spain

Background: The interrelationships between body weight and thyroid status are complex. Serum TSH is typically increased in obese compared with lean individuals. Several mechanisms leading to hyperthyrotropinemia have been hypothesized. **Objective and hypotheses:** To compare thyroid function and autoimmunity in normal, overweight and obese healthy children and adolescents in our population. To analyse any metabolic risk factor related to hyperthyrotropinemia. **Method:** Cross-sectional epidemiological study. By a multistage probability sampling 1317 children and adolescents aged between 2 and 16 were selected. Physical and laboratory examination were performed including weight, height, waist circumference, neck palpation, blood pressure, glucose, insulin, triglycerides, HDL-cholesterol, urinary iodine, free thyroxine (T_4), TSH, antiperoxidase, and antithyroglobulin antibodies. Thyroid autoimmunity was diagnosed when any antibody was positive. BMI was calculated and obesity and overweight were diagnosed using the threshold proposed by the International Obesity Task Force for children and adolescents.

χ^2 and ANOVA tests were used. **Results:** TSH levels (mU/l) were significantly higher in the obese (3.12 (2.44)) (mean (s.d.)) than in the overweight (2.79 (1.51)) and normal children and adolescents (2.73 (1.30)) ($P=0.02$), while T_4 and urinary iodine levels did not differ. Prevalence of thyroid autoimmunity was lower in normal (2.9%) than in overweight (6.3%) and obese individuals (5.6%) ($p=0.02$). When excluding subjects with autoimmunity, TSH levels were less different comparing the three groups: obese 2.98 (1.17), overweight 2.73 (1.17), and normal weight 2.72 (1.19) ($P=0.09$). Hyperthyrotropinemia in obese and overweight children and adolescents was not related to any variable. **Conclusion:** TSH levels are significantly higher in obese than in overweight and normal children and adolescents. Significance is statistical but not clinical. Hyperthyrotropinemia in obese and overweight children and adolescents is not related to any cardiovascular risk factor.

P2-D1-587

Mutation of the TSH Receptor Gene: a Longitudinal Study in Children with Non-Autoimmune Subclinical Hypothyroidism

Maria Cristina Vigone^a, Micol Sonnino^a, Fabiana Guizzardi^c, Marianna Di Frenna^a, Silvana Caiulo^a, Giulia Gelmini^c, Luca Persani^{b,c}, Giovanna Weber^a

^aDepartment of Pediatrics, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy; ^bDepartment of Clinical Sciences and Community Health, University of Milan, Milan, Italy; ^cLaboratory of Endocrine and Metabolic Diseases, IRCCS Istituto Auxologico Italiano, Milan, Italy

Background: Neonatal screening strategies revealed an increase in hypothyroidism associated with an in-situ thyroid gland due to TSH receptor (TSHR) mutations. While there are many genetic and functional studies regarding TSHR mutations, few are found concerning the clinical course and long-term outcome of TSH resistance involving the pediatric population. **Objective and hypotheses:** To determine the impact of TSHR mutations on clinical course, biochemical parameters and therapeutic approach in children carrying this mutation. **Method:** Data regarding diagnosis, etiological reevaluation, family history, thyroid function, thyroid ultrasound, clinical and auxological parameters, were collected and evaluated in a group of 33 children with non-autoimmune subclinical hypothyroidism (SH) due to a TSHR mutation. DEXA scan, bone age, biochemical parameters, and questionnaire on QOL were also administered. Fifty-four children, negative for a TSHR mutation, were enrolled as our controls. **Results:** Fourteen different mutations (five new) of the TSHR gene were identified. Only 45% of TSHR+ patients were identified at screening while the remaining 55% were diagnosed in early childhood. All patients at diagnosis demonstrated FT_4 values within range with the exception of one patient. 60% of our TSHR+ patients began treatment, however only 35% within

one month of age. Diagnostic re-evaluation, carried out in 15 patients, demonstrated that TSHR+ patients had a greater tendency of discontinuing treatment compared to TSHR- patients (60 vs 43%). The six patients who resumed treatment were either compound heterozygous for the mutation, SGA or both. During follow up, we analyzed different aspects of thyroid hormone competence and no significant alterations were found. **Conclusions:** We found different arguments in favor of avoiding substitute hormonal treatment in patients carrying a single heterozygous TSHR mutation.

P2-D1-588

Investigation of Autoimmune Diseases Accompanying Hashimoto's Thyroiditis in Children and Adolescents and Evaluation of Cardiac Signs

Veysel Nijat Bas^a, Sebahat Yilmaz Agladioglu^a, Senem Ozgur^b, Selmin Karademir^b, Zehra Aycan^{a,c}

^aClinics of Pediatric Endocrinology, Dr Sami Ulus Research and Training Hospital of Women's and Children's Health and Diseases, Ankara, Turkey; ^bClinics of Pediatric Cardiology, Dr Sami Ulus Research and Training Hospital of Women's and Children's Health and Diseases, Ankara, Turkey; ^cYildirim Beyazit University Medical School, Ankara, Turkey

Objective: In the present study, it was aimed to investigate the concomitance of additional cardiac problems, mainly mitral valve prolapse, in adolescents and pediatric patients with Hashimoto's thyroiditis, by screening autoimmune markers. **Methods:** Euthyroid 57 patients, who applied to the Pediatric Endocrinology clinic at our institution with marked symptoms of hypothyroidism at the time of diagnosis, and were diagnosed and treated for Hashimoto's thyroiditis, were included in the present study. All patients were evaluated by performing non-organ specific autoantibodies which could be tested at our institution, thyroid ultrasonography, two dimensional echocardiography, and 24-h holter monitorization. **Results:** Of the 57 cases with Hashimoto's thyroiditis, 48 (84.2%) were female, and 9 (15.8%) were male. In the echocardiographic evaluation, mitral valve prolapse (MVP) was detected in 10 (17.5%) of all cases; mitral valve prolapse (MVP) was diagnosed in eight (seven females and one male) cases, and mitral insufficiency (MI) was diagnosed in two female cases. First-degree atrioventricular (AV) block was observed in only two patients during 24-h holter monitorization. Different non-organ specific autoantibody positivity was distributed as antinuclear antibody in 15 (26.3%) cases, anticardiolipin IgG in 2 cases, anticardiolipin IgM in three cases, tissue transglutaminase IgA in one, glutamic acid decarboxylase in one, anti-insulin antibody in 4 cases, antiphospholipid IgG in one, and antiphospholipid IgM in 1 case. **Conclusion:** It should be underlined that patients with Hashimoto's thyroiditis should to be followed up closely for MVP and accompanying autoimmune diseases.

P2-D1-589

No Difference in Cognitive Development of Young Adults and Adolescents Affected by Congenital Hypothyroidism Compared to Their Sibling Controls Despite High Dose L-Thyroxin Treatment

Paulina Aleksander, Oliver Blankenstein, Annette Grüters, Heiko Krude

Institut Exp.Päd.Endocrinology, Charite-Universitymedicine-Berlin, Berlin, Germany

Background: An early diagnosis and treatment based on neonatal screening offers a normal cognitive development in patients affected with congenital hypothyroidism (CH). However, several studies within cohorts of young adults have shown a still existing difference compared to control groups of up to eight IQ points. Moreover it has been claimed recently that a high L-T₄ dose with subsequent episodes of overtreatment results in less favourable IQ outcomes (Bongers-Shokking, *J Clin Endocrinol Metab*, 2013). **Objective and hypotheses:** We tested the cognitive outcome in the cohort of CH patients diagnosed in the Berlin screening program born from 1979 to 2003 who were treated early and with a high L-T₄ dose. **Method:** We recruited 74 patients, nine were not euthyroid and two had conductive hearing problems who were excluded and 36 control siblings. We performed a variety of cognitive tests. Episodes of over- and undertreatment were calculated based on the individual TSH ssc (steady state concentration) (Bongers-Shokking, *J Clin Endocrinol Metab*, 2013). **Results:** Mean initial L-T₄-dose was 12.8 µg/kg at mean age of 9 days; TSH normalization at median treatment-time of 13.5 days. We did not find a significant difference of global IQ in CH patients compared to their sibling control group (102.98 vs 99.19). We did not find a correlation of the number of suppressed TSH ssc with IQ. **Conclusion:** Early treatment of CH patients with a high dose of 12.8 µg/kg that normalize TSH within 14 days lead to a normal IQ without difference to sibling controls although such treatment is associated with episodes of suppressed TSH.

P2-D1-590

Thyroid Disorders in Siblings of CH Patients with Thyroid Dysgenesis

Alessandra Cassio, Valentina Di Ruscio, Federico Baronio, Ilaria Bettocchi, Antonella Cantasano, Milva Orquidea Bal, Antonio Balsamo, Giulio Maltoni, Laura Mazzanti

Pediatric Unit, Program of Endocrinology, Department of Medical and Surgical Sciences, University of Bologna and S. Orsola-Malpighi Hospital, Bologna, Italy

Background: Thyroid dysgenesis has been considered a sporadic disease, but recent observations suggested a possible genetic basis. **Objective and hypotheses:** The aim of our report is to evaluate the incidence of hormonal and ultrasound thyroid anomalies in siblings of CH patients with thyroid dysgenesis. **Method:** In Emilia-Romagna Region (Italy) 328 CH infants were

diagnosed by neonatal screening between January 2000 and December 2012. 122 cases of permanent CH due to thyroid dysgenesis were enrolled in this study (63 ectopic gland, 28 athyreosis, and 31 hypoplasia). Inclusion criteria were: confirmation of CH diagnosis at our screening centre, parents' informed consent, and availability of thyroid hormonal and US data in siblings of CH cases. **Results:** In 49/122 families 65 siblings (seven twins) over the CH patient were found. 19/65 subjects (29.2%) showed subclinical hypothyroidism (TSH range 5.38–113.4 mU/l; FT₄ range 10.1–16.6 pmol/l; thyroid antibodies negative in all cases) with thyroid *in situ* (normal volume in 14 cases, hypoplasia in four cases and goiter in one case). Thyroid anomalies were found in all twins examined. L-Thyroxine therapy was needed in seven cases. The median age at diagnosis was 5.5 years (range 14 days–19 years). CH screening test was negative in all siblings. The frequency of positive history for thyroid diseases was similar in each group. **Conclusion:** Monitoring of thyroid function is strongly recommended in siblings of patients with thyroid dysgenesis regardless of the result of the screening test. The type of thyroid disorders found in our sample of siblings seems to suggest a multifactorial origin of CH in which genetic and environmental risk factors can play a role.

P2-D1-591

Trends in Median Age at Guthrie Sampling, Laboratory Receipt, Notification, and Start of Treatment for Infants with TSH Elevation on Newborn Screening

Chourouk Mansour^a, Yasmine Ouarezki^b, Jeremy Jones^c, Sarah Smith^d, Malcolm Donaldson^c, Avril Mason^c

^aUniversity Hospital of A. Harouchi, Casablanca, Morocco; ^bEPSP BARAKI, Algiers, Algeria; ^cChild health Glasgow School of Medicine, Glasgow, UK; ^dScottish Newborn Screening Laboratory, Glasgow, UK

Background: Screening for congenital hypothyroidism (CH) has virtually eradicated the severe mental handicap associated with late or absent treatment. We have previously reported two audits of newborn screening for CH between 1979 and 2003 showing significant improvement from the first to more recent period. **Objective and hypotheses:** We aimed to audit the period 2004–2013 and report trends in timing of sampling, laboratory processing, delay between first and subsequent sample, notification of abnormal results and replacement therapy initiation. We hypothesise that sample timing is similar but it is taking longer for samples to reach the laboratory ameliorated by more rapid laboratory processing. **Method:** All data was extracted from the national CH database. Patients consisted of those who were referred after one abnormal result (TSH > 25 mIU/l) or those who required a second sample. Processing of data was carried out using Minitab 15.1. Kruskal–Wallis and Mann–Whitney *U* tests were used to compare data between years. **Results:** Median (range) time to first sample, receipt by laboratory, notification of abnormal result and start of treatment were 5 (1–12), 8 (4–13), 10 (5–17), and 11 (1–24) days of life respectively. Sampling was significantly

slower in 2004. Laboratory receipt occurred on day 9 in 2004 and 2006, improved to day 7 for 2005 and 2007–2008 and 2010 but worsened to day 8 in 2011–2013 and day 8.5 in 2009. Notification delay reflects slow laboratory receipt (2004, 2006, and 2009 being the slowest). Treatment start was also slowest in these 3 years with the median being 12.5 days in 2004. However in recent years this has improved to day 10 in 2012 and day 9 in 2013. The median (range) delay in obtaining a second screening sample was 9 (2–55) days but has improved by 2 days compared to the last audit period. **Conclusion:** Despite a recent worsening in the day of receipt by the laboratory, start of treatment continues to get earlier, suggesting that the laboratory has indeed improved processing time for samples. It is heartening that the delay between first and second samples has improved in this audit period.

P2-D1-592

Iodine-Deficiency Levels in Schoolchildren Aged Between 6 and 12

Ana Muñoz-Serrano^a, Abel González-González^b, José María Tenías-Burillo^c, Piedad Falero-Gallego^a, Ramon Cañete^d

^aServicio de Pediatría, Hospital General La Mancha Centro, Alcázar de San Juan, Ciudad Real, Spain; ^bSección de Endocrinología y Nutrición, Hospital General Universitario de Ciudad Real, Ciudad Real, Spain; ^cUnidad de Investigación, Hospital General La Mancha Centro, Alcázar de San Juan, Ciudad Real, Spain; ^dUnidad de Endocrinología Pediátrica, Hospital Universitario Reina Sofía (IMIBIC), Córdoba, Spain

Background: Iodine deficiency is the main cause of endemic goitre. A total of 29.8% of the world's school-age children insufficient iodine intake. A population is deemed iodine-sufficient when median iodine levels are over 100 µg/l; measured iodine deficiency serves as a diagnostic criterion for determining the extent to which goitre is endemic, and also as an indicator of the gradual eradication of iodine-deficiency disorders. **Patients, material, and methods:** Transversal study. Population of 13 896 children, representative of the school-age population of the Central La Mancha Healthcare Region, Spain. A survey was carried out, including questions on dietary iodine intake. First morning urine samples were kept frozen until processing. Urine iodine levels were measured using the modified Benotti and Benotti method. **Aims:** To measure the degree of iodine deficiency in this school-age population. To assess intake of iodised salt, sea fish, and goitrogenic foods. **Results:** Urine iodine levels were measured in 1110 children. The median level was 184 µg/l. A total of 14.1% of subjects displayed iodine deficiency, with levels lower than 100 µg/l. Iodine deficiency levels were greater in boys than girls, and were closely linked to the consumption of certain foods. Iodine levels were higher amongst children consuming iodised salts and dairy products. Iodine levels and external iodine supply displayed a somewhat seasonal pattern; deficiency levels were lower and intake of salt and fish higher in November. A linear correlation was recorded with age; iodine deficiency levels dropped slightly but steadily with each additional year of age. Half the schoolchildren surveyed consumed iodised salt. A somewhat

larger percentage ate fish, and a smaller percentage consumed goitrogenic foods. **Conclusion:** This school-age population displayed adequate iodine intake. A positive correlation was noted between iodine levels and intake of iodine-rich foods. The foods most influencing iodine levels proved to be dairy products. Age- and sex-related differences were found for iodine deficiency.

P2-D1-593

Incidence of Thyroid Nodules in Children Affected by Hashimoto's Thyroiditis: a 12-Year Survey of 567 Children

Silvia Longhi^a, Tommaso Aversa^c, Milva Bal^d, Antonella Cantasano^d, Marco Cappa^e, Alessandra Cassio^d, Andrea Corrias^f, Valeria D'Antonio^a, Filippo De Luca^c, Raffaella Di Mases^a, Roberto Gastaldi^h, Chiara Guzzetti^h, Sandro Loche^b, Mariacarla Salerno^g, Giulia Maria Tronconiⁱ, Maria Cristina Vigoneⁱ, Giovanna Weberⁱ, Giorgio Radetti^a

^aDepartment of Paediatrics, Regional Hospital of Bolzano, Bolzano, Italy; ^bPaediatric Endocrinology Unit, Microcitemico Hospital, ASL Cagliari, Cagliari, Italy; ^cDepartment of Paediatrics, University of Messina, Messina, Italy; ^dDepartment of Paediatrics, S. Orsola Malpighi Hospital, Bologna, Bologna, Italy; ^eUnit of Endocrinology and Diabetes, Bambin Gesù Children's Hospital, IRCCS Roma, Roma, Italy; ^fDepartment of Paediatric Endocrinology, Regina Margherita Children Hospital, Torino, Torino, Italy; ^gDepartment of Paediatrics, University of Naples Federico II, Napoli, Italy; ^hDepartment of Paediatrics, Institute G. Gaslini, University of Genova, Genova, Italy; ⁱDepartment of Paediatrics, Institute San Raffaele, Milano, Milano, Italy

Background: Hashimoto's thyroiditis (HT) has been linked to papillary cancer in adults but not in children and adolescents. Moreover, there is no agreement on the more appropriate frequency of thyroid ultrasound (TS) in the follow-up of children with HT. **Objective and hypotheses:** The aim of the study was to investigate the incidence of thyroid nodules and of thyroid cancer in a large group of children and adolescents (567) with HT followed-up for a mean period of 4.6 years (1.2–11.8 years). **Method:** At each visit the auxological data were recorded, TSH, fT₄, TPO- and TG-antibodies were measured and a TS was performed to assess the thyroid volume, detect nodules > 0.5 mm and to classify the echographic changes (score 1–5). The presence of lymphadenopathy or palpable nodules, treatment with L-thyroxine, results of eventual fine needle biopsy (FNB) were also recorded. 567 patients (440 females and 127 males, mean chronological age at diagnosis 10.7 ± 3.0 years) participated to the study. Median period of follow-up was for 4.6 years (1.2–11.8 years). **Results:** At the time of diagnosis, TSH was 16.0 ± 69.1 µIU/ml (range 0–1000; nv 0.3–3.69), fT₄ 9.2 ± 6.4 pg/ml (range 0.46–67.4; nv 9–17.7). At ultrasound, 35 patients (6.17%) showed nodules with a diameter > 5 mm, and 145 patients had a thyroid volume greater than +2 s.d. 17 FNB were performed based on TS findings. The incidence of nodules was 3.5% per year and only a thyroid score more than 2 (severe parcelled hypoechogenicity) was predictive for the appearance of new nodules. Papillary cancer was found in one girl who did not show

lymphadenopathy. **Conclusion:** Thyroid nodules are relatively frequent in HT children, particularly in those showing the most hypoechoic pattern at ultrasonography. However, papillary cancer seems to be a rare condition in this age group.

P2-D1-594

The Evolution of Iodine Status in Schoolchildren Living in a Formerly Iodine-deficient Region of Mures County, Romania

Zsuzsanna Szántó^a, Zsuzsanna Réti^a, Jolán Balló^b, Attila Csiszér^c, Elod Nagy^a, Ildikó Kun^d, Imre Zoltán Kun^a

^aUniversity of Medicine and Pharmacy, Targu Mures, Romania;

^bGeneral Practitioner Unit, Glajarie, Romania; ^cRegional Center of Public Health, Targu Mures, Romania; ^dDentalin, Budapest, Hungary

Background: Some hilly-mountainous regions of Mures County, located in the geographical center of Romania, were known as moderately mild iodine-deficient areas before the universal use of iodized alimentary salt was compulsorily implemented in practice in 2003. A partial evaluation was performed in 2006, but the sustainability of this prophylactic program was not evaluated afterward. **Objective and hypotheses:** To assess the current iodine status of schoolchildren living in three rural localities of formerly iodine-deficient endemic area Gurghiu valley, and to evaluate the changes of iodine status in the last 7 years. **Material and methods:** Schoolchildren aged between 6 and 14 years were investigated during October–November 2013, physical examination and thyroid ultrasound being performed in 95, urinary iodine excretion (UIE) in 120 and hormone investigations (TSH and free-T₄) in 84 cases. **Results:** According to the age- and gender-related thyroid volume measured ultrasonographically, the frequency of goiter was 6.2% in 2013, which is a significant reduction compared to the 20% seen in 2006 ($P=0.0038$; $RR=1.49$; 95% $CI=1.21-1.83$). The mean UIE was $337 \pm 190 \mu\text{g/l}$ in 2013 (35% of the children having elevated IUE), which shows a normal, even an almost increased iodine-supply in this region. This is a significant elevation compared to that of $73.7 \pm 52.5 \mu\text{g/l}$ obtained in 2006. In 2013 seven children (7.1%) had subclinical hypothyroidism, which is a significant reduction compared to the frequency of 17.7% registered in 2006 ($P=0.038$, $RR=1.38$; 95% $CI=1.10-1.74$). **Conclusion:** Regions of Mures County known as iodine-deficient in 2003–2006 became now iodine-sufficient areas, even observing in 35% of the children high iodine supply.

P2-D1-595

Papillary Thyroid Cancer with Diffuse Pulmonary Metastasis: How to Manage?

Serpil Basa^a, Saygin Abali^a, Yasemin Gokdemir^b, Belma Haliloglu^a, Zeynep Atay^a, Bulent Karadag^b, Abdullah Bereket^c, Serap Turan^a

^aMarmara University, Department of Pediatric Endocrinology, Istanbul/Pendik, Turkey; ^bMarmara University, Department of Pediatric Pulmonology, Istanbul/Pendik, Turkey

Background: Papillary thyroid cancer (PTC) is the most common endocrine malignancy in children. PTC shows more aggressive progress in children than in adults in respect to local and distant metastases. Here we presented a PTC case with primary pulmonary symptoms and pulmonary metastasis. **Case:** A 15.5-year-old male patient presented to the clinics with cyanosis and respiratory difficulty for the last 2 years. He had dyspnea, central cyanosis, clubbing, and decreased lung sounds bilaterally. Additionally, 3×3 cm hard and immobile thyroid nodule was palpated on physical examination. Oxygen saturation was 70%. Thorax CT showed diffuse infiltration of both lungs with multinodular parenchymal infiltrations, the largest being 12 mm in diameter and mediastinal lymph nodes. Lung biopsy showed metastatic papillary thyroid cancer. Thyroidectomy and deep lymph node dissection with subtotal tumor resection could be performed due to invasion of tumor to carotid artery and trachea and deterioration of oxygenation during the operation. Radioactive iodine (RI) treatment could not be performed in the early postoperative period due to oxygen requirement and tracheostomy. Sorafenib (a multikinase inhibitor) was given for 4 weeks. Thyroglobulin levels decreased to 600 ng/ml from 18 000 ng/ml and oxygen requirement of the patient was significantly reduced. Ablative RI (175 mCi) treatment could be given 10 days after discontinuation of Sorafenib after preparation with recombinant TSH. Diffuse uptake in neck and lung were detected on whole body scan after RI ablation. Sorafenib was restarted 5 weeks after radioactive iodine treatment. The patients' oxygen requirement gradually decreased, tracheostomy is closed and his saturations are normal on room air now. **Conclusions:** Although sorafenib is indicated for undifferentiated thyroid cancer it could be an adjunctive treatment option for differentiated thyroid cancers when RI treatment can not be given or delayed for any reason.

P2-D1-596

Factors Useful to Distinguish between Children with Permanent Congenital Hypothyroidism and Transient or Permanent Hyperthyrotropinemia

Maria Francesca Messina, Vincenzo Ramistella, Tommaso Aversa, Mariella Valenzie, Filippo De Luca

Department of Pediatrics, University of Messina, Messina, Italy

Background: Screening for congenital hypothyroidism (CH) with the possibility of an early treatment has transformed the outlook for children with CH. Despite the unquestioned public health success of newborn screening programs, the management of CH is still controversial. Most patients with positive screening have permanent hypothyroidism but some of them may have transient hyperthyrotropinemia, so it is important to identify these patients in order to avoid lifelong unnecessary treatment. **Objective:** To identify factors useful to distinguish between children with permanent congenital hypothyroidism and transient

Table 1. (for abstract P2-D1-596)

	TH (n=23)	PH (n=10)	CH (n=21)	P
Gestational age (weeks)	36.4	37.5	38.1	0.117
Birth weight (g)	2590	2700	2900	0.270
TSH at diagnosis (mIU/ml)	81.5	105.2	82.4	0.842
FT ₄ at diagnosis	9.5	9.0	12.7	0.720
Levo-thyroxine at diagnosis (µg/day)	31.19	32.0	29.81	0.899
Levo-thyroxine adjustment	0/23 (0%)	0/10 (0%)	12/21 (57%)	0.0001
Levo-thyroxine at 1 years (µg/kg per day)	2.31	2.93	3.02	0.154
Levo-thyroxine at 3 years (µg/kg per day)	1.33	1.70	2.67	0.0001

(TH) or permanent hyperthyrotropinemia (PH). **Method:** We enrolled 54 children with positive screening test for CH. All these patients have been treated with levo-thyroxine at a dose of 10–12 µg/kg per day up to three years when treatment has been discontinued and the diagnosis was rechecked. Comparison between different parameters in the three groups was performed by one-way ANOVA and χ^2 . **Results:** Table 1. **Conclusion:** Our data demonstrate that none of the considered parameters was able to predict differential diagnosis among CH and either TH or PH before the age of 3 years, with the only exception of levo-thyroxine dose adjustments that were necessary only in CH patients; as a consequence of levo-thyroxine adjustment, levo-thyroxine dose at the age of therapy withdrawal was significantly higher in CH patients than in the other groups. When TH or PT is suspected early cessation of therapy should be considered in order to reduce medical expenses and parental anxiety.

24 (33.8%), and 21 (29.5%) of the patients. In 18 patients FNAB was performed and in 7 (9.8%) patients carcinoma (papillary (n=3), follicular (n=2), follicular variant papillary (n=1) and hurthle cell (n=1)) was diagnosed. Adenoma and chronic lymphocytic thyroiditis (CLT) were diagnosed in 7 (9.8%) and 4 (5.6%) of the patients. All of the patients with carcinoma had nodule size > 1 cm and none of them had thyroid dysfunction at the diagnosis. In two patients with papillary carcinoma there were microcalcifications in the preoperation ultrasound in whom one also had CLT. Three patients with nodule size between 0.5 and 1 cm and had FNAB were diagnosed as CLT. Overall etiological distribution was as adenoma, carcinoma, CLT, congenital hypothyroidism and nodular goiter in 7 (9.8%), 7 (9.8%), 22 (30.9%), 2 (2.81%), and 33 (46.7%) of the patients. **Conclusion:** Although in most of the patients we couldn't identify a specific etiology, significant amount of patients had carcinoma, that should attract attention.

P2-D2-597**Thyroid Nodules in Childhood and Adolescence; Clinical, Radiologic and Etiological Evaluation**

Olca Evliyaoglu, Bahar Ozcabi, Ayse Tekin, Feride Bucak, Oya Ercan
Cerrahpasa Medical School, Istanbul, Turkey

Background: Thyroid nodules are less common in childhood but it has higher risk of malignancy. In this study, we aimed to evaluate children and adolescents with thyroid nodules, clinically, radiologically and histopathologically to determine etiological distribution. **Method:** Seventy-one patients (46 females) with the mean age of 10.41 ± 5.03 (0.04–21) years with thyroid nodules were involved in this study. Patients were evaluated by their complaints at admission, physical examination, thyroid functions and autoantibodies, and thyroid ultrasounds. Fine needle aspiration biopsy (FNAB) was suggested in the patients with nodule size ≥ 1 cm or 0.5–1 cm and if there is family history of thyroid ca, increased vascularity in doppler usg or microcalcification. **Results:** The most frequent complaint was swelling of neck (n=20.27%). Thyroid nodule was diagnosed incidentally in 16 (22%) patients. In 12 (16.4%) patients, family history of thyroid disease was observed. Hypothyroidism, subclinical hypothyroidism, hyperthyroidism and subclinical hypothyroidism were determined in 6 (8.2%), 3 (4.1%), 1 (1.36%) and 3 (4.1%) of the patients respectively. In the ultrasonographic evaluation, nodule size was ≥ 1 cm, 0.5–1 cm, and <0.5 cm in 26 (36.6%),

P2-D2-598**An Unusual Presentation of Acquired Hypothyroidism: the Van Wyk–Grumbach Syndrome**

Pinar Isguven, Nefise Uluc, Mustafa Kosecik, Mehmet Karacan, Bahri Ermis

Department of Pediatric Endocrinology, Faculty of Medicine, Sakarya University, Sakarya, Turkey

Background: Van Wyk–Grumbach syndrome (VWGS) is characterized by breast development, uterine bleeding and multicystic ovaries in the presence of long-lasting primary hypothyroidism. **Objective and hypotheses:** The pathophysiology of VWGS involves a complex mechanism, which is at least partly mediated by the direct action of TSH and FSH receptors. **Method:** We present a girl with Down syndrome having typical features of VWGS. The girl, aged 9 years and 7 months, was referred to our endocrinology department with the suspicion of precocious puberty after having had first episode of vaginal bleeding lasting 4 days. Her poor growth and inactivity were previously thought to be due to her Down syndrome. **Results:** On examination, her height was 117 cm (<3p) and weight was 30 kg (50p). She had breast development at Tanner's stage 3, but no pubic and axillary hair development. Baseline LH was 0.15 U/l, FSH 5.4 U/l, oestradiol was 94 mIU/ml and prolactin was 140 mU/l. Morning cortisol, 17-hydroxyprogesteron, and androgens were normal.

Primary hypothyroidism was demonstrated by a free $T_4 < 2$ pmol/l and TSH > 100.000 mU/l. Positive thyroid peroxidase antibodies confirmed autoimmune thyroiditis. LHRH test showed FSH dominated prepubertal response. A pelvic ultrasound showed a pubertal uterus in size and appearance, and large cystic ovaries with multiple follicles. Cardiac echography yielded moderate pericardial effusion. Her bone age was compatible with 6 years. Her clinic and laboratory findings were in agreement with VWGS. T_4 replacement was started at a very low dose, 25 mg, because of pericardial effusion, and was increased gradually. She had no further episodes of vaginal bleeding. **Conclusion:** The combination of delayed bone age with vaginal bleeding is one of the important diagnostic clues of the VWGS.

P2-D2-599

Severe Urticaria in Graves' Disease: is Carbimazole to Blame?

Caroline Ponmani, Martin Mcclatchey, Shilpa Kanzaria, Morgan Keane, Kausik Banerjee

Queens Hospital Romford, London, UK

Background: Carbimazole is widely used in the treatment of Graves' disease and is well tolerated but can produce adverse effects in 5% of cases. Urticaria, which can develop as a drug reaction to carbimazole responds to withdrawal of the drug and symptomatic management. Urticaria is also a rare manifestation of thyrotoxicosis and does not respond to treatment, but regresses rapidly with the control of underlying hyperthyroidism. **Objective and hypotheses:** We present two cases with Graves' disease and severe urticarial rash. **Method:** A 15-year old diagnosed with Graves' disease was commenced on carbimazole and propranolol. After 10 days she developed an intensely pruritic maculopapular rash affecting trunk and limbs. Her FT_4 was 17.3 pmol/l. Carbimazole was stopped, propranolol was continued and antihistaminics and steroids were commenced. The rash improved rapidly. She however became clinically and biochemically thyrotoxic. Three weeks later she was recommenced on carbimazole. Within 24 h she developed the rash which subsided after carbimazole was stopped. She subsequently underwent radioiodine treatment. A 12-year-old with a background of epilepsy was diagnosed with Graves' disease. Previously she had reactions to anti-epileptic drugs resulting in DRESS syndrome. She was started on propranolol, then cautiously started on carbimazole. Within 24 h she developed an urticarial rash on the face and limbs. Antihistaminics and steroids were commenced but the rash persisted. Carbimazole was continued as her FT_4 was 66 pmol/l. The rash subsided after 3 weeks. Her FT_4 then was 18 pmol/l. **Results:** In the first case symptoms were distressing and subsided with withdrawal of the drug. In the second, carbimazole was continued and the symptoms subsided with improvement of thyrotoxicosis. **Conclusion:** Often there is a diagnostic dilemma whether the urticaria is secondary to thyrotoxicosis or a drug reaction to carbimazole. In the event of distressing urticaria as illustrated by the first case we recommend discontinuation of carbimazole.

P2-D2-600

Low Serum Free T_4 Concentration in a Girl with McCune-Albright Syndrome

Aleksandr Peet^{a,b}, Mart Roosimaa^{c,d}, Anett Pajuväli^e, Vallo Tillmann^{a,b}

^aDepartment of General Paediatrics, Children's Clinic of Tartu University Clinic, Tartu, Estonia; ^bDepartment of Paediatrics, Tartu University, Tartu, Estonia; ^cTartu University Hospital, Tartu, Estonia; ^dInstitute of Biomedicine and Translational Medicine, University of Tartu, Tartu, Estonia; ^eTartu University, Tartu, Estonia

Background: McCune-Albright syndrome (MAS) is a rare disease with a prevalence of < 1 to 100 000. It is caused by early post-zygotic mutations in the GNAS1 gene. Classically it presents with precocious puberty, fibrous dysplasia and café-au-lait spots. Other endocrinopathies may be hyperthyroidism, GH excess, Cushing syndrome, and renal phosphate wasting. **Case report:** A 17-year-old girl diagnosed with MAS at the age of 11 on basis of all three classical signs and hypophosphatemia who had been lost to the follow-up during the next 6 years. At age of 17 years she appeared having short stature (< 5 th percentile), frequent bone fractures and bone deformations. Endocrine investigations revealed low free T_4 (fT_4 4.9, reference range 12.6–21.0 pmol/l) with an inappropriately normal TSH (2.2, ref. 0.5–4.3 mU/l) and low IGF1 (67, ref. 194–680 μ g/l). Clinically euthyroid. Her cortisol, prolactin, FSH, LH and oestradiol levels were normal. Due to the very low free T_4 , she was started with levothyroxine 50 μ g/die. Due to the poor growth, low IGF1 and low TSH, arginine stimulation test and pituitary MRT were done to rule out GH deficiency and pituitary lesion. Both were normal (peak GH 56 mU/l). Thyroid ultrasound was normal and no anti-TPO antibodies were present. One month after commencing levothyroxine treatment, serum free T_4 concentration remained low (fT_4 9 pmol/l and TSH 0.96 mU/l) and her levothyroxine dose was increased to 75 μ g/die. Clinically she was euthyroid. After 1 month, free T_4 remained still below reference range (9.6 pmol/l), but her free T_3 , measured first time, was increased (8.35 pmol, ref. 3.93–7.70 pmol/l) and TSH became suppressed (0.03 mU/l). Clinically slight tachycardia occurred. Iatrogenic hyperthyroidism was diagnosed and treatment with levothyroxine was stopped. **Conclusions:** In patients with MAS free T_3 should be always measured together with free T_4 and TSH to estimate the thyroid function. Low free T_4 in our case was probably due to the increased T_3 to T_4 ratio due to a cAMP-mediated intrathyroidal increased activity of type 1 and type 2 5'-deiodinase (Celi *et al.*, JCEM 2008).

P2-D2-601

Long Term Anti-Thyroid Drug Therapy in a Paediatric Population with Down Syndrome: an Irish Experience

Niall Johnston^a, Meenal Mavinkurve^a, Nuala Murphy^a, Sinead Moloney^a, Colm Costigan^b, Declan Cody^b

^aEndocrine Department, Temple Street Childrens University Hospital, Dublin, Ireland; ^bEndocrinology Department, Our Lady's Children's Hospital, Crumlin, Dublin, Ireland

Background: Ireland has the highest prevalence of Down syndrome (DS) in Europe, affecting ~1 in 500 live births. Patients with DS are at increased risk of developing thyroid disorders during childhood. Hyperthyroidism can be difficult to recognise and treat in this population. First-line therapy with anti-thyroid drugs (ATDs) may help achieve remission, but relapse is common following discontinuation of medication. Definitive treatment with radio ablation or surgery is often considered but may have additional risks in the DS population. **Objective:** We report a case series of infants with DS who developed hyperthyroidism and were treated with successfully anti-thyroid drugs. **Methods:** Five children with DS had hyperthyroidism confirmed at our centre. Information regarding clinical features at presentation, diagnostic testing and management was recorded. **Results:** Thyrotoxicosis was confirmed in five children (two females and three males) at a mean age of 5.5 years (range 3.7–8.0 years). Behaviour disturbance and disordered sleep were the presenting symptoms in 4/5. Diagnostic testing confirmed an increased thyroxine level (T_4 , mean 36.4 pmol/l, range 25.9–49.4 pmol/l), suppressed TSH level (<0.01 mIU/l) and TSH receptor antibody (TRAb) positivity (TRAb, mean 92.0 U/l, range 6.4–400 U/l). All children were treated with ATDs with a mean duration of 2.6 years (range 0.25–4 years). After 24 months of therapy, consideration was given to a trial off treatment for four of five children but all became clinically or biochemically hyperthyroid when ATD dose was reduced. All children currently remain clinically and biochemically euthyroid on ATDs and none have proceeded to definitive therapy. ATDs were well tolerated in our cohort, with no serious side effects noted. **Conclusion:** Anti-thyroid drugs should be considered a safe and effective option for long-term management of hyperthyroidism in the DS population and may be preferable to more definitive treatments.

P2-D2-602

Influence of Amiodarone on Thyroid Function in Children

Irina Nikitina, Elena Vasichkina, Irina Artemeva, Anastasia Liskina, Dmitri Lebedev

Almazov Federal Medical Research Centre, Saint-Petersburg, Russia

Background: Unlike to adults, the side effects of long-term administration by amiodarone (A) of life-threatening arrhythmias (LThA) on thyroid function still is not studied exactly in children. **Methods:** Twenty-six children with LThA aged 1 week to 16 years (mean 10 years) treated by A were examined. The mean duration of oral treatment ranged from 1 month to 47 months (mean 12.5 months). We estimated serum level of T_4 , T_3 , TSH, antibodies (TPO-Ab, TSH-Ab) and performed ultrasound diagnostics of thyroid before and during the therapy and then in 6 months after stop of therapy. **Results:** All patients had not any thyroid pathology before starting of the therapy and thyroid function during A treatment did not change in majority of them (85%). Transient subclinical hypothyroidism non-required T_4 treatment has been observed in 7.5% (two children) and we found out the

same amount cases (two) of amiodarone induced hyperthyroidism (AIH). One of them was mild AIH began 1.5 month later stopping oral A. Another case was presented by severe AIH type 2 in 17th year old boy with arrhythmogenic right ventricular cardiomyopathy. At the beginning, the dose of A was 500 mg/day and it was decreased later, but the duration of the therapy was more than 3 years. His hormones were increased (FT_4 58.87 pmol/l, FT_3 6.82 pmol/l, FT_4/FT_3 – 8, no TPO-Ab, TSH-Ab). He has been treated by prednisolone (0.6 mg/kg) and methimazole (20 mg), A was stopped, but life-threatening ventricular tachycardia progressed. Surgical treatment is considering. **Conclusion:** AIH can accompany and complicate the treatment of LThA in children. It may be caused by long-term duration or/and high doses of amiodarone.

P2-D2-603

Euthyroid Sick Syndrome in Children with Diabetic Ketoacidosis

Yanyan Hu, Guimei Li, Qian Wang, Zengmin Wang, Fengxue Wang

Shandong Provincial Hospital Affiliated to Shandong University, Jinan, Shandong, China

Background: The correlation between free thyroid hormones and poor diabetic control in children with diabetic ketoacidosis (DKA) and the effects of thyroid hormone therapy on euthyroid sick syndrome (ESS) remain unclear. **Objective and hypotheses:** To investigate characteristics of ESS in children with DKA and the effects of thyroid hormone therapy on ESS. In children with DKA, free thyroid hormones may be associated with the severity of DKA and thyroid hormone therapy may have effects on ESS. **Method:** Children with DKA were divided into two groups: euthyroidism (group 1, $n=25$) and ESS (group 2, $n=30$). All children were treated with insulin, and levothyroxine was added in 21 children in group 2. C-peptide, insulin, HbA1c, bicarbonate, anion gap (AG), free triiodothyronine (FT_3), free thyroxine (FT_4), and TSH levels were measured before and after 7 days of treatment. Daily blood glucose (BG) profiles were recorded. **Results:** HbA1c, AG and the mean daily BG levels were higher and bicarbonate, FT_3 , FT_4 , and TSH levels were lower in group 2 than in group 1 (all $P<0.05$). FT_3 and FT_4 levels were positively correlated with bicarbonate ($r=0.409$, $P=0.002$, $r=0.324$, $P=0.016$) and negatively correlated with HbA1c ($r=-0.561$, $P<0.0001$, $r=-0.302$, $P=0.025$) and AG ($r=-0.344$, $P=0.010$, $r=-0.428$, $P=0.001$). There were no statistically differences in laboratory parameters between ESS with and without levothyroxine after treatment (all $P>0.05$). However, fasting blood glucose (FBG) levels were lower in ESS with levothyroxine than without levothyroxine ($P=0.007$). The coefficient of variation of the mean daily BG and FBG levels were lower in ESS with levothyroxine than in ESS without levothyroxine ($P=0.037$, $P=0.037$). **Conclusion:** DKA children with ESS have a poor diabetic control. Free thyroid hormones are associated with the severity of DKA. Thyroid hormone therapy may improve glycemic control for ESS.

P2-D2-604**Levothyroxine Requirement in Congenital Hypothyroidism: 12-year Longitudinal Study**

Maria Cristina Vigone^a, Rosa Lapolla^b, Maurizio Delvecchio^c, Mariacarla Salerno^d, Malgorzata Wasniewska^e, Pietro Pio Popolo^b, Alessandro Mussa^f, Giulia Maria Tronconi^a, Raffaella Di Mase^d, Ida D'Acunzo^d, Rosa Maria Falcone^g, Andrea Corrias^f, Filippo De Luca^e, Giovanna Weber^a, Luciano Cavallo^g, Maria Felicia Faienza^g

^aDepartment of Pediatrics Endocrinology, IRCCS Vita-Salute San Raffaele University, Milan, Italy; ^bDepartment of Pediatrics, University of Foggia, Foggia, Italy; ^cPaediatrics Unit IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, Foggia, Italy; ^dDepartment of Pediatrics, University of Naples Federico II, Naples, Italy; ^eDepartment of Pediatrics, University of Messina, Messina, Italy; ^fDivision of Pediatric Endocrinology, Department of Pediatrics, University of Turin, Turin, Italy; ^gSection of Pediatrics, Department of Biomedical Sciences and Human Oncology, University of Bari Aldo Moro, Bari, Italy

Background: The replacement therapy with levo-thyroxine (LT4) in congenital hypothyroidism (CH) aims to ensure normal growth and neuropsychological development. Few data are available about the appropriate dose during childhood and early adolescence. **Objective and hypotheses:** i) To evaluate LT4/kg per day requirement from diagnosis until 12 years of age; ii) to assess any differences in relation to the different etiology of CH as concerns the LT4/kg per day requirement. **Method:** Multicentric observational study; 216 patients (142 females) with permanent CH classified as athyreosis, ectopia, *in situ* gland, on the basis of the thyroid imaging; LT4 dose was recorded from 6 months to 12 years of age and the LT4/kg per day calculated. **Results:** The LT4/kg per day requirement statistically decreased year by year, irrespective of etiology. It was about 3–4 µg/kg per day from 1 to 5 and about 2–3 µg/kg per day from 6 to 12 years of age. It was significantly lower in patients with *in situ* gland than with athyreosis and with ectopic gland from the age of 1 year. Only at 1, 2, and 10 years the LT4/kg per day requirement was higher in athyreotic than in ectopic patients. The LT4/kg per day requirement at 6 months of age was correlated with the requirement at each later time point. The LT4/kg per day dose was modified less frequently in patients with *in situ* thyroid (40.5%) than in patients with ectopic gland (47.4%) or with athyreosis (48.9%). **Conclusion:** Euthyroidism may be achieved by 3–4 and 2–3 µg/kg per day of LT4 in preschool and in school CH patients. The LT4/kg per day dose is affected by the etiology: patients with *in situ* gland require a lower dose than the other ones. The patients with ectopia or athyreosis require more frequently a change in the daily dose, and thus such patients have to be followed up more frequently. Since the age of 6 months, some patients require higher doses than other ones, irrespective of etiology.

P2-D2-605

Abstract withdrawn.

P2-D2-606**Genetic Studies in Congenital Hypothyroidism: a Regional Study**

Mahin Hashemipour^{a,b}, Silva Hopvsepian^{a,b}

^aIsfahan Endocrine and Metabolism Research Center, Isfahan University of Medical Sciences, Isfahan, Iran; ^bChild Growth and Development Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

Background: Congenital hypothyroidism (CH) is considered as the most common endocrine disorder in neonates. CH may be caused by defects in the thyroid gland (dysgenesis) or in one of the stages in the synthesis of thyroid hormones (dyshormonogenesis). Early diagnosis and treatment of neonates with CH is crucial for their neurological development and preventing its related mental retardation. CH screening program have made the opportunity to achieve the mentioned goals. CH screening program in Isfahan-Iran was initiated in 2002 and continued until 2005 when it integrated with the nationwide CH screening. Results of CH screening indicated that prevalence of CH is high in Isfahan. Moreover the etiologic feature of CH with higher rate of dyshormonogenesis was not similar to that reported by other studies worldwide. To determine the causes of mentioned differences as well as pathophysiology of CH many genetic studies was performed in Isfahan. In this review, the findings of the genetic studies are presented. The role of thyroid transcription factor 1 (TTF1) and TTF2, TSH receptor (TSHR) and paired box transcription factor 8 (PAX8) genes studied among CH patients with dysgenesis. We found a known polymorphism in ser 273 of TTF2 gene in 74% unrelated patients and a heterogen polymorphism for TSHR gene. In dyshormonogenetic CH patients, thyroid peroxidase (TPO), two mutations (T354P and G395R) of sodium/iodide symporter (NIS) and four mutations (R434X, Q36H, R376W, and D506N) of dual oxidase 2 (DUOX2) were studied. One homozygous missense mutation at exon 15 in one patient and seven different single nucleotide polymorphisms in exons 1, 7, 8, 11, and 15 of TPO gene were detected. **Conclusion:** Though some mutations in both dysgenetic and dyshornrmonogenetic CH patients were detected but it seems that screening of the whole length of the involved genes can be helpful to determine the cause of CH in our patients.

P2-D2-607**Premature Menarche Associated with Hashimoto Thyroiditis at 2 Years 9 Months: Case Report**

Meliksah Keskin, Semra Cetinkaya, Elif Sagsak, Zehra Aycan, Senay Savas Erdeve

Background: Primary hypothyroidism is frequently associated with delayed puberty. However, precocious puberty is known to occur in some rare cases of hypothyroidism untreated for a long time. Differently from the cases suffering from precocious puberty due to other causes, linear growth and bone age are retarded in children developing precocious puberty associated with hypothyroidism. There are no definite data about the incidence of precocious puberty associated with hypothyroidism. Knowledge about the long-term follow-up of these patients is still limited. **Objective and hypotheses:** Untreated hypothyroidism can cause menarche even at an early age. **Method:** A female patient with Down syndrome aged 2 years and 9 months was referred with the symptom of vaginal bleeding continuing for 1 week. In her history, there were no symptoms suggesting trauma, foreign body, urinary tract infection or intracranial mass. The patient exhibited the phenotypic features of Down syndrome and her height and weight were within 5–25% percentiles and 25–50% percentiles, respectively, regarding the growth curves generated for children with Down syndrome. Breast development was at Tanner stage 3 bilaterally, and she had no axillary or pubic hairs. Suprapubic ultrasonography revealed cystic lesions in the right lower quadrant and left adnexial region. **Results:** She was diagnosed with Hashimoto thyroiditis hypothyroidism as result of the tests and was started on Na L-thyroxine replacement therapy. In our patient, all examination findings relevant to precocious puberty, laboratory parameters and adnexial cystic lesions returned to normal in the sixth month of the treatment. **Conclusion:** Hypothyroidism is common in childhood due to many reasons. However, premature menarche is a rarely seen clinical presentation of hypothyroidism. Contrary to the other cases of precocious puberty due to other reasons, linear growth is stunted and bone age is retarded. This knowledge alone is enough to draw attention once more to the importance of monitoring the growth curves of children.

P2-D2-608

Iodine Nutrition and Neonatal Thyrotropin Levels in Lucknow, India

Vijayalakshmi Bhatia^a, Vignesh Gopalakrishnan^a, Kriti Joshi^a, Shubha Phadke^a, Preeti Dabadghao^a, Meenal Agarwal^a, Cynthia Mootheden^b, Vinita Das^c, Amita Pandey^c

^aSanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India; ^bBCM Hospital, Khairabad, India; ^cKing George Medical University, Lucknow, India

Introduction: In India, newborn screening (NBS) for congenital hypothyroidism (CH) is not yet a national government policy. Preliminary information suggests neonatal TSH levels to be higher in expatriate Indian babies than those in European

populations in developed countries. **Objectives:** To evaluate maternal urinary iodine and cord blood TSH in a subset of women participating in a postnatal NBS program for CH. **Methods:** Cord blood (CB) and postnatal (PN) NBS samples (>24 h of age) were collected on Whatman 903 filter paper. Dried blood spot TSH assay was performed by immunofluorometry and urine iodine (UI) was estimated by the ammonium persulfate method. **Results:** Mean \pm s.d. TSH in 4200 CB samples was 7.9 ± 7.4 mU/l. TSH > 20 mU/l was found in 4.6% of CB and 1.39% of 13 426 PN samples. Median UI in 350 mothers was 189 μ g/l. Insufficient UI (<150 μ g/l) was present in 42% women. Intake above normal (UI 150 to <250 μ g/l) and excessive intake (UI > 250 μ g/l) were found in 22 and 20% of women respectively. TSH was weakly negatively correlated with birth weight, rural residence, and normal delivery, but not with UI. **Conclusion:** Locally derived TSH cut offs are needed to deal with high recall rate. Iodine deficiency and low birth weight may be two contributory factors for high recall. Iodine nutrition is extremely inconsistent and variable in our women.

P2-D2-609

Auxological Pattern, BMI and Endocrine Follow Up in Children with Congenital Hypothyroidism: the Data of the Pediatric Clinic of Palermo

Maria Cristina Maggio, Mariagrazia Irene Mineo, Marilena Maltese, Giovanni Corsello

University Department Pro.Sa.M.I. 'G. D'Alessandro', University of Palermo, Palermo, Italy

Background: Congenital hypothyroidism (CH) has a high incidence, with a local increase in our screening relieves in the last years. **Objective and hypotheses:** An accurate follow up and an appropriate treatment guarantee an adequate neurological and auxological development. **Method:** We describe the personal report of 74 children (27 males and 43 females) with CH, diagnosed by neonatal screening and followed for 8.5 ± 5.3 years. **Results:** Their TSH, fT₃, fT₄ levels were in the range of normality, except in two adolescents with transient TSH increase. During the follow up a program of education to physical activity and/or sport, correlated to age of the children and adequate to their familial possibilities, was promoted. The SDS of stature ranged between -0.45 ± 1.13 and -0.35 ± 1.07 ; SDS of weight ranged between -0.43 ± 1.34 and -0.17 ± 1.32 ; the SDS of BMI ranged between -0.12 ± 1.38 and -0.05 ± 1.35 . All the patients showed an adequate statural and ponderal growth; every patient was in the normal range for SDS BMI, even during adolescence. **Conclusion:** Our patients did not present an early adiposity rebound, whereas reported in other studies. Our data confirm the utility of a programmed follow up in children and especially in adolescents with CH, with the finality of the maintenance of an adequate surveillance on growth and BMI. The education to the utility of physical activity can contribute to prevent a precocious adiposity rebound and to maintain a regular growth and weight.

P2-D3-610

Therapeutic Effects of GH Combined with Low-Dose Stanozolol on Growth Velocity and Final Height of Girls with Turner Syndrome

Hong-Shan Chen, Min-Lian Du, Yan-Hong Li, Hui Xiong, Hua-Mei Ma, Qiu-Li Chen

Pediatric Department, The First Affiliated Hospital of Sun Yat-sen University, GuangZhou, China

Objective: This study aimed to investigate the therapeutic effects of recombinant human GH (rhGH) combined with low-dose stanozolol on the growth and final adult height (FAH) of girls with Turner syndrome (TS). **Method:** A total of 47 girls with TS were treated with rhGH (47.6–52.4 µg/kg per day) and low-dose stanozolol (20–35 µg/kg per day), starting at a mean age of 12.57 ± 1.96 year. The control group consisted of 26 girls with TS, who did not receive treatment. Subjects' growth velocity (GV) was investigated. Height SDS (HtSDS), as referenced by the healthy Chinese girls (HtSDS_{Nor}) and as well as the untreated Chinese girls with TS (HtSDS_{TS}), were calculated. Post-treatment follow-up was performed until the subjects achieved FAH or near-FAH. **Results:** FAH was significantly higher in subjects receiving treatment compared to the untreated controls (151.42 vs 136.72 cm, $P < 0.001$). GV was significantly higher in the first to fourth years of treatment compared to baseline values ($P < 0.001$); it was significantly lower in the second to fifth years of treatment compared to the first year ($P < 0.001$). **Conclusions:** In girls with TS 9–12 years of age, rhGH combined with low-dose stanozolol may effectively increase growth. At least a 2-year course of this treatment may effectively improve FAH with proper delay of estrogen-induced development.

P2-D3-611

Epidemiology of Turner Syndrome in Iceland 1968–2012

Arndis Audur Sigmarsdóttir^a, Johann Heidar Johannsson^{b,d}, Helga Augusta Sigurjonsdóttir^{c,d}, Arni V Thorsson^{a,d}

^aChildren's Medical Center, Landspítali University Hospital, Reykjavik, Iceland; ^bDepartment of Genetics and Molecular Medicine, Landspítali University Hospital, Reykjavik, Iceland; ^cDepartment of Endocrinology, Landspítali University Hospital, Reykjavik, Iceland; ^dFaculty of Medicine, University of Iceland, Reykjavik, Iceland

Introduction: Turner syndrome (TS) is a common genetic disorders with an estimated range of occurring in 25–210 per 100 000 liveborn females. In Denmark the prevalence of TS has been found to be 40 per 100 000 liveborn females. Our aim was to study the epidemiology of TS in Iceland for the period of 1968–2012. **Methods:** Primary source of data were hospital records and records from all pediatric endocrinologists in Iceland. To validate the data the karyotypes were obtained from the chromosomal

laboratory which is the only cytogenetic laboratory in Iceland, serving all hospitals and private physicians since 1968. **Results:** A total of 51 females were diagnosed with TS during the 45 year period. Cases diagnosed in the first year of life were 16 (31%). The median age of diagnosis was 7 years. Five were diagnosed after the age of 16, the oldest at 59 years. The incidence of TS, computed for 5 year periods, was on average one per 2103 liveborn females and the prevalence 53 per 100 000 females. Induced abortions on TS diagnosed fetuses were 19. Almost half of the TS females (49%) had the classical karyotype 45,X, whereas in fetuses the 45,X karyotype was found in nearly 80% of cases. Various mosaic karyotypes were seen, most commonly 45,X/46,XX (11%) and 45,X/46,XiX (isochromosome q) (10%). **Conclusions:** The prevalence of TS in Iceland is higher than that reported from Denmark. A higher percentage of the classical 45,X karyotype was seen in the aborted fetuses. For the last two decades most of the girls have been diagnosed in the first year of life or at a relatively young age. A diagnostic delay was seen in many cases in the earlier years as some females were not diagnosed until adulthood. Clinical vigilance is important for early diagnosis of Turner syndrome.

P2-D3-612

Anti-Mullerian Hormone: a Marker of Premature Ovarian Insufficiency in Girls with Turner Syndrome

Catarina Mendes^a, Liliana Pinho^a, Teresa Borges^a, Maria João Oliveira^a, Helena Cardoso^b

^aDepartment of Child and Adolescent, Centro Hospitalar do Porto, Porto, Portugal; ^bDepartment of Endocrinology, Diabetes and Metabolism, Centro Hospitalar do Porto, Porto, Portugal

Background: Turner syndrome (TS) patients typically exhibit short stature and gonadal dysgenesis with pubertal delay and infertility. Up to 30% of these girls will have spontaneous pubertal development, however only 2% achieve a spontaneous pregnancy. Biochemical markers reflecting the ovarian reserve in girls and adolescents with TS are therefore needed. **Objective and hypotheses:** Evaluation of the ovarian reserve in girls and adolescents with TS using serum AMH and simultaneously comparing this value with other markers, including serum FSH, number of ovarian follicles on transabdominal gynecologic ultrasound and karyotype. **Method:** Prospective study investigating TS girls followed at the Pediatric Endocrinology Unit of a Portuguese General Hospital between April and August 2013. **Results:** Twenty girls aged 3–15 years were included (median age 10 years). Normal serum AMH levels were observed in 35% of TS girls. There was a strong correlation between AMH and FSH levels: all patients with normal serum AMH had also normal serum FSH whereas all girls with low serum AMH showed high serum FSH ($P < 0.001$). Ovarian follicles were present in 86% of girls with normal AMH and absent in 69% with low serum AMH. Ovarian follicles were detectable in only 25% of girls with karyotype 45,X and in 67% with karyotype 45,X/46,XX or other cytogenetic abnormalities. Five girls showed spontaneous puberty, one of which had abnormal FSH and AMH levels despite detectable

ovarian follicles. **Conclusion:** Serum AMH correlated well with serum FSH and appears to be a useful marker of the follicle pool. Nevertheless, complementary imaging study is still needed. Karyotype is a good predictive marker of premature ovarian insufficiency when considered together with other parameters.

P2-D3-613

Nationwide Study of Turner Syndrome During Childhood in Turkey: Evaluation of Associated Problems

Ediz Yesilkaya^a, Feyza Darendeliler^b, Abdullah Bereket^c, Firdevs Bas^b, Sukran Poyrazoglu^b, Banu Kucukemre Aydin^b, Sukran Darcan^d, Bumin Dundar^e, Muammer Buyukinan^f, Cengiz Kara^g, Erkan Sari^h, Erdal Adal^h, Aysehan Akinciⁱ, Mehmet Emre Atabekⁱ, Fatma Demirel^k, Nurullah Celik^l, Behzat Ozkan^m, Bayram Ozhanⁿ, Peyami Cinaz^l, Pediatric Endocrinology Turner Study Group^o

^aGulhane Military Medicine Academy, Ankara, Turkey; ^bIstanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey; ^cFaculty of Medicine, Marmara University, Istanbul, Turkey; ^dFaculty of Medicine, Ege University, Izmir, Turkey; ^eFaculty of Medicine, Katip Celebi University, Izmir, Turkey; ^fKonya Training and Research Hospital, Izmir, Turkey; ^gFaculty of Medicine, 19 Mayıs University, Samsun, Turkey; ^hKanuni Sultan Suleyman Education and Research Hospital, Istanbul, Turkey; ⁱFaculty of Medicine, İnönü University, Malatya, Turkey; ^jFaculty of Medicine, Necmettin Erbakan University, Konya, Turkey; ^kFaculty of Medicine, Yildirim Bayezid University, Ankara, Turkey; ^lFaculty of Medicine of Medicine, Gazi University, Ankara, Turkey; ^mDr Behçet Uz Children Hospital, Izmir, Turkey; ⁿFaculty of Medicine, Pamukkale University, Denizli, Turkey; ^oFAVOR for Pediatric Endocrinology, Ankara, Turkey

Background: Turner syndrome is one of the most common chromosomal disorders and is seen in 1:2500 female live births. The disease manifests with various clinical features and can be classified according to karyotype as monosomy, mosaicism, numeric, and structural abnormalities. **Objective and hypotheses:** Patients with Turner syndrome have complicated with various manifestations congenital or acquired. In this study we aimed to emphasise the importance of awareness of all these findings and follow-up in adulthood. **Method:** Study was performed via FAVOR Research Centre in which 842 patients from 35 centers in Turkey were registered. **Results:** Mean age at diagnosis was 10.5 ± 4.8 years. The most common complaints were short stature, delayed puberty, and dysmorphic appearance. Karyotype was 45,X in 50.7% of the patients. Other common karyotypes were 45,X/46,XX in 10.8%, 46,X,i(Xq) in 10%, 45,X/46,X,i(Xq) in 9.5%, 45,X/46,X,r(X) in 3.4%, 45,X/46,XY in 2.7%, 45,X/46,X,idi(Y) in 1.3%, and 45,X/46,X,+mar in 1.2%. SRY was searched in 125 patients and were positive in 24 (19.2%). Urinary system abnormalities were present in 16.4% of the patients and the most common abnormalities were horseshoe kidney, collecting system and rotation anomalies. Cardiac abnormalities were detected in 25%, the most frequent being bicuspid aorta followed by coarctation of the aorta and aortic stenosis. Thyroid abnormalities were detected in 16.5% of patients

including hypothyroidism and autoantibody positivity. Patients with isochromosome X (Xi) had higher frequency of autoantibody positivity compared to other karyotype groups, although all karyotype groups were comparable for hypothyroidism. Gastrointestinal (GI) pathologies were present in 9%. The most common GI pathologies were high transaminase levels, celiac diseases and/or celiac antibody positivity and hepatosteatosis. Ear problems were found in 22% including recurrent otitis media, deafness, and history of tympanostomy. Psychosocial problems were encountered in 29.2%. Physical appearance and infertility risk were the most important factors to cause low self-esteem. Eye problems (strabismus, myopia, and ptosis) were seen in 8.8%. Dermatologic problems like nevus, psoriasis, alopecia, vitiligo, and keloid were seen in 21.8%. Insulin resistance and impaired fasting glucose frequencies were 3.3 and 2.2% respectively. Patients with Xi abnormality had more frequently insulin resistance ($P=0.042$) and impaired fasting glucose ($P=0.003$). Dyslipidemia prevalence was 11.3%. **Conclusion:** This study demonstrates the frequency of abnormalities in a large group of patients with TS. Patients should to be examined periodically for these comorbidities in childhood and in transition to adulthood.

P2-D3-614

Aortic Dilation in a Large Cohort of Paediatric and Young Adult Patients with Turner Syndrome

Nadia Geniuk, Elisa Vaiani, Ana Rizzi, Gabriela Guercio, Monica Warman, Diego Michelli, Marco Rivarola, Alicia Belgorosky Hospital de Pediatria Garrahan, Buenos Aires, Argentina

Background: Aortic dilation (AD) occurs in Turner syndrome (TS) increasing the risk of aortic dissection at all ages. There are no current guidelines on what specific aortic diameter measurement should provoke concern in pediatric TS. Because of their small stature, an aortic size index (ASI) has been proposed to normalize the ascending aorta (AA) to body size in young adults' with TS. However, a more reliable index has been also proposed: the ratio of vascular diameter to thoracic vertebra (TV) diameter, which is constant through age in normal children (AVI). **Objective and hypotheses:** To evaluate AD using these two different methods. **Method:** TS patients ($n=87$) were studied. Ages ranged from 3.2 to 25.7 years. According to chronological age they were divided in three groups (Gr). Gr1 ($n: 11$): 1–7.9 years, Gr2 ($n: 42$): 8–15.9 years, and Gr3 ($n: 34$): ≥ 16 years. Simple chest computed tomography were done in all patients. AA and TV diameters were measured. AD was defined as $ASI > 2 \text{ cm/m}^2$ and $AVI > 2$ SDS according to published reference values. **Results:** AD was significantly greater ($P < 0.01$) in all groups. Gr1=81 and 18%, Gr2=47 and 2.3%, and Gr3=23 and 2.9% of patients, using ASI and AVI respectively. All patients with severe AD ($ASI > 2.5 \text{ cm/m}^2$) presented $AVI > 2$ SDS. **Conclusion:** We found a high prevalence of AD in our population of TS. ASI overestimates the risk of AD in all Grs, particularly in younger patients. AVI seems to be a more useful tool to assess AD in the pediatric population. Additional follow up is necessary to evaluate the long time consequences of these findings.

P2-D3-615

Aortic Dimensions and Cardiac Anomalies in a Cohort of Children with Turner Syndrome

Nimasari Ginige, Shamyra de Silva, Shehan Perera

Lady Ridgeway Children's Hospital, Colombo, Sri Lanka

Background: The increased risk for congenital heart malformations in Turner syndrome (TS) is well established with a prevalence ranging from 17 to 45%. The associated cardiac anomalies and normal parameters for aortic dimensions in TS have not been previously reported from Sri Lanka. **Objective and hypotheses:** To document parameters for aortic dimensions and describe structural and functional cardiac abnormalities in a cohort of children with TS. **Method:** Girls with karyotype proven TS, attending an Endocrinology Clinic were evaluated by a pediatric cardiologist using two-dimensional and colour Doppler echocardiography. Aortic annulus, aortic sinus, sino tubular junction, and ascending aortic dimensions were measured. Dysmorphic features and blood pressure were documented. **Results:** 28 patients (5–20 years) with a karyotype distribution of: 45,X (75%), X-mosaicism (14%), and X-structural abnormalities (10%). Eleven of 28 (39.2%) had cardiovascular abnormalities: 9 (81%) were structural and 2 (18%) were functional (hypertension and mitral valve prolapse). Coarctation of aorta (COA) and bicuspid aortic valve (BAV) alone or in combination comprised 45% of the cardiac malformations. Fifteen (53%) had neck webbing of which 5 (33%) had associated BAV or COA. Bilateral SVC and PAPVD were seen in 10.7% each. Three had aortic annulus diameter above normal range. All had aortic sinus diameter in the normal range while diameters of ascending aorta had a wide variation with 5 (17%) being above normal range. One patient (20 years) who underwent surgical VSD closure had all aortic dimensions above normal range. **Conclusion:** Echocardiography is recommended in TS to detect the presence of structural cardiac anomalies. Abnormal aortic dimensions were seen in 25% of our study population highlighting the importance of serial echocardiography in follow up of patients with TS.

P2-D3-616

Improvements in Bone Mineral Density in Girls of Prepubertal Age with Turner Syndrome

Oleg Malievskiy^a, Natalya Volevodz^b, Valentina Peterkova^b

^aBashkir State Medical University, Ufa, Russia; ^bEndocrinological Research Center, Moscow, Russia

Background: Patients with Turner's syndrome (TS) develop osteoporosis, resulting from chromosomal deficiency and estrogen deficiency by gonadal dysgenesis. **Objective and hypotheses:** The aim of this study was to assess bone mineral density (BMD) and parameters of bone remodeling during somatropin therapy in prepubertal girls with TS. **Population and/or methods:** We examined 22 girls with TS of the age of 11–15 years (the mean age

of 13.1 ± 0.9 years), treating by somatropin 'Rastan' (Pharm-standart, Russia) daily at a dose of 0.05 mg/kg subcutaneously (group 1). The comparison group was composed of 11 girls of the same age, not receiving somatropin (group 2). All patients were diagnosed with TS at chromosomal examination of peripheral blood. 19 (57.6%) patients had 45, XO and 14 (42.4%) patients had mosaicism. All girls with TS underwent measurement of areal BMD using dual-energy X-ray absorptiometry (DXA) to obtain anteroposterior lumbar spine values at L1–L4 before treatment and 12 months after beginning of therapy with recombinant GH. We defined osteoporosis as a Z-score < -2.5 and osteopenia as < -1 and ≥ -2.5 . Girls with hypothyroidism were not included in the study. Statistical significance of parameters before and after treatment was evaluated by Wilcoxon's single-rank test. **Results:** In groups 1 and 2, the median Z-score was -1.9 and -1.8 , respectively; osteoporosis was revealed in 2 (9.1%) and 1 (9.1%) girls respectively, osteopenia – in 5 (22.7%) and 3 (27.3%) girls, respectively. The median Z-score rose from -1.9 to -1.7 after 12 months ($P < 0.019$). In group 2, change of Z-score at dynamic follow-up were statistically non-significant. **Conclusions:** Prepubertal TS patients are very likely to develop osteopenia as they reach pubertal age. GH treated prepubertal girls with TS showed improvements in BMD.

P2-D3-617

Early Occurrence of Gonadoblastoma Found at Elective Gonadectomy in Turner Syndrome Mosaic for Y Chromosome

J MacMahon^a, R Morrissey^a, M McDermott^b, M O'Sullivan^b, F Quinn^c, A Green^d, S A Lynch^d, S M O'Connell^a

^aDepartment of Paediatrics and Child Health, Cork University Hospital, Cork, Ireland; ^bDepartment of Histopathology, Our Lady's Children's Hospital, Crumlin, Dublin, Ireland; ^cDepartment of Paediatric Surgery, Our Lady's Children's Hospital, Crumlin, Dublin, Ireland; ^dNational Centre for Medical Genetics, Our Lady's Children's Hospital, Crumlin, Dublin, Ireland

Background: Turner syndrome (TS) is one of the most common genetic disorders in females and occurs in phenotypic females who are missing all or part of one sex chromosome. While the most common mosaic forms of the disorder are 45,X/46,XX and 45,X/46,Xiq, mosaicism for cells containing Y chromosome material is well documented. **Objective and hypotheses:** Owing to increased risk of gonadoblastoma (GB), current recommendations are for elective gonadectomy following diagnosis. But there are no recommendations on lower age limits. **Method:** A review of TS patients attending the Paediatric Endocrinology Clinic ($n=9$) was conducted specifically looking for those with mosaicism for Y chromosome (TSMY). Three cases were identified and all underwent elective gonadectomy. **Results:** Case 1 was diagnosed with TSMY at 2 years. Peripheral blood karyotype showed mosaicism for 45,X (25 cells) and an isodicentric Y chromosome made of Yp and proximal Yq material (25 cells). Gonadectomy at 6 years revealed extensive unilateral GB.

Interphase FISH of the GB tissue showed isodicentric Y chromosome in 43% of GB cells. Case 2 presented with dysmorphic features at birth. G banded karyotype and interphase FISH of blood showed 45,X in 95% and 47,XY+18 (Edwards syndrome) in 5% of cells analysed. Interphase FISH of buccal cells showed 45,X only. Gonadectomy at 13 months revealed bilateral GB, interphase FISH was similar to blood: 45,X(86%), 47,XY+18(14%). Case 3 presented with severe neonatal aortic stenosis. Peripheral blood karyotype showed 45,X (29 cells) and a pseudoisocentric Y chromosome with breakpoint at Yq11.23 (six cells), confirmed on buccal and skin karyotyping. Gonadectomy revealed unilateral GB, karyotype pending. **Conclusion:** All three patients with TSMY were found to have GB at elective gonadectomy. This highlights early age of occurrence of GB despite low mosaicism for SRY cell lines and would support a recommendation for early surgery in such cases, regardless of age.

P2-D3-618

GH Deficiency as a Cause of Persistent Hypoglycaemia in a Child with Turner Mosaic and Kabuki Syndrome

Michal Ajzensztejn^a, Pratik Shah^b, Noina Abid^c, Jane Hurst^b, Deborah Morrogh^b, Shane McKee^c, Khalid Hussain^b

^aThe Evelina London Children's Hospital, London, UK; ^bGreat Ormond Street Hospital for Sick Children, London, UK; ^cThe Royal Belfast Hospital for Sick Children, Belfast, UK

Introduction: We report the first known case of a child with mosaic Turner syndrome (TS) with ring X chromosome abnormality and Kabuki syndrome (*KDM6A* deletion) presenting with hypoglycaemia secondary to severe GH deficiency. Ring X Turner's mosaic have the XIST locus, so the chromosome is inactivated, however the *KDM6A* gene deletion associated with Kabuki syndrome escapes X-inactivation as it falls below the threshold required to manifest inactivation. This results in a more severe phenotype than Turner's monosomy. **Case history:** We describe a girl diagnosed antenatally with a lumbar myelomeningocele and spina bifida. She was born at term with intra-uterine growth restriction and noted to be dysmorphic. Karyotype confirmed Turner's mosaic syndrome 46,XrX(p11;q13)(22)/45,X(8)arrXp22.33p11.2x1,Xp11.1q13.3x2-3,Xq13.3q28x1 with a small r(X). Her features were consistent with Kabuki syndrome. CGH array confirmed the known *KDM6A* deletion associated with Kabuki syndrome. She developed recurrent asymptomatic hypoglycaemia around the ages of 20–25 weeks with concurrent gastroenteritis, which was resistant to treatment with standard TS dose GH therapy. She underwent formal pituitary assessment aged 18 months confirming severe GH deficiency. **Discussion:** Children with TS develop postnatal short stature. They usually have normal GH levels but show end organ resistance to it. Hypoglycaemia has been associated with Kabuki syndrome from various aetiologies including GH deficiency. Two recent case reports describe children with combined Turner mosaic and Kabuki syndrome presenting with hyperinsulinaemic

hypoglycaemia, but no reported cases due to severe GH deficiency alone. The combination of GH deficiency and end organ GH resistance is likely to have led to the severity and resistance to treatment seen in this case, which rectified on treatment with a high dose of GH given in two divided doses (0.07 mg/kg per day). **Conclusion:** From this case, we recommend a low threshold for monitoring blood glucose levels in children with this phenotype and if evident, growth hormone provocation testing should be performed.

P2-D3-619

A Child with Clinical and Cytogenetic Features of Male Edward Syndrome and Turner Syndrome with Bilateral Gonadoblastoma in Infancy

J MacMahon^a, R Morrissey^a, M McDermott^b, F Quinn^c, A Green^d, SM Lynch^a

^aDepartment of Paediatrics and Child Health, Cork University Hospital, Cork, Ireland; ^bDepartment of Histopathology, Our Lady's Children's Hospital, Crumlin, Dublin, Ireland; ^cDepartment of Paediatric Surgery, Our Lady's Children's Hospital, Crumlin, Dublin, Ireland; ^dNational Centre for Medical Genetics, Our Lady's Children's Hospital, Crumlin, Dublin, Ireland

Background: Mosaic Turner syndrome (TSM) commonly occurs in the form of 45,X/46,XX and 45,X/46,Xiq, although mosaicism including the presence of a Y chromosome has been well documented. It is associated with increased risk of gonadoblastoma (GB). **Objective and hypotheses:** To date, there are only six reported cases of TSM with a trisomy 18 karyotype, and only two of these were phenotypically female with 45,X, 47,XY+18 karyotype. **Method:** We present the case of an infant born with dysmorphic features noted at birth (webbed neck, low set ears and broad chest). G banded karyotype and interphase FISH of blood showed 45,X in 95% and 47,XY+18 (Edwards syndrome) in 5% of cells analysed. However, interphase FISH of buccal cells showed only 45,X. Increased nuchal fluid, suggestive of Edward's syndrome had been detected at 13 weeks gestation on ultrasound but had resolved on follow-up scan at 15 weeks hence amniocentesis was not preformed. Renal ultrasound and echocardiogram were normal. Owing to presence of SRY, an elective gonadectomy was performed at 13 months of age. There were bilateral streak ovaries with early evidence of GB bilaterally, rudimentary uterus and bilateral fallopian tubes with unilateral ectopic adrenal tissue identified. Interphase FISH of the gonadal tissue was similar to the blood findings with 45,X in 86% of cells and 47,XY+18 in 14% of cells analysed. **Results:** She is now 2 years old, growing and developing well. **Conclusion:** This case highlights a rare karyotype of TSM and Edwards syndrome in the same patient. Current investigations are ongoing as to the possible causes for this unusual finding. This case was also associated with a finding of bilateral gonadoblastoma. To the authors' knowledge this is the only case with the above karyotype with gonadoblastoma reported.

P2-D3-620

Turner Syndrome: Analysis of Changes in the Age at Diagnosis and Phenotypic and Genotypic Description of 174 Patients

Julie Auger^a, Abderrahim Oussalah^b, Laetitia Lambert^c,
Jacqueline Vigneron^c, Philippe Jonveaux^d, Bruno Leheup^a

^aService de Médecine Infantile et Génétique Clinique, Centre Hospitalier Universitaire de Nancy, et U954, Université de Lorraine, Vandoeuvre les Nancy, France; ^bInserm U954, Nutrition Génétique et Exposition aux Risques Environnementaux (NGERE), Faculté de Médecine, Université de Lorraine, Vandoeuvre les Nancy, France; ^cUnité de Génétique Maternité Régionale de Nancy CHU de Nancy, Vandoeuvre les Nancy, France; ^dLaboratoire de Génétique Médicale, EA 4368, Centre Hospitalier Universitaire de Nancy, Université de Lorraine, Vandoeuvre les Nancy, France

Background: Turner syndrome, characterized by complete or partial absence of second sexual chromosome, is responsible for phenotype of variable severity. **Objective and hypotheses:** The main objective of this work is to describe the evolution of the age at diagnosis of Turner syndrome over time. We also performed a phenotypic and genotypic description and we assessed evolution over time. **Method:** It is a monocentric descriptive observational epidemiological study of a serie of cases. We included a total of 174 female patients followed since 1969 in the center of reference of Nancy (France) for which time of diagnosis was known and karyotype available. **Results:** The median age at diagnosis was 100 months (0–150 months). 10.3% of patients were diagnosed in antenatal period, 24.1% before 6 months, 29.9% between 1 and 11 years, and 35.6% after 11 years. There is a statistically significant inverse correlation between age at diagnosis and time since 1985 ($P=0.0290$). The median age at diagnosis decreased until 2000, but then increased back: 2.5 years between 2000 and 2004, vs 8.3 years between 2005 and 2012. 48.9% of all the patients had a 45,X homogeneous karyotype but the proportion of monosomy X decreased significantly over time ($P=0.016$). **Conclusion:** In this study about evolution of the age at diagnosis of Turner syndrome, we showed a historical evolution with a significant decrease over time which may be related to an effect of prenatal diagnosis and the resulting abortions. The postnatal proportion of 45,X karyotypes, responsible for most of sonographic signs, tends to decrease. It is necessary to pay greater attention to early diagnosis of some moderate forms of expression.

P3-D1-621

The Effect of Working in a Children's Hospital on Urinary Catecholamine Excretion Rates in Male and Female Physicians

Claudia Boettcher^a, Mirko Peitzsch^b, Graeme Eisenhofer^b,
Stefan A Wudy^a

^aCentre of Child and Adolescent Medicine, Paediatric Endocrinology and Diabetology, Justus Liebig University, Giessen, Germany; ^bInstitute of Clinical Chemistry and Laboratory Medicine, University Hospital Carl Gustav Carus at the TU Dresden, Dresden, Germany

Background: Working as a physician is accompanied by emotional and physical stress. **Objective and hypotheses:** Our study aimed to investigate the effect of working day and night in a children's hospital on catecholamine excretion as a marker for acute stress and to work out possible gender differences. **Methods:** 22 paediatricians (ten females, 12 males) aged 27–41 years collected four 12-h urine samples: two during a 24 h-shift at the Children's Hospital Giessen ('on-duty') – the first sample from 0800 till 2000 h the second from 2000 till 0800 h the following morning – and another two on a free weekend ('off-duty'). Urinary excretion rates (ER) per m² body surface (BS) for epinephrine (EPI), norepinephrine (NEPI), normethanephrine (NMN), metanephrine (MN), dopamin (DA), and 3-methoxytyramine (MTY) were determined by liquid chromatography–mass spectrometry (LC–MS). **Results:** The group of physicians as a whole had significantly higher nightly ERs for all metabolites 'on duty' than 'off duty' (EPI, NMN, $P<0.001$; NEPI, MN, $P<0.01$; MTY: $P<0.05$), except DA. Comparing the ERs during the day 'on duty' with those 'off duty', only the ER of EPI was significantly higher 'on duty' ($P<0.001$). When divided into a 'male' and a 'female' group, there were significant differences between days 'on' compared to 'off duty' in the male group detectable for EPI ($P=0.001$) and MN ($P<0.001$), whereas the females showed no differences at all. Similar results gave the comparison of the nights 'on' and 'off duty': there was a significant difference for all ERs except DA in the male group (EPI, NMN, NEPI $P<0.01$; MN, MTY $P<0.05$), but in the female group only EPI was higher 'on duty' ($P<0.05$). **Conclusion:** Working in a children's hospital, especially overnight activates the adrenal medulla resulting in increased catecholamine excretion. Female physicians react differently from males, possible indicating a higher stress resistance to acute stress.

P3-D1-622

Body Composition Analysis in Girls With Premature Adrenarche

Ayse Nurcan Cebeci^a, Aysegul Tas^b

^aPediatric Endocrinology, Derince Training and Research Hospital, Kocaeli, Turkey; ^bPhysiology, Derince Training and Research Hospital, Kocaeli, Turkey

Background: Idiopathic premature adrenarche (PA) in girls refers to the presence of androgenic signs before the age of 8 years in the absence of thelarche. Increased adrenal androgens lead to changes in body composition and transient growth acceleration without effecting final height. Although the association between PA and some components of the metabolic syndrome is well

known, total body fat and body composition analysis are not widely studied. **Subjects and methods:** We examined 38 girls with new-onset PA and 64 age-matched controls. For PA group the inclusion criteria were the appearance of pubic/axillary hair before 8 years of age, the absence of central puberty and absence of any long-term medication. Steroidogenic enzyme defects and virilizing tumors were excluded by hormonal studies and by adrenal ultrasonography. The control group was built from healthy female volunteers of first-second grades of an elementary school from the same district. Height, weight, waist circumference (WC), and hip circumference (HC) were measured. Body composition analysis was executed by bioelectrical impedance method. **Results:** Median ages were 7.44 years in PA group and 6.78 years in controls ($P=0.065$). In PA group, both weight-SDS and height-SDS were significantly higher than controls ($P<0.001$ for both). Although WC was found similar between groups (median 60.5 vs 57 cm in PA group and controls, $P=0.101$), median HC was higher in PA group (69 vs 64 cm, $P=0.003$). While fat percentage was significantly increased in PA group (median 23.05 vs 20.3%, $P=0.010$), fat free mass percentage was significantly decreased (median 77.0 vs 79.5%, $P=0.017$). **Conclusion:** Our findings confirm that PA causes acceleration in body weight and longitudinal growth and significant changes in body composition. The increase in body weight is more prominent in total body fat percentage with a concomitant decrease in fat free mass percentage.

P3-D1-623

Pseudohypoaldosteronism Type 1: Role of Urinary Steroid Profiling in Specific and Early Diagnosis: Lessons in Differential Diagnosis of PHA1 vs PHA2 (Renal Tract Anomaly)

V Abbot, L Ghataore, D J Pieterse, S Chapman, R R Kapoor, N F Taylor, C R Buchanan

KCH, London, UK

Background: Pseudohypoaldosteronism type 1 (PHA1) is a rare disorder of neonatal salt loss unresponsive to mineralocorticoids, requiring salt supplementation. It results from resistance of kidney and/or other tissues to mineralocorticoids, arising from mutations in genes encoding mineralocorticoid receptor (MR: *NR3C2*; autosomal dominant), or epithelial sodium channel (ENaC) genes (*SCNN1A/B/G*; autosomal recessive). Milder clinical phenotype associates with renal PHA1 (*NR3C2*) and shows variable penetrance. PHA1 may be distinguished from PHA2 (2ary to urinary tract abnormalities) by urinary steroid profiling (USP). **Objectives, hypotheses and methods:** Case reports: two families/three patients. **Results:** Pt 1: female, BWt 3.1 kg, 1st child non-consanguineous Caucasian parents. Presented at 3 weeks below BWt with Na 125 mmol/l; K 6.5 mmol/l; glucose, cortisol post-Synacthen, blood gas: Normal. USP diagnostic of PHA1; Aldo 36 000 ($n<2000$) pmol/l, PRA 61 ($n<3$ pmol/ml per h). Stabilised with oral NaCl supps after IV saline treatment.

Subsequently thriving, now age 2 years on ~ 1 mmol/kg per day oral NaCl. Diagnosis presumed *NR3C2* clinically. Neither parent has relevant childhood history. Pt 2: male, newborn sib. Pt 1. BWt 4.1 kg, 39 weeks, Feb/2014 – prospectively evaluated for possible PHA1, even though parental history negative. Day1&2 U/Es and USP normal. Day7 U/Es Na 136/K 5.3 mmol/l; USP diagnostic of PHA1. Day15: Wt loss to 3.88 kg, NA 139/K 4.2 mmol/l started NaCl supps 5 mmol/l per kg per day; Aldo 3670 pmol/l ($n<800$) /PRA 282 mU/l ($n<60$). Clinically well since. Pt 3: female, born 36 weeks, Romanian/Indian parents. EmLSCS for PROM. Admitted with 7% wt loss at 12 days; Na 132/K 6.3 mmol/l. Considered PHA2 (no maternal infection proven)/congenital adrenal hyperplasia (but no virilising signs). Cortisol response to Synacthen, renal USS and MSU normal. Antibiotic treatment and improved feeding. U/Es normalised. Patient discharged by General Team at 1 week pending endocrine (Aldo/PRA) results. Readmitted recurrent salt-wasting crisis/collapse. Initial USP consistent with PHA1 or PHA2 – Subsequent definitive USP supports diagnosis PHA1. Genetic analysis is in process with both families. **Conclusion:** USP analysis is a critical and essential component for diagnosis of salt-wasting disorders in neonates.

P3-D1-624

Genotype-Phenotype Correlations in Bulgarian Patients with c.293-13A/C>G Splice Mutation of 21CYP2A2 Picked up by Neonatal Screening (NS)

Iva Stoeva^a, Ganka Dineva^a, Andrey Kirov^{b,c}, Antoaneta Kostova^a, Tihomir Todorov^c, Ani Aroyo^a, Albena Todorova^{b,c}, Vanio Mitev^b

^aUniversity Pediatric Hospital Sofia/Medical University Sofia, Screening and Functional Endocrine Diagnostics, Sofia, Bulgaria;

^bDepartment of Medical Chemistry and Biochemistry, Medical University Sofia, Sofia, Bulgaria; ^cGenetic Medico-Diagnostic Laboratory Genica, Sofia, Bulgaria

Background: Congenital adrenal hyperplasia (CAH) comprises a group of autosomal recessive disorders caused by defects in one of the several adrenal steroidogenic enzymes. 80–95% of CAH are due to mutations in *CYP21A2* gene encoding 21 hydroxylase. Its residual activity defines the clinical form. Except deletions and large gene conversions, nine pseudogene-derived mutations are responsible for 95% of all CAH alleles. The mutational distribution varies between different populations. c.293-13A/C>G may give either salt wasting (SW) or simple virilizing (SV) forms due to enzyme residual activity. **Objective and hypotheses:** To study genotype-phenotype correlations in Bulgarian patients with homozygous c.293-13A/C>G *CYP21A2* mutations. **Method:** Newborns and siblings with elevated 17-OHP picked up by NS; 17-OHP (Delfia), clinical evaluation, electrolytes; MLPA (multiplex ligation-dependent probe amplification) – first step genetic screening strategy, second direct sequencing of *CYP21A2*. **Results:** 222 827 screened newborns (coverage 82.5%); 22 patients with *CYP21A2* mutations were characterized (two of them previously undiagnosed older

brothers); c.293-13A/C>G is the most common mutation found in this study (59% frequency, one of the highest reported). Ten patients are homozygous for c.293-13A/C>G (seven male and three female). The SW form was clear in nine patients; CAH was late diagnosed in an older brother with history of failure to thrive, frequent vomiting, hospital admissions until early childhood, no regular corticosteroid treatment; at 6 years of age he developed pseudoprecocious puberty. The clinical form, despite the genotype, is difficult to be classified. Virilisation (Prader 2–4) was evident in all of the diagnosed girls. The 17-OHP screening levels were elevated: average 398.2 nmol/l (s.d. ±224), but varied widely (median 414, range 69.9–703). **Conclusions:** c.293-13A/C>G homozygous patients showed variability at manifestation and evolution, even within a family; the c.293-13A/C>G splice mutation is the most common in Bulgaria; our mutational screening strategy needs adaptation.

P3-D1-625

A Pediatric Case of Cushing's Disease Presenting with Diabetic Ketoacidosis

Gonul Catli^a, Ozgur Tarrisever^b, P Sule Can^a, Bumin Nuri Dundar^{a,c}

^aPediatric Endocrinology Unit, Tepecik Training and Research Hospital, Izmir, Turkey; ^bDepartment of Pediatrics, Tepecik Training and Research Hospital, Izmir, Turkey; ^cDepartment of Pediatric Endocrinology, Katip Celebi University, Izmir, Turkey

Background: Cushing syndrome is very rare in childhood and adolescence and often occurs with iatrogenic causes. The major cause of endogenous Cushing syndrome is Cushing's disease, which results due to excessive ACTH secretion from pituitary cells (corticotroph adenoma). **Objective and hypothesis:** Cushing syndrome cases, which presented with diabetic ketoacidosis (DKA) in adulthood have been rarely reported. However, to our knowledge, there is no report of a pediatric case of Cushing's disease presenting with DKA. **Methods:** A 16-year-old girl suffering from polyuria and polydipsia for the last 2 weeks, was admitted with menstrual irregularity and oral moniliasis. Due to her hyperglycemia (venous glucose 556 mg/dl), ketonuria, glucosuria, and metabolic acidosis on arterial blood gas, she was diagnosed with DKA. **Results:** Her weight was 95 kg (+2.89 s.d.), height was 156 cm (–1.03 s.d.), and BMI was 36.98 kg/m² (+3.30 s.d.), with a normal blood pressure. On physical examination; bilateral exophthalmos, oral moniliasis, acanthosis nigricans, moon face, central obesity and striae were detected. Her HbA1c level was 10.4%, C-peptide level was 11.4 ng/ml (0.9–7.1 ng/ml) and diabetes autoantibodies were negative. Her serum cortisol levels at 0800 and 2300 h were high (respectively 31.7 and 26.3 µg/dl), ACTH level was 46.7 pg/ml, and 24-h urinary free cortisol excretion level was 151 µg/m² per day ($n < 70$ µg/m² per day). Based on the results of overnight and low-dose dexamethasone suppression tests, which both failed to suppress endogenous cortisol secretion, the patient was diagnosed with Cushing syndrome. In high-dose dexamethasone suppression test, free

urinary cortisol excretion rate was suppressed by 80%, and a pituitary MRI revealed a 4 mm microadenoma thus she was diagnosed as Cushing's disease. **Conclusion:** Although very rare in childhood, Cushing syndrome should be kept in mind in pediatric patients with obesity, acanthosis nigricans, moniliasis and striae. Diabetic ketoacidosis may be the presenting clinical picture in patients with impaired glucose metabolism.

P3-D1-626

Cyp21a2 Mutation Spectrum in Bulgarian Cah Patients

Albena Todorova^{a,b}, Andrey Kirov^{a,b}, Iva Stoeva^c, Tihomir Todorov^b, Ganka Dineva^a, Antoaneta Kostova^c, Ani Aroyo^c, Vanio Mitev^a

^aDepartment of Medical Chemistry and Biochemistry, Medical University, Sofia, Bulgaria; ^bGenetic Medico-Diagnostic Laboratory Genica, Sofia, Bulgaria; ^cUniversity Pediatric Hospital, 'Screening and Functional Endocrine Diagnostics' Medical University, Sofia, Bulgaria

Background: Congenital adrenal hyperplasia (CAH) is a group of inborn errors of steroidogenesis. It is mainly caused by steroid 21-hydroxylase coding gene (*CYP21A2*) mutations. More than 30% of the *CYP21A2* mutations are deletions, with ethnic specific differences. The Bulgarian mutational spectrum of *CYP21A2* gene is unknown. **Objective and hypotheses:** To determine *CYP21A2* mutation spectrum in Bulgarian CAH patients. **Method:** Nineteen patients, picked up by the 17-OHP neonatal screening (nation-wide implementation 2010), were enrolled in the study. The multiplex ligation-dependent probe amplification (MLPA) was chosen as a first step genetic testing. In many cases targeted sequencing may prove point mutation detected by MLPA. Sequencing of the whole gene was chosen as a second step. **Results:** The molecular genetic testing detected a heterozygous deletion of *CYP21A2* gene in 47% (9/19) of the patients (23.5% allele frequency). The whole gene sequencing revealed the splice site mutation c.293-13A/C>G (allele frequency 57.8%), missense mutations – c.518T>A; p.I173N (13%); c.334G>A, p.Asp112Asn (2.6%), nonsense mutation 955C>T, p.Gln319* (2.6%) and frame shift mutation c.923dupT, p.Leu308-Phefs*6 (2.6%). The total percent is more than 100 because one of the patients carries three mutations. This patient reveals classic salt-wasting CAH phenotype caused by a homozygous c.923dupT mutation and a heterozygous mutation c.334G>A. The double mutated allele was inherited from the mother and it is most probably formed due to non-allelic homologous recombination between the *CYP21A2* and its pseudogene. **Conclusion:** Our results showed that the screening in Bulgarian patients for *CYP21A2* gene mutations should begin with screening for mutations c.293-13A/C>G and c.518T>A; p.I173N, followed by MLPA analysis and whole gene sequencing as a last step. Nevertheless, we should keep in mind that due to possible recombination some of the patients may carry more than two mutations in the *CYP21A2* gene which is important for genetic testing in relatives and prenatal diagnosis.

P3-D1-627

A Rare Cause of Congenital Adrenal Hyperplasia due to P450 Oxidoreductase Deficiency: a Case Report

Peyami Cinaz, Hamdi Cihan Emeksiz, Nurullah Çelik, Esra Döğer, Özge Yüce, Orhun Çamurdan, Aysun Bideci

Gazi University, Ankara, Turkey

Background: P450 oxidoreductase (POR) deficiency is the newest form of congenital adrenal hyperplasia first described in 2004. POR is a protein that transfers electrons from NADPH to all 50 microsomal forms of cytochrome P450. Mutations that cause POR deficiency result in partial deficiency of the enzymes 21-hydroxylase and 17 α -hydroxylase. Remarkable clinical features of the POR deficiency are genital ambiguity in both sexes, glucocorticoid deficiency and Antley-Bixler skeletal malformations. Mild mutations may give rise to polycystic ovary syndrome in women and gonadal insufficiency in men. **Case:** The patient was brought to hospital at the age of 5 years due to micropenis. There was no parental consanguinity. The karyotype analysis of the patient revealed 46,XY. He had a bifid scrotum and a micropenis. The left testicle was palpated in the scrotum and the right one in the inguinal canal. His baseline 17-OH progesterone and ACTH levels (9.16 ng/ml, 110 pg/ml, respectively) were high and cortisol level (10 μ g/dl) was normal. A standard dose ACTH stimulation test was performed and test results revealed a peak cortisol level of 10.2 μ g/dl and peak 17-OH progesterone level of 14.12 ng/ml. The patient was started on hydrocortisone treatment. Molecular genetic analysis of the patient demonstrated a c.1329_1330insC (p.I444Hfs*6) heterozygous mutation which was a previously described and well-known mutation for POR deficiency. **Conclusion:** As in our case, 12% of the reported patients have only one identified mutation for POR deficiency. This rare disorder should be born in mind in 46,XY cases with ambiguous genitalia and hormonal profiles compatible with partial deficiencies of 21-hydroxylase and 17 α -hydroxylase/17,20-lyase.

P3-D1-628

Familial Glucocorticoid Deficiency: Masked Diagnosis by Hydrocortisone Life-Saving Treatment

Federico Baronio^a, Angelica Marsigli^a, Ilaria Bettocchi^a, Davide Tassinari^b, Laura Mazzanti^a, Louise Metherell^c, Antonio Balsamo^a

^aPediatric Unit, Department of Medical and Surgical Sciences, Program of Endocrinology, University of Bologna and S.Orsola-Malpighi Hospital, Bologna, Italy; ^bEmergency Pediatric Unit, University of Bologna and S.Orsola Malpighi Hospital, Bologna, Italy; ^cWilliam Harvey Research Institute, Centre for Endocrinology, Queen Mary University of London, London, UK

Background: Familial glucocorticoid deficiency (FGD) is a rare and potentially life-threatening disease, characterized by

adrenal insufficiency without mineralocorticoid deficiency. It is diagnosed during the neonatal period but also in childhood. Manifestations are recurrent hypoglycemia, seizures or even coma, chronic fatigue, recurrent infections and skin hyperpigmentation. Mutations on mineralocorticoid receptor 2 (*MC2R*) gene and on melanocortin-2 receptor accessory protein (*MRAP*) gene have been described in 25 and 15–20% of cases respectively. **Method:** We report a girl, second child of (probably) related Pakistani parents, with previous unremarkable pathological history. She was evaluated at 2.3 years of age for severe drowsiness (GCS < 8), ketotic hypoglycemia (1 mmol/l), hypotension, developed in course of febrile gastroenteritis. Hyperpigmentation was not recognized.

Euglycemia was restored with i.v. glucose and bolus of hydrocortisone. Cerebral infarction, poisoning, infectious encephalopathy, hyperinsulinism were excluded. Reduced serum cortisol (12 ng/ml) and ACTH levels were considered unreliable due to hydrocortisone treatment. Dexamethazone was early started for cerebral edema and continued for laryngeal edema, due to intubation. The child fully recovered and corticosteroid was tapered. **Results:** The subsequent endocrine studies showed serum cortisol < 2 ng/ml, ACTH > 1250 pg/ml, with normal renin, aldosterone and electrolytes; FGD was suspected and the patient started regular treatment with hydrocortisone. Adrenal hypoplasia and Allgrove syndrome were excluded. Molecular analysis of *MC2R* gene showed a novel mutation (L283R) in homozygosis (confirmed in both parents). **Conclusion:** Our case confirms that FGD is a rare cause of adrenal insufficiency in some cases triggered by infection. Corticosteroid treatment did not allow us to early reach the diagnosis, but saved the child. We suggest, in the case of pediatric ketotic hypoglycemia, to collect few ml of plasma for adrenal function evaluation, and then consider to promptly start corticosteroid treatment.

P3-D1-629

Clinical and Genetic Diagnosis of Allgrove Syndrome

Zdravka Todorova, Elissaveta Stefanova, Ivan Litvinenko, Krasimira Kazakova, Penka Yaneva, Desislava Yordanova, Mihaela Dimitrova

Endocrinology Department, University Children's Hospital, Sofia, Bulgaria

Background: Allgrove syndrome (triple A, 4 A syndrome) is a rare autosomal recessive disorder, characterized by the triad of ACTH resistant adrenal insufficiency, alacrima and achalasia. In addition many patients show progressive neurologic impairment such as progressive peripheral polyneuropathy, hyperreflexia, nasal speech and disautonomia. It is now known that mutations of the *ADRACALIN* (*AAAS*) gene on the 12q13, that encodes the protein ALADIN, are responsible for the clinical presentation. **Objective and hypotheses:** An 18 years old girl, from normal pregnancy of no consanguineous parents, who came at our hospital for first time at the age of ten, with complain of lower limb weakness. In the next 2 years present neurologic symptoms

progressed and new ones appeared. There was an episode of severe hypoglycemia and several ones with serious vomiting imposing hospital admission. In addition hyperpigmentation, hypotension, alacrima and mild optical atrophy were observed in the following years. **Method:** Clinical evaluation, laboratory tests of hormones, electrolytes, biochemical indices, electromyography, ophthalmologic examination, barium esophagography and molecular genetic analysis. **Results:** Laboratory testing proved the ACTH resistant adrenal insufficiency with extremely high ACTH 600 ng/l (7.20–63.3), low free urine cortisol 35 nmol/24 h (100–379), alacrima, motor and sensory peripheral polyneuropathy and excluded achalasia of the cardia. Normal values of very long chain fatty acids in serum excluded adrenoleucodystrophy. A molecular genetic analysis showed two heterozygous mutations of the AAAS gene, which confirmed the clinical diagnosis. The patient receives treatment with hydrocortisone, fludrocortisone, topical eye lubricants and rehabilitation. She is now 18 years old with normal height, weight, mental development and still mild neurologic symptoms. **Conclusion:** There is great variability in the time and order of presentation of symptoms. It is crucial for the patient's quality of life and lifespan to receive an early diagnosis and efficient treatment in order to avoid life threatening complications as in presented case.

P3-D1-630

Clinical Case of Cushing Syndrome in Secreting NET

Gianluca Musolino^a, Marzia Pirana^a, Stefano Chiaravalli^{a,b}, Luigi Nespoli^a, Alessandro Salvatori^a

^aInsubria University, Varese, Italy; ^bFondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy

Background: Neuroendocrine tumors (NETs) represent a complex entity of neoplasm arising from different cell types of neural crest origin. They can produce and/or secrete various hormones or vasoactive substances. Usually sporadic, they can occur in association with other cancers, as part of a multiple endocrine neoplasia type 1 (MEN1), von Hippel–Lindau disease, von Recklinghausen, tuberous sclerosis. **Case report:** We report a case of neuroendocrine tumor in a 15-year male adolescent referred to our clinic for tarry stool, weakness, paleness and significant weight gain (13 kg in the last 8 months). Nine months before he had been hospitalized for acute anemia due to a 18-mm ulcerative lesion of the duodenal bulb, successfully treated with PPI. **Clinical features:** He showed pale skin and mucous membranes. He had protruding abdomen for fat, with palpable liver 1 cm from costal arch. BMI 25 kg/m². Blood pressure: 125/85 mmHg. Laboratory tests confirmed severe anemia (Hb 6.3 g/dl) and showed moderate hypokalemia (3.34 mEq/l) and hyperglycemia (9.8 mMol/l). EGDS revealed two ulcers, the former on upper duodenal bulb with evidence of recent bleeding and the latter in the second duodenal tract. **Laboratory and imaging exams:** The MRI showed normal anatomy of the hypothalamic–pituitary region, increased liver size, with numerous nodular lesions (size from 2 to 24 mm) normal adrenal glands

and a 4-cm solid neof ormation located between the body and the tail of pancreas. Secondary-level laboratory exams demonstrated very high urinary free cortisol/die (> 1000 µg/24 h), salivary cortisol (> 36 ng/ml), ACTH (412 pg/ml), free testosterone androstenedione, high level of chromogranin A (> 1000 ng/ml) and gastrin (> 1000 pg/ml). **Conclusion:** Ultrasound-guided biopsy of hepatic lesion (segment VI) confirmed the pancreatic origin of a gastrin-secreting neoplasm (immunophenotype: CDX2, synaptophysin and gastrin +). The patient underwent distal pancreatectomy, splenectomy, multiple hepatic biopsies and transcatheter arterial chemoembolization (TACE) via the femoral artery, followed by liver transplantation. The histological confirmed well-differentiated pancreatic endocrine carcinoma with gastrin-secreting G cells (T3N1M1). The treatment was successful in normalizing all clinical features and lab parameters.

P3-D1-631

Homozygous c.923dupT Combined with Heterozygous c.334G>A CYP21A2 Mutation: a Case Report from the Bulgarian CAH Screening Programme

Antoaneta Kostova^a, Iva Stoeva^a, Andrey Kirov^{b,c}, Ganka Dineva^a, Tihomir Todorov^c, Albena Todorova^{b,c}, Elissaveta Stefanova^d, Krassimira Kazakova^d, Ani Aroyo^a, Vanio Mitev^b

^aUniversity Pediatric Hospital, 'Screening and Functional Endocrine Diagnostics', Medical University Sofia, Sofia, Bulgaria; ^bDepartment of Medical Chemistry and Biochemistry, Medical University Sofia, Sofia, Bulgaria; ^cGenetic Medico-Diagnostic Laboratory Genica, Sofia, Bulgaria; ^dUniversity Pediatric Hospital, Clinic of Pediatric Endocrinology and Genetics, Medical University Sofia, Sofia, Bulgaria

Background: This case underlines the importance of a newborn screening programme combined with genotyping for confirmation and prognosis of disease severity. **Objective and hypotheses:** Case presentation of a girl with three CYP21A2 mutations. **Method:** Girl, born from first uneventful pregnancy per vias naturalis. Birthweight 3200 g, birthlength 50 cm. Intensive jaundice, start at d3, necessitating phototherapy. Discharged from the neonatal ward on the 7th day, clinically healthy, weight 2970 g. Breastfed. From the 9th day on begin to vomit a little after each feeding. **Results:** 17-OH-progesterone from dried blood spot (taken on the 4th day) > 285 (578.7) nmol/l. The excessively elevated 17-OH-progesterone was highly suspicious for CAH and necessitated immediate referral to the Screening Unit at the University Pediatric Hospital, Sofia. The evaluation at the 11th day revealed: delayed weight gain, jaundice, decreased skin elasticity, 2nd virilisation grade (Prader), hyperpigmented areoles and labia. Hyponatremia (Na-129 mmol/l), hypokaliemia (K-8.1 mmol/l), a high hematocrit (64%), no metabolic acidosis, further increasing of 17-OHP levels (dried blood spot and serum), normal sized adrenals on ultrasound were evident. The girl was classified as salt wasting form of CAH and after informed consent blood for CYP21A2 molecular genetic studies of the family was drawn.

Therapy started at day 11 (Urbason, Cortineff, iv rehydration); switch to oral hydrocortisone three times daily was performed later on with regular adaptations of the dosages according to 17-OHP profiles. Growth and development are according to that of healthy children, no new salt waste crisis occurred until 2 years of age. Sequencing of *CYP21A2* revealed homozygous c.923dupT mutation and a heterozygous mutation c.334G>A. **Conclusion:** The double mutated allele was inherited from the mother and it is most probably formed due to non-allelic homologous recombination between the *CYP21A2* and its pseudogene. The c.923dupT mutation belongs to group Null *CYP21A2* mutations.

P3-D1-632

Secondary Pseudohypoaldosteronism Type 1: the Role of a Urinary Steroid Profile

M L Grace^a, D M Murray^{a,d}, C Joyce^b, N F Taylor^c, L Ghataore^c, S M O'Connell^{a,d}

^aDepartment of Paediatrics and Child Health, University College Cork, Cork, Ireland; ^bDepartment of Clinical Biochemistry, Cork University Hospital, Cork, Ireland; ^cDepartment of Clinical Biochemistry, King's College London, London, UK; ^dDepartment of Paediatrics and Child Health, Cork University Hospital, Cork, Ireland

Background: Secondary pseudohypoaldosteronism (PHA) type 1 is an uncommon salt losing condition of infancy caused by transient resistance of the mineralocorticoid receptors (MR) of the renal tubule to aldosterone. This can be secondary to urinary tract infection (UTI), urinary tract malformation (UTM) or obstructive uropathy. Ninety percent of reported cases present before 3 months and nearly all are under 7 months of age. **Objective and hypotheses:** The commonest clinical presentation is failure to thrive and salt-wasting, associated with metabolic acidosis. The initial presentation may mimic that of congenital adrenal hyperplasia (CAH) with shock, acidosis and hyperkalaemia. Definitive diagnosis can be difficult, but is crucial to guide management. The urinary steroid profile (USP) has a very specific pattern in PHA, with increase of both corticosterone and aldosterone metabolites. This is useful in the exclusion of salt wasting forms of CAH and aldosterone synthase defects. PHA secondary to a UTI is further distinguished by a relative increase in urinary cholesterol. Normalisation of the USP following treatment of the underlying cause confirms resolution of secondary PHA. **Method:** We report findings in two infants with secondary PHA type 1 who presented at 5 and 8 weeks with failure to thrive, profound salt wasting and metabolic acidosis. The two cases had confirmed UTI and UTM. We describe clinical course, management and follow up over a 1-year period focusing on the use of the urinary steroid profile (USP) for the investigation and follow-up of both patients. **Results:** Secondary PHA type 1 is a transient salt losing condition of infancy and the USP offers a reliable non-invasive method for definitive diagnosis. **Conclusion:** We report a new finding that PHA secondary to a UTI can be further distinguished by a relative increase in urinary cholesterol, with

normalisation following treatment of the underlying cause to confirm resolution.

P3-D1-633

Steroid 11 β Hydroxylase Deficiency in Egyptian Children

Noha Musa, Isis Ghali, Sara Farag, Maha Amin, Mona Hafez

Diabetes, Endocrine and Metabolism Pediatric Unit (DEMPU), Children Hospital, Cairo University, Cairo, Egypt

Background: Congenital adrenal hyperplasia (CAH) is one of the most common inherited endocrinal disorders. Steroid 11 β hydroxylase deficiency (11 β OHD) is the 2nd most common form of CAH. It is a rare AR disorder caused by *CYP11B1* mutations with an incidence of 100 000–200 000 in overall population. **Objective and hypotheses:** To detect 11 β hydroxylase deficiency in patients presenting with clinical manifestations and hormonal findings suggestive of CAH. **Method:** The study was cross sectional, including 22 patients (16 females and six males) with CAH, divided into two groups (11 β hydroxylase deficiency and 21 hydroxylase deficiency) according to 11 deoxycortisol/cortisol ratio. Both groups were studied regarding history (demographic data, family history, age at presentation, different presentations), examination (BP measurement, auxology, genitalia, pubertal staging) and investigations including laboratory tests (adrenal precursors, PRA, Na, K) and imaging (pelvic U/S). **Results:** Both studied groups showed no statistically significant difference regarding age at presentation, sex, consanguinity, different clinical presentations, BP assessment, auxology, Prader scoring in females with atypical genitalia, adrenal precursors (except for 11 deoxycortisol level and 11 deoxycortisol/cortisol ratio which were highly significant with a *P* value of <0.001), PRA, Na and K levels. Two 11 β OHD cases had molecular studies done, their sequence analysis revealed a single base substitution in exon 8, codon 448 from arginine (CGC) to histidine (CAC). **Conclusion:** Differentiation is very difficult between 21OHD and 11 β OHD and in order to properly diagnose 11 β OHD, measurement of 11 deoxycortisol is mandatory for all cases with suspected CAH, especially that routine use of mineralocorticoids in 21OHD might be injurious in 11 β OHD prone to hypertension. Furthermore, the need for genetic studies is increasing especially for those patients with atypical presentation (salt wasting 11 β OHD).

P3-D2-634

Prenatal Dexamethasone Use for the Prevention of Virilization in Pregnancy at Risk for Classical Congenital Adrenal Hyperplasia

María Sanz Fernández, Esther González Ruíz de León, Elena Dulín Iñiguez, Begoña Ezquieta Zubizaray, Dolores Rodríguez Arnao, Amparo Rodríguez Sánchez

Hospital General Universitario Gregorio Marañón, Madrid, Spain

Background: The most common form of congenital adrenal hyperplasia (CAH) is 21-hydroxylase deficiency, which in its severe form can cause genital ambiguity in females. This can be ameliorated by administering dexamethasone to the mother. **Case:** This is a family whose index case is a first son diagnosed by Madrid Newborn Screening Program of CAH with salt-wasting form due to 21-hydroxylase deficiency. Mutation analysis revealed: 'hybrid deletion' includes the 655G splicing mutation at intron 2 and 8 pairs deletion of exon 3 from paternal line and a 'large conversion' of the gene in maternal line. Both mutations are a severe type and involve significant virilization. In her second pregnancy, dexamethasone treatment is initiated at 4+5 weeks gestation. The dose administered was 23 µg/kg per day. At 9 week gestation chorionic villous sampling confirmed female foetus affected (46XX) by CAH (same mutations as her brother) so mother was treated until term. Pregnancy was unremarkable until 31 weeks' gestation when spontaneous rupture of membranes. Birth weight was 950 g (-2.06DS) and height 35.5 cm (-2.47DS). Genitalia was assessed as normal at birth, with hypertrophied clitoris according to her prematurity. At 16 days of age her 17OHP concentration was elevated (163 µg/l) and symptoms of salt-losing form were detected. She was administered hydrocortisone (150 mg/m² per day), fludrocortisone (0.025 mg/day) and ClNa (4-5 mEq/kg per day). Maternal side effects of dexamethasone administration were weight gain and facial acne. Gestational diabetes was not attributed clearly to the treatment performed. Foetal exposure to dexamethasone may be related to intrauterine growth restriction and preterm labour. **Conclusion:** Prenatal treatment seems to prevent the gender ambiguity sometimes seen in CAH females. Treatment is offered to women who have previously given birth to a child with severe CAH. Treatment should only be undertaken when the follow-up in the newborn is documented by competent pediatricians experienced with CAH.

P3-D2-635

Congenital Adrenal Hyperplasia: Survey of the Management in Children Across UK

Usha Niranjana^a, Anuja Natarajan^b

^aSheffield Children's Hospital, Sheffield, UK; ^bDoncaster Royal Infirmary, Doncaster, UK

Background: The ultimate goal in the management of congenital adrenal hyperplasia (CAH) in children is to achieve normal growth and development which can be a challenge. The consensus guidance recommends hydrocortisone (10-20 mg/m² per day) and fludrocortisone (50-200 µg/day) therapy titrated carefully with regular monitoring. **Objective and hypotheses:** To determine the current practise in UK regarding the management of CAH in children as there is ongoing debate about the optimal management. **Method:** A survey was mailed to all the members of the British Society of Paediatric Endocrinology

(n=440) asking for a response regarding CAH management from each centre (n=92). **Results:** The response rate was 38% (n=35). Tertiary paediatric endocrine centres constituted 63% while 23% provided tertiary service in a district general hospital (DGH). The number of children with CAH managed by each centre varied from 15 to 120 for tertiary centres to 5-13 for DGH. The dose of hydrocortisone varied significantly from 6-8 µg/m² per day to 12-20 mg/m² per day with majority (71%) using 10-15 mg/m² per day. Similarly fludrocortisone dose varied from 50-300 µg/day with majority (26%) using 50-100 µg/day. The frequency of clinic visits was controversial and centres felt it varied depending on the child's age and clinical status. The majority (46%) did 3 monthly reviews while others did 4-6 monthly (54%) reviews. The frequency and type of investigations: 17 hydroxyprogesterone (63% 6 monthly; 34% yearly), testosterone/DHEAS (37% 6 monthly; 51% yearly), renin/aldosterone (31% 6 monthly; 69% yearly) and bone age (83% yearly, 6% 2 yearly, 9% as indicated) varied with centres. Genetic counselling was provided at diagnosis in 69% of centres while surgical (66%) and psychology (80%) input were primarily as required. **Conclusion:** This pilot survey across the UK highlights the on-going lack of consensus on a unified guidance for managing patients with CAH in the paediatric population. The survey also points to the lack of consistent involvement of other specialists which is an essential part of the management in this group of patients.

P3-D2-636

Neonatal Hypercalcaemia Associated with Congenital Adrenal Hyperplasia

Cigdem Binay, Enver Simsek, Neslihan Tekin, Meliha Demiral

Eskisehir Osmangazi University School of Medicine, Eskisehir, Turkey

Background: Adrenal insufficiency is an important and potentially life-threatening condition, and it is also known as a rare cause of hypercalcaemia. **Objective and hypotheses:** Resistant hypercalcaemia may be associated with hypocortisolism. **Method:** A 18-day-old male infant was born at 36 weeks by emergency cesarean section for fetal distress and intrauterine growth retardation. He was referred to paediatric endocrinology because of the resistant hypercalcaemia. His parents are first degree cousins. On physical examination, the infant was appearing ill with the vital signs, heart rate of 160 beats/min; respiration rate of 68 breaths/min and blood pressure 90/65 mm/Hg, bilateral palpable gonads, a 3 cm phallus and scrotal hyperpigmentation. **Results:** The laboratory evaluation revealed serum glucose, 58 mg/dl; calcium, 12.8 mg/dl; phosphorus, 6 mg/dl; sodium, 134 mEq/l; potassium, 6.8 mEq/l; alkaline phosphatase, 1100 U/l; ACTH, 104 pg/ml; morning (0800 h) cortisol, 4.4 µg/dl; 17-hydroxyprogesterone (17-OHP), 1900 ng/dl, DHEAS, 1000 µg/dl; total testosterone, 306 ng/dl. Standard-dose ACTH test revealed peak cortisol level 12 µg/dl and the peak 17-OHP and

11-deoxycortisol levels were 4800 ng/dl and 37.1 ng/ml respectively. He was diagnosed with congenital adrenal hyperplasia (11 β -hydroxylase deficiency). Serum 25-OH vitamin D and PTH levels were 10.5 ng/ml and 4.8 pg/ml, respectively. Although i.v. saline infusion and furosemid treatment, hypercalcemia was persisted above 12.0 mg/dl. When he was diagnosed with oral hydrocortisone treatment at the dose of 20 mg/m² per day was commenced. Hypertension and hypercalcemia were corrected by hydrocortisone replacement therapy. On the follow-up the patient did not develop hypercalcaemia or hypertension. **Conclusion:** This case report confirms that, CAH may be one of the rare causes of neonatal hypercalcaemia. Neonatologists should consider CAH as a differential diagnosis of neonatal hypercalcaemia.

P3-D2-637

Abstract withdrawn.

P3-D2-638

Addison Disease and Atrophic Gastritis: High Persistent ACTH Levels Although an Adequate Treatment

Eugenia Prinzi, Francesca Serraino, Maria Cristina Maggio, Giovanni Corsello

University Department Pro.Sa.M.I. 'G. D'Alessandro', Palermo, Italy

Background: Primary Addison's disease (AD) is a rare endocrine condition, with reduced or absent secretion of adrenal hormones. Steroid replacement therapy normalizes endocrine assess and the quality of life. More than a half of patients display additional autoimmune conditions, which represent a considerable clinical concern. **Objective and hypotheses:** Antiparietal cells antibodies (APC-Ab) are commonly found in patients with autoimmune Addison's disease, usually pointing to autoimmune atrophic gastritis and pernicious anemia. **Method:** A 12-year-old girl, with a diagnosis of Addison disease made 1.6 years previously (anti-adrenal Ab negative) attended her routine clinic appointment. She had a history of good adherence. Regular medications were: hydrocortisone 10 mg morning, 5 mg afternoon and evening, fludrocortisone 100 μ g morning and 50 μ g evening. On examination she presented with increasing darkening of the skin and easy fatigue. Investigations showed: plasma cortisol h. 8: in the normal range (29 μ g/dl); raised ACTH levels (2976 pmol/ml). PTH, TSH, fT₃, fT₄, anti-TG and anti-TPO antibodies were within the normal range. She presented anemia with the following parameters: Hb 11 g/dl MCV 74fL, ferritin 18 ng/ml.

Autoimmunity tests showed APC 1:640. She is waiting for gastroscopy. **Results:** It was therefore necessary to increase the corticosteroid replacement therapy in order to obtain an appropriate reward: Hydrocortisone 10 mg three times per day, fludrocortisone 100 μ g morning and 50 μ g evening. After 1 and 3 months examinations she showed a progressive reduction of ACTH levels (ACTH 127 pg/ml cortisol 16.9 μ g/dl). **Conclusion:** Autoimmune atrophic gastritis (AAG) is common in patient with AD and may coexist with various hematological presentations. Iron deficiency is often associated with AAG. Addison's patients with coexisting elevated gastric APC-Ab are at risk of enterochromaffin-like cells hyper/dysplasia. In case of rapid onset of anemia and/or iron deficiency we should exclude the presence of gastric adeno-carcinoma or gastric carcinoid. Probably in our patient the concomitant atrophic gastritis, suggested by the appearance of AAG, has been the trigger that required an increased hydrocortisone dose.

P3-D2-639

Four Cases of Ovarian Adrenal Rest Tumors in Chinese Girls with Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency

Su Zhe, Zhang Jun, Ma Huamei, Chen Qiuli, Du Minlian, Li Yanhong, Chen Hongshan

The First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, Guangdong, China

Background: Ovarian adrenal rest tumors (OART) is a rare complication of congenital adrenal hyperplasia (CAH) and is not very well characterized yet. **Objective and hypotheses:** We report four cases of OART in Chinese girls with CAH due to 21-hydroxylase deficiency (21 OHD). **Method:** We describe the clinical, imaging, and surgical findings of the patients. **Results:** The four cases of CAH with OART included three salt wasters and one simple virilizer. The median age of OART diagnosis was 12.5 years. The median follow-up period of OART was 3.6 years. There were histories of CAH poor control, the median persisted period was 6.5 years, before the diagnosis of OART in all of the four patients. Their clinical presentations included severe acne (4), deepened voice (1), accelerated growth (1), primary (1), or secondary (1) amenorrhea. Rectal ultrasonography and MRI scan can find the mass in only one case. All the four girls underwent surgical removal and confirmed the diagnosis of OART. The OARTs could be a big mass or several small nidus with diameter ranging from 0.3 to 0.6 cm. OART located in broad ligament of uterus, between the fimbriae of uterine tube and ovary, and rectal bladder pit. The patients showed clinical relief after the operations. **Conclusion:** OART is rare and much more difficult to diagnose compared to testicular ART. The diagnosis of OART can remain unconfirmed before the operation. Surgical removal is effective.

P3-D2-640

Therapeutic Troubles of Cushing's Disease in Adolescence: Report of a Case

Manuela Deiana^a, Marco Losa^b, Adolfo Trettene^a,
Alessandra Scolari^a, Alessandro Salvatori^a

^aPediatric Clinic, Insubria University, Varese, Italy; ^bNeurosurgery Clinic, IRCCS, San Raffaele Hospital, Milan, Italy

Background: Cushing's disease, due to ACTH-secreting pituitary adenomas, is rare in the pediatric age (0.2–0.5/ million people per year), although accounts for 75–80% of Cushing syndrome in childhood compared to 49–71% in adulthood. We report clinical presentation, diagnostic workup and treatment of a new case with major therapeutics problems. **Case report:** A 15-year-old girl was referred to our clinic because of secondary amenorrhea, acne, hirsutism, and rapid weight gain (15 kg in few months). The physical examination revealed height 157 cm, weight 69.6 kg, BMI 28 kg/m², blood pressure 140/95 mmHg, 'full-moon face', central obesity, wide purple striae on thighs, abdomen and arms and terminal hair on the upper abdomen, sacral region, cheeks and chin. Endocrine findings showed loss of ACTH-cortisol circadian rhythm (67 pg/ml–194 µg/ml 0800 h, 109 pg/ml–255 µg/ml at 1600 h), very high levels of midnight salivary cortisol (25.86 µg/ml) and urinary free cortisol (357 µg/24 h). High dose (8+8 mg/24 h), but not low dose (1 mg), dexametason suppression test suppressed both serum and urinary cortisol and serum ACTH. MRI showed a 0.45 cm adenoma at the left side the anterior pituitary gland. Transsphenoidal adenomectomy was unsuccessful in reducing the levels of ACTH and cortisol and histological examination did not show the presence of ACTH-secreting cells. Three months later a bilateral inferior petrosal sinus sampling for ACTH, indicated lateralization of ACTH secretion to the right side the pituitary gland. Subsequent treatment options may be a new attempt of adenomectomy, a partial hypophysectomy or adrenalectomy. The latter option may cause Nelson syndrome. **Conclusion:** Cushing's disease in the pediatric age range may be a difficult therapeutic challenge. Transsphenoidal surgery is now considered first-line therapy, but selective microadenomectomy can be technically very difficult and an appreciable rate of failure exists.

P3-D2-641

Congenital Hypoaldosteronism of Unknown Etiology in Five Half-Siblings

Jan Foote^{a,b}, Jennifer Cook^a

^aBlank Children's Endocrinology Clinic, Des Moines, Iowa, USA;
^bThe University of Iowa College of Nursing, Iowa City, Iowa, USA

Background: The children had normal 21-hydroxylase screening. An atypical form of congenital adrenal hyperplasia was initially suspected. The first child (female) had hyponatremia, hyperkalemia, elevated ACTH, and elevated androgens at birth. The second child (male) presented at 16 days with hyponatremia,

hyperkalemia, normal cortisol, very elevated renin, low aldosterone, and elevated deoxycortisol. The third (female) and fourth (male) siblings had similar electrolyte abnormalities. The fifth child (male) was treated immediately at birth due to family history. The females had no ambiguous genitalia. The third child died of adrenal crisis associated with acute gastroenteritis. Mother had normal puberty and no history of salt wasting, electrolyte disturbance, or blood pressure abnormality. All three fathers were reportedly healthy. **Objective and hypotheses:** The objective is to determine the etiology of congenital hypoaldosteronism. The hypothesis is that etiology is a rare genetic disorder transmitted by the mother. **Method:** These children have been treated with daily mineralocorticoid therapy and as needed stress steroid therapy. Only the first child received daily cortisol replacement therapy but she was able to be weaned off. The oldest two siblings (different fathers) were evaluated by genetics. The mother and first, second, and fourth siblings (all different fathers) were evaluated by the National Institutes of Health. **Results:** The oldest two siblings had unremarkable CYP11B1 genetic analysis. Mother and three of the siblings had chromosomal microarray testing with normal results. Mother's evaluation was not consistent with hypoaldosteronism or any adrenal insufficiency. Testing for CYP11B2 in one child is pending and if positive, the others may be tested. **Conclusion:** An autosomal recessive disorder is extremely unlikely since all five children have the same mother but there are three different fathers. Differential diagnoses include de novo autosomal dominant or X-linked genetic disorders, or mitochondrial disease.

P3-D2-642

X-Linked Adrenoleukodystrophy in eight Patients

Zhe Meng, Liyang Liang, Lina Zhang, LeLe Hou, Zulin Liu

Department of Pediatrics, Sun Yat-Sen Memorial Hospital,
Sun Yat-Sen University, Guang Zhou, China

Background: Adrenoleukodystrophy (ALD) is a genetic disease associated with demyelination of the CNS, adrenal insufficiency, and accumulation of very long-chain fatty acids in tissue and body fluids. **Objective:** To research the clinical features, laboratory tests, imaging examinations and treatment on children who suffer from X-linked ALD. Also aim at revealing the correlation between the severity of disease and level of very long chain fatty acids (VLCFAs) or MRS. **Methods:** Analyze Eight cases of X-ALD patients' clinical data, laboratory and imaging results, and make a review of related literatures. **Results:** Eight patients were male, onset age ranged from 5 to 11 years old, and the course of disease was from 4 months to 3 years. Three patients presented with reduced vision, two patients presented with hyperpigmentation and all patients show different degree nervous system symptoms, such as intelligence breakdown, attention deficit, coordination, and communication ability decrease, etc. The measurement of VLCFA revealed that low level of C22:0 and high level of C24:0 and C26:0, what's more, we can find increases in the C26:0/C22:0 and C24:0/C22:0 ratios. Cranial MRI showed typical lesion. MRS also demonstrated abnormal image. **Conclusion:** Major clinical features of ALD were demyelination of white matter and adrenal insufficiency, generally with rapid development.

Serum VLCFA is a specific indicator for diagnosis of ALD, and MRS can find lesion in an early phase. The treatment of ALD is difficult, and some researchers demonstrated that application of hematopoietic stem cell transplantation in the early stage is the most effective way until now.

P3-D2-643

The Ganglioneuromas: About Eight Cases

Ali el Mahdi Haddam^a, Soumeya Fedala^b, Djamilia Meskine^a, Farida Chentli^b, Amina Laloui^b, Leila Ahmed Ali^b

^aBologhine Hospital, Algiers, Algeria; ^bBab el Oued Hospital, Algiers, Algeria

Background: The ganglioneuroma (GN) is a benign tumor of the sympathetic nervous system following the sympathogones that affects children and young adults. This is a rare tumor (7/1 000 000) which can be located along the sympathetic chain from the neck to the pelvis. In 20% of cases, the GN is localized in the adrenal. **Objective and hypotheses:** Report observations of eight patients with GN. **Observations:** Eight patients (two boys and six girls) with a mean age of 12 years (4–17) hospitalized for exploration discovered adrenal mass on ultrasound after the onset of abdominal pain (*n*: 8) associated with partial subocclusif syndrome in one case (patient aged 4 years old). clinical and laboratory exploration did not reveal hormonal hypersecretion. All tumors were large (≥ 6 cm), heterogeneous and invasives. Retroperitoneal localization was observed in three patients. The fixing MIBG scintigraphy was observed only in two cases. Seen surgery was too risky because of the close relationship of the tumor with large vessels. Monitoring shall be decided in the younger, while other patients were referred for embolization (*n*: 5) or radiotherapy (*n*: 2). **Conclusion:** GN preferentially affects children and adolescents. 3/5 of them occur before the age of 20. Women are more affected than men. They are voluminous tumors most often found incidentally during a radiological examination or a palpable mass. They can be revealed by non-specific pain or signs of compression. Some GN are hyperfunctioning (catecholamines, VIP, or testosterone) The diagnosis of GN is histopathological. The evolution of these tumors is slow and the prognosis is mainly due to mechanical complications of infectious or order related to tumor volume.

P3-D2-644

Cushings Syndrome without Origin

Sara Queirolo, Piero Balice

Pediatric Endocrinology and Diabetes Unit, Pediatric Department, Civico Hospital, Lugano, Switzerland

Background: Cushings syndrome is a rare entity in children and generally it presents a female to male predominance. The most common cause in childhood is iatrogenic Cushings syndrome

related to chronic administration of glucocorticoids or ACTH. Endogenous Cushings syndrome is divided into ACTH dependent (ACTH overproduction due to pituitary adenoma or ectopic production) and in ACTH independent causes (surrenal adenoma, carcinoma, or bilateral hyperplasia). **Objective and hypotheses:** We describe a case of a previously healthy 10-year-old boy presented with a rapid weight gain associated with growth retardation, facial plethora, and acne. He also complained of palpitations, sleep disruption, and muscular weakness. On clinical evaluation he presented central obesity, hypertension, excess sweating, acne, moon facies, and hirsutism. **Method:** Biochemical investigation showed an elevation of ACTH, cortisol, and other androgen hormones. A low dose dexamethasone suppression test was performed and showed a persistent high level of cortisol and ACTH and loss of cortisol circadian rhythm. Cerebral and abdominal magnetic resonance imaging was performed and both resulted normal. Bilateral inferior petrosal sinus sampling has been done and did not demonstrate the presence of an ACTH pituitary microadenoma. Total body octreotide scanning and repeated positron-emission tomography were also normal and have failed to determine the source of ACTH hypersecretion. **Results:** A therapy with ketoconazole was started with gradual increase of the dose with a good clinical and biochemical response for 2 years. But at the dosage of 1200 mg/day (maximal adult dose) the patient presented relevant bone retardation, hypertension, and hyperinsulinism with a high possibility of multiorgan failure. Finally a bilateral total adrenalectomy was done and an adequate corticosteroid replacement therapy was started with a good outcome. **Conclusion:** However the origin of ACTH hypersecretion, that is most likely cancerogenous, remain still unknown.

P3-D2-645

Untreated Congenital Hyperplasia with Central Precocious Puberty

Mihaela Dimitrova, Elisaveta Stefanova, Krasimira Kazakova, Desislava Yordanova, Zdravka Todorova

University Endocrinology Department, Children's Hospital, Sofia, Bulgaria

Background: Congenital adrenal hyperplasia (CAH) may cause early maturation of hypothalamic-pituitary-gonadal axis when the initiation of corticosteroid treatment is late or/and there is poor compliance. The latter sometimes leads to a lack of treatment. In most cases, if the child survives, he or she develops central precocious puberty. **Case report:** We present a 12-year-old boy born of a normal pregnancy and delivery. In the first months of life he was admitted to children's wards with poor weight gain, vomiting and electrolyte abnormalities. He was thought to have dehydration and treated with electrolyte solutions. At the age of 6 the boy had testicular enlargement and premature pubarche, but no medical advice was requested. When the child was 9 years old the family was born another male with CAH. This led to the diagnosis of toddler with CAH and precocious puberty.

At that time he already had advanced pubertal development with testicular volume 25 ml; penis of 11/3 cm and pubic hair Tanner stage grade V. Levels of 17-OHP and sex hormones were high. However, the boy was not followed up and his parents refused the prescribed therapy. His present age is 12 years, height and weight are 156 cm (0.73 SDS) and 54 kg (1.05 SDS). Serum concentration of 17-OHP is 2551 nmol/l (normal range <30 nmol/l), sex hormone levels are typical for puberty. His pubertal development Tanner stage is grade V. Bone age is 17 years, growth plates are closed. His final height will remain low. **Conclusion:** Timely diagnosis of CAH, as well as good compliance are crucial for normal physical development and prevention of central precocious puberty, short stature, psychological disturbances, and bad quality of life.

P3-D3-646

Hypothyroidism in Anorexia Nervosa due to Primary Autoimmune Pathogenesis

Rajesh Chidanandaswamy^{a,b}, Mars Skae^a

^aDepartment of Paediatric Endocrinology, Royal Manchester Children's Hospital, Manchester, UK; ^bDepartment of Paediatrics, University Hospital of South Manchester, Wythenshawe, Manchester, UK

Background: Anorexia nervosa (AN) is associated with a number of endocrine abnormalities including a low serum free thyroxine level. Hypothyroidism in AN is a recognised condition which is associated with a low normal free thyroxine and triiodothyronine levels (FT₄, FT₃) with an elevated reverse T₃ (rT₃). Serum TSH levels are normal or slightly reduced, suggesting a hypothalamic origin to the suppressed thyroid function which is normally left untreated. It is very rare for patients with AN to have low serum T₄ and elevated serum TSH levels. To date, there are only two published (Matsubayashi S, *et al. Psychosom Med.* 1988; Haraguchi K, *et al. Endocrinol Jpn.* 1986) of a total of five patients in the literature with similar biochemical picture. All these patients however were reported as being thyroid autoantibody negative. It is usual practice to leave such cases untreated as thyroxine therapy may risk increased weight loss. **Cases:** We report two females who presented with intentional rapid weight loss and primary autoimmune hypothyroidism with elevated serum TSH (32.5 ± 18.5 mu/l) and low FT₄ (10.5 ± 3.5 pmol/l) levels. Both patients were found to have positive serum thyroid peroxidase (TPO) antibodies but no goitre. Following replacement with levothyroxine (up to 100 µg daily) both patients demonstrated improved appetite and weight gain whilst undergoing psychiatric interventions for their eating disorder. Long-term follow up of both patients has demonstrated complete resolution of anorexia nervosa and both remain in thyroxine replacement. **Conclusion:** Children with AN with elevated serum TSH levels should prompt further testing for thyroid autoantibodies. We recommend that antibody positive

patients should have thyroxine replacement in a specialist setting as it may enhance metabolic rate, cardiac function, appetite, psychological affect and aid recovery.

P3-D3-647

Autoimmune Disease and Arnold Chiari Syndrome: Any Correlation?

Federica Ortolani^a, Albina Tummolo^b, Stefania Fedele^a, Maristella Masciopinto^a, Sabino Pesce^a, Francesco Papadia^a, Domenica Cornacchia^c, Arianna Labbate^c, Marcella Vendemiale^c, Elvira Piccinno^c

^aMetabolic Diseases, Clinical Genetics and Diabetology, Pediatric Hospital Giovanni XXIII, Bari, Italy; ^bUOC Hereditary Metabolic Diseases, Azienda Ospedaliera Policlinico di Padova, Padova, Italy; ^cClinical Psychology, Pediatric Hospital 'Giovanni XXIII', Bari, Italy

Introduction: Type 1 Arnold Chiari syndrome (extension of cerebellar tonsils into the foramen magnum without involving the brain stem) causes ataxia, dysphagia, headache, breathing problems... So far, an association between Arnold Chiari and autoimmune diseases has not yet been described in literature.

Case 1 description: M.V., on term third born, spontaneous delivery, non complicated pregnancy, normal physical and psychological development stages. Healthy father, mother diagnosed with type 1 Arnold Chiari at 41 years old and Hashimoto's thyroiditis treated with levothyroxine, 25-year-old brother with Raynaud syndrome and type 1 Arnold Chiari, 19-year-old sister with celiac disease, Raynaud syndrome and type 1 Arnold Chiari. Reported parental familiarity with type 1 diabetes mellitus. Since the age of 11, M.V. complained frontal-occipital headache, nausea, photophobia, sonophobia, tinnitus, hypoglycemic episodes, cervical pain, hand paresthesia, lumbalgias irradiating into both thighs, diplopia, and equilibrium problems. NMR confirmed herniation of cerebellar tonsils and rise of the medullary cone between L1 and L2. Like her mother, brother and sister, M.V. underwent section of the filum terminale at 'Istituto Chiari e Siringomielia e Escoliosis De Barcelona'. Total relief of symptoms following surgery. After few months polyuria, polydipsia, 3 kg weight loss. Diagnosis of type 1 diabetes mellitus (HbA1c 13.2%, positive GAD). Negative serology for celiac disease (homozygous DR3-DQ2). Normal thyroid function, negative thyroid autoantibodies. Actually good metabolic control (HbA1c ≤ 6.1%), multiple daily insulin injections. **Case 2 description:** D.H., on term first born, caesarean section, non complicated pregnancy. Healthy parents and younger sister. Not reported familiarity for any autoimmune disease. Diagnosed with autoimmune thyroiditis and type 1 diabetes mellitus at the age of 10 years, actually in good metabolic control. Brain NMR performed few months earlier for persistent headache underlined type 1 Arnold Chiari malformation. **Conclusion:** In literature there are still no clear evidences about a correlation between Arnold Chiari and autoimmune diseases, but we really think it is important to focus our attention on this.

P3-D3-648

Genetically Proven APS Type 1 in Two Siblings

Desislava Jordanova, Elisaveta Stefanova, Krasimira Kazakova, Zdravka Todorova, Mihaela Dimitrova

Endocrinology Department, University Children's Hospital, Sofia, Bulgaria

Background: APS type 1 is characterized by an autosomal recessive inheritance. The clinical diagnosis is based on the presence of at least two of the three following diagnostic criteria: chronic mucocutaneous candidiasis, chronic hypoparathyroidism, and autoimmune adrenal insufficiency. Patients often develop other autoimmune diseases. APS type 1 is caused by mutations in the AIRE gene which encodes the AIRE protein. The protein probably acts as a transcription factor. **Case:** A 10-year-old girl with hypoparathyroidism from the age of 3 years. One year later she developed dystrophic nail changes, mucocutaneous candidiasis, and alopecia areata. The girl presented to us with adrenal insufficiency when she was 4 years and 9 months. From the age of 5 years she was also found to have autoimmune thyroiditis with normal thyroid function. Her treatment includes 1,25-dihydroxy calciferol, magnesium, hydrocortisone, and fludrocortisone. We also evaluated her 6-year-old brother, born without the recommended prenatal diagnosis. He is with hypoparathyroidism since he was 3 years old. From the age of 4 years the boy also has dystrophic nail changes, mucocutaneous candidiasis, and alopecia areata. His therapy is with 1,25-dihydroxy calciferol and magnesium. In January, 2014 molecular-genetic analysis of the AIRE gene was performed in the two siblings and it indicated the presence of a homozygous mutation in exon 6 of the AIRE gene. The results confirm the clinical diagnosis of APS type 1. Their parents are heterozygous carriers of the same mutation. **Conclusion:** Mutation analysis of the AIRE gene will help in early diagnosis of the disease and prevention of serious and fatal complications. In our case the disease has an early onset and rapid manifestation of the autoimmune diseases.

P3-D3-649

Rare Association of Diabetes Insipidus with Autoimmune Thyroiditis

Mirjana Kocova^a, Daniela Pop Gjorceva^b

^aMedical Faculty, University Pediatric Clinic, Skopje, Macedonia;

^bInstitute of Pathophysiology and Nuclear Medicine, Skopje, Macedonia

Background: Diabetes insipidus of central origin has been described in association with other endocrine autoimmune diseases as a rare condition in adults. In children this association is extremely rare. **Objective and hypotheses:** To present a girl with a concurrent appearance of diabetes insipidus and autoimmune thyroiditis. **Method:** Diagnostic approach for both diseases. **Results:** A girl of 11 years presented with polyuria and

polydipsia of 4–6 l/day. She was a well developed child with a height at the 75%. She also had enlarged thyroid gland. The urine osmolality was 104 mOs/l for the normal plasma osmolality. Electrolytes, urea, creatinine, renal ultrasound as well as FSH, LH, and cortisol were normal. Test with Adiuretin confirmed diabetes insipidus of central origin. MRI of the pituitary showed normal size of the anterior pituitary, missing bright signal of the neurohypophysis and slight enlargement of the pituitary stalk. Normal β hCG and α -foetoprotein excluded hypothalamic germinoma. No histiocytosis was confirmed. Ultrasound of the thyroid gland was typical for Hashimoto's thyroiditis. TPO antibodies were >1000 IU/ml, whereas antithyroglobulin antibodies were within normal range as well as T₄, T₃, and TSH. Diabetes insipidus was well controlled with 10 μ g of adiuretin two times per day. The evolution of the thyroiditis was unusual. Three years after the diagnosis, significant hyperechogenic nodule with cystic degeneration was seen on ultrasound in the right lobe that was benign on biopsy. One year thereafter due to the growth of the nodule a scintiscan was performed and it showed a 'cold' – nonfunctioning nodule in the right lobe. Histology confirmed one group of thyrocytes with oncocytic metaplasia and diffusely dispersed inflammatory infiltration. **Conclusion:** Although association of hypophysitis with autoimmune thyroiditis usually appears with affected anterior pituitary, neurohypophysis might be affected also. When no other cause for central diabetes insipidus is found, thorough search for multiple endocrine deficiencies of autoimmune origin should be warranted.

P3-D3-650

Coexistence of Unusual and Distinctive Initial Clinical Manifestations of Systemic Lupus Erythematosus (SLE): a Child Case Presentation and Evaluation of Polyglandular Autoimmune Syndrome in SLE

Murat Karaoglan, Mehmet Keskin, Sibel Öztürk, Ozlem Kesin

Gaziantep Medical Faculty, Gaziantep, Turkey

Background: Involvement of multiple specific endocrine organs in systemic lupus erythematosus (SLE), as initial manifestations, are quite rare. These manifestations can appear singly or combined. But they have been usually reported singly. We report a child case who coexists many of rare clinical features of SLE at the same time at onset. **Objective and hypotheses:** Polyglandular autoimmune syndrome may be a part of SLE. Coexistence of many polyglandular autoimmune diseases as initial manifestations at onset is extremely rare. In that instance, to make diagnosis can be very difficult. **Method:** A 3.5-year-old boy was diagnosed with adrenal insufficiency and treated with hydrocortisone at Children's Hospital of City about 1 year ago. The patient was admitted to our department with history abdominal pain, abdominal distention, and irritability. Physical examination on admission was unremarkable except for massive hepatomegaly, abdominal distention, and photosensitivity. Further investigations showed a patient who represents quite rare features of SLE.

Results: Any autoimmune disorder can involve any endocrine organ. Any autoimmune disorder can contribute or trigger another autoimmune disorder. SLE can be concomitant with polyglandular autoimmune syndrome. **Conclusion:** The initial manifestations of childhood-onset SLE are miscellaneous and serious. Therefore, if any autoimmune endocrine disease with unexpected manifestations was described in any child patient, SLE should be urgently investigated.

considered in patients who have undergone HSCT. Periodic screening with basal glucose is recommended.

P3-D3-651

Diabetes Mellitus after Hematopoietic Stem Cell Transplantation

Karla Maria Narvaez Barros, Ariadna Campos Martorell, Maria Clemente Leon, Izaskun Elorza Alvarez, Diego Yeste Fernandez, Antonio Carrascosa Lezcano

Hospital Universitari Vall d'Hebron, Barcelona, Spain

Background: Patients who have received an hematopoietic stem cell transplantation (HSCT) have more risk of endocrine complications (hypothyroidism, hypogonadism, and growth retardation) but the incidence of diabetes after HSCT is not as well known. The pathogenesis of the diabetes is not well established, and is believed to be multifactorial: chemotherapy, pancreatic irradiation, inflammatory cascade and cytokines, steroids and predisposing genetic factors. **Objective and hypotheses:** Describe the incidence of DM after HSCT. **Method:** Retrospective analysis of 14 patients who received HSCT and who have developed diabetes following ADA's criteria in the last 2 years (2011–2013). **Results:** 16% of patients who received HSCT developed diabetes. Eight patients were women (57%). Mean age at HSCT: 13.2 years (7–18 years). Two had family history of DM2 (14.3%). Anthropometric data at HSCT: normal weight. Three patients were prepubertal. Indication for HSCT: acute lymphoblastic leukemia (5), acute myelogenous leukemia (3), acquired aplastic anemia (3), thalassemia major (1), Fanconi anemia (1), and lymphoma (1). 6 (45%) received an HLA identical HSCT of bone marrow and 8 (55%) unrelated donor (six bone marrow and two cord blood). Maximum dose of corticosteroids before diabetes diagnosis: 1.6 mg/kg per day. Diagnosis of hyperglycemia without ketosis after HSCT: 166.5 days (range 15–902 days). Average glycemia: 329 mg/dl, HbA1c: 7.2% (NV: 4.7–6.4%), C peptide: 3.2 ng/ml (NV 0.81–3.85 ng/ml), and insulinemia 24.3 mU/l. Study of antibodies prior to insulin therapy was performed in eight patients remain positive in one case for antiGAD65. Treatment: MDI with basal-bolus, short acting insulin and basal insulin (glargine (71%) and detemir (29%)). If insulin dose was >1.5 U/kg per day, metformin (35.7%, five patients) was added. Comorbidities: 100% arterial hypertension and hypertriglyceridemia. **Conclusion:** Diabetes after HSCT is associated with metabolic syndrome with insulin resistance, dyslipidemia, and hypertension associated relative insulinopenia. Some patients benefit from coadjuvance with metformin. Diabetes must be

P3-D3-652

Preservation of Ovarian Function in Young Females Cancer Survivors with Risk of Ovarian Failure

Maria Chueca, Sara Berrade, Isabel San Miguel, Mirentxu Oyarzábal, Maria Sagaseta de Ilurdoz, Teodoro Dura, Javier Molina

S^o Pediatría, Complejo Hospitalario de Navarra, Pamplona, Navarra, Spain

Background: Ovarian function in young females with cancer can be damaged due to chemo-radiotherapy. One option to preserve fertility in these patients is the cryopreservation of ovarian tissue, but this is still experimental. **Objective and hypotheses:** Evaluate our experience with cryopreservation (indications, complications, and reimplantation). Through surveys, understand patient perspectives. **Method:** A total of 63 women were diagnosed with cancer (2006–2013). 25 were peripubertal (>9 years old). Nine presented with high risk of ovarian failure (eight Hodgkin's disease and one metastatic rhabdomyosarcoma but was not a candidate due to her advanced condition); cryopreservation was offered to these eight patients including one with a medium risk for osteogenic sarcoma, and all accepted. Patient opinion of the procedure is evaluated, and gonadal function is analyzed through hormonal analysis. **Results:** Characteristics of the nine patients in which cryopreservation was conducted: age at diagnosis 11–15 years old, current age 14–23 years old. FSH levels were from 2.7 to >200 mU/ml and 17 β -estradiol 5–77 pg/ml. Inhibin B ranged from 77 to <10 pg/ml, and AMH 8.1 to <0.1 ng/ml. One patient had ovarian failure, FSH >200, estradiol 5, inhibin B 4 and is under replacement therapy. The cryopreservation was conducted at a specialty clinic via laparoscopy with general anesthesia. In 1–3 days, without delay of oncological treatment, they returned to our center. Patients positively reviewed the procedure conducted and none of them had undergone reimplantation at the time of the survey. **Conclusion:** Given the potential risk of oncological treatment, the cryopreservation of ovarian tissue in high-risk adolescents is an option to consider. The procedure is minimally invasive and well-received by the patients. The procedure should be considered on a case-by-case basis, and patients should be informed of the risks/benefits associated with the procedure.

P3-D3-653

Late Endocrine Effects in Children and Adolescents Submitted to Allogeneic Bone Marrow Transplantation

Hilton Kuperman^a, Lilian Argentino Pinchiri^a, Caroline Kupsch Medrado^a, Claudilene Battistin^a, Thais Della Manna^a, Vaê Dichtchkenian^a, Hamilton Cabral de Menezes Filho^a, Leandra Steinmetz^a, Louise Cominato^a, Juliana Folloni Fernandes^b, Lillian Maria Cristofani^b, Vicente Odone Filho^b, Durval Damiani^a

^aPediatric Endocrine Unit, Instituto da Criança Hospital das Clínicas Faculdade de Medicina USP, São Paulo, São Paulo, Brazil; ^bPediatric Oncology Unit, Instituto da Criança Hospital das Clínicas Faculdade de Medicina USP, São Paulo, São Paulo, Brazil

Background: Pediatric bone marrow transplantation (BMT) can lead to endocrine dysfunctions due to common pre-operative regimens involving chemo and radiotherapy. **Objective and hypotheses:** To evaluate the prevalence and time-of-onset of endocrine dysfunctions after BMT in children and adolescents. **Method:** A retrospective cohort-study design was performed. The inclusion criteria were: <18 years of age at the time of their allogenic BMT program, which started in 2010 in our institution. The patients started their follow-up 100 days after BMT (time 0) and every 6 months, when possible. Height (cm), weight (kg), BMI, and respective z scores (NCHS 2000) as well as their pubertal status (Tanner) were obtained. Lab and imaging data for endocrine diseases (GH deficiency; precocious/delayed puberty, thyroid dysfunctions, adrenal diseases, diabetes insipidus, bone diseases, and metabolic syndrome) were collected. **Results:** From 45 patients submitted to allogenic BMT, 28 (14F) were referred to endocrine evaluation. Their primary disease was diagnosed at 5.5 (± 4.0) years old (range 0.0–13.5). BMT was performed at 8.7 (± 4.3) years (0.8–17.8). Bone marrow donors were: siblings (15), bone bank (6), umbilicus cord (5), and parents (2). The patients were referred for endocrine evaluation at 10.2 (± 4.0) years (2.0–18.0). The prevalence of endocrine complications were: growth disorders ((5), four with GH deficiency under treatment), hypercholesterolemia (4), hypothyroidism (3), amenorrhea (2), obesity (2), precocious puberty (1), delayed puberty (1), and diabetes mellitus (1). 15 patients are still under follow-up with no endocrine disease detected so far. **Conclusion:** These findings emphasize the importance of screening for endocrine complications, particularly growth disorders and metabolic syndrome, in children who have undergone BMT. Children require an early and long follow up so that endocrine complications can be diagnosed and promptly treated.

P3-D3-654

Adrenocortical Tumor: a Case Report

Elisa Guidoni, Renato Scarinci, Giovanna Municchi

University of Siena, Siena, Italy

Background: The annual worldwide incidence of childhood adrenocortical tumors (ACT) ranges from 0.3 to 0.38/million children below the age of 15 years. Only 1–2% of them are feminizing ACT occurring in prepubertal boys and presenting with gynecomastia that normalizes after tumor removal. **Case report:** We present a case of a feminizing ACT. The boy was referred for bilateral gynecomastia, appeared 6 months before, at the chronological age (CA) of 7.5 years. Height was 139 cm ($>97^{\circ}$ ct), weight 27.5 kg (50° – 75° ct), Tanner stage 2 bilateral gynecomastia was present along with prepubertal testes of normal

consistency. Baseline investigations showed normal blood count, electrolytes, liver, and renal function. Serum FT₄, TSH, prolactin, and cortisol were normal; serum FSH, LH, and testosterone were within the prepubertal range. Serum levels of DHEAS and androstenedione were mildly increased: 221 μ g/ml (<15 – 120 μ g/dl) and 3.08 ng/ml (0.09–0.31) respectively. Serum levels of estradiol were elevated: 56.6 pg/ml (prepubertal values <15 pg/ml). Abdominal ultrasound revealed the presence of a mass in the left adrenal gland. A transabdominal adrenalectomy was then performed. Histological examination of the surgical specimen showed an adrenal cortical adenoma with low malignant potential. Two months after surgery gynecomastia regressed and serum estradiol levels normalized. The ongoing follow up includes abdominal ultrasound and estradiol serum levels measurements. **Conclusion:** Unlike pubertal gynecomastia, which is physiological and appears in about 60% of adolescents, prepubertal gynecomastia is a rare disorder that can be associated with severe underlying diseases as adrenal or testicular tumors. Since the behavior of ACT can be unpredictable and very aggressive, early diagnosis with thorough clinical and laboratory examination and surgical excision plays a key role in the management of these rare tumors.

P3-D3-655

A Conservative Approach to the Management of Endocrine Neoplasia in Carney Complex in an Adolescent Male

Carley Frerichs^a, Mohammed Didi^a, Laurence Abernethy^a, Simon Kenny^a, Ian Ellis^b, Joanne Blair^a

^aAlder Hey Children's Hospital NHS Foundation Trust, Liverpool, UK; ^bLiverpool Women's NHS Foundation Trust, Liverpool, UK

Background: Carney complex (CC) is a rare, dominantly inherited condition due to mutations of the tumour suppressor gene PRKAR1A. Endocrine manifestations include: Cushing's syndrome (CS) due to primary pigmented nodular adrenocortical disease, pituitary adenomas, testicular neoplasms, thyroid tumours, and ovarian cysts. The management of some of these tumours is controversial. **Objective and hypotheses:** To describe conservative management of CC. **Method:** The male patient presented age 7 years with a painful tibial lesion, subsequently found to be an osteomyxoma. Age 10 years a myxoma was excised from his neck. Genetic testing demonstrated a mutation of the PRKAR1A gene (frameshift mutation c.18delC.). **Results:** At referral age 12.5 years growth and puberty were normal: Ht SDS 1.29, BMI SDS 2.08, target Ht SDS 0.13, Tanner stage A2, G4, TV 8 ml/8 ml. Pituitary MRI, baseline pituitary profile, thyroid ultrasound (US), and echocardiogram were normal. 24-h urinary cortisol:creatinine ratio on 3 consecutive days was modestly elevated: 30, 34, and 35 nmol/mmol (NR 0–25), but then normalised. Multiple, bilateral, large cell calcifying Sertoli cell tumours were demonstrated on testicular US age 13 years

and have been monitored by US every 6 months. Appearances are unchanged 1.5 years later. Age 14 years he complained of depressive symptoms. BMI SDS increased 0.69 and height SDS decreased 0.25 over the preceding 3 months. Diurnal rhythm of cortisol secretion was lost: 0900 h, 239 nmol/l; midnight, 192 nmol/l; 0900 h, 162 nmol/l; midnight, and 179 nmol/l. ACTH was undetectable. 0900 h cortisol was 144 nmol/l following dexamethasone 2 mg at 2300 h. Adrenal vein sampling indicated focal right-sided origin of cortisol excess. Right-sided retroperitoneoscopic adrenalectomy restored normal, diurnal patterns of ACTH and cortisol secretion. **Conclusion:** This patient has been managed conservatively, in accordance with the family's wishes, to preserve testicular and adrenal function, with close surveillance of testicular appearances and cortisol profiles. This approach is controversial, with bilateral orchidectomy and adrenalectomy being advocated by some.

P3-D3-656

Two Cases of Thyroid Carcinoma in Children

Bethany Mitchell^a, Noina Abid^a, Fiona Eatock^b, Deirdre Donnelly^b

^aThe Royal Belfast Hospital for Sick Children, Belfast, Northern Ireland, UK; ^bThe Royal Victoria Hospital, Belfast, Northern Ireland, UK

Background: Whilst thyroid carcinoma is rare in children, thyroid nodules in children have an increased risk of being malignant. Two 10-year-old patients with thyroid nodules presented to the Royal Belfast Hospital for Sick Children in December 2013. **Objective and hypotheses:** Illustration of sporadic and genetic presentations of thyroid carcinoma in children. **Method:** Presentation of two cases of thyroid carcinoma in children. **Results:** The first case is a previously well 10-year-old girl who presented with a firm, asymmetrical nodular goitre. Ultrasound scan showed an enlarged, abnormal thyroid with multiple abnormal lymph nodes. Fine needle aspiration stained positive for TTF1 and CK19 but negative for calcitonin – in keeping with papillary thyroid carcinoma. She proceeded to total thyroidectomy and bilateral cervical lymph node dissection. On histology, tracheal margin was positive and 18 of 66 lymph nodes were positive. She is currently awaiting radioactive iodine treatment. The second case is a 10-year-old boy who presented to ophthalmology with painful eyes. He was found to have limbic hyperplasia and other features in keeping with multiple endocrine neoplasia type 2B (MEN2B). No family history of note. Ultrasound scan of neck revealed suspicious solid nodules within both lobes of the thyroid and extensive cervical lymphadenopathy. Ultrasound scan of liver was normal, calcitonin markedly elevated and catecholamines normal. He proceeded to total thyroidectomy and bilateral cervical lymph node dissection. On histology, confirmed to be thyroid medullary carcinoma with positive margins and 26 of 60 lymph nodes positive. On genetic testing, a missense mutation in RET gene demonstrated (exon 16, c.2753T>C, codon 918),

confirming a diagnosis of MEN2B. **Conclusion:** These two cases clearly illustrate both sporadic and genetic presentations of thyroid carcinoma in children and that genetic cases can arise *de novo*.

P3-D3-657

Is There Any Correlation Between Height and Pediatrics' Malignancy

Bahram Darbandi, Maryam Jafrودي, Adel Baghersalimi, Shahin Koohmanaee, Afagh Hassanzadeh Rad, Setila Dalili

Pediatrics Growth Disorders Research Center, School of Medicine, 17th Shahrivar Hospital, Guilan University of Medical Sciences, Rasht, Iran

Background: Recent studies had been demonstrated that raised height could be related with Hodgkin lymphoma (HL). In addition, increased osteo-sarcoma had been indicated in taller individuals and those with earlier pubertal growth spurts. However, some investigators obtained no significant relation between elevated height and childhood malignancy. **Objective and hypotheses:** We aimed to investigate whether there is any correlation between height and pediatrics' malignancy or not. **Method:** This is a prospective study which included children and adolescents aged 14 years and less with newly diagnosed malignancies who were admitted to pediatric oncology ward in 17 Shahrivar Children Hospital during October 2009–October 2013 in north part of Iran, Rasht. Height was measured by tape meter and the comparison between height and 25th and 50th NCHS was evaluated. Data were reported by descriptive statistics and analyzed by Regression tests in SPSS version 19. **Results:** Malignancy had been observed in 78 (38.6%) boys and 124 (61.4%) girls with the mean age of 74.76 ± 44.06 months. Results showed that leukaemia was the most common cause of malignancy. Mean heights in most children with malignancies were more than 20th percentile and under 50th percentile of the NCHS. **Conclusion:** Although, in this article there was significant correlation between height and cancer but it could be better if larger sample size matched for sex was assessed in a cohort study. Also, if the correlation between height and cancer could be acceptable, cancer could be prevented by measuring IGF1 and GFBP3 factors.

P3-D3-658

Increasing Testicular Size due to Bilateral Large Cell Calcifying Sertoli Cell Tumours in a Peri-Pubertal Child with Carney Complex

Sarah Geoghegan^a, Rose Morrissey^a, Michael Moore^b, M O'Sullivan^c, Michelle Murphy^d, Alan Irvine^e, Stephen O'Riordan^a, Fergal Quinn^f, Susan O'Connell^a

^aDepartment of Paediatrics and Child health, Cork University Hospital, Cork, Ireland; ^bDepartment of Radiology, Cork University Hospital, Cork, Ireland; ^cDepartment of Histopathology, Our Lady's

Hospital Crumlin, Dublin, Ireland; ^dDepartment of Dermatology, South Infirmery Victoria University Hospital, Cork, Ireland; ^eDepartment of Paediatric Dermatology, Our Lady's Hospital Crumlin, Dublin, Ireland; ^fDepartment of Paediatric Surgery, Our Lady's Hospital Crumlin, Dublin, Ireland

Background: Carney complex (CNC) is a rare multi endocrine neoplasia syndrome associated with endocrine and non-endocrine tumours. Three types of testicular tumour have been described; large cell calcifying Sertoli tumours (LCCST), Leydig cell tumours and testicular tumours of adrenal origin. LCCST is a rare benign stromal tumour, which has been observed in 41% of males affected with CNC, usually appearing in the first decade of life. It can be hormonally active, presenting with gynaecomastia or gonadotropin-independent precocious puberty. It is generally benign although malignant transformation has been described. In pre-pubertal patients conservative management is preferred, with anti sex steroid therapy as needed, to manage secondary sexual characteristics. LCCST can cause replacement obstruction of seminiferous tubules leading to reduce fertility. CNC patients have morphologically reduced sperm and abnormal sperm number. Testicular sparing surgery is often not suitable due to the multifocal nature of the tumour. **Objective and hypotheses:** To describe the presentation of LCCST in a peripubertal boy. **Method:** A 11-year-old boy diagnosed with CNC 1 year previously with multiple lentiginoses and blue naevi was referred for endocrine management. He was heterozygous for a known nonsense mutation of the PPKAR1A gene (p.R42). Height was <2nd centile. Bone age was normal. Testicular volume was 4 ml bilaterally, suggesting early pubertal onset. Six months later testicular volume had increased and appeared bulky. Height velocity was 5.6 cm/year (+0.8 SDS). **Results:** A 11-year-old boy diagnosed with CNC 1 year previously with multiple lentiginoses and blue naevi was referred for endocrine management. He was heterozygous for a known nonsense mutation of the PPKAR1A gene (p.R42). Height was <2nd centile. Bone age was normal. Testicular volume was 4 ml bilaterally, suggesting early pubertal onset. Six months later testicular volume had increased and appeared bulky. Height velocity was 5.6 cm/year (+0.8 SDS). **Conclusion:** A 11-year-old boy diagnosed with CNC 1 year previously with multiple lentiginoses and blue naevi was referred for endocrine management. He was heterozygous for a known nonsense mutation of the PPKAR1A gene (p.R42). Height was <2nd centile. Bone age was normal. Testicular volume was 4 ml bilaterally, suggesting early pubertal onset. Six months later testicular volume had increased and appeared bulky. Height velocity was 5.6 cm/year (+0.8 SDS).

P3-D3-659

Evaluation of the Relation between Thyroid Dysfunction and Oxidant/Antioxidant Status in Obese Children

Ali Ascı^a, Derya Bulus^b, Nesibe Andiran^c, Belma Kocer-Gumusel^d

^aDepartment of Toxicology, Faculty of Pharmacy, Atatürk University, Erzurum, Turkey; ^bDivision of Pediatric Endocrinology,

Keçiören Research and Educational Hospital, Ankara, Turkey; ^cDivision of Pediatric Endocrinology, Keçiören Research and Educational Hospital, Yildirim Beyazit University, Ankara, Turkey; ^dDepartment of Toxicology, Faculty of Pharmacy, Hacettepe University, Ankara, Turkey

Background: Obesity has been defined as 'abnormal or excessive fat accumulation that may impair health' by World Health Organization. **Objective and hypotheses:** Although the role of oxidative stress in obesity has been interest of subject in recent studies, comprehensive studies evaluating parameters of oxidant/antioxidant status in children are limited. Moreover, there has been an increasing focus on the relationship between obesity and thyroid function. This study was aimed to evaluate the role of oxidative stress in obesity and to investigate the possible relationship between thyroid hormones and oxidative stress parameters in obese children. **Method:** The changes in oxidant/antioxidant status (lipid peroxidation (plasma MDA and urine F2 isoprostane); plasma carbonyl; erythrocyte antioxidant enzyme activities (glutathione peroxidase 1 (GP×1), superoxide dismutase (SOD), and catalase (CAT))) and thyroid hormone parameters (TSH and sT4) were measured in the newly diagnosed obese children (n=33, mean age=13.4). **Results:** Indicate that the equilibrium between oxidants and antioxidants is deteriorated in obese children. SOD activity was found to be increased (33.7%; P<0.05) and CAT activity decreased significantly (12.8%; P<0.05) in obese children compared to control group (n=31; mean age=13.8). No changes were observed in GP×1 activity. Significant increases were found in carbonyl, MDA and F2-isoprostane levels of obese group when compared to control children. Significant alterations in thyroid hormone status were also detected in obese children. While levels of TSH elevated, levels of sT4 decreased significantly in obese children according to control (57 and 14% respectively). **Conclusion:** These alterations might occur as an adaptive response to increase the energy expenditure in obesity or the oxidative stress observed in obesity might be a possible underlying mechanism in the disruption of thyroidal functions. The findings that contribute to the definition of pathophysiology of childhood obesity may have marked importance in preventing cardiovascular diseases that might arise in older ages and in developing preventive approaches.

P3-D1-660

Normal Serum Calcium Levels and Vitamin-D Dependent Rickets Type 2 (VDDR-II): a Novel Vitamin D Receptor Mutation

Damla Goksen^a, Samim Ozen^a, Sachiko Kitanaka^c, Tsuyoshi Isojima^c, Ozgur Cogulu^b, Sukran Darcan^a

^aDepartment of Pediatric Endocrinology, Ege University School of Medicine, Izmir, Turkey; ^bDepartment of Pediatric Genetics, Ege University School of Medicine, Izmir, Turkey; ^cDepartment of Pediatrics, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

Background: VDDR-II, is an autosomal recessive disorder characterized by the early onset of rickets with hypocalcemia, secondary hyperparathyroidism and hypophosphatemia and is caused by mutations in the vitamin D receptor (VDR) gene. **Objective and hypotheses:** 2 years old Turkish girl first offspring of consanguineous parents admitted to the hospital for the evaluation of total alopecia and bilaterally genu varum deformity. She was born with normal pilosity, hair loss was observed at 3 months, and alopecia was completed by 6 months. Her motor and mental development was normal and she had used daily oral 400 IU vitamin D regularly until 1 year old. **Method:** In her physical examination; weight was 9.2 kg (SDS: -2.1), height was: 78.5 cm (SDS: -1.31). She had frontal bossing, prominence of costochondral junctions, widening of wrists, and bilaterally genu varum deformity. **Results:** She had serum calcium of 9.4 mg/dl (8.5-10), phosphorus of 2.2 mg/dl (3-5.5), ALP of 988 U/l (100-350), PTH of 778 pg/ml (12-60), 25(OH) D3 of 32 pg/ml (20-100). Blood gas analyses, renal and tubular functions tests were normal. X-ray of the left hand wrist and lower extremities were compatible with severe rickets. Molecular analysis of VDR gene revealed the presence of a novel homozygous missense mutation (S360P). Her parents were heterozygote for the same mutation. Functional analysis is continuing for this mutation. **Conclusion:** The clinical spectrum of VDDR-II varies widely, probably reflecting the type of mutation within the vitamin D receptor and the amount of residual vitamin D receptor activity. S360P mutation in the vitamin D receptor may be associated with normocalcemic VDDR-II.

Results: This 8 year girl was referred for first seizures with loss of consciousness. She also had headache and vomiting, without papilledema. The height and intelligence were normal. There was no mucocutaneous candidiasis or cataracts. The serum calcium level is low (1.57 mmol/l (normal 2.10-2.55)), and the phosphorus level elevated (3.76 mmol/l (normal 0.85-2.15 mmol/l)). Blood levels of ionized calcium was low (0.65 µmol/l), magnesium normal (0.7 mmol/l (normal 0.7-1.0)). Urine calcium excretion was low. The serum alkaline phosphatase level is age-appropriate, 1,25[OH]₂D₃ was not measured, while blood magnesium was normal. Levels of intact PTH were low (<3.0 (normal 10.0-69.0 pg/ml) on an immunometric assay). Radiograph of the wrist was normal. CT scans revealed calcifications in the basal ganglia. TORCH and ultrasound of the kidneys were uneventful. Calcitriol and calcium were recommended. **Conclusion:** Idiopathic IHPT is rare in childhood. Although no alteration in eleven IHPT related genes was found, further follow-up is needed to elucidate the genetic and/or autoimmune etiology of IPPT in this child.

P3-D1-661

No Gene Alterations in 11 Genes Associated with Isolated Hypoparathyroidism

Zoran Guceva^a, Vesna Sabolic^a, Velibor Tasic^a, Toshikatsu Mitsui^b, Toshikatsu Hasegawa^b

^aMedical Faculty Skopje, University Paediatric Clinic, Skopje, Macedonia; ^bPaediatrics, Keio University School of Medicine, Tokyo, Japan

Background: Idiopathic isolated hypoparathyroidism is rare in children. Most often aetiology is autoimmune or genetic. **Objective and hypotheses:** To sequence eleven genes (*AIRE*, *CASR*, *GATA3*, *GCM2*, *PCLN1*, *PTH*, *TBCE*, *TRPM6*, *GNAS*, *PRKARIA*, *PDE4D*) associated with hypoparathyroidism in a child with isolated hypoparathyroidism (IHPT) in order to find a specific gene alteration in IHPT. **Method:** We systematically sequenced the 11 genes associated with hypoparathyroidism. A total of 1321 genomic regions comprising 246 158 bp were captured with use of custom-designed SureSelect kit (Agilent, Santa Clara, CA, USA). To search structural mutations (e.g., gene deletion and duplication) including the 11 hypoparathyroidism-related genes, we performed aCGH (Agilent Technologies).

P3-D1-662

Hypercalcemia due to Subcutaneous Fat Necrosis in a Newborn Successfully Treated with Pamidronate Infusion Therapy

Ali Atas^a, Suleyman Geter^a, M Emin Guldur^b

^aDepartment of Pediatric Endocrinology, University of Harran, Sanliurfa, Turkey; ^bDepartment of Pathology, University of Harran, Sanliurfa, Turkey

Introduction: Subcutaneous fat necrosis (SFN) of the newborn is an inflammatory disorder of the adipose tissue that rarely disease which may be complicated with potentially life-threatening hypercalcemia. The etiology of hypercalcemia was related to persistently elevated 1,25-dihydroxyvitamin D₃ levels. **Case:** The case 47 days (length 0.3 SDS; weight -1.48 SDS) who presented sucking difficulty and debility duo to hypercalcemia with an initial physical examination determined indurated plaques over the back and buttocks without erythema. The baby girl at 38 weeks, weighing 4000 g were born by cesarean section. Newborn with complicated meconium aspiration syndrome had received treatment in new-born-service for 15 days. Laboratory and imaging tests revealed severe hypercalcemia (19.92 mg/dl), normal serum phosphorous (4.0 mg/dl), suppressed parathyroid hormone (3 pg/ml), hypercalciuria (2.37 urinary calcium (mg)/creatinine ratios (mg)), elevated 1,25-dihydroxyvitamin D₃ levels (112 pg/ml) and nephrocalcinosis. Despite treatment with IV fluids, and furosemide, calcium levels remained high. The patient was given one doses (1 mg/kg per dose) of pamidronate. Calcium/creatinine ratios and calcium levels decreased within 72 h. Clinical symptoms resolved rapidly after normalization of serum calcium levels. A punch biopsy specimen showed

multinucleated giant cells. No persistent nephrocalcinosis was observed. The usual treatment of hypercalcemia includes hyperhydration, corticosteroids and diet. This treatment is not always effective in normalizing plasma calcium concentration. Recently, pamidronate has been used in the treatment of hypercalcemia associated with many disorders. **Conclusions:** We report a 47-day-old baby who developed subcutaneous fat necrosis presented with symptomatic hypercalcemia which successfully treated with pamidronate infusion therapy. Pamidronate is effective, well-tolerated in the short-term.

P3-D1-663

Hypovitaminosis D: Factors Affecting in Spanish Children and Adolescents

Rosaura Leis^a, Rocio Vazquez^a, Luisa Maria Seoane^b, Silvia Barja-Fernandez^{a,b}, Isabel Martinez-Silva^c, Concepcion M Aguilera^d, Josune Olza^d, Mercedes Gil-Campos^e, Lidia Castro-Feijoo^f, Carmen Cadarso-Suarez^c, Angel Gil^g, Rafael Tojo^a

^aUnit of Investigation in Nutrition, Growth and Human Development of Galicia, Pediatric Department (USC), Complejo Hospitalario Universitario de Santiago (IDIS/SERGAS), Santiago de Compostela, Spain; ^bEndocrine Physiopathology Group, Complejo Hospitalario Universitario de Santiago (IDIS/SERGAS), Santiago de Compostela, Spain; ^cUnit of Biostatistics, Department of Statistics and Operations Research (USC), Santiago de Compostela, Spain; ^dDepartment of Biochemistry and Molecular Biology II, Institute of Nutrition and food Technology, Center for Biomedical Research (UGR), Granada, Spain; ^ePediatric Research and Metabolism Unit, Reina Sofia University Hospital (IMIBIC), Cordoba, Spain; ^fPediatric Endocrinology, Pediatric Department (USC), Complejo Hospitalario Universitario de Santiago (IDIS/SERGAS), Santiago de Compostela, Spain

Background: Vitamin D adequate concentration is essential for growth, development and health during vital cycle. Hypovitaminosis D pandemic is associated with a wide range of pathologies. **Objective and hypotheses:** The objectives of the present study were to characterize vitamin D status in children and adolescents residing in Galicia (Northwest of Spain, latitude 43°N) and to determine if serum 25-hydroxy-vitamin D (25(OH)D) concentration is related to age, gender, pubertal period and adiposity. **Method:** Serum 25(OH)D levels were measured by LIAISON method in 471 children and adolescents (2–18 years age) and analyzed in correlation to age, gender, pubertal period and adiposity, measured by BMI. **Results:** An overall prevalence of hypovitaminosis D was present in the 67.1%. Females had significantly lower serum 25(OH)D levels (25.56 ± 14.03 ng/ml) than males (29.71 ± 17.10 ng/ml) ($P=0.004$). Lower 25(OH)D levels were found in pubertal (25.52 ± 13.97) than prepubertal (29.21 ± 16.83 ng/ml) ($P=0.011$) children. In children, an inverse lineal effect of BMI ($P=0.015$, lineal coefficient (β) = -0.3191)

and age ($P=0.043$, lineal coefficient (β) = -0.4109) on 25(OH)D concentration was observed. **Conclusion:** In conclusion, it was found a high prevalence of low vitamin D status levels in children and adolescents from Galicia. The association of age, gender, pubertal period and adiposity with 25(OH)D levels was established. Obese pubertal males are special risk group of hypovitaminosis D, so it is necessary to control their vitamin D levels to establish intervention and prevention strategies including vitamin D supplements.

P3-D1-664

Abstract withdrawn.

P3-D1-665

Survey of Vitamin D Status in Breastfeeding Infants Under the Age of 6 Months Attending the Growth Monitoring Clinic at Rubaga Hospital

Nalunkuma Cissy^a, Laigong Paul^b, Mworozzi Edison^b, Larry Fox^a

^aPETCA, Nairobi, Kenya; ^bMakerere medical School, Kampala, Uganda

Background: Vitamin D deficiency has been found to occur in peoples of all ages worldwide, including those living in sunny climates. Sun exposure is the main source of this vitamin for many people but its utilization is influenced by many factors such as lifestyles and availability of sunlight. The breastfeeding infant is particularly at increased risk of deficiency because of its dependence on maternal stores. **Objective and hypotheses:** The hypothesis for this study was that vitamin D deficiency is uncommon in the breast feeding infants under the age of 6 months. The study objectives were to find the prevalence of vitamin D deficiency and associated risk factors in breastfeeding infants under the age of 6 months attending the immunization and growth monitoring clinic. **Method:** It was a cross-sectional study with an analytical component. Questionnaires and physical exams were used to obtain information on neonatal events and feeding practices in infants and mothers, and examinations for any signs of vitamin D deficiency respectively. Serum samples were taken to determine the levels of 25 hydroxy vitamin D, calcium, phosphorus and alkaline phosphatase. **Results:** A total of 154 children aged between 6 weeks and 6 months were enrolled into the study. Nineteen were excluded from the final analysis because of incomplete data. The prevalence of vitamin D deficiency (< 20 ng/dl) in this study was 83.7% (113/135). Elevated alkaline

phosphatase levels were found to be significantly associated with vitamin D deficiency. None of the other factors were found to be associated with hypovitaminosis. **Conclusion:** The prevalence of vitamin D deficiency (<20 ng/ml) was 83.7% in this study. Alkaline phosphatase was significantly associated with hypovitaminosis.

P3-D1-666

Hypercalciuria in Patients with Coexisting Osteogenesis Imperfecta and Renal Tubular Acidosis

Luisa Aguiar, Gregory Braden, Holley Allen

Baystate Children's Hospital, Springfield, Massachusetts, USA

Background: Hypercalciuria, short stature and low bone mineral density are features of distal renal tubular acidosis (dRTA) and osteogenesis imperfecta (OI). If untreated, the presence of dRTA in patients with OI may worsen the prognosis and lead to poorer height outcomes. We describe two unrelated children with an unusual association between OI and dRTA. **Cases:** Patient 1 is a 7-year-old female diagnosed prenatally with a COL1A2 mutation and postnatally with type IV OI who presented at 20 months of age with metabolic acidosis and inappropriately alkaline urine, in the setting of family history for dRTA. She had a low urine PCO₂ (maximum 28 mmHg; normal >60–70 mmHg) and low urine-blood PCO₂ after acetazolamide test and has since been on potassium citrate treatment with correction of the acidosis. Patient 2 is a 13-year-old male diagnosed with type I OI at 16 months of age (COL1A1 mutation) who had an abnormal acetazolamide test a few months later (maximum urine PCO₂: 29 mmHg; normal >60–70 mmHg). He received therapy with potassium citrate until 10 years of age, when it was successfully discontinued. Patients 1 and 2 both had intermittent hypercalciuria, but distinct OI severity: patient 1 is growing below the 3rd percentile and has frequent fractures requiring bisphosphonate therapy, while patient 2, who never received bisphosphonates, is growing at the 50th percentile with no recurrent fractures. **Conclusion:** Case reports in the literature describe dRTA initially misdiagnosed as OI, but this is, to our knowledge, the first description of coexistence of the two conditions. The etiology of hypercalciuria in OI has not been fully elucidated. We hypothesize that in some patients it may be secondary to dRTA, and alkali therapy could

prevent nephrocalcinosis and nephrolithiasis along with improving height attainment and bone disease.

P3-D1-667

Metabolic and Bone Disorders in Vertically HIV-Infected Children

Maritza Vivanco^{a,b}, Constanza Riveros^c, Paulina Balboa^{a,b}, Mariana Hevia^{b,d}, Eloisa Vizueta^f, Ana Maria Chavez^g, Julia Villarroel^h, Ana Maria Alvarez^e, Claudia Torrejon^{a,b}

^aUniversity of Chile, Santiago, Chile; ^bRoberto Del Rio Hospital, Santiago, Chile; ^cInta, University of Chile, Santiago, Chile,

^dUniversity of Andes, Santiago, Chile; ^eSan Juan De Dios Hospital, Santiago, Chile; ^fSan Borja Arriaran Hospital, Santiago, Chile;

^gExequiel Gonzalez Cortez Hospital, Santiago, Chile, ^hFelix Bulnes Hospital, Santiago, Chile

Background: Life expectancy of children with human immunodeficiency virus (HIV) has increased due to highly active antiretroviral therapy. Metabolic disorders and changes in bone mineral density (BMD) are common in adult patients with HIV. There are few studies evaluating metabolic and bone involvement in children. **Objective and hypotheses:** To evaluate metabolic disorders and BMD in vertically HIV-infected children in four Chilean hospitals. **Method:** A total of 68 children with HIV were studied (35 women), 12.2 years (3.8–18.5). We determined disease stage, zBMI, zHeight, vitamin D levels and BMD. Energy, protein and calcium intake were recorded. Spearman and partial correlations were used. **Results:** 5-13-4-23-4-1-11-4 and 3 patients were in stage N1, A1, A2, B1, B2, B3, C1, C2 and C3 respectively. 68% were normal weight (46/68), 7% underweight, 18% overweight and 6% obese. 49% (32/66) had body fat >30%, 44% (26/59) elevated triglycerides, 22% had a height/age <–2 SD. Vitamin D levels were <20 ng/ml in 28% of patients, 30% between 20 and 30 ng/ml. Spine BMD was <–1.5 SD in 16% (11/68) and 7.3% (5/68) <–2 SD. Hip BMD was <–1.5 SD in 2% (2/68) and 6% (4/68) <–2 SD. All patients consumed about 2.5 times their protein requirements, 27 and 68 <75% of their energy and calcium requirements. Significant correlations were found between BMD and zheight, zBMI, CDC disease classification at diagnosis $r < 0.26$ ($P < 0.05$), Current classification $r < 0.3$ ($P < 0.01$), worst CDC classification presented $r < 0.3$ ($P < 0.05$), and years of treatment $r < 0.4$ ($P < 0.01$). **Conclusion:** Paediatric patients with vertically HIV infection have a high percentage of body fat mass and altered triglycerides and bone involvement correlated with disease severity. This would increase the risk of chronic diseases in adulthood.

P3-D1-668

Lumbar Spine Areal Bone Mineral Density and 25-Hydroxyvitamin D Serum Concentrations at 2-Year Follow-up in Patients with Osteogenesis Imperfecta

Claudia Piona, Giovanni Moser, Diego Ramaroli, Malesani Francesca, Grazia Morandi, Rossella Gaudino, Franco Antoniazzi

Department of Life and Reproduction Sciences Pediatric Clinic, University of Verona, Verona, Italy

Background: Cyclic treatment with bisphosphonates (BP) is now considered a 'standard care' for children with osteogenesis imperfecta (OI). Vitamin D is a necessary nutrient for bone health for all children but especially for those with OI. In the literature few studies have considered the relationship between bone mineral density, vitamin D and pubertal stage in children treated with BP for OI. **Objective and hypotheses:** The purpose of this study is to evaluate the vitamin D status and to assess the relationship between 25-hydroxyvitamin D (25OH-D) level, pubertal stage and the variation in lumbar spine areal bone mineral density (LS-aBMD) measurements during a 2-year follow-up in children with OI. **Method:** This retrospective study comprised 28 patients affected by OI treated with neridronate for at least 4 years. Charts of these 25 patients were reviewed for mean 25OH-D level and mean variation in LS-aBMD (% Δ BMD) in 2-years follow-up. The patient cohort was divided into three groups according to pubertal stage: prepubertal group (SP1), pubertal group (SP2) and postpubertal group (SP3). Each group was divided into two subgroups numerically similar according to 25OH-D serum concentrations (A: >26 ng/ml; B: <26 ng/ml). **Results:** Almost 60% of our patients have insufficient (<30 ng/ml) or deficient (<20 ng/ml) level of 25OH-D. The mean serum 25OH-D concentrations was 28.9 ng/ml (SP1 35.58 \pm 15.48 ng/ml; SP2 25.24 \pm 5.62 ng/ml; SP3 25.9 \pm 8.81 ng/ml). In prepubertal SP1 and postpubertal SP3 subgroups BMD improved, but not significantly, during the 2-years follow-up (% Δ BMD SP1 A:18%, B:14%, P:0.271; % Δ BMD SP3 A:5%, B:6.93%, P:0.322). In pubertal subgroup SP2 % Δ BMD increased more in patients of subgroup A respect patients of subgroup B, with a significantly difference between the two subgroups (% Δ BMD SP2 A: 27.72%, B:11.84%, P:0.029). **Conclusion:** We find a positive association between high vitamin D status and LS-aBMD in pubertal patients with OI. Stable vitamin D level above 30 ng/ml during pubertal development may keep low PTH level decreasing bone resorption and potentially stimulate the increase of bone mass during treatment with BP in adolescents with OI.

P3-D1-669

Achondroplasia and Neurological Disorders

Fatima Saraoui^a, Soumeiya Fedala^a, Ali el Mahdi Haddam^b, Farida Chentli^a, Djamilia Meskine^b, Leila Ahmed Ali^a

^aBab el oued Hospital, Algiers, Algeria; ^bBologhine Hospital, Algiers, Algeria

Background: Achondroplasia is the most common cause of genetic dwarfism with a prevalence of 1/10 000 to 30 000 birth. It is a pathology of dominant inheritance linked to the mutation of the receptor gene growth factor on chromosome 4p16 fibroblasts FGFR3 responsible rhizomelic dwarfism and multiple complications likely to compromise the functional and vital prognosis of patients. **Objective and hypotheses:** Find the frequency of neurological complications in children and adolescents with achondroplasia and specify scalability. **Method:** Twenty patients with achondroplasia were hospitalized in our department between 2000 and 2013. In addition to clinical examination, paraclinical was performed with X-rays of the skeleton, brain and spinal MRI. **Results:** The mean age of patients was 7 \pm 1.4 years (4–18). Six patients had an age \geq 15 years. The neurological examination and neuroophthalmologic were normal in all cases. 33% had a non-active hydrocephalus. One patient had a narrowing of the foramen magnum by atlando - odontoidienne hypertrophy and narrowing of the foramen magnum requiring only monitoring. A narrowing of the spinal canal observed only in a patient aged 16 years old. **Conclusion:** The molecular defect is responsible for rhizomelic dwarfism. Bone growth is done in the width direction, and not of a length which causes the short bone. At the spine, the growth of vertebrae can cause a narrowing of the spinal canal with the risk of compression and hydrocephalus. Neurological complications appear at the age adults but can occur earlier. clinical and neuroradiological monitoring are required.

P3-D1-670

Primary Hypomagnesaemia with Secondary Hypocalcaemia (HSH): an Uncommon Diagnosis for a 2 Month Old Afro-Caribbean Formula Fed Infant Presenting with Seizures

Chibuzor Ihe, Jennifer Kalitsi, Ritika Kapoor, Charles Buchanan
Kings College Hospital, London, UK

Background: HSH is a rare condition, first described by Paunier *et al.* (1968). It is an autosomal recessive disorder arising from impaired intestinal absorption of magnesium (Mg) together with renal Mg loss due to a re-absorption defect in the distal convoluted tubule. Mutations in the TRPM6 gene (Chr9q21) (OMIM #607009) have been identified as the underlying genetic defect. A review of 28 affected individuals (21 families) showed median age of diagnosis of 2 months, all but one presenting with seizures. Other modes of presentation include tetany, and associated clinical findings include mental retardation, cardiac arrhythmias, hyperactivity and failure to thrive. We report the only case known to our regional centre over a 20 year period. **Objective/hypotheses/method:** Case report and literature review. **Results:** A 2 month old Afro-Caribbean infant presented with history of apnoea, limb twitching, drooling of saliva, eye rolling and subsequent floppiness. He was thriving (weight 50th–75th centile) and fully established on formula feed. Examination revealed no dysmorphism, otherwise unremarkable. Initial bloods:

Ca 1.59 mmol/l, Phos 2.82 mmol/l, Mg 0.13 mmol/l, ALP 324 IU/l, Vit D 23 µg/l (normal) with PTH 74 ng/l. A standard IV dose of Mg was given with two further repeats to achieve physiologic levels. Renal ultrasound normal; wrist X-ray showed no features of rickets. He was discharged on maintenance oral Mg glycerophosphate (Mg level >0.7 mmol/l). He is now 7 year old and has had five further inpatient admissions for HSH, arising from non-adherence to treatment, the longest interval between each being 30 months. Genetic studies on his TRPM6 gene identified a homozygous splice site mutation, consistent with clinical diagnosis of HSH. **Conclusion:** The commonest differential for hypocalcaemia with seizures in an Afro-Caribbean infant in Northern Europe would be vitamin D deficiency. However, atypical biochemical profile, notably hypocalcaemia with severe hypomagnesaemia, should prompt early consideration of the alternative diagnosis of HSH.

P3-D1-671

A Challenging Diagnosis of Pseudohypoparathyroidism Type 1a and Practical Management: a Case Report

M L Grace^a, S O'Riordan^b, S M O'Connell^{a,b}, C Bogue^c, C Joyce^d, J Allgrove^e

^aDepartement of Paediatric and Child Health, University College Cork, Cork, Ireland; ^bDepartement of Paediatric and Child Health, Cork University Hospital, Cork, Ireland; ^cDepartment of Paediatric Radiology, Cork University Hospital, Cork, Ireland; ^dDepartment of clinical Biochemistry, Cork University Hospital, Cork, Ireland; ^eDepartment of Endocrinology and Diabetes, Great Ormond Street Hospital, London, UK

Background: PHP is a rare heterogeneous genetic disorder causing parathyroid hormone (PTH) resistance. This condition is caused by deficiency of the α subunit of the protein Gs, encoded by GNAS gene. Clinical classification is based on presence or absence of Albright hereditary osteodystrophy (AHO) and multiple or single hormone resistance, to PHP1a/1c and PHP1b respectively. **Objective:** To describe the clinical and practical management of a case of PHP1a in a challenging clinical context. **Method:** Case review of clinical notes and investigations in 8 year old girl with recent hypothyroidism and severe hypocalcaemia. A previous clinical diagnosis of Beckwith Wiedemann syndrome (BWS) was made in the neonatal period, however genetic analysis was negative. At 6 years she was referred to endocrinology services with new onset hypothyroidism. **Results:** Severe hypocalcaemia calcium 1.63 mmol/l (RR 2.1–2.62), high PTH 613 ng/l (RR 15–65), and high phosphate 3.10 mmol/l (RR 1.0–1.8), were found, with normal renal function, ultrasound and urinary calcium 0.04 mmol/l. She was commenced on calcium and vitamin D supplements; however the PTH (319 ng/l) remained elevated. Clinical and radiological features were consistent with AHO, PTH resistance with coexisting TSH resistance made the diagnosis of BWS doubtful and PHP1a was considered. The introduction of calcium supplementation generated painful subcutaneous calcinosis in her feet. Daily activities were restricted due to severe

pain. She improved only when calcium supplements were stopped and 1,25-dihydroxyvitamin D (One Alpha 25 ng/kg per day) was started. Analgesia and orthotics were an essential part of management. GNAS1 gene and methylation (imprinting defect in PHP1b) defects were negative. **Conclusion:** When making a new diagnosis of PHP1a, excess calcium supplementation should be avoided, with a goal to maintain calcium in the low normal range and focus on careful 1,25-dihydroxyvitamin D dose adjustment. Aiming to minimize bone demineralisation and optimize normal PO4, PTH thereby avoiding excessive calcium deposition.

P3-D1-672

Obese Adolescent with Gait and Depression

Vera Zdravkovic^{a,b}, Vladan Zivaljevic^{b,c}, Vadislav Bojic^a, Maja Jesic^{a,b}, Natasa Dragutinovic^a, Silvija Sajic^{a,b}

^aUniversity Children Hospital, Belgrade, Serbia; ^bFaculty of Medicine, University of Belgrade, Belgrade, Serbia; ^cCentre for Endocrine Surgery, Clinical Centre of Serbia, Belgrade, Serbia

Introduction: Hypercalcaemia is an uncommon electrolyte disorder, frequently discovered incidentally based on routine blood chemistry results. **Case report:** A 14-year-old adolescent was admitted to the Endocrinology Department due to obesity, gait and depression. His weight had been gradually increasing over the previous 2 years, and on admission his BMI was 31.5 kg/m². The pain in his legs started a year ago, but worsened progressively and in the months prior to admission, the patient could not walk without the aid of crutches. He was on antidepressant therapy due to adjustment disorder. oGTT showed impaired glucose tolerance, but incidental finding was hypercalcemia. A detailed family history ruled out the possibility of various forms of familial hyperparathyroidism and since a neck ultrasound did not show any abnormalities, Technetium-99m sestamibi scintigraphy was performed, which demonstrated a right-sided parathyroid adenoma. Minimally invasive parathyroidectomy was performed successfully with a decrease in PTH levels (from 640.7 to 6.55 pg/ml). Seven days after surgery, biochemical test results indicated hungry bone syndrome (serum calcium level 1.9 mmol/l, serum phosphate level 1.0 mmol/l). After 4 weeks calcium supplementation therapy and antidepressants were stopped. One year

Biochemistry	Normal values	
Calcium (mmol/l)	3.54 ↑	2.02–2.60
Phosphate (mmol/l)	0.92	1.0–2.0
Alkaline phosphatase (U/l)	982 ↑	< 618
Ca/Cr urine	0.17	< 0.01
iPTH (pg/ml)	503.1 ↑	10–60

after surgery, he walks normally, no signs of depression and calcium levels are normal. The remaining problem is his struggle to loose weight, his BMI is 34.8. **Conclusion:** Hyperparathyroidism is rare in children, but we have to consider measurement of calcium in a child with pain in legs and mood changes.

P3-D2-673

Normal Bone Mineral Acquisition in Korean Adolescents; Korea National Health and Nutrition Examination Surveys

Hye Won Park^{a,b}, Byung Ok Kwak^a, Kyo Sun Kim^{a,b}, Sochung Chung^{a,b}

^aKonkuk University Medical Center, Seoul, Republic of Korea;

^bKonkuk University School of Medicine, Seoul, Republic of Korea

Background: The large portion of bone mass is acquired with body growth during adolescent period and peak bone mass is achieved in early adulthood. Body composition is known as predictor of bone health. **Objective and hypotheses:** The aims of this study were to evaluate normal bone mineral acquisition during adolescent period and to determine the factor that affects on it in Korean. **Method:** This study was based on data from the Fourth and Fifth Korea National Health and Nutrition Examination Surveys (KNHANES) that conducted by Korea Centers for Disease Control and Prevention. We used bone mineral content (BMC), bone mineral density (BMD), fat free mass (FFM), and fat mass (FM) of whole body and regional data (head, arms, legs, lumbar spine and pelvis in BMC and BMD; trunk instead of spine, and pelvis in FM and FFM) using dual-energy X-ray absorptiometry. **Results:** A total 2120 adolescents (1112 male, 1008 females) between the age of 10 and 19 years were included. Whole body BMC (WBMC) was lowest at 10 years (1226.8 g in male and 1220.7 g in female) and highest at 19 years (2556.6 g in male and 2089.5 g in female). During adolescent period WBMC were increased 2.1 times in male and 1.7 times in female. Whole body BMD (WBMD) was lowest at 10 years (0.86 g/cm² in male and 0.84 g/cm² in female) and highest at 19 years (1.16 g/cm² in male and 1.10 g/cm² in female). WBMD were increased 1.3 times during this period. The WBMC fraction of FFM were 4.4 – 4.9% in male and 4.7–5.6% in female, and higher in female ($P < 0.001$). WBMC and WBMD were strongly associated with FFM than FM, especially FFM of trunk in both genders. **Conclusion:** Significant increases in BMC and BMD were observed during adolescent periods in both genders and FFM was the strongest predictor of WBMC and WBMD acquisition.

P3-D2-674

Klippel-Trenaunay-Weber Syndrome: the First Case Report in an African Child

Olumide Jarrett, Kehinde Fasina

University of Ibadan, Ibadan, Nigeria

Background: Klippel-Trenaunay-Weber syndrome is characterized by a triad of port-wine stain, venous malformation, and bony and soft tissue hypertrophy. Most patients would have two out of the three features. It is a rare disorder occurring in one out of 100 000 live births. Diagnosis is largely clinical. The cause is unknown but could be due to a sporadic genetic mutation. Management is conservative. **Objective and hypotheses:**

We report a case of a 4month-old-boy with clinical features in keeping with Klippel-Trenaunay-Weber syndrome. **Method:** Case report. **Results:** Product of a full term uneventful pregnancy period delivered to non consanguineous apparently healthy parents. He weighed 6.72 kg (5th centile) and his length was 60.5 cm (25th centile). The child was dysmorphic with flattened nasal bridge, low set ears, widened anterior fontanelle with metropic sutural diastasis. There was facial asymmetry with the left side larger than the right. There was crossed hemihypertrophy with the right limbs larger than the left. The child also had a capillary haemangioma over the lateral surface of the right upper limb. Systemic review was normal. The child has remained clinically stable while investigations have been hampered by financial constraints as there is no medical insurance. Main problem is cosmetic as parents are concerned about his appearance. Child is being managed by a multidisciplinary team comprising endocrinologists, plastic and orthopaedic surgeons. The child is currently being followed up closely on out-patient basis. **Conclusion:** This is an interesting case of crossed hemihypertrophy and also the first case of Klippel-Trenaunay-Weber syndrome reported in Africa. This report is to increase awareness of this rare condition and to motivate research.

P3-D2-675

FGFR3 Gene: a Very Rare Mutation

Magdalena Hawkins^a, Ana Alcalde^a, Julia Yebra^a, Victor Quintero^a, María Jose Trujillo-Tiebas^b, Alfonso Cañete^a

^aHospital Infanta Sofía, Madrid, Spain; ^bFundación Jiménez Díaz, Madrid, Spain

Background: Achondroplasia and hypochondroplasia are more frequent types of skeletal dysplasia. *De novo* mutations in the fibroblast growth factor receptor 3 (FGFR3) gene are the principal cause. More than 95% of the cases of achondroplasia result from a mutation G1138A (Gly380Arg). In hypochondroplasia we usually (50–70%) found the change C1620A y C1620G, N540K (*Asn540Lys*). **Objective and hypotheses:** We describe an skeletal dysplasia with a very rare mutation of FGFR3 gene. We describe the same mutation in his mother, with mild phenotype of disharmonic short stature. **Methods:** A 5 month-old-boy referred to our clinic due to short stature with short legs and arms. Normal delivery. 37 weeks of GA. BW 2625 gr (p16, –1DE). BL 49 cm (p49, –0.04DE). Neonatal jaundice needed intensive phototherapy. Hiperbilirubinemia neonatal que precisó fototerapia intensiva. Father height 163 cm (p2, –2.23DS). Mother height 147 cm ($P < 1$, –2.85DS). Short stature in mother's family. At 5 months age: weight 7.1 kg (p18, –0.92DE), height 62 cm (p2, –2.13DE). CP: 42.5 cm (p12, –1.2DE). Short legs and arms, due to proximal segments (mesomelia). No bizarre appearance, just frontal bossing. Blood test: normal systematic exams. Negative ATG, normal IGF1 e IGFBP3, and normal bone age. Normal ultrasounds. Normal karyotype 46,XY. Normal SHOX gene sequencing. X-ray: shorter proximal segments of legs and arms. Molecular study of FGFR3 gene (PCR+sequencing exon 8): heterozygous mutation c.1150T>C. Mother carries the same

heterozygous mutation. **Conclusions:** We describe a rare mutation of FGFR3 gene. A T to C change at 1150 nucleotides of the FGFR3. This mutation provokes an change in the sequence of amino acids (pPhe384Leu) previously described in two families with skeletal dysplasia, with a variable expression, from soft to severe forms.

P3-D2-676

Abstract withdrawn.

P3-D2-677

Risk Factors Affecting the Development of Nephrocalcinosis, the Most Common Complication of Hypophosphatemic Rickets

Meliksah Keskin, Senay SavaS Erdev, Elif Sagsak, Zehra Aycan, Semra Cetinkaya

Dr Sami Ulus Kadın Dogum, Çocuk Saglığı ve Hastalıkları Eğitim ve Arastırma Hastanesi, Ankara, Turkey

Background: Hypophosphatemic rickets is a clinical picture with inadequate bone mineralization that develops following renal phosphate loss. One of the most common complications in this group of patients is nephrocalcinosis. However, the mechanisms causing nephrocalcinosis are not clear. **Objective and hypotheses:** The aim of our study was to define the risk factors affecting the development of nephrocalcinosis, which is reported to be seen at a rate of 50% in this patient group, and to enable preventive measures to be taken. **Method:** A total of six patients diagnosed with hypophosphatemic rickets at Dr Sami Ulus Training and Research Hospital and then followed up for at least 3 years were included in the study. The patients were evaluated at 3-month periods. Serum calcium, phosphorus, alkaline phosphatase, bicarbonate, creatinine, BUN, PTH, and spot urine Ca/cr ratios were recorded. Renal and urinary system ultrasonography was performed at the beginning and then at 6-month intervals. The patients were treated with calcitriol and phosphate supplementation. **Results:** Nephrocalcinosis developed in three of the six cases with at least 3 years (range 36–60 months) of follow-up. The mean phosphate dose was higher in the group that developed nephrocalcinosis than the group without nephrocalcinosis ($P < 0.05$). The calcitriol dose was also higher in the nephrocalcinosis group but the difference between the two groups was not significant ($P > 0.05$). There was no relationship between the hypercalcemia and hypercalciuria episodes detected in the two groups and nephrocalcinosis development ($P > 0.05$). **Conclusion:** A high phosphate dose is generally seen as a risk factor for nephrocalcinosis ($P < 0.05$). We had four cases consisting of two groups of siblings. The fact that only one sibling developed nephrocalcinosis in both these sibling groups indicates that the treatment agents used are more effective than genetic

factors in these patients. However, new studies with a larger number of patients are needed to enable more definite conclusions on this issue.

P3-D2-678

When is Epilepsy Not Epilepsy

Richard Lloyd-Nash, Tabitha Randell

QMC, Nottingham, UK

Background: We present four patients who presented with seizures and their journey to diagnosis. All were managed for some time as epilepsy before the diagnosis of hypocalcaemia was made.

Objective and hypotheses: To confirm not all seizures are epileptiform. **Method:** Case reports. **Results:** Case 1. Seen at age 4 with seizures. EEG normal. Mild language delay. Seizures continued intermittently on anti-epilepsy medication and was seizure free until age 12, when had prolonged tonic-clonic seizure. Calcium 1.37 at time of seizure, with inappropriately low PTH. Genetic analysis showed 22q deletion. Case 2. Presented age 2 with muscle cramps and afebrile seizure. No investigations done at first presentation. Had second seizure several months later and found to have low calcium and low PTH. Autoimmune hypoparathyroidism diagnosed. Subsequently developed Addison's disease age 6 and AIRE gene mutation confirmed. Case 3. A 12 year-old-boy presented with dystonic movements, muscle spasms, and parasthesiae. MRI showed extensive intracerebral calcification. Calcium not checked. Started on L-DOPA but as symptoms persisted, referred to tertiary neurology clinic at age 14. Calcium then checked; 1.24 with PTH of 223 (markedly elevated). Subsequent genetic testing showed pseudohypoparathyroidism type 1b. Case 4. A 9-year-old girl presented with numbness, tetanic episodes, and seizures. Older brother known to have Addison's disease. Difficult family circumstances and labelled as pseudoseizures. After 18 months, presented with prolonged seizure and calcium checked at that time; found to be low, with inappropriately low PTH. Also noted to have low sodium but not investigated further. Subsequently confirmed to have Addison's disease and AIRE gene deletion identified. **Conclusion:** Seizures are common in childhood. NICE guidance has recommended since 2004 that all children presenting with a first afebrile seizure should have baseline investigations; two of these cases presented initially before this guidance was published but two others presented in 2008 and 2010 respectively. A baseline calcium level is mandatory in all children presenting with afebrile seizures and if low, must be investigated further.

P3-D2-679

Evaluation of Patients with Stunting in Armenia

Renata Markosyan^a, Natalya Volevodz^b, Anush Perikhanyan^a

^aYerevan State Medical University, Yerevan, Armenia; ^bMoscow State Medical Academy, Moscow, Russia

Background: We analyzed characteristics of patients with stunting admitted at Endocrinology Department of Muratsan University Medical Settings, the only specialized center in Armenia. No similar study was carried out in this region. **Objective and hypotheses:** Patients ($n=102$) were evaluated prospectively. **Method:** The following parameters were used for statistical analysis- demographic information, diagnosis, anthropometric data of children and their parents with consideration of SDS, gestation and birth history, bone age, retardation bone age, hormones, IGF1, IGFBP3, atherogenic risk, history of MRI, and, etc. **Results:** The mean age of children was 9.2 ± 3.62 years (3–17); 66 (64.7%) were boys, mean SDS height was -3.4 ± 1.1 ; the following cases were identified – 28.57% idiopathic short stature (ISS), 16.40% with GH deficiency, 15.34% primary hypothyroidism, 14.29% constitutional delay of growth and puberty, 10.58% genetically determining stunting, 8.99% systemic bone disease, 3.70% intrauterine growth delay, and 2.12% somatogenically conditioned stunting. ISS and GH deficiency were more frequently seen in boys (4:1 and 3:1 respectively). In GH deficiency group there were strong correlation between low GH and low IGF1, IGFBP3 levels ($P=0.000$). 77.42% of these patients had combined dyslipidemia. Hypo- and dyslipidemia were frequently identified in ISS group (28%). Among 22.2% ($n=12$) ISS patients we observed, other patients' 77.8% ($n=42$) IGF1 levels corresponded to the norm. IGFBP3 levels in ISS patients 16.7% ($n=42$) were also lower. We did not find any correlation between the maximal concentration of GH and IGF1 in ISS patients ($r=-0.02$; $P=0.148$). **Conclusion:** Blood lipid control is very important for patients with GH deficiency and ISS. We recommend the development of national registry and common guidelines in Armenia which can help practitioners easily identify the cases of stunting and accompanying risk factors.

P3-D2-680

Fluctuation in Cerebral Calcification in a Patient with Pseudohypoparathyroidism Type 2

Elena Sukarova-Angelovska, Mirjana Kocova, Olivera Lekovska
University Pediatric Clinic, Skopje, Macedonia

Background: Pseudohypoparathyroidism is a rare genetic disorder that is characterized by unresponsiveness to parathyroid hormone and abnormal calcium regulation. Several subtypes have been established according to clinical appearance, resistance of other hormones, and recent genetic findings. Although little is known about the pathogenesis of heterotopic calcifications of soft tissues and brain, they are frequently found. **Objective and hypotheses:** Evaluation of cerebral calcification during 15-year period in a patient with pseudohypoparathyroidism. **Method:** We present a male patient with pseudohypoparathyroidism and basal ganglia calcification. This is the first child in a family with unaffected parents. Hypocalcemic convulsions occurred in the neonatal period, considered as transient and no further investigations were made. At the prepubertal age hypocalcemic convulsions occurred. Examination didn't reveal dysmorphism or skeletal anomalies. Biochemical evaluation established the

diagnosis of pseudohypoparathyroidism – severe hypocalcemia (1.7 mmol/l), hyperphosphatemia (2.9 mmol/l), and high levels of PTH (1050 pg/ml). No other hormone resistances except to PTH were found. CT scan has been done several times from establishing the diagnosis. **Results:** CT of the brain that has been made at the beginning before treatment showed slightly dispersed calcification spread radially between gray and white matter. In the following years, after initiation and prompt titration of the therapy with calcium carbonate and calcitriol, several other scans have been made, all showing fluctuation in calcifications towards basal ganglia. The extent of calcification broadened in the first years, followed by reduction after the stabilization of PTH level. **Conclusion:** Although calcification of basal ganglia is a well-established feature in pseudohypoparathyroidism, there are very few studies in the literature showing the changes in the amount of the calcified regions during the treatment. Monitoring of calcification is an important tool in titrating the therapy in patients.

P3-D2-681

Variability in Clinical and Genetic Spectrum in Hypophosphatasia: Natural History in Two Patients

Gabriel Á Martos-Moreno^{a,b}, Sergio Lerma^c, Elena García-Esparza^d, Jesús Argente^{a,b}

^aEndocrinology Department, IIS La Princesa, Hospital Infantil Universitario Niño Jesús, Universidad Autónoma de Madrid, Pediatrics Department, Madrid, Spain; ^bInstituto de Salud Carlos III, CIBER Fisiopatología de la Obesidad y Nutrición, Madrid, Spain; ^cOrthopedic Department, IIS La Princesa, Hospital Infantil Universitario Niño Jesús, Madrid, Spain; ^dRadiology Department, IIS La Princesa, Hospital Infantil Universitario Niño Jesús, Madrid, Spain

Background: Hypophosphatasia (HPP) is inherited in an autosomal recessive fashion, although symptoms in heterozygous carriers are described. Age at symptom onset determines six clinical forms with different severity and prognosis, but showing phenotypic overlapping. **Objective:** We aimed to show this genetic and clinical variability by analyzing two cases. **Case 1:** Male, born at 38+5 weeks with 2250 g (-2.22 SDS) and 45 cm (-2.60 SDS), without familial bone disease background. Started rachitic chest deformity at 4 months, left coronal craniosynostosis at 10 months. At 17 months (73.9 cm (-2.65 SDS); 8.4 kg (-2.43 SDS); head circumference: 49 cm ($+2$ SDS height-adjusted)), he added axial hypotonia (not standing), dolichocephaly, delayed tooth eruption and distal metaphyseal widening in the forearms, with radiological flaring. Repeatedly minimal alkaline phosphatase (ALP) serum activity (23–31 U/l), with high serum pyridoxal phosphate (PLP >300 mcg/l) and urine phosphoethanolamine (PEA 1395 mmol/mol Creat) were the only abnormal analytical findings. He showed compound heterozygosity (c.542C>T (p.S181L)/c.644T>C (p.I215T)) for *ALPL* (infantile HPP). At 4.5 years hypotonia, growth impairment (weight -3.00 SDS and height -3.80 SDS); chest deformity (involving functional impairment (forced-vital.capacity 54.2%)), skeletal and tooth impairment (precocious teeth decay, typically described in juvenile

HPP) had worsened; determining a typical gait pattern (video and movement analysis study available to display), initiating treatment on recombinant ALP (phase-II clinical trial). **Case 2:** A 9-month-old female, born full-term with suitable anthropometry, exclusively showing moderately low ALP serum activity (72–100 U/l) without bone deformities (lacking tooth eruption). Serum PLP was >300 µg/l, and she was heterozygous for the deletion c.217-219delCTC (p.L73del) in *ALPL*. Her mother (also carrying the deletion) complained from muscle fatigue and pain after long walk (typical symptom in adult HPP). **Conclusion:** HPP shows a wide and overlapping clinical phenotype, with variable genotype-phenotype correlation. PLP serum level quantification upon reduced ALP activity allows for the suspicion of HPP in patients with suggestive symptoms.

P3-D2-682

Cautionary Tales in the Management of Transient Neonatal Hypoparathyroidism

Ian Robert Mulvey, Carley Frerichs, Poonam Dharmaraj, Renuka Ramakrishnan

Alder Hey Children's Hospital, Liverpool, UK

Background: Transient hypoparathyroidism is a recognised cause of hypocalcaemia during the neonatal period and difficult to differentiate from permanent forms. **Objective and hypotheses:** We present the challenges of monitoring and managing neonates with hypocalcaemia and inappropriately low PTH. **Method:** Cases 1 and 2 had congenital heart disease (CHD) but were FISH negative for 22q11 deletion. Both were treated with supplemental doses of calcium and magnesium with Case 2 needing alfacalcidol to normalise calcium. By 3 weeks of age both showed high calcium levels (Case 1 AdjCa 2.85 and Case 2 AdjCa 2.97). All supplements were discontinued. Case 3: A 7-day-old ventilated for persistent pulmonary hypertension presented with hypocalcaemic seizures. He received calcium supplements and alfacalcidol which were stopped after 3 months due to rising calcium (AdjCa 2.59). Case 4: 33/40-gestation infant with oesophageal atresia, radial abnormalities and CHD presented with neonatal hypocalcaemia requiring calcium and alfacalcidol. After 6 weeks supplements were stopped due to rising calcium (AdjCa 2.85). Case 5: A 2-year-old male presented with severe symptomatic hypercalcaemia having been taking calcium and alfacalcidol for isolated hypoparathyroidism diagnosed in the neonatal period, monitored 3 monthly once levels were stable. He developed nephrocalcinosis. In all cases calcium remained normal off treatment. **Results:**

Conclusion: Cases of transient hypoparathyroidism require close monitoring and alfacalcidol should be used with caution to prevent the long-term complications of unrecognised hypercalcaemia including nephrocalcinosis.

P3-D2-683

Two Different Diagnosis of Pseudohypoadosteronism

Derya Bulus^a, Nesibe Andiran^b, Elif Yagli Colakoglu^a, Nilgün Altuntas^c

^aDivision of Pediatric Endocrinology, Keçiören Research and Educational Hospital, Ankara, Turkey; ^bDivision of Pediatric Endocrinology, Keçiören Research and Educational Hospital, Yıldırım Beyazıt University, Ankara, Turkey; ^cDivision of Neonatology, Keçiören Research and Educational Hospital, Ankara, Turkey

Background: Pseudohypoadosteronism (PHA) is a disorder caused by aldosterone resistance with impaired sodium reabsorption and potassium excretion from the body. PHA is subdivided into primary (genetic) and secondary (transient) forms. Primary PHA is caused by mutations in genes encoding epithelial sodium channel or mineralocorticoid receptors. The secondary PHA may occur due to urinary tract malformations, urinary tract infections (UTI), drugs, etc. We present here two cases with salt wasting crisis due to primary PHA in one case and due to secondary PHA associated with urosepsis in the other. **Case 1:** A 7-day-old female child was brought to the hospital with poor feeding and hypotonia. She was born at term after an uneventful pregnancy with a birth weight of 3720 g. She was the fifth child of first degree consanguineous parents with a brother who was died of adrenal disease at 6 months of age. On admission, she was pale, lethargic, and hypotonic. Her weight was 3200 g with decreased skin tonus and depressed eye-balls. External genitalia was appropriate with female, with no palpable or pigmentation. On laboratory at admission, Na: 129 mEq/l, K: 11 mEq/l, BUN: 71 mg/dl, Cr: 1.14 mg/dl, pH: 7.1, HCO₃: 16, urine Na: 116, and K: 6.1. Urgent treatment for adrenal crisis and hyperkalemia (Ca gluconate i.v. bolus; NaHCO₃ infusion; glucose/insulin infusion; salbutamol and kayexelate) had began. Resistance of hyperkalemia was remarkable despite aggressive treatment. Results on admission: cortisol: 46 µg/dl, 17 OHP: 8 ng/ml, 11 DOC: 9.2 ng/ml, aldosteron: 1800 (n: 5–120) pg/ml, and renin 45 ng/ml. As the clinical course and

Table of initial results at presentation (for abstract P3-D2-682)

Case	Symptomatic	AdjCa (2.2–2.79 mmol/l)	PTH (1.1–6.9 pmol/l)	Vitamin D	Urine Cal:creat
1	No	1.75	4.2	Insufficient	Normal
2	Yes	1.61	2.5	Insufficient	High
3	Yes	1.60	2.4	Sufficient	High
4	No	1.45	3.7	Sufficient	–
5	Yes	1.38	1.7	–	–

investigations were suitable with PHA, hydrocortisone was stopped. Now she is 3 months of age, weighted 5.6 kg, she is taking oral salt, kayexalate and anti-acidosis. Genetic analysis have been sent. **Case 2:** 50 days of age girl with urosepsis, had resistant hyponatremia. She was the first child of a first degree consanguineous parents. On laboratory at admission, Na: 125 mEq/l, K: 5.1 mEq/l, cortisol: > 62 µg/dl, renin 500 ng/ml, aldosterone: > 150 pg/ml, urine Na: 17, and K: 44.6. She was started oral salt and mineralocorticoid after 2 months follow-up, the therapy could be stopped. **Discussion:** Although congenital adrenal hyperplasia is a frequent and important reason for salt wasting in early infancy; none etiology PHA should be kept in mind especially in cases with poor response to cortisol treatment and resistant hypercalemia.

P3-D2-684

Clinical Phenotype and Molecular Studies in Patients with Hypophosphatemic Rickets

Monika Obara-Moszyńska^a, Aleksandra Rojek^{a,b}, Zofia Kolesinska^a, Malgorzata Slomko-Jozwiak^a, Marek Niedziela^{a,b}

^aDepartment of Pediatric Endocrinology and Rheumatology, Poznan University of Medical Sciences, Poznan, Poland; ^bMolecular Endocrinology Laboratory, Poznan University of Medical Sciences, Poznan, Poland

Background: Hypophosphatemic rickets (HR) is a group of rare disorders caused by excessive renal phosphate wasting. The dominant form of HR is X-linked HR (XLHR) caused by mutation in the phosphate-regulating endopeptidase gene *PHEX*. There is also autosomal dominant form of HR caused by mutation in *FGF23* gene or rare autosomal recessive form caused by *DMP1* mutation. The phenotype can vary from very delicate to severe bone disease. **Objective and hypotheses:** The aim of the study was to investigate the clinical and molecular background of HR in five patients. **Method:** Five patients aged 2–8 years (two girls and three boys) were diagnosed with HR due to clinical and biochemical picture. In each of these patients three exons of the *FGF23* gene were directly sequenced after PCR amplification of the entire coding region. Additionally, in one patient *PHEX* gene was also analyzed by direct sequencing (in the four remaining the analyses are ongoing). **Results:** i) Bowing of legs was the dominant symptom in all patients. ii) All patients presented hypophosphatemia, increased loss of phosphorus with urine, increased alkaline phosphatase with normal serum calcium and 25OHD3. The TRP was low only in two children. iii) In one patient analysis of the *FGF23* gene revealed the presence of one polymorphism c.C716>T, p.T239M. The remaining four patients were *FGF23* mutation-negative. In one patient the already known *PHEX* gene deletion was found encompassing exons 17–22. **Conclusion:** The early diagnosis of HR is very important for proper treatment and to prevent bone deformities. The molecular analysis of *FGF23* and *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.

P3-D2-685

Autosomal-Dominant Hypocalcaemia, New Clinical Features

Isabel Leiva Gea^a, Noemi Auxiliadora Fuentes-Bolaños^b, Araceli Muñoz-Garach^c, Luis Castaño González^d, Maria Jose Martinez-Aedo Ollero^a, Juan Pedro Lopez-Siguero^a

^aHospital Regional Universitario, Malaga, Spain; ^bHospital Materno Infantil, Badajoz, Spain; ^cHospital Universitario Virgen de la Victoria, Malaga, Spain; ^dHospital de Cruces, Vizcaya, Spain

Introduction: The extracellular calcium-sensing receptor (CaSR) enables the parathyroid glands and other CaSR-expressing cells involved in calcium homeostasis to sense alterations in calcium serum concentrations. Mutations in the CASR gene may produce gain or loss in its activity. Activating mutations cause a hypocalcaemic syndrome of varying severity, as autosomal-dominant hypocalcaemia or Bartter's syndrome. **Case report:** We describe a 6 months infant who was admitted to undergo a corrective surgery for tetralogy of Fallot. His mother, and four other relatives, were diagnosed with hypoparathyroidism and receiving treatment with calcium and calcitriol. Physical examination did not show dysmorphic features neither other significant findings. Postoperative and follow-up care showed hypocalcemia (8 mg/dl), hyperphosphatemia (up to 8.5 mg/dl), persistent hypercalciuria (ratio Ca/Cr 0.63 mg/mg) and low serum PTH (7 pg/ml). The CASR gene study detected a pathogenic mutation in heterozygous (c2488a G>A) designated as probably pathogenic. It was also presented in his mother. Currently, the patient is treated with calcium carbonate and calcitriol. **Conclusions:** The prevalence of autosomal dominant hypocalcaemia is unknown and probably underdiagnosed. Recognition of patients with an activating mutation of the CaSR has great relevance in prognosis as they present special vulnerability to treatment with calcium and vitamin D, so it should be included in the differential diagnosis of hypocalcemia. We present a case associated with Tetralogy of Fallot, not previously described which makes more difficult the diagnosis because the orienting toward the Di George syndrome.

P3-D2-686

I.V. Zoledronic Acid: Experience of Treatment of Children with Osteogenesis Imperfecta in Indonesia

A Pulungan^{a,b}, M Zacharin^c, K Armstrong^d, F Soesanti^{a,b}, D L Pramesti^b

¹Department of Child Health, Faculty of Medicine, Cipto Mangunkusumo Hospital, University of Indonesia, Jakarta, Indonesia; ²Faculty of Medicine, University of Indonesia, Jakarta, Indonesia; ³Department of Endocrinology, Royal Children's Hospital, Melbourne, Victoria, Australia; ⁴Caring and Living as Neighbours, Sydney, New South Wales, Australia

Background: The incidence of osteogenesis imperfecta (OI) worldwide is unknown. In the USA, the incidence is ~1/20 000

live births: for Indonesia (population 240 million) this should extrapolate to 12 000 OI patients rather than the 35 patients currently registered with the Indonesian Pediatrics Society (IPS), Faculty of Medicine, University of Indonesia-Cipto Mangunkusumo Hospital (RSCM). This enormous disconnect signifies many missed diagnoses, mortality or both. **Objective and hypotheses:** To raise awareness of OI, assert zoledronic acid (ZA) as an effective treatment; and provide ZA as an essential medicine, with consensus from IPS guidelines for Indonesia. **Method:** IPS working with CLAN and RCH, undertook a 2 days community-building, information and education course for families of children with OI and for pediatricians. Approval was granted to treat children with OI using ZA every 4–6 months. ZA (0.05 mg/kg per dose) was administered to 15 patients (nine females), ages 0.9–18.2 years. Patients were observed for 24 h. Total calcium examination was performed after 24–48 h. **Results:** To date, 39 new patients with OI have been registered nationally; 14 patients have received one dose of ZA and one patient received two. Well recognized mild acute phase reactions occurred in the first 24 h after treatment, fever (5), fatigue (1), bone pain (1), and abdominal pain (1). Asymptomatic mild reduction in serum calcium was seen in eight. **Conclusion:** Treatment has been successful to date, with minimal discomfort, as previously described. It is anticipated that ongoing OI community building and dissemination of patient information throughout Indonesia will raise public awareness and result in larger numbers of affected individuals seeking treatment, further improving quality of life and reducing morbidity. It is proposed ZA be included in the national list of essential medicines and covered by health insurance, resulting in general availability of ZA for OI treatment in Indonesia. Currently, ZA is already used for treating OI at RSCM.

P3-D3-686

Bone Health in a Cohort of Irish Spinal Muscular Atrophy Patients

Niamh Mc Sweeney^a, Malachi Mc Kenna^{b,c}, David Webb^d, Susan van der Kamp^b, Mark Kilbane^c, Myra O' Keane^c, Bryan Lynch^{a,e}

^aDepartment of Paediatric Neurology, The Central Remedial Clinic, Dublin, Ireland; ^bDXA Unit, St Vincent's University Hospital, Dublin, Ireland; ^cMetabolism Laboratory, St Vincent's University Hospital, Dublin, Ireland; ^dDepartment of Paediatric Neurology, Our Lady's Children's Hospital, Dublin, Ireland; ^eDepartment of Paediatric Neurology, The Children's University Hospital, Dublin, Ireland

Background: Spinal Muscular Atrophy (SMA) is characterised by progressive muscle weakness, resulting from loss of anterior horn cells in the spinal cord and the brain stem nuclei. Survival motor neuron levels (SMN) are reduced due to mutations in the SMN1 gene. SMN function has been implicated in poor bone health. SMA is classified according to age of onset and clinical course accordingly: type 0 (prenatal), type 1 (onset <6 months, severe, never sit unsupported), type 2 (onset 6–12 months, intermediate, sit unsupported but never walk) and type 3 (onset >12 months and mild, walk). Congenital bone fractures

have been described in type 1 SMA. Patients with SMA are at increased risk of osteoporosis, but there are very few studies quantifying this risk. **Objective and hypotheses:** We sought to determine the prevalence of low bone mineral density (BMD) and to assess bone remodelling indices. **Method:** BMD was measured at spine and whole body. Early morning fasting blood samples were obtained: 25-hydroxyvitamin D (25OHD), calcium, parathyroid hormone (PTH), procollagen type 1 N-terminal propeptide (P1NP), and timed-urine for N-terminal telopeptides of type 1 collagen (NTX). **Results:** We studied ten patients (mean age 7 years (2–18 years)); eight had SMA type 2 and two were type 3. Median (range) for tests was as follows: 25OHD was 55.9 (34.2–74.5) nmol/l; P1NP was 353.5 (61.8–711) µg/l; NTX was 1058.7 (512–3081) nMBCE/mMCR; and spine Z-score –3.8 (–4.3 to –1.1). WB Z score could not be evaluated due to spinal surgery prosthesis. **Conclusion:** Our patients frequently had low 25OHD, low bone formation and high bone resorption. Spine BMD was also suboptimal and lower than spinal BMD that we observed in boys with Duchenne muscular dystrophy. We suggest that bone health should be closely monitored in SMA.

P3-D3-687

Endocrinological Assessment of Children with Bronchiectasis

Ilker Tolga Ozgen, Erkan Cakir, Hakan Gedik, Selim Gökce, Mustafa Atilla Nursoy, Yasar Cesur

Department of Pediatrics, Bezmialem Vakif University, Istanbul, Turkey

Background: Bronchiectasis is a result of recurrent pulmonary infections and chronic inflammation. **Objective and hypotheses:** Chronic inflammation may lead some endocrinological disorders. The consequences of the bronchiectasis on the endocrinological system and on the bone health in childhood were investigated in this study. **Method:** The medical records of the 64 children with bronchiectasis (32 females and 32 males) at the mean age of 11.12 ± 3.21 were investigated retrospectively. **Results:** The ratio of the children with short stature was only 7.8% ($n=5/64$), but the ratio of the children who had worse height status than their target height z-score (target height z-score-current height z-score >0.5) was 25%. According to Gomez classification 17.5% of the children had mild and 4.8% of the children had moderate or severe malnutrition. Girls' and boys' mean ages at the pubertal stage 2 were 9.45 ± 0.48 and 11.78 ± 0.55 years old respectively. There were not any cases of retarded or precocious puberty. Four of the 64 children had subclinical hypothyroidism (6.2%) and five children (7.8%) had lower serum cortisol levels than $5 \mu\text{g/dl}$. Assessment of bone mineral density revealed that the ratio of osteoporosis and osteopenia were 23.1% (9/39) and 30.8% (12/39). Vitamin D deficiency and insufficiency ratio were 14.1% (9/58) and 51.7% (30/58) respectively. **Conclusion:** Children with bronchiectasis may have some endocrinological complications such as failure of thrive and osteoporosis. Therefore, evaluation of the nutritional status, bone health status and the endocrinological system should be considered to the children with bronchiectasis.

P3-D3-688

Infantile Hypophosphatasia

Nevenka Slaveska^{a,b}, Marina Krstevska-Konstantinova^{a,b},
Zoran Trajkovski^{a,b}

^aPediatric Clinic, Skopje, Macedonia; ^bInstitute of Radiology,
Skopje, Macedonia

Background: Hypophosphatasia (HP) is a rare inherited disorder characterised by defective bone and teeth mineralization because of deficient serum and bone alkaline phosphatase activity due to mutations in the tissue-nonspecific ALP (TNALP) gene. Infantile HP (IHP) is one of the six recognized clinical forms according to age at presentation and clinical features. IHP is characterised by skeletal abnormalities due to demineralization and rachitic changes in the metaphyses, premature craniostylosis, respiratory problems, and failure to thrive. Serum alkaline phosphatase (AP) activity is markedly reduced, which leads to increased serum/urine phosphoethanolamine (PEA), inorganic pyrophosphate (PPi), and pyridoxal-5'-phosphate (PLP). **Objective and hypotheses:** We report a 4.5-month-old female infant with the infantile form of HP. The patient was hospitalized due to failure to thrive, growth retardation, severe bone deformities, and hypotonia. **Method:** The diagnosis was based on physical findings, haematological investigations, and radiographic skeletal features. **Results:** The examinations revealed short stature and severe skeletal deformities: short and bowed limbs, an abnormally shaped chest, and an abnormal skull shape with soft skull bones. Radiographic diagnostic findings showed decreased ossification of the skull, generalized demineralization of the bone, defective metaphyseal modelling, and rachitic changes in the metaphyses. Laboratory investigations showed hypercalcemia (2.8 mmol/l), reduced serum alkaline phosphatase activity (33 U/l), and increased urine PEA (1855 mmol/l). **Conclusion:** Infantile HP is a rare inherited disorder presented with severe bone deformities. The biochemical diagnosis is based on laboratory assays on markedly reduced serum AP, and increased urinary PEA.

P3-D3-689

Vitamin D Levels in Short Prepubertal Children Born Small for Gestational Age

Maria Korpal-Szczyrska

Clinic of Pediatrics, Diabetology and Endocrinology, Medical
University of Gdansk, Gdansk, Poland

Background: Adequate vitamin D level is essential for optimal child's growth. Small for Gestational Age (SGA) is a common cause of short stature in childhood. Being born SGA is associated with a risk of developing insulin resistance. **Objective and hypotheses:** The aim of the study was to evaluate serum vitamin D levels in short children born SGA and appropriate for

gestational age (AGA) and to assess their relationship with insulin sensitivity. **Method:** In 59 short prepubertal children: 31 SGA (15 boys) and 28 AGA (14 boys) aged 6.69 ± 2.1 years fasting serum 25-hydroxyvitamin D (25(OH)D), parathyroid hormone (PTH), glucose, and insulin levels were assessed. Insulin sensitivity was calculated with the homeostasis model assessment (HOMA). **Results:** The mean serum 25(OH)D level in SGA children was 22.5 ± 4.6 ng/ml and was significantly higher than in AGA children (15.3 ± 4.6 ng/ml). 74% SGA children showed 25(OH)D level above 20 ng/ml, 10% above 30 ng/ml, 10% below 15 ng/ml, and none below 10 ng/ml. In AGA group only 21% showed 25(OH)D level above 20 ng/ml (none above 30 ng/ml), 36% below 15 ng/ml, and 14% below 10 ng/ml. PTH level did not differ between groups. Mean fasting insulin level and HOMA was significantly higher in SGA group than in AGA group (4.69 ± 1.13 vs 2.74 ± 0.87 mU/l and 0.99 ± 0.26 vs 0.55 ± 0.21). No differences between fasting glucose levels were shown. In SGA children no correlations between fasting blood glucose, insulin, HOMA, and 25(OH)D levels were found. **Conclusion:** Inadequate vitamin D levels are prevalent in prepubertal short children. Prepubertal short SGA children show higher vitamin D levels than AGA children.

P3-D3-690

Prospective Evaluation of Bone Mineralization, PTH Regulation, and Metabolic Profile in Adult Patients with Hereditary Hypophosphatemic Rickets

Emese Boros^a, Anya Rothenbuhler^b, Hazar Haidar^c, Dominique Prie^c,
Pol Harvengt^d, Lavinia Vija^e, Sylvie Brailly-Tabard^c,
Philippe Chanson^f, Agnès Lingart^b, Peter Kamenicky^f

^aService D'endocrinologie Pédiatrique, Hôpital Universitaire des Enfants Reine Fabiola Avenue J J Crocq 15, Bruxelles, Belgium; ^bCentre de Référence des Maladies Rares du Métabolisme du Calcium et du Phosphore, Service d'Endocrinologie et Diabétologie de l'Enfant, Université Paris Sud, Hôpital Bicêtre, APHP, 78 Rue du Général Leclerc, Paris, France; ^cService de Pharmacogénétique, Biochimie Moléculaire et Hormonologie, Service GMPH, Hôpital Bicêtre, APHP, Université Paris Sud, 78 Rue du Général Leclerc, 94270 Paris, France; ^dReprésentant Association Pour les Personnes Atteintes de Rachitisme Vitamino-résistant Hypophosphatémique, Paris, France; ^eUnité Inserm 693, Faculté de Médecine Paris-Sud, 63 Rue Gabriel Péri, 94276 Le Kremlin-Bicêtre, Paris, France; ^fCentre de Référence des Maladies Rares du Métabolisme du Calcium et du Phosphore, Service d'Endocrinologie et des Maladies de la Reproduction, Hôpital Bicêtre, APHP, 78 Rue du Général Leclerc 94270, Paris, France

Background: Hereditary hypophosphatemic rickets (HHR) is a rare genetic disease characterized by renal phosphate wasting, caused by elevated circulating FGF23. Despite the current available treatment complications include short stature,

	All patients	Treated	Non treated	P*
Blood pressure systolic/diastolic (mmhg)	116/72	108/65	120/74	0.1044
BMI (kg/m ²)	27.5	27.8	27.3	0.7997
HOMA	1.3	2.7	1.0	0.0057
Urinary calcium (mg/kg per day) (n < 4)	2.5	1.8	2.8	0.1365
PTH (pg/ml) (n 15–60)	36.0	46.5	52.5	0.7082
L1–L4 T score	2.4	2.7	2.3	0.4980
Femoral neck T score	–0.1	0.7	–0.4	0.0174

hyperparathyroidism, pseudofractures, bone pain, bone demineralization and osteoporosis, nephrocalcinosis and enthesopathies. Elevated circulating FGF23 was recently involved in glucose metabolism and cardiovascular function. **Objective and hypotheses:** Our objective was to prospectively evaluate complications of the disease and patients' metabolism. **Method:** Twenty-eight patients with HHR were prospectively evaluated (six males and 22 females). **Results:** Mean age (min-max) of adult HHR patients was 39 years (19.4–69.3). The mean height for males was 160.6 cm and for female 147.0 cm. 9 (32.1%), 9 (32.1%), and 10 (35.8%) patients were obese, over weighted and had a normal BMI respectively. Two patients had glucose intolerance. One patient had a parathyroid adenoma. Two patients had renal lithiasis, none had nephrocalcinosis. The spinal T score correlated with FGF23 values. Femoral neck T score was higher in patients who received vitamin D analogues during childhood. **Conclusion:** Overweight and obesity is frequent in HHR patients. Vitamin D analogues treatment improves cortical bone mineral density. Complications like nephrocalcinosis and hyperparathyroidism are rare.

P3-D3-691

Bone Mineral Density and Vitamin D Status in Girls and Adolescents with Turner Syndrome

Ouidad Baz^a, Mourad Semrouni^a, Samia Sakher^a, Lakhdar Griene^b, Nadir Hammomraoui^c, H Djoudi^c

^aEndocrinology Department, Pierre and Marie Curie Center, Algiers, Algeria; ^bHormonology Laboratory, Pierre and Marie Curie Center, Algiers, Algeria; ^cRheumatology Department, Douera, Algiers, Algeria

Background: Low bone mineral density (BMD) in patients with Turner syndrome (TS) has been reported in a considerable number of previous studies. Cortical and trabecular bone have been involved. Osteoporosis can be over diagnosed in TS patients with a short stature unless BMD measurements are adjusted for body size. Optimization of bone health in girls with TS requires a healthy active lifestyle, including adequate calcium, vitamin D, and

hormonal replacement therapy, according to consensus guidelines. **Objective and hypotheses:** The aim of this study is to evaluate BMD and vitamin D status in our population of TS and follow this group after substitution. **Method:** A group of 32 girls and adolescents diagnosed as TS by karyotype, age ranged between 12 and 32 years, we had 14 monosomy, 07 mosaisms, and 11 structural abnormalities. Evaluated by osteodensitometry, measurement of vitamin D, PTH, calcium, and phosphorous. The age of spontaneous or induced puberty, the GH treatment and fracture history were precise. **Results:** The mean age of this group is 21 years, The BMD was low in all patients with osteopenia in 35% and osteoporosis in 57% and normal BMD in 7% of cases this group had treated early by GH and their puberty are early induced, vitamin D status is very low in all patients, calcium was low in just three cases and PTH was high in two patients with normal calcemia and very low vitamin D. Seven patients received take vitamin D orally and have standardized their rates. The others patients received also vitamin D and their results are pending. osteodensitometries of control for all patients are ongoing. **Conclusion:** Achieving optimal bone density is of critical importance for fracture prevention in TS, and should be pursued by timely introduction of hormone replacement therapy, adequate dose of estrogens during the young adult life, optimal calcium and vitamin D intake and regular physical exercise.

P3-D3-692

Vitamin D Deficiency in Children

Andreea Dobrescu^{a,b}, Adela Chirita-Emandi^a, Maria Papa^{a,b}, Maria Puiu^{a,b}

^aVictor Babes University of Medicine and Pharmacy, Timisoara, Romania; ^bLouis Turcanu Children Emergency Hospital, Timisoara, Romania

Background: Vitamin D deficiency has a high prevalence in children. It is produced by the skin from exposure to sunlight but its synthesis is influenced by many external and internal factors. **Objective and hypotheses:** The study aims to evaluate vitamin D in children with different pathology and highlights the influencing factors of it. **Method:** We evaluate 25-hydroxyvitamin D levels in 84 patients, sex ratio 1.15:1, aged between 3 month and 17.9 years old, using high-performance liquid chromatography method. 39 patients had a genetic disease. We divided the tested period in two parts according with the sun exposure: the group tested from March to August, 55 samples, compared with the group tested from September to February, 29 samples. We evaluated the differences of vitamin D levels and we correlated it with the season and medical condition. **Results:** We diagnosticated 42 patients, with vitamin D deficit, 19 with genetic disease 74.35% of total belonged the first group. The mean for the first group was 30 ± 17.29 with 56.36% affected patients and 40.75 ± 24.29 with 37.93% for the second group. The smaller value was 4.9 µg/l, a 4.6 years old boy from the second group. The higher value was 105 µg/l recorded in the second

group also in a boy with an aggressive prophylactic treatment. 33.33% of the total number of girls and 64.44% of boys had vitamin D deficit. 53.84% of patients with genetic disease had low level of vitamin D. **Conclusion:** The recorded values were smaller for the hot season even if the sun exposure is the most important stimulant factor for vitamin D synthesis. Patients with genetic disorders had a higher prevalence of vitamin D deficit, their special condition can decrease the sun exposure. The low levels of vitamin D were correlated with clinical symptoms in genetically patients.

P3-D3-693

The Use of Pamidronate in Pediatric Patients with Disease of Other than Osteogenesis Imperfecta: the Experience of Our Center

Ayla Güven, Didem Helvacioğlu, Suna Hancili, Metin Yıldız

Göztepe Education and Research Hospital, Pediatric Endocrinology Clinic, Istanbul, Turkey

Background: Bisphosphonate treatment for bone fragility has expanded beyond the children with osteogenesis imperfecta (OI) to those with other causes of low bone mass. Pamidronate is effective such as Paget's disease, hypercalcaemia of malignancy, osteolytic bone metastasis, steroid-induced osteoporosis and idiopathic osteoporosis. **Objective and hypotheses:** The experience with bisphosphonates treatment other than OI in children is limited although there are a growing number of publications showing their usefulness in several bone and metabolic diseases. Our objective is to demonstrate the efficacy of pamidronate other than OI. **Methods:** The i.v. administration of pamidronate in children in our institute is analyzed: 2 McCune-Albright (MCA), 1 Tripple A syndrome (TA), 1 glycogene storage disease (GSD) type 0. Pamidronate 0.5 mg/kg per day, 3-consecutive-days were given for 3 months interval (6 mg/kg per years). **Results:** We have two cases (19 and 5 old ages) of fibrous dysplasia due to MCA who had severe bone pain showing remarkable clinical improvement with pamidronate. We used pamidronate treatment 18-aged-male with TA syndrome that had osteoporosis (BMD-Z score was -3.0) and severe back pain. His BMD-Z score was -2.08 after the treatment. We also treated nine aged-girl with GSD type 0, who had osteopenia (BMD-Z score -1.2 end of the therapy Z score was: -0.5) and chronic bone pain because of restricting diary product in her diet. All patients had normal levels of calcium, phosphorus, and vitamin D, and proper nutrient intake. No adverse effects of pamidronate treatment were identified and subjective skeletal pain diminished in all patients. All children had a positive response to the treatment, with rapid and marked clinical improvement in their mobility. **Conclusion:** Our experience with the use of bisphosphonates in pediatric patients with diseases other than OI. Intravenous bisphosphonates are well tolerated, and reduce the risk of fracture and ameliorate bone related clinical symptoms.

P3-D3-694

McCune-Albright Syndrome Associated to Hypophosphatemic Rickets

Tiago Jeronimo dos Santos, Caroline Passone, Hamilton Menezes Filho, Hilton Kuperman, Thaís Della Manna, Leandra Steinmetz, Louise Cominato, Vaê Dichtchekenian, Joyce Pupo, Nuvarte Setian, Durval Damiani

Instituto da Criança, HCFMUSP, São Paulo, Brazil

Introduction: McCune-Albright syndrome (MAS) is a genetic disorder characterized by constitutive activation of $G\alpha$, resulting in excessive activity of multiple hormones. The most known clinical characteristics are the presence of polyostotic fibrous dysplasia (FD), hyperpigmented skin spots, and gonadotropin-independent precocious puberty (PP). However, other endocrine manifestations can be found like hypophosphatemic rickets due to FGF-23-induced renal phosphate wasting. **Case report:** A 7-year-old girl was diagnosed with MAS at 4.9 years, with vaginal bleeding at 1.7 years, associated to large and irregular skin spots and fibrous dysplasia. This patient also has facial dysmorphisms, as 'saddle nose'. No other endocrine manifestation was identified. Bone scintigraphy with technetium 99 showed increased uptake tracer with heterogeneous pattern in skull, ribs, hipbone and limbs, especially in facial bones. A cranium CT was performed due to migraine. Microcephaly and diffuse bone enlargement were noted, with global small tapering of bone foramina with accommodation of periencephalic spaces. She developed genu valgus, fibrous dysplasia and decreased cortical bone. As phosphate serum level was low, associated to increased renal phosphate wasting, hypophosphatemic hyperphosphaturic rickets was diagnosed. She was treated with calcium carbonate and tamoxifen and, due to bone dysmorphism, calcitriol, phosphate, and pamidronate were introduced. **Conclusion:** Despite MAS is known by its most known characteristics, such as PP, FD, and skin spots, the screening for other endocrine disorders is mandatory. The presence of polyostotic fibrous dysplasia does not exclude the findings of rickets. It has been suggested that the large skin spots may alert us to overproduction of FGF-23 that could be a marker of the condition of phosphate wasting. Therefore, a special attention about the phosphate metabolism should be done in these patients.

P3-D3-695

Clinical Effects of Vitamin D in Asthma

Mahmut Dogru^a, Heves Kirmizibekmez^b, Gul Yesiltepe Mutlu^b, Alev Aktas^c

^aDepartment of Pediatric Allergy, Zeynep Kamil Woman's and Children's Diseases Training and Research Hospital, Istanbul, Turkey; ^bDepartment of Pediatric Endocrinology, Zeynep Kamil Woman's and Children's Diseases Training and Research Hospital, Istanbul, Turkey; ^cDepartment of Pediatrics, Zeynep Kamil Woman's and Children's Diseases Training and Research Hospital, Istanbul, Turkey

Background: In both asthma and vitamin D deficiency is common. The results from studies examining the relationship between them is contradictory. **Objective and hypotheses:** The aim of this study was to investigate the relationship vitamin D levels and clinical parameters of asthma in children. **Method:** One hundred twenty children with asthma, followed up in Pediatric Allergy and Immunology Department were included. Seventy-four children with no evidence of allergic disease, were included as the control group. The eosinophil counts, immunoglobulin (Ig) E levels and serum 25OHD levels were measured. Skin prick tests were applied using same allergens to all patients. **Results:** This study consisted of 73 (60.8%) male and mean age of 4.4 ± 1.2 years as patient group. There was no significant difference between patient and control groups in respect to gender, age. Mean 25OHD3 level was 21.49 ± 7.74 ng/ml in study group and 23.94 ± 8.97 ng/ml in control group. The difference was not significant ($P=0.094$). The patients with asthma were grouped according to vitamin D status as 'deficient (Group-1)', 'insufficient (Group-2)' and 'normal (Group-3)'. Total number of the exacerbations, asthma severity, and systemic glucocorticoid need in the previous year were significantly higher in deficiency group. ($P < 0.05$). Vitamin D levels were negatively correlated with severity of asthma ($r: -0.310$; $P: 0.001$), duration of wheezing ($r: -0.297$; $P: 0.001$), total number of exacerbations ($r: -0.441$; $P: 0.000$), number of exacerbations in the previous year ($r: -0.307$; $P: 0.001$) and systemic glucocorticoid need in the previous year ($r: -0.347$; $P: 0.000$). **Conclusion:** Vitamin D levels were not significantly different in patients with asthma, since vitamin D deficiency was common in study group and also in the control group. Clinical severity of disease, the number of exacerbations, and systemic glucocorticoid need were related with vitamin D level.

P3-D3-696

A Korean Boy with Pseudohypoparathyroidism Type Ia Presenting with Congenital Megacolon and Spinal Stenosis: Identification of a Novel GNAS Gene Mutation

J E Lee^a, S H Lee^a, S Y Chob^b, C S Ki^b, D K Jin^b

^aINHA University Hospital, Incheon, Democratic People's Republic of Korea; ^bSamsung Medical Center, Seoul, Democratic People's Republic of Korea

Pseudohypoparathyroidism (PHP) is a disease of rare frequency. There are five subtypes with each having different phenotypes and blood laboratory test results, which depend on gene mutation and hereditary styles. Among them, the most common type is PHP Ia which inherits maternal gene mutation and expresses Albright's hereditary osteodystrophy (AHO) appearance, hypocalcemia, hyperphosphatemia and serum parathyroid hormone elevation. Another type, pseudo-pseudohypoparathyroidism (PPHP), inherits the same paternal gene mutation and expresses AHO appearance, except abnormal blood test

results. We report a novel GNAS gene mutation found cases of AHO phenotype in a son with PHP Ia and his mother with PPHP.

P3-D3-697

A Case with Odontohypophosphatasia and Family Investigation

Esra Deniz Papatya Cakir^a, Mehmet Tureb, Halil Saglam^b, Seyit Ahmet Ucakurkc, Sahin Erdolb, Erdal Erenb, Tahsin Yakutb, Omer Tarimb

^aSevket Yilmaz Education and Research Hospital, Bursa, Turkey; ^bFaculty of Medicine, Uludag University, Bursa, Turkey; ^cMersin Maternity and Children Hospital, Mersin, Turkey

Background: Early tooth loss could be the consequence of the local or systemic diseases. We present an odontohypophosphatasia case with otosomal dominant mutation in ALPL gene. **Objective and hypotheses:** We report a case with odontohypophosphatasia and his family investigation. **Method:** Three-years-old boy admitted to our pediatric endocrinology clinic with toothloss without any other dental or gingival disease. His serum levels calcium, phosphorus, alkaline phosphatase, parathormone and 25 hydroxy vitamin D levels were 9.7 mg/dl, 5.9 mg/dl, 70 U/l, 32.2 pg/ml, 18.9 ng/ml, respectively. We considered that the patient have odontohypophosphatasia. We performed ALPL gene analysis. PCR techniques were used to amplify the all translated exons of the ALPL gene. Sanger sequencing technique was used for mutation analysis and ALPL gene analyzed with ABI 3130 Sequencer device. **Results:** Heterozygous otosomal dominant c.346G>A (p.A116T) mutation was detected in fifth exon of ALPL. ALPL gene analysis was performed to all members of the family. While his father has no mutation, his mother, brother and sister have same heterozygous mutation in the same locus. **Conclusion:** Odontohypophosphatasia should be considered in patients with early tooth loss. It can be presented without extremely low alkaline phosphatase levels.

P3-D3-698

TSH/ft₄ Ratio as a Marker of TSH Resistance in Pseudoparathyroidism 1A and Obesity

Aurélia Alimi^a, Danielle Rodrigue^a, Agnès Linglart^{a,b}, Gianpaolo De Filippo^a

^aAssistance Publique - Hôpitaux de Paris, Hôpitaux Universitaires Paris Sud, Hôpital Bicêtre, Service d'Endocrinologie et Diabétologie de L'enfant, Le Kremlin-Bicêtre, France; ^bCentre de Référence des Maladies Rares du Calcium et du Phosphore, Le Kremlin-Bicêtre, France

Introduction: Gsα is imprinted in human thyroid glands and this appears to be important in the development of moderate TSH

resistance in pseudohypoparathyroidism (PHP) 1A and less severe TSH resistance in some, but not all, other forms of PHP. Obesity is a clinical condition in which subclinical alterations of thyroid function have been reported, although the relationship between thyroid status and obesity remains unclear. It is uncertain if this biochemical abnormality may be a secondary phenomenon of obesity or a real hypothyroid state. **Methods:** To investigate the correlation between TSH and circulating levels of fT_4 (i.e. TSH/ fT_4 ratio; mUI/l per pmol/l) in patients with mild hypothyroidism (i.e. TSH value $<10 \mu\text{IU/ml}$) affected with PHP1A ($n=7$: mean age 7.3 ± 5.6 years), obesity ($n=8$: mean age 10.4 ± 3.2 years) and hypothyroidism secondary to Hashimoto's thyroiditis ($n=8$: mean age 11.3 ± 3.6 years). Subjects were matched for TSH levels (mean TSH 5.4 ± 2.4 , 5.5 ± 1.5 and $4.9 \pm 0.6 \mu\text{IU/ml}$, respectively; $P=0.533$ ANOVA). Patients with PHP1A or obesity were negative for thyroid autoimmunity. Ten healthy age and fT_4 matched subjects were included as controls. **Results:** The TSH/ fT_4 ratio was higher in hypothyroid patients (0.45 ± 0.16) than in PHP and obese subjects (0.37 ± 0.18 and 0.38 ± 0.13) showing a trend without reaching statistic significance. The latter subjects presented a very similar hormonal phenotype. TSH/ fT_4 ratio in control subjects was 0.15 ± 0.06 ($P < 0.001$ vs patients with mild hypothyroidism). The observed trend could suggest that a ratio < 0.40 in presence of TSH levels higher than 2.5 could indicate a resistance phenotype requiring further explorations. **Conclusions:** The strong similarity between PHP and obese thyroid hormonal phenotype could be supplementary evidence that obesity is associated with TSH resistance rather than a real hypothyroid state.

clinical forms according to age at presentation, and clinical features. IHP is characterised by skeletal abnormalities due to demineralization and rachitic changes in the metaphyses, premature craniosynostosis, respiratory problems and failure to thrive. Serum alkaline phosphatase (AP) activity is markedly reduced, which leads to increased serum/urine phosphoethanolamine (PEA), inorganic pyrophosphate (PPi), and pyridoxal-5'phosphate (PLP). **Objective and hypotheses:** We report a 4, 5 month old female infant with the infantile form of hypophosphatasia. The patient was hospitalized due to failure to thrive, growth retardation, severe bone deformities, and hypotonia. **Materials and methods:** The diagnosis was based on physical findings, haematological investigations, and radiographic skeletal features. **Results:** The examinations revealed short stature and severe skeletal deformities: short and bowed limbs, an abnormally shaped chest, and an abnormal skull shape with soft skull bones. Radiographic diagnostic findings showed decreased ossification of the skull, generalized demineralization of the bone, defective metaphyseal modelling, and rachitic changes in the metaphyses. Laboratory investigations showed hypercalcemia (2.8 mmol/l), reduced serum alkaline phosphatase activity (33 U/l), and increased urine phosphoethanolamine ($1.855 \mu\text{mol/l}$). **Conclusions:** Infantile hypophosphatasia is a rare inherited disorder presented with severe bone deformities. The biochemical diagnosis is based on laboratory assays on markedly reduced serum alkaline phosphatase (AP), and increased urinary phosphoethanolamine (PEA).

P3-D3-699

Infantile Hypophosphatasia

Nevenka Slaveska^a, Marina Krstevska-Konstantinova^b, Trajkovski Zoran^c

^aPediatric Clinic, Metabolism, Skopje, Macedonia, FYrom; ^bPediatric Clinic, Endocrinology and Genetics, Skopje, Macedonia, FYrom;

^cInstitute of Radiology, Skopje, Macedonia, FYrom

Background: Hypophosphatasia (HP) is a rare inherited disorder characterised by defective bone and teeth mineralization because of deficient serum and bone alkaline phosphatase activity due to mutations in the tissue-nonspecific ALP (TNALP) gene. Infantile hypophosphatasia (IHP) is one of the six recognized

P3-D1-699

Efficacy and Safety of CSII Treatment in Paediatric Age: Long Term Experience of a Tertiary Care Centre in Spain

Belen Roldan, Esmeralda Colino, Maria Martin-Frias, Angeles Alvarez, Rosa Yelmo, Raquel Barrio

Ramon y Cajal Hospital, Alcala University, Madrid, Spain

Aims: The aims of the study are to evaluate the efficacy and safety of CSII treatment in paediatric patients, to determine if ISPAD criteria for good metabolic control are achieved and to define the general and specific characteristics depending on age and pubertal stage. **Methods:** Charts of all the patients who started CSII in the last 10 years were reviewed. The cohort consisted of 90 patients (age 10.1 ± 4.4 years, 58% males). Age at

Table 1. (abstract for P3-D1-699)

	Prior HbA1c	HbA1c 1 year	HbA1c 4 year	Prior SH	SH CSII	IDd %	B/TI % 1y	% Hb <7.5 CSII follow
Total	7.0 ± 0.8	$6.7 \pm 0.5^*$	6.9 ± 0.7	18.9	6.9	16	41	91
<6 year	7.1 ± 0.8	$6.8 \pm 0.4^*$	6.8 ± 0.9	4.8	0	0	35	94
6 year-Tann2	6.8 ± 0.6	6.6 ± 0.5	6.7 ± 0.7	7.1	5.3	16	37	91
\geq Tanner2	7.1 ± 0.9	$6.7 \pm 0.5^*$	7.0 ± 0.6	34.1	12	20	47	91

start, DM duration, pubertal stage, HbA1c (HPLC (Menarini) (normal value $5.1 \pm 0.31\%$), insulin dose decrease (IDd), number of glycemic controls (GC), number of basal rates (BR), % basal/total insulin (B/TI), insulin to carbohydrate ratio at different meals, severe hypoglycaemia (SH episodes/100 patients years) and DKA events were analyzed. Subgroup analysis based on age and pubertal stage was made. Statistical analysis was performed by SPSS. **Results:** HbA1c decreased the first year to 6.7%. Afterwards, it remained under 7% during the follow-up (mean 3.5 ± 1.8 , range 1–8 years). Prior to CSII, 76% of the subjects met ISPAD criteria. At 1 year, 96% had HbA1c < 7.5%. GC per day were 8.7 ± 1.7 . BR were 5.6 ± 1.8 at 1 year, increasing progressively to 6.7 ± 2.1 at 5 years of CSII. There were only two episodes of DKA. Insulin needs at breakfast were bigger for all the subgroups. **Conclusions:** CSII is effective and safe in the paediatric age. It allows to achieve and maintain good metabolic control (based on ISPAD criteria) without increasing adverse effects. Smaller children need less basal insulin. *statistically significant.

P3-D1-700

Diabetic Ketoacidosis in Children with T1DM: an Italian Multicentre Survey

Stefano Zucchini^a, Riccardo Bonfantini^b, Pietro Buono^c, Francesca Cardella^d, Vittoria Cauvin^e, Valentino Cherubini^f, Giovanni Chiari^g, Giuseppe D'Annunzio^h, Anna Paola Frongiaⁱ, Dario Iafusco^j, Giulio Maltoni^k, Patrizia Ippolita Patera^k, Andrea Scaramuzza^l, Sonia Toni^m, Stefano Tuminⁿ, Ivana Rabbone^o

^aDepartment of Women's and Children's Health, S.Orsola-Malpighi H., Bologna, Italy; ^bDiabetes Research Institute, San Raffaele H., Milan, Italy; ^cDepartment of Pediatrics, University of Naples Federico II, Naples, Italy; ^dPediatric Diabetology Unit Children H. G Di Cristina, Palermo, Italy; ^ePediatric Diabetology Unit, S.Chiera H., Trento, Italy; ^fDepartment of Women's and Children's Health, AOU Ancona, Ancona, Italy; ^gDepartment of Pediatrics, Pediatric Diabetes Regional Center, General Hospital of Parma, Parma, Italy; ^hDepartment of Pediatrics, Pediatric Diabetes Regional Center, Gaslini H., Genova, Italy; ⁱPediatric Unit, Brotzu H., Cagliari, Italy; ^jDepartment of Pediatrics, Second University of Naples, Naples, Italy; ^kEndocrinology and Diabetology Unit, Bambino Gesù Children's H., Rome, Italy; ^lDepartment of Pediatrics, Diabetology Unit, Sacco H., Milan, Italy; ^mPediatric Diabetology Unit, Meyer Children H., Florence, Italy; ⁿDepartment of Pediatrics, University of Chieti, Chieti, Italy; ^oDepartment of Pediatrics, University of Turin, Turin, Italy

Background: Data regarding epidemiology and management of Diabetic Ketoacidosis (DKA) in Italian children with T1D at disease onset are lacking. **Method:** From 1/1/2012 to 31/12/2013 a survey on DKA was conducted in all paediatric Centres belonging to the Italian Society for Pediatric Diabetology and Endocrinology. DKA was defined according to the ISPAD criteria. The following data were collected: treatment according ISPAD protocol yes or not, type of rehydrating solution used, bicarbonates use yes or not

and amount of insulin infused. **Results:** Data were returned from 68/77 Centres (87%) for a total of 14.493 patients with T1D. We recorded 2453 children with T1D onset, with DKA in 945 (38.5%) (severe in 10.3%). Considering only preschool children DKA was observed in 72% (severe in 16.6%). Cerebral oedema following DKA treatment was observed in five cases (0.5%). DKA treatment according ISPAD guidelines was adopted in 67% of the Centres, while 11% did not follow any specific guidelines. In the first 1–2 h, rehydration was started with normal saline, at different rates: 5–10 ml/kg per h in 71%, 10–20 ml/kg per h in 16%, < 5 ml/kg per h in 4%. After the first hours, differences among Centres were observed regarding the type of solutions used: saline 0.9–0.45% in 75%, 5–10% glucose solution in 19%, irrespective of glycemic values. Potassium supplementation was performed at the rate of 20–40 mEq/l in 63% of Centres. Bicarbonates were never used in 17% of Centres, while in 68% were exceptionally used according to pH and clinical conditions. Insulin was infused starting from 2nd–3rd hour at the rate of 0.05–0.1 U/kg per h in 63% of Centres, while others used infusion rate lowest as 0.025 U/kg per h. **Conclusion:** Notwithstanding prevention campaign, DKA is still observed at clinical diabetes onset in Italian children. Despite international guidelines (ISPAD), significant variability in DKA treatment still exists, underlying the need to share them among Centres.

P3-D1-701

Changing Presentation of Type 1 Diabetes to a Tertiary Paediatric Centre

Niamh Mc Grath, S M Mc Glacken-Byrne, C P Hawkes, N P Murphy
Children's University Hospital, Temple St, Dublin, Ireland

Background: The prevalence of childhood type 1 diabetes mellitus (T1DM) is increasing and the age at presentation is falling. Late presentation with diabetic ketoacidosis (DKA) is more common in younger children who are at increased risk of cerebral oedema. **Objective and hypotheses:** To describe the clinical presentation of new onset T1DM to our centre and report time to diagnosis, incidence of DKA, requirement for intensive care and complications. **Method:** Retrospective case review of all children with new onset T1DM from 2004–2012 at The Children's University Hospital, Temple Street, Dublin. DKA was classified as mild (pH < 7.3), moderate (pH < 7.2) and severe (pH < 7.1). **Results:** Over the study period 281 patients (129 males) presented with new onset T1DM (87 0–5 years, 120 6–11 years, and 74 12–16 years). Twenty-two patients presented in 2004 compared with 46 in 2012. Mean age at diagnosis was 8.8 years (range 0.66–15.6 years). Most (95%) presented with classical symptoms. DKA was seen in 31% of the cohort at presentation (45.9% mild, 26.4% moderate, and 27.5% severe) but occurred more commonly in younger children (68% of those < 2 years). Eleven percent of all children and 44% of those < 2 years required intensive care. Two patients (0.71%) developed cerebral oedema. The mean time to diagnosis from first contact with health care professional (HCP) was 20.6 days (range 2–140 days). Factors associated with early diagnosis were having a family member with type 1 diabetes ($P = 18$) and older age. **Conclusion:** The incidence of T1DM in

our centre is rising rapidly and the age at presentation is falling. Younger children tend to present later and are more often in DKA. Recognition is more difficult in the young child. Greater HCP awareness and implementation of national guidelines for management of DKA are critical to good outcomes.

P3-D1-702

Abnormal Blood Glucose as a Prognostic Factor for Adverse Clinical Outcome Among Children with Acute Medical Conditions in Ghana

Emmanuel Ameyaw

Komfo Anokye Teaching Hospital, Kumasi, Ghana

Background: Abnormal blood glucose in sick children is known to be common and carries a poor prognosis being associated with increased morbidity and mortality. **Aim:** To compare the clinical outcome in children admitted to the PEU of KATH with normal and abnormal blood glucose (hypoglycaemia or hyperglycaemia). **Method:** Prospective cohort study involving 430 children, 215 each with normal and abnormal blood glucose, selected from screening a total of 800 participants. They were matched for age group and diagnosis and clinical outcome compared. Participants were followed up till discharge. Complications, mortality and final diagnoses were recorded. **Results:** Twenty seven percent (116/430) of patients had at least one complication on admission and 22% (96/430) had abnormal blood glucose ($P=0.000$). The commonest complications were shock, intravascular haemolysis and acute renal failure. At the end of the study, 89% (382/430) were discharged well, 9% (40/430) died and 2% (8/430) were discharged with complication(s). 75% (6/8) of those discharged with complication(s), and 75% (30/40) of those who died had abnormal blood glucose ($P<0.001$). Of those with abnormal blood glucose who died, 36% (10/28) had hypoglycaemia and 11% (20/187) had hyperglycaemia ($P=0.000$). The risk ratio of patients with abnormal blood glucose dying was three (95% CI: 1.5–6.0) ($P<0.001$). The risk ratio of developing a complication was 4.8 (95% CI: 3.1–7.5) ($P=0.000$). **Conclusion:** Abnormal blood glucose was a common finding in children admitted to PEU, KATH, with acute medical conditions and was associated with increased complications including mortality. Hypoglycaemia on admission was a greater predictive factor of complications and mortality than hyperglycaemia.

P3-D1-703

Urinary c-Peptid/Creatinine Ratio in Children and Adolescents Diagnosed with Maturity-Onset Diabetes of the Young

Sebahat Yilmaz Agladioglu, Zehra Aycan

Dr Sami Ulus Children's Health and Disease Training and Research Hospital Clinics of Pediatric Endocrinology, Ankara, Turkey

Background and hypotheses: Urinary C-peptide creatinine ratio (UCPCR) is a new, non-invasive, economical test recommended in differential diagnoses of maturity-onset diabetes of the young (MODY). There are a few studies on this topic. UCPCR values were determined as >0.2 and >0.7 nmol/mmol with a high specificity and sensitivity in differential diagnosis in the previous two studies, the values were evaluated in only three MODY types (HNF1A/HNF4A/GCK-MODY). We investigate UCPCR changes in six different MODY types along with the availability of previously defined UCPCR values in different MODY types. **Methods:** A total of 28 patients genetically diagnosed with MODY were included in the study. Urine samples were collected 2 h after a standard lunch, which contained an appropriate calorie content consistent with patients' ages and weights. UCPCR values were calculated for all cases, and correlations between them as wells as ratios reported from previous studies were analyzed alongside data about each patient's MODY type and diabetes duration. **Results:** Patient UCPCR was defined as 1.22 ± 1.03 (0.1–3.97) nmol/mmol. The duration of diabetes in patients with $UCPCR < 0.7$ nmol/mmol was 3.08 ± 1.04 years, and it was 2.43 ± 2.72 years in patients with $UCPCR \geq 0.7$ nmol/mmol ($P=0.044$). There was a negative correlation between duration of diabetes and UCPCR. Among all patients, it was determined that 26 (93%) had $UCPCR \geq 0.2$ nmol/mmol, whereas 16 (57%) had $UCPCR \geq 0.7$ nmol/mmol. **Conclusions:** It was determined that UCPCR values might change in relationship with MODY type and diabetes duration. It was observed that, in the differential diagnosis of MODY, if $UCPCR > 0.7$ nmol/mmol is used only 57% of patients could be defined and if $UCPCR > 0.2$ nmol/mmol is used 93% of patients could be defined. It was deduced that an interpretation of UCPCR alongside other clinical and laboratory tests defined for MODY would strengthen the diagnosis.

P3-D1-704

A Case with Neonatal Diabetes and Congenital Hypothyroidism due to Glis3 Gene Deletion

Ilker Tolga Ozgen^a, Mehmet Küçüköç^a, Jayne Houghton^b, Selim Gökçe^a, Yasar Cesur^a

^aDepartment of Pediatrics, Medical Faculty, Bezmialem Vakif University, Istanbul, Turkey; ^bUniversity of Exeter Medical School, Molecular Genetic, Exeter, UK

Background: Neonatal diabetes is a rare disease having usually a genetic origin. Defects in *KCNJ11*, *ABCC8*, *INS*, *GCK*, and *PDX1* genes are more frequent and may lead non-transient, non-syndromic neonatal diabetes, whereas defects in *PTF1A*, *FOXP3*, *EIF2AK3*, *GLIS3*, *RFX6*, and *NEUROD1* genes are very rare and may lead neonatal diabetes as a part of a syndrome. **Objective and hypotheses:** We present a patient with *GLIS3*

gene deletion in this case report. **Method: Results:** Patient presented with prematurity, intrauterine growth retardation, respiratory distress syndrome, neonatal diabetes mellitus, severe resistant hypothyroidism with normal thyroid anatomy, neonatal cholestasis, isolated renal cyst, facial dysmorphism had been admitted to our hospital. Genetic analysis revealed that PCR amplification was successful for exons 1–2 and 5–11 of the *GLIS3* gene but not for exons 3–4, suggesting the homozygous partial gene deletion. This result confirmed a diagnosis of neonatal diabetes and congenital hypothyroidism due to a *GLIS3* gene mutation. The patient died at 5 months of age from measles infection. **Conclusion:** There are a few patients with *GLIS3* mutation reported in the literature. Some authors have emphasized different genotype may lead different clinical phenotype. Regarding to our patient, the *GLIS3* gene, exon 3–4 mutation may lead to intrauterine growth retardation, respiratory distress syndrome, neonatal diabetes mellitus, severe resistant hypothyroidism with normal thyroid anatomy, neonatal cholestasis, isolated renal cyst, facial dysmorphism without glaucoma, osteopenia or severe renal cystic diseases.

P3-D1-705

Glycemic Control of Patients with Type 1 Diabetes Using Automated Bolus Calculator Glucometer

Jaime Cruz Rojo, Lucía Garzón Lorenzo, Jaime Sánchez del Pozo, M^a Elena Gallego Gómez

Hospital 12 de Octubre, Madrid, Spain

Background: In the past years, new glucometers with integrated automated bolus calculator, are available in the market for patients with type 1 diabetes (DM1) in multiple daily injections (MDI) therapy. The limited bibliography about the use of these meters in the pediatric population with DM1, suggests that it may have beneficial effects in terms of glycaemic control and improved quality of life. **Objective and hypotheses:** The use of a glucometer with an integrated automated bolus calculator (Accu-Chek[®] Aviva Expert), improves glycaemic control in children and adolescents with DM1. **Method:** Data of children and adolescents diagnosed with DM1 followed in a tertiary hospital in were collected. Only the patients who performed at least four capillary blood glucose tests per day, and who had a knowledge on the carbohydrate counting calculation. Se collected data Hb1ACantes start using the meter, at 3 months and the last HbA1c disponible. Se sought significant differences between the three HbA1c, by Student's *t* for paired samples. **Results:** Data from 38 patients receiving treatment with MDI with insulin analogues (55% male, 45% female, age 12 ± 4.5 years) were collected. We did not find any statistically significant difference in HbA1c values measured before they started using the glucometer, 3 months later and at the last

HbA1c measurement (initial A1c: $6.9\% \pm 0.6$ DE; 3 months $6.8\% \pm 0.5$ ($P > 0.05$), HbA1c $6.9 \pm 0.5\%$ at the end of). The patients with poorest metabolic control (HbA1c $> 7.5\%$, $n = 7$), were the ones who most improved (initial HbA1c 7.8 ± 0.6 DE; 3 months 7.05% ($P > 0.05$), HbA1c $7.2 \pm 0.5\%$ at the end of the study ± 0.5 DE), but the differences founded were not statistically significant (probably due to the small sample size). **Conclusions:** In our study has not been able to show improvement in HbA1c after using a glucometer with recommender bolus, although this is possibly because the population included previously showed good glycaemic control. We have yet to analyze whether HbA1c beyond the use of these meters can decrease glycaemic variability or hipoe hyperglycaemic excursions.

P3-D1-706

Congenital Hyperinsulinism Linked to INS-R Mutation: Case Report

Marcello Vitaliti^d, Maria Cristina Maggio^a, Giuliana Vitaliti^a, Valeria Grasso^b, Amalia Ciofalo^d, Grazia Rinaudo^a, Elisa Tranchina^d, Giuseppina Costantino^d, Giovanni Corsello^a, Fabrizio Barbetti^{b,c}

^aUniversitary Department Pro.Sa.M.I. 'G. D'Alessandro', University of Palermo, Palermo, Italy; ^bBambino Gesù' Pediatric Hospital IRCCS, Rome, Italy; ^cTor Vergata' University, Rome, Italy; ^dNeonatology Intensive Care Unit, ARNAS Civico, Palermo, Italy

Background: Leprechaunism, also known as Donohue syndrome, is due to a severe congenital insulin-resistance, with prenatal and neonatal growth retardation, typical dysmorphic features, glycaemic dysregulation with hyperinsulinism and hyperandrogenism. **Objective and hypotheses:** These patients have a poor prognosis with death in the first year of life. **Method:** We report the case of a newborn (35.4 weeks) with severe fetal growth restriction (weight: 1149 g; length: 38 cm; and cranial circumference: 28 cm), facial dysmorphic features with low implant ears, low implant hairs, hypertrichosis, hypertrophic external genitalia, and postnatal growth failure. This patient showed significant hyperglycaemic (327 mg/dl) alternated with hypoglycaemic values (10 mg/dl) also during infusion of significant dose of i.v. glucose (12 mg/kg per min), significant hyperinsulinism (1000 μ U/dl) with elevated C peptide levels (43.41 ng/ml), persistent hypertension (113/74 mmHg). He has consanguineous parents (cousins). **Results:** A treatment with diazoxide (5 mg/kg per day) was tried with limited efficacy. He was treated with ACE-inhibitor (Captopril) at the dose of 0.02 mg/kg per day with a low response. The Captopril dose was increased at 0.04 mg/kg per day with a regulation of the blood pressure (76/54 mmHg). **Conclusion:** The genetic study of INS-R was performed. He presented a homozygote mutation in the insulin receptor (INS-R) gene. The mutation reported was c.3289C>T (CAG \rightarrow TAG) p.Gln1097Stop (Q1097X).

P3-D1-707

The Lung Endothelin System: a Potent Therapeutic Target with Bosentan for the Amelioration of Lung Alterations in a Rat Model of Diabetes Mellitus

Atila Cayir^a, Zekai Halic^b, Erol Akpınar^b, Zafer Bayraktutan^c, Mustafa Kara^d

^aDepartment of Pediatric Endocrinology, Regional Training and Research Hospital, Erzurum, Turkey; ^bDepartment of Pharmacology, Faculty of Medicine, Ataturk University, Erzurum, Turkey; ^cDepartment of Biochemistry, Regional Education and Research Hospital, Erzurum, Turkey; ^dDepartment of Pediatrics, Faculty of Medicine, Ataturk University, Erzurum, Turkey

Background: Endothelial dysfunction underlies lung and other organ complications developing in associated with diabetes. Endothelial dysfunction leads to an increase in cytokine levels and oxidative stress. Studies have shown that the endothelin plays significant roles in the development of diabetic complications.

Objective and hypotheses: The aim of this study is to show the effect of a new mechanism on endothelin receptors in the physiopathology of diabetes-related pulmonary injury. **Methods:** The rats were separated into four groups: group 1 (SHAM): control group; group 2 (DM): streptozotocin 60 mg/kg (i.p.); group 3 (DM+BOS-1): streptozotocin 60 mg/kg (i.p.) + bosentan 50 mg/kg peros; group 4 (DM+BOS-2): streptozotocin 60 mg/kg (i.p.) + bosentan 100 mg/kg peros. The bosentan treatment was initiated immediately after occurred STZ induced diabetes and continued for 6 weeks. **Results:** In the treatment group, SOD activity was significantly increased, although GSH and MDA levels and TNF α and TGF β gene expression were decreased. BOS-1 and BOS-2 showed a significantly down-regulatory effect on ET-1, ET-A, and ET-B mRNA expression. **Conclusion:** Following bosentan therapy, improvement in endothelial dysfunction, histopathological marked, and a decrease in cytokine levels were recorded, and the antioxidant balance progressed.

P3-D1-708

Clinical Significance of Typing Fulminant Type 1 Diabetes in Children and Adolescents

Yi Wang, Chunxiu Gong

Beijing Children's Hospital, The Capital Medical University, Beijing, China

Background: Fulminant type 1 diabetes (FT1D) is presented as a severe diabetes subtype among adults, however, we have no idea whether it's worth being taken seriously among children and adolescents. **Objective and hypotheses:** We aim to clarify the clinical significance of the subtype. It's supposed that we may needn't pay special attention to the subtype. **Method:** Case-control study design. Data from hospitalized all new type 1

diabetes (T1D) patients from January 2004 to December 2012. We obtain 11 cases as experimental group, whereas the classic type as control group. We match controls according to sex, age, onset season, and year with a ratio of 1:4. We study the clinical features, laboratory parameters and follow-up for 1 year in both groups. **Results:** Among 853 cases, there are 468 classic T1D patients onset with DK or DKA. Eleven cases (boys vs girls = 6:5) are in line with FT1D criteria. FT1D incidence is account for 1.29% of all classic T1D, and 2.35% of T1D with DK or DKA onset. Five patients with FT1D have honeymoon period. Compared with the control group, BMI (17.89 ± 2.64) vs (15.33 ± 1.90), $P < 0.05$. Incidence of FT1D group vs control group: severe DKA 40 vs 17%, insulin dose when the patients were discharged from hospital for 3–4 weeks 0.63 vs 0.59 (IU/kg per day), honeymoon period rate 45 vs 43% and average duration 113 vs 135 days, electrolyte index when diagnosed initially K⁺ (4.2 ± 1.0) vs (4.3 ± 0.6) mmol/l, Na⁺ + 135 (118–144) vs 134 (119–143) mmol/l, P values are ≥ 0.05 . **Conclusion:** Incidence of FT1D below 18 years old is very low. We find that additional stratification of the subtype among children and adolescents has little clinical significance.

P3-D1-709

Continuous Subcutaneous Insulin Infusion Therapy in Preschool Children with Type 1 Diabetes Mellitus

Rita Moinho^a, Dora Martins^a, Ângela Almeida^b, Estefânia Maia^a, Nanci Batista^a, Lina Aveiro^a, Rita Capitão^a, Rita Cardoso^a, Isabel Dinis^a, Alice Mirante^a

^aHospital Pediátrico – Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal; ^bHospital Infante D. Pedro – Centro Hospitalar do Baixo Vouga, Aveiro, Portugal

Background: A good metabolic control in preschool children with type 1 diabetes (DM1) is particularly challenging, being easier and safer with continuous subcutaneous insulin infusion (CSII) compared with multiple daily injections (MDI). **Objective and hypotheses:** Evaluate and compare metabolic control of preschool children with DM1, before and 9 months after CSII therapy. **Method:** Analytical retrospective study of children under the age of 6 when diagnosed with DM1 that began CSII therapy in 2013 first semester. Included variables: age at diagnosis and at CSII initiation, gender, insulin daily dose (IDD), mean blood glucose (previous 14 days), A1c and mean percentage of hypo and hyperglycemia (previous 14 days). Variables were analyzed in the previous 3–3M) and after 3 (+3M), 6 (+6M); and 9 (+9M) months of CSII initiation. **Results:** Fourteen children were included, 57% male. Mean age at diagnosis was 2.7 ± 1.3 years and mean age for CSII therapy initiation 5.1 ± 1.7 years. Mean IDD remained constant: –3M (0.8 ± 0.14 U/kg per day); +3M (0.75 ± 0.17 U/kg per day, $P = 0.1$); 6M (0.84 ± 0.2 U/kg per day, $P = 0.44$); and 9M (0.84 ± 1.6 , $P = 0.37$). Mean blood glucose did not change significantly over time: –3M (159 ± 27 mg/dl); +3M (163 ± 27 mg/dl, $P = 0.6$); +6M (165 ± 18 mg/dl, $P = 0.4$); and +9M (167 ± 20 mg/dl, $P = 0.4$). A1c levels decreased until 6M:

-3M ($7.1 \pm 0.6\%$); +3M ($6.95 \pm 0.6\%$, $P=0.37$); +6M ($6.87 \pm 0.4\%$, $P=0.18$); and +9M ($7.04 \pm 0.6\%$, $P=0.69$). Hypoglycemia percentage decreased significantly over time: -3M ($10.6 \pm 7.3\%$); +3M ($5.9 \pm 4.1\%$, $P=0.038$); +6M ($6.02 \pm 4.5\%$, $P=0.026$); and +9M ($6.8 \pm 5.9\%$, $P=0.05$). There was no significant variation in hyperglycemia percentage: -3M ($44.6 \pm 13.8\%$); +3M ($44.3 \pm 14.4\%$, $P=0.59$); +6M ($44.35 \pm 9.8\%$, $P=0.95$); and +9M (46.8 ± 11.9 , $P=0.58$). **Conclusion:** With CSII the good metabolic control that already existed with MDI was kept. There was also a trend of decreasing in A1c, with significant reduction of hypoglycemia, that is particularly feared in this age group. Under close medical supervision and continuous education, CSII therapy allows to maintain good metabolic control, reducing hypoglycemia and providing improved quality of life.

P3-D1-710

Health-Related Quality of Life Among Turkish Children and Adolescents with Type 1 Diabetes

Turgay Aydin, Cengiz Kara

Faculty of Medicine, Ondokuz Mayıs University, Samsun, Turkey

Background: Health-related quality of life (HRQOL) is defined as a patient's subjective perception related to the satisfaction with own health. There is no enough data on HRQOL of children and adolescents with type 1 diabetes (T1D) living in Turkey. **Objective:** To evaluate HRQOL in children and adolescents with T1D compared with healthy controls in Turkey, and to identify HRQOL determinants. **Method:** A total of 133 children and adolescents with T1D aged 6-18, and 133 matched healthy peers participated. KINDL (KINder Lebensqualitätsfragebogen) quality of life questionnaire was applied to all subjects. In addition, the patients completed a second questionnaire for the disease state. The patients' hospital records were examined to identify possible factors affecting HRQOL including age, gender, duration of diabetes, HbA1c, and the frequency of hypoglycemia and diabetic ketoacidosis (DKA). **Results:** Mean age was 12.5 ± 2.8 years, 54% were girls and mean duration of diabetes was 4.3 ± 2.7 years. Mean HbA1c was 9.1 ± 2.0 , but no patient had overt diabetes complication. Total HRQOL scores of the patients were lower than those of healthy peers ($P=0.044$). Sub-dimension scores including physical well-being, emotional well-being and self esteem were lower in the patient group compared to the control group ($P=0.008$, 0.032 , and 0.003 respectively). However, there were no statistically significant differences regarding family, school and friend sub-dimensions between two groups. Total HRQOL scores of both diabetic and healthy adolescents (aged 12-18) were poorer than those of children (aged 6-11) ($P=0.01$). Lower HRQOL scores were significantly associated with longer duration of diabetes, older age (being adolescent) and experience of DKA. **Conclusion:** Our study showed that T1D among Turkish children and adolescents had negative impact on physical and emotional well-being, rather than social well-being. HRQOL was related to older age, duration of diabetes and experience of DKA, but not to gender, metabolic control and hypoglycemia in our population.

P3-D1-711

Autoimmune Thyroiditis in Georgian Children and Adolescents with Type 1 Diabetes Mellitus

Nino Abdushelishvili^a, Marine Gordeladze^b

^aChildren's New Clinic, Tbilisi, Georgia; ^bPediatric Clinic, Tbilisi State Medical University, Tbilisi, Georgia

Background: Over the recent years there have been more and more cases with DM type 1 and thyroid autoimmune diseases. **Objective:** To study course of autoimmune thyroiditis in children and adolescents with DM type 1. **Methods:** From 758 children with DM type 1 we identified high risk cohort (thyroid gland palpation and clinical symptoms) and performed thyroid US and TSH, fT₄, anti-TPO, anti-TG, and HbA1c testing. Cohort group, 84 patients were followed for 2-5 years. Treatment with l-thyroxine was administered in cases of enlarged gland and/or TSH elevation (tested twice, with elevation above 4.5 mU/l). Diabetes compensatory markers were compared with control group of same age with DM type 1 and no autoimmune thyroiditis. **Results:** Autoimmune thyroiditis was found in 38 cases: girls 22 (57.9%), boys 16 (42.1%). Prevalence of thyroiditis in study population was 5 vs 1.2% in general population. Stratification according to age 3-10 years - 15 patients (39.5%), 11-18 years - 23 patients (60.5%). **US results:** Enlarged gland - 78.9%, normal volume - 15.8%, and decreased volume - 5.3%. US changes - 94.7% and structural changes - 65.8%. Elevated anti-TPO - 92.1%, anti-TG - 57.8%, both - 50% of case. Anti-TPO was high in 11-18 years old group ($P<0.05$). Hypothyreosis was found in 13.2%, subclinical hypothyreosis - 26.3%, euthyreosis - 57.9%, and hyperthyreosis - 2.6%. Fourteen patients received treatment with l-thyroxine. Statistically significant difference was not found between HbA1c level and insulin requirement in study as well as control group. **Conclusion:** Autoimmune thyroiditis is more prevalent in DM type 1 patients than in general population of same age. Prevalence increases with age and diabetes duration. Thyroid disease in euthyroid state does not cause worsening of DM.

P3-D2-712

Audit of the Use of Integrated Care Pathway in the Management of Diabetic Keto Acidosis in Children

Ravi Palakurthi, Kamal Weerasinghe

Wrexham Maelor Hospital, Wrexham, UK

Background: Diabetic keto acidosis is a complex metabolic state of hyperglycaemia, ketosis, and acidosis. Integrated care pathway for the management of DKA was introduced in 2007. At our hospital we use potassium infusion prepared by pharmacy that allows us to alter the rate of infusion for variable potassium delivery. **Objective and hypotheses:** To check the adherence to integrated care pathway. To identify whether alteration of the

rate of potassium infusion was needed in these children. **Method:** Retrospective review of case notes of children admitted with DKA from April 2011 to July 2013. **Results:** Nine out of 16 children (six males) were admitted with DKA as their first presentation. One hour interval from the start of rehydration fluid to the start of insulin was maintained in seven out of 16 children. Change of insulin infusion from 0.1 to 0.05 U/kg per hour was needed in 13 out of 14 children. One child who had GCS of 10/14 was treated for possible cerebral oedema and two children with GCS of 14/15 did not need specific treatment. Two of the three children on admission received insulin bolus subcutaneously, deviating from guideline. No other adverse outcomes were noted. **Conclusion:** Adherence to the integrated care pathway facilitated appropriate management of children presenting with DKA. Areas for improvement in practice including need for effective documentation were identified. Alteration of potassium infusion rate was not needed and episodes of hypokalemia were not documented. This led us to reconsider our practice of providing potassium infusion prepared in-house in the pharmacy. Standard replacement fluid with 40 mmol/l may be sufficient. All teams who could potentially get involved in the management of children with DKA need to be familiar with the guidelines to optimise their care.

P3-D2-713

Development of Diabetes Mellitus after Hematopoietic Stem Cell Transplantation for Childhood Leukemia

In Ah Jung, Yeon Jin Jun, Won Kyoung Cho, Jae Wook Lee, Nak Gyun Chung, Min Ho Jung, Bin Cho, Byung Kyu Suh

College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

Background: Hematopoietic stem cell transplantation (HSCT) recipients are at risk of endocrine complications as a result of chemotherapy and radiation therapy. Development of diabetes mellitus (DM) after HSCT is less frequently reported compared with other complications. **Objective and hypotheses:** We investigated clinical features of newly diagnosed DM after HSCT for treatment of childhood leukemia. **Method:** Between April 1999 and March 2013, total 112 patients (63 males and 49 females) were visited the Clinic of Pediatric Endocrinology for routine follow-up check after HSCT for leukemia. Among them, four patients developed DM (three males and one female). We retrospectively reviewed medical charts including laboratory findings. **Results:** Three patients were diagnosed as acute lymphoblastic leukemia who received total body irradiation and chemotherapy. The other one patient diagnosed as acute myeloblastic leukemia received only chemotherapy for conditioning. The mean age at HSCT was 7.75 ± 4.21 years. All four patients developed chronic graft-vs-host disease (GVHD) and treated with steroid. The mean age at diagnosis of DM was 16.25 ± 1.48 years and the time interval between HSCT and DM was 8.5 ± 4.2 years. Three patients showed obesity depend on BMI

(>95th percentile for sex and age). No one showed antibodies related with pancreatic β -cell. The mean fasting insulin levels at diagnosis were 13.24 ± 9.17 μ IU/ml and the mean homeostasis model assessment indexes of patients was 4.5 ± 2.0 . Three patients who showed obesity were treated with metformin only or metformin and insulin injection, and the other one was treated with insulin injection only. After the treatment, the diabetic control of all patients was improved. **Conclusion:** GVHD, long-term steroid treatment and insulin resistance seem to be close related to develop of DM after HSCT for treatment of childhood leukemia.

P3-D2-714

Case of Family Neonatal Diabetes with *KCNJ11* Gene Mutation

Svitlana Chumak, Olena Budreiko, Evgeniy Globa

State Institution 'Institute of Children and Adolescents Health Care' of NAMS of Ukraine, Kharkov, Ukraine

Background: Neonatal diabetes is a rare pathology occurring in around one in every 200 000–400 000 live births. The most common cause of permanent neonatal diabetes (PNDM) is heterozygous activating mutations in the *KCNJ11* gene encoding the pore-forming Kir6.2 subunit of the pancreatic β cell KATP channel. **Objective and hypotheses:** To determine the dynamic of carbohydrate metabolism in family transferred from insulin to sulphonylureas (SU). **Method:** We studied a family (mother and child) with PNDM diagnosed within the first 6 months of life. Carbohydrate metabolism was studied by iPro-2 monitoring, HbA1c, C-peptide, and insulin levels during 8 months of SU therapy. The *KCNJ11* gene was sequenced by Sanger. **Results:** A mutation in *KCNJ11*, R201H was identified in both patients. Transfer from insulin to SU tablets was done in child and mother at the age of 2 months and 28 years old accordingly. At the start of transfer process in child the daily dose of SU was divided into six doses (0.27 mg/kg per day), every feeding, but after 8 months of SU treatment frequency of dosing is reduced to four doses with decreasing of SU daily dose (0.17 mg/kg per day). The child's mother at 28 years old stopped insulin (45 units/day) and went on to SU in dose 15 mg/day. After 8 months of SU treatment HbA1c improved in both patients (in child 5.15 vs 13.9% and in mother 6.5 vs 8.9% accordingly). Daily monitoring (iPro-2) in child showed a marked reduction in the fluctuations as well as an overall lower level of glycaemic control (13.8 (2.6–26.6) mmol/l before SU treatment to 6.0 (3.3–10.2) mmol/l after). C-peptide level increased from 0.09 to 0.5 ng/ml in child and from 0.009 to 0.35 ng/ml in mother after 8 months of SU treatment accordingly. **Conclusion:** Patients with diabetes presenting within the first 6 months of life should receive genetic testing to prescribe the pathogenetic treatment. Daily dose of SU in child during 8 months decreased by 37% on a background of improving of carbohydrate metabolism, HbA1c. A good response on SU treatment was observed even after 28 years of insulin therapy.

P3-D2-715

Insulin Pump Therapy in One Case of 6q24 Transient Neonatal Diabetes for 3 Years

Liu Wangkai^a, Li Xiaoyu^a, Su Yihua^b, Zhuang Siqi^a, Li Yijuan^a,
Ma Huamei^a, Du Minlian^a, Chen Weiqi^a

^aDepartment of Pediatrics, The First Affiliated Hospital, Sun Yat-Sen University, Guangzhou, China; ^bDepartment of Ophthalmology, The First Affiliated Hospital, Sun Yat-Sen University, Guangzhou, China

Background: Management of transient neonatal diabetes mellitus is complex. Conventional insulin therapy may be increase additional medical problems. From the case is presented, We suggested s.c. insulin pump therapy of neonatal diabetes is a safe and effective approach to management. **Objective and hypotheses:** To evaluate the therapeutic effect of continuous s.c. insulin infusion with insulin pump in a case with transient neonatal diabetes mellitus (TNDM). **Method:** A 2-month female infant patient, presented with postnatal persistent hyperglycemia, received a diagnostic workup in the newborn department of our hospital. Methylation-specific PCR showed complete loss of methylation at the TND differentially methylated region on chromosome 6q24, which was consistent with 6q24 transient neonatal diabetes. Thus a diagnosis of TNDM was confirmed genetically. This patient, previously treated with multiple daily insulin injections and glibenclamide, which proved to be ineffective, was then given continuous s.c. insulin infusion with insulin pump. Insulin dose and infusion mode were adjusted based on blood glucose profiles. The patient has been followed up for 3 years. **Results:** Blood glucose levels were significantly improved within 2 weeks. Basal and bolus infusion mode had been maintained for 2 years and subsequently switched to a mode with basal insulin infusion only for 2 months, which was then discontinued and followed by a single injection of basal insulin until now. Blood glucose levels fluctuated from 4.1 to 11.2 mmol/l. Hypoglycemia was minimal. The patient thrives well, with her weight and height around the 50th percentage in her age group. **Conclusion:** Continuous s.c. insulin infusion with insulin pump provided optimal and safe control of blood glucose in TNDM, and might also shorten length of hospital stay, prevent relevant complications and reduce mortality rate.

P3-D2-716

Uptake of a Novel Tool to Adjust Insulin Boluses, Based on CGM Trend Arrows and Insulin Sensitivity (Trend Arrow Adjustment Tool); in Children with Type 1 Diabetes, Who are Using Insulin Pump Therapy and Continuous Glucose Monitoring

Emmeline Heffernan, Margaret Lawson

Children's Hospital of Eastern Ontario, Ottawa, Ontario, Canada

Background: Real-time CGM data includes 'trend arrows' which indicate when the blood glucose is rapidly falling or rising

thus enabling the pump user to make immediate adjustments in insulin delivery to prevent subsequent low or high blood sugars. However, effective strategies for adjusting insulin boluses based on CGM trend arrows are lacking. Previous studies recommended that boluses be adjusted based on trend arrows using a standard 10–20% increase/decrease of the bolus dose (10% for one arrow up or down and 20% for two arrows up or down), with the original bolus dose calculated by the pump calculator. However, the original recommended bolus dose is dependent on the amount of food to be consumed and the current blood glucose, and therefore increasing or decreasing the total recommended bolus by 10–20% could potentially overcompensate for the trend arrows and result in postprandial hypoglycemia. This formula also requires the pump user, or the caregiver, to perform mathematical calculations with each trend arrow. Attempts to use the 10/20% formula resulted in low acceptance and adherence by CGM users. Dissatisfaction with the 10/20% formula led to the development of an innovative tool for adjusting boluses for CGM trend arrows based on the patient's insulin sensitivity factor. **Objective and hypotheses:** We aimed to assess patient uptake of the Trend Arrow Adjustment Tool (TAAT) and whether its use is sustained. **Method:** A retrospective audit of CGM data; examining the uptake of the TAAT, in 40 patients, over a 3-month period. **Results:** Uptake of the TAAT was very good, with use being sustained over a 3-month period. **Conclusion:** We plan a more detailed evaluation of TAAT, to assess effectiveness and patient satisfaction.

P3-D2-717

Diabetes Mellitus a Late Complication in Glycogen Storage Disease Type 1b

Kiran Kumar, Pooja Sachdev, Tabitha Randell, Louise Denvir

Nottingham University Hospital NHS Trust, Nottingham, UK

Background: Diabetes mellitus is a late complication in glycogen storage disease type 1 (GSD1). Patients with GSD1 who are poorly controlled have prolonged periods of low glucose levels. As they grow older they become tolerant to these hypoglycaemic episodes, and may be mildly symptomatic or asymptomatic even with low glucose levels. This results in adaptive mechanisms, mediated through down regulation of glucose receptor on the β -cell membrane (GLUT2) to reduce insulin secretion. In time these patients develop a permanent state of insulinopaenia and lose their ability to secrete appropriate amounts of insulin in response to transient elevations of blood glucose. This hypothesis is the basis for the inclusion of GSD1 among genetic syndromes associated with secondary diabetes mellitus. **Case series:** Patient one is a male who had first liver transplant at age of 11 years because of poor metabolic control secondary to GSD. He had rejection of his transplant following reactivation of CMV 4 years post-transplant and developed diabetes mellitus. He has been on twice daily insulin injections and his latest HbA1c is 81 mmol/mol. He has had two further transplants and has developed epilepsy,

cataract and stage four kidney disease. Patient two is a female sibling who had liver transplant at age of 8 years for poor metabolic control secondary to GSD. She had few episodes of rejection but has recovered. She presented acutely unwell at 17 years with polyuria, polydipsia and acute abdominal distension and found to have graft dysfunction, acute renal failure and hyperglycaemia. She settled following insulin therapy and currently on insulin pump. Her latest HbA1c is 38 mmol/mol. She developed acute kidney injury during this episode but recovering well. **Summary:** Only few cases have been reported so far. In our series siblings with GSD1b developed diabetes and it should be considered among the late complications of GSD-1b.

P3-D2-718

Incidence of Diabetes Mellitus and Associated Complications Among Children: Results from Azerbaijan Diabetes Registry 1997–2007

Gunduz Ahmadov

Azerbaijan Medical University, Baku, Azerbaijan

Background: Diabetes prevalence is increasing globally, and Azerbaijan is no exception. Poorly controlled diabetes is associated with increased long-term micro-vascular and macro-vascular complication risk, leading to an increased morbidity and mortality. **Objective and hypotheses:** The purpose of this study was to estimate incidence of diabetes mellitus (DM) among children aged 0–18 years and to assess growth, glycaemic control, complications, risk factors and mortality associated diabetes mellitus, based on prospective registration of patients in National Diabetes Registry during the period 1997–2007 in the Azerbaijan Republic. **Method:** We performed a comparative clinic-based study of 1194 patients with diabetes from over the country. Retinopathy was assessed by seven-field stereoscopic retinal photography; albumin excretion rate from three consecutive, timed, overnight urine collections; peripheral neuropathy by thermal and vibration threshold. HbA1c and lipids were measured in all patients. **Results:** Complications were determined in subgroups serving as cohorts by screening tests and based on physicians' report. There were 1194 patients (550 boys and 644 girls) registered during the period 1997–2007. The overall incidence/prevalence of T1DM (per 100 000 persons) was 3.5 (0.32/10(5)/year). Incidence was increasing from 3.5 to 11.5% during the period 1997–2007. On cross-sectional analysis of different cohorts, 65% were below 50th percentile height, 85% were <50th percentile of weight. 12.5% patients had poor glycaemic control (HbA1c >9%). The prevalence of different complications were as follows: neuropathy 18.9%, retinopathy 1.2%, nephropathy 1.3%, and diabetic cataract 1.3%. The percentage of patient with micro-albuminuria, high sensitive C-reactive protein was 29.6 and 44.4% respectively. Poor glycaemic control, hypertension, and duration were strong consistent predictors of all complications. Eleven patients died during the period of which ten deaths were related to diabetes. **Conclusion:** Though the incidence of diabetes

in the children is low in our population compared to the western population, the burden of diabetes is high due to large population in our country.

P3-D2-719

Arabic Translation and Validation of the Newest Vital Sign Health Literacy Tool: a Pilot Project to Test Health Literacy of Caregivers of Children with Type 1 Diabetes in Kuwait

Dalia Al-Abdulrazzaq^a, Muneera Al-Haddad^b,
Majedah AbdulRasoul^a, Iman Al-Basari^b, Abdulla Al-Taiar^a

^aKuwait University, Kuwait, Kuwait; ^bMinistry of Health, Kuwait, Kuwait

Introduction: Health literacy is a recognized concept in diabetes care. The newest vital sign (NVS) is an English instrument established to test health literacy using a nutrition label. No studies looked into health literacy in the Arab world. Our aim is to translate and validate the NVS tool to Arabic then test it on a pilot of Arabic-speaking caregivers of children with type 1 diabetes. **Methods:** i) Production of the Arabic version: the English version of NVS was translated to Arabic then reviewed by a panel of expertise. Then the modified Arabic version was created and back-translated to English. ii) Translation validation: the original and back-translated to English versions were compared based on the comparability of language and similarity of interpretation by fluent English speaking assessors. iii) Pilot project: the Arabic version is used to measure health literacy among 20 caregivers of pediatric patients of type 1 diabetes. **Results:** The mean age for the pilot group was 38.5 ± 6.6 years. The mean duration of the test in Arabic was 4.0 ± 1.2 min. Mean NVS score for the sample 3.2 ± 2.1 . None of the children of caregivers with limited literacy score had a good control (HbA1c $\leq 7.5\%$). **Conclusion:** The Arabic version of the NVS tool seems to be an accepted tool to measure health literacy. Although bases on small numbers, limited health literacy of caregivers seems to be linked to inadequate glycemic control of their children. Further link should be studies on a larger sample to be generalized to Arabian populations.

P3-D2-720

Anti-Cyclic Citrullinated Peptide Antibodies are not Frequent in Children with Type 1 Diabetes

Melek Yildiz^a, Figen Isleten^b, Korcan Demir^a, Nilüfer Celik^b,
Hüseyin Anil Korkmaz^a, Birsan Tuglu^b, Özlem Nalbantoglu Elmas^a,
Behzat Özkan^a

^aDivision of Pediatric Endocrinology, Dr Behçet Uz Children's Hospital, Izmir, Turkey; ^bDivision of Biochemistry, Dr Behçet Uz Children's Hospital, Izmir, Turkey

Background: Type 1 diabetes mellitus is characterized by presence of several organ specific autoantibodies. Anti-cyclic citrullinated peptide (anti-CCP) antibody is a promising marker of rheumatoid arthritis (RA) which is known to coincide with autoimmune diabetes. Presence of these antibodies was not investigated in children with type 1 diabetes. **Objective and hypotheses:** To evaluate presence of anti-CCP antibodies in children with type 1 diabetes compared to healthy subjects. **Method:** Ninety children with type 1 diabetes known to be positive for at least one of the pancreatic islet autoantibodies (group 1, M/F: 46/44; mean age 10.5 ± 3.9 years; diabetes duration 2.1 ± 1.9 years) and 76 control cases (group 2, M/F: 34/42; mean age 9.8 ± 3.7) were included. Presence of antithyroid antibodies and coeliac antibodies were recorded for cases with type 1 diabetes. The groups were compared regarding family history for RA, anti-CCP, as studied by ELISA, and rheumatoid factor levels. **Results:** The groups were similar regarding age and gender ($P=0.196$ and $P=0.507$ respectively). In group 1, one case (1.1%) was positive for anti-CCP antibody (5 U/ml, normal < 4.00 U/ml) while none of the controls was positive ($P=0.999$). The case, who was 9.5 years old, had no relevant joint complaints or findings. He was diagnosed with type 1 diabetes 2 months ago and showed positivity for anti-islet cell antibody, anti-gliadin IgA, and tissue transglutaminase IgA antibodies. However, intestinal biopsy for coeliac disease and RF were negative. Family history for RA and RF positivity was not different between groups 1 and 2 ($P=0.626$ and $P=0.999$ respectively). In group 1, positivity rates of antithyroid and coeliac autoantibodies were 19.8 and 10%, respectively. **Conclusion:** During childhood, anti-CCP antibodies are rare in type 1 diabetes of short duration. The single case with high anti-CCP level will be followed for rheumatoid arthritis however this positivity might be nonspecific and transient as well.

P3-D2-721

Glycemic Variability and Metabolic Control in Pediatric Patients with Type 1 Diabetes Mellitus

Maria Martin-Frias, M Belen Roldan, M Milagros Alonso, Yoko Patricia Oyakawa, Daniel Alonso, Raquel Barrio

Ramon Cajal Hospital, Madrid, Spain

Introduction: Recently, the impact of glycemic variability in the development of chronic complications of diabetes has been put in question. The gold-standard method to quantify glycemic variability is not well established. **Objective:** To analyze the relationship between HbA1c and glycemic variability as determined from self-monitoring blood glucose (SMBG) in type 1 diabetes (T1D) pediatric population. **Patients/methods:** Cross-sectional study in 175 T1D patients with a mean age of 12.2 ± 4.2 years, 50% female. Variables analyzed were: age at diagnosis, time from diagnosis, and metabolic control (HbA1c, HPLC-Menarini, VN $5.31 \pm 0.31\%$). As parameters of glycemic variability we used: mean blood glucose (MG, mg/dl), s.d., percentage hypoglycaemia (< 70 and < 50 mg/dl) and hyperglycaemia (> 180 mg/dl) during the last 1 and 3 months. As indices of glycemic variability: MG/2

relative to s.d. (adequate if $MG/2 \geq s.d.$) and J index ($0.001 \times (MG + s.d.)^2$: ideal 10–20, adequate 20–30, and inadequate > 40). Statistical analysis: SPSS, version 17.0 program. **Results:** Mean age at diagnosis was 6.2 ± 4.2 years, mean time T1D duration 6.0 ± 3.9 years and mean HbA1c $6.7 \pm 0.6\%$. Mean SMBG per day and patient 7.6 ± 2.3 . Mean capillary glycemia in last 3 months 150 ± 70 mg/dl. The 61 and 63% of patients had a $MG/2 \geq s.d.$ in last 1 and 3 months respectively. Patients with $MG/2 \geq s.d.$ relation had significantly lower MG and s.d., hyper and hypoglycaemia percentage and HbA1c, with no differences in the number of daily capillary glycemic controls. Patients with inadequate J index had significant worse glycemic control. We found a positive correlation between HbA1c and MG, s.d., and J index. **Conclusion:** The presence of inadequate glycemic variability is associated with worse glycemic and metabolic control in pediatric patients with T1D.

P3-D2-722

Knowledge Base and Attitudes of Senior Medical Staff to Insulin Therapy in Children with Diabetes

Amith Nuti, Christopher Bidder, Geraldine Phillips, Puvaneswary Vamadevan, Carol Fraser

Abertawe Bro Morgannwg University Health Board, Swansea, South Wales, UK

Background: Knowledge on multiple daily injections (MDI) and continuous subcutaneous insulin infusion (CSII) regimen impacts on the out-of-hours advice given to families of children with diabetes. As such, knowledge base and attitudes of senior medical staff particularly middle grades regarding insulin therapy is paramount. **Objective:** Assessing confidence levels of middle grade doctors to provide advice on insulin regimens. We conducted a questionnaire based survey to assess knowledge base and followed it up with training sessions delivered by the diabetic team. **Method:** A SurveyMonkey based questionnaire was circulated to all middle grades and consultants in the paediatric department. Questions included: i) Calculation based scenarios. ii) Confidence levels at managing DKA. iii) Trouble shooting insulin pump queries. iv) Future training sessions content. Free text option for responses were provided. **Results:** Three consultants, five middle grades (ST4-8), and two associate specialist doctors responded. 67% were not confident on starting MDI for newly diagnosed cases although majority were confident of managing DKA and provide advice over 'sick day rules'. 57% were unable to advise change from CSII to MDI regimen and 85% were not confident on providing advice over the phone regarding pump use. Training sessions on the insulin pump improved confidence in diabetes management. **Conclusion:** There is significant lack in knowledge base regarding insulin pump therapy. There is scope for guideline development on different pumps used in CSII. Structured education teaching on diabetes should include basic insulin pump training. Confidence in managing common insulin pump queries improved in post-teaching survey.

P3-D2-723

Estimation of Compensation and Prevalence of Chronic Complications of Type 1 DM in Children According to the Screening Data

Nasiba Alimova, Gulnara Rakhimova

Center for the Scientific and Clinical Study of Endocrinology, Tashkent, Uzbekistan

Objective and hypotheses: The work was initiated to comparatively assess degree of compensation and prevalence of complications of type 1 DM in children in Uzbekistan from 1998 to 2012 according to the screening data. **Method:** 950 children (coverage of 80.3%) with type 1 DM were screened in 2012 within the WDF grant 'Children's Diabetes in Uzbekistan', the degree of compensation and prevalence of type 1 DM chronic complications were compared with those obtained for 618 children (coverage of 98%) examined in 1998. Compensation level was estimated according to ISPAD criteria (2011). **Results:** In 2012 target levels of therapy in children (HbA1c <7.5%) were reached in 24.3% comparing with 16% in 1998, mean level of HbA1c decreased from 12.7 to 9.6% ($P < 0.001$). The comparative analysis showed significant decrease in prevalence of physical retardation by 3.45 times in children ($P < 0.0001$) and decrease of sexual retardation by 3.4 times ($P < 0.0001$). In children prevalence of diabetic complications reduced as follows, by 7.9 times for retinopathy ($P < 0.0001$), by 1.6 times for neuropathy ($P < 0.0001$), by four times for diabetic nephropathy with ESRD ($P < 0.0001$), and by 2.3 times for diabetic hairopathy ($P < 0.001$). Occurrence of cataract has the tendency to reduce. **Conclusion:** The analysis of screening results showed efficiency of the National Register and a correct choice of strategy and tactics on optimization of quality of care for children with type 1 DM in Uzbekistan.

P3-D3-724

Prevalence of Impaired Glucose Tolerance and Insulin Resistance in a Sample of the 6- to 16-Year-Old Overweight or Obese Pediatric Population

Fatemeh Saffari^a, Mahmood Vandaei^b, Sonia Oveis^a, Neda Esmailzadeh^a

^aMetabolic Diseases Research Center, Qazvin University of Medical Sciences, Qazvin, Iran; ^bQazvin University of Medical Sciences, Qazvin, Iran

Background: Prevalence of obesity and its complications including type 2 diabetes mellitus, impaired glucose tolerance and insulin resistance have been increased among children and adolescents during recent decades. **Objective and hypotheses:** The aim of this study was to determine the prevalence of impaired glucose tolerance and insulin resistance among overweight or obese children and adolescents. **Method:** This cross sectional

study was conducted in 199 children and adolescents aged between 6 and 16 years with BMI above the 85th percentile for their age and sex referred to the endocrine clinic of Qazvin children hospital during 2012. Physical examination including evaluation of weight, height, BMI was performed. Overweight was defined as a BMI between the 85th and 95th percentiles for children of the same age and sex; obese was defined as a BMI over the 95th percentile for children of the same age and sex. Blood levels of fasting glucose and insulin were measured after an 8 h overnight fast. An oral glucose tolerance test was performed with 1.75 g/kg glucose for all the participants. Participants were characterized as having normal glucose metabolism, impaired fasting glucose, impaired glucose tolerance or diabetes according to American Diabetes Association criteria. Homeostatic model assessment (HOMA) more than three was used to estimate insulin resistance. Data were analyzed using descriptive statistics. **Results:** Mean age was 10.94 ± 2.56 . 17.6 and 82.4% of the participants were obese and overweight, respectively. Prevalence of impaired fasting glucose, impaired glucose tolerance and diabetes were found to be 15.6, 7.5 and 4%, respectively. 51.3% of the participants were insulin resistant. **Conclusion:** High prevalence of insulin resistance indicates the future burden of diabetes and emphasizes the importance of prevention programs in overweight or obese children and adolescents from early age in order to promote their present and future health.

P3-D3-725

Differences in Pubertal Development and Anthropometry Between Normal Population and Type 1 Diabetic Child at Debut in Spain

Ignacio Diez-Lopez, Ainhoa Sarasua-Miranda, Sonia Sanchez-Antonio, Isabel Lorente-Blazquez

Children's Endocrinology Section, Pediatric Service, University Hospital of Alava, Vitoria/Basque Country, Spain

Background: The deterioration caused DM1 anthropometric and pubertal development. With intensive treatment, improved HbA1c and less microvascular complications should be similar to normal population. **Objective:** To study the pubertal development in our population with DM1 and final somatometric variables reached in relation to the normal population. **Material and methods:** Retrospective study of DM1A debut from diagnosis to final height. Inclusion: Historical Unit Patients from 1973 to 2000 DM1a. Exclusion: other DM, no final height or V. Tanner Studio and bilateral Student' *t*-test Samples T IBM SPSS 18.0. Comparative longitudinal half somatometry Orbegozo 2004 (OL) to final height. Pubertal development Ferrandez 2002 (DPF). **Results:** 82 cases initially selected (38/82 ♂ -46%). Average age debut 8.24aDS4.27 (0.3-15). 16.98 kg/m² average BMI (-0.2 SDS) DS4.27, mean height of 132 cm. (+0.3 SDS) DS27.92. Tanner I.HbA1c debut DS2.37 11.11% (8-15.5), differences ♂ ♀ 10.79 vs 11.87 $P: 0.032$ target height of 171.5 cm. DS2.1 with normal population difference $\Delta -2.6$ cm $P 0.01$ and ♀ 159.3 cm. SDS difference for OL 2.3 with $\Delta -2.5$ cm $P: 0.01$. Evolutionary

average 9.6 years follow DS2.8 with the high average age of 17.91 years SDS3.1. SDS1. 16 mean HbA1c 7.30% (5.8–9.6) along the track. No differences between sexes. To start T2 ♂ mean age 12.48 years, SD 1.2 (+0.8 years for PDF P : 0.02) and T5 14.60 years (like PDF). Final height reached 174.33, gain +2.8 cm. TD regarding size and equivalent to OL. 23.48 kg/m² BMI (Z -score +0.51 SDS respect OL P : 0.001). To start T2 ♀ mean age 10.49 years, SD 1.1 (−0.2 years for PDF P : 0.45) and menarche at 13.31 years (+0.7 years for PDF P : 0.02). Final height reached 161.74, gain +2.5 cm. TD respect and respect OL +1.0 cm P : 0.010. BMI 23.59 kg/m² (Z -score +0.85 SDS regarding OL P : 0.001). **Conclusions:** DM1 children start puberty a little later, ending an age and final height equivalent to normal population, but there is more tendency to be overweight, perhaps influenced by insulin therapy. Girls enter telarquia a normal age but more than half year delay menarche, finishing in a normal size but with tendency to overweight.

P3-D3-726

Effect of Vitamin D Treatment on Glucose and Insulin Metabolism, and Bone Turnover in Children with Symptomatic Vitamin D Deficiency

Nagla El-fakhria, Martin McMillana, Jane McNeillyc, S F Ahmeda, Helen McDevitt^{a,b}

^aSchool of Medicine, Royal Hospital for Sick Children, University of Glasgow, Glasgow, UK; ^bNeonatal Unit, Royal Hospital for Sick Children, Glasgow, UK; ^cDepartment of Biochemistry, Southern General Hospital, Glasgow, UK

Background: There are limited data in paediatric population on the association between vitamin D deficiency/treatment and glucose/insulin metabolism. **Objective and hypotheses:** This study aimed to investigate the effect of vitamin D therapy on glucose homeostasis, insulin resistance and bone turnover, in children with vitamin D deficiency. **Method:** 22 children aged 3 months to 10 years (nine male) who were diagnosed with vitamin D deficiency were recruited from August 2011 to October 2013. Treatment consisted of 6 weeks of 5000 IU units cholecalciferol orally once a day. At baseline and completion of treatment serum 25 hydroxyvitamin D (25OHD), parathyroid hormone (PTH), alkaline phosphatase (ALP), serum collagen type I cross-linked C-telopeptide (CTX), HbA1c, sex hormone binding globulin (SHBG), fasting insulin, fasting blood glucose, and homeostasis model assessment index-estimated insulin resistance (HOMA-IR) were measured. **Results:** After treatment, 25OHD had increased to a median of 126 from 28 nmol/l (P =0.00). PTH decreased from a median of 5.5 to 4.1 pmol/l (P =0.001). ALP also decreased significantly, median 236 to 195 u/l (P =0.03). There was a non-significant reduction in CTX from a median of 1.98 to 1.76 ng/ml (P =0.4) and SHBG from a median of 121 to 116 nmol/l (P =0.3). There was no change in fasting glucose (median 4.3 and 4.4 mmol/l, P =0.8) or HbA1c (median 33.5 and

34 mmol/l, P =0.5), There was a trend towards a reduction in both insulin levels and insulin resistance, with the median insulin falling from 11.1 to 8.1 μ IU/ml and HOMA-IR falling from 1.84 to 1.59, however this was not statistically significant (P =0.7 and 0.9 respectively). There was a weak negative correlation between vitamin D deficiency and elevated PTH at the base line (r_s , −0.19) and insulin level after treatment (r_s , −0.22). **Conclusion:** There is no clear evidence of an abnormality of insulin sensitivity with no significant change on vitamin D replacement.

P3-D3-727

Evaluation of HbA1c Measurement in Trinidad and Tobago

Maynika Rastogi^a, Paul Ladenson^b, David Goldstein^c, Randie Little^c

^aSangre Grande Hospital Eastern Regional Health Authority, Sangre Grande, Trinidad and Tobago; ^bJohn Hopkins Medicine International, Baltimore, Maryland, USA; ^cDiabetes Diagnostics Laboratory at the University of Missouri, Columbia, Missouri, USA

Introduction: The prevalence of diabetes in Trinidad and Tobago (T&T) exceeds 12%. Monitoring of HbA1c is standard of care to assess diabetes control but assay reliability requires high precision and standardization to either DCCT or IFCC values and results should be monitored through proficiency testing (PT). In T&T a developing country there is no existing data on HbA1c precision and accuracy. Johns Hopkins Medicine International and the Diabetes Diagnostic Laboratory, University of Missouri studied the accuracy and precision of HbA1c testing to determine the clinical utility of HbA1c measurements in T&T. **Methods:** Sets of ten samples containing blinded duplicates were created from five whole blood pools with HbA1c levels from 5.1 to 9.3% HbA1c and shipped to the five public hospitals and two large volume private laboratories. To assess within-day imprecision, the pooled estimate of the SDs between the duplicates (S_p) was calculated; 0.229 was the acceptable limit based on the current NGSP HbA1c standardization program monitoring criterion. To assess accuracy, each laboratory's results were compared to an NGSP Secondary Reference Laboratory (SRL9 using Tosoh G8) with $\pm 6\%$ bias considered acceptable. **Results:** Methods included Roche Tina quant on Cobas Integra, Cobas 6000 and Hitachi 911, Sebia Minicap, and Axis-Shield NycoCard. One laboratory reported results as IFCC %HbA1c; these were aligned to NGSP using the NGSP/IFCC master equation ($NGSP\% = 0.915(IFCC\%) + 2.15$) for consistency of reporting. All laboratories except the two using the NycoCard showed acceptable precision and accuracy. **Conclusions:** All but two participating T&T laboratories met acceptable criteria for HbA1c measurement. Since inaccurate HbA1c reporting negatively impacts diabetes care, we recommended that all laboratories report HbA1c in the same units and that only methods shown to report within acceptable limits of precision and accuracy be used. Continuous oversight of HbA1c testing is recommended.

P3-D3-728

The Result of Sulphonylureas Treatment in Patients with Neonatal Diabetes Mellitus due to *kcnj11/abcc8* Gene Mutations in Vietnam

Ngoc Can Thi Bich^a, Dung Vu Chia^a, Thao Bui Phuong^a, Khanh Nguyen Ngoc^a, Dat Nguyen Phu^b, Sian Ellard^c, Maria Craig^d, Hoan Nguyen Thi^a

^aNational Hospital of Pediatrics, Hanoi, Viet Nam; ^bHanoi Medical University, Hanoi, Viet Nam; ^cRoyal Devon and Exeter Hospital, Exeter, UK; ^dThe Children Hospital at Westmead, Sydney, New South Wales, Australia

Background: Neonatal diabetes may be defined as hyperglycemia diagnosed within the first 6 months of life which is permanent neonatal diabetes or transient neonatal diabetes. They can result from some gene mutations such as *KCNJ11*, *ABCC8*, *INS*, *GCK*, ... In there, the most common cause of neonatal diabetes mellitus is associated with activating mutations in the *KCNJ11* gene, which encodes Kir6.2-a subunit of the ATP-sensitive potassium channel (KATP) of the β cell and *ABCC8*, which encodes the sulphonylurea receptor (SUR1)-the other subunit of the β -cell KATP channel. *ABCC8* and *KCNJ11* are located on chromosom 11. **Objective:** Determine gene mutation of *KCNJ11* and *ABCC8* in patients with neonatal diabetes mellitus; assess the results of oral sulphonylureas therapy replacing insulin injection. **Subject:** 11 neonatal diabetes mellitus patients with *ABCC8* or *KCNJ11* mutations are treated in National Hospital of Pediatrics. **Methods:** Case series study, collect the symptoms and investigation, DNA was extracted from lymphocyte and analysed gene mutation by PCR or sequencing of *KCNJ11*, *ABCC8*. Results: six patients has *KCNJ11* mutation: one heterozygous for a missense mutation, R201H (p.Arg201His), two heterozygous for a missense mutation R201C (p.Arg201Cys), one heterozygous for missense mutation R50Q (p.Arg50Gln), one heterozygous for missense mutation p.G1229Lys, one heterozygous for missense mutation E292G (p.Glu292Gly); five patients with *ABCC8* mutations: one missense R1183W (p.Arg1147Trp), one nonsense E747X, one compound heterozygote for missense E747X and nonsense E128K, one heterozygous for A1153G, one compound heterozygous for splicing c.3401-1G>A and novel missense E1507Q (p.Glu1507Gln). 10/11 patients successfully transferred to sulphonylureas and did not need insulin injections, and one patient with novel mutation is treating with insulin. **Conclusion:** It is important for patients with neonatal diabetes mellitus to analysis mutations for choosing a suitable therapy and progress.

P3-D3-729

Prevalence of Secondary Diabetes and Related Factors in China Hospitalized Children

Li Yu-Chuan, Cao Bing-yan, Gong Chun-xiu, Liang Xue-jun

Beijing Children's Hospital, Capital Medical University, Beijing, China

Background: Secondary diabetes in children, often rising from the treatment of the primary disease. However, not enough attention has been paid. We analyze the cases of secondary diabetes in children identified from 2002 to 2010 in our hospital for the frequency and clinical features, so as to gain a better understanding of the disease. **Objective and hypotheses:** To investigate the prevalence and association factors of secondary diabetes in Chinese hospitalized children. **Method:** It is a case-control design, retrospective study on paediatric patients <18 years, who were hospitalized in our hospital from 2002 to 2010. Diabetes was diagnosed according to the criteria of WHO, 1999. Control cases were chosen with 1:4 ratio and matched in the primary diseases, age, gender. The risk factors of secondary diabetes were investigated with logistic analysis. **Results:** Total 33 cases (aged 7.1–16.4 years, 15 boys and 18 girls) of secondary diabetes were identified among 9657 inpatients suffering the corresponding primary diseases. The total prevalence was 0.34%, the highest was 4.17% in lymphoma leukemia, then 3.70% in acute lymphoblastic leukemia (ALL) after hematopoietic stem cell transplantation, 1.67% in multiple sclerosis and < 1.0% in SLE, dermatomyositis, ALL without hematopoietic stem cell transplantation, histiocytosis, ITP, nephropathy and purpuric nephritis. The prevalence of secondary diabetes was lower in boys than that in girls (0.24 vs 0.53%, $\chi^2=4.79$, $P=0.028$). None of them had typical symptoms and diabetic ketone acidosis. Logistic regression showed that age and obesity or overweight were the risk factors for secondary diabetes (the odds ratio was 1.24 and 5.08 respectively, both $P<0.05$). **Conclusion:** It's indicated that the prevalence of secondary diabetes in hospitalized children was lower in China than that in western countries and differs with gender, age and various primary diseases. Secondary diabetes can be easily misdiagnosed due to the atypical symptoms. It is necessary to monitor glucose during the whole course of the primary diseases.

P3-D3-730

Wolcott-Rallison Syndrome in Two Siblings with no Implication of *EIF2AK3* Mutation

Ayca Altincik^a, Bayram Ozhan^b, Sarah Flanagan^c, Sian Ellard^d

^aDenizli State Hospital, Denizli, Turkey; ^bFaculty of Medicine Pamukkale University, Denizli, Turkey; ^cPeninsula College of Medicine and Dentistry, Peninsula, UK; ^dPeninsula Medical School Department of Molecular Genetics, Peninsula, UK

Background: Wolcott-Rallison syndrome (WRS) which is characterized with permanent neonatal diabetes mellitus (PNDM), epiphyseal dysplasia, recurrent hepatitis and is caused by *EIF2AK3* mutations. **Objective and hypotheses:** There is a possibility of a variant form of WRS, not caused by *EIF2AK3* mutation. **Method:** Case 1: She was born at term from consanguineous parents. Family history was unremarkable. She had been diagnosed as diabetes mellitus at 1 years old and had been on insulin therapy since then. Liver biopsy was performed due to recurrent hepatitis and was reported as unremarkable. She also had been on L-thyroxine therapy with the diagnosis of hypothyroidism. At 7 years old,

she was admitted to our hospital with the complaints of abnormal walking and hip pain, macroscopic steatore. Her pelvic X-ray films were consistent with skeletal dysplasia. Her weight was.kg (-4.5 SDS), height was 108 cm (-5.2 SDS). Laboratory tests revealed fT_4 : 1.08 ng/dl, TSH: 4.26 uIU/ml, AST: 73 IU/l, ALT: 76 IU/l, HbA1c: 9.2%. She had no retinopathy and microalbuminuria. She had mild mental retardation. Case 2: He was the brother of the first case. He was born at term after an uneventful pregnancy. Neonatal diabetes was diagnosed at 4 months of age and he was on insulin therapy since then. He was admitted to our hospital at 2 years old. His weight was 10 kg (-2.05 SDS), height was 96 cm (-2.65 SDS). Laboratory tests revealed HbA1c: 9.6%, liver and thyroid function tests were normal. His pelvic X-ray films were consistent with skeletal dysplasia. **Results:** No mutation was determined at *EIF2AK3* gene with sequence analysis. *ABCC8*, *KCNJ11* ve *INS* genes were also examined and no mutations were also detected. **Conclusion:** Genetic counselling of WRS in PNDM patients born from consanguineous parents is strongly recommended.

P3-D3-731

Prevalence of Atopic Diseases in Diabetic Children and Adolescents

Hildegard Jasser-Nitsche, Eva-Maria Varga, Elke Fröhlich-Reiterer, Julia Höntzsch, Lisa Pieringer, Alexander Avian, Martin Borkenstein
Medical University, Graz, Austria

Background: In the last decade, an increase in the incidence of type 1 diabetes mellitus (T1D) has been observed worldwide, as well as an increase in the incidence of allergies in childhood. Both diseases are characterized by an imbalance between Th1- and Th2 cells. Autoimmune disorders are considered to be associated with a Th1 immune response while allergic diseases with a Th2 response. However, studies conducted to find a correlation between T1D and atopic diseases are heterogeneous and controversial. **Objective and hypotheses:** The aim of the study was to investigate if children with T1D tend to have a greater risk to develop allergies than children without T1D. **Method:** We asked 179 patients with T1D (mean age 14.5 years, ± 6.3 ; mean duration of diabetes 6.5 years, ± 5.0 ; mean HbA1c 8.25%, ± 1.12) to fill out a questionnaire about allergic symptoms. Questions on the family history, duration of breast feeding, nicotine exposure and pets were also included. In addition, blood tests of each patient were taken to analyze sensitizations against 20 common allergens (Phadia-CAP). To compare our results, we asked a control group of 88 healthy children (mean age 10.8 years, ± 4.7) to fill out the same questionnaire and had them tested on the same allergen sensitizations in the blood. **Results:** According to the questionnaires, the control group reported slightly more allergic symptoms than our patients with T1D. However, the difference was not statistically significant ($P=0.366$). On the other hand, the blood tests showed a tendency ($P=0.059$) to be more often positive (44%) in T1D patients than in healthy controls (31%). **Conclusion:** We found some evidence for a higher rate of atopic patients among our patients with T1D than in a healthy

control group. These results indicate a growing importance of environmental factors causing an increase in both T1D and atopic diseases.

P3-D3-732

The Pattern of Body Composition Change in Type 1 Diabetes by Gender

Yong Hyuk Kim^a, Hye Won Park^b, Kyo Sun Kim^b, Sochung Chung^b

^aDepartment of Pediatrics, Wonju College of Medicine, Yonsei University, Wonju, Gangwon-do, Republic of Korea; ^bDepartment of Pediatrics, Konkuk University School of Medicine, Seoul, Republic of Korea

Background: Childhood period is associated with growth accompanied by rapid change of body composition. Excessive fat gain and followed increased insulin resistance is an obstacle in controlling blood sugar for type 1 diabetic patients. **Objective and hypotheses:** This study was designed to understand the gender difference in the patterns of body composition change along the growth process of newly diagnosed type I diabetic children and adolescents. **Method:** Ten type I diabetic boys (median age 12.3 ± 3.5 years at diagnosis) and 13 girls (median age 12.3 ± 3.3 years at diagnosis) were included in the study. The median follow-up period was 3.2 ± 2.3 and 2.2 ± 2.1 years, respectively. Height, weight, body compartment of fat mass and fat free mass were measured in minimum 6 month to maximum 12 months interval in each patient. We also checked glucose, blood chemistry and HbA1c to monitor glucose control. BMI, fat mass index (FMI), fat free mass index (FFMI) and percent body fat (PBF) were calculated and coordinate of each component was plotted on the body composition chart and traced during follow up period. **Results:** BMI increased as the children aged in both genders (male 1.7 ± 1.8 kg/m² and female 2.1 ± 2.3 kg/m², respectively) but no significant difference in BMI Z-scores was observed. The body composition chart showed that the fraction of FMI increment contributing to BMI increase was higher in girls while that of the FFMI was higher in boys. **Conclusion:** The juvenile body composition change of type 1 diabetic patients progressed differently by gender. Evaluation of body compositional change using body composition chart in pediatric type 1 diabetic patients may be a useful method for the monitoring of diabetes control and promote adequate growth.

P3-D3-733

Transient Neonatal Diabetes and Intermediate DEND Phenotype with KCNJ11 Mutation

Ana Laura Fitas^a, Rita Belo Morais^a, Eulália Viveiros^b, Anabela Simões^a, Ana Raposo^b, João Anselmo^b, Catarina Limbert^a, Lurdes Lopes^a

^aHospital de Dona Estefânia, CHLC – EPE, Lisbon, Portugal;

^bHospital do Divino Espírito Santo – EPE, Ponta Delgada, Portugal

Background: Neonatal diabetes (ND) is a rare condition (1:160.000-260.000 live births) associated with diabetes onset within the first 6 months of life. It can be permanent (PNDM) or transient (TNDM), and several genes can be implicated in both, namely KCNJ11. Clinical phenotypes usually correlate to the causal gene. KCNJ11 mutations are usually associated with PNDM whilst the most frequent cause of TNDM is disordered imprinting in the 6q24 locus. **Objective and hypotheses:** To report a case with uncommon features. **Method:** Case report. **Results:** A male infant (DOB:04.04.2013), second child of a consanguineous couple, was born at the term of an uneventful pregnancy by vaginal delivery, adequate for gestational age, with Apgar 5/9/10. Minor dysmorphies, hypotony and feeding difficulties were noticed. He was readmitted on the 11th day of life because of failure to thrive and clinical deterioration; 6 days later, severe diabetic ketoacidosis was diagnosed (pH 7.0, glucose 1421 mg/dl, Na^+ 172 mmol/l). Glycemic control was difficult to achieve under i.v. and subsequently s.c. insulin. He was transferred to our level III center at 2 months of age and started on continuous s.c. insulin infusion with improved glycemic control. Neurologically, he maintained axial hypotony and poor-for-age interaction, without seizures. Electroencephalogram and intracranial ultrasound were normal. Insulin requirements progressively diminished and he was discarded without insulin 1 month afterwards. Since then, he has remained normoglycemic with peaks of glycemia during infectious episodes. A KCNJ11 mutation was identified both on the infant and his mother (c.679G>Ap.E227K). **Conclusion:** The association of ND with developmental delay, without seizures, raised the hypothesis of intermediate DEND syndrome. KCNJ11 mutations only cause TNDM in 10% of cases. To our knowledge this is the first reported case of TNDM associated with DEND features. Due to the elevated risk for diabetes recurrence, close long-term surveillance is mandatory.

P3-D3-734

Offspring of Parents with Obesity, Complex Investigations Risk of Carbohydrate Disturbances and Diabetes

Renata Wasik^a, Maria Dziura^b, Aleksander Basiak^a

^aMedical University, Wrocław, Poland; ^bPublic Hospital, Lubin, Poland

Aim: To examine offspring of patients with simple obesity. To ascertain, if there are some disturbances in the carbohydrate or lipid metabolism or unknown type 2 diabetes in these subjects. **Method and subjects:** Examined were 132 families, 108 families with obesity, and 24 families without obesity, the control group. 14 additional were excluded because of ascertained at the time of examination unknown type 2 diabetes in the parents. In all of the offspring and their parents performed were: weight, height, BMI, WHR HDL, TGD, LDL, glycaemia HbA1c, in the offspring additional HOMA. The control group included 30 healthy subjects with a negative anamnesis of obesity and/or diabetes in the family.

Results: Observed was overweight and obesity in a high percentage, increased BMI, WHR, significant differences in the level of HDL, TGD, LDL and HOMA between the examined and control group. Additional introduced was $\text{HHR} < \text{HWRWMI} < \text{HJMI} < \text{Zot} < \text{Zot}4, \text{ZL}$. In seven of the examined offspring ascertained was unknown type 2 diabetes, in eight morning hyperglycaemia, in five glucose intolerance. **Conclusion:** i) In offspring of obese parents observed are obesity and disturbances in the carbohydrate, lipid metabolism and unknown diabetes. ii) in offspring of obese patients very important and necessary are repeated prophylactic investigations. iii) useful will be an education about the prevention of obesity and diabetes. For a better analysis of the obesity is in our opinion important the examination of height to hip ratio (HHR) and height to waist ratio (HWR).

P3-D3-735

Metabolic Control in a Pediatric Population with Type 1 Diabetes Mellitus

Joana Andrade, Clara Gomes, Assunção Luís, Gabriela Laranjo, Joana Campos

Tondela-Viseu Central Hospital, Viseu, Portugal

Background: Type 1 diabetes mellitus (T1DM) is one of the most frequent chronic diseases in childhood and adolescence. Poor metabolic control is associated with numerous and onerous consequences. HbA1c levels are important in the assessment and monitoring of metabolic control in T1DM. Therefore, it is essential to know the causes of its variability. **Objective and hypotheses:** Determine the impact of age and time of disease in the value of HbA1c in children and adolescents with T1DM, as well as appreciate the relationship between HbA1c/dyslipidemia and HbA1c/microalbuminuria. **Method:** We designed an observational, transversal, and retrospective analysis of the files of a pediatric population with T1DM followed in a Pediatric Diabetic Consult in a Tertiary Hospital in Portugal. The studied variables were: gender, age, age at diagnosis, metabolic control and metabolic complications. **Results:** Our population consisted of 104 T1DM patients (47.1% female, and 52.9% male). The HbA1c mean value in the last year was 7.8% (<7.5% in 43.3%). We realized that adolescents' HbA1c was not higher than in children (7.8 vs 7.9%). Patients with T1DM duration of disease higher than 5 years had greater HbA1c values (8 vs 7.7%). 13.5% ($n=14$) of patients had microalbuminuria and 12.5% ($n=13$) had dyslipidemia. Besides, those with microalbuminuria did not had higher values of HbA1c (7.7 vs 7.9%) and the values were not significantly different in patients with or without dyslipidemia (7.8 vs 7.9%). **Conclusion:** In this study, we confirmed that patients with longer diabetes duration had the highest HbA1c values. We also verified that the consequences of a poor metabolic control, like microalbuminuria and dyslipidemia, can occur even at pediatric age.

P3-D2-736

Metabolic Compensation Correlation with Chronic Complications of Type 1 Diabetes in Children in Latvia

Zane Eglite^{a,b}, Iveta Dzivite-Krisane^{a,b}, Una Lauga-Tunina^a, Inara Kirilova^a

^aChildren's Clinical University Hospital, Riga, Latvia; ^bRiga Stradins University, Riga, Latvia

Background: Type 1 diabetes is the most common chronic disease in the childhood. As young patients have to live with diabetes most of their lives they have higher risk of complications. HbA1c has been approved as indicator of metabolic compensation in the guidelines. So if we control the level of HbA1c we can predict and avoid the early development of diabetes chronic complication. **Objective and hypotheses:** The aim of the research was to explore the structure of complications of type 1 diabetes and its connection with metabolic compensation of diabetes. Hypothesis to prove: children in Latvia with type 1 diabetes have poor metabolic compensation. **Method:** The methods used in the research were analysis of literature and statistical analysis of data taken from ambulatory cards of patients (age 0–18) with type 1 diabetes in year 2011–2012 using Microsoft Excel and SPSS. **Results:** There were 317 patients of age 0–18 (average age 11.30 ± 4.18 years) collected. It was found out that average HbA1c = $9.3 \pm 2.18\%$ and for 79% of patients it is higher than the standard mentioned in guidelines 7.5%. Worse situation is in age range 13–18 where 90% of patients have HbA1c > 8%. 59% of patients have at least one complication. The most common chronic complication is lipohypertrophy (53% of patients). The earliest clinically apparent long-term complication is lipohypertrophy (in average 2.43 years after the manifestation) but the latest is diabetic retinopathy in average 10.4 years after the manifestation. **Conclusion:** The results of the research lead to conclusion that hypothesis has been approved. The children in Latvia have poor compensation of diabetes that is closely related to the HbA1c that brings to earlier chronic diabetic complications, early evolution and patient's life quality deterioration. Required National Diabetes program to improve diabetes care.

P3-D2-737

IGF1 Levels in Children with Type 1 Diabetes are Primarily Related to Glycemic Control and Residual β Cell Mass, and not Affected by Different Modalities of Insulin Therapy

Carla Bizzarri, Danila Benevento, Ippolita Patrizia Patera, Romana Marini, Marzia Bongiovanni, Marco Anziano, Marco Cappa
Bambino Gesù Children's Hospital, IRCCS, Rome, Italy

Background: Impaired linear growth and low IGF1 levels, strictly related to poor glycemic control have been reported

in children with type 1 diabetes (T1DM). **Objective and hypotheses:** We studied growth and growth factors in 91 T1DM young patients, 54 males (age: 11.73 ± 3 years, disease duration: 5.2 ± 2.9 years). All subjects were on intensive insulin therapy: 72 children by multiple injection therapy (MI), 19 children by continuous subcutaneous insulin infusion (CSII). Twenty-seven subjects were pre-pubertal, 64 were pubertal. **Method:** Anthropometric and biochemical parameters (HbA1c, C-peptide, IGF1, and IGFBP3) were recorded at 6-month intervals. Duration of follow-up was 2.9 ± 0.28 years. **Results:** Height velocity (HV) SDS was found higher in females than in males (females: 0.6 ± 2.4 vs males: -0.45 ± 2.3). Growth factors levels were higher in females than in males (IGF1 SDS: females -1.0 ± 0.5 vs males -1.4 ± 0.6 , $P: 0.02$; IGF1/IGFBP3 molar ratio: females 0.26 ± 0.1 vs males 0.21 ± 0.08 , $P: 0.04$) and in pubertal children compared to pre-pubertal children (IGF1 SDS: pre-pubertal -1.58 ± 0.4 vs pubertal -1.1 ± 0.6 , $P: 0.03$; IGF1/IGFBP3 molar ratio: pre-pubertal 0.16 ± 0.08 vs pubertal 0.26 ± 0.09 , $P < 0.001$). No differences in terms of HV SDS, IGF1 SDS, and IGF1/IGFBP3 molar ratio were evident between children treated with different therapeutic modalities (CSII vs MI therapy). Multivariate analysis showed that HV SDS was positively affected by IGF1 SDS ($P: 0.04$) and negatively related to T1DM duration ($P: 0.01$). IGF1 SDS was positively affected by female gender ($P: 0.02$), puberty (0.01) and C-peptide levels ($P < 0.001$), and inversely related to HbA1c levels ($P: 0.04$). **Conclusion:** A negative impact of T1DM on growth and growth factors remains evident despite intensive insulin therapy, probably due to a defect of portal insulinization. The effect seems to be independent from treatment modalities and primarily related to glycemic control and residual β cell mass.

P3-D2-738

When Should We Suspect Maturity Onset Diabetes of the Young in Children and Adolescents

Sarar Mohamed^a, Iman Talaat^b, Ali Hellani^b

^aKing Saud University, Riyadh, Saudi Arabia; ^bSaad Specialist Hospital, Alkhobar, Saudi Arabia

Background: The prevalence of maturity-onset diabetes of the young (MODY) in Saudi population remains unknown and data on molecular etiology of this condition is limited. **Objective and hypotheses:** The present study was undertaken to elucidate the clinical and molecular characteristics of a Saudi family with MODY1. **Method:** A 12-year-old female presented to us with symptoms suggestive of diabetes. Investigations revealed hyperglycemia, glycosuria, and ketonuria with no acidosis. Pancreatic antibodies were negative. She responded well to s.c. insulin. Her family history revealed that two of her siblings were diagnosed with type 1 diabetes (T1DM) while her father and mother have T2DM. In view of this strong family history, the possibility of monogenic diabetes was raised, namely hepatocyte nuclear factor 1 α and 4 α genes (HNF4 α and HNF4 α 1). Accordingly, genomic DNA was isolated from peripheral blood lymphocytes of the eight members

of this family, PCR was carried out, and sequencing of the whole HNF1 α and HNF4 α gene was done. **Results:** DNA study of the proband revealed heterozygous substitution at position-nt5 in intron 1 of the HNF4 α gene. This mutation was identified in other five members of the family. **Conclusion:** This report highlights the importance of considering MODY in any individual diagnosed with either T1DM or T2DM, who have atypical features for these polygenic disorders. The red flags for prediction of monogenic diabetes include strong family history of diabetes and early presentation in young age group especially when ketoacidosis, anti-islet antibodies, and obesity are not features. Confirming this diagnosis at molecular level facilitates management, improves outcome and provides effective genetic counselling.

P3-D2-739

Cystic Fibrosis-Related Diabetes in Children and Adolescents in the Russian Federation

Elena Kondratyeva, Nicolay Kapranov, Victoria Sherman

Medical Genetics Research Center, Moscow, Russia

Background: Disorders of carbohydrate metabolism in children and adolescents with cystic fibrosis occur from 5 to 12.6%, significantly increasing during the teenage period and reaching 24–50% in adults. **Method:** An analysis of 499 medical records was conducted. All the patients were treated in the Russian Children's Clinical Hospital in 2012. The survey was carried out on carbohydrate metabolism and indications according to children after 12 years (Management of Cystic Fibrosis Diabetes Mellitus, 2011) and as recommended by WHO (1999). **Results:** Violation of carbohydrate metabolism was detected in 5.1% (29 children). In addition, the frequency of cystic fibrosis-related diabetes (CFRD) was 2.8% (14 children), while the insulin requirement was observed in 2.2% of children, intermittent postprandial hyperglycemia find impaired glucose tolerance (IGT), CFRD without fasting hyperglycaemia was registered in 3% (15 children). Most often the disorders of carbohydrate metabolism were observed in 27% of adolescents, in the general group of patients with impaired glucose metabolism they was 86%, at that, girls were 83% and overpass the boys were 17%. All children (100%) had a mutation F508del, while 30% in the homozygous state. Underweight was observed in 60% of children, stunting – 40%. 30% of children (all getting insulin) had FEV1 < 50%. 30% of children were receiving systemic glucocorticoids. In 90% of cases, in sputum were detected

associations of two to four microorganisms. HbA1 was above 7% in 25% of children. **Conclusion:** It is established that glucose intolerance and diabetes are most often observed during adolescence, among girls, with exacerbation of bronchopulmonary process and receiving glucocorticoids.

P3-D2-740

Continuous Glucose Monitoring System in the Diagnosis of Early Glycemic Abnormalities in High-Risk Groups

Ashraf Soliman^a, Mohamed Yassin^b, Ahmed Elawwa^a, Rania Elalaily^c, Vincenzo De sanctis^d

^aHamad Medical Center, Doha, Qatar; ^bAlamal Hospital HMC, Doha, Qatar; ^cPrimary Health Care PHC, Doha, Qatar; ^dQuisisana Hospital, Ferrara, Italy

Background: Continuous glucose monitoring (CGM) systems are an emerging technology that allows frequent glucose monitoring in real time. **Objective and hypotheses:** To assess the value of using CGM system (Medtronic) versus oral glucose tolerance (OGT) and HbA1c in the diagnosis of glycemic abnormalities (Prediabetes) in high-risk groups. **Methods:** We performed OGT and monitored glucose for 72 h using CGMS combined with four to five times/day SGM (before three meals and mid-night) and measured HbA1c concentration in three groups of children and adolescents with high-risk to develop glycemic abnormalities including: ten with morbidly obesity, 16 with thalassemia major (on repeated blood transfusion and iron chelation) and ten with nephrotic syndrome on high dose glucocorticoids for 4 weeks or more as well as ten normal children (controls). The diagnosis of glycemia status whether normal, impaired fasting glucose (IFG), impaired glucose tolerance (IGT) (2 h after oral glucose load in the OGTT or after a CGMS recording) diabetic (DM), was done according to the American diabetes association criteria. **Results:** Glycemic abnormalities detected in all groups are summarized in Table. None of the children and adolescents had elevated HbA1c level > 5.7%. CGMS diagnosed more glycemic abnormalities in the three high-risk groups compared to OGTT (Table 1). **Conclusion:** Our data suggest CGMS is more sensitive method to diagnose glycemic abnormalities (Prediabetes) in high risk patients compared to OGTT and HbA1c. Further studies are required to improve the criteria of early diagnosis of glycemic abnormalities using CGMS.

Table 1. (abstract for P3-D2-740)

	OGTT-IFG	OGTT-IGT	OGTT-DM	CGM-IFG	CGM-IGT	CGM-DM
Normal (%)	0	0	0	0	0	0
Thalassemia	4/16	2/16	1/16	6/16	9/16	4/16
Obese	0/10	1/10	0/10	1/10	3/10	1/10
Corticosteroid	0/10	0/10	0/10	0/10	3/10	2/10

P3-D2-741

Incidence of Dyslipidemia and its Association with Glycemic Control in Adolescents and Young Adults with Type 1 Diabetes

Shin-Hee Kim, In-Ah Jung, Won Kyoung Cho, Kyoung Soon Cho, So Hyun Park, Min Ho Jung, Byoung Kyu Suh

Department of Pediatrics, The Catholic University of Korea School of Medicine, Seoul, Republic of Korea

Background: Hyperglycemia and dyslipidemia are metabolic abnormalities commonly found in type 1 diabetes. **Objective and hypotheses:** Limited data are available on the relationship between glycemic control and dyslipidemia in patients with type 1 diabetes. We aimed to investigate the incidence of dyslipidemia and its association with glycemic control in adolescents and young adults with type 1 diabetes. **Method:** This cross-sectional study included 29 Korean patients with type 1 diabetes aged 10–25 years. Eighteen (62%) patients were female and median duration of diabetes was 7.5 years (range: 0.2–15.6). We compared the lipid profiles of patients with dyslipidemia and those of patients without dyslipidemia. In addition, correlations between HbA1c and lipid profiles (total cholesterol (TC); LDL cholesterol (LDL-C); HDL cholesterol (HDL-C); and triglyceride (TG)) were determined by linear regression analysis. **Results:** Of 29 patients with type 1 diabetes, 11 (38%) had dyslipidemia. There were no statistically significant differences between dyslipidemia and non-dyslipidemia group regarding age, duration of illness, and microalbuminuria. HbA1c level was positively correlated with TC ($P=0.03$; $R^2=0.395$) and TG ($P=0.005$; $R^2=0.51$). Patients with dyslipidemia were more likely to have the higher median values of HbA1c than those without dyslipidemia (9.2% (range: 7.5–13.3) vs 7.9% (range: 6.6–10.8); $P=0.002$). Patients with dyslipidemia were more likely to have the higher median values of BMI z-score than those without dyslipidemia (0.7 (range: -0.57 to 2.6) vs -0.4 (range: -2.5 to 2.2); $P=0.02$). There were no differences among the groups with respect to age, disease duration. **Conclusion:** A substantial proportion of adolescents and young adults with type 1 diabetes had dyslipidemia. We found a correlation between poor glycemic control and poor lipid profiles in young patients with type 1 diabetes.

P3-D2-742

'Learning by Doing Approach': Use of Multimedia Applications in Type 1 Diabetic Children

Federica Ortolani^a, Marcella Vendemiale^b, Albina Tummolo^d, Pierpaolo Di Bitonto^c, Veronica Rossano^c, Teresa Roselli^c, Elvira Piccinno^a

^aMetabolic Diseases, Clinical Genetics and Diabetology, Pediatric Hospital Giovanni XXIII, Bari, Italy; ^bClinical Psychology, Pediatric Hospital 'Giovanni XXIII', Bari, Italy; ^cInformatics Department, University 'Aldo Moro', Bari, Italy; ^dUOC Hereditary Metabolic Diseases, Azienda Ospedaliera Policlinico di Padova, Padova, Italy

Background: Virtual environments have proved to be successful for educational purposes in different fields. Multimedia applications might be used to consolidate and internalize informations and behavioral strategies in type 1 diabetic children. **Aim:** In the last years our Diabetology Division and the Department of Informatics co-created many multimedia applications (edutainments, virtual environments, role serious games, electronic diary smartphone apps, and tutorial teaching). **Methods:** In 'Treasure Hunter' young users (8/12 years) are trained to control the balance between energy/physical activity. The player learns that physical activity causes energy consumption and energy stocks must be periodically renewed. The energy available increases and decreases in relation to the care that he/she has in balancing supply (a correct diet) and physical activity. 'Diabetland' is an open simulator game (virtual 3D world) in which 12/14-year-old patients become familiar with terms commonly used when discussing diabetes, learn to choose healthy foods and follow a correct diet. The game is structured in different levels: the player has to complete the mission before proceeding to the next level. With 'Diabetes diary', app for Android/Iphone, 13/15-year-old patients can record glycaemic values and communicate them to their physician in real time. Hyper/hypoglycaemic episodes might be reduced, patients have greater peace of mind knowing that their physician is watching over their diabetes self-management decisions. In 'Serious Mika' the 7/10 year-old-children take care of a virtual ant affected by type 1 diabetes. 'Smile D' is a tutorial teaching (for Android) in which the protagonist explains symptoms and situations that he/she experienced before being diagnosed with diabetes (for 4/8 year-old children). **Conclusions:** Educational applications motivate young patients and improve their therapy compliance, reaching and keeping a good metabolic control, minimizing the risk to develop acute and chronic complications, modifying the 'destiny of the disease' and therefore reducing health care costs in the future.

P3-D2-743

Seip Berardinelli Syndrome Case Report

Doly Pantoja^a, Liliana Mejia^b

^aHospital Departamental de Nariño, Pasto – Nariño, Colombia;

^bFundación Valle de Lili, Cali – Valle, Colombia

Background: Congenital generalized lipodystrophy (LCG) or Seip Berardinelli Syndrome is an autosomal recessive rare disease with a prevalence of one in 10 million live births and characterized an absence of adipose tissue and alterations in carbohydrates metabolism and diabetes mellitus, hypertriglyceridemia, hypertrophic cardiomyopathy, hepatomegaly caused by fatty infiltration which may lead to cirrhosis and polycystic ovary syndrome. The challenge is to prevent these complications thereby preventing death. Current management consists of metformin and recombinant leptin but the latter is associated with resistance due to antibody formation. The low prevalence of the disease prevents the

findings of new therapies. **Objective and hypotheses:** To describe a case of Seip Berardinelli syndrome. **Method:** A 15-year-old adolescent female presents with severe acanthosis nigricans and amenorrhea. Height 147 cm, weight 41 kg, triangular fascies, absence of Bichat's ball, micrognathia, acromegaloid features of hands and feet, severe acanthosis in neck, axillary folds, thorax, perineal region, absence of subcutaneous tissue, and athletic body with marked muscular hypertrophy. Laboratory: fasting blood glucose 128 mg/dl, postprandial blood glucose 234 mg/dl. HbA1c 8.1%, triglycerides 358 mg/dl, pelvic ultrasound polycystic ovaries, echocardiogram normal. Patient did not respond to metformin so insulin was instituted with improvement of the diabetes. **Results:** We present this case to make physicians aware of its existence and indicate the therapeutic option of insulin.

P3-D2-744

Nine-Year-Old Boy with Wolfram Syndrome: Case Report

Ewa Jakubowska^a, Justyna Michalak^a, Bożena Florys^a,
Wojciech Młynarski^b, Agnieszka Zmysłowska^b,
Agnieszka Szadkowska^b, Włodzimierz Łuczyński^a,
Barbara Olszewska-Głowińska^a, Artur Bossowski^a

^aDepartment of Pediatrics, Endocrinology, Diabetology with Cardiology Division, Medical University of Białystok, Białystok, Poland; ^bDepartment of Pediatrics, Oncology, Hematology and Diabetology, Medical University of Łódź, Łódź, Poland

Background: Wolfram syndrome is a rare progressive genetic neurodegenerative disorder connected with diabetes mellitus, diabetes insipidus, optic atrophy, deafness, neurologic, and endocrine abnormalities. Wolfram syndrome is inherited in autosomal recessive manner – due to mutation of the WFS1 gene which is located on chromosome 4. **Objective and hypotheses:** A 9-year-old boy, diagnosed with diabetes mellitus at the age of 5.5 years, was admitted to hospital for further investigation of optic atrophy and polydipsia with polyuria while euglycaemic. Patient did not necessitate pharmacological treatment (unless having increased insulin requirement – such as during infection) for diabetes mellitus, only followed diabetic diet. Blood samples were taken for the genetic tests on appointment to outpatient clinic – as presented symptoms grew suspicion for Wolfram syndrome. **Method:** Physical examination revealed correct psychomotor evaluation, lateral nystagmus and malocclusion. Laboratory tests showed anaemia and thrombocytopenia. Hormonal tests excluded central diabetes insipidus. Abdominal ultrasound and MRI scan of central nervous system showed no abnormalities. Laryngological examination demonstrated sensorineural hearing deficits of high-frequency in left ear and mixed deficit in right ear. **Results:** Ophthalmic examination and optical coherence tomography of the optic nerve discs revealed optic nerve discs thinning, global thinning of bundles of neural fibres – confirming the diagnosis of optic nerve neuropathic atrophy. During hospitalisation results of genetic tests were obtained and the diagnosis of Wolfram syndrome was acknowledged.

Conclusion: Wolfram syndrome may be a rare cause of diabetes mellitus, and patients with such diagnosis require multispecialist care and genetic counselling.

P3-D2-745

A Case of Type 2 Diabetes Associated with Ichthyosis: Chanarin–Dorfman Syndrome

Nihal Hatipoğlu, Deniz Ökdemir, Leyla Akın, Songül Gökay,
Fatih Kardaş, Mustafa Kendirci, Ülkü Gül, Selim Kurtoğlu

Erciyes Universities, Kayseri, Turkey

Background: Chanarin–Dorfman syndrome is a rare autosomal recessively inherited neutral lipid disorder which is characterized by congenital ichthyosis and multiple system involvement. It is diagnosed by visualization of lipid vacuoles in neutrophils (Jordon anomaly) in suspicious cases. This syndrome can be associated with type 2 diabetes. **Aim:** We wished to remind this very rare disease in differential diagnosis of ichthyosis associating with diabetes mellitus. **Case:** A 16-year-old girl was presented with polyuria and polydipsia for a month. She had a diagnosis of congenital ichthyosis since neonatal period. The parents were consanguineous and family history was negative for diabetes mellitus. Physical examination revealed generalized ichthyosis and hepatomegaly. On laboratory investigation, blood glucose was 600 mg/dl, blood ketone negative, C-peptide, and blood gases were in normal range and fasting triglyceride and aminotransferases were elevated. Liver biopsy revealed mild hepatic fibrosis and Moriac findings. Blood smear showed lipid vacuoles in neutrophils. **Conclusion:** Chanarin–Dorfman syndrome should be kept in mind in patients with congenital ichthyosis associated with diabetes mellitus due to insulin resistance or pancreatic involvement.

P3-D2-746

Current Status of Diabetes Management, Glycemic Control and Complications in Children and Adolescents with Diabetes: a Registry-Based Study in Egypt: Where Do We Stand Now? and Where Do We Go from Here?

Nancy Elbarbary, Mona Elsamahy, Hala Elmorsi

Ain Shams University, Cairo, Egypt

Background: Given that diabetes is an extremely common disorder in Egypt, the Diabetes Registry was designed by Pediatric Diabetes Clinic, Ain Shams University Hospital in the year 2010. **Aim:** Identify risk factors related to poor glycemic control and to provide data to health professionals for use in planning, evaluation, and optimizing diabetes care in those patients.

Subjects and methods: The registry was designed to provide information on current clinical status, metabolic control, acute and long-term complications, presence of concomitant autoimmune diseases, and psychological disturbances in patients. **Results:** Mean age of patients was 13.29 ± 5.05 years, mean duration of diabetes was 6.37 ± 3.64 years, mean HbA1c was $8.81 \pm 4.59\%$, and 71% had poor glycemic control. Acute complications included ketoacidosis in 19.7% and severe hypoglycemia in 2.83%. Chronic complications including peripheral neuropathy, retinopathy, and persistent microalbuminuria were present in 6.33, 1.83, and 6.83% respectively. The majority (97.17%) of patients are on intensive regimen of therapy. Patients with poor glycemic control had higher disease duration, DKA frequency, and microvascular complications. However, regular education lecture attendance and regular SMBG were found to have better glycemic control. **Conclusions:** These data from registry indicate that although the majority of the patients were on intensive insulin therapy, poor glycemic control was common, and chronic complications were encountered. These findings will provide potential avenues to improve quality of care and also could be the first step in the development of a national registry system for diabetes in Egypt.

P3-D2-747

Comparison the Clinical Efficacy of Autologous Hematopoietic Stem Cell Transplantation and Traditional Insulin Therapy in Newly Diagnosed Primary Childhood Type 1 Diabetes

Gu Yi, Gong Chunxiu, Peng Xiaoxia, Wei Liya, Su Chang, Li Fengting, Wang Yi

Director of Endocrinology, Genetics and Metabolism, Beijing Children's Hospital, The Capital Medical University, Beijing, China

Objective: Evaluation the clinical efficacy of autologous hematopoietic stem cell transplantation and traditional insulin therapy. **Methods:** This is a case-control study. The subject investigated were diagnosed primary childhood type 1 diabetes in Beijing Children's Hospital Endocrinology Centre, and there are 14 cases did the immune intervention combined with autologous hematopoietic stem cell transplantation in other hospital during the first 3 months of diagnosis, then came back to our hospital diabetes clinic due to poor glycemic control or reuse insulin again. The 14 cases were set to the case group. Using 1:2 matches, we select the 30 cases of newly diagnosed type 1 diabetes in the corresponding period in our hospital as the control group, and compare the effect of diabetes control between the case group and control group. We also observed the diabetes control levels of restoring traditional treatment and duration of 4.2 ± 1.8 years time in case group. **Results:** The average time they once again to our hospital were at the duration of 10.7 ± 4.2 months of the 14 cases in case group. Of which 11 cases had never been deactivated insulin replacement therapy, three cases have been treated with insulin were deactivated for the 2, 3, and 11 months, both in the

diagnosis of diabetes duration of 1 year. All children in case group did not occur diabetic ketoacidosis after transplantation. At the time of restoring traditional treatment and the average duration of 4.2 years, we compare the same period of diabetes outpatient data with the control group, found that HbA1c of the control group was significantly lower than the case group, with a statistically significant difference ($P < 0.01\%$), while there is no significant difference ($P > 0.05$) of insulin dosage and serum C-peptide level between the two groups; compare the current diabetes outpatient data of the case group and the control group over the same period, we found that HbA1c of the control group is still lower than case group ($P < 0.01\%$), while no significant difference ($P > 0.05$) in insulin dosage, serum C-peptide level between the two groups. Compare the insulin dosage before and after AHST treatment, no significant difference ($P > 0.05$). **Conclusion:** At present, AHST treatment cannot significantly improve the diabetes control on the recent and long-term. Conventional insulin therapy remains the preferred treatment for children with primary type 1 diabetes. Attaches great importance to the 'five carriages' comprehensive treatment.

P3-D3-748

Monogenic Diabetes in a Paediatric Population: Finding the Needle in the Haystack

M Mavinkurve^a, N Johnston^a, A Carroll^a, C Mc Donnell^{a,c}, M M Byrne^b, N P Murphy^{a,b}

^aEndocrinology Department, Children's University Hospital, Temple Street, Dublin, Ireland; ^bEndocrinology Department, Mater Misericordiae University Hospital, Dublin, Ireland; ^cEndocrinology Department, Adelaide and Meath National Children's Hospital, Dublin, Ireland

Background: Ireland has a high incidence of type 1 diabetes in childhood (16.8/100, 000 per year (1)). A small percentage of children with diabetes have maturity onset diabetes of the young (MODY) (2). Establishing the correct diagnosis is critical to optimal therapy and future genetic counselling (3). **Objective and hypothesis:** To review the cohort of children attending our tertiary diabetes service and describe the clinical features of those where MODY was confirmed. **Methods:** We performed a retrospective chart review of children attending our service over a 5 year period. Clinical presentation, family history, autoantibody status and insulin therapy were noted. Gene sequencing was performed on genomic DNA. **Results:** Six patients (2%), all initially diagnosed with type 1 diabetes, had MODY confirmed. Four of the six had no osmotic symptoms at presentation but had hyperglycaemia detected incidentally; one child presented in DKA. A positive family history was present in 5/6 cases. All children had negative autoantibody screens. Five of six children were initially treated with insulin and four were successfully switched to oral sulphonylurea therapy. **Conclusions:** Childhood diabetes is not always type 1 diabetes and rarer aetiologies should be considered. Accurate diagnosis has implications for future management.

P3-D3-749

Hyperglycemia: MODY: a Diagnosis to Remember

Ricardo Monteiro^a, Ana Laura Fitas^b, Marta Amado^c, Rosa Pina^b, Lurdes Lopes^b

^aPediatric Department, Centro Hospitalar de Leiria, Leiria, Portugal;

^bPediatric Endocrinology Unit, Hospital Dona Estefânia, Centro Hospitalar Lisboa-Central, Lisboa, Portugal; ^cPediatric Department, Centro Hospitalar do Algarve, Faro, Portugal

Background: The detection of hyperglycemia on occasional evaluation raises the diagnosis of diabetes mellitus (DM). Maturity onset diabetes of the young (MODY), namely glucokinase deficiency, should be considered in cases of non-progressive hyperglycemia associated with a positive family history. **Objective and hypotheses:** We describe two unrelated cases of asymptomatic hyperglycemia where glucokinase mutations were detected. **Method:** Case report. **Results:** *Case 1:* Female child. Family history: the father has impaired fasting glucose and hepatic steatosis; paternal grandparents have type 2 DM. At 3 years of age, hyperglycemia (195 mg/dl) was detected; this evaluation was repeated and fasting glycemia were always high (110–128 mg/dl); 3 years later, an OGTT (fasting – 122 mg/dl; 120' – 144 mg/dl) was performed and she was referred to our center. Clinical observation was negative; BMI was 21.6 kg/m² (75th centile). Laboratory evaluation confirmed the previous results: glycemia – 121 mg/dl, A1cHb 6.6%, HOMA 1.3. Anti-GAD antibody was positive (5.4 U/ml) and ICA and IAA autoantibodies were undetectable. The possibility of a glucokinase mutation was considered and a new mutation was detected. *Case 2:* Male child. Family history: mother had had gestational diabetes and currently has DM treated with gliclazide; maternal grandmother and great-grandfather had type 2 DM. At 3 years of age, during acute gastroenteritis, hyperglycemia (169 mg/dl) was detected. Repeated home monitoring showed both fasting (104–117 mg/dl) and postprandial (120–160 mg/dl) hyperglycemia. He was referred at 5 years of age; clinical observation was normal. Laboratory evaluation revealed: OGTT – glycemia: 109 mg/dl (fasting) and 162 mg/dl (120'); A1cHb: 6.3%, HOMA: 0.4; negative autoantibodies. The molecular study confirmed a described mutation in the glucokinase gene. In both cases, only dietetic measures have been used so far. **Conclusion:** In patients with asymptomatic hyperglycemia, MODY diagnosis should be considered as it has both prognostic and therapeutic implications. The genetic characterization of the subtype is essential.

P3-D3-750

A Case of Type 1 Diabetes Associated with Cerebellar Ataxia: Stiff-Person Syndrome

Selim Kurtoğlu, Deniz Ökdemir, Nihal Hatipoğlu, Leyla Akın, Ülkü Gül, Mehmet Canpolat, Mustafa Kendirci

Erciyes University, Kayseri, Turkey

Background: Stiff-person syndrome (SPS) is a rare disorder which is characterized by muscle rigidity, spasm and cerebellar abnormalities. The etiology is not clarified yet. 80% of cases are caused by an autoantibody against GAD that inhibits synthesis of GABA. Other autoimmune diseases such as type 1 diabetes mellitus and thyroiditis are often associated. **Aim:** To underline the importance of considering SPS in differential diagnosis of patients with type 1 diabetes associated with neurological abnormalities. **Case:** A 10-year-old girl was referred to our department due to hyperglycemia. The diagnosis of type 1 diabetes was made upon clinical and laboratory findings. Blood glucose was 500 mg/dl, HbA1c 8%, and serum anti-GAD antibody was positive. Serum thyroid autoantibodies were also elevated. She had been diagnosed with cerebellar ataxia 1 year ago but the etiology could not be established. She had no muscle rigidity or spasm. On follow-up, cranial MRI revealed atrophic changes in cerebellum. Cerebrospinal fluid examination was negative for anti-GAD antibodies. **Conclusion:** Although the etiology of SPS is undefined and clinical spectrum is large, this syndrome should be considered in the differential diagnosis of patients with type 1 diabetes associated with neurological abnormalities.

P3-D3-751

Continuous Glucose Monitoring vs Oral Glucose Tolerance Test and HbA1C in the Evaluation of Glycemic Abnormalities in an Obese Adolescent Before vs After Partial Gastrectomy

Ashraf Soliman, Aml Sabt, Fawzia Alyafei, Nagwa Eldarsy

Hamad General Hospital, Doha, Qatar

Background: We compared continuous glucose monitoring (CGMS) (Medtronic) to oral glucose tolerance test (OGTT) and HbA1c in the follow-up of glycemic abnormality in an adolescent

Table 1

	Normal values (mg/dl)	Before surgery (mg/dl)	8 weeks after surgery (mg/dl)
Mean blood glucose (MBG) for 24 h	<117	92	78
BG 1 h before breakfast	<108	89	69
BG 1 h before lunch	<113	99	70
BG 1 h before dinner	<108	101	74
MBG 3 h after breakfast	<126	105	81
MBG 3 h after lunch	<121	145	69
MBG 3 h after dinner	<126	162	130
s.d. of blood glucose (SDBG)	<25	42	17
Number of high excursions/day	0	2	0
The % of time > 7.8	<9	19	0
OGTT – 0 h	<111	121	109
OGTT – 2 h	<140	225	140
HbA1c %	<6	9.10	6.70

girl with morbid obesity and glycemic abnormalities before and after 2 months of partial gastrectomy. This 16-year-old adolescent girl presented with obesity (weight 98 kg, height 158 cm, BMI=39.2 kg/m²), acanthosis nigricans and nocturnal polyuria and polydipsia. Trials to reduce weight through dieting, exercise and use of metformin was not successful; (patient lost 3 kg in 4 months). Her fasting BG=102 mg/dl but 2 h BG after oral glucose (75 g)=225 mg/dl. She underwent partial gastrectomy surgery. Two months after surgery her weight=70 kg and BMI=28 kg/m². **Results:** A comparison of her glycemic data using CGMS (for 5 days), OGTT and HbA1c before and 2 months after surgery is shown in Table 1. **Conclusion:** Before surgery this obese patient with morbid obesity had normal FBG but abnormal OGTT which was confirmed with CGMS criteria. After surgery CGMS showed correction of her glycemia both during basal and postprandial in real-life settings.

P3-D3-752

The Psychological Impact of Diabetes on Glycaemic Control in Affected Saudi Children at Different Developmental Age Groups

Amir Babiker^a, Mona El Rashid^a, Nasir Al Jurayyan^a, Maralyn Druce^b, Aban Bahebri^c, Mohamed El Ahmedi^d, Ahmed H Errasoule^e, Hala Gasim^a, Simon Coppack^b

^aPaediatric Endocrine Division, King Khalid University Hospital, College of Medicine (39), King Saud University, PO Box 2925, 11461 Riyadh, Saudi Arabia; ^bQueen Mary University (Msc in Endocrinology and Diabetes), London, UK; ^cKing Saud University (Medical Students), Riyadh, Saudi Arabia; ^dKing Saud University (Obesity Chair – Statistics), Riyadh, Saudi Arabia; ^eRoscommon County Hospital (Consultant Psychiatrist), Roscommon, Ireland

Background: Diabetes is the third commonest chronic disease of childhood. When a child or an adolescent is diagnosed with type 1 diabetes (T1D), adaptation to a new life is usually a challenge for the whole family. There are specific challenges posed by T1D on the affected children, and their families, at different developmental age groups. The correlation between HbA1c and age specific psychological challenges, to our knowledge, has not been previously explored in the Middle East. **Objective/hypotheses:** To assess the correlation between children's HbA1c and the psychological impact of T1D on affected Saudi children and their parents at King Khalid University hospital, Riyadh, Saudi Arabia. Also to explore any variation, between children and their parents and between the children at different age groups, in the psychological impact scores of different aspects of T1D. **Method:** In this cross sectional study, the psychological impact of T1D on children and their parents was assessed using a standard quality of life diabetes specific questionnaire for children – (PedQoL DM V3.0 – Arabic translation). The total and individual impact scores of different domains in the questionnaire were calculated from children's and parents' responses. Data were statistically analysed using Pearson's correlation, ANOVA and t-2 tests. **Results:** There were significant variations in the mean HbA1c between different age groups. Though statistically not significant, the HbA1c showed

more of negative correlations with the psychological impact scores of parents compared to very poor correlations with children's scores. There were variations, but not statistically significant, in the correlations of HbA1c with parents' and children's impact scores of individual domains at different age groups. **Conclusion:** Identifying age specific challenges in children with T1D may help focusing on relevant areas of concern in their management. Larger studies may be required to better highlight the relationship of these challenges with HbA1c in affected Saudi children.

P3-D3-753

Type 1 Diabetes Mellitus in Pediatric Population: Chronic Complications and Associated Diseases

Joana Andrade, Clara Gomes, Assunção Luís, Gabriela Laranjo, Joana Campos

Tondela-Viseu Central Hospital, Viseu, Portugal

Background: Type 1 diabetes mellitus (T1DM) is the second most frequent chronic disease in childhood and adolescence. Chronic hyperglycemia is responsible for numerous long term complications, not only microvascular (retinopathy, nephropathy and neuropathy), but also macrovascular (ischemic cardiopathy, cerebrovascular disease and peripheral vascular disease). On the other hand, the T1DM immune modification is responsible for an increased incidence of other autoimmune diseases. **Objective and hypotheses:** The aim of this study is to describe the prevalence of overweight and obesity in a group of patients with T1DM and to determine the consequences of the lipid profile and metabolic control. **Method:** We designed an observational, transversal and analytic study, based on patient data from the Pediatric Diabetic Consult in a Tertiary Hospital in Portugal. The studied variables were: gender, age, age at diagnosis, weight, height, BMI, blood pressure (BP), HbA1c, total cholesterol (TC), HDL cholesterol (cHDL), LDL cholesterol (cLDL) and triglycerides (TG). **Results:** A 104 T1DM population was obtained with a median age of 12.5 years (3.3–17.9 years). The prevalence of overweight was 13.5% ($n=14$), 50% male, and obesity was 4.8% ($n=5$), 80% male. Hypertension was only observed in those patients with overweight ($n=2$; 14%). 12.5% ($n=13$) of our T1DM population had dyslipidemia. 15.8% of 19 patients with overweight/obesity had dyslipidemia. There were not significant differences in HbA1c control between obese patients and the rest of the sample (7.9 vs 7.8%). **Conclusion:** Overweight and obesity in children and adolescents has increased dramatically since the 1980s. Although it is known that diabetes and elevated BMI increases cardiovascular risk factors, in our study we did not verified these results.

P3-D3-754

Ketoacidosis-Associated Stroke: Cerebral Infarction

Zerrin Orbak, Hakan Doneray, Seda Yesilcibik, Mecit Kantarci, Huseyin Tan, Nuran Kucuk, Celalettin Kosan

Medical Faculty, Ataturk University, Erzurum, Turkey

Background: Type 1 diabetes mellitus (T1DM) is a common autoimmune condition in childhood and may be complicated by episodes of diabetic ketoacidosis (DKA). DKA is a state of severe insulin deficiency, resulting in hyperglycemia, ketonemia, acidemia, and systemic inflammation. This is predominantly attributable to intracerebral complications. We report a girl with a newly diagnosed T1DM who presented with DKA and cerebral infarction. **Case:** A 13-year-old previously healthy girl with DKA became unconsciousness and anisocoria. Babinski reflex was positive on the right side of the body. She was treated for DKA and cerebral edema. Magnetic resonance imaging provided evidence for lacunar subcortical infarcts and deep white matter changes. **Conclusion:** Children and adolescents who present with DKA should be monitored for neurologic deficits and must be investigated for both stroke and cerebral edema in the event of neurologic deterioration.

P3-D3-755

Multiple Daily Injections Since the Diagnosis of Type 1 Diabetes Mellitus in Children and Adolescents: Assessment of 3 Years

Rita Cardoso, Dora Martins, Nanci Batista, Lina Aveiro, Rita Capitão, Helena Ribeiro, Filomena Freitas, Luisa Simão, Isabel Dinis, Alice Mirante

Coimbra Pediatric Hospital, Coimbra, Portugal

Background: Functional insulin therapy allows precise insulin adjustments to achieve normoglycaemia. **Objective and hypotheses:** To assess metabolic control (A1c) and lipid profile in children and adolescents with DM1 in a 3-year period under multiple daily injections (MDI) since the diagnosis. **Method:** Retrospective analysis of children and adolescents under functional insulin therapy since the diagnosis of DM1. The variables studied were: age at diagnosis, gender, pubertary stage; insulin daily dose (IDD), average blood glucose, A1c, hypo and hyperglycemias and lipid profile in the first 3 years of disease. **Results:** Forty-six children and adolescents were included, 26 (56.5%) females, age at diagnosis was 8.9 ± 3.4 years, 69.6% pre-pubescent. IDD increase significantly over the years: year 1 (0.64 ± 0.19 U/kg per day) and year 3 (0.88 ± 0.24 ; $P < 0.001$), and average blood glucose (140.85 ± 26.8 mg/dl vs 157.13 ± 29.4 ; $P < 0.001$). In the pre-pubertal group, there was no significant increase in the first 2 years (142.53 ± 23.9 vs 150.9 ± 27.2 ; $P = 0.057$). A1c did not vary significantly: year 1 ($7.18 \pm 0.99\%$) and year 3 ($7.4 \pm 0.84\%$; $P = 0.139$). In the pubescent group A1c increased significantly (6.86 ± 0.93 vs 7.6 ± 1.09 ; $P = 0.037$). Hyperglycemia increased significantly: year 1 ($31.9 \pm 18.1\%$) and year 3 ($44.3 \pm 15.3\%$; $P < 0.001$), without variation in hypoglycemia rate: year 1 ($9.1 \pm 4.4\%$) and year 3 ($9.1 \pm 5.8\%$; $P = 0.979$). There was no significant variation of LDL cholesterol and triglycerides (2.1 ± 0.57 vs 2.2 ± 0.57 mmol/l; $P = 0.41-0.71 \pm 0.29$ vs 0.80 ± 0.37 mmol/l; $P = 0.113$). **Conclusion:** Functional insulin therapy contributes to good metabolic control with low frequency of hypoglycemia, even in pre-pubertal children. Therapeutic education is needed on

how to adjust insulin to avoid hyperglycemia increasing. This therapy is safe since the diagnosis of DM1.

P3-D3-756

Haemolysis and Acute Pancreatitis During Diabetic Ketoacidosis Treatment in a 14-Year-Old Boy with Unknown Glucose-6-Phosphate Dehydrogenase Deficiency

Federica Ortolani^a, Albina Tummolo^b, Cataldo Torelli^a, Maristella Masciopinto^a, Stefania Fedele^a, Maria Paola Lanzillotto^d, Francesco Nicastro^a, Francesco Papadia^a, Marcella Vendemiale^c, Elvira Piccinno^a

^aMetabolic Diseases, Clinical Genetics and Diabetology, Pediatric Hospital Giovanni XXIII, Bari, Italy; ^bUOC Hereditary Metabolic Diseases, Azienda Ospedaliera Policlinico di Padova, Padova, Italy; ^cClinical Psychology, Pediatric Hospital 'Giovanni XXIII', Bari, Italy; ^dUOC Pediatric Surgery, Pediatric Hospital Giovanni XXIII, Bari, Italy

Background: G6PD deficiency is conventionally affiliated with drug induced oxidative stress, but an association with diabetes mellitus is seldom reported. Hypertriglyceridemia from insulin deficiency can be the cause of severe pancreatitis complicating DKA in children. **Case report:** A 14-year-old Bulgarian boy, no significant past medical history, hospitalized in Pediatric Surgery Department for abdominal pain, hematemesis inserted during a cruise trip. Referred recent use of aspirin, clarithromycin, vitamin C. Started i.v. physiologic saline solution and omeprazole. Naso-gastric tube drained hematic material. AP 146/83 mmHg, HR 142 b.p.m., and BR 42/min. Venous blood gas analysis: pH 6.867, Hb 15 g/dl, K 4 mmol/l, glucose 462 mg/dl, lactate 2.9 mmol/l, and BE - 30.1 mmol/l. Capillary ketonemia 4.2 mmol/l, HbA1c 10.4%. I.v. sodium bicarbonate (50 mEq HCO₃), transferred to diabetology department (glycemia 486 mg/dl, and ketonemia 2.4 mmol/l), continued on i.v. fluids. Regular insulin was started (0.04 U/kg per h). Suspecting cerebral edema (lethargy, neurological state deterioration) mannitol i.v. infusion (18 g/100 cc in 20 min). Brain CT scan confirmed edema. Low grade fever (37.7 °C) PCR 170.5 mg/l: started i.v. meropenem. On day 2 venous blood pH 7.3, alpha amylase 1077 U/l (<90), and lipase 882 U/l (7-60). Ultrasound: mild heterogeneously enlarged and hypoechoic pancreas. Started gabexate mesilate and parenteral feeding. Serum triglyceride 168 mg/dl (70-150), normal total cholesterol. On day 4 jaundice and pallor. Hematological assessment: RBC 1 500 000/mm³, reticulocytes 8.7%, Hb 4.8 g/dl, Hct 14.4%, total bilirubin 5.45 mg/dl, LDH 866 U/l. G-6-PD was measured and found to be deficient (1 IU/10⁹). Transfused with red blood cells. Antibiotic therapy integrated with clarithromycin after detection of IgM positivity for micoplasma pneumoniae. On day 7 suspended parenteral nutrition, transitioned to s.c. insulin. Continued gabexate mesilate for other 5 days. Dismissed after 18 days of hospitalization in good general condition. Now in follow up for type 1 (positive insulin autoantibodies) diabetes mellitus.

P3-D3-757

Pneumothorax, Pneumomediastinum, and Subcutaneous Emphysema: Complications of Severe DKA in T2DM Obese Patient

Federica Ortolani^a, Albina Tummolo^c, Cataldo Torelli^a,
Maristella Masciopinto^a, Stefania Fedele^a, Francesco Nicastro^a,
Francesco Papadia^a, Marcella Vendemiale^b, Elvira Piccinno^a

^aMetabolic Diseases, Clinical Genetics and Diabetology, Pediatric Hospital Giovanni XXIII, Bari, Italy; ^bClinical Psychology, Pediatric Hospital 'Giovanni XXIII', Bari, Italy; ^cUOC Hereditary Metabolic Diseases, Azienda Ospedaliera Policlinico di Padova, Padova, Italy

Case presentation: G. 15 years 8 months; H 180 cm; P 149.6 kg, BMI 46 kg/m², second born, father obese, healthy mother and two brothers, no familiarity for T1DM/T2DM, no gestational diabetes. Bronchial asthma, since 2-year-old important weight increase. Flue, polyuria, polydipsia, 12 kg loss in 15 days, anorexia since 5 days, vomit. Hospitalized for tachycardia, dyspnea, and asthenia. On arrival: serious dehydration, Kussmaul breathing, neck subcutaneous emphysema, tachycardia 130/min, A.P. 125/70 mmHg. **Diagnostic procedures, therapy, and follow up:** Glycemia 663 mg/dl, ketonemia 4.8 mmol/l, anion gap 24 mEq/l, K 2.5 mEq/l, HbA1c 11.4%, GOT 77 UI/l, GPT 73 UI/l, amilase 204 U/l, lipase 723 U/l, cholesterol 250 mg/dl, tryglicerides 301 mg/dl, C-peptide 0.37 ng/ml, negative IAA, GAD and IA2. Chest CT scan: large anterior pneumomediastinum, left apical pneumothorax, neck subcutaneous emphysema. Abdomen ultrasound: steatotic enlarged liver. I.v. therapy on arrival: physiologic saline solution, potassium, 15 fl of sodium bicarbonate, subcutaneous rapid insulin 20 U. 12 h later transferred to our department, metabolic-hydroelectrolytic correction for DKA with i.v. insulin 12–18 U/h. Equilibrium in 48 h, potassium normalisation in 4 days, amilase and lipase in 1 week. Seven days later, insulin pump implantation (total insulin: 5 U/h + three bolus), started therapy with metformin (1500 mg/day). Dismissed with insulin pump (basal + two bolus), after 1 month infused only low basal insulin, suspended after 6 months (pre-prandial C-peptide 3.5 ng/ml and HbA1c 5.3%). Metformin suspended after 16 months (weight 90 kg, BMI 27.8%, and HbA1c 5.1%), 30 months later normal OGTT and insulinemia, C-peptide 2.7 ng/ml, and HbA1c 4.9%. **Considerations:** The severe outset might have suggested T1DM diagnosis (negative family history for T2DM). Importance of insulin pump therapy for preserving pancreatic β cells activity. Hypocaloric diet and adequate lifestyle determined weight loss and the patient did not require any therapy: total remission or healing?

P3-D3-758

Diabetes Insipidus in Pediatric Practice

Shakhrizada Sultanova^a, Shakhlo Bobohodzhaeva^b

^aThe Centre of Scientific and Clinical Study of Endocrinology in Republic of Uzbekistan, Tashkent, Uzbekistan; ^bTashkent Pediatric Medical Institute, Tashkent, Uzbekistan

Background: In pediatric practice, as a rule, differential diagnostics between the three main types of diabetes insipidus DI is to be made: central DI, renal DI and physiological polydipsia of infants – the separation of which is extremely important for the prescription of pathogenetic treatment. **Objective:** To make a differential diagnostics of various forms of DI. **Methods:** The study involved 14 patients (ten girls and four boys) aged from 1 to 4 years, directed to the Department of Pediatric Endocrinology RSPCEMHRU diagnosed with DI (central form). They were treated with different doses of desmopressin. To all patients, there were conducted Zimnitsky's test, blood electrolytes (calcium, phosphorus, sodium, and alkaline phosphatase) and daily urine (calcium and phosphorus), ultrasound of renal, MRT of hypophysis, X-ray of the hand to detect rachitic changes; consulting a nephrologist and genetics. **Results:** On the basis of complaints, anamnesis, Zimnitsky's test (urine specific gravity fluctuations were 1001–1005; daily urine output ranged from 1.7 to 8.5 l); electrolyte composition data of blood and urine, ultrasound of renal were diagnosed as $n=11$ (71%); cases of various kinds of tubulopathy made up, $n=1$ (7.1%) of dismetabolic nephropathy, $n=1$ (7.1%) of multi enzyme failure and $n=1$ (7.1%) of physiological polydipsia infants. When prescribing desmopressin an increase of the relative density of urine is not observed. As a result of pathogenetic treatment, there was a significant decrease of polydipsia and polyuria. **Conclusions:** The study shows that the use of relative density of urine for the diagnostics of DI in children is entailed with hyper diagnostics of the disease in all patients studied. Taking into account a huge group of genetically determined diseases associated with defects of tubular transport of electrolytes and high frequency in our study (71%), it is necessary to make a deep survey of patients in this age group for the purpose of pathogenetic treatment, prevention of potentially dangerous side effects of improperly prescribed treatment (desmopressin) and for further search of causes of disease.

P3-D3-759

Diabetes Mellitus Type 2 in Pediatrics: an Emerging Reality in Our Country: First Described in Spain

Ignacio Diez-Lopez, Ainhua Sarasua-Miranda,
Isabel Lorente-Blazquez

Endocrinology Section, Pediatric Service, Vitoria, Basque Country, Spain

Background: The diagnosis of increasingly serious in the early years of life obesity has experienced a large epidemiological increased worldwide in recent decades, and especially in our country and in some groups. Many of the metabolic complications (SM) and cardiovascular have their origins in childhood and are closely related to the presence of insulin resistance (IR), which associated complications: hepatic steatosis, endothelial dysfunction, polycystic ovary syndrome (PCOS) dyslipidemia, prediabetes, type 2 diabetes, and asthma. To date there have been described in our type 2 DM in children associated with obesity.

Objective: To study within our cohort of obese children followed in the prevalence of RI Hospital and DMtipo2. **Material and methods:** Retrospective cohort of obese children consultation (2000–2012). BMI > P97 (Orbegozo 2004). Making OGTT (ADA criteria) and criteria for Metabolic Syndrome IFD 2007 (MS). IBM SPSS 18.0 statistical descriptive. **Results:** Two hundred and fifty cases initially selected. 54% ($n=135$) 46% girls ($n=115$) children. First consultation age: 10.1 ± 2.2 (6–17). Weight and height at birth: 92% PAEG, 2.7% PEG, 5.4% MEG. BMI (kg/m^2) average Z-score +2.8, with DS 0.75 (2–8.5). Tanner 1 (61%) T2–4 (35%), T5 (4%). Obesity grade I (44%), grade II (46%), and grade III (7%) severe/morbid (3%). Intolerant OGTT 30/250 (12%), criteria MS 12/250 (5%), and DMtipo2 2/250 (0.8%). Description cases (iconography is provided). Case 1: ♂ 12a7m. Fragile – X (+). Disharmonious PEG. Debut glucose 580 mg/dl, insulinemia 29 $\mu\text{U}/\text{ml}$, HbA1c 11.8%. HLA DR3/DR4 (–/–). Ac GAD/IAA (–) requires intensive insulin (glargine–lispro) + metformin. Initial BMI SDS +4.3. Weight loss +2.2 SDS. Now exercise + metformin treatment. Case 2: ♀ 13th 8m. Disharmonious PEG. Debut glucose 385 mg/dl, insulinemia 33 $\mu\text{U}/\text{ml}$, HbA1c 10.6%. Requires intensive insulin (glargine–glisulide) + metformin. HLA DR3/DR4 (–/–). Ac GAD/IAA (–) initial BMI SDS +3.4. Weight loss +2.8 SDS. Now treatment liraglutide + metformin + exercise test. **Conclusions:** Childhood obesity in our country has reached such prevalence and intensity which gives rise to cases of type 2 DM, as described in other age groups and regions.

P3-D1-760

Association of Ghrelin Gene Polymorphisms with Obesity in Japanese Children

Ikuyo Itoh, Hisakazu Nakajima, Kazuki Kodo, Satoru Sugimoto, Kitaro Kosaka, Hajime Hosoi

Department of Pediatrics, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan

Background: Recently, ghrelin has attracted attention as a hormone connected with appetite. The relationship between ghrelin genetic polymorphisms and obesity has been analyzed in adults, but the influence of these SNPs on obesity in children is uncertain. **Objective:** We perform SNP analysis of the ghrelin gene and examine its relationship with the childhood obesity. **Population:** We analyzed 35 patients (27 boys, eight girls) treated in our pediatric obesity clinic from 2010 to 2014. The average age at the first visit was 10.9 years old (range, 6–18 years old). **Method:** We selected three SNPs of the ghrelin gene: g.A-604G (rs27647), g.C-501A (rs26802), and g.C247A Leu72Met (rs696217). The SNPs were genotyped using ABI 7500 Fast Real-Time PCR System and Taqman[®] SNP Genotyping Assays. **Results:** The ghrelin variant, Leu72Met, showed associations with total serum cholesterol ($P=0.003$) and LDL cholesterol level ($P=0.007$). The mean levels of each tended to be higher in obese children with heterozygous Leu72Met. The relationship between the SNPs and HOMA-IR index was not seen in children, although g.A-604G and Leu72Met were related to the insulin resistance in

adults. Fasting glucose levels tended to be high in obese children with heterozygous g.C-501A, compared with those with homozygous g.C-501A ($P=0.05$). **Conclusion:** Our observation suggests a protective role of Leu72Leu against hypercholesterolemia in childhood obesity. However, significant associations between SNPs of ghrelin gene and BMI were not observed. We are planning to examine the relationship between diet and SNPs in childhood obesity. Future studies on a larger sample size are needed for more definitive conclusions.

P3-D1-761

25-Hydroxy Vitamin D Deficiency and its Relationship to Obesity and Other Risk Factors in a Group of Iranian Children and Adolescents

Heshmat Moayeri, Maral Ghasemzadeh

Tehran University of Medical Sciences, Tehran, Iran

Background: There is increasing evidence of vitamin D deficiency world-wide resulting in nutritional rickets. With increasing use of fast foods and reducing appropriate physical activity. Our world is encountered with the problem of obesity which increases the risk of 25-hydroxy vitamin D deficiency. **Objective and hypotheses:** The aim of this study was to determine the status of serum 25(OH)D level in children 2–14 years old who visited in a pediatric endocrinology clinic between 2012 and 2014. We also examined the relationships between serum 25(OH)D deficiency and obesity, age, sex, skin color, season, sun exposure index, and dairy intake. **Method:** Using a cross sectional design, serum 25(OH)D level, the amount of dairy intake, BMI percentile and BMI Z-score for age and sex, sun exposure index, were measured in 170 children (2–14 years old) living in Tehran. Our data was analysed using Pearsons correlation test, linear regression test, independent *t*-test, χ^2 -test and ANOVA test. All the children were divided into four groups according to their level of 25(OH)D. On the base of our review of literatures, we use the cut off 30 ng/ml as the optimal level of 25(OH)D, 20–30 ng/ml as 25(OH)D insufficiency, 10–20 ng/ml as moderate deficiency and under 10 ng/ml as severe vitamin D deficiency. **Results:** The mean serum 25(OH)D level was 21.37 ± 11.54 ng/ml, and 23% of subjects had severe vitamin D deficiency and 78% of subjects did not have optimal 25(OH)D level. 25(OH)D levels were negatively and significantly correlated with BMI, BMI percentile, BMI Z-score and age. 25(OH)D level was positively and significantly correlated with dairy intake and sun exposure index. Prevalence of severe vitamin D deficiency was significantly higher among girls than the boys and prevalence of severe vitamin D deficiency was significantly higher during winter. Prevalence of severe 25(OH)D deficiency was significantly higher in obese group. Overall we can conclude that our children especially obese, girls, those who are in pre pubertal and pubertal age with rapid growth, are at high risk of 25(OH)D deficiency and its subsequence and prevalence of severe vitamin D deficiency in subjects whose 25(OH)D were measured during summer was significantly higher than winter group (P value = 0.03). Prevalence

of severe 25(OH)D deficiency was significantly (P value <0.001) higher in obese group (BMI percentile for age and sex >95 and BMI Z-score >1.5). Overall we can conclude that our children specially obese, girls, those who are in prepubertal and pubertal age with rapid growth, are at high risk of 25(OH)D deficiency and its subsequence.

P3-D1-762

A Rare Case of Sea-Blue Histiocytosis Associated with Niemann–Pick Disease Type B in a 8-year and 9-month Old Boy with Hypertension

Hua-mei Ma, Zhe Su, Yan-hong Li

The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China

Background: Sea-blue histiocytosis is a morphological finding that can be associated both with acquired conditions of increased cellular turnover and inborn errors of lipid metabolism. **Objective and hypotheses:** To present a Chinese boy of hypertension and sea-blue histiocytosis secondary to Niemann–Pick disease type B. **Methods:** Diagnosis was confirmed by the bone marrow aspiration and the specific enzyme assay of leukocytes (deficiency in sphingomyelinase activity). **Results:** The 8-year and 9-month old boy was the first child of non-consanguineous parents of Chinese Han ethnicity, who presented with hepatosplenomegaly for 4 years. General physical examination showed short stature with Ht 106 cm (-5 s.d.) and abdominal distention. On systemic examination, hypertension with BP 158/119 mmHg was noted, and hepatosplenomegaly measuring 10 cm below costal margins, respectively was present. Neurological examination and respiratory function tests were normal. Chest X-rays revealed diffuse reticular pattern. The echocardiography showed a thickening (8 mm) of the interventricular septum. Ultrasonography showed a bright liver, which is usually fatty tissue. Coagulation function tests showed slightly prolonged activated partial thromboplastin time (APTT), lipid profile showed elevated LDL (3.57 mmol/l), elevated TG (2.37 mmol/l), and decreased HDL (0.54 mmol/l). Other admission laboratory data include following: white blood cell count, hemoglobin, platelet count, serum total bilirubin, aspartate aminotransferase, alanine aminotransferase, serum albumin, were all within normal ranges. Hematoxylin–eosin staining of bone marrow showed scattered foci of foamy histiocytes. May-Giemsa staining of the bone marrow smear showed multiple blue-colored granules were found in the cytoplasm of histiocytes. Histiocytes were stained blue by the Schmorl reaction. The acidic sphingomyelinase activity seen in peripheral blood leukocytes was lower (4.75 nmol/mg per h) than normal (40.29 nmol/mg per h), confirming a diagnosis of sea-blue histiocytosis secondary to Niemann–Pick disease. **Conclusion:** We report a rare case of sea-blue histiocytosis associated with Niemann–Pick disease type B in a 8-year and 9-month old boy with hypertension.

P3-D1-763

Association of Lifestyle with Metabolic Syndrome in Children

Maria Efthymia Katsa, Sofia Zyga, Maria Tsironi, Anastasios Ioannidis, Athanasios Sachlas, Petros Kolobos, Maria Magana, Anna Maria Pistikou, Dafni Eleni Kougioumtzi Dimoliani, Andrea Paola Rojas Gil

Department of Nursing, School of Human Movement and Quality of Life, University of Peloponnese, Sparta Lakonias, Greece

Background: Metabolic syndrome (MetSyn) is defined as a group of disorders including diabetes mellitus, central obesity, dyslipidaemia, and hypertension. **Aim:** To investigate the role of lifestyle habits in correlation with MetSyn in children. **Methods:** In our research, 480 students, 6–12 years old, were participated living in Sparta–Greece. During 2011–2012, a specially designed questionnaire was used and anthropometric and biochemical analyzes were performed. **Results:** 22.7% of children had BMI% ≥ 90 %. 67.9% had WC% ≥ 95 %. 35.6% of children had elevated, for their age, systolic blood pressure, 31.5% had LDL ≥ 100 mg/dl, 33.5% glucose ≥ 100 mg/dl, 3.6% triglycerides ≥ 150 mg/dl, 4.4% cholesterol ≥ 200 mg/dl and no children had HDL ≤ 40 mg/dl. 15% were predisposed for MetSyn. With statistically importance $P \leq 0.05$ we found: reduced vegetable and cereal consumption increased glucose level. Reduced fruit consumption increased triglycerides. Lack of sleep increased cholesterol. The hour when children go to bed was positively correlated with BMI%, waist circumference % (WC%) and glucose. Studying separately children with (MTS) and without predisposition (WMTS) for MetSyn we found that in MTS: fruit and vegetable consumption increased glucose and Ca respectively. Legume consumption increased total protein, CRP and decreased urea. Dairy product consumption increased WC%. Regarding WMTS we found: meat consumption increased LDL. Cereals consumption increased WC%. Oil/olive consumption increased HLD, albumin, and BMI%. In MTS: BMI% was increased in children who sleep after 2200 h. Nap increased glucose, LDL and decreased total protein and ALT/SGPT. In WMTS: lack of sleep is positively correlated with diastolic blood pressure (DP), urea and creatinine. Nap decreased systolic blood pressure (SP), DP, and creatinine. The hour when children go to bed was positively correlated with WC%, DP, urea, and glucose. **Conclusion:** Childhood obesity and predisposition for MetSyn are in high percentage. In an effort to prevent metabolic complications is necessary to preserve an appropriate diet and also keep adequate sleep hours.

P3-D1-764

Prevalence of Metabolic Syndrome and Insulin Resistance Among Aged 3–9 Children

Nihal Hatipoglu^a, Selim Kurtoglu^b, Mumtaz Mazicioglu^a, Deniz Okdermir^a, Ulku Gul^a

^aDepartment of Pediatric Endocrinology, Medical Faculty, Erciyes University, Kayseri, Turkey; ^bDepartment of Family Medicine, Medical Faculty, Erciyes University, Kayseri, Turkey

Background: Metabolic syndrome (MS) is increasingly reported in obese children. So far, MS evaluations were performed for children at the age of 10 and over. **Objective and hypotheses:** Our aim is to evaluate the prevalence of MS and insulin resistance (IR) in obese children between 3 and 9 years old according to modifying National Cholesterol Education Program Adult Treatment Panel-III (NCEP-III) and International Diabetes Federation (IDF) criteria. **Methods:** Two hundred twenty-two obese children aged 3–9 were included. Blood pressure, waist circumference, fasting triglycerides (TG), HDL, insulin and blood glucose levels (FBG) were obtained. IR was defined with HOMA-IR. MS was defined by modification of NCEP-III and IDF criteria. **Results:** IR was found 25%. MS prevalence was found 24% by NCEP-III, 18.7% by IDF criteria. According to NCEP-III criteria, rates were high FBG: 0.5%, high TG: 45.2%, and low HDL: 12.3%. According to IDF criteria, these rates were 5.8, 15.5, and 22.7% respectively. Systolic and diastolic hypertension ratio was 17.2 and 22.4% respectively by both criteria. Considering to both of criteria, MS was 10%. Considering puberty, in prepubertal, IR was 22.7%. MS was 23.2 and 15.8% depending on NCEP-III, IDF criteria respectively. These rates were 34.1, 27.3, and 29.5%, respectively in puberty. **Conclusion:** The early diagnosis of obesity and its complications are very important in term of treatment and prevention. It was found that one-fifth of obese children had IR and one of their four had MS in between 3 and 9. These high rates are quite alarming.

P3-D1-765

The Relation of Serum Leptin and Soluble Leptin Receptor Levels with Metabolic and Clinical Parameters in Obese and Healthy Children

Gönül Çatlı^a, Ahmet Anık^a, Hale Ünver Tuhan^a, Tuncay Kume^b, Ece Böber^a, Ayhan Abacı^a

^aDepartment of Pediatric Endocrinology, School of Medicine, Dokuz Eylül University, Izmir, Turkey; ^bDepartment of Biochemistry, School of Medicine, Dokuz Eylül University, Izmir, Turkey

Background: In blood, leptin is suggested to circulate both in the free form as well as bound to soluble leptin receptor (sLR) and possibly also to other as yet unidentified binding protein. However, the role of the sLR in the regulation of the physiological function of leptin is until now unclear. **Objective and hypotheses:** We aimed to investigate the relation of serum leptin and sLR levels with metabolic and anthropometric parameters in obese and healthy children. **Methods:** The study included obese children with a BMI >95th percentile and healthy children with a BMI <85th percentile. The height, weight and waist circumference

(WC) of the patients was measured for anthropometric evaluation. Fasting serum glucose, insulin, lipid profile, leptin, and sLR levels were measured to evaluate the laboratory parameters. **Results:** The study included 35 obese and 36 healthy children. The obese children had significantly higher BMI, BMI-SDS, WC, triglyceride (TG), homeostasis model assessment of insulin resistance (IR), fasting glucose, and insulin levels compared to the healthy children ($P < 0.05$). In the obese children serum leptin levels, free leptin index (FLI) and leptin/BMI ratio were found significantly higher, while sLR level was found significantly lower than the healthy children ($P < 0.05$). Leptin level, FLI and leptin/BMI ratio were significantly higher among insulin-resistant obese children ($P < 0.05$), while sLR level was similar between the groups when compared regarding the presence of IR ($P > 0.05$). In the obese children, sLR level was negatively correlated with only total cholesterol and TG levels ($P < 0.05$). **Conclusions:** Findings of this study suggest that in obese children and adolescents decreased sLR level together with increased leptin level and FLI might be a compensatory mechanism for increasing leptin effect in peripheral tissue. Besides, in the obese group dyslipidemia and insulin resistance contributes toward the development of leptin resistance.

P3-D1-766

Positive Association of Pro-Oxidative Stress Markers with Adipose Mass in Pre- and Early-Pubertal Boys

George Paltoglou^{a,b}, Maria Schoina^c, George Valsamakis^a, Alexandra Avloniti^c, Athanasios Chatzinikolaou^c, Antonis Kambas^c, Dimitris Draganidis^c, Ioannis Papassotiropoulos^d, Alexandra Margeli^d, Nicolaos Salakos^e, Maria Papagianni^f, Christina Kanaka-Gantenbein^b, George P Chrousos^b, Ioannis G Fatouros^c, George Mastorakos^a

^aEndocrine Unit, Second Department of Obstetrics and Gynecology, Aretaieion Hospital, Athens University Medical School, Athens, Greece; ^bFirst Department of Pediatrics, 'Aghia Sofia' Children's Hospital, Athens University Medical School, Athens, Greece; ^cSchool of Physical Education and Sports Sciences, Democritus University of Thrace, Komotini, Greece; ^dDepartment of Biochemistry, 'Aghia Sofia' Children's Hospital, Athens, Greece; ^eSecond Department of Obstetrics and Gynecology, Aretaieion Hospital, Athens University Medical School, Athens, Greece; ^fPediatric Endocrinology Unit, Third Department of Pediatrics, Hippokrateion General Hospital of Thessaloniki, Aristotle University of Thessaloniki, Thessaloniki, Greece

Background: Oxidative stress and adipocytokines are associated with obesity. **Objective and hypotheses:** To investigate the association of adipocytokines with markers of pro- and anti-oxidation at baseline and their change and correlations during acute aerobic exercise in normal weight and obese pre- and early-

pubertal boys. **Method:** Fifty healthy pre- and early-pubertal, normal weight and obese boys, underwent a baseline blood sampling followed by an aerobic exercise bout until exhaustion at 70% VO_2max and a subsequent (post-exercise) sampling for the measurement of pro-oxidation markers (TBARS, PCs); anti-oxidation markers (GSH, GSSG, GPX, catalase, and TAC) and adipocytokines (lipocalin-2, RBP4, hsCRP, hsIL6, adiponectin, and leptin). **Results:** No difference was found between pre- and early-pubertal subjects in pro- and anti-(except baseline TAC) oxidation markers and adipocytokine concentrations. Baseline pro-oxidation markers, hsCRP, hsIL6, and leptin concentrations were greater in obese than normal weight subjects, whereas the reverse was true for anti-oxidation markers. Post-exercise concentrations of pro- and anti-oxidation markers, RBP4 and hsIL6 were significantly different compared to baseline in all subjects groups. In all subjects baseline TBARS and PCs correlated positively with leptin and hsCRP while post-exercise PCs correlated positively with post-exercise hsIL6. Also, baseline TAC correlated negatively with RBP4 and hsIL6 while baseline GSH correlated negatively with hsIL6, hsCRP, and leptin. Furthermore, baseline and post-exercise GPX was negatively correlated to hsCRP and hsIL-6 respectively. **Conclusion:** Pro-oxidation markers, inflammatory adipocytokines and leptin are greater in obese compared to normal-weight pre- and early-pubertal boys whereas anti-oxidation markers are greater in normal weight boys. Post-exercise both pro- and anti-oxidative stress markers change significantly in all subjects. In all subjects pro- and anti-oxidation markers are positively and negatively correlated, respectively, with inflammatory adipocytokines and leptin, a marker of adipose mass. These findings indicate the deleterious association of pro-oxidation with adipose tissue in pre- and early-pubertal boys.

P3-D1-767

Prevalence Metabolic Syndrome and Its Components Among Children with Obesity

Oleg Latyshev^a, Elena Kiseleva^a, Goar Okminyana^a,
Lubov Samsonova^a, Irina Kolomina^b

^aRussian Medical Academy of Postgraduate Education, Moscow, Russia; ^bTyshinskaya Children City Hospital, Moscow, Russia

Background and aims: To study the prevalence of metabolic syndrome and its components (impaired fasting and after overload glucose, type 2 diabetes mellitus, low cholesterol HDL, and high triglycerides) in children with obesity. **Methods:** This research includes 550 (65.8% boys) children, recruited from Pediatric Endocrinology Department, with abdominal obesity. We measured BMI, waist circumference, blood pressure with standard instrumentation and glucose (fasting and after overload with 1.75 g/kg glucose), cholesterol HDL, and triglycerides. **Results:** The overall prevalence of metabolic syndrome was 33.1% (182 of 550). The patients were divided into two groups. In the first group,

182 patients (66.5% boys) were included with metabolic syndrome (IDF, 2007). In the group with metabolic syndrome, components of syndrome were diagnostic: impaired fasting and after overload glucose – 62.1% (111 of 182), type 2 diabetes mellitus – 1% (two of 182), hypertensive 83.0% (151 of 182), and dyslipidemia – 65.4% (119 of 182). Second group – 368 children without metabolic syndrome. In the second group, one component of metabolic syndrome was diagnostic in 41% (153 of 368): impaired fasting and after overload glucose – 14.1% (52 of 368), hypertensive 25.8% (95 of 368), and dyslipidemia – 1.6% (6 of 368). **Conclusion:** Metabolic syndrome is formed in childhood, in children with obesity. In children with and without metabolic syndrome, the most frequent symptom is hypertensive. The most rare component in group with metabolic syndrome – impaired fasting and after overload glucose, type 2 diabetes mellitus; in group with obesity – dyslipidemia.

P3-D1-768

Serum Omentin-1 and Vaspin Levels in Obese Children and Their Correlation with Lipid Metabolism

Hong-Shan Chen^a, Ling-Ling Xu^a, Shun-Ye Zhu^{a,b}, Si-Nian Pan^{a,b},
Min-lian Du^a, Zhe Su^a

^aPediatric Department, The First Affiliated Hospital of Sun Yat-sen University, GuangZhou, China; ^bPediatric Department, The Third Affiliated Hospital of Sun Yat-sen University, GuangZhou, China

Objective: To investigate the serum levels of omentin-1 and vaspin in obese children and their correlation with lipid metabolism. **Methods:** Fifty-nine children participated in the study, among the 59 subjects, 30 of were obese [(9.43 ± 2.02) years old] and 29 were non-obese controls [(10.3 ± 2.2) years old], there was no statistical difference in age between the two groups. Serum levels of omentin-1 and vaspin were measured by ELISA method. The concentrations of triglyceride (TG), cholesterol (TC), fasting plasma glucose (FPG) and fasting insulin (FINS) were also measured. Body mass index standard deviation score (BMI-SDS) and homeostasis model assessment of insulin resistance (HOMA-IR) were calculated for all participants. **Results:** A significant difference of BMI between obese group and control group (24.8 ± 3.4 vs 16.2 ± 3.2, $P=0.000$) was observed. Serum levels of TC, LDL-C, FINS, HOMA-IR were significantly higher in obese group than those in control group (all $P<0.05$). Serum level of omentin-1 was positively correlated with HDL-C ($r_s=0.405$, $P=0.026$) in obese children. The positive correlations between serum omentin-1 and TC ($r_s=0.614$, $P<0.05$) in obese girls. There was negative correlation between serum vaspin and TC ($r_s=-0.621$, $P=0.031$), LDL-C ($r_s=-0.678$, $P=0.015$) in obese girls. **Conclusion:** Serum omentin-1 and vaspin may take part in the lipid metabolism pathogenesis in obese children.

P3-D1-769

The Importance of Weight for Height for Prediction of Metabolic Syndrome in Obese Children and Adolescents: Impact of Gender and Pubertal Status

Bayram Özhan^a, Betül Ersoy^b, Seniha Kiremitçi^b

^aSchool of Medicine, Division of Pediatric Endocrinology and Metabolism, Pamukkale University, Denizli, Turkey; ^bDivision of Pediatric Endocrinology and Metabolism, School of Medicine, Celal Bayar University, Manisa, Turkey

Background: We aimed to assess whether or not anthropometric indices such as weight circumference (WC), waist/hip ratio (WHR), waist-height ratio (WHtR), and weight for height (W/H) are predictors for metabolic syndrome (MetS) among obese children and adolescents. We aimed to describe effects of gender and pubertal status on these anthropometric indices. **Method:** A total of 291 obese children and adolescents (160 girls and 131 boys, age range: 6–16 years, mean age: 11.84 ± 2.62 years) were included in this study. Anthropometric and biochemical parameters were evaluated in all participants. MetS was defined according to the International Diabetes Federation (IDF) criteria. **Results:** The prevalence of metabolic syndrome was 22.3% (65) in all participants. Significantly higher WC and W/H were found in obese with MetS ($P < 0.05$). The prevalence of MetS was significantly higher in pubertal obese children than pre-pubertal ones ($P = 0.004$). W/H in both pubertal and prepubertal obese children with MetS was significantly higher compared to obese without MetS. Significantly higher W/H was found in obese girls with MetS. However, difference for W/H were not significant between obese boys with and without MetS ($P > 0.05$). Multiple regression analysis revealed that W/H was the most important predictor of MetS in obese children and adolescents except obese boys ($P < 0.05$). **Conclusion:** Frequency of MetS is common in pubertal period among obese children. Anthropometric parameters, particularly weight for height must be evaluated in all obese children. Weight for height can be used as a predictor for MetS in obese children and adolescents except obese boys.

P3-D1-770

Understanding How Race Influences Plasma Peptide YY in the Aging Population

Kamille Camacho-Monclova^{a,b}, Dillip Jeste^a, Pei-an Betty Shih^a

^aUniversity of California–San Diego, San Diego, California, USA; ^bUniversity of Puerto Rico at Cayey, Cayey, Puerto Rico

Background: Appetite change and metabolic complications have been studied to understand implications in the elderly cardiometabolic health. Peptide YY (PYY) plays an important role in appetite regulation; therefore is associated with obesity risks and metabolic syndrome (MetS). MetS risk reported to differ in multiple racial categories, yet the mechanisms that drive this risk are not well understood. **Objective and hypotheses:** Our overall

research aim is to understand MetS risk in a cohort of psychiatric patients. PYY is a risk factor for MetS. The specific goal of my summer project is to assess how race influences PYY. MetS differs in severity and prevalence across different racial groups, therefore our hypothesis is that PYY. Level may also be different across different racial groups. **Method:** We utilized a pre-existing clinical data set containing patients with multiple self-reported racial categories (predominately Caucasian and African American) who are at increased risk of MetS from factors associated with their mental illnesses. A total of 174 older patients (60 females/114 males, mean age = 66.74 ± 13.07) with major psychiatric illnesses were included in the statistical analysis. The subjects are 139 Caucasians, 24 African Americans, and 11 others (ethnic minorities combined). Two different types of statistical analysis were performed. ANOVA and analysis of covariance (ANCOVA). **Results:** Race does appear to have a significant association with PYY levels even after removing the confounding effect of the covariates. The literature shows that MetS risk varies by racial groups. In our data, PYY level varies significantly by racial groups, even after accounting for the effects of conventional covariates. Caucasians appear to have the highest level of plasma PYY compared to African American and individuals from other minority races. Understanding how PYY contributes to the risk of MetS may aid in reducing the morbidity and mortality associated with MetS. Understanding how PYY level observed in each racial group corresponds to differential race-based MetS risk profile and outcome, may lead to better public health intervention and health management. **Conclusion:** This research is part of the foundation needed to research the mechanisms of PYY that can lead to a therapeutical strategy to prevent or treat metabolic risks in people with different racial backgrounds.

P3-D1-771

Level of Non-HDL Cholesterol and its Related Factors in Chinese Han Students

Fang Yanlan^a, Liang Li^a, Fu Junfen^b

^aThe First Affiliated Hospital of College of Medicine, Zhejiang University, Hangzhou, China; ^bChildren's Hospital of Zhejiang University School of Medicine, Hangzhou, China

Background: Cardiovascular disease is one of the most prominent causes of mortality world widely. A key related factor of atherosclerotic cardiovascular disease is the presence of dyslipidemia. Together with elevated blood pressure, obesity, and diabetes mellitus, dyslipidemia is a component of metabolic syndrome and associated with an increasing incidence of coronary heart disease. **Objective and hypotheses:** The aim of this study was to investigate the concentration of non-HDL cholesterol in Chinese Han students of varying ages and genders, and to find out its related factors. **Methods:** We examined 20 208 Han students (10 573 boys and 9635 girls) aged between 6 and 17 years old who came from six districts throughout China. The examination, performed during 2009–2010, involved a clinical examination and self-administered questionnaire. Based on the criteria defined by the American Academy of Pediatrics for children and adolescents

in 2011, we defined high non-HDL cholesterol (total cholesterol minus HDL cholesterol) at a level ≥ 3.75 mmol/l. We set gender, age, obesity, physical activities, sleep duration, eating patterns and sedentary activities as related factors and performed logistic regression analysis. **Result:** The percentage of high non-HDL cholesterol was 4.1% in 6–17 years old children and adolescents in China. Non-HDL cholesterol concentration was significantly higher in girls than boys. Biological maturity was positively associated with non-HDL cholesterol concentration. Gender, weekly sport frequency, eating patterns, biological maturity and obesity were the related factors of high non-HDL cholesterol concentrations. **Conclusion:** The concentrations of non-HDL cholesterol in children and adolescents are strongly determined by gender. Obesity, gender and biological maturity contributed to the variance in non-HDL cholesterol and should be considered in future evaluation of non-HDL cholesterol status. Children and adolescents who did more sports and ate more vegetables were less likely to have a higher non-HDL cholesterol level.

P3-D1-772

Do Children with Down Syndrome Show Lipid Profile Disorders?

Dominika Zimny, Marta Szatkowska, Julian Maciaszek, Mikolaj Machaj, Ewa Barg

Wroclaw Medical University, Wroclaw, Poland

Background: People with Down syndrome (DS) are considered to be atherosclerosis-free. However, obesity predispositions and thyroid gland dysfunction that accompanies this syndrome can influence on the heart ischemic risk. **Aim:** The aim of the study was the evaluation of lipid profile of children with DS and estimation of omega-3 supplementation effect on serum lipid profile. **Materials and methods:** The group constituted 69 children with DS (41 boys), average age 4.1 (± 3.5) years. 102 tests of lipid profiles were obtained – total cholesterol, LDL, HDL, and triglycerides (TG). The children were divided into two groups A – (36.4%) supplemented, B – (63.6%) not supplemented. Statistica 10 was used to perform the statistical analysis. **Results:** Concentration of lipids was evaluated basing on sex and age centile charts. It was stated: Total cholesterol - 22.8% above 75 percentile (pc.) and 11.4% above 95 pc.; LDL–25% above 75 pc. and 8.3% above 95 pc.; TG–25.7% above 75 pc. and 17.6% above 95 pc.; HDL–24.7% under 25 pc. and 11.7% under 5 pc. Negative correlation between the level of TG and the age of children ($P < 0.05$; $R = -0.297$) was found. Average value of the total cholesterol/HDL ratio (cholesterol/HDL) was 3.52 (± 1.09), that is increased in 42.5% children. Children with DS had pharmacologically aligned thyroid function. Group A in comparison to group B was characterized with a significantly lower level of TG, a significantly higher level of HDL and lower chol/HDL ratio of 3.48 (vs 3.99 in group B). **Conclusion:** Performed study confirmed the presence of serum lipid profile disorders in children with DS. Taking all this into account, some recommendations should be done in order to enable monitoring and treatment of lipid disorders in this group of patients. In the context of this research,

supplementation of children with DS using preparations containing polyunsaturated fatty acids omega-3 is justified, due to its beneficial effects on lipid disorders.

P3-D2-773

Trends in Obesity Prevalence and BMI among Pre-Pubertal Bulgarian Children, 1990–2007

Violeta Iotova^a, Sonya Galcheva^a, Yoto Yotov^b, Kera Grozdeva^a, Velin Stratev^b

^aDepartment of Pediatrics, Varna Medical University, Varna, Bulgaria; ^bDepartment of Internal Diseases, Varna Medical University, Varna, Bulgaria

Background: Obesity prevalence is increasing among young children in both developed and developing countries, showing a tendency to persist with age and lead to early morbidity and mortality. **Objective and hypotheses:** The aim of this study is to present the most recent trend in obesity prevalence and to investigate the changes in BMI among Bulgarian pre-pubertal children for a period of 17 years (from 1990 to 2007). **Method:** Three cross-sectional surveys of random representative samples of 7–9 years old urban schoolchildren were conducted in 1999/2000 ($n = 1162$), 2001/2002 ($n = 1004$), and 2006/2007 ($n = 1043$) respectively. Body weight and height were measured by trained personnel using standard procedures and BMI was calculated. The obesity prevalence was defined according to the International Obesity Task Force age- and gender-specific BMI cut-off points. **Results:** There was a significant upward trend in the obesity prevalence over a 17-year period both among boys and girls. It was more pronounced in boys (3.2 vs 9.2 vs 10.6%, $P < 0.001$) compared to girls (4.9 vs 4.3 vs 10.4%, $P = 0.003$). No gender related difference in obesity prevalence was found during the last survey conducted in 2006/2007 (10.6 vs 10.4%, $P > 0.05$). Mean BMI also steeply increased in the last 5 years both among males (16.7 ± 2.8 in 2001/2002 vs 18.7 ± 3.5 kg/m² in 2006/2007, $P < 0.001$) and females (16.9 ± 2.7 in 2001/2002 vs 18.8 ± 3.8 kg/m² in 2006/2007, $P < 0.001$). **Conclusion:** The present study presents evidence of a significant increase in obesity prevalence and mean BMI among pre-pubertal children over time. Active preventive measures and regulations are needed to halt this positive trend of increasing childhood obesity and alleviate the burden of future diseases.

P3-D2-774

The Prevalence of 25-Hydroxyvitamin D Insufficiency and Deficiency Among Overweight and Obese Children and Adolescents in Greece

Christos Giannios, Ioanna Farakla, Georgios Papadopoulos, Ioanna Bakopoulou, Nicolas C Nicolaidis, Chryssanthi Papathanasiou, Maria Drakopoulou, George P Chrousos, Evangelia Charmandari

Background: The prevalence of obesity has increased dramatically in Greece in the last decades, and more than 30% of children and adolescents are currently overweight or obese. Obesity is associated with decreased circulating 25-hydroxyvitamin D concentrations, which might predispose to metabolic syndrome and cardiovascular morbidity and mortality. **Objective and hypotheses:** To determine serum 25-hydroxyvitamin D concentrations and their relationship to cardiometabolic parameters in overweight and obese children and adolescents. **Patients and methods:** One hundred thirty-three ($n=133$) children and adolescents (79 females (F), 54 males (M)) were recruited to participate in the study during the autumn months. Of these, 49 were overweight (age: 9.78 ± 0.45 years, BMI: 23.29 ± 0.37 kg/m², F: 32, M: 17) and 84 obese (age: 10.49 ± 0.4 years, BMI: 28.7 ± 0.62 kg/m², F: 47, M: 37). Blood samples for determination of liver and renal function, 25-hydroxyvitamin D, bone profile and cardiometabolic parameters were determined at 08:00h following a 12-h fast. Systolic and diastolic blood pressure was determined twice and the mean was calculated. **Results:** The concentrations of 25-hydroxyvitamin D were sufficient (≥ 30 ng/ml) in 45 (33.8%) children and adolescents, insufficient (20–29 ng/ml) in 46 (34.6%) and deficient (<20 ng/ml) in 42 (31.6%) subjects. There was no significant difference in 25-hydroxyvitamin D concentrations between overweight and obese (27.08 ± 1.4 vs 25.74 ± 1.11) subjects. A significant negative correlation between serum 25-hydroxyvitamin D concentrations and diastolic blood pressure ($r = -0.169$, $P = 0.046$) was noted. **Conclusions:** Our findings indicate that 25-hydroxyvitamin D insufficiency or deficiency is observed in approximately two thirds (66.2%) of overweight and obese children and adolescents in Greece.

P3-D2-775

Metabolic and Lifestyle Correlates of Health-Related Quality of Life Among Taiwanese Obese Adolescents

Meng-Che Tsai, Yen-Yin Chou

Department of Pediatrics, College of Medicine, National Cheng Kung University Hospital, National Cheng Kung University, Tainan, Taiwan

Background: Recent research has focused on the association between obesity and health-related quality of life (HRQoL). However, the results are mixed when addressing this issue in youth and in different cultural contexts. Little is known about the impact of obesity on HRQoL of Asian adolescents. **Objectives:** To determine the metabolic and lifestyle correlates of HRQoL among Taiwanese obese adolescents in a hospital setting. **Methods:** Obese (age 11–19 years) with BMI >95 th percentile for sex and age were compared to non-obese counterparts in aspects of anthropometric measurements, biochemical testing, and items on lifestyles and

HRQoL. Insulin sensitivity was represented by homeostasis model assessment-insulin resistance (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI). Body composition was measured by the dual-energy X-ray absorptiometry (DXA). HRQoL was assessed by the pediatric quality of life inventory (PedsQL). Student *t*-test and Mann-Whitney *U* test were used to compare the differences in the PedsQL scores between groups. Ordinal logistic regression model was further applied to identify significant factors associated with PedsQL. **Results:** Obese adolescents ($n=46$) reported a lower PedsQL score in the physical domain only, as compared to that of non-obese participants ($n=16$). Further stratifying subjects by metabolic and lifestyle factors, we observed a higher emotional PedsQL subscales among those with HOMA-IR >2.8 and daily sleep >8 h/day and also a higher social PedsQL subscales among those with trunk fatness $<25\%$. In the multivariate analysis, trunk fatness is associated with physical, emotional, and school domains, while duration of sleep and sun exposure are associated with social domains of HRQoL. **Discussion:** Taiwanese obese adolescents had similar HRQoL, except physical subscales, as compared to non-obese adolescents. Metabolic and lifestyle factors correlated with HRQoL in this Asian context. Understanding the biopsychosocial impact of obesity may benefit in adolescent weight management.

P3-D2-776

Prevalence of Dyslipidemia and Associated Factors Among Obese Turkish Children

Selin Elmaogullari, Derya Tepe, Ahmet Ucakturk, Fatma Demirel

Pediatric Endocrinology Department, Ankara Children's Hematology and Oncology Training Hospital, Ankara, Turkey

Background: Obesity prevalence among children increased worldwide in last three decades. Childhood onset obesity is associated with increased mortality and morbidity related to cardiovascular diseases during adulthood. Dyslipidemia has a fundamental role in the pathogenesis of cardiovascular diseases. **Objective and hypotheses:** This study is designed to evaluate the prevalence and related factors of dyslipidemia among obese children and adolescent. **Method:** In this study obese cases of endocrinology out-patient clinic were evaluated retrospectively for dyslipidemia and related factors. In total, 823 obese individuals aged 2–18 years (mean 10.8 ± 3.1 years, 55.8% female, 60.8% pubertal) with age and sex matched BMI above 95 percentile were included in the study. Mean BMI and BMI SDS was found 28.3 ± 4.8 kg/m² and 2.4 ± 0.6 respectively. Dyslipidemia was defined as total cholesterol >200 mg/dl, triglycerides >150 mg/dl, LDL >130 mg/dl or HDL <40 mg/dl. Insulin resistance was evaluated using HOMA-IR index. **Results:** Patients with both dyslipidemia and hepatosteatosis had higher levels of ALT, AST and TSH, and lower levels of free T₄. **Conclusion:** Dyslipidemia prevalence increases with obesity degree and older age. Dyslipidemia with concomitant hepatosteatosis influences both liver and thyroid function tests significantly.

P3-D2-777

The Interaction of Exophthalmos with Obesity in Turkish Children and Adolescents

Betul Cicek^a, Ahmet Ozturk^b, Mumtaz Mazicioglu^c, Selim Kurtoglu^d, Tuncay Kara^c, Nihal Hatipoglu^d

^aDepartment of Nutrition and Dietetics, Faculty of Health Sciences, Erciyes University, Kayseri, Turkey; ^bDepartment of Biostatistics and Medical Informatics, Faculty of Medicine, Erciyes University, Kayseri, Turkey; ^cDepartment of Family Medicine, Faculty of Medicine, Erciyes University, Kayseri, Turkey; ^dDepartment of Pediatric Endocrinology, Faculty of Medicine, Erciyes University, Kayseri, Turkey

Background: Many clinicians are aware of the systemic complications of obesity, however there are few studies on the effect of the ocular manifestations of obesity. The ocular complications of obesity include diabetic retinopathy, high intraocular pressure, cataracts, macular degeneration, floppy lid syndrome, pseudotumor cerebri, and exophthalmos. All of these complications can have serious consequences to the individual's ocular health and visual well-being. **Objective and hypotheses:** This study was performed to find out the interaction of exophthalmos with obesity in Turkish children and adolescents. **Methods:** In this cross-sectional study, a total of 4294 children and adolescents aged between 6 and 17 years were included. Hertel exophthalmometry provides the simultaneous projection measurement of both eyes. The distance between the lateral orbital rim and corneal apex is measured on a mirror plane scaled in millimetres. When measurements were being taken, the child/adolescent stood upright on a chair with his/her back leant against the wall and looked straight ahead. Participants were positioned with heels, buttocks, back and head against the upright surface of the wall, with the head positioned in the Frankfurt horizontal plane. All measurements were obtained by two observers with the same device, twice in daytime in a 6-month period, and then the mean of these two measurements was calculated. **Results:** For boys; exophthalmos of the right and left eyes were significantly different for 10, 12, 15, 16 years in normal weight vs overweight/obesity. For girls; exophthalmos of the right and left eyes were significantly different for 6, 8, 9, 10, 12, 14 years in normal weight vs overweight/obesity. **Conclusion:** The cause of exophthalmos is still unknown. One theory is increased retro-orbital fat. We did not explore any relationship between exophthalmos and obesity. Consequently, it was found that the amount of body fat has a few or nearly no effect in exophthalmos.

P3-D2-778

Reproducibility of the Glucose Tolerance Test in Overweight Children

Shokery Awadalla

Hospital San Jose, Bogota, Colombia

Background: Fasting blood glucose has been questioned as a sensitive screening method of dysglycemia in obese children, as

good percentage with normal fasting glucose can had altered glucose tolerance test (GTT). **Objective and hypotheses:** Evaluate the reproducibility of the results of the GTT in overweight children. **Method:** We studied 120 children, 55 girls and 65 boys with BMI \geq P85. No genetic or hormonal abnormalities were detected. After a normal diet for the last 3 days and 8 h fast the day of the test, fast glucose was measured and a glucose load of 1.75 mg/kg body weight was given and new glucose sample was measured after 3 h. After 7 days, without any change in diet or physical activity, a new test was done in the same way. **Results:** 18 children (15%) (ten boys and eight girls) had abnormal glucose tolerance test with glucose post load of 168 ± 15 mg/dl, ten of them had normal fasting blood glucose. In the second test of those only 6 (33%) had similar results and three of the normal results previously showed altered results with glucose post load of 155 ± 14 mg/dl. No difference by sex was detected, and no correlation was found between BMI and the results of the GGT. **Conclusion:** Fasting blood glucose may be insufficient in some cases to detect dysglycemia, however, GGT results are not reproducible. Decision to do one or another test should be evaluated individually.

P3-D2-779

Younger Age and BMI > 3SD are Risk Factors for Mortality in Children with Hypothalamic Obesity

Belma Haliloglu, Serap Turan, Zeynep Atay, Tulay Guran, Saygin Abali, Serpil Bas, Abdullah Bereket

Pediatric Endocrinology Department, Marmara University School of Medicine, Istanbul, Turkey

Background: Hypothalamic obesity is the most flagitious endocrinologic problem following surgical intervention for childhood brain tumors. Thus, recognition of this condition and identification of risk factors for mortality is important. **Objective and hypotheses:** In this study, we have shared our single center experience in obesity-related mortality in children with hypothalamic obesity. **Method:** We retrospectively analyzed 20 patients with HyOb in whom we had minimum follow-up of 3 years. **Results:** The mean age was 6.36 ± 3.60 (0.50–13.82) years, BMISDS was 0.80 ± 1.25 (-1.74 ± 2.55) at diagnosis. The mean duration of follow-up was 6.02 ± 2.5 years (3.3–11.9 years). The most common histologic diagnoses were optic glioma (45%) and craniopharyngioma (40%). Δ BMISDS 0–6 months (difference between BMI SDS at diagnosis and 6 months after tumor therapy) was very high (1.89 SDS), but this rapid increment in weight did not continue on 6–12 months after treatment (Table 1). Δ BMISDS 0–6 months was significantly higher in patients younger than 6 years at diagnosis compared to those who were older than 6 years at diagnosis ($P < 0.001$) (Table 1). Four cases died during follow-up and mortality rate was 4.5-fold higher in patients younger than 6 years compared to those older than 6 years at the time of diagnosis (37.5 vs 8.3%). Mortality rate was also 3.7-fold higher in patients whose maximum BMISDS ≥ 3 at anytime during first 3 years after tumor therapy. **Conclusion:** This study underlined the importance of first 6 months after tumor therapy in regards to weight gain. It also identifies for the first time that children who

Table 1. BMI SDS and Δ BMI SDS values (abstract for P3-D2-779).

	All patients (n=15)	Age at diagnosis		P value
		(≤ 6 years (n=5))	> 6 years (n=10)	
BMI SDS at diagnosis	0.77 \pm 1.26	0.10 \pm 1.63	1.14 \pm 0.91	0.074
BMI SDS 6 months	2.66 \pm 1.45	3.82 \pm 1.86	2.02 \pm 0.63	0.01
BMI SDS 12 months	2.73 \pm 1.35	3.78 \pm 1.59	2.09 \pm 0.61	< 0.01
Δ BMI SDS 0–6 months	1.79 \pm 1.85	3.71 \pm 1.96	0.83 \pm 0.73	< 0.001
Δ BMI SDS 6–12 months	0.04 \pm 0.42	-0.04 \pm 0.50	0.07 \pm 0.38	0.36

were diagnosed younger than 6 years old and max BMISDS ≥ 3 at anytime during first three years after therapy are at risk for increased mortality.

and juices, fried products contribute to the development of obesity in children.

P3-D2-780

Age-Related Characteristics of Nutritional Status in Children with Alimentary Obesity

Nataliya Volkova, Anzhalka Solntsava, Olga Zagrebaeva

Belarusian State Medical University, Minsk, Belarus

Background: Among alimentary factors leading to obesity in children, the main ones are: consumption of high-calorie foods with high content of carbohydrates and getting more calories during the second half of the day. **Objective:** To study feeding habits in children of different ages with alimentary obesity compared with normative values. **Methods:** We compared 3-day food diaries of 115 children with alimentary obesity with nutritional standards of healthy children recommended by Belarusian National Center for Hygiene, Epidemiology and Public Health – control (K). Patients were divided into three age groups: 1st 5–6 years (6.17 \pm 0.68 years; BMI 24.59 \pm 4.00 kg/m²) – 13 people (11.3%); 2nd 7–11 years (9.74 \pm 1.08 years; BMI 26.74 \pm 4.07 kg/m²) – 47 people (40.9%); 3rd 12–17 years (14.71 \pm 1.89 years; BMI 32.81 \pm 8.72 kg/m²) – 55 people (47.8%). The frequency of different food groups, main meals, snacks consumption were studied with the assessment in points (p) 0p – a child didn't eat products of this group, 1p – ate every day, 2p – ate 1–2 times a day, 3p – ate three or more times a day. Results were processed using SPSS 18.0. **Results:** Obese children showed a significant decrease in consumption of porridges and pasta (p (three groups)=0.0001), fiber vegetables (p2- κ =0.0003, p3- κ =0.0001), fruits (p2- κ =0.0001, p3- κ =0.0001), dairy products (p1- κ =0.022, p2- κ =0.0001, p3- κ =0.0001); with increasing – sweet beverages and juices (p1- κ =0.0008, p2- κ =0.0001, p3- κ =0.0001) and fried products (p1- κ =0.0008, p2- κ =0.0001, p3- κ =0.0001). The frequency of snack consumption were less in children with obesity vs the standard ratios (group 1 2.10 \pm 0.57, group 2 1.57 \pm 0.1p, group 3 1.26 \pm 0.80p, norm 3) (p1-K=0.022, p2-K=0.001 and p3-K=0.0001). **Conclusions:** Reduced consumption of pasta and porridges, vegetables, fruits, dairy products, reducing the frequency of snacking and increased consumption of sweet drinks

P3-D2-781

Relationship Between Adiposity Degree and Physical Activity and Inactivity Among Children and Adolescents

Rosaura Leis^a, Rocío Vázquez-Cobela^a, Juan José Bedoya^a, Luisa María Seoane^b, Silvia Barja-Fernández^{a,b}, Concepción Aguilera^c, Josune Olza^c, Gloria Bueno^d, Mercedes Gil-Campos^e, Lidia Castro-Feijoo^f, Luis Moreno^g, Angel Gil^h, Rafael Tojo^a

^aUnit of Investigation in Nutrition, Growth and Human Development of Galicia, Pediatric Department (USC), Complejo Hospitalario Universitario de Santiago (IDIS/SERGAS), Santiago de Compostela, Spain; ^bEndocrine Physiopathology Group, Complejo Hospitalario Universitario de Santiago (IDI/SERGAS), Santiago de Compostela, Spain; ^cDepartment of Biochemistry and Molecular Biology II, Institute of Nutrition and Food Technology, Center for Bimedical Research-UGR, Granada, Spain; ^dDepartment of Pediatric, Hospital Lozano Blesa, Zaragoza, Spain; ^eUnit of Research Pediatric and Metabolism, Hospital Reina Sofía, Córdoba, Spain; ^fPediatric Endocrinology, Pediatric Department (USC), Complejo Hospitalario Universitario de Santiago (IDIS/SERGAS), Santiago de Compostela, Spain; ^gDepartment of Public Health, Universidad de Zaragoza, Zaragoza, Spain

Introduction: The highest prevalence of children and adolescents with obesity in Europe is observed in the south countries. This epidemic is related to unhealthy eating patterns, decreased physical activity and increased inactivity. **Objective:** To determine the relationship between adiposity degree and physical activity and inactivity in children and adolescents. **Methods:** 338 children from 6 to 8 years of age ($x=11.11$ years); boys 52.4% ($n=177$), girls 47.6% ($n=161$) attended in a Pediatric Nutrition Unit. Adiposity degree (BMI, Cole *et al.* 2000) was stratified. Physical activity and inactivity was evaluated using a validate questionnaire. The date analysis were conducted with Statistical SPSS 19. **Results:** 60.4% ($n=204$) are obese. 69.9% ($n=200$) use any type of public transport or by car. Only 12.2% ($n=36$) walking 15 min or more to school. 55.8% ($n=189$) not belong a sports club. 58.6% ($n=198$) watch television while eating. The number of

obese who walk to school is greater than non obese (37.1% ($n=59$) vs 21.3% ($n=2$)) $P=0.002$. Although 91.2% ($n=166$) of obese children walk <15 min and non obese 82.3% ($n=93$) $P=0.023$. The number of obese who belong to a sports club is less than non-obese (39.2% ($n=80$) vs 51.9% ($n=70$)) $P=0.022$. The number of obese who watch television while eating is greater than non-obese (60.8% ($n=124$) vs 55.2% ($n=74$)) $P=0.33$. **Conclusion:** A significant proportion of children start their day without physical activity, do not belong to any sports club and eat in front of television, these unhealthy habits are more frequent in the obese group. Thus the action on aspects must be part of the prevention and intervention strategies.

P3-D2-782

Antenatal and Early Childhood Determinants of the Development of Obesity in Children

Yauhenia Dzmitrovich^a, Anzhaliika Solntsava^a, Olga Zagrebaeva^a, Hanna Mikhno^a, Yuliya Tkachova^b, Katsiaryna Konchyts^a

^aBelarusian State Medical University, Minsk, Belarus;

^b8 State Children of Patient Clinic, Minsk, Belarus

Aim: To identify early risk factors of the development of alimentary obesity in adolescence. **Methods:** We analysed retrospectively 375 histories of development of adolescents: group 1 – 206 obese children (14.55 ± 2.06 years, BMI 32.9 ± 5.1 kg/m²), group 2 – 169 normal-weight patients (12.6 ± 2.2 years ($P=0.2$); BMI 20.5 ± 1.2 kg/m² ($P=0.0001$)) from the University Hospital (Minsk). We collected anamnesis clarifying gestational age, account and complications of pregnancy and delivery, presence/absence of chronic intrauterine hypoxia, family obesity, parental smoking, feeding until 4 months; anthropometric data at birth, 4–12 months; 1.5; 2–6; 12 years were estimated. **Results:** Birth weight in obese children were higher than in normal-weight ($P=0.0001$). Complicated pregnancy in group 1 were detected in 63% (preeclampsia – 34.8%, iron deficiency anaemia (IDA) 4.3%, infections 8.7%, threatened miscarriage 15.2%) in group 2 – 32.5% (preeclampsia 17.8%; IDA 14.8%) ($P=0.0001$); chronic intrauterine fetal hypoxia – 34.8 and 5.9% ($P=0.0001$); complications in delivery – 35.6 and 20.7% ($P=0.049$). Parent's obesity of group 1 were noted in 75.9% of cases, control 1.8% ($P=0.0001$). There were the increasing BMI in obese girls in comparison with controls in 4 ($P=0.01$), 5 ($P=0.005$), 6 years ($P=0.005$). The age of adiposity rebound was 2 years ($P=0.05$). BMI in obese boys were higher than in normal-weight in 6 ($P=0.0001$)–8 ($P=0.003$), 10 ($P=0.01$)–12 ($P=0.02$) months; 2–6 years ($P(2y)=0.006$; $P(3y)=0.04$; $P(4y)=0.0001$; $P(5y)=0.03$; $P(6y)=0.001$). Adiposity rebound in obese boys was 2 years ($P=0.001$). There were no significant differences between the groups in the nature of delivery, pregnancy and delivery account; parental smoking, birth height and gestational age, feeding until 4 months of age. **Conclusions:** Large birth weight, early age at adiposity rebound, early increasing of BMI comparison with normal-weight children, complications of pregnancy and delivery, chronic intrauterine foetal hypoxia; obese

parents are related to perinatal risk factors for obesity development in adolescence.

P3-D2-783

The Association Hypothyroidism: Obesity in a Group of Children and Adolescents

Corina Paul^{a,b}, Mirela Mogoja^{a,b}, Iulian Velea^{a,b}

^aUniversity of Medicine and Pharmacy Victor Babes, Timisoara, Romania; ^bClinic II Pediatrics, Emergency Clinical County Hospital, Timisoara, Romania

Background: Several studies suggested that hypothyroidism, especially subclinical hypothyroidism (SH), is rather a consequence than one of the causes of excessive weight. **Objective and Hypotheses:** We analyzed if there is a correlation between serum TSH, free thyroxine (FT₄) and anthropometric measures in a group of overweight and obese children. **Method:** The study included 92 children (46 girls and 46 boys), mean age: 11.79 ± 3.40 years, evaluated for obesity in 2010–2013. The first evaluation included: anthropometric indexes (weight, height, BMI, waist circumference), complete clinical exam, biochemical tests (glucose and lipid metabolism, TSH, FT₄, anti Tg and anti TPO antibodies in selected cases). **Results:** Three age groups were formed: Ist: <10 years ($n=32$), IInd: 10.1–13 years ($n=26$), IIIrd: 13.1–18 years ($n=34$). Hypothyroidism was found in three children (3.26%), two girls and one boy, one from each group. Anti Tg and anti TPO auto-antibodies were found positive in two of these cases. 18.75% of children from the first group, 30.76% from the second and 35.29% from the third were with SH. So, 26 children (28.26%) had slightly high TSH levels (mean: 4.66 ± 0.77 μ U/ml) but with FT₄ in normal range. Another five children had TSH level near the upper limit. We couldn't find a positive correlation ($P>0.05$) between BMI and serum TSH and FT₄ levels. We observed, in the SH group, that children with severe obesity had lower TSH levels than one with mild obesity. **Conclusion:** There is no general recommendation for treatment with (L-thyroxin) in obese children with SH. The standard evaluation for overweight and obese children should include thyroid function evaluation even if there are no clinical signs. Evaluation of TSH and FT₄ levels should be also included in the follow-up protocol for these children.

P3-D2-784

A New Lipodystrophy Syndrome?

Julia von Schnurbein^a, Pamela Fischer-Posovszky^a, Abhimanyu Garg^b, Martin Wabitsch^a

^aUniversity Medical Center of Ulm, Ulm, Germany; ^bUniversity of Texas Southwestern Medical Center, Dallas, Texas, USA

Background: Congenital generalized lipodystrophy (CGL) is characterized by the absence of most adipose tissue at birth due to

an adipocyte differentiation block. For several forms of CGL, the underlying mutation and pathophysiological pathway has been identified. However, for many cases the genetic cause is still unknown. **Objective and hypotheses:** We report a patient with CGL who showed a complete absence of fat apart from protective fat pads in a postnatal MRI. Adipocyte precursor cells prepared from his subepidermal tissue differentiated into adipocytes in the presence of a peroxisome proliferator-activated receptor (PPAR) γ agonist. Further symptoms of the patient included a short stature, mental retardation, progressive contractions of his joints, muscular weakness, pronounced scoliosis, obstructive cardiomyopathy, multiple naevi, eruptive xanthoma, umbilical hernia, singular palmar grease and a triangular face with low sitting ears. Blood analysis showed a mild hypertriglyceridemia and a microcytic anemia. At the age of 8 years, the patient developed a pilocystic astrocytoma grade I^c which was surgically removed. Within the next 2 years, two relapses occurred during which the tumor progressed to an anaplastic astrocytoma. Despite the normally severe diagnosis, after a radio-chemotherapy no relapse occurred in the last 3 years. It seems unlikely that the patient developed two rare diseases unconnected to each other. **Method:** We screened for mutations known to cause CGL (BSCL 2, AGPAT, Caveolin 1, PTRV Cavin) and performed an array CGH. **Results:** No pathological changes could be found. **Conclusion:** Though we did not find a mutation, a hypothetical mutual cause might lie in the PPAR γ pathway, since PPAR γ is essential for adipocyte differentiation and its expression is increased in human glioma tissue. However so far, a mutation in this pathway has not been described either for anaplastic astrocytoma or for generalized lipodystrophy (in contrast to partial lipodystrophy).

P3-D2-785

Prevalence of Excessive Body Mass and Obesity Among Children and Adolescents Residing in Tashkent, Uzbekistan

Shakhnoza Azimova, Gulnara Rakhimova

Center for the Scientific and Clinical Study of Endocrinology, Tashkent, Uzbekistan

Background: Having the onset in childhood or adolescence obesity in one third of adult people is known to progress resulting in complications. A number of studies demonstrated preservation of excessive weight in 80% of obese adolescents. **Objective and Hypotheses:** The work was initiated to analyze prevalence of excess body mass and obesity among children and adolescents residing in Tashkent, Uzbekistan. **Method:** We examined 3140 children and adolescents aged from 6 to 18 (mean age 13.4 years, *Me* 14.0; IQR10.0–17.0). The study was designed to include anthropometric parameters, such as, body mass, height, BMI and waist circumference. Excess weight and obesity were verified by means of international BMI criteria with age and sex of the patient taken into account. BMI ranging from 85th to 97th percentiles, body mass was assessed as the excessive one, those above the 97th indicated obesity. **Results:** There were 1613 boys and 1527 girls (51.4 and 48.6%, respectively). Excessive body and obesity was

registered in 239 and 48 patients (7.6 and 4.1%, respectively). Obesity was found in boys insignificantly less frequently than in girls (2.2 vs 1.9%, $P=0.69$). Obese persons of 10 years of age or older were more frequently registered both among boys (76.8 vs 23.2%, $P<0.0001$) and girls (70.0 vs 30.0%, $P<0.0001$). Excessive body mass was found in 4.1 and 2.2% of cases among boys and girls, respectively. Prevalence of excessive body mass was observed more frequently among boys (86.1 vs 13.9%, $P<0.0001$) and girls (79.8 vs 2.2%, $P<0.0001$) above ten. **Conclusion:** Prevalence of excessive body mass and obesity among children and adolescents aged from 6 to 18 years residing in Tashkent, Uzbekistan, was 7.6 and 4.1%, respectively. Gender differences in the prevalence of obesity were not found. Excessive body mass and obesity was registered more frequently among persons above ten.

P3-D3-786

Hypothalamic Obesity in Children and Adolescents: a Multi-Disciplinary Approach and Novel Therapeutic Tools

Daniele Tessaris^a, Antonella Tuscano^a, Ivana Rabbone^a, Antonella Lezo^b, Giorgia Fenocchio^c, Fabio Broglio^d, Alessandra Spinardi^e, Roberto Lala^a, Patrizia Matarazzo^a

^aPediatric Endocrinology and Diabetology, Regina Margherita Children Hospital, University of Turin, Torino, Italy; ^bPediatric Clinical Nutrition, Regina Margherita Children Hospital, University of Turin, Torino, Italy; ^cClinical Psychology, Regina Margherita Children Hospital, Torino, Italy; ^dEndocrinology, Health and Science City, University of Turin, Torino, Italy; ^eSUISM, University of Turin, Torino, Italy

Background: Hypothalamic obesity (HO), due to midline congenital malformations, genetic diseases or hypothalamo-hypophysis tumours, is severe and difficult to treat. Patients are scarcely compliant to diet and physical activity, for disabilities often affecting them. Drugs have been rarely employed. **Objective and hypotheses:** Aim of the study was to treat hypopituitary children and adolescents affected by severe HO with a multi-disciplinary approach including endocrine, dietary, physical exercise, psychological measures and, in case of failure, pharmacological and surgical treatment. **Method:** Fourteen hypopituitary (five congenital and nine acquired) subjects (six males and eight females), age range from 8 to 16 years, have been enrolled between July 2013 and February 2014. At 0–3–6 months, height, weight, BMI, serum glucose, insulin, triglycerides, cholesterol, and HOMA-index have been evaluated. At time 0 they received: personalized diet, USB digital support monitoring daily physical exercise, psychological evaluation. Therapeutic efficacy was defined after 6 months: 'good' in case of BMI improvement; 'inefficacy' in case of BMI worsening and/or HOMA index >4 . In the four not responsive adolescents, we employed metformin (500 mg twice/daily) for 3 months, when they were re-evaluated and shifted to GLP-analogue if still not responsive. **Results:** Time 0: 14/14 BMI $>90^{\circ}$ (of whom 11 $>97^{\circ}$), HOMA >4 in 3/14 patients. At 3 months: 2/10 BMI stability or reduction and/or HOMA improvement. At 6 months: 0/5 BMI stability or reduction

and/or HOMA improvement, 4/5 started metphormine treatment. After 3 months of metphormine treatment 2/4 showed BMI stability or reduction and/or HOMA improvement. Patients that are not responsive are starting GLP-analogue. The follow-up of the other patients is ongoing. **Conclusion:** Multidisciplinary approach to HO including physical exercise, diet, psychological support and drugs can give partial favourable results in these challenging condition. This kind of treatment should be started as soon as possible to prevent severe deterioration of BMI and metabolism.

P3-D3-787

Obese Teenagers and Risk of Injuries During School Physical Activity

Francesco Lemma^a, Beatrice Messini^b

^aUSL 2, Foligno, Umbria, Italy; ^bGeneral Hospital, Foligno, Umbria, Italy

Background: Injuries occur frequently in the obese young population even if they need to practice physical activity. The greatest part of Italian adolescents plays sports only at school. **Objective and hypotheses:** The aim of the study was to investigate the relationship between overweight and obesity, and the risk of injuries in adolescents during school physical activity. **Method:** This is a retrospective cohort study utilizing the electronic emergency room data of Umbria's hospitals. The patients' lists were taken from the data base of a family doctor and the pediatric endocrinology ambulatory of Foligno's hospital. 12–17 years old adolescents who reported injuries related to the physical activity at school. The period considered was between the 1st January 2008 and 31st March 2011. 111 patients met the inclusion criteria. The group with a BMI ≥ 85 th percentile included 51 patients (26 males and 25 females). The average BMI was 28.86 kg/m^2 (s.d. ± 4.31), the average age at the first visit was 13 years and 4 months. The group with a BMI < 85 th percentile included 60 patients. The injury incidence among the overweight/obese was 15.6%, while among the normal weight was 3.3%. The relative risk was 4.705 (1.04–21.17, $P < 0.05$). **Results:** Sports played during school hours could be not adequate for overweight/obese adolescents. It's necessary to elaborate and apply different gym plans to put this group at the same level of the normal weight. The obesoes probably avoid practicing sport outside school.

P3-D3-788

Erythrocyte Sedimentation Rate and CRP Levels in Childhood Obesity

Dilek Ozcelik Ersu, Lale Seren, Rahime Gul Yesiltepe Mutlu, Heves Kirmizibekmez

Zeynep Kamil Obstetric and Pediatrics Education and Research Hospital, Istanbul, Turkey

Background: Childhood obesity is one of the most important public health problems at 21st century. Obesity is an inflammatory process that leads to the impairment of health. Increasing prevalence of obesity will be a worldwide problem in the next generation, leading to serious health care and economical burden.

Objective and hypotheses: The aim of this study was to investigate the relationship between childhood obesity and erythrocyte sedimentation rate and C-reactive protein level.

Method: In this study, 49 obese children and adolescents (16 boys and 33 girls) between 8 and 18 years (mean age 12.4 ± 2.6) were included. The control group was consisted of 24 age-matching (mean age 12.5 ± 2.9) children and adolescents (non-obese and healthy, 13 boys, 11 girls). BMI, above the 95th percentile for age and gender, was considered as obesity. In both groups, the erythrocyte sedimentation rate and C-reactive protein (CRP) levels were measured. **Results:** Mean CRP level was significantly higher in the obese group than the control group ($P = 0.001$) independent of age and gender. Erythrocyte sedimentation rate (levels at 1 and 2 h) was not significantly different in the obese group than the control group ($P > 0.005$). **Conclusion:** Compared with overweight children, normal weighted children had lower CRP levels. This study revealed a significant increase in CRP levels, while no difference in erythrocyte sedimentation rates in obese children. Measuring CRP levels in obese children is not a routine approach, but elevated levels of CRP can be an important marker of inflammatory process in obesity.

P3-D3-789

Bone Age Advancement in Prepubertal Children with Overweight and Obesity

Hae Sang Lee^a, Jung Sub Lim^b, Jin Soon Hwang^a, Eun Young Kim^c

^aAjou University School of Medicine, Suwon, Republic of Korea;

^bKorea Cancer Center Hospital, Seoul, Republic of Korea; ^cCollege of Medicine, Chosun University, Gwangju, Republic of Korea

Objective: Obesity is associated with bone age (BA) advancement of unclear etiology. In animal study, insulin may directly modulate skeletal growth. Our objective was to investigate the association with BA maturation and insulin levels in children with overweight and obesity. **Methods:** In this cross-sectional study of 42 prepubertal children, anthropometric data and hormonal values during oral glucose tolerance test were measured. Subjects were divided into two groups by the difference between BA and chronological age (CA) (noted as BA-CA). **Results:** The study population included 26 (61.9%) males and 16 (38.1%) females with a mean age of 7.8 ± 2.0 years. The advanced bone age group defined as BA-CA > 1 year ($n = 25$) had significantly higher HOMA-IR, fasting insulin levels and lower quantitative insulin sensitivity check index (QUICKI). Also, BA-CA was significantly correlated with weight SDS and QUICKI. **Conclusion:** Skeletal age is more advanced in overweight and obese children with hyperinsulinemia and insulin resistance. These findings suggest that insulin may modulate skeletal growth.

P3-D3-790

Obesity Correlates in Adolescence

Ioannis Papandreou, Eleni Kotsalidou, Aikaterini Tselenti, Zoi Gerle
Tzaneio General Hospital, Piraeus, Greece

Background: Adolescence represents a period of one's life when profound mental and physiological adjustment take place marking the transition to adult life. Obesity is a common health issue amongst Greek adolescents often following an obese childhood. **Objective and hypotheses:** We intended to assess the dietary, lifestyle, and metabolic profile of adolescents followed at the outpatient clinic of our hospital. **Methods:** 253 adolescents aged 13.9 ± 2.01 (mean \pm s.d.), followed in the outpatient clinic of our hospital were included. The BMI was calculated from weight and height measurements and was used to divide the adolescents into two groups, obese and non-obese. Blood pressure, fasting insulin, glucose and lipid blood levels were measured. Estimates of insulin resistance homeostatic model assessment (HOMA-IR) and the quantitative insulin sensitivity check index (QUICKI), were derived from fasting measurements. All adolescents were given a standard questionnaire about dietary and lifestyle habits. For the statistical analysis we used SPSS 20.0 (IBM Corp.). Mann-Whitney and Spearman tests were applied. **Results:** 94 adolescents were obese and 45 were also obese during their childhood. The reported consumption of snacks/fast food ($P < 0.03$) and soda beverages ($P < 0.001$) was higher among obese. Additionally all obese adolescents reported < 1 h of daily physical activity. A higher systolic and diastolic blood pressure ($P < 0.001$ and $P: 0.03$ respectively), higher blood levels of fasting insulin ($P < 0.001$) and lower HDL ($P < 0.05$) were associated with obesity. Insulin resistance and insulin sensitivity indexes were associated with obesity (HOMA-IR, $P < 0.001$, QUICKI $P < 0.001$). **Conclusion:** It is therefore necessary to screen for high blood pressure and hyperlipidemia among obese adolescents but it is equally important to try and make them adopt healthy dietary habits and increase their physical activity.

P3-D3-791

Correlation Between Fasting Blood Glucose and Glucose Tolerance Test in Overweight Children

Shokery Awadalla

Hospital San Jose, Bogota, Colombia

Background: Fasting blood glucose (FBG) is the recommended test to evaluate dysglycemia in overweight children, while the glucose tolerance test (GTT) is preferred in adults. FBG may be normal in dysglycemic children while GTT is abnormal. **Objective and hypotheses:** Evaluate the correlation between fasting blood glucose and glucose tolerance test in overweight children. **Method:** Fasting blood glucose were measured and in a different day a glucose tolerance test was done after 8 h of fasting

using a glucose load of 1.75 g/kg with a maximum of 75 g. Blood glucose was measured before and after 2 h. **Results:** We studied 214 children how were referred for weight management. Genetic and hormonal abnormalities were excluded. There were 124 girls and 90 boys. Age was 13 ± 1.2 years. All children had $BMI \geq P85$. 40 boys and 32 girls were obese with $BMI \geq 95$. Total 85 (55 boys and 30 girls) 40% had abnormal fasting glucose values 105 ± 15 mg/dl. There were no difference between obese and overweight, of those only 11 boys and ten girls had abnormal tolerance test with glucose level of 160 ± 18 -mg/dl. (10% of the total number, 25% of those with impaired fasting glucose). Of those with normal fasting glucose (total 129, 94 girls, 35 boys) 7 (5%) (four boys and three girls) had impaired glucose tolerance test. Impaired fasting blood glucose and glucose tolerance test was more frequent in boys than in girls ($P < 0.05$). No difference were found between overweight and obese children. **Conclusion:** Fasting glucose is an easy cheap and good screening method for detecting dysglycemia in overweight children. Glucose tolerance test should be restricted to individualized cases.

P3-D3-792

Frequency of Vegetable and Fruit Consumption in Overweight Children and Their Parents

Sandra Beatriz Escobar Escobar, Shokery Awadalla

Hospital San Jose, Bogota, Colombia

Background: Increased incidence of obesity is related to increased consumption of fast and processed food and decreased consumption of fruits and vegetables. **Objective and hypotheses:** Evaluate the habit of fruit and vegetable consumption in children with overweight. **Method:** A questionnaire was designed in which the frequency and quality of these habits were recorded and anthropometric data also. Parent's habits regarding fruit and vegetable consumption were also evaluated. **Results:** 422 children with overweight was included (250 boys, 172 girls) the age of children was 13 ± 0.9 years. BMI was $\geq P85$. Hormonal and genetic abnormalities were excluded. None of the children take fruits and vegetables the five servings daily as recommended. 210 children (110 girls and 100 boys) 55% do not consume fruits or vegetables, parents do not offer them as they do not like it, only they carry a fruit for snack in school and we were told that bring it back. Parents of this group informed that they take only fruit juice in the morning. 82 children 19% (50 girls and 32 boys) take fruit only in breakfast. Parents of this group informed they take fruit and vegetables twice a day. 130 children (30%) take a fruit in breakfast and some vegetables at dinner. Their parents take three to four serving of fruit and vegetables. Parents took fruit juice consumption as part of fruit consumption. **Conclusion:** Children with overweight do not consume enough fruits and vegetables. There is a strong correlation between parents and children's habits. Encouraging fruit and vegetable consumption should be part obesity prevention in children.

P3-D3-793

Prevalence of Abnormalities of Glucose Metabolism in Obese Greek Children and Adolescents

Feneli Karachaliou^a, Irene Kaloumenou^a,
Elpis-Athina Vlachopapadopoulou^a, Paraskevi Katsixti^a,
Aspasia Fotinou^b, Stefanos Michalacos^a

^aEndocrinology-Growth and Development Department, 'P & A Kyriakou' Children's Hospital, Athens, Greece; ^b'P & A Kyriakou' Children's Hospital, Microbiology, Athens, Greece

Background: Obesity is associated with alterations in glucose metabolism, often present from childhood. **Objective and hypotheses:** To assess the prevalence of glucose metabolism alterations and insulin resistance in a group of obese, otherwise healthy children and adolescents from Greece. **Method:** It is a retrospective study of 130 obese children and adolescents, 79 girls (61%), aged 5.4 to 15.2 years (mean \pm s.d.: 10.8 ± 2.1). Obesity was defined according to IOTF criteria. All subjects underwent an oral glucose tolerance test (OGTT). Fasting insulin, HOMA index and insulin values on OGTT were used as indexes of insulin resistance. **Results:** No case with impaired fasting glucose was detected. Impaired glucose tolerance was observed in 15.5% of subjects. Only one boy aged 13.5 years had diabetes type 2. Insulin resistance was found in 29% of subjects by the use of HOMA index and in 48% by the insulin response in OGTT. **Conclusion:** Disturbances in glucose metabolism are present in a considerable number of young subjects and insulin resistance is the earlier abnormality in glucose homeostasis. This emphasizes the usefulness of OGTT as a screening tool for identification of subjects with small disturbances of glucose metabolism and prevention of type 2 diabetes through intensive intervention.

P3-D3-794

Prader-Willi Syndrome: Reports of Two Patients with Congenital Abnormalities of Kidney and Urinary Tract

Federica Tamburrino^a, Emanuela Scarano^a, Francesca Mencarelli^b,
Annamaria Perri^a, Angela Colangiulo^a, Benedetta Siroli^a,
Anna Lisa Martini^a, Laura Mazzanti^a

^aRare Diseases Unit, Department of Pediatrics, S.Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy; ^bPediatric Nephrology, Department of Pediatrics, S.Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy

Background: Prader-willi syndrome (PWS) is characterized by decreased fetal activity, obesity, muscular hypotonia, MR, short stature, hypogonadism and small hands and feet. Little information is available concerning PWS and kidney involvement. **Objective and hypotheses:** We report two patients with PWS and congenital abnormalities of kidney and urinary tract (CAKUT). **Method:** First case: male, born at 35 weeks with caesarian section, normal pregnancy. Birth weight 2090 g, length 47 cm, severe neonatal hypotonia. PWS was confirmed by

maternal UPD15. GH therapy started at 3 years, stopped after 9 months for hypertrophic cardiomyopathy. At 7 years endocranial hypertension, MRI showed Arnold-Chiari malformation, surgically treated. Second case: male, born at 42 weeks, normal pregnancy, decreased fetal activity. Birth weight 3100 g, length 49 cm, severe neonatal hypotonia. PWS was confirmed by maternal UPD15. GH-therapy started at 10 years of age and continued until 18 years. Now undergoing testosterone therapy for hypogonadism. **Results:** First case: Renal echography and renal MRI: hypo-dysplastic kidneys. At 12 years of age he developed mild chronic kidney disease (stage 2) with high blood pressure and proteinuria. Second case: Nephro-urological imaging showed: monolateral high grade vesicico-ureteral reflux and right kidney hypoplasia. In the follow-up normal renal function with hypertrophic single kidney. **Conclusion:** We report two patients with PWS and CAKUT. A literature review showed few cases with CAKUT: a patient with horseshoe kidney, an other with bilateral hydronephrosis and the last with dilated pelvis (Liu AP *et al.*, *Am J Med Genet A.* 2013). At the moment the relation between congenital abnormalities of kidney and urinary tract and PWS is not clear.

P3-D3-795

Response to Treatment in a Group of Patients with Childhood Obesity

Concepción Freijo Martín, María Laura Bertholt Zuber,
Inmaculada Palenzuela Revuelta, Ana Rebollo Rebollo

Hospital Univ. Marques de Valdecilla, Santander, Spain

Background: The childhood obesity is a common reason for consultation, due to the increase of this disease in our society, the instruction of the patient and the family consumed many resources. **Objective:** Study the obese children who attended during the year 2012 valuing the results at 4 and 8 months. **Method:** 37 obese children (SDS >2), valuing sex, age, family history (FH), anthropometrics measures at birth and the time of the study, relationship W/H, BMI and SDS, type of diet, exercise performed, blood pressure (BP), analytics TC (total cholesterol), HDL-C and LDL-C, TGR (Triglycerides), insulin, HOMA and not endocrinology associated diseases. Indicated guidelines of diet, exercise and they were helped by the educator. Evolution to the 4 and 8 months. The statistical analysis was performed SPSS.15.

Evolution	Aggravate BMI	Same = BMI	Little improvement BMI (0.5-1)	Adequate improvement BMI (> 1)
4 Months	18.9%	24.3%	32.4%	24.3%
8 Months	45.9% (70% males)	32.4%	16.2%	5.4%

Results: 37 children, 22 males (59.5%), ages 10.61 (4.6–15.2), there were FH 32 (86.5%), at birth 25 (67.6%) had a AGA, 11 (29.7%) were macrosomics, weight at the beginning 63.67 (32.8–101 kg), SDSp 2.98 ± 1 , height 1.45 (1.13–1.77 cm), SDSt 0.84 ± 1 , W/H $145.17 \pm 13.9\%$, BMI $28.25 \pm 2.71 \text{ kg/m}^2$, SDS-BMI 2.72 ± 0.87 , carbohydrates rich food in 97.3%, did not take fruits and/or vegetables 73%, ate between meals 65%, and not performing any exercise 40.5%. Systolic BP 113.16 ± 10.43 , diastolic 63.92 ± 9.3 . Analytical: CT 160.25 ± 30 , HDL-C 51.43 ± 12.14 , LDL-C 92.69 ± 22.47 , TGR $81.97 \pm 44.3 \text{ mg/dl}$, insulinemia $15.68 \pm 8.9 \mu\text{U/ml}$, HOMA 3.41 ± 2.12 , being 13(35%) > 3 , predominance in males (61.5%). The frequent disease associated was asthma 21.6%. **Conclusions:** Eating habits and life style produced an increase in childhood obesity, with the future risk of diabetes type II especially in males. The results achieved are bit rewarding, it would be necessary to devote more resources to try to decrease this pathology.

P3-D3-796

Prevalence of Overweight and Obesity in Children and Adolescents at Public and Private Schools from Uberaba Brazil

Adriana Paula Silva, Taciana Carla Maia Feibelmann,
Daniela Cristina Silva, Heloisa Marcelina Cunha Palhares,
Lúcia Marina Scatena, Maria de Fátima Borges

Universidade Federal DO Triângulo Mineiro, Uberaba State of Minas Gerais, Brazil

Background: In Brazil there is a nutritional transition between child malnutrition and increasing prevalence of obesity. **Objective and hypotheses:** The study aims to identify the prevalence of overweight and obesity in children aged 5–18 years in five private and 15 public schools from city of Uberaba Brazil. **Method:** Anthropometric data, inventories physical activities and socioeconomic aspects were evaluated from 1125 individuals, 681 girls and 444 boys. Comparisons between groups by ANOVA; correlation between variables by Pearson's test and significant level was $P < 0.05$. **Results:** Undernutrition was 36 (3.2%), eutrophic 725 (64.4%), overweight 195 (17.33%) and obesity 169 (15.02%). It was observed that overweight was more prevalent between girls 127 (59.91%) and obesity between boys 84 (55.26%) $P = 0.0042$. **Conclusion:** Obesity is becoming an important public health problem and warns for the need of policies that encourage healthy eating and physical activity, reducing sedentary lifestyle.

P3-D3-797

Gene Mutation and Clinical Characteristics Analysis in Progressive Familial Intrahepatic Cholestasis

Ruizhu Lin, Li Liu, Huiying Sheng

Guangzhou Women And Children's Medical Center, Guangzhou, China

Background: Progressive familial intrahepatic cholestasis (PFIC) is an autosomal recessive diseases. **Objective and hypotheses:** To explore the characterization of ATP8B1, ABCB11 and ABCB4 gene mutational spectrum in children from South China. **Method:** By using PCR combined with direct DNA sequencing for 32 patients. **Results:** Six patients were diagnosed as PFIC. **Conclusion:** Six novel mutations were identified.

P3-D3-798

Characteristics of a Population of Obese Children and Adolescents: Suggesting a New Paradigm

Quentin Van Meter^{a,b}, Bethany Welstead^c, Joey Low^b

^aEmory University School of Medicine, Atlanta, Georgia, USA;

^bVan Meter Pediatric Endocrinology, P.C., Atlanta, Georgia, USA;

^cCollege of William and Mary, Williamsburg, Virginia, USA

Background: Obese children come from families where either one or both parents are obese, suggesting obesity is the result of exposure to detrimental environment. **Objective and hypotheses:** We propose that inherited insulin resistance is the core which promotes development of obesity and that allergic airway obstruction stalls development of obesity, while peptic gastritis promotes over-eating by confounding portion control. **Method:** We reviewed 384 new patient records with a diagnosis of abnormal weight gain (ICD-9 783.1) and conducted descriptive statistical analysis. **Results:** Of 384 obese patients, 79.1% had at least one obese parent, and 31.5% had two obese parents. More importantly, 51.1% of obese patients with full siblings had one full sibling who was not obese. Although 16% of the patients were described by their parents as obese in infancy, 53.9% became obese between ages 5 and 10 years, but were previously lean. 62% suffered with allergic diatheses, and 25.5% had peptic symptoms. **Conclusion:** Obese children are born insulin resistant and gain body fat when they finally eat sufficiently.

P3-D3-799

Effects of GnRH Analogue Treatment on Internal Genitales of Girls with Central Precocious

Havva Nur Peltek Kendirci, Zehra Aycan, Elif Sagsak,
Yasemin Tasci Yildiz

Dr. Sami Ulus Women Health, Children's Training and Research Hospital, Ankara, Turkey

Background: The GnRH analogues have been used to treat many diverse reproductive system disorders, including precocious

puberty. **Objective and hypotheses:** The present study aims to investigate the effects of GnRH analogue (GnRHa) treatment on internal genitals of girls with central precocious puberty (CPP). **Method:** The study included 40 girls who were diagnosed as CPP and treated with GnRH analogue (leuprolide acetate, Lucrin depot[®], 3.75 mg of i.m. or s.c. injections once every 28 days). Patients' age, bone age, puberty stage, LH, FSH and estradiol levels were noted retrospectively. Ovarian and uterin volumes were calculated in both initial and post-treatment ultrasounds, uterin corpus/cervix differentiation, endometrium and follicles presence were evaluated. Values before and after therapy were compared. **Results:** Chronological ages of forty girls with CPP was 8.0 ± 1.2 , bone age was 9.7 ± 1.8 . They were treated with GnRH analogue for 13.6 ± 2.0 (12–18) months. Basal LH, FSH and estradiol levels and puberty stages after therapy decreased significantly compared with the initial values ($P=0.00$). Initial mean ovarian volume was $2.4 \pm 2.1 \text{ cm}^3$ and regressed to $1.6 \pm 1.1 \text{ cm}^3$ and uterin volume regressed from 4.9 ± 4.9 to $3.6 \pm 3.7 \text{ cm}^3$ after treatment ($P=0.01$, $P=0.00$ respectively). Endometrial thickening existed at 30% of patients and uterin corpus- cervix differentiation at 25% initially and regressed to 12.5% ve 7.5% respectively, and it was statistically significant ($P=0.01$). It is observed that number and sizes of ovarian follicles decreased significantly ($P=0.01$). **Conclusion:** GnRH analogue treatment regresses puberty stage by repressing gonadotropin levels, and also decrease uterin and ovarian sizes, regresses uterin pubertal alterations and decreases number and sizes of ovarian follicles.

P3-D3-800

Ovarian Tumors Observed in Endocrinology

Amina Laloui^a, Soumeya Fedala^a, Ali El Mahdi Haddam^b, Farida Chentli^a, Djamilia Meskine^b, Leyla Ahmed Ali^a, Fetta Amel Yaker^a

^aBab El Oued Hospital, Algiers, Algeria; ^bBologhine Hospital, Algiers, Algeria

Background: Ovarian tumors are rare in the pediatric age and are represented primarily by functional cysts and benign tumors, the most common is the mature teratoma. **Objective and hypotheses:** Assess clinical, radiological, etiological and scalable characteristics of ovarian tumors in the pediatric age. **Method:** Retrospective study of seven cases of ovarian tumors collected over a period of 20 years. All children received complete clinical, hormonal balance with tumor markers (hCG, α fetoproteins ACE) and an abdominopelvic imaging (CT and magnetic resonance imaging) At the end of the exploration patients were operated and monitored. **Results:** The average age of our patients was 8 years (5–15). reasons for consultation are abdominal pain (70%) and hyperandrogenism (30%). Abdominopelvic CT showed a large mass in all cases (> 5 cm) cyst in 23.1%, and heterogeneous tissue in the remaining cases. The treatment was surgical: Tumorectomy in most cases. A single patient with Peutz Jeghers syndrome (PJ)

was ovariectomized. Histological study concluded the diagnosis of cystic mature teratoma in 50% of cases, arrénoblastome in 25% of cases and granulosa cell tumors in 25% of cas. post opératoir evolution was marked 2 years after by a contralateral recurrence in the patient carrying PJ syndrome requiring further surgery (oophorectomy and adnexectomy) with chemotherapy. **Conclusion:** The ovarian tumors in children are benign in most cases. Their diagnosis is based on histological and treatment given is usually surgical. A long-term follow-up is necessary in these.

P3-D3-801

The Usefulness of the Leuprolide Stimulation Test as a Diagnostic Method of Idiopathic CPP in Girls

Joan Bel, Marta Murillo, Federico Carretto, Maria Martinez, Marisa Granada, Isabel Salinas

Hospital Germans Trias i Pujol, Badalona, Barcelona, Spain

Background: The central precocious puberty (CPP) diagnosis is usually based on clinical evaluation but in its soon phase this evaluation is difficult so laboratory confirmation is crucial. **Objective and hypotheses:** To evaluated the usefulness of the Leuprolide stimulation test as a diagnostic method of idiopathic CPP. **Method:** Sixty-one girls, aged 5–8 years, were evaluated retrospectively for premature breast development. Girls were divided in two groups, according to the clinical characteristics evolution in 6 months, in *progressive puberty* ($n=28$) and *nonprogressive puberty* ($n=33$). In the first visit we measure serum concentration of FSH, LH and estradiol and we also measure serum concentration of FSH, LH at 3 h and estradiol at 24 h, after a s.c. injection of 0.5 mg of aqueous leuprolide. Receiver operating characteristic (ROC) curves were used to select the best criterion and cut-off point to predict progressiveness of puberty. In both groups we evaluated the sensitivity and especificity of the leuprolide test to predict puberty evolution. **Results:** A pubertal hormonal pattern was defined as at least one of the following values: baseline LH: >0.1 mUI/l, baseline FSH: >2.3 mUI/l, peak LH: >5.5 mUI/l, baseline estradiol >12 pg/ml, peak estradiol: >79.67 pg/ml. baseline LH/FSH ratio >0.23, and stimulated LH/FSH ratio >0.24. Stimulated and baseline concentration of LH, stimulated and baseline estradiol and the stimulated and baseline LH/FSH ratio were significantly higher in girls with progressive puberty with respect to girls with nonprogressive puberty group. The measurement LH/FSH ratio post stimulation with Leuprolide had 100% of sensitivity and 94.3% of specificity (based on the ROC curve with an area under the curve of 0.992) to classify progression puberty. **Conclusion:** Although measuring basal gonadotropins could allow discrimination between pubertal and prepubertal values, the measurement of LH/FSH ratio, LH and estradiol post stimulation with Leuprolide could be very useful in the diagnosis of CPP in the early phase. However clinical judgment and follow up continues to be of great importance in the evaluation of precocious puberty.

P3-D3-802

The Effects of Rhythmical Massage Therapy and Heart Rate Variability-Biofeedback on Primary Dysmenorrhea a Qualitative Study

Anna Böning^a, Aurelia Karutz^a, Jan Vagedes^{a,c}, Bettina Berger^b, David Martin^a

^aTübingen University Children's Hospital, Tübingen, Germany;

^bChair of Medical Theory, Integrative and Anthroposophic Medicine, University Witten/Herdecke, Witten/Herdecke, Germany;

^cARCIM-Institute Filderlinik, Filderstadt, Germany

Aim: This study investigated rhythmical massage therapy (RMT) and heart rate variability-biofeedback (HRV) to treat dysmenorrhea. **Methods:** As a part of a randomized controlled trial, 60 patients were allocated to one of the two intervention groups or the crossover control group. For the qualitative study, before and after the 3-month intervention, the women drew their pain into a body silhouette. With the aid of these drawings, half-structured interviews were conducted, in which the patients described their body perceptions and effects of the treatment. All interviews were audio-recorded and analyzed with qualitative methods using the software MAXQDA. **Results:** Dysmenorrhea can be associated with marked functional and psychological stress. RMT and HRV can reduce the pain and enable the women to sense their body in a more differentiated way. They can thereby understand the correlations between their symptoms and their cycle and achieve higher self-awareness. The women can feel a better regulation of the body warmth and have fewer limitations in their daily life. Relief on these different levels can result in a better quality of life. **Conclusions:** The stress of the affected women through dysmenorrhea needs to be taken more seriously than is often done. RMT and HRV can be very helpful and without side effects. The analysis also shows the importance of the emotional condition.

P3-D3-803

Menstrual Regularity Among Early Menarche Girls and CPP or EFP Girls Treated with GnRHa

Chen Qiuli, Li Yanhong, Su Zhe, Ma Huamei, Chen Hongshan, Zhang Jun, Du Minlian

The First Affiliated Hospital of Sun Yat, Sen University, Guangzhou, China

Objective: We assessed in a retrospective unicenter study the effect on menstrual regularity of early menarche and treatment with GnRH analogs (GnRHa) in central precocious puberty (CPP) or early and fast puberty (EFP) girls. **Methods:** Six hundred and ten healthy girls were interviewed and their menarche age and menstrual interval were recorded. One hundred and sixty-nine CPP or EFP girls who were treated with GnRHa were followed up, and their menarche age and menstrual interval were also recorded. **Results:** The menarche age of 610 healthy girls were 12.3 ± 1.0 years. One hundred and thirty girls among all healthy girls (21.3%)

and 12 among 44 early menarche girls (27.3%) had irregular menstruation. There were no significant difference between them. The ratio of dysmenorrhea were 41.1% in normal girls and 50.0% in early menarche girls. The difference were not significant. The menarche age of 113 CPP girls and 56 EFP girls who were treated with GnRHa were 12.2 ± 1.0 years. Fifty-seven among them (33.7%) had irregular menstruation, which were higher than healthy girls ($P < 0.05$) and were similar with early menarche girls ($P > 0.05$). Fifty-seven among them (33.7%) were dysmenorrhea, which had no significant difference with healthy girls and early menarche girls. **Conclusion:** The ratio of irregular menstruation in early menarche girls was slightly higher than normal girls, but not significant. CPP and EFP girls with GnRHa treatment had a significant higher irregular menstruation rate than normal girls. It was probably because of premature puberty plus GnRHa treatment, rather than because of GnRHa treatment alone. Early menarche and GnRHa treatment did not affect the ratio of dysmenorrhea.

P3-D3-804

Complete Blood Count Parameters in Girls with Polycystic Ovary Syndrome

Ahmet Ucakturk, Fatma Demirel, Meltem Tayfun, Derya Tepe, Selin Elmaogullari, Ozlem Kara

Pediatric Endocrinology Department, Ankara Children's Hematology and Oncology Training Hospital, Ankara, Turkey

Background: Polycystic ovary syndrome (PCOS) is characterized by ovulatory dysfunction and excess androgen secretion. Androgens may affect bone marrow cells via androgen receptor which expressed in the bone marrow. Also it is known that especially testosterone increases hemoglobin and hematocrit concentrations. **Objective and hypotheses:** Our aim in this study is to describe the relation between hyperandrogenism and complete blood count (CBC) parameters in adolescents with PCOS. **Method:** The study group was consisted of 80 cases. Forty adolescents with PCOS were compared with an age- and BMI-matched group of 40 obese girls without PCOS. BMISDS in PCOS and obesity groups were 2.56 ± 0.78 and 2.52 ± 0.67 respectively ($P > 0.05$). The mean age of patients with PCOS was 15.2 ± 1.4 years, and in the obesity group it was 14.8 ± 1.19 years ($P > 0.05$). CBC parameters were compared between PCOS and obesity groups. Also the relationship between androgen levels and CBC parameters in the patients with PCOS was investigated. **Results:** In PCOS patients, mean testosterone level was 0.75 ± 0.18 ng/ml, free testosterone was 3.4 ± 0.83 pg/ml and DHEAS was 294 µg/dl. There were no significant differences in hemoglobin (14.1 ± 0.8 vs 13.8 ± 0.94 g/dl), erythrocyte counts (5.03 ± 0.66 vs 4.85 ± 0.32 $10^6/\mu\text{l}$), hematocrit (5.03 ± 0.66 vs $41.2 \pm 2.66\%$), thrombocyte counts (283 ± 72 vs 298 ± 52 $10^3/\mu\text{l}$), leukocyte counts (8.43 ± 1.51 vs 8.2 ± 2.02) between the PCOS and obesity groups without PCOS ($P > 0.05$). There was no correlation between the level of testosterone, DHEAS and CBC parameters. **Conclusion:** Effect of the testosterone on erythropoiesis dependent on dosage. Low level endogenous androgens may not affect CBC parameters in patients with PCOS.

P3-D3-805

The Genotypic and Phenotypic Variability of Mixed Gonadal Dysgenesis

Chelsey Grimby, Robert Couch, Rose Girgis

Department of Pediatrics, University of Alberta, Alberta, Edmonton, Canada

Background: Mixed gonadal dysgenesis is most commonly associated with 45,XO/46,XY karyotype. **Objective and hypotheses:** We report three cases that illustrate the genotype and phenotype variability of mixed gonadal dysgenesis. **Methods:** Data was extracted from Pediatric Endocrinology charts in a tertiary care centre after consenting the parents. **Results:** i) A 13 year old patient, 45,XO/46,X, isodicentric Y chromosome, was diagnosed antenatally by amniocentesis for advanced maternal age. He has normal male external genitalia. He is followed for short stature responsive to GH. He had spontaneous puberty, currently Tanner stage 3. He has behavioural problems including conduct disorder, aggression, and learning difficulties. ii) A 3-year-old patient presented at birth with hypospadias, 2.5 cm phallus, bifid scrotum and left cryptorchidism. The right testis is located in the bifid scrotum. Pelvic ultrasound revealed a persistent uterine structure. He underwent hernia repair and an inguinal gonad was removed. Pathology showed no ovarian stroma and was consistent with a rete testis. Karyotype is 45,XO/46,XY and the child is raised as a boy. iii) A 17 year old phenotypic female presented with delayed puberty, subtle Turner syndrome features, normal stature, and was found to have primary gonadal failure. She has cerebral palsy and developmental delay. Her karyotype was complex and consisted of 46,XY with isodicentric Y chromosome (90%), 47,YYY with two isodicentric Y chromosomes (4%), and 45,XO (4%) despite her father's normal 46,XY karyotype. She underwent gonadectomy bilaterally. The pathology report to rule out gonadoblastoma is pending. **Conclusion:** Mixed gonadal dysgenesis has a wide spectrum of clinical presentations and needs to be managed on a case-by-case basis. This includes karyotype, monitoring of growth and puberty, and assessment for pelvic structures with surveillance for gonadal pathology.

P3-D3-806

A Rare Cause for 46,XX Ovarian Dysgenesis: Perrault Syndrome

Gülşay Karagüzel^{a,b}, Aysenur Ökten^{a,b}

^aSchool of Medicine, Karadeniz Technical University, Trabzon, Turkey; ^bDepartment of Pediatric Endocrinology, Trabzon, Turkey

Background: Perrault syndrome (PS) is a rare autosomal recessive condition characterized by sensorineural deafness and gonadal dysgenesis in females. The most commonly reported additional manifestations are neurological, including mental retardation, cerebellar hypoplasia, and neuropathy. **Objective and hypotheses:** Although sensorineural hearing impairment and ovarian dysgenesis are the cardinal signs of PS in females, PS is a genetically and clinically heterogeneous disorder and its

pathogenetic basis is still unclear. We present a case of Perrault syndrome in a girl with ovarian dysgenesis and normal karyotype. **Method:** A 12-year-old girl referred to our department with thyroid dysfunction. She was the first child of non-consanguineous parents. Her height was 139 cm (< 3.p), weight 31 kg (3.p), height SDS -2.93, and her vitals were normal. She had mental retardation and hearing loss. She had normal external genitalia and she was prepubertal, other systems were normal. Her hemogram, blood glucose, renal and liver function tests were normal. Levels of free-thyroxine 1.29 ng/dl and TSH 8.4 µIU/ml were consistent with subclinical hypothyroidism. Thyroid ultrasound and metabolic screening were normal. She had low levels of estradiol (5.7 pg/ml) and elevated gonadotropins (FSH 119.7 mIU/ml; LH 34.8 mIU/ml) considered primary ovarian insufficiency. **Results:** Pelvic ultrasound showed atrophic uterus and ovaries were not visualised. Her karyotype was 46,XX. She was diagnosed with ovarian dysgenesis. Brain MRI showed vermis hypoplasia. Audiometric evaluation revealed of bilateral sensorineural deafness and completed the diagnosis of PS. **Conclusion:** PS is a rare cause of ovarian dysgenesis, but should be considered in a girl with deafness. It has been identified mutations in *CLPP*, *HARS2*, and *LARS2* genes, but no definitive gene mutation for PS and further studies are needed to establish of the underlying molecular defect. However, PS can be diagnosed by a careful clinical evaluation.

P3-D3-807

A Rare Cause of Ovarian Failure; Ovarioleucodystrophy

Erkan Sari^a, Mutluay Arslan^b, Ediz Yesilkaya^a, Sebahattin Vurucu^b, Murat Kocaoglu^c, Bulent Una^b

^aGülhane Military Medical Academy Pediatric Endocrinology, Ankara, Turkey; ^bGülhane Military Medical Academy Pediatric Neurology, Ankara, Turkey; ^cGülhane Military Medical Academy Radiology, Ankara, Turkey

Background: Ovarioleucodystrophies are one of the rarest leucodystrophies associated with primary ovarian failure. Patients may present with variable disease manifestations such as neurologic, psychiatric or ovarian failure. Disease onset may occur in infancy, adolescence or adulthood caused by mutation in the eukaryotic initiation factor 2B (eIF2B) which has a poor prognosis. **Objective and hypotheses:** Seventeen-year-old girl was brought with tremor, gait difficulty, dysarthria and tingling. She was born at term with a birth weight of 2500 g. and her parents were cousins. It was learned that telarche started when she was 12 years old and was evaluated for primary amenorrhea when she was 16 years old. Her chronological age was 17 years, height 162 cm (46 p), weight 51.5 kg (35 p), and puberty was consistent with Tanner stage 5. She had no signs of hyperandrogenism and it was thought that she had premature ovarian failure with high gonadotropin levels. FSH: 112 U/l, LH: 42 U/l, estradiol: <11 pg/ml, thyroid functions, prolactin, α -fetoprotein

ve β -HCG were in normal ranges. Uterus sizes were $50 \times 15 \times 17$ mm with bilateral atrophic ovaries and karyotype was 46,XX. Brain MRI tested for neurologic symptoms was compatible with leucodystrophy. Ovarian failure and leucodystrophy key words led us to conclusion. **Conclusion:** A global view prevents to be drown in details. Symptoms should be assessed totally instead of separately. This autosomal recessive entity should be kept in mind before further investigation.

P3-D3-808

Phenotypic and Genotypic Characteristics of Patients with Turner Syndrome

Soumeya Fedala^a, Mahdi Haddam^b, Farida Chentli^a,
Djamila Meskine^b, Lyna Akkache^a, Hafsa Si Youcef^b

^aBab El Oued Hospital, Algiers, Algeria; ^bBologhine Hospital, Algiers, Algeria

Background: Turner syndrome (TS) is the most common chromosomal abnormality in females (prevalence 1/2500 births). It is related to the absence or abnormality of one of the two X chromosomes. It is characterized by a short stature, gonadal failure and a many diseases that reduce life expectancy of patients. **Objective and hypotheses:** Report Clinical, hormonal, Cytogenetics and evolutionary ST characteristics then correlate the karyotype and clinical expression of ST. **Method:** Retrospective study on 50 cases of patients with ST and followed between 2000 and 2013. Incomplete records ($n=40$) were not included in the study. All patients underwent a clinical examination, radiological assessment., Hormonal exploration and cytogenetic assessment: test BARR, karyotype. **Results:** The average age at diagnosis is 14 years (20j - 33 years). The time between recognition of the disorders and the first consultation is 5.22 years (0–18 years). 65% of patients consulted for growth retardation associated with a impuberism in 35% of cases. There was a dysmorphic syndrome in 30% of cases. 41.6% of patients had a monosomy, 50% have a mosaïque. In the others cases, there were a structural abnormalities of the X chromosome. A genotype phenotype correlation is observed in all cases. **Conclusion:** ST is expressed variably depending on the age at diagnosis. However despite often suggestive clinic al picture, diagnosis is often delayed. Recent molecular approaches have identified many chromosomal formulas correlation with phenotype and genotype.

P3-D3-809

Three Siblings with Gonadal Dysgenesis

Fatma Dursun, Heves Kirmizibekmez

Pediatric Endocrinology, Istanbul, Turkey

Background: Gonadal dysgenesis in female is defined as absent or insufficient development of ovaries. The patient with gonadal dysgenesis presents with primary amenorrhea and lack

of development of secondary sexual characteristics. The patterns of inheritance is thought to be autosomal recessive. **Case 1:** A fourteen and half year-old-girl, presented with delayed puberty. She was born from consanguineous parents. Pelvic ultrasonography revealed streak ovaries and hormone profile was consistent with hypergonadotropic hypogonadism. Thyroid, adrenal and GH levels were normal. Karyotype was that of a normal female, 46,XX. **Case 2 and 3:** We subsequently examined the proband's sisters who were then 11 and 22 years old. Their laboratory and imaging results were similar to those of the proband. 22-year-old girl, sibling of the first patient, was investigated because of primary amenorrhea. She was receiving oral contraceptives therapy for primary amenorrhea of unknown cause. Genetic analyses of cases for SF- 1 mutation are in progress. **Conclusion:** A rare disease of gonadal dysgenesis in three siblings is presented.

P3-D1-810

The Role of IGF1R Gene Mutation in the Development of Oligodendrocytes

Fan Yang, Mei Tang, Hedong Li

West China 2nd University Hospital, Sichuan University, Chengdu, Sichuan, China

Background: IGF1R gene mutation usually cause IUGR. The children born with IUGR were prone to some kinds of brain function disorders. **Objective and hypotheses:** The dysfunction of the brain was caused by the abnormal oligodendrocyte development. To establish lentivirus vector of IGF1R gene mutation (R709Q) and transfect oligodendrocyte precursors (Ge6). Observe the IRS/MAPK and PI3K/Akt/PKB signaling pathway and the change of proliferation, differentiation, and apoptosis of oligodendrocyte. **Method:** Synthesise IGF1R (R709Q) gene *in vitro* and clone in lentivirus vector with resistance to puromycin (puro). R709Q gene was mediated by lentivirus and to transfect Ge6 cells. Target cells were selected by puro. The experimental group R709Q cells and the control group Ge6 cells were culture *in vitro*. IGF1 were used respectively. Immunofluorescent staining were applied to observe the positive rate of caspase-3 and O4; western blot were applied to observe the IRS/MAPK and PI3K/Akt/PKB signaling pathway, which is the proportional change of p-Erk1/Erk2, p-Akt, p-Bad and Erk1/Erk2, Akt, Bad. **Results:** Immunofluorescent staining indicated that the caspase-3 positive rate of experimental group increased compared to the control group ($P < 0.05$). The other Immunofluorescent staining indicate that the O4 positive rate of experimental group decreased compared to the control group ($P < 0.05$); Western blot indicated that p-Erk1/Erk2/ Erk1/Erk2 Protein expression levels of experimental group are higher than that control group ($P < 0.05$), however P-Akt/Akt, p-Bad/Bad protein expression levels of experimental group are lower in control group ($P < 0.05$). **Conclusion:** The expression of IRS/MAPK and PI3K/Akt/PKB signaling pathway is changed in mutated oligodendrocytes which lead to abnormal proliferation, differentiation and apoptosis.

P3-D1-811

A Novel GHR Mutation, c.439 + 1g > a; in a Family with Laron Syndrome

Mona Attia^a, Atef Abeer^a, Ibrahim Makarem^c, Malcolm Donaldson^d, Lou Metherelle^e, Sameh Tawfik^b, Wafaa Dowedar^b

^aCairo University, Cairo, Egypt; ^bMaadi, Cairo, Egypt; ^cMinistry of Health, Cairo, Egypt; ^dYorkhill, Glasgow, UK; ^eQueen Mary University, London, UK

Background: Mutations in the human GH receptor gene (GHR) are the most common cause of GH insensitivity (GHI) syndrome and IGF1 deficiency. The extracellular domain of GHR (encoded by exons 2–7 of the GHR gene) can be proteolytically cleaved to circulate as GH-binding protein. **Objective:** To evaluate the cause of classical GHI (Laron) phenotypes in two siblings and their parents. **Method:** We observed clinical characteristics of two sibs with extreme short stature, assessed the function of GH–IGF1 axis, and surveyed their parents. Genomic DNA was extracted from peripheral blood, GHR mutation gene was amplified by PCR for sequencing, including exons and splicing areas. **Results:** Two full term brothers with average birth weight (aged 9.4 and 6.23 years) presented with extreme short stature. Height SDS, SDS, was (–6.42 and –5.50 s.d. respectively). The parents were consanguineous with normal stature (mother 156 cm, father 165 cm). Children's weight: –5.49 and –2.81 s.d. respectively). Chronological age–bone age(–5.2 and –2.53 years respectively). Peak GH for the two sibs; by glucagon was 33.3 and 15.7 ng/ml respectively. IGF1 for the older brother was: 9.5, 23.8, and 18.2 ng/ml; while IGF1 for the younger was: 18.1, 28.6, and 22.2 ng/ml; during IGF-1 generation test (reference range 98–156 ng/ml). **Mutation:** The two brothers were homozygous GHR mutation c.439 + 1G > A, so a splice site mutation at the junction of exon 5/intron 5. It's novel and would be predicted to lead to skipping of exon 5, a frameshift and premature truncation of the protein also both parents were heterozygous for the same mutation. **Conclusion:** The clarification of the molecular genetics for these defects will contribute to our future understanding of both normal and aberrant growth and avoid miss-diagnosis and mal-treatment.

P3-D1-812

Maternal Inheritance of an Heterozygous Exon 4 IGF1 Gene Mutation (g.65941 G > A) in an IUGR Child with Mild Post Natal Growth Retardation

Muriel Houang^a, Frédéric Brioude^{a,b}, Salah Azzi^b, Nathalie Thibaud^a, Laurence Perin^a, Yves Le Bouc^{a,b}, Irène Netchine^{a,b}

^aAP-HP Hôpital Armand Trousseau, Explorations Fonctionnelles Endocriniennes, Paris 75012, France; ^bINSERM Unit 938-UPMC, Paris 75012, France

Background: We already described a partial IGF1 primary deficiency due to an exon 4 homozygous missense mutation (g.65941 G > A). A few patients are now described with a heterozygous IGF1 deletion or mutation, questioning about IGF1 haplo insufficiency role in short stature. **Results:** We describe a boy born from consanguineous parents, with an intra uterine growth restriction (IUGR). Birth weight: 2520 g (–1 SDS) birth length: 46 cm (–2 SDS), and head circumference: 33.5 cm (–1 SDS) at 39 weeks. Mother's height was 147 cm (–2.9 SDS) and father's height was 173 cm (0 SDS). This child had a history of failure to thrive. At presentation at 2 years, he had post natal growth failure, his height was at 80.5 cm, (–2 SDS) and weight at 8.720 kg (–2 SDS), and a normal head circumference. He had no frontal bossing and no hemi hypotrophy. Penis and testes were normal. Usual nutritional markers and free T₄, TSH levels were normal, IGF1 was at 33 ng/ml (*n*: 13–136) in the lower range contrasting with a mildly elevated IGFBP3 at 3 µg/ml (*n*: 0.95–3.35). Direct sequencing of IGF1 gene revealed an exon 4 heterozygous mutation g.65941 G > A that we had previously identified in some relatives of this new patient. We had demonstrated that the resulting protein (IGF1-R36Q) had a 4 times lower affinity to the IGF Receptor than the WT. In this new patient, the molecular defect inherited probably from his mother, raises the question of its repercussion on the placenta function and on the foetal growth when present even at a heterozygous status only. **Conclusion:** We speculate that IGF1 signaling may act in a dose-dependent way leading to a mild impaired growth phenotype in this case.

P3-D1-813

BMI, IGF1–SDS, and rhGH Treatment

Ioannis Anargyros Vasiliakis, Ruth Gausche, Christoph Beger, Jürgen Kratzsch, Wieland Kieß, Roland Pfäffle

Childrens Hospital, University of Leipzig, Leipzig, Germany

Background: CrescNet is a large data base used to document children's growth and weight development in more than 300 primary care practices and in eight specialized paediatric endocrinological centres in Germany. **Aims and method:** We investigated 3281 patients with IGF1 measurements during their consultations and subsequent checkups. We analysed 2269 children without an indication for rhGH treatment and 1012 who were subsequently treated with rhGH. A linear model was used to assess the correlation between BMI–SDS and IGF1 SDS. In a group of 1724 rhGH-treated patients we also investigated the correlation between BMI–SDS and IGF1–SDS before and after 3 and 12 months of rhGH treatment. **Results:** As expected, a significant correlation between BMI status and IGF-1 serum levels was observed ($r_s=0.321$; $r_p=0.315$; slope=0.317; $P < 0.001$) in the group of untreated patients. For patients subsequently treated

Table 1. (abstract for P3-D1-813)

<i>x</i>	<i>y</i>	r_s	r_p	Slope	P_s and P_p
T0 BMI–SDS	T0 IGF1–SDS	0.060	0.014	0.019	> 0.005
T1 BMI–SDS (3 months)	T1 IGF1–SDS	0.284	0.216	0.292	< 0.001
T2 BMI–SDS (1 year)	T2 IGF1–SDS	0.300	0.280	0.313	< 0.001

with rhGH, the correlation was not significant and the slope of the linear relationship was flatter (Table 1). In addition, a change in the relationship between BMI and IGF-1 serum values was seen in patients under rhGH treatment. The correlation became statistically significant and the slope more parallel to that of the control patients. **Conclusion:** The correlation between BMI and IGF1 levels is significantly lower in patients with growth failure who need treatment with rhGH than in control patients but it increases under treatment with rhGH. The BMI-SDS of a patient should be considered in the clinical interpretation of IGF-1 measurements before and after rhGH therapy has been initiated in a patient.

P3-D1-814

A Novel GH1 Functional Mutation in a Family with Isolated GH Deficiency

Bilgin Yuksele^a, Fatih Gurbuz^a, Atıl Bisgin^b, Eda Mengen Ucakturk^a, Ali Kemal Topaloglu^a

^aPediatric Endocrinology, Cukurova University, Adana, Turkey;

^bDepartment of Genetics, Cukurova University, Adana, Turkey

Background: The familial type of isolated GH deficiency (IGHD) is characterized by a variable degree of growth restriction, low but detectable GH serum concentrations. The recessive type 1A and 1B, the autosomal-dominant type 2, and X-linked recessive type 3. Phenotype-genotype correlations are notoriously difficult to be established. **Objective and hypotheses:** Herein, we described the variable clinical status of a family with a novel GH1 mutation which is likely lead to GH dysfunction. **Method:** *Case:* The proband was 8-years and 9-month-old boy who presented with short stature. His height was 108.5 cm (-4.15 SDS) and his weight was 14.5 kg (-5.6 SDS), MPH was 164.9 (-1.8 SDS), bone age was 6 years. Interestingly, two GH stimulation tests had normal peak GH value of 12.6 ng/ml (with clonidine) and 12.1 ng/ml (with insulin). Other pituitary hormones and magnetic resonance imaging (MRI) of the pituitary region was normal. The proband received recombinant human GH (rhGH) treatment (30 μ g/kg per day) and he grew 5.1 cm in 6 months. **Results:** Sequencing of the GH1 gene revealed a novel heterozygous mutation in patient, his mother and sister with severe short stature, no phenotypic characteristics of GHD (p.Q110E). **Conclusion:** Establishing the genetic diagnosis of GHD is a challenge but clinical feature exceptions have to be considered.

P3-D1-815

Insulin Tolerance Test and GHRH Plus Arginine in the Reassessment of Pituitary Function at Adult Height Achievement

Natascia Di Iorgi^{a,b}, Maria Carolina Salerno^c, Marco Cappa^d, Sandro Loche^e, Giorgio Radetti^f, Donatella Capaldo^c, Flavia Napoli^a, Annalisa Calcagno^a, Anna Elsa Maria Allegrì^a, Ofelia Bianca Iovovich^a, Serena Noli^{a,b}, Stefano Parodi^g, Mohamad Maghnie^{a,b}

^aGiannina Gaslini Institute, Genova, Italy; ^bUniversità degli Studi di Genova, Genova, Italy; ^cOspedale Federico II, Napoli, Italy; ^dOspedale Bambin Gesù, Roma, Italy; ^eOspedale Microcitamico, Cagliari, Italy; ^fOspedale Regionale, Bolzano, Italy; ^gInstitute of Electronics, Computer and Telecommunication Engineering, Genova, Italy

Background: There is still need to define permanent GHD after adult height achievement in young adults with childhood-onset GHD (COGHD). **Objective and hypothesis:** To reassess GH response during transition. **Method:** We present the final data of 129 subjects (71M) recruited from a multicenter cross-sectional observational study, in whom anthropometrics, ITT ($n=99$), GHRH-arginine ($n=122$), IGF-1 evaluations were undertaken at a mean age of 17.5 ± 2.1 years. Fifty had idiopathic (iGHD), 49 secondary to brain tumors or LMA ($n=1$) (TGHD) and 30 congenital GHD (CGHD). Isolated GHD (IGHD) was found in 83 ($n=49$ iGHD, $n=19$ secondary GHD (SGHD), $n=15$ CGHD), and MPHD in 46 ($n=1$ iGHD, $n=30$ SGHD, $n=15$ CGHD). Peak GH values >6 μ g/l for ITT and >19 μ g/l for GHRH-arginine were considered normal. **Results:** As TGHD and CGHD subjects had comparable peak responses to ITT, GHRH-arginine and IGF1 SDS they were combined as secondary GHD (SGHD); this latter showed lower values compared to iGHD subjects (ITT: 5.0 ± 5.3 and 18.7 ± 13.3 μ g/l; GHRH-arginine: 15.8 ± 19.5 and 49.2 ± 34.7 μ g/l; and IGF1 -2.2 ± 2.2 and -0.4 ± 1.3 SDS, respectively; all P 's < 0.0001). Patients with SGHD and IGHD showed higher GH responses after GHRH-arginine compared to those with MPHD ($P=0.0001$). ROC analyses identified a GH value of 5.26 μ g/l after ITT discriminating SGHD from iGHD (AUC 0.88, $P < 0.00001$; sensibility (Se), 66% and specificity (Sp), 94%); a GH value of 31.2 μ g/l after GHRH-arginine (AUC 0.85, $P < 0.00001$; Se 89%, Sp 74%) and an IGF1 of -1.9 SDS (AUC 0.76, $P < 0.00001$; Se 49%, Sp 96%). The best cut-offs discriminating IGHD from MPHD were a GH value of 5.26 μ g/l after ITT (AUC 0.79, $P < 0.00001$, Se 78%, Sp 63%), 13.7 μ g/l after GHRH-arginine (AUC 0.86, $P < 0.00001$, Se 79%, Sp 82%) and an IGF1 of -1.5 SDS (AUC 0.75, $P < 0.00001$; Se 69%, Sp 75%). GH responses to ITT and GHRH-arginine were inversely correlated to BMI SDS ($r^2 -0.44$ and -0.40 , respectively, P 's < 0.00001). **Conclusion:** Patients with childhood-onset SGHD and MPHD are at higher risk of permanent GHD compared to iGHD and IGHD. ITT confirms to be reliable in the identification of patients who may need rhGH treatment in adult life. BMI may affect GH response after both stimulation tests.

P3-D1-816

The Level and Conformation of Blood Plasma Carotenoids in Girls with Turner Syndrome After 1 Year of GH Therapy

Maria Pankratova^a, Maria Faassen^a, Svetlana Kovalenko^b, Alexander Yusipovich^b, Adil Baizhumanov^b, Tatyana Shiryayeva^a, Georgy Maksimov^b

^aDepartment of Pediatric Endocrinology, Endocrinology Research Centre, Moscow, Russia; ^bBiophysics Department, Faculty of Biology, Moscow State University, Moscow, Russia

Background: The concentration and conformation of carotenoids and blood plasma in girls with Turner syndrome (TS) were observed. **Objective and hypotheses:** The level and conformation of blood plasma carotenoids could be used as markers of overall condition of patients. The obtained data was compared with the parameters of antioxidant status before and after 1 year of GH therapy. **Method:** 12 prepubertal girls (median 13.2 years) with TS were included in the study. All of them have not been treated with GH before. The conformation and total concentration of carotenoids were examined using Raman spectroscopy. Blood antioxidant system was examined using activity of superoxide dismutase (SOD) and catalase, thiobarbituric acid reactive substances (TBARS) and ceruloplasmin level and total antioxidant capacity of plasma evaluated by FRAP. All parameters were measured before and after 1 year treatment of GH in dose 0.05 mg/kg per daily. **Results:** The concentration of plasma carotenoids in girls with TS after 1 year treatment GH was significantly higher about 30% (2.15 ± 0.18 and 2.86 ± 0.19 $\mu\text{g/ml}$ correspondingly). The mean values of band ratio I1525/I1008 after treatment was significantly less about 60%. The values of SOD and catalase activities were significantly decreased during the course of treatment (about 25% in both cases) and also the significantly elevated level of TBARS after treatment was observed (about 30%). **Conclusion:** The changing of antioxidant status parameters may be interpreted as development of chronic oxidative stress. The increasing the total carotenoids concentration in plasma correlated with value of TBARS. This may be interpreted as a protective mechanism for scavenging of reactive oxygen species. The decrease of the band ratio at I1525/I1008 was by changing of carotenoids conformation probably in results of oxidative alterations of lipoproteins structure.

P3-D1-817

Increased Required Dose of GH in Children with Inborn Panhypopituitarism

Michael Wurm, Natascha van der Werf-Grohmann, Alexandra Krause, Cordula Roemer-Pergher, Karl Otfried Schwab
University Childrens Hospital, Freiburg, Germany

Introduction: Standard dose for GH deficient children is 0.025 mg/kg per day given subcutaneously once daily. Inborn panhypopituitarism is a special subset of GH deficiency. Its management is difficult because several hormones need to be replaced. We present three patients with perinatal onset panhypopituitarism. **Case reports:** Case 1 is a 7-year-old boy who had hypoglycaemic seizure with reanimation due to circulatory arrest shortly after birth. Panhypopituitarism was diagnosed as hypoglycemia was ongoing during intensive care treatment. After initiation of treatment with GH and cortisol hypoglycemia ceased. GH-therapy was initiated and was increased up to a dose of 0.036 mg/kg per day to achieve good growth velocity and IGF1 in the upper normal range. Since the age of 4, dose/kg was slowly reduced to 0.026 mg/kg per day maintaining good growth velocity and good IGF1 levels. The patient's prospective length is normal. Case 2 is a 4-year-old girl who was born after fetal hydrops and

emergency C-section. In the first few weeks of life hypothyroidism and hypocortisolism was diagnosed and treatment initiated. MRI showed aplastic hypophysis, hormonal testing showed panhypopituitarism. Treatment with GH (0.025 mg/kg per day) was started, but no catch-up growth was reached and IGF1 remained low. GH-dose was increased in several steps to a dose of 0.052 mg/kg per day to achieve good growth velocity and IGF1 levels in the normal range. Case 3 is a 20-year-old man with hypoplastic pituitary gland of unknown cause. Treatment for panhypopituitarism was initiated at the age of 11. He was treated with GH in a dose of 0.025 mg/kg per day, but catch up-growth and normal IGF1 levels were only achieved with a dose of 0.035 mg/kg per day. The patient is still growing due to constitutional delay of growth and will reach his genetic length. **Conclusion:** Our cases show that in patients with panhypopituitarism much higher doses may be (initially) necessary to achieve appropriate growth velocity, normal IGF1 levels and normal length. We conclude that these patients need to be closely monitored and GH-dose must be increased if growth velocity and IGF1 levels are not within normal limits. Further studies are necessary to evaluate the reason for these findings.

P3-D1-818

Assessment of Compliance with GH Therapy

Chrysoula Drosatou, Feneli Karachaliou, Elpis-Ahina Vlachopapadopoulou, Vassileios Petrou, Eirini Kaloumenou, Stefanos Michalakos

Department of Endocrinology–Growth and Development, 'P & A Kyriakou' Children's Hospital, Athens, Greece

Background: Treatment compliance is one of the most important practical aspects in long-term treatments such as GH therapy. **Objective and hypotheses:** To evaluate the level of compliance and its association with duration of treatment and other demographic factors. **Method:** A prospective study with the use of validated questionnaires was conducted in the Endocrinology Department of one of the two main Pediatric Hospitals in Athens. The study included 66 children (43 boys), with mean age 13.2 (2.5) years and mean duration of treatment 3.5 (3.2) years. The level of compliance was considered to be high if the child missed less than three doses, medium between three and five doses and low more than five doses per month. χ^2 test was used for the comparisons of proportions while Mann–Whitney *U* test was used for continuous variables. Multiple regression analysis was used with stepwise methods. **Results:** The level of compliance with GH treatment was high in the majority of children (78.5%). In 66.2% of the cases, there was a loss of at least one dose and the number of missed injections was independently associated with father's educational level ($P=0.021$) and treatment duration ($P=0.015$). The most common reason for omitting a dose was being away from home (30.8%) followed by forgetfulness (24.6%). Only 54.6% of the cases were confident enough that they injected themselves properly. Children whose parents were satisfied from their training were five fold more likely to have a high level of compliance (odds ratio: 5.07, 95% CI: 1.2–25). Most of the children (76%) found the use of the injection device easy/very easy. These children had

almost double duration of treatment compared to the rest (4.0 (3.7) vs 1.9 (3.7), $P=0.025$). **Conclusion:** Level of compliance seems to be positively affected from parent's educational level and satisfaction from training and negatively affected from the increase in the duration of the treatment.

P3-D1-819

Body Composition in GH Deficient Children: Effects of GH Therapy and Comparison Between DXA and Anthropometric Data

Donatella Capalbo^a, Andrea Esposito^a, Manuela Cerbone^a, Martina Rezzuto^a, Rosita Di Pinto^a, Ciro Mainolfi^b, Mariacarolina Salerno^a

^aPediatric Endocrinology Unit, Department of Translational Medical Sciences, University 'Federico II' of Naples, Naples, Italy;

^bDepartment of Advanced Biomedical Sciences, University 'Federico II' of Naples, Italy, Naples, Italy

Background: GH deficiency (GHD) in adults has been consistently associated with increased adiposity and decreased lean mass. Data in childhood are still scanty and the most appropriate tools to assess body composition in these children remain to be established. **Objective and hypotheses:** To evaluate the effects of GHD and GH replacement therapy (GHRT) on body composition in GHD children and make a comparison between DXA and anthropometric measures in evaluating adiposity in these patients. **Method:** Twenty pre-pubertal children (10.36 ± 3.58 years) with GHD were evaluated before and after 2 years of GHRT. Patients underwent measurement of height, weight, BMI, waist circumference (WC), hip circumference, waist to hip (WHR), and waist to height ratio (WHtR). DXA analysis was performed to evaluate fat mass percentage (FM%) and lean mass percentage (LM%). Anthropometric measures were also evaluated in 20 healthy children, comparable for age, sex, and height with the patients. **Results:** At baseline WHtR was significantly higher in GHD children (0.49 ± 0.05 vs 0.44 ± 0.03 , $P < 0.01$), whereas no differences were found in BMI, WC, hip circumference, and WHR. GHRT was associated with a significant reduction in WHtR (0.45 ± 0.03 , $P < 0.01$). Furthermore, GHRT was associated with a reduction in FM% ($27.57 \pm 7.46\%$ vs 22.15 ± 6.49 , $P < 0.0001$) and an increase in LM% (68.62 ± 7.13 vs 74.62 ± 6.55 , $P < 0.0001$). Correlation studies revealed that WHtR significantly correlated with FM% and LM% evaluated by DXA at study entry ($r = 0.61$, $P < 0.01$; $r = -0.60$, $P < 0.001$ respectively) and after GHRT ($r = 0.61$, $P < 0.05$; $r = -0.58$, $P < 0.05$ respectively), whereas no correlations were found between DXA measurements and other parametric indices. **Conclusion:** Untreated GHD in children is associated with increased abdominal adiposity in comparison to healthy, matched controls. GHRT improves body composition increasing lean mass and decreasing fat mass.

In our study the evaluation of WHtR yielded to results comparable to DXA measurements thus leading to conclude that WHtR may represent a simple clinical tool which accurately reflects fat distribution.

P3-D1-820

Socioeconomic Factors Influence rhGH Treatment Adherence and its Response in Children

Joan Bel, María Martínez, Marta Murillo, Silvina de Pedro, Maria Luisa Granada

Hospital Germans Trias i Pujol, Badalona/Barcelona, Spain.

Background: GH treatment requires regular, daily s.c. injections for very long periods of time when not virtually for a lifelong period. The mean final height attained with GH therapy is influenced by poor adherence to treatment. **Objective and hypotheses:** The main aim of this study was to identify non-adherent patients to GH therapy and to determine the influence of compliance in response to the treatment (IGF1 serum levels and growth velocity). We also evaluated the influence of socioeconomic factors on the therapeutic adherence. **Method:** 165 children treated with rhGH were included. Age, gender, etiology, Tanner state, duration of treatment, growth rate, IGF1 serum values, daily dose and annual dose data were collected. The prescribed dose and the dose administered by the hospital pharmacy were compared. Poor adherence was defined as a rate below 92% of prescribed dosage. A subgroup of 106 patients (53 poor-adherent patients and 53 good-adherent ones) was asked to answer a questionnaire to assess social and environmental factors. **Results:** 34% of the patients showed moderate-low adherence to rhGH treatment. There was a decrease in adherence associated with age ($P < 0.04$) and treatment duration ($P < 0.001$), but no differences were found in relation to GH deficiency diagnosis. The median HV-SDS (height velocity SDS) in patients who showed good adherence to therapy was higher (1.29 vs 0.47) when compared to the group of poor adherence ($P < 0.001$). Adherence was significantly related to IGF1 (1.3 vs 0.4 ; $P < 0.001$) and with the level of education of the mother ($P < 0.007$). **Conclusion:** One-third of our patients presented poor adherence to GH therapy, which results in suboptimal growth. IGF1 levels could be helpful to identify patients with lower adherence. Physicians should pay special attention to certain characteristics of the patient and their environment to encourage desirable therapeutic compliance.

P3-D1-821

Study of GH Receptor exon 3 Polymorphism in Children With Prader-Willi Syndrome

Feihong Luo, Wei Lu, Zhou Pei, Zhangqian Zheng

Children's Hospital of Fudan University, Shanghai, China

Background: Prader-Willi syndrome (PWS) is a genomic imprinting disorder due to loss of paternally expressed genes in the 15q11-q13 region and characterized by hypotonia, a poor suck, hypogonadism, GH deficiency (GHD), learning and behavioural problems. GH acts as a ligand for the GH receptor (GHR) coded by a gene polymorphism for an exon-3 deletion (d3) seen in about 50% of Caucasians and associated with an increased response to GH (GH) therapy. **Objective and hypotheses:** We designed the present study by analyzing those polymorphisms in Chinese PWS

patients. By comparing our results with previous studies, we aimed to identify the association between the effect of recombinant human GH (rhGH) and genetic polymorphism in Chinese PWS patients. **Method:** We designed the present retrospective study involved 57 PWS patients diagnosed genetically. We used a multiplex PCR method for the genotyping of polymorphisms in exon 3 of GHR gene. We then compared out genotype results with data from previous studies on patients with obesity or short stature. **Results:** In our PWS patient cohort, the genotype frequencies of fl/f, fl/d3, and d3/d3 in GHR exon 3 (70%, 23%, and 7% respectively) were not different from general population in Chinese. However the frequencies of d3/d3 and fl/d3 genotype were lower than European general population. We did not find difference between genotype distribution when compared either with patients with idiopathic short stature and Turner syndrome or with patients with obesity and overweight. However, difference in genotype distribution was found in comparison with GHD patients. **Conclusion:** No differences in distribution of GHR exon 3 polymorphisms were found between Chinese PWS patients and general population. Less common phenotype of short stature manifested among Chinese PWS patients could be due to the lower frequency of d3 genotype in GHR gene.

P3-D1-822

Auxological Evaluation of 'Non-Identical Twins'

Raluca-Monica Pop, Marian Pop, Ionela Pascanu

University of Medicine and Pharmacy Tirgu Mures, Tirgu Mures, Romania

Background: Multiple external influences have proved to be of importance in auxology. Sub-group analysis can identify specific factors involved in normal children development. **Objective and hypotheses:** The main objective of the study was to identify differences in development in children born the same day from different parents. Our hypothesis was that there are identifiable general factors that predict the growth of a child. **Method:** Type of study: cross-sectional; target population: children aged 6–15 born on the same day. Sample: non-randomized, composed of 377 children from four urban and four rural areas of Mures county. Inclusion criteria: identical birth date; exclusion criteria: children born small for gestational age, cardiac, renal disorders, malabsorption, and rickets. Variables: sex, environment, birth length, birth weight, height, weight, waist, arm span, sitting height, and breastfeeding period. The study was approved by the Local Ethics Committee and a written consent was obtained for every child. Children refusing the evaluation were excluded from the final analysis. Statistical analysis used M.O. Excel and Graph Pad InStat with a level of significance 0.05. **Results:** 64 pairs of the same sex were identified; children from rural areas were significantly taller than those from urban areas ($P < 0.001$), regardless of the sex. The environment had no influence on other anthropometric variables. Breastfeeding according to WHO recommendations had no significant influence on the height and weight, even after adjusting for sex and environment. No other anthropometric measurements were influenced by the environment or the breastfeeding status. **Conclusion:** Children born on the same day tend to be taller in rural areas but do not differ in other anthropometric factors: weight, waist, arm span, and sitting height.

P3-D1-823

Three-Years Height Outcome During rhGH Therapy in Severe Short Subjects Affected by Skeletal Dysplasias

F Massart^a, L Gnesi^a, A Baggiani^b, M Miccoli^b

^aPediatric Unit, Maternal and Infant Department, St Chiara University Hospital of Pisa, Pisa, Italy; ^bEpidemiology Unit, Department of Experimental Pathology M.B.I.E., University of Pisa, Pisa, Italy

Background: Skeletal dysplasias comprise heterogeneous disorders often characterised by short stature with abnormalities of one or more of epiphysis, metaphysis or diaphysis. Over 200 types of skeletal dysplasias are identified, most of which are autosomal dominantly inherited. Actually, surgery has attempted to correct bone deformities but drug therapy for improving their severe short stature has been rarely attempted. **Objective and hypotheses:** Administration of recombinant human GH (rhGH) increases height (Ht) among subjects with achondroplasia and hypochondroplasia, who are the most common short-limb dwarfism. For other skeletal dysplasias, however, the efficacy of rhGH remains substantially unknown for disorder rarity. **Method:** After thorough search of pertinent English-language literature, our meta-analysis examined the rhGH therapy efficacy to improve height growth over 3-year period in short stature subjects with skeletal dysplasia. From eligible studies, we excluded data regarding ACH and HCH subjects. **Results:** In total sample, mean Ht at rhGH therapy start (rage dosage 0.23–0.46 mg/kg per week) was subnormal ($n = 79$; Ht -3.685 SDS (95% CI -3.899 to -3.472)) in all the studies. Ht scarcely improved during 12 months of rhGH treatment with no catch-up growth ($n = 79$; Ht -3.551 SDS (95% CI -3.737 to -3.366); $P < 0.0001$). Then, Ht trend appeared constant at 24 months ($n = 39$; -3.047 SDS (95% CI -3.439 to -2.655)) and until 36-months ($n = 21$; -2.513 SDS (95% CI -2.702 to -2.323)). Episodic adverse effects were reported. **Conclusion:** Although our meta-analysis does not indicate convincing benefits of rhGH treatment in severe short individuals with skeletal dysplasias, larger randomized studies are needed to assess the Ht gain in regard to higher rhGH dosages or longer treatment. Furthermore, careful consideration of indications for rhGH administration as surgery therapy adjuvant is crucial when attempting to treat advanced bone deformities.

P3-D2-823

Correlation Between Initial Treatment Effect of Recombinant Human GH and Exon 3 Polymorphism of GH Receptor in Chinese GH Deficiency Children

Zhangqian Zheng^a, Linfeng Cao^b, Zhou Pei^a, Feihong Luo^a, Dijing Zhi^a, Zhuhui Zhao^a, Rong Ye^a, Ruoqian Cheng^a, Xiaojing Li^a

^aChildren's Hospital of Fudan University, Shanghai, China;

^bInstitute of Pediatrics of Fudan University, Shanghai, China

Objective and hypotheses: To investigate the frequency distribution of exon 3 deleted (d3-GHR) genetic polymorphism of GH receptor (GHR) in GH deficient (GHD) Chinese children and

to explore the correlation between the growth promoting effects of recombinant human GH (rhGH) and exon 3 genetic polymorphism of GHR in GHD children. **Method:** 111 GHD (excluded small for gestational age) children were treated with rhGH (0.20 mg/kg per week) for 6 months. The body height (Ht), body weight, bone age (BA) and growth velocity (GV) were measured before and after 6 months of treatment. The d3-GHR and full length GHR (fl-GHR) were analyzed to detect the frequency distribution of two isoforms and their influence on growth promoting effect of rhGH. **Results:** The frequencies of fl/fl, fl/d3 and d3/d3 GHR genotypes were 67.6, 18.9 and 13.5%. After 6 months of GH therapy, there were significant differences of Δ GV (Δ GV: 10.77 ± 3.40 vs 12.18 ± 3.08 cm/year) ($P < 0.05$) and Δ Ht (Δ Ht: 5.38 ± 1.70 vs 6.09 ± 1.54 cm) ($P < 0.05$) were found among GHD children with different genotypes (fl/fl vs fl/d3 and d3/d3). **Conclusion:** The frequencies of fl/fl, fl/d3 and d3/d3 GHR genotypes were 67.6, 18.9 and 13.5%. After 6 months of GH therapy, there were significant differences of Δ GV (Δ GV: 10.77 ± 3.40 vs 12.18 ± 3.08 cm/year) ($P < 0.05$) and Δ Ht (Δ Ht: 5.38 ± 1.70 vs 6.09 ± 1.54 cm) ($P < 0.05$) were found among GHD children with different genotypes (fl/fl vs fl/d3 and d3/d3).

P3-D2-824

GH Deficiency in a Case with Neurofibromatosis-Noonan Syndrome

Dogus Vurallı^a, E Nazli Gonca^a, Dominique Vidaud^b, Z Alev Ozon^a, Ayfer Alikasifoglu^a, Nurgun Kandemir^a

^aDepartment of Pediatric Endocrinology, Hacettepe University, Ankara, Turkey; ^bGroupe Hospitalier Cochin-Broca-Hôtel-Dieu Service de Biochimie et Génétique Moléculaire, Paris, France

Background: Neurofibromatosis-Noonan Syndrome (NFNS) is a distinct entity which has variable features of both neurofibromatosis 1 (NF1) and Noonan syndrome (NS). In majority of cases NF1 mutations have been demonstrated. Short stature is one of the major causes for these patients requiring medical attention. GH deficiency (GHD) may accompany in some cases with NF1 or NS cases, however there are rare case reports on NFNS receiving GH therapy. **Objective and hypotheses:** We hypothesized that GHD may accompany NFNS and the patients with NFNS should be evaluated for GHD. **Method:** A case with NFNS having NF1 gene defect and fulfilling the criteria of GHD is presented. **Results:** A 13-year-old girl presented with short stature. Physical examination revealed multiple café-au-lait spots, axillary freckling, relative macrocephaly suggesting NF1, and dysmorphic facial features, short and webbed neck, low posterior hairline, cubitus valgus, brachy and clinodactyly, widely spaced nipples suggesting NS. Her height SDS was -4.4 and height velocity SDS -3.4 . Puberty was at Tanner stage 3. Karyotype analysis was 46,XX. Her father also had features of both NF1 and NS. The genetic analysis of the patient and the father both revealed a truncating mutation in the NF1 gene c.7846C>T(M82814), p.Arg2616X (AAA59924). Peak GH response was 3.9 ng/ml in stimulation tests; IGF1 and IGFBP3 SDS levels < -3 . She had neither hypothyroidism nor adrenal insufficiency. MRI of cranium showed lesions of NF in cerebral

peduncles and globus pallidus, and pituitary gland was hypoplastic. Since the patient fulfilled the criteria of GHD, GH treatment was started. Height velocity during the first year of GH treatment was 8 cm/year. **Conclusion:** Short stature is a feature of NFNS, however in some cases it can be caused by GHD. GH therapy may be beneficial in patients with NFNS who are diagnosed as GHD.

P3-D2-825

Monitoring of GH Treatment by the Electronic Auto-Injection Device Easypod™ Allows to Improve the Outcome and Maximize Adherence in Patients with Generally High Adherence Rates

Klaus Hartmann

Medical Center of Adolescence and Childhood, Frankfurt, Germany

Background: We recently described that 27.8% of patients treated with recombinant human GH (r-hGH) using the easypod had an adherence (AD) rate of $< 85.7\%$ i.e. missing one r-GH dose per week. Overall AD of all investigated patients during the first 2 years of treatment was generally high (mean 90.2%). **Objective:** To evaluate the importance of high AD rate of r-GH administration over the first 2 years of r-hGH treatment on growth velocity and increase of height-SDS in patients with GH deficiency (GHD) and small for gestational age (SGA). **Methods:** Retrospective, observational, open-label, non-controlled, multi centre study in patients diagnosed as GHD or SGA. Patients were treated with r-hGH using the easypod injection device. **Results:** 53 patients (36 GHD and 17 SGA), mean chronological age (CA) 10.7 ± 3.7 years (mean \pm s.d.)(y) were treated with an average prescribed r-hGH dose of 32.9 mg/kg per day. (In consideration of the AD the real administered GH dose was 28.7 ± 5.4 ng/kg per day. 40 patients 25 GHD and 15 SGA), mean CA 9.6 ± 3.5 year had an AD of $> 85.7\%$ and received an administered GH dose of 30.2 ± 4.8 ng/kg per day. After 2 years of treatment these patients showed a GV of 8.2 ± 1.8 cm/year and an increase of height-SDS of 0.99 ± 0.69 . 13 patients with an AD $< 85.5\%$, mean 14.2 ± 1.4 year, received 23.9 ± 4.0 ng/kg per day GH and had a GV of only 7.6 ± 2.2 cm/year with an increase of height SDS of 0.76 ± 0.66 . **Conclusion:** Easypod is an important device that allows to achieve an accurate recording of GH dose and adherence rate and maximize the impact of adherence on the outcome of GH treatment in GHD and SGA patients.

P3-D2-826

Usability and Safety of FlexPro® PenMate® in Patients, Caregivers and Healthcare Professionals (HCPs)

Yanhong Wen^a, Conny Nøhr Korsholm^b, Rasmus Klinck^a, Anne-Marie Kappelgaard^b

^aNordisk A/S, Hillerød, Denmark; ^bNovo Nordisk A/S, Søborg, Denmark

Introduction: FlexPro[®] PenMate[®] (PenMate[®]) (Novo Nordisk A/S, Denmark) aims to reduce needle anxiety by hiding the needle during injection. This usability test validated the safe and effective use of PenMate[®] and the instructions for use (IFU) in patients with growth hormone (GH) deficiency (GHD), Turner syndrome (TS), Noonan syndrome (NS) and children born small for gestational age (SGA). **Methods:** Participants were selected according to FDA Human Factors Engineering (HFE) guidelines: children/adolescents (10–17 years) with GHD/SGA ($n=16$), TS/NS ($n=15$), adult patients/caregivers of patients with GHD/SGA/TS/NS (≥ 18 years) ($n=19$), and HCPs ($n=15$) managing patients with GHD/SGA/TS/NS. All performed four scenarios after training: first-time use of PenMate[®]; replace a depleted FlexPro[®] pen in PenMate[®]; check GH and wipe the front stopper; and one IFU comprehension scenario. Participants completed post-test questionnaires on PenMate[®] use, training and IFU. Questionnaires used a seven-point scoring scale: 1 = strongly disagree, 7 = strongly agree. Task failures, use errors, close calls and operational difficulties were recorded by observers. Root causes of all observations were evaluated by subjective feedback from participants. **Results:** Participant demographics (mean [range]) were: GHD/SGA (88% male; age 14 years [10–16]), TS/NS (100% female; age 14 years [11–17]), adult patients/caregivers (58% female; age 44 years [18–71]), HCPs (80% female; age 44 years [25–59]). No task failures, potential serious or non-serious errors were recorded. Eighteen handling-use errors (committed by 14 participants) (no potential for harm), 11 close calls (committed by 11 participants) and 19 operational difficulties (committed by 17 participants) were recorded. Participants provided positive ratings for PenMate[®] use, training and IFU (mean ratings, 6–7). Participants correctly interpreted five out of six IFU excerpts. **Conclusions:** PenMate[®] was considered easy to use and the IFU was considered helpful. No potentially serious or non-serious user errors were recorded. Handling use errors were not related to PenMate[®].

P3-D2-827

Impairment of Glucose Metabolism in GH Deficient Children Under GH Replacement

Maria Xatzipsalti^a, Vasiliki-Ioanna Mitravela^a, Ioulia Polichroni^a, Dimitrios Delis^b, Andriani Vazeou^b, Lela Stamogiannou^a

^aA¹ Department of Pediatrics, P&A Kyriakou Children's Hospital, Athens, Greece; ^bA¹ Department of Pediatrics, Diabetes Center, P&A Kyriakou Children's Hospital, Athens, Greece

Background: GH replacement therapy in children with GH deficiency (GHD) mainly promotes linear growth. There are few studies fully analyzed the metabolic consequences of GH therapy. **Objective and hypotheses:** To study the effects of GH replacement therapy on glucose metabolism in patients with GHD. **Method:** Sixty two children {mean age (s.d.) 8.6 (3.3) years; 35 boys, 10 SGA, 50 prepubertal who were under treatment with GH (for a median duration of 2.5 years (range 0.43–10.5) were studied. Height SDS was -1.9 (0.71) and BMI SDS -0.35 (1.2) before treatment. Fasting blood glucose, HbA1c, lipid profile was evaluated annually at 0, 1, 2, and 3 years. **Results:** Fasting blood glucose levels were significantly increased during GH replacement therapy for 3 consecutive years within the normal range. (Mean \pm s.d.) $81.8 \pm$

11.34 vs 88.0 ± 8.94 vs 88.8 ± 8.3 vs 95.0 ± 10.5 at 0, 1, 2, and 3 years after GH treatment ($P=0.005$ for 0 vs 1, $P=0.002$ for 0 vs 2, $P<0.0005$ for 0 vs 3 years, $p=0.032$ for 1 vs 3 years). HbA1c was not different among the different groups. The difference in blood glucose was not related to BMI SDS and to Tanner stage. Cholesterol levels were increased above 170 mg/dl in 45% of treated patients, however, triglyceride and HDL levels were within normal range. **Conclusion:** Children with GHD who are on GH replacement show an increase in their fasting blood glucose over the years of treatment possibly due to GH therapy, although this increase was within the normal range in this group of patients.

P3-D2-828

Growth Response After 1 Year of GH Treatment in Children Born Small for Gestational (SGA) Without GH Deficiency: our Experience

Giisella Garbetta, Gabriella Pozzobon, Sara Osimani, Chiara Damia, Maria Piera Ferrarello, Andrea Voto, Giulia Pruccoli, Cristina Partenope, Giovanna Weber, Giuseppe Chiumello

Department of Pediatrics, San Raffaele Scientific Institute, Milan, Italy

Background: Many studies have shown that GH therapy can increase final height in children born SGA. Adult height and growth velocity can be improved in these subjects even if there is not a deficiency of endogenous GH (GHD). **Objective and hypotheses:** We aimed to analyze growth response after 1 year of GH treatment in children born SGA without GH deficiency. **Method:** Ten patients (six M, four F) born SGA (according to Gagliardi *et al*) treated with GH for 1 year (mean GH dose: 0.2 mg/kg per week) were included. Eight patients were prepubertal, two patients were pubertal stage 2 (according to Tanner). One patient showed clinical aspects suggestive for Silver–Russell syndrome. Two patients were late preterm (34 and 35 GA). GH stimulation tests excluded GH deficiency. **Results:** Mean age at start of treatment was 8.5 ± 3.4 years. Mean height at start was -3.17 ± 0.49 SDS. After 1 year of treatment, change in height SDS (Δ HtSDS) was $+0.50 \pm 0.22$ SDS. Mean height velocity improved from -1.5 ± 0.92 SDS to $+2.8 \pm 2.24$ SDS. Mean height corrected for mid-parental height at start was -2.05 ± 0.60 SDS, after treatment was -1.55 ± 0.69 SDS. **Conclusion:** GH treatment in children born SGA without GHD improves height and height velocity after 1 year. When anamnestic and auxological data are suggestive of growth impairment in SGA, GH treatment must be started as soon as possible to optimize growth outcomes.

P3-D2-829

Cross-Sectional and Prospective Study of the Effects of GH Therapy on Metabolic Panel in Children with GH Deficiency

Vincenzo Ramistella, Malgorzata Wasniewska, Mariella Valenzise, Tommaso Aversa, Stefania Arasi, Maria Rosa Velletri, Filippo De Luca

Department of Pediatrics, Gynecology, Microbiology and Biomedical Sciences, University of Messina, Messina, Italy

Background: Numerous studies have shown that GH, in addition to promoting linear growth, exerts a key role in many metabolic processes. However, there are only few studies aiming at evaluating the metabolic panel of children with GH deficiency (GHD). The aims of the study were: to verify the presence of metabolic alterations in GHD children in comparison with age-matched controls and to check the possible effects of 2 year GH therapy on the metabolic parameters in GHD. **Study design:** Cross-sectional and prospective; one center experience. **Population and methods:** We enrolled 32 pediatric GHD patients (group A) and 33 sex- and age-matched healthy controls (group B). Baseline serum assays (lipid, insulin, glucose) were performed in both groups. GHD children underwent replacement therapy with GH. The same assays were repeated after 12 and 24 months of GH treatment. **Results:** No differences, in basal assays were found between the two groups. In group A, after initiation of GH, there was a significant increase of basal insulin and HOMA-insulin resistance (IR) index ($P < 0.001$). In children with severe GHD (peak GH < 3 ng/ml), after beginning of GH therapy a significant improvement in the lipid profile was found ($P < 0.05$). **Conclusions:** (i) At the time of diagnosis GHD children had a metabolic picture that was not different from non-GHD group; (ii) in children with severe GHD, the metabolic profile showed a trend towards at improvement after the initiation of replacement therapy with GH, with beneficial effects in terms of total cholesterol, LDL cholesterol and cardiovascular risk indices; (iii) GHD patients with unfavorable metabolic profile (high BMI and hypercholesterolemia) need a monitoring of glucose metabolism by periodical evaluations of insulin and HOMA – IR.

P3-D2-830

Prader-Willi Syndrome and GH Therapy: valuable Effects and Adverse Events

Magdalena Wilk^b, Katarzyna Wzorek^b, Ewa Tobór^b, Barbara Dejniak^b, Anna Wedrychowicz^a, Katarzyna Dolezal-Oltarzewska^a, Agata Zygmunt-Gorska^a, Jerzy Starzyk^a

^aDepartment of Pediatric and Adolescent Endocrinology Polish-American Pediatric Institute, Medical College, Jagiellonian University in Cracow, Cracow, Poland; ^bStudents' Scientific Group, Department of Pediatric and Adolescent Endocrinology, Polish-American Pediatric Institute, Medical College, Jagiellonian University in Cracow, Cracow, Poland

Background: Prader-Willi syndrome (PWS) is a genetic disorder with hypothalamic-pituitary dysfunction, in which obesity, excess fat to lean body mass cause metabolic complications. For the purpose of these disorders normalization, PWS patients have been treated with recombinant human GH (rhGH). Long-term tolerance in PWS children treated with rhGH is not well known and the data are still required. **Objective and hypotheses:** To evaluate effects of rhGH treatment in PWS patients. **Method:** Twelve patients (pts) with genetically confirmed PWS: eight boys, median age 13.4 ± 5.64 years (5–17 years), treated with rhGH in 2013, were included to the study. Treatment duration was 5.9 ± 2.62 years (2–11 years). The study was conducted on a basis of data from patients medical records. **Results:** During treatment weight SDS increased from 0.16 to 0.93 and height SDS from -1.38 to 0.55. Weight SDS raised after

median 3 years of treatment (to 1.15) and noted downturn (0.93) during next year. BMI-SD at the beginning of the treatment was 1.31, now totals 1.29. Most pts required decreasing of rhGH dose: 8/12 due to high IGF1 values, 2/12 due to glucose intolerance and one pt due to the rapid acceleration of growth. One pt discontinued therapy due to an excessive increase in body weight (weight-SDS from 0.99 to 2.53 during 3 years). Mean pts HbA1c level was 5.37% (57 mmol/mol), no diabetes was observed. Glucose intolerance was observed in two pts, who developed obesity (BMI-SD from 1.025 to 2.522 during 6 years of treatment and from 0.01 to 0.556 during 7 years), Lipids profiles was within normal ranges in all cases except this one who discontinued rhGH therapy. In 2/12 pts tonsillar hypertrophy and in 1/12 pt the progression of scoliosis were observed. **Conclusion:** In PWS pts treated with rhGH, BMI-SD should be strictly monitored, not to allow develop obesity and severe metabolic disorders as a result.

P3-D2-831

Recovery of Central Fever After GH Therapy in a Patient with GH Deficiency Secondary to Posttraumatic Brain Injury

Hale Unver Tuhan, Ahmet Anik, Gonul Catli, Ayhan Abaci, Ece Bober
Department of Pediatric Endocrinology, Faculty of Medicine, Dokuz Eylul University, Balcova, Turkey

Background: Hypopituitarism, which is a heterogeneous disorder with diverse underlying etiologies, has been increasingly recognized following traumatic brain injury. **Objective and hypotheses:** In some patients, central fever associated with GH deficiency have been rarely reported. In this case report we presented a case with central fever associated with GH deficiency. **Method:** A 7-year-old boy, who was involved in a traffic accident, presented with coma. Multiple skull fractures, hydrocephalus, pneumocephalus and subarachnoid hemorrhage were present on cranial computed tomography. **Results:** On the second day following head trauma, he was diagnosed with central diabetes insipidus (DI), and desmopressin treatment was initiated. Owing to the presence of DI, anterior pituitary functions were investigated and revealed central hypothyroidism and hypocortisolism. Treatment with hydrocortisone and L-thyroxine, was initiated. During the past 6 months, he also had recurrent episodes of a prolonged febrile illness of unknown origin. All investigations related to infectious, autoimmune and neoplastic diseases were negative and the fever was considered to be of central origin. On follow-up, the patient had a decreased height velocity together with reduced IGF 1 and IGFBP 3 concentrations and insufficient growth hormone (GH) responses in two provocative tests thus GH deficiency was confirmed. He was started on rhGH at a dose of 25 µg/kg per day. On the fifth day of the rhGH treatment, his fever was controlled. **Conclusion:** It has recently been shown that patients with GH deficiency have a reduced sweating capacity which increases the risk of developing hyperthermia. This case report describes a patient with prolonged febrile illness of unknown origin, who presents with GH deficiency possibly due to a previous head trauma. With this report, we would like to emphasize that in cases with a fever of unknown origin and traumatic brain injury, GH deficiency should be considered, and complete pituitary evaluation should be performed.

P3-D2-832

The Impact of GH Replacement Therapy in Children Born Small-for-Gestational-Age: growth Response and Safety Profile

Irina Oana Chifu, Ioana Bodescu, Ioana Vasiliu, Jeanina Idriceanu, Alina Fadur, Ana Hreniuc, Maria Christina Ungureanu, Letitia Leustean, Voichita Mogos, Carmen Vulpoi

University of Medicine and Pharmacy 'Gr.T. Popa', Iasi, Romania

Background: Children born small-for-gestational-age (SGA) have a birth weight below 2,500 g at a gestational age over 37 weeks or a birth weight or length below the 3-rd percentile for gestational age. They usually recover growth during the first 6–12 months of life, but if not so, it is unlikely the recovery to happen after the age of two unless GH replacement therapy is initiated. **Objective:** The aim of this study was to evaluate the 1-st year growth response obtained with recombinant rhGH treatment in children with SGA. **Methods:** We performed a prospective study to analyse the pattern of growth in ten prepubertal children (seven boys and three girls) with SGA, in the first year of treatment with rhGH. **Results:** All children met the criteria to receive rhGH treatment. Chronological age at the initiation of therapy was between 3 and 9 years old. The mean dose of rhGH the children received was 0.036 mg/kg per day. In the 1-st year of treatment, the mean height velocity was 0.67 cm/month, similar in boys and girls (0.65 cm/month in girls, 0.68 cm/month in boys, $P < 0.05$), with a medium height gain of 8 cm (± 2.5). Height s.d. of subjects improved throughout the studied period and the medium height increase was approximately +0.5 s.d. in the first year. The increase in IGF1 levels during treatment was positively correlated to heights s.d. gain ($r = 0.415$, $P = 0.006$). No impairments in hematologic and metabolic profiles were observed during treatment and the thyroid function maintained normal. **Conclusion:** Growth promoting effects of rhGH therapy in short children born SGA were confirmed, with a good safety profile in the 1-st year of treatment.

P3-D2-833

GH Treatment in 50 Child with Short Stature: Lebanese Experience

Elie Abi Nader^{a,b}, Imad Melki^a, Carlo Akatcherian^a, Bernard Gerbaka^a, Eliane Khallouf-Callas^a

^aHotel-Dieu de France Hospital, Beirut, Lebanon; ^bNecker Enfants Malades Hospital, Paris, France

Background: GH treatment in childhood is proven to increase adult final height in many indications. In Lebanon, no other study was done to evaluate the response to GH treatment. **Objective and hypotheses:** Identify the prevalence of each indication and evaluate the annual response to treatment based on growth velocity, bone age (BA), bone age on height age (BA/HA) and bone

age on chronological age (BA/CA). **Method:** The population is 50 child, presented at Hotel-Dieu de France hospital for short stature. Information is collected on diagnosis and annual evaluations during treatment: weight, height, value of IGF1 and BA. **Results:** GH deficiency (CGHD and PGHD) is the main indication (50%) followed by intrauterine growth retardation (IUGR) (36%), idiopathic short stature (ISS) (8%) and lastly comes Turner syndrome (6%). The age of onset of treatment is earliest in IUGR where stature delay is between -2.8 and -3 SDS and their treatment was for the longest period in our study. BA/HA and BA/CA ratios are lowest in IUGR (< 1) where it is expected the best response to treatment. Growth velocity during the first year of treatment is 11 cm in CGHD followed by ISS (10.3 cm). Catch-up growth after 2 years of treatment is the best in Turner patients ($+1.7$ SD) followed by IUGR ($+1.5$ SD). It gradually decreases with time in all indications. It is the best during the first year of treatment in children under 6 years of age compared to children over 6 years. No adverse effects were noted in our population. **Conclusion:** The response to GH treatment is good in its various indications, especially in children treated early. A study on the national level should be considered to identify the various factors that influence final height in children treated with GH.

P3-D2-834

Effectiveness of GH Therapy in Children with Short Stature and Decreased GH Peak in Stimulating Tests is Independent from GH Secretion After Falling Asleep

Maciej Hilczer^{a,b}, Joanna Smyczynska^a, Renata Stawerska^a, Andrzej Lewinski^{a,c}

^aDepartment of Endocrinology and Metabolic Diseases, Polish Mother's Memorial Hospital - Research Institute, Lodz, Poland;

^bDepartment of Pediatric Endocrinology, Medical University of Lodz, Lodz, Poland; ^cDepartment of Endocrinology and Metabolic Diseases, Medical University of Lodz, Lodz, Poland

Background: GH deficiency (GHD) is routinely diagnosed on the basis of decreased GH peak in two stimulating tests (GHST). In Poland, few years ago, an assessment of nocturnal GH secretion after falling asleep (noctGH) has been introduced as a screening test in diagnosing GHD. **Objective and hypotheses:** The aim of the study was to assess GH therapy effectiveness in children with decreased GHST with respect to noctGH. **Method:** Retrospective analysis comprised 150 children with GHST in standard tests with clonidine and with glucagon < 10.0 ng/ml, including 116 patients with noct GH < 10.0 ng/ml (GHD1 Group) and 34 patients with noctGH > 10.0 ng/ml, recruited prior to the introduction of screening test (GHD2 Group). First-year response to treatment: height velocity (HV) increase and IGF1 SDS increase was assessed in all the patients, while final height (FH) was attained by 32 patients in GHD1 Group and 16 ones in GHD2. **Results:** In GHD1 Group, GH peak in stimulating tests (GHST) was 6.9 ± 2.3 ng/ml, height SDS before treatment (hSDS-0) was -2.95 ± 0.85 ,

in 1st year of treatment HV increased from 3.8 ± 1.4 to 9.8 ± 2.0 cm/year, IGF1 SDS increased from -1.92 ± 1.11 to 0.44 ± 0.87 , FH SDS was -1.23 ± 0.68 . In GHD2 Group, GHST was 8.2 ± 1.9 ng/ml, hSDS-0 was -2.84 ± 0.62 , HV increased from 3.6 ± 1.2 to 10.1 ± 2.2 cm/year, IGF1 SDS increased from -1.84 ± 1.18 to 0.70 ± 0.92 , FH SDS was -1.34 ± 0.64 . The differences in age, GH dose, therapy duration and all the analysed indices of GH therapy effectiveness between the Groups were insignificant, despite normal noctGH and significantly higher GHST ($P < 0.001$) in GHD2 Group. **Conclusion:** Assessment of GH secretion after falling asleep should no longer be the screening procedure in diagnosing GHD in children with short stature. Normal result of this test is not the sufficient basis for disqualification children with decreased GH peak in stimulating tests from GH therapy.

P3-D2-835

An Unusual Case of a Child with GH Deficiency and Arnold-Chiari Malformation Type I

Maria Xatzipsalti^a, Ioulia Polychroni^a, Andriani Vazeou^b, Lela Stamogiannou^a

^aA' Department of Pediatrics, P&A Kyriakou Children's Hospital, Athens, Greece; ^bDiabetes Center, A' Department of Pediatrics, P&A Kyriakou Children's Hospital, Athens, Greece

Background: Arnold-Chiari malformations (CM), types I-IV, refer to a spectrum of congenital hindbrain maldevelopments characterized by downward herniation of the cerebellar tonsils. CM-I is defined as tonsillar herniation of 3–5 mm below the foramen magnum and is the most common and the least severe of the spectrum. **Objective and hypotheses:** Children with CM-I usually are asymptomatic and often diagnosed in adulthood, therefore early presentation of the disease with GHD is unusual. **Method:** We report a case of a 3.5 years old girl who was referred to our Department because of short stature and vomiting. She had a history of full term normal delivery without any trauma, birth weight 2510 g (-2.85 sds) and length 48 cm (-2.08 sds). At the age of 7 weeks she was hospitalized because of afebrile seizure with normal electroencephalography. She had also reduced food intake and frequent vomiting since infancy. A thorough investigation of malabsorption (hematologic and serum biochemical tests, barium swallow and esophagram test) was normal. **Results:** At the age of 3.5 years she was referred to us because of short stature. Her height was 90 cm (<3 rd percentile), her weight 13 kg (15th percentile), growth rate 3.9 cm/year and bone age 3 years. GH peak levels in two provocative tests were both <10 ng/ml and the rest endocrine evaluation revealed only increased TSH 5.6 μ IU/ml with normal autoantibodies. A brain magnetic resonance showed pituitary hypoplasia and CM-I. At the age of 4 years she presented with dysphagia and frequent mild headaches and a decompressive surgery was performed to her due to syringomyelic cavity. **Conclusion:** We report an unusual case of a toddler female with GHD and CM-I who presented with neurologic symptoms and growth retardation very early in life in contrast to majority of cases.

P3-D3-836

What is the Profile of Gigantism: Seven Observations

Samia Achir, Mourad Semrouni

Pierre and Marie Curie Center, Algiers, Algeria

Background: Gigantism is a condition characterized by excessive growth and height significantly above average; it is usually caused by a tumor on the pituitary gland. In some cases the condition can be passed on genetically through a mutated gene. **Objective and hypotheses:** Describe clinical, hormonal, and morphological profile of seven children with gigantism. Mean age = 14 years (9–16), age of onset of symptoms 12 years. Tall stature (50%), and brain tumor syndrome (50%). Discrete dysmorphic syndrome ($n=1$). Delayed puberty ($n=4$) a McCune-Albright syndrome ($n=1$), no signs of MEN type 1. **Method:** Laboratory studies used in the diagnosis: of gigantism: OGTT/GH and IGF1 of hypopituitarism: cortisol, ACTH, FT₄, TSH, FSH, LH, E₂, TESTO, PRL. Imaging studies include Magnetic resonance imaging (MRI): to image pituitary adenomas. **Results:** Average of GH = 110 μ UI/ml and high IGF1. Hyperprolactinemia ($n=2$), gonadal failure ($n=3$), hypothyroidism ($n=1$ case), and normal cortisol level ($n=7$). Hypothalamic-pituitary - MRI: locally invasive pituitary adenoma ($n=4$) and aggressive ($n=2$). Treatment: surgery ($n=6$), second surgery ($n=3$), surgery + radiotherapy ($n=4$), surgery + radiotherapy + somatostatin analogs (AS) ($n=3$), surgery + AS ($n=1$ case), and AS ($n=1$). **Conclusion:** Gigantism is a rare disease of the child. A monitoring of growth allows early diagnostic and early treatment; because the Treatment is difficult and requires a combination of several treatment arms. In addition there is no indication of AS before age = 15 years. The genetic study is required.

P3-D3-837

GH Treatment in Dent's Disease: a Case Report

Simona Falcone, Elisa Guidoni, Giovanna Municchi, Maddalena Cioni

University of Siena, Siena, Italy

Background: Dent's disease is an X-linked recessive proximal tubulopathy characterized by low molecular weight proteinuria, hypercalciuria, nephrocalcinosis, nephrolithiasis, and progressive renal failure. Growth retardation, due to resistance to GH action is a feature commonly associated with Dent's disease. **Case report:** We describe a boy diagnosed with Dent disease, treated with recombinant human GH. He was initially referred at 6 years of age for genetic evaluation due to the presence of dysmorphism. Pediatric and nephrologic evaluations led to the diagnosis of Dent disease 1, caused by an inactivating mutation in CLCN5 gene. The boy had also mild mental retardation and, in addition to the typical renal alterations of the syndrome, presented short stature (-3 SDS) and IGF1 levels. GH therapy was started at a chronological age of 11 years and 6 months. Bone age was

9 years. After 6 months of GH treatment (40 mcg/kg per day), height increased from 124 cm (-3.6 s.d.) to 128.5 cm (-3.3 s.d.), IGF1 levels increased from 57.8 ng/ml (88–770) to 150 ng/ml and creatinine clearance improved from 28 cc/ml (70–120) to 30 cc/ml. Our preliminary findings showed beneficial effects of GH treatment on growth velocity and renal function parameters. Further follow-up is needed in order to confirm these preliminary positive results. **Conclusion:** GH treatment should be considered in children with Dent's disease and short stature because it may have positive effects on longitudinal growth and renal function parameters. To the best of our knowledge, only three cases with Dent's disease treated with GH have been reported in the literature, showing encouraging results. Unfortunately, the small sample size does not allow us to reach definitive conclusions on the beneficial effect of GH treatment.

P3-D3-838

Analysis of the Effectiveness of Treatment with GH in a Tertiary Hospital in the Last 30 Years

Jaime Cruz Rojo, Lucía Garzón Lorenzo, M^a Elena Gallego Gómez, Jaime Sánchez del Pozo

Hospital 12 de Octubre, Madrid, Spain

Objective: To analyze the efficacy of GH treatment in pediatric patients in a hospital from 1982 to 2013. **Material and methods:** Retrospective study whose population are patients who have been or are being treated with GH in a Tertiary Hospital. The following data were collected: indication of treatment, years of treatment, genetic target height, height at start and the end of treatment, with their corresponding s.d.. A simple linear regression model was applied to explore the effect of duration of treatment with GH (measured in years) in the increase of height (s.d. of stature in last visit $-$ s.d. of stature at start). In patients with treatment completed, treatment success, measured as the difference between the s.d. of Adult Height reached and the s.d. of genetic target height, was analyzed. **Results:** Data from 162 patients (58.6% boys) were obtained. GH treatment was indicated for GH deficiency in a 36.4, 33.3% for small for gestational age (SGA), 23.5% for Turner syndrome and 6.8% for Prader-Willi. 57 patients had completed the treatment. Treatment was withdrawn due to side effects in two cases (1.2%; epiphysiolysis and intracranial hypertension). Final height was more than 1 s.d. below the genetic target height, in 8.5% of children treated because of GH deficiency, 5.5% of PEG and 23.7% of Turner. The regression model applied to the whole group of treated patients or in treatment shows significant association between treatment duration and variable gain of Talla in all diagnostic groups (except s.d. Prader-Willi) the resulting predictive equations are: all treatments: DE height gain = $0.87 + 0.17$ siloxanes of treatment ($P < 0.01$, $r^2 = 0.23$), GH deficiency: DE height gain = $1.04 + 0.19$ siloxanes of treatment ($P < 0.01$, $r^2 = 0.25$), PEG: DE height gain = $0.82 + 0.16$ siloxanes of treatment ($P < 0.01$, $r^2 = 0.14$). **Conclusions:** GH treatment in children is safe and effective in

the vast majority of patients. Treatment duration is associated with a significant gain of stature. The simple regression model obtained, applied to all patients studied, explains 23% ($r^2 = 23$) the increase of the size obtained.

P3-D3-839

A Rare Syndrome Benefits from GH Therapy: Hypotonia-Cystinuria Syndrome

Onur Akin, Bulent Hacıhamdioğlu, Ediz Yeşilkaya

Gulhane Military Medical Academy, Ankara, Turkey

Background: Hypotonia-Cystinuria syndrome (HCS), characterized by hypotonia at birth, poor feeding and growth retardation is an autosomal recessive disorder caused by homozygous microdeletions of PREPL and SCL3A genes. Increase in the urinary amino acids including cystine, lysine, arginine, and ornithine is the main laboratory finding. **Objective and hypotheses:** HCS was described in 17 patients so far and previous reports with favorable responses to GH treatment are present. Herein, we report a case with HCS who were successfully treated with GH. **Method:** A 8-year-old girl was referred to Pediatric Endocrinology outpatient department because of short stature. She was born at 38 weeks after a normal pregnancy and her birth weight was 2400 g. She was evaluated by Department of Pediatric Metabolism for poor feeding and hypotonia when she was 2 months old and her urinary levels of cystine and dibasic amino acids were found to be increased. Diagnosis of HCS was confirmed by detection of SLC3A/PREPL deletions. Hypotonia and poor feeding has improved by age. Physical examination revealed mild facial dysmorphism, proximal weakness, nasal speech, and mild learning disability along with short stature. Her height was 112.5 cm (SDS -3.47). Her serum IGF1 level was 37 ng/ml (SDS -2.9). Peak GH levels after provocation tests were 1.1 and 1.7 ng/dl. **Results:** GH treatment (0.2 mg/kg per week) was initiated. Her height reached to 125.9 cm (SDS -1.72 , growth velocity: 13.4 cm/year) after 1-year treatment. **Conclusion:** The clinical findings of HCS may resemble to Prader-Willi Syndrome (PWS) in terms of poor feeding, hypotonia at birth improving by age and gradually increasing risk of obesity. It should be considered in the differential diagnosis of patients who present symptoms similar to PWS. GH replacement therapy for short stature is a well established treatment in patients with HCS.

P3-D3-840

Changes in BMI in GHD and SGA Children in the First Year of Treatment

Juan-Pablo Llano^{a,b}, Teresa Ortiz Picon^a, Mauricio Llano^a

^aLaboratorio de Investigacion Hormona, Bogota, Colombia;

^bEsimed, Bogota, Colombia

Background: The effect of GH has been classically described as anabolic which should lead to changes in body composition in children during treatment. Likewise, GHD typically occurs in children with short stature and increased BMI. **Objective and hypotheses:** The aim of this study was to assess changes in BMI in children before and after initiation of treatment with GH in patients with GH deficit in small for gestational age and year. Starting variables as age, sex, dose and growth rate and evaluating criteria were included. **Method:** One year prospective follow-up study in 106 patients with GH deficit and 44 small for gestational age patients with assessment of BMI at baseline and every 3 months during treatment with GH. All patients gave informed consent. Variables such as growth rate, changes in BMI and gain in net weight were analysed. **Results:** At the beginning of treatment, the mean height SDS was -2.63 and -2.36 after 12 months SDS. The average BMI was -0.6 SDS without significant difference after 12 months. Despite a good estatural gain no net changes in body composition in patients treated with somatropin after 12 months. In our population GHD patients tend to have BMI below the mean for age and sex unlike classically described. Small for gestational age patients had similar results. **Conclusion:** The effects of GH on body composition do not occur during the first year of treatment in patients with GH deficit or small for gestational age despite changes in the growth rate. Likewise, at the beginning of treatment BMI is less than expected for age and sex.

P3-D3-841

Study of the Effect of GH Treatment on Growth in Patients Affected by the Inherited Metabolic Disease Methylmalonic Acidemia

Francois Eyskens

UZA, Antwerp, Belgium

Background: Methylmalonic acidemia (MMA) is an inborn error of metabolism affecting the catabolism of essential amino acids: valine, isoleucine, methionine, and threonine. A great problem in these children is that of a growth abnormality with progressive slowing of the statural growth rate, in contrast with a normal or even accelerated weight gain. These abnormalities are accompanied by bone demineralization and muscle hypotonia. **Objective and hypotheses:** We propose conducting a prospective study to determine the metabolic effects and effects on growth of 2-year treatment with recombinant human GH (rhGH) in five children presenting with vitamin B12 non-responsive methylmalonic aciduria in the age group of 2–12 (prepubertal) age. Course will be assessed longitudinally with each patient acting as his/her own control. The primary goal of this study is that rhGH treatment, by increasing protein anabolism, enables an improvement in growth rate and a gain of at least 1 s.d. in 1 year. The secondary goal is that rhGH treatment improves metabolic equilibrium due to enhanced protein synthesis. **Method:** The children will receive rhGH at a dose of 0.05 mg/kg per day as a single s.c. injection daily, 7 days a week. A glucagon test for GH should be performed since an important proportion of patients with organic acidurias suffer from partial or total GH deficiency.

The analysis will be conducted after 1 year. If the treatment is shown to be effective, the children will be treated with rhGH for a further period of 1 year. An extension should be provided for patients with a favourable response. **Results:** Proof of concept for therapy with rhGH in children with methylmalonic aciduria has already been achieved by several authors, the largest cohort has been treated in Paris where the primary end point unfortunately was not the stimulation of growth in these patients but rather focused on improvement of the metabolic parameters. One patient of ours has received rhGH according to the protocol described above and manifested improvement of growth of 2 cm during a period of 3 months. **Conclusion:** Patients affected by MMA are prone to growth abnormalities. Therapy with rhGH of these patients is promising, but should be studied in a prospective manner in order to get guidelines in starting this adjuvant treatment in this particular patient population.

P3-D3-842

Pubertal Development of Isolated GH Deficient Patients

Soumeya Fedala^a, Mahdi el Mahdi Haddam^b, Farida Chentli^a

^aBab El Oued Hospital, Algiers, Algeria; ^bBologhine Hospital, Algiers, Algeria

Background: Hormone deficiency no or late treated causes delayed puberty and reduced final height. **Objective and hypotheses:** Assess the progress of puberty in isolated GH deficient (GHD) patients. **Method:** 34 patients with GHD in puberty were followed in endocrinology. The average age at diagnosis of GH deficiency was 8 ± 2.4 (7–19) in girls and 9 ± 1.2 (8–18) in boys. The majority of patients received an irregular GH treatment. The assessment of puberty studied: the Age at puberty and its progress and age ménarchie. **Results:** Delayed puberty is reported in all patients. Age of pubertal development was 16.44 ± 2.36 years for boys and 13.88 ± 2.96 years for girls. The mean age of $15.46 \pm$ ménarche is delayed 2.00. The course of puberty was normal except for five patients precociously treated with GHR (average 2 years) **Conclusion:** Early treatment with GHR allows normal pubertal development by inducing local production of IGF1 in the gonads by promoting local production of sex steroid and follicular development. Whether puberty occurs normally in patients treated precociously, an advance of puberty and reduced the duration of the course of puberty may even. It is linked to the action of GH on bone maturation.

P3-D3-843

Two Years of GH Therapy in Children with Growth Deficiency

Mimouna Bessahraoui, Sakina Niar, Malika Naceur, Karim Bouziane-Nedjadi

Department of Pediatrics 'C', CHU, Oran, Algeria

Background: GH therapy improves height outcome in children with GH deficiency (GHD). Height velocity (HV) is maximum in the first year of treatment. Early diagnosis and therapy initiation optimize growth outcomes. **Objective and hypotheses:** Of this study was to evaluate growth during the first 2 years of GH treatment in 33 GHD children and evaluated the height velocity. **Method:** The study enrolled 54 children (29 boys, and 25 girls) with GHD. All of them were treated with a mean dose of GH = 0.035 mg/kg per day and followed for at least 2 years. We register the following parameters at baseline and every 6 months: – height – height SDS – weight – height velocity (HV). Bone age. **Results:** Mean age at diagnosis was 10 ± 3 years. The mean height SDS at diagnosis was: -3.2 ± 1.2 DS and the mean weight SDS was: -2.5 ± 0.4 DS. 73% of children with isolated GH deficiency (IGHD) and 27% of children with multiple pituitary hormone deficiency (MPHD). The mean height SDS improved by 0.6 ± 0.2 DS after 2 years of traitement. HV is maximum in the first year of treatment (0.4 ± 0.1 DS). Bone age improved by 1.7 years. **Conclusion:** GH treatment significantly improves growth of GHD children, with a favorable safety profile. The maximum height velocity was observed in the first year of therapy; the second year of treatment resulted in a lower height velocity.

P3-D3-844

WHO Growth Charts Replacing National Reference Data: Their Influence on Screening for Over- or Underweight and of Growth Disorders

Celine Eisenegger, Sarina Allenspach-Moser, Dagmar Lallemand
Children's Hospital of Eastern Switzerland, St Gallen, Switzerland

Background: In 2011, nationwide growth charts were introduced, replacing different regional references (ZLS, Prader 1989; Sempé 1979 and, for BMI only, Kromeyer 2001). **Objective and hypotheses:** The aim was to examine the influence of new growth charts (WHO 2010) on the prevalence of nutrition- and growth-related disorders compared the 'old' references. **Method:** 6007 anonymised weight and height datasets of children measured between 2000 and 2012 in one center were included. Precision of measurement was below 0.1% or 0.5 cm, respectively The degree of deviation of the 'new' from the 'old' percentile charts was assessed by the kappa measurement of agreement for different age groups. **Results:** WHO-percentiles for length/height show a broader normal range and a good agreement with ZLS charts (κ 0.88–0.83) in boys and girls. Yet 2–9% of boys aged 2–15 years are now classified as normal, while they would have been defined as short statured before. Female height charts are broader now and, except for the age of puberty, classify more girls as normal, namely 4.7% of those having been short statured and 1.4% of those classified as too tall before. WHO-weight percentiles, of boys and girls, are shifted to a higher normal range than ZLS curves. In the first year of life, the new BMI-percentiles find 4% less obese infants, but at school age, obesity was identified by WHO-BMI-references in up to 10% more boys and 2% more girls than with references from Kromeyer. **Conclusion:** For public health, the implementation of 'new' growth charts has an important impact on prevalence of

growth-related disorders and obesity. WHO percentiles find less short statured and more obese school aged children than 'old' references, the additional use of further markers of growth or obesity should be added, such as parental target height or waist circumference.

P3-D3-845

Skeletal Maturity of Radius, Ulna, and Short Bones in TW3 Method for Children in Korea

Jieun Lee, Jaesuk Kim, Jurae Cho

INHA University, Incheon, Democratic People's Republic of Korea

Purpose: The Tanner-Whitehouse (TW) system is the method of choice for skeletal maturity assessment in both clinical practice and auxological research (Tanner *et al.* 1983), and it has been used to estimate skeletal maturity in groups of children from all over the world. This study aimed on analyzing the characteristic of the RUS maturity of Korea children by evaluating RUS maturity of Korea children using the TW3 method, compared with children in China and Japan. **Methods:** Left hand including wrist radiographs of normal children (643 boys and 837 girls) who had visited several local clinics and University Hospital were obtained in five cities. Their RUS maturity was estimated using the TW3 method and 50th percentiles of the RUS scores classified by sex and age were compared with TW3 standards and study results of Beijing in China and Tokyo in Japan. **Result:** The RUS maturity of Korea children was similar to the TW3 standard until the age of 12 years in boys and 9 years in girls. The age of full maturity was 16-year-old in boys and 15-year-old in girls. **Conclusion:** The RUS maturity of Korea children showed a sharp increase after the age of 12 years in boys and 9 years in girls, compared with the TW3 standard. RUS maturity of Korea children was more similar to that of Beijing (China) children than that of Tokyo (Japan) children.

P3-D3-846

Design and Recruitment of a Longitudinal Cohort Study of Growth and Puberty in Russian Boys

Oleg Sergeev^a, Thuy Lam^b, Paige L Williams^c, Jane S Burns^b, Susan A Korrick^{b,d}, Russ Hauser^b, Boris Revich^e, Yury Dikov^a, Lyubov Sergeeva^a, Mary M Lee^f

^aChapaevsk Medical Association, Chapaevsk, Samara Region, Russia; ^bDepartment of Environmental Health, Harvard School of Public Health, Boston, Massachusetts, USA; ^cDepartments of Biostatistics and Epidemiology, Harvard School of Public Health, Boston, Massachusetts, USA; ^dChanning Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA; ^eCenter for Demography and Human Ecology of the Institute of Forecasting, Russian Academy of Sciences, Moscow, Russia; ^fPediatric Endocrine Division, Departments of Pediatrics and Cell and Developmental Biology, University of Massachusetts Medical School, Worcester, Massachusetts, USA

Introduction: There are few longitudinal male cohort studies with serial assessments of growth and puberty. **Objective:** To describe the design and implementation of a longitudinal cohort study of Russian boys evaluated annually for growth, development and puberty. **Design/methods:** We assembled a multi-disciplinary team of U.S. and Russian researchers to design and conduct a longitudinal boys' cohort study in Chapaevsk, Russia with the primary goal of evaluating associations of environmental exposures with growth and puberty. At annual study visits scheduled at each subject's birth month, the same study physician (O.S.) assesses pubertal staging and one nurse (L.S.) measures anthropometric variables. Pubertal assessments are based on a 1–5 scale for genitalia and pubic hair staging by visual inspection, testicular volume is measured using orchidometers, and penile length is measured with a ruler. Blood and urine samples for hormonal, chemical and genetic analysis were collected at baseline and biennially. **Results:** In 2003–2005, 516 prepubertal boys were recruited at ages 8–9 years (86% of all eligible Chapaevsk boys) and will be followed annually for at least 10 years. The participation rate has remained high with over 75% followed for 6 years and 64% at 9 years of follow-up with 4319 visits as of February 2014. A core set of 23 anthropometric indices measured at annual visits (e.g., height, weight, segment lengths and diameters, circumferences, skinfolds) are available, as well as an additional 30 measures conducted biennially. Longitudinal curves for selected anthropometric and pubertal measures will be constructed. **Conclusions:** To our knowledge, this longitudinal male cohort is the first to have serial assessments of growth and puberty performed by the same physician and nurse followed for over 10 years, from prepuberty to young adulthood. This cohort provides an excellent foundation for describing growth and pubertal development trajectories and evaluating associations with environmental exposures.

P3-D3-847

Multiple Endocrinopathies in a Case with H Syndrome due to a Novel *slc29a3* Mutation

Gul Yesiltepe Mutlu^a, Heves Kirmizibekmez^a, Elif Ozsu^b, Abraham Zlotogorski^c, Sukru Hatun^b

^aDepartment of Pediatric Endocrinology, Zeynep Kamil Woman's and Children's Diseases Training and Research Hospital, Istanbul, Turkey; ^bDepartment of Pediatric Endocrinology and Diabetes, Kocaeli University, Medical School, Kocaeli, Turkey; ^cDepartment of Dermatology and the Center for Genetic Diseases of the Skin and Hair, Hadassah-Hebrew University Medical Center, Jerusalem, Israel

Background: H syndrome (OMIM #602783) is an autosomal recessive syndrome resulted from mutations in the *SLC29A3* gene, encoding hENT3 protein. Characteristic findings are cutaneous hyperpigmentation, hypertrichosis, hepatosplenomegaly, hypogonadism, hyperglycemia/diabetes mellitus, cardiac anomalies, hallux valgus and short stature. Herein we report a girl with multiple endocrinopathies due to H syndrome. **Case:** Ten year and

5 month old girl was referred because of short stature. Her height was 115 cm (–3.8 SDS), weight was 20 kg (–2.8 SDS). She had fixed flexion contractures of the fingers and toes, and bilateral hallux valgus. Cutaneous induration, hyperpigmentation and hypertrichosis was evident on the thighs and external genitalia. Her pubertal stage was 1 according to Tanner staging. Mutation analysis of the *SLC29A3* gene revealed a homozygous mutation in exon 6. Her thyroid function tests and morning cortisol levels were normal. She had high anti-tissue-transaminase levels and small intestine biopsy revealed celiac disease. On the 10th month of gluten-free diet, her growth rate was still low despite negative serologic markers of celiac disease. IGF1 level was 7.4 ng/ml and the peak GH level was 3.4 ng/ml. Although fasting serum glucose level was normal initially, it increased to 116 mg/dl in the follow-up period. Oral glucose tolerance test revealed impaired glucose tolerance and anti-GAD level was found very high (>200 U/ml). At the age of 12 years and 2 month old she still had no breast development and her peak LH level was detected as 3.19 mIU/ml in GnRH stimulation test. Impaired glucose tolerance, GH deficiency and possible hypogonadotropic hypogonadism are the main endocrinopathies in this case. **Conclusion:** Seventy-nine cases with H syndrome were reported so far and some of these are noted to have various endocrinopathies, however etiopathogenesis of endocrinopathies associated H syndrome has not been lightened, yet. To our knowledge, this is the first report emphasising endocrinopathies related H syndrome.

P3-D3-848

Severe Short Stature with Features of Achondroplasia, Later Diagnosed as Panhypopituitarism: a Case Report

Cristina Matei^a, Maria Karam^a, Catherine Peters^b

^aEast and North Hertfordshire NHS Trust, Stevenage, UK; ^bGreat Ormond Street Hospital NHS Trust, London, UK

Background: Severe short stature is considered when height falls below –4 SDS. When infants with extreme short stature are evaluated, often multidisciplinary input is required, before a formal diagnosis is met. **Objective and hypotheses:** We want to learn from delayed diagnosis of child with panhypopituitarism and review subsequent difficulties in starting GH treatment. **Method:** Retrospective review of notes, investigations and patient clinical progress. **Results:** Our patient was born at 31 weeks gestation with birth weight of 1.935 kg. During follow-up it became gradually apparent that he was short. At 8 months, his weight was 5.2 kg and length 55.5 cm both –5 SDS with head circumference 44.5 cm on 50th centile. His disproportionate skeletal appearance was suggestive of achondroplasia. His skeletal survey reported osteopenia, hence hypothyroidism was suspected. At age 10 month his thyroid function showed a TSH 1.13 IU/l and a free T₄ of 3.6 pmol/l, suggestive of secondary hypothyroidism.

Synacthen test demonstrated an inappropriate response and hydrocortisone treatment was started. MRI brain demonstrated a small anterior pituitary and his IGF1 was low. He was considered GH deficient, but this could not be more clearly demonstrated as GH stimulation was considered unsafe. As a consequence, funding for GH was refused by local services. Due to recurrent severe hypoglycaemia GH treatment was finally initiated, which resolved the hypoglycaemic episodes. **Conclusion:** No screening programme is perfect and in this case was falsely reassuring. Thyroid function should be checked in all cases of short stature. Funding for GH treatment can be difficult to obtain from commissioning groups if need not clearly demonstrated by dynamic testing. However, medicine is an art as well as science and each patient has to be treated individually.

treatment significantly improves growth of GHD children, with a favorable safety profile. The maximum height velocity was observed in the first year of therapy (10.59 cm/year); the following years of treatment resulted in a lower height velocity (7.48 cm/year, 6.04 cm/year, 6.76 cm/year respectively). No severe adverse events were observed.

P3-D2-849

GH Therapy in Prepubertal Children: Results After 4 Years

Corina Galesanu^a, Andra Iulia Loghin^a, Ilinka Grozavu^a, Luminita Apostu^a, Didona Ungureanu^a, Mihail Romeo Galesanu^b

^aUniversity of Medicine and Pharmacy, Iasi, Romania; ^bRomanian Academy of Medical Sciences, Iasi, Romania

Background: GH therapy is being used worldwide to improve height outcome in children with GH deficiency (GHD), with minimal serious side effects. Early diagnosis and therapy initiation optimize growth outcomes. **Objectives:** To evaluate growth and safety during the first 4 years of GH treatment in 33 GHD children. **Methods:** We reviewed clinical data of 33 prepubertal children (23 boys and ten girls): 30 with isolated GH deficiency (IGHD), three with multiple pituitary hormone deficiency (MPHD). All of them were treated with a mean dose of GH = 0.035 mg/kg per day and followed for at least 4 years (mean 5.98 years). **Results:** The mean height SDS increased from -2.76 at baseline to -0.73 at 4 years; the change in height SDS decreased with time Table 1. Within first 4 years of therapy none of these children developed diabetes mellitus, seven patients (21.21%) presented transient increase in fasting glucose (>100 <126 mg/dl), two patients (6.06%) had transiently impaired glucose tolerance (<140 <200 mg/dl at OGTT), three patients (9.09%) developed hypothyroidism and one patient (3.03%) had transiently increased TSH levels (normal fT₄ values, no clinical signs). No malignancies were observed to date. **Conclusions:** GH

P3-D2-850

A Follow-up Study up to Adult Height of the Patients Included in the Phase iii Clinical Trial with the Biosimilar Human Recombinant GH (omnitrope[®]) on the Treatment of Spanish Children with GH Deficit

Victoria Borrás^a, Juan Pedro Lopez Siguero^b, Gabriela Martínez^c, Raquel Corripio^d, Juan Fernandez^e, Jose Labarta^f, Marta Ferrer^f, Nuria Cabrinety^g, Pablo Prieto^h, Marta Ramonⁱ, Jordi Bosch^j, Rafael Espino^k, Margarida Palla Garcia^l

^aHospital General Granollers, Barcelona, Spain; ^bHospital Universitario Carlos Haya, Malaga, Spain; ^cHospital Ciudad de Jaén, Jaen, Spain; ^dCorporación Sanitaria Parc Tauli, Barcelona, Spain; ^eHospital San Cecilio, Granada, Spain; ^fHospital Universitario Miguel Servet, Zaragoza, Spain; ^gHospital Sacrat Cor, Barcelona, Spain; ^hHospital Universitario de Salamanca, Salamanca, Spain; ⁱHospital San Joan de Deu, Barcelona, Spain; ^jHospital Universitario Arnau Villanova, Lérida, Spain; ^kHospital Nuestra Sra Valme, Sevilla, Spain; ^lSandoz Farmacéutica, Madrid, Spain

Introduction: The results of the phase III clinical trial that evaluated the efficacy and safety of the biosimilar recombinant human GH - rhGH - (Omnitrope[®], Sandoz) on the treatment of Spanish children with GH deficiency were published in 2011. At the end of the study those patients that were still growing remained on treatment within the usual clinical practice. **Objective:** To know the values of adult height of the children who participated in the Spanish phase III clinical trial. To ascertain the long term safety of treatment with Omnitrope[®]. **Method:** This study was a multicentre, observational, retrospective follow-up study of the patients that participated in the Spanish phase III clinical trial (70 patients recruited). Height data up to adult height was obtained from 39 patients. **Results:** Data from 27 men and 12 women was gathered. The mean age of the patients was

Table 1. Growth data during first 4 years of GH therapy in 33 GHD children (abstract for P3-D2-849).

Parameter	Baseline	1 year	2 years	3 years	4 years
Chronological age (years)	7.89	8.89	9.89	10.89	11.89
Bone age (years)	5.76	6.62	7.44	9.46	11.07
IGF-1 mean values (ng/ml)	64.64	221.8	205.7	265	338
Height SDS	-2.76	-2.12	-1.55	-1.14	-0.73
Height velocity (cm/year)	-	10.59	7.48	6.04	6.76
Weight SDS	-1.94	-1.28	-0.94	-0.46	-0.12

18.5 ± 2.7 years (men 18.5 ± 2.8; women 18.5 ± 2.6). At the end of the phase III clinical trial the mean height was 144.8 ± 13.9 cm (men 145.1 ± 14.3, women 144.1 ± 13.3) and the height SDS was -1.16 ± 0.63 (men -1.11 ± 0.69, women -1.26 ± 0.50). The mean adult height was 163.1 ± 7.6 cm (n = 36; men 165.5 ± 7.8, women 157.6 ± 3.2) and the adult height SDS was -1.01 ± 0.59 (n = 36; men -1.07 ± 0.52, women -0.86 ± 0.72). Two patients have not yet reached adult height and in one patient adult height could not be measured. 23.1% of patients (9) changed from Omnitrope® to an original rhGH. No adverse events were reported. **Conclusions:** The patients recruited in the Spanish phase III clinical trial had a positive growth achieving an adult height SDS of -1.01 ± 0.59 (men: -1.07 ± 0.52 and women: -0.86 ± 0.72). No adverse events were reported.

P3-D2-851

Growth pattern of the Nigerian child compared to international references

Jerome Elusiyan^a, MaryAnn Ugochi Ibekwe^b, Y Alkali^c, J. Chizo Agwu^d

^aDepartment of Paediatrics and Child Health, Obafemi Awolowo University, Ile-Ife, Nigeria; ^bDepartment of Paediatrics, Federal Teaching Hospital, Abakaliki, Ebonyi State, Nigeria; ^cDepartment of Paediatrics, Federal Medical Centre, Gombe, Gombe, Nigeria;

^dDepartment of Paediatrics, Sandwell and West Birmingham NHS Trust, West Bromwich, UK

Background: There are currently no specific growth charts for use in Nigerian children over the age of 5 years. Health workers rely on charts developed by the Center for Disease Control for children in USA (2000CDC US) or the UK 1990 growth charts for British children. It is unknown whether Nigerian children grow to the same height or at the same tempo as American or British children. **Objective and hypotheses:** To compare the growth of the Nigerian child to the 2000CDC US and UK 1990 growth references **Method:** Healthy Nigerian children (5-16years) were recruited from local schools in Gombe (Northern Nigeria), Abakaliki (Eastern Nigeria) and Ile-Ife (Western Nigeria). Height and weight were measured. The results were expressed as SD scores relative to the 2000CDC US and the UK 1990 growth reference data. The timing of pubertal growth spurt (PGS) was estimated by calculating the difference between the annual stature medians at each age. **Results:** 2,856 Children (1246 girls and 1612 boys) were measured. Overall, girls had a similar height to both UK and American girls with the mean height being only 0.04 SD and 0.008SD below the 2000CDC US and the 1990 UK references respectively. The timing of PGS occurred later in the Nigerian girl between 12-13yrs. The girls were lighter with mean BMI being 0.8SD less than both UK and US reference data. Nigerian boys were shorter with mean height being 0.4 SD and 0.5 SD below the UK and US references respectively but with estimated timing of PGS between age 13 and 14 years. They were also lighter with

mean BMI being 0.7 SD and 0.9SD less than both the UK and US references respectively. **Conclusion:** There are important differences in the growth pattern of the Nigerian child when compared to US and UK growth references.

P3-D2-852

Evaluation of Potential Waste of GH Across Available GH Pen Devices and an Electronic GH Delivery Device

JC Locklear^a, NC Edwards^b, AL Phillips^a

^aEMD Serono, Inc., Rockland, Massachusetts, USA; ^bHealth Services Consulting Corporation, Boxborough, Massachusetts, USA

Background: Several somatotropin products are available as pen and electronic devices. When administering the last dose from a device, patients may have an insufficient amount of GH remaining for a full dose. **Objective and hypotheses:** The aim of this analysis was to estimate the potential GH waste per patient with pen devices and the easypod® device, and to quantify the potential economic impact of expected GH waste from patient and health care organization perspectives. **Method:** A Waste Calculator Model was developed to examine GH waste. All somatotropin products available in pen or electronic devices were included in the model. The user may define distribution across cartridges sizes (where applicable). The mechanical/priming loss applied to each product was based upon each product's prescribing information and/or instructions for use. The base case model utilizes a US patient daily dose of 1.4 mg. The model assumes that the easypod® dose adjustment feature (± 10 , ± 25 , or $\pm 50\%$) is activated by the clinician (base case model utilizes $\pm 25\%$). Model assumes that 42.6% of caregivers will discard the remaining amount left in the cartridge (e.g. waste) if less than a full dose. Annual amount of GH waste (mg, cartridges, dollars) per patient and per population (based on US national market shares) for each pen/device is reported. Costs are based on USD 2013 wholesale acquisition cost (WAC) pricing, exclusive of discounts. **Results:** The expected annual amount of waste per patient was lowest for easypod®. The expected annual amount of waste per patient was highest for Omnitrope®. The expected annual amount of waste ranged from 0 to 38.9 mg per patient per year, which is equal to 0 to 8 cartridges per patient per year and/or 0 to \$2935 per patient per year. For a patient population of 100 GH-treated patients, the annual amount of waste is estimated at 2009 mg, which can be translated into approximately 342 cartridges or about \$162 000 per year. There are several modifiable inputs to allow for examination of other scenarios. The results in GH waste fluctuated depending upon daily dose, cartridge size, and dose spread assumptions; however easypod® consistently had the lowest amount of expected annual waste. **Conclusion:** The expected annual amount of GH waste evaluated in this Waste Calculator was lowest with easypod®. Cost of GH waste can be an important consideration when evaluating GH delivery devices.

P3-D2-853

Switching From the Original to the Biosimilar Recombinant Human GH – Omnitrope®: an Experience of a Single Paediatric Centre in Spain

Ana Gomez Gila^a, Margarida Palla Garcia^b

^aHospital Universitario Virgen del Rocío, Sevilla, Spain; ^bSandoz Farmacéutica, Madrid, Spain

Introduction: In 2009/2010 Hospital Virgen del Rocío, Seville, Spain changed the treatment of patients with GH deficiency (GHD) from various original recombinant human GH (rhGH) to a biosimilar rhGH (Omnitrope[®], Sandoz). **Objective:** To evaluate the consequences on growth parameters of switching treatment, from original rhGHs to Omnitrope[®] in children with GHD, in a window period of 36 months. **Method:** This study was a single centre, retrospective, observational study. It included children with GHD treated with an original rhGH at least 2 years before the switch. Auxological data was obtained from 20 patients. **Results:** Data from 15 boys (75%) and five girls (25%) was gathered. The mean age of the patients was 14.5 years. 65% (13) had idiopathic GHD. The mean duration of treatment prior to switching was 38,3 months. At the beginning of treatment the mean height was 105.5 ± 16.2 cm and the height SDS (HSDS) was -3.25 ± 0.93. Eighteen months before the switch the mean height was 118.5 ± 10.9 cm, the HSDS was -2.16 ± 0.80, the HV was 8.77 ± 2.04 cm/year and the HVSDS was 3.87 ± 2.66. At the time of the switch to Omnitrope[®] the mean height was 128.1 ± 10.6 cm, the HSDS was -1.82 ± 0.88, the HV was 6.20 ± 1.39 cm/year and the HVSDS was 1.03 ± 1.80. Eighteen months after the switch the mean height was 139.4 ± 12.9 cm, the HSDS was -1.41 ± 0.91, the HV was 6.92 ± 2.88 cm/year and the HVSDS was 0.89 ± 1.57. No adverse drug reactions were reported after the switch and three patients had transitory problems with the Omnitrope[®] device. **Conclusion:** The switch from the original to the biosimilar rhGH, Omnitrope[®], had no negative impact on the growth of children with GHD. No adverse drug reactions were reported after the switch.

P3-D2-854

Descriptive Analysis of Medication Adherence for Patients Treated with GH Therapy

S L Michels^a, C Uribe^a, Y Li^a, D M Meletiche^b, F F Velez^c, J C Locklear^b

^aCompetitive Health Analytics – A Humana Company, Louisville, Kentucky, USA; ^bEMD Serono, Inc., Rockland, Massachusetts, USA;

^cFormerly EMD Serono, Inc., Rockland, Massachusetts, USA

Background: GH deficiency (GHD) occurs in one in 4000–one in 10 000 children, but can also be diagnosed in adults.¹ GHD therapy typically requires injections over a period of years.² Adherence to long-term GHT presents a challenge. **Objective and hypotheses:** This study describes the rates of adherence to GHT among patients with GHD. **Method:** Members who were

continuously enrolled 6 months pre- and 12 months post-initiation of GHT (generic product identifier code, 3010002000) aged <65 years with a diagnosis of GHD during the study period (January 1, 2007–December 31, 2011) were identified from the Humana administrative claims database. Member demographic, clinical and GHT adherence information was described. New and existing users were classified on the presence of a claim for GHT before the index date. Proportion of days covered (PDC) was calculated as the number of days with GHT on hand as identified in the pharmacy claim divided by 365 (i.e. the total number of days in the measurement period). The PDC was calculated overall and stratified by user type and age category. PDC ≥ 0.8 was considered adherent. **Results:** In total, 417 patients were identified. The cohort was, on average, 23.9 years (median 14.7) of age, predominantly male (67.1%) and mainly covered under commercial insurance (85.1%). Overall mean PDC was 0.69 (± 0.27) to GHT in the first 12 months after initiation of a GHT. Less than 10% of patients overall were considered nonadherent (PDC < 0.2), 46.8% considered adherent and 44.9% considered partially adherent. Children < 12 years had higher overall average PDC (0.79 ± 0.28) than children 12–17 years of age (0.69 ± 0.27) and patients > 18 (0.60 ± 0.28). **Conclusion:** There is room for improvement in adherence, consistent with published data.

P3-D2-855

Effect of Cyanotic and Acyanotic Congenital Heart Disease on Placental and Birth Size

Ashraf Soliman^a, Emad Shatlah^b, Aml Sabt^a, Fawzia Alyafei^a, Mohanad Alqadi^a

^aDepartment of Pediatrics Hamad Medical Center, Doha, Qatar;

^bNeonatal ICU Hamad Medical Center, Doha, Qatar

Background: Abnormal cardiac development leading to CHD can be associated with abnormal placental development with abnormal trophoblast invasion and remodeling resulting in abnormal transfer of nutrients and oxygen. **Objective and hypotheses:** We measured the anthropometric parameters (length, weight, and head circumference) and the placental weight of 49 FT newborns (gestation period > 36 weeks) infants with CHD ((cyanotic ($n=8$) and acyanotic ($n=41$)) diagnosed clinically and by echocardiography and compared these data with those for randomly selected normal FT newborns ($n=104$). **Results:** Newborn infants with CHD were significantly shorter

	Placental wt (g)	Birth wt (g)	Birth length (cm)	Head circumference (cm)
Normal, NB=104	677.6	3185	50.6	34.0
CHD newborns, $n=49$	597.3*	2600*	46.4*	31.7*
Acyanotic, $n=41$	588.64	2510	46	31.5
Cyanotic, $n=8$	640.00	2870	48.6	32.6

* $P < 0.05$

and had lower birth weight and smaller head size compared to normal newborns (Table). Their placental weights were significantly decreased compared to those for normal newborns. However, there was no statistically significant difference in the anthropometric parameters of infants with cyanotic vs acyanotic heart disease. **Conclusion:** The intrauterine growth restriction in newborn infants with CHD may represent an adaptive mechanism to cope with the compromised perfusion caused by the congenital cardiac anomaly. Restricted uterine growth can pose a risk for postnatal development. In this study CHD was associated with significant affection of birth weight, length, and head circumference and lower placental weight compared to normal newborns.

P3-D2-856

Anthropometric Evaluation of a Cohort of School-Aged Children: the Need for National Growth References in Romania

Raluca-Monica Pop, Ionela Pascanu, Marian Pop

University of Medicine and Pharmacy Tirgu Mures, Tirgu Mures, Romania

Background: For children above 5 years of age no specific national growth charts are available in our country, the most widely used being the Swiss ones (Prader, 1989). Previous studies have shown significant differences between the various international standards available regarding. The incidence of growth disorders. **Objective and hypotheses:** Our aim was to compare the recommended growth reference with a new one based on a national representative sample. Our hypothesis was that the available growth references do not reflect the local reality regarding auxological data. **Method:** Type of study: cross-sectional; target population: children 6–15 years of age. **Sample:** Random stratified, composed of 1168 children selected from four rural and four urban areas of Mures county. Variables: age, sex, environment, height, weight, arm span, head circumference, and waist. The evaluation was performed by two trained endocrinologists using verified instruments. Exclusion criteria: small for gestational age, cardiac or renal failure, malabsorption, and rickets. The study was approved by the Local Ethics Committee and a written consent was obtained for every child. Children refusing the evaluation were excluded from the final analysis. Statistical analysis used M.O. Excel and Graph Pad InStat with a level of significance 0.05. A mean and SDS was computed for every year of age for both sexes. **Results:** General characteristics: environment ratio urban:rural was 1.07; sex ratio boys:girls was 1.01. For every anthropometric parameter evaluated there are significant differences between the available Swiss references and the new computed means and s.d.s ($P < 0.001$), for each age and sex, regardless of other factors. Moreover, using the new means resulted in a much smaller number of pathological results that needed further medical evaluation (2 vs 18.9% respectively). **Conclusion:** This study proves the need for constructing national growth references giving the important differences existent between the recommended growth curves and the current national reality reflected by our representative sample.

P3-D2-857

Differences in Personality of Monozygotic Twins can be Predicted by Difference in Birth Weight in Teen Monozygotic Twins

Lioba Wimmer^a, Joachim Woelfle^a, Peter Bartmann^b, Sandra Schulte^a, Bettina Gohlke^a

^aPediatric Endocrinology Division, Children's Hospital, University of Bonn, Bonn, Germany; ^bDepartment of Neonatology, Children's Hospital, University of Bonn, Bonn, Germany

Background: Low birth weight and unfavourable intrauterine conditions are associated with long-term effects on life. The influence of intrauterine conditions on personality might be underestimated. **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 (tts) from birth until puberty. **Method:** 23 pairs of monozygotic twins with intra-twin bw-differences were seen at birth, 2.8 and 15.25 (during/post-puberty) years. Auxiological data were collected at all occasions; we differentiated between donators (lower birth weight) and acceptors (higher birth weight). Additionally at 15.25 years, two psychological questionnaires were issued: the Strength and Difficulties Questionnaire (SDQ-self and -parent, Goodmann, 2000) and the Kidscreen-52 (Health Related Quality of Life, The Kidscreen Group Europe, 2006). **Results:** Parents saw significantly more emotional problems and hyperactivity in donators (each $P < 0.05$). In contrast to this, in self-assessment donators and acceptors did not report significant differences of their strength and difficulties. Similar, self-perceived quality of life in the two groups did not differ significantly. Differences in bw-SDS correlated significantly with differences regarding hyperactivity (self ($r = 0.91$; $P < 0.01$) and parents ($r = 0.93$; $P < 0.001$)), and external assessment of behavioural problems (parents, $r = 0.74$; $P < 0.05$). No significant correlations occurred between differences in twin pairs regarding height and weight-SDS and scores of SDQ-self/-parent and Kidscreen-52. Again, there were no significant correlations with quality of life. **Conclusion:** Psychological data of adolescent monozygotic twins with tts suggest that parents view the former smaller twin (the donator) to be more hyperactive and suffer from more emotional problems than the former larger co-twin (the acceptor). Quality of life appears to be unaffected by this. Differences in birth weight can predict intra-twin differences in personality.

P3-D2-858

The Growth Speed of Late Preterm Infants Aged 1 Year

Cheng Qian

Department of Primary Child Health Care, Children's Hospital, Chongqing Medical University, Chongqing, China

Background and aims: The physical growth of late preterm infants (LPI) is unknown, to investigate the growth of LPIs to provide the basis for growth evaluation of LPI. **Methods:** Infants

were recruited for a cohort study in Department of Primary Child Health Care, Children's Hospital, Chongqing Medical University from May 2010 to November 2011. LPI and full term infants (FTI) were compared in terms of weight for age Z-scores (WAZ), length for age Z-scores (LAZ), head circumference for age Z-scores (HCZ), weight for length Z-scores (WLZ), and the velocity of all physical growth indicators (Δ WAZ, Δ LAZ, and Δ HCZ). **Results:** 309 LPI and 418 FTI were included. The LPI gained obviously more in weight, length and head circumference than FTI within 1 year of age ($P < 0.0001$). Δ WAZ1-4, Δ LAZ1-4, Δ LAZ4-8, and Δ HCZ1-4 were 1.74 ± 0.89 , 1.24 ± 0.79 , 0.79 ± 0.7 , and 0.98 ± 0.83 respectively. **Conclusions:** LPI grow faster than FTI, and there is a 'catch-up growth' in LPI.

P3-D2-859

Response of GH Therapy in Six Children with Achondroplasia

Yoon Jung Kim^a, Byung Wook Cho^a, Ji Yoon Kim^a, Heung Sik Kim^a, Hee Jung Lee^b

^aDepartment of Pediatrics, Keimyung University School of Medicine, Daegu, Republic of Korea; ^bDepartment of Radiology, Keimyung University School of Medicine, Daegu, Republic of Korea

Background: Achondroplasia is the most common condition characterized by disproportionate short stature. Patients with achondroplasia progressively fall below normal standards for length and height. GH has been widely used to treat short stature with or without GH deficiency (GHD). **Objective and hypotheses:** The purpose of the present study was to clarify the effectiveness of GH therapy on short stature in achondroplasia. **Method:** The study included six children (four males and two females, age 2 years–2 months to 7 years–10 months) with achondroplasia. We reviewed height, weight, MRI finding, FGFR3 gene mutation, bone age, IGF1, and growth rate of the patients. GH response to provocation tests with insulin and L-DOPA were evaluated. All six patients were treated with recombinant human GH. **Results:** Heights of all patients were under three percentile. Weights were under three percentile in three patients, 3–10 percentile in one patient, 10–25 percentile in one patient, 50–75 percentile in one patient. Brain MRI showed narrowing of foramen magnum in three patients, hydrocephalus in two patients and periventricular leukomalacia in one patient. Four patients underwent decompressive suboccipital craniotomy. FGFR3 mutation showed in five patients and one patient was negative. Bone age was from 1 year–3 months to 7 years–2 months (delayed in four patients). Mean IGF1 level was 50.8 ng/ml and GHD was notified in four patients. The annual height gains after the therapy were 6.8 ± 2.5 cm/year (7.4 ± 0.9 cm/year in patients with GHD and 5.8 ± 1.5 cm/year in patients without GHD). **Conclusion:** Based on our findings, for the management of short stature in children with achondroplasia, response of GH therapy was minimal. Further management for height gain should be considered in achondroplasia patient.

P3-D2-860

Clinical Expression of Familial Williams–Beuren Syndrome in a Turkish Family

Mesut Parlak^a, Banu Guzel Nur^b, Ercan Mihci^b, Erdem Durmaz^a, Sibel Berker Karaüzüm^c, Sema Akcurin^a, Iffet Bircan^a

^aDepartment of Pediatric Endocrinology, Akdeniz University School of Medicine, Antalya, Turkey; ^bDepartment of Pediatric Genetics, Akdeniz University School of Medicine, Antalya, Turkey; ^cDepartment of Medical Biology and Genetics, Akdeniz University School of Medicine, Antalya, Turkey

Background: WBS is a rare genetic disorder characterized by distinctive facial features, intellectual disability, cardiovascular anomalies, and infantile hypercalcemia. **Objective and hypotheses:** Majority of WBS cases occur sporadically, only five families with clinically confirmed WBS have been identified by molecular cytogenetic analysis. Here, we report on the three molecular cytogenetically confirmed familial WBS detected in a family with familial short stature. **Method:** FISH analysis in metaphase spreads and interphase nuclei showed microdeletion in the chromosomal band 7q11.23, using the commercial Williams–Beuren probe (Cytocell, cat. no: LPU011-S). This probe contains three clones that are situated at: Chr7: 72851047–72999295 (148 kb), Chr7: 73508472–73652590 (144 kb), Chr7: 73709072–73912798 (204 kb). **Results:** FISH analysis showed microdeletion in the chromosomal band 7q11.23 with all cases. **Case 1:** Eight-year-old female patient height and weight were 109.5 cm (< -2 s.d., WBS), 17 kg (< -2 s.d., WBS). Elfin face, 2/6 pansystolic murmur and hoarse voice were detected. Breast development and pubic hair were of Tanner stage 1. Serum free T_4 (fT₄): 1.17 ng/dl, TSH: 7.77 μ IU/ml (n : 0.27–4.20), calcium level 10.6 mg/dl, and echocardiogram showed a patent foramen ovale. **Case 2:** Three-year-old male patient height and weight were 83.7 cm ($-1/-2$ s.d., WBS) and 12 kg ($-1/0$ s.d., WBS). Elfin face, 2/6 systolic murmur, hoarse voice were detected. Serum fT₄: 1.19 ng/dl, TSH: 8.66 μ IU/ml, calcium level 9.4 mg/dl, and echocardiogram showed moderate aortic stenosis. **Case 3:** The father of the two siblings was evaluated at 44 years old age. His height and weight were 156 cm (< -2 s.d., WBS) and 45 kg ($0/-1$ s.d., WBS). **Conclusion:** Feeding problems, cardiac abnormalities, celiac disease, subclinical hypothyroidism, and GH deficiency (GHD) may be the reasons of short stature in WBS. We suggest that parents with WBS may affect height extension of their children and a decrease of their final height.

P3-D2-861

Abstract withdrawn.

P3-D3-862

Mucopolysaccharidose and Hypopituitarism:

a Case Report

Saida Kabour, Soumeya Fedala, Farida Chentli, Fetta Amel Yaker, Leila Ahmed Ali

Bab El Oued Hospital, Algiers, Algeria

Background: Mucopolysaccharidosis 6 (MPS6) (or Maroteaux-Lamy syndrome) is a rare genetic disease characterized by progressive systemic disease caused by a deficiency of 4-N-acetylgalactosamine 4-sulfatase which causes an accumulation of dermatan sulfate (DS). It is due to mutations in the BRSA gene, located on chromosome 5. In severe cases, the accumulation of DS in the body cells occurs mainly in bones, joints, eyes, heart and brain. Its association with anterior pituitary deficiency has been rarely reported. **Objective and hypotheses:** Report an observation of mucopolysaccharidosis. **Observation:** AN, aged 3 years old was admitted for congenital hypothyroidism. Clinical examination revealed a significant growth retardation (−3DS/M and TC) psychomotor retardation, signs of somatotrophic insufficiency a dysmorphic syndrome characteristic of MPS, a sleep apnea syndrome with hepatomegaly, splenomegaly and an umbilical hernia. Urinary GAG assay and hypophysioigramme confirmed diagnosis of MPS and dissociated hypopituitarism. Exploring brain imaging showed hydrocephalus. **Conclusion:** Among the lysosomal storage diseases, the MPS 6 causes characteristic skeletal dysplasia with small stature, dysostosis multiplex and degenerative arthropathy. Other clinical manifestations may involve: valvulopathy, mixed pulmonary syndrome, obstructive and restrictive, hepatosplenomegaly, sinusitis, otitis media, hearing loss, sleep apnea, corneal clouding, carpal tunnel syndrome, inguinal or umbilical hernia. Neurological manifestations are possible spinal compression spinal instability, meningeal thickening and/or spinal stenosis and hydrocephalus. The existence of the latter must consider hormonal explorations to detect precociously hypopituitarism and treat. The course is variable, sometimes slowly, sometimes rapidly progressive. Death occurs before the 2nd or 3rd decade. The therapeutic management includes symptomatic treatment and transplantation of hematopoietic stem cells.

P3-D3-863

Costello Syndrome: What About GH Treatment?

Adina Manolachie^a, Cristina Rusu^b, Alina Fadur^a, Ioana Bodescu^a, Elena Braha^b, Voichita Mogosa^a, Carmen Vulpoi^a

^aDepartment of Endocrinology, University of Medicine and Pharmacy 'Gr.T.Popa', Iasi, Romania; ^bDepartment of Genetics, University of Medicine and Pharmacy 'Gr.T.Popa', Iasi, Romania

Background: Costello syndrome (CS) is a rare autosomal dominant genetic disease, first described in 1971, part of neuro-cardio-facio-cutaneous syndrome (with RAS pathway genes

mutations of MAPKinase-RASopathies), characterized by short stature, delayed mental development, joint hyperlaxity, papillomas, congenital heart defects and increased risk to develop benign or malignant solid tumors. **Case:** We present the case of a teenaged girl (15 years 7 months), the second child of an apparently healthy couple, evaluated at the Endocrinological Department in February 2014 for short stature. She presented congenital heart malformations (pulmonary valvular stenosis, interatrial septal defect type ostium secundum – operated at 1 year and 3 months, with persistent slight pulmonary valvular stenosis), delayed psychomotor development and physical dysmorphies: curly hair, high forehead, thick eyebrows and lips, down implanted ears, dysplastic nails, multiple palmar skin folds. She was later genetically diagnosed with CS (HRAS gene mutation – 11p 15.5). Physical exam confirmed the developmental delay – height 142 cm (−3.81 SD), weight 33 kg, BIII PII–III pubertal development. Bone age was delayed ~11 years. Hormonal balance revealed low basal GH 1.49 ng/ml, with insufficient response to induced hypoglycemia – max value 9.95 ng/ml, low IGF1 level 114 ng/ml. GH treatment was decided in order to improve final height. **Conclusions:** Patients with CS have high risk of developing malignancies or hypertrophic cardiomyopathy which may be (at least theoretically) favoured by the GH treatment. Actual studies did not show an increase of these complications in children with CS treated with hGH. However, due to the small number of treated children, it is not possible to exclude such an evolution. Given the important growth delay, the slight cardiac defect and the absence of solid tumors, together with the reduced risk and potential high benefits of the GH treatment, we decided to start it, with periodic evaluations.

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The Establishment of a New Paediatric Endocrinology Training Programme in South Africa

François de Villiers

MEDUNSA Campus, University of Limpopo, Pretoria, South Africa

Background: During the 1980s there were no officially accredited training programmes for subspecialty training in South Africa. Accordingly, doctors with accreditation from other countries, or with extensive experience in the subspecialty, were recognised as subspecialists, based on peer review. **Objective and hypotheses:** The objective of this poster was to document the development of a new Paediatric Endocrinology programme in a previously disadvantaged medical school. **Method:** In preparation for the HPCSA inspection (Health Professions Council of South Africa) scheduled for early 2012, a new Paediatric Endocrinology programme was developed at our university. **Results:** The Department of Paediatrics and Child Health of the MEDUNSA campus of the University of Limpopo planned a new training programme for a Paediatric Endocrinology fellow, and applied to the HPCSA for accreditation. The programme outline is as follows: the fellow will be available for endocrine and metabolic consultations during the week, and will be directly involved with all in-patient admissions. The outpatient clinic dealing with

sufficient patients for training will be handled by the fellow under supervision. During the weekly metabolic ward round patients in the wards with metabolic problems will be identified, investigated and managed by the Endocrinology fellow. A weekly postgraduate discussion will be jointly held with the Department of Chemical Pathology. A Paediatric Endocrinology journal club will alternate with endocrinology case discussions between the endocrinologists and the chemical pathologists every second week. **Conclusion:** The HPCSA panel indicated that the application was meritorious. Following further discussions, we re-submitted our application. This was successful, and we started training a fellow in January 2014. We are particularly proud of this unit, as we are only the third Paediatric Endocrinology Unit (after the Universities of Cape Town and the Witwatersrand) to be accredited in South Africa.

P3-D3-865

Side Effect of Treatment with rGH

Belacel Merouane, Baz O' Achir Samia

Pierre et Marie center, Algiers, Algeria

Background: Stunting is a common reason for consultation in pediatrics, several etiologies are responsible, although endocrine causes is rare, it is important to make the diagnosis in order to provide early adequate treatment. However the treatment by rGH is usually well tolerated, side effects should be known, including the possibility of retinal edema revealing intracranial hypertension. **Objective and hypotheses:** Our purpose is to report a side effect occurred during the initiation of treatment with GH. **Method:** We report the case of BK, aged 16 years explored for late growth without personal antecedents, parental target height 169 cm, insulin hypoglycemia test, bone age and pituitary MRI were performed. **Results:** Income in favor of GH deficiency without other abnormalities of endocrine axes, bone age estimated at 13 years and empty sella in the pituitary MRI. A treatment is conducted by NORDILET 5 mg 0.10 UI/kg per day, (22 clicks/day), the patient presented headache and visual disturbances associated with papillary edema of the retina. The treatment was stopped, symptoms disappeared. A review of control after 3 months, papillary edema disappeared, the patient is given under treatment at 0.07 IU/kg per day (15 clicks/day). The subsequent control were satisfactory. **Conclusion:** The appearance of visual disturbances and headache in children treated with rGH for growing deficit should suggest an intracranial hypertension, although this is a rare side effect, it must be evaluated, treatment should be stopped, a subsequent recovery may be considered after stabilization.

P3-D3-866

GH Treatment Adherence in Children in Latvia

Zane Eglite^{a,b}, Iveta Dzivite-Krisane^{a,b}, Una Lauga-Tunina^a, Inara Kirilova^a

^aChildren's Clinical University Hospital, Riga, Latvia; ^bRiga Stradins University, Riga, Latvia

Background: Children with different growth disorders need therapy with recombinant human GH. Although mostly therapy leads to good results there are clinical cases when the therapy is not working. One of the reasons is patient's and patient's family's adherence. That's why it is necessary to explore what are the adherence and its impact on therapy's outcome. Growth disorders can make an influence to all humans' life, that's why if it is possible to do something to change it must be done. It is necessary to explore the situation in Latvia so that we can make conclusions and recommendations how to improve the situation. **Objective and hypotheses:** There is hypothesis to prove that children in Latvia with GH therapy have bad adherence and it impacts the therapy's outcome. **Method:** Research is still going on. It is retrospective-prospective research. Literature of the last 5–10 years has been analysed. Statistical analysis is made with material that is taken from Children Clinical University Hospital ambulatory cards after special questionnaire. Patients aged 0–18 years are included, who are on GH treatment on years 2013–2014 and uses Easypod device. **Results:** As the research continues, the final results will follow. **Conclusion:** Already from the first results we can conclude, that adherence to the treatment with Easypod device is quite well. We can also see that pubertal children have worse adherence than smaller children, because in pubertal period parents don't have so big influence on therapy and the therapy is more superficially done. The research must be continued to see if in Latvian population computerized and controlled therapy really gives better results.

P3-D3-867

The Effect of GH and Pubertal Induction Therapy in Turner Syndrome

Sukran Darcana^a, Samim Ozen^a, Ozge Koprulu^c, Tahir Atik^b, Ferda Ozkinay^b, Damla Goksen^a

^aDepartment of Pediatric Endocrinology, Ege University School of Medicine, Izmir, Turkey; ^bDepartment of Pediatric Genetics, Ege University School of Medicine, Izmir, Turkey; ^cDepartment of Pediatrics, Ege University School of Medicine, Izmir, Turkey

Background: The most prominent clinical feature in patients with Turner syndrome (TS) is short stature. **Objective and hypotheses:** To assess the effect of GH and pubertal induction therapy on height gain in patients with TS. **Method:** 58 TS patients with a mean age of 18.9 ± 7.2 years were documented retrospectively. Clinical findings, karyotype, impact of baseline age, dosage, baseline bone age, duration of the GH and pubertal induction therapy was investigated. **Results:** On admission mean age and height SDS was, 9.6 ± 4.2 years and -3.1 ± 1.1 s.d. respectively. Difference between chronologic and bone age (CA–BA) was -2.3 ± 1.5 years. GH therapy (0.038 ± 0.008 mg/kg per day) was initiated in 52 of the patients (89%) (mean height SDS: -3.3 ± 1.1) at an age of 10 ± 3.3 years and a bone age of 7.9 ± 2.9 years. CA–BA was: -2.3 ± 1.5 years. Estrogen treatment for

pubertal induction was given at an age of 14.6 ± 1.5 years and bone age of 11.6 ± 1.6 years. Mean final height was 147 ± 5.5 cm (final height SDS -2 ± 0.95) in the 21 patients who had achieved final height. 32 of the patients were diagnosed below 10 years (group 1) and 26 above 10 years (group 2). Six of the patients (18.7%) from group 1 and 15 of the patients (57.6%) from group 2 reached to final height. Final height SDS of the two groups did not reach to statistical significance ($P=0.133$). Positive correlation was found between height gain and baseline age, initial age of GH and CA-BA ($P<0.05$). Height gain in patients treated with GH was 0.9 ± 1.2 s.d. while in patients untreated was 0.2 ± 1.5 s.d. ($P=0.18$). **Conclusion:** Early diagnosis, early initiation of GH therapy and the delay of initial bone age are important for height gain.

progression of hearing loss, whether conductive or sensorineural. Once hearing loss is recognized, patients should be fully investigated to exclude other causes, especially in cases of unilateral SNHL.

P3-D3-868

Hearing Loss in Turner Syndrome

Ouidad Baz, Mourad Semrouni, Samia Sakher

Endocrinology Department, Pierre and Marie Curie Center, Algiers, Algeria

Background: Hearing problems and ear malfunctions are frequent in Turner syndrome (TS) and correlate with the karyotype. As a result of the frequent otitis media, conductive hearing loss is common in girls with TS. Sensorineural hearing loss is also common and may occur as early as 6 years of age. **Objective and hypotheses:** This study reviewed a cohort of children to clarify the incidence and pattern of conductive and sensorineural hearing loss in girls with TS. **Method:** Retrospective cohort study of 27 girls with TS was identified by karyotype 14 monosomy, four mosaisms and nine structure anomalies – mean age 11 years 4 months. A retrospective review was undertaken and otologic status assigned. **Results:** Middle ear disease affected 30% of patients. 34% of this children demonstrated hearing loss attributable to TS. Sensorineural hearing loss was found in 31% of them and conductive hearing loss in 44% of cases. Cholesteatoma was found in one girl aged 12 years and was cure by surgery at 7 years. **Conclusion:** The only possible intervention to reduce hearing loss in girls and women with TS remains the assiduous treatment of ear problems in childhood. All Turner individuals should be screened second yearly for onset and

P3-D3-869

Genotype-Phenotype Correlation in Turner Syndrome

Adel Djermane^a, Asmahane Ladjouze^b, Yasmine Ouarezki^c, Belaid Ait-Abdelkader^d, Leila Kedji^b, Abdeljalil Maoudj^b, Karima Berkouk^b, Lakhder Griene^d, Abdennour Laraba^b

^aDepartment of Paediatrics, EPH Gouraya, Tipaza, Algeria;

^bDepartment of Paediatrics, CHU Bab El Oued, Algiers, Algeria;

^cDepartment of Neonatology, EPSP Baraki, Algiers, Algeria;

^dLaboratory of Hormonology, CPMC, Algiers, Algeria

Background: Short stature and gonadal dysgenesis are the two characteristic clinical features of Turner syndrome (TS), but multiple systems may be affected. **Aims:** To evaluate TS prevalence in girls presenting with short stature; and to establish a correlation between karyotype and associated features. **Subjects and methods:** Retrospective study of all patients diagnosed with TS (December 2007–March 2013). **Results:** (as mean \pm s.d.) Of 469 girls referred with short stature, 46 (9.8%) were diagnosed with TS on the basis of clinical features and elevated FSH, with karyotype confirmation in 39 (8%). Age at diagnosis was 8.6 ± 5.3 years, with four girls (9%) diagnosed during infancy and delayed diagnosis until adolescence in 17 (37%). Height at diagnosis was -3.07 ± 1.14 SDS. After infancy, short stature was the most common presenting feature (89%). Girls with 45,X/46,X, iXq or 46, XiXq karyotypes were i) shorter than 45,X girls (height SDS 3.35 ± 1.3 vs -2.81 ± 1.4); ii) more likely to have hypothyroidism (7%), and iii) sensori-neural deafness (15%). **Conclusions:** A significant proportion of girls referred with short stature have TS. Mosaic karyotypes are most common. Phenotypic features including renal malformations, cardiac disease, and dysmorphic features are correlated with degree of X chromosome loss; structural anomalies with thyroid disease. Mean age at diagnosis of TS is relatively late, a situation which could be improved by providing appropriate measuring equipment for school doctors to the existing community child health program in Algeria.

Table 1. (abstract for P3-D3-869)

Karyotype	n	Cardiac disease	Renal malformation	Thyroid disease	Clinical features	Deafness (audiogram)	Height SDS
No assessed	39	32	23	29	39	13	-3.07 ± 1.14
45,X	9	4	1	0	5	1	-2.81 ± 1.4
45,X/46,XX	11	3	1	0	2	1	-2.54 ± 0.67
45,X/46, XiXq	8	1	0	2	2	2	-3.35 ± 1.3
Other	11	5	1	1	3	2	-3.53 ± 1.1

P3-D3-870

Primary Amenorrhea with Normal Stature: Why Not Turner Syndrome?

Ioana Hristov^a, Ana Hreniuc^a, Simona Gherasim^a,
Maria-Christina Ungureanu^{a,b}, Cristina Preda^{a,b}, Carmen Vulpoi^{a,b},
Voichita Mogos^{a,b}, Letitia Leustean^{a,b}

^aEndocrinology Department, 'St Spiridon' Hospital, Iasi, Romania;

^bUniversity of Medicine and Pharmacy 'Gr. T. Popa', Iasi, Romania

Background: Turner syndrome is the most common sex chromosome disorder in females and occurs in about 1/2500 newborn girls worldwide. On chromosomal analysis, the various karyotypes observed are: 45,X (50%); 45,X/46,XX (20%); 46,X,i(Xq) (15%); 46,X,r(X) or 46,X,del(X) (10%); and others (5%). **Objective and hypotheses:** We present the case of a 17-year-old girl referred to our service for primary amenorrhea. Clinical examination: height = 163 cm (62nd percentile), weight = 59 kg. Sexual development was: PIII BII. She associates several suggestive clinical aspects for Turner syndrome even if there is no stature deficit. **Method:** The result of the Barr test (sexual chromatin) was positive, so an X chromosome monosomy (45,XO) was not confirmed. We continued the genetic investigation with a karyotype analysis, followed by a structural analysis of the X chromosomes, confirming a structural anomaly of the X chromosome: long arm deletion of X chromosome (46,X,del(X) (q13-qter)). Primary amenorrhea associated with a hormonal profile of hypogonadotropic hypogonadism is suggestive for a gonadal dysgenesis. Pelvis ultrasonography revealed a hypoplastic uterus, absence of the right ovary and a small left ovary, with three to four follicles. No associated cardiac or renal malformations were revealed. **Results:** Under oestro-progestative substitution treatment, menarche, sexual development (PIV BIII), and additional stature gain (5 cm/6 months) were obtained. The hand bone age of 14 years shows an additional growth potential. **Conclusion:** No stature deficit (non-mutated SHOX gene) associated with clinical features of Turner syndrome. Rare structural anomaly of the X chromosome: long arm deletion, usually associated with secondary amenorrhea (DAX1 gene responsible for ovaries development being situated on the short arm of the X chromosome). Studies revealed that large Xq deletions proximal to Xq21 led to gonadal dysgenesis, and half of these patients showed Turner syndrome stigmata. In the literature we find several cases of Xq deletion.

P3-D3-871

The Causes of Short Stature in Turner Syndrome

Ruimin Chen, Ying Zhang, Xiaohong Yang, Xiangquan Lin, Xin Yuan
Fuzhou Children's Hospital of Fujian, Fuzhou, Fujian, China

Background: Turner syndrome (TS) is due to complete or partial deletion of an X chromosome. The most common clinical features encountered in TS patients were short stature and primary

amenorrhea. **Objective and hypotheses:** The purpose of this study was to investigate the causes of short stature in TS. **Method:** 86 patients with TS were diagnosed by karyotypes from 2004 to 2013, the karyotypes distribution were as follows: 64 patients with total haploinsufficiency of the short arm of chromosome X, 18 patients with partly haploinsufficiency of the short arm of chromosome X, and four patients without haploinsufficiency of the short arm of chromosome X. All patients received GH stimulated test, 47 patients were GH deficiency (GHD) and 39 patients were normal. All patients detected IGF1, and divided into three groups according to different IGF1 level. 86 patients divided into two groups according to thyroid function. **Results:** Ht SDS in three groups according to the deletion of the X chromosome short arm were (-4.39 ± 1.08), (-3.26 ± 1.25), and (-2.84 ± 0.15) ($P < 0.05$). The proportion of GHD in the three groups were 62.5, 38.9, and 0% ($P < 0.05$). Ht SDS of different IGF1 degree groups were (-4.37 ± 1.10), (-3.82 ± 1.07), and (-3.25 ± 0.91) ($P < 0.05$). Ht SDS in GHD group and non-GHD group were (-4.24 ± 1.00) and (-4.02 ± 1.32) ($P > 0.05$). Ht SDS of hypothyroidism group was not different from the non-hypothyroidism group ($P > 0.05$). **Conclusion:** The deletion of X chromosome short arm may induce the short stature in TS. The GH-IGF1 axis in TS was impaired but GHD and hypothyroidism were not related to degree of short stature in TS.

P3-D3-872

Descriptive Analyses of Turner Syndrome

Mimouna Bessahraoui, Malika Naceur, Sakina Niar, Amel Zennaki,
Farouk Arbi, Meriem Ousaleh, Karim Bouziane-Nedjadi

Department of Pediatrics 'C', CHU Oran, Oran, Algeria

Background: Turner syndrome (TS) is a genetic syndrome caused by complete or partial absence of an X chromosome. It is the most common diagnosed sex chromosome abnormality in women, affecting 1/2000–2500 female live births. **Objective and hypotheses:** To determine to establish the clinical, hormonal, cytogenetic, and evolutive pattern of children with TS and to establish for correlations between genotype and phenotype. **Method:** We describe a retrospective study (2007–2013) on 29 patients with TS. **Results:** Mean age at diagnosis was 9 ± 4 years. A significant short stature at diagnosis (-4 ± 1 DS), it was more frequent among the youngest and monosomics. The dysmorphic syndrome was observed in 40% of cases; it was significantly more frequent in monosomics. Delayed puberty was present in 28% of cases, it was almost constant in monosomics. Consanguinity was found in 40% of cases. The karyotype revealed a monosomics in 22% of cases and mosaicism in 88% of cases. Delayed bone age revealed in 55% of cases. Our results report a high frequency of autoimmune diseases (40% of cases) including dysthyroidism and celiac disease. Disorders of sex development was found in three cases. **Conclusion:** Our study reported a higher frequency of short stature related to delayed age of diagnosis and we noted a high frequency of autoimmune diseases. TS is the main problems a multidisciplinary team monitors and manages during childhood.

P3-D3-873

Phenotypic and Genotypic Characteristics of Patients with Turner Syndrome

Soumeya Fedala^a, Ali el Mahdi Haddam^b, Farida Chentli^a,
Djamila Meskine^b, Lyna Akkache^a, Hafsa Siyoucef^b

^aBab el Oued Hospital, Algiers, Algeria; ^bBologhine Hospital, Algiers, Algeria

Background: Turner syndrome (TS) is the most common chromosomal abnormality in females (prevalence 1/2500 births). It is related to the absence or abnormality of one of the two X chromosomes. It is characterized by a short stature, gonadal failure and a many diseases that reduce life expectancy of patients. **Objective and hypotheses:** Report clinical, hormonal, cytogenetics, and evolutionary TS characteristics then correlate the karyotype and clinical expression of TS. **Method:** Retrospective study on 50 cases of patients with TS and followed between 2000 and 2013. Incomplete records ($n=40$) were not included in the study. All patients underwent a clinical examination, radiological assessment, hormonal exploration, and cytogenetic assessment: test BARR, karyotype. **Results:** The average age at diagnosis is 14 years (20–33 years). The time between recognition of the disorders and the first consultation is 5.22 years (0–18 years). 65% of patients consulted for growth retardation associated with a impuberism in 35% of cases. There was a dysmorphic syndrome in 30% of cases. 41.6% of patients had a monosomy, 50% have a mosaïque. In the others cases, there were a structural abnormalities of the X chromosome. A genotype–phenotype correlation is observed in all cases. **Conclusion:** TS is expressed variably depending on the age at diagnosis. However despite often suggestive clinical picture, diagnosis is often delayed. Recent molecular approaches have identified many chromosomal formulas correlation with phenotype and genotype.

P3-D1-874

Clinical Characteristics and Phenotype–Genotype Analysis in Turkish Patients with Congenital Hyperinsulinism; Predominance of Recessive K_{ATP} Channel Mutations

Huseyin Demirbilek^{a,c}, Ved Bhushan Arya^{a,b}, Mehmet Nuri Ozbek^d,
Aysehan Akinci^e, Murat Dogan^f, Fatma Demirel^c, Jayne Houghton^g,
Sultan Kaba^f, Fatma Guzel^c, Riza Taner Baran^c, Sema Unal^c,
Selahattin Tekkes^h, Sarah E Flanagan^g, Sian Ellard^g,
Khalid Hussain^{a,b}

^aDepartment of Paediatric Endocrinology, Great Ormond Street Hospital for Children NHS Trust, London, UK; ^bThe Institute of Child Health, University College London, London, UK; ^cDepartments of Paediatric Endocrinology, Ankara Pediatric Hematology and Oncology Research and Training Hospital, Ankara, Turkey; ^dDepartments of Paediatric Endocrinology, Children State Hospital, Diyarbakir, Turkey; ^eDepartments of Paediatric Endocrinology, İnönü University, Malatya, Turkey; ^fDepartments of Paediatric Endocrinology, Yüzüncü Yıl University, Van, Turkey; ^gInstitute of

Biomedical and Clinical Science, University of Exeter Medical School, Exeter, UK; ^hDepartment of Medical Biology and Genetics, Dicle University, Diyarbakir, Turkey

Background: Congenital hyperinsulinism (CHI) is the most common cause of hyperinsulinaemic hypoglycaemia in the neonatal, infancy, and childhood periods. Its clinical presentation, histology and underlying molecular biology are extremely heterogeneous. **Objective and hypotheses:** To describe the clinical characteristics, analyse the genotype–phenotype correlations and describe the treatment outcome of Turkish CHI patients. **Method:** Thirty-five patients with CHI were retrospectively recruited from four large paediatric endocrine centres in Turkey. Detailed clinical, biochemical and genotype information was collected. **Results:** Diazoxide-unresponsiveness was observed in nearly-half of the patients ($n=17$; 48.5%). Among diazoxide-unresponsive patients, mutations in *ABCC8/KCNJ11* were identified in 16 (94%). Among diazoxide-responsive patients ($n=18$), mutations were identified in two patients (11%). Genotype–phenotype correlation revealed that mutations in *ABCC8/KCNJ11* were associated with increased birth weight and early age of presentation. Five patients had p.L1171fs (c.3512del) *ABCC8* mutations, suggestive of a founder effect. The rate of detection of a pathogenic mutation was higher in consanguineous families compared to non-consanguineous families (87.5 vs 21%; $P<0.0001$). Among diazoxide-unresponsive group, ten patients were medically managed with octreotide therapy and carbohydrate rich feeds and six patients underwent subtotal pancreatectomy. There was high incidence of developmental delay and cerebral palsy among diazoxide-unresponsive patients. **Conclusion:** This is the largest study to report genotype–phenotype correlations among Turkish patients with CHI. Mutations in *ABCC8* and *KCNJ11* are the most common causes of CHI in Turkish patients (48.6%). There is higher likelihood of a genetic diagnosis in patients with early age of presentation, higher birth weight and those from consanguineous pedigrees.

P3-D1-875

Clinical Remission in a Patient with Congenital Hyperinsulinism due to Paternally Inherited Two Novel Mutations in *KCNJ11* Gene

Ayşe Nurcan Cebeci^a, Jayne Houghton^b, Sian Ellard^b

^aDerince Training and Research Hospital, Pediatric Endocrinology, Kocaeli, Turkey; ^bInstitute of Biomedical and Clinical Science, University of Exeter Medical School, Exeter, UK

Background: Congenital hyperinsulinism (CHI) is the most common cause of persistent and profound hypoglycemia in infants. There are two distinct histologic forms of CHI, diffuse and focal. The distinction between these forms is important in patients who fail medical therapy since surgical strategies may vary. Focal lesions occur due to paternally inherited recessive mutation in *ABCC8* or *KCNJ11* genes with somatic loss of the maternal 11p15

region (paternal uniparental disomy). Patients with focal CHI can be cured with partial pancreatectomy, but a few cases with focal lesion have been reported to have spontaneous resolution. **Case report:** Twenty-seven months old male patient has been diagnosed with diazoxide unresponsive CHI in neonatal period in another center. He has been using octreotide treatment since discharge. His parents were consanguineous with no family history of diabetes. On physical examination the patient had microcephaly, bilateral medial strabismus, and neuromotor retardation. His height was 83.5 cm (−1.98 SDS), weight: 10.8 kg (−1.86 SDS). The patient was subjected to genetic analysis for determining long-term therapeutic approach. Mutational analysis revealed paternally inherited two novel mutations of KCJN11 gene (p.L270M and p.E288K). A maternally inherited KCJN11 mutation has not been found and therefore a focal lesion is highly suspected. Since 18-Floro-L-DOPA positron emission tomography (PET) is not available in our country, the focal lesion could not be identified. In the clinical course we observed that the patient tolerated overnight fasting under very low dose octreotide and consider clinical remission. He has been receiving no medications for the last ten months and is still euglycemic. **Conclusion:** Genetic analysis is very useful to identify focal CHI in those patients who could be not subjected to 18-Floro-L-DOPA-PET. Although very rare, patients with paternally inherited KCJN11 mutations might respond to medical treatment and subsequently clinical remission might be observed.

P3-D1-876

Biochemical Studies in Patients with Hyperinsulinaemic Hypoglycaemia

Hessah Al Otaibi^a, Senthil Senniappan^b, Syeda Alam^b, Khalid Hussain^b

^aKing Khalid University Hospital, Riyadh, Saudi Arabia; ^bGreat Ormond Street Hospital for Children, London, UK

Background: Hyperinsulinaemic hypoglycaemia (HH) is characterized by the dysregulated secretion of insulin from the pancreatic β -cell. It is a major cause of severe and persistent hypoglycaemia in the newborn period. The rapid diagnosis and avoidance of recurrent episodes of hypoglycaemia are vital in preventing brain damage. **Objective and hypotheses:** To assess if the serum insulin measured at the time of hypoglycaemia in neonates with HH could be correlated with the severity of the disease or any of the other biochemical parameters. **Method:** Retrospectively biochemical data was collected on 90 neonates (gestational age 32–42 weeks and birth weight 2–5.6 kg) with a diagnosis of HH based on (glucose requirement <8 mg/kg per min, low β -hydroxybutyrate and fatty acid concentrations) who had undergone fasting studies. Also, other parameters like birth weight and gestational age were compared to the serum insulin level at the time of hypoglycaemia. **Results:** There was no correlation between the serum insulin level and severity of hypoglycaemia and some of the patients have undetectable serum insulin despite severe hypoglycaemia and a high glucose

infusion rate. Also we observed a greater effect of insulin on ketogenesis than on the lipolysis. We noticed no correlation between birth weight and the serum insulin or glucose level at the time of hypoglycaemia or on the glucose infusion rate. **Conclusion:** We have shown in a large cohort study that the diagnosis of HH should not be based on an isolated serum insulin concentration but on clinical findings (glucose requirement <8 mg/kg per min) and the biochemical of insulin action (low β -hydroxy butyrate and fatty acid concentration).

P3-D1-877

Congenital Hyperinsulinism: Clinical and Molecular Characteristics of Brazilian Patients

Raphael Liberatore Jr^a, Carlos Martinelli Jr^a, Gil Guerra Jr^b, Thais Della Manna^c, Ivani Silva^d

^aFMRP-USP, Ribeirao Preto, Brazil; ^bUNICAMP, Campinas, Brazil; ^cICr-HC-FMUSP, Sao Paulo, Brazil; ^dUFMG, Belo Horizonte, Brazil

Background: Congenital hyperinsulinism (CH) is the most common cause of persistent hypoglycemia in neonatal period. The inadequate secretion of insulin leads to high morbidity and mortality in those newborns. Despite the recent progress in the diagnosis and management of CH, until recently, the situation in Brazil has been that of early 1990's. The epidemiology is unknown and state-of-the art management has not been available. **Objective and hypotheses:** We proposed to review clinical and molecular data from the cases of Brazilian patients with CH. **Method:** All centers of pediatric endocrinology were invited to participate, and except the north region of the country, all center sent clinical data and blood species. **Results:** 61 cases of CH were reviewed, 36 (59%) male, gestational age ranged between 32 and 41 weeks (M: 37,6). Macrosomia occurred in 14 cases (28%) and the age at the diagnosis ranged from 1 to 1080 days (M: 75.13) and more than 90 days in 28% of the cases. Glucose level at diagnosis range from 5 to 77 mg/dl (28.5) and insulin level 2.5 to 147 mU/ml. Cetone, ammonia and free fat acid levels were achieved in only 14% of the cases. Most part of the cases used prednisone as the first treatment although 40 cases used diazoxide. In 40% of the cases medical treatment was not effective and surgery was necessary. All histological forms were diffuse. Molecular analysis were made in 53/61 cases. ABCC8 mutations were found in 15/53 cases and KCNJ11 mutations in 6/53. Together, ABCC8 and KCNJ11 mutations occurred in 40% of the cases. Clinical and molecular correlations were impossible as 68% of the cases that used diazoxide the dosage were too small to check clinical response. Also all surgery cases were diffuse. GLUD1 mutations were found in 9/53 cases, no one with result of ammonia level. GCK mutations were found in 3/53 cases, and none mutations were found at HADH, SLC16A1, and HNF4A genes. **Conclusion:** Mutations were found in 63% of the cases, but no clinical and molecular correlations were possible caused by a no patronization of the diagnostic exams and medical treatment.

P3-D1-878

Clinical and Genetic Analysis of 95 Cases of Congenital Hyperinsulinism

Shuyue Huang, Chunxiu Gong, Chang Su, Zhan Qi, Di Wu, Bingyan Cao, Yi Gu, Wenjing Li, Min Liu, Xuejun Liang

Beijing Children's Hospital, Beijing, China

Background: We want to know the clinical presentation and genetic mutation of congenital hyperinsulinism (CHI) patients in our country. **Objective and hypotheses:** To investigate the clinical outcomes and gene mutations related to CHI in our patients. **Method:** We studied the therapeutic outcomes of 95 cases of CHI and analyzed the associations between gene mutations and clinical features in 55 cases. **Results:** Among all 95 CHI cases, 36 (38%) experienced misdiagnosis. 82 (86%) children were given diazoxide therapy based on an age-dependent feeding frequency, and 54 (66%) cases showed effective. Five patients were treated with octreotide for 1–4 months, and four showed a positive response. Non-surgical therapy was effective in 71 (75%) cases. Four children received subtotal pancreatectomy, and three had abnormal glucose metabolism. The side-effects of diazoxide treatment included: sodium and water retention in 55 (67%) cases, four cases showing intolerance; gastrointestinal reactions in 41 (50%) cases, eight intolerance and stopped; polytrichia in 25 (30%) cases; and thrombocytopenia in five cases. One patient complicated syndrome of inappropriate antidiuretic hormone. The remission rate of hypoglycemia was 59 and 71% for children over 2 and 3 years old respectively. Thirty-five (37%) patients had nervous complications. The identified gene mutation rate was 38% for CHI-related genes and 33% for K channel-related genes. Early onset and lower diazoxide respond rate were associated with gene mutations. **Conclusion:** Therapeutic outcomes based on age-dependent feeding were positive but varied greatly with subtotal pancreatectomy. The effectiveness of non-surgical therapy may partially be the result of a low K channel gene mutation rate. Hence, we do not recommend operation before typing can be clarified.

P3-D1-879

Congenital Hyperinsulinism: a Single-Center Experience

Murat Dogan, Sultan Kaba, Keziban Bulan

Yuzuncu Yil University, Van, Turkey

Background: Clinically, hyperinsulinemic hypoglycemia (HH) can cause apnea, growth retardation and learning disorders. Early diagnosis and meticulous follow-up are of importance to prevent undesired neurological outcomes. Congenital hyperinsulinism results from eight distinct gene defects. These genes include ABCC8, KCNJ11, GLUD1, GCK, HADH, SLC16A1, HNF4A, and UCP2. The most common causes are autosomal recessive

mutations of ABCC8 and KCNJ11 genes (5). **Material and method:** In this study, we retrospectively reviewed seven patients with HH who was diagnosed before May 2013 and have been followed in Pediatric Endocrinology Department of Van Yüzüncü Yil University, Medicine School. All eight patients and their parents and siblings were screened for genetic defect. **Findings:** In the present study, seven patients with HH, who was diagnosed before May 2013 and have been followed in Pediatric Endocrinology Department of Van Yüzüncü Yil University, Medicine School, were reviewed. There was consanguinity (first cousins) between parents in one patient, while there was no consanguinity in remaining seven patients. There were three girls and five boys. Age at onset of HH was within first 4 weeks of life in five patients while it was 6 weeks of age in one patient. Of the remaining patients, one was diagnosed at 6 months of age while other was diagnosed at 11 months of age. All patients were term infants with normal birth weight except two preterm boys delivered by cesarean section. In one patient (preterm infant), hyperinsulinism was resolved on the month 3 of age during follow-up and medical therapy was no longer necessary. All eight patients and their family were screened for mutations in eight distinct genes. ABCC8 and KCJN11 gene studies were completed and mutations were detected in three patients who had undergone subtotal pancreatectomy. A novel mutation (p.L26K homozygote) was detected in KCJN11 gene in one patient. Parents were first cousins in the patient with mutation in XXX gene. Screening for mutations in GLUD1, GCK, HADH, SLC16A1, HNF4A, and UCP2 genes is still proceeding. **Conclusion:** In the management of preterm infants with hypoglycemia, hyperinsulinism must be excluded before suggesting prematurity as the cause of hypoglycemia. Blood sampling for metabolic markers at the time of hypoglycemia and assessment of glucagon responsiveness are indispensable for diagnosis of hyperinsulinemia. Screening patients with persistent HH for gene defects will guide for genetic counseling as well as management.

P3-D1-880

Persistent Hyperinsulinemic Hypoglycemia of an Infancy Carrying *abcc8* arg598stop Mutation

Jianfang Zhu^a, Weifen Zhu^b, Chunlin Wang^a, Li Liang^a

^aThe First Hospital of Zhejiang University School of Medicine, Hangzhou, China; ^bZhejiang University School of Medicine, Hangzhou, China

Background: Congenital hyperinsulinism (CHI) is the most important causes of persistent hypoglycemia in infants during the first few days after birth. **Objective and hypotheses:** We report an 11-day-old female infant admitted with persistent hypoglycemia since 11 h after born. **Method:** Multiple tests and imageological examinations were used to detect the cause of hypoglycemia. A whole-body PET CT-scan with [¹⁸F]-L-dihydroxyphenylalanine (DOPA) to detect lesions of organs. PCR and directly sequencing for mutation detection of all the

39 exons and the flanking intron–exon boundaries of ABCC8 gene. **Results:** Blood biochemical examinations shown CHI was diagnosed definitely. Genetic analysis of the infant revealed a new heterozygous ABCC8 Arg598stop mutation, but not in the parents. The whole-body PET CT-scan with [D]-L-DOPA revealed a mildly hypermetabolic lesion in distal part of the body of pancreas. Then partial lesion resection of pancreas was performed, and the infant remained euglycemic with normal feeding. Clinicopathologic and immunohistochemical analysis prompted focal nesidioblastosis. **Conclusion:** We reported a novel Arg598stop mutation of ABCC8 gene in an infant of CHI. [D]-L-DOPA PET can help to identify of focal and diffuse forms of CHI effectively. Indeed, the high sensitivity of this method could aid surgeons to perform a curative partial resection of pancreas without the high risk of long-term diabetes mellitus.

P3-D1-881

A Case of Hyperinsulinism/Hyperammonemia Syndrome

Young Suk Shim^a, Hwal Rim Jeong^a, Hae Sang Lee^a, Jung Sub Lim^b, Jin Soon Hwang^a

^bDepartment of Pediatrics, Ajou University Hospital, Ajou University School of Medicine, Suwon/Gyeonggi-do, Republic of Korea; ^bDepartment of Pediatrics, Korea Cancer Center Hospital, Seoul/Seoul, Republic of Korea

Background: Hyperinsulinism/hyperammonemia (HI/HA) syndrome is a form of congenital hyperinsulinism (CHI) caused by a mutation in the GLUD1 gene. It is characterized by hyperinsulinemic hypoglycemia accompanying hyperammonemia. **Objective and hypotheses:** We report HI/HA syndrome with a 4-month-old male who hypoglycemic seizure. **Method:** A 4-month-old male infant presented with seizure caused by fasting-induced hypoglycemia. At the time of seizure, the serum glucose, ammonia, insulin, and C-peptide levels were 49 mg/dl, 216 $\mu\text{mol/l}$, 7.1 $\mu\text{U/ml}$, and 2.54 ng/ml respectively. Even though he was fed as usual, his blood glucose level reduced to below 50 mg/dl with an increased plasma insulin level. **Results:** He was thought to have hyperinsulinemic hypoglycemia associated with hyperammonemia. He was administered diazoxide, following which his blood glucose levels were maintained within the normal range. **Conclusion:** HI/HA syndrome is a diazoxide-responsive form of CHI, early detection and appropriate management are important to prevent brain injury.

P3-D1-882

Project Episga: PreMeb Presentation, Subject Recruitment, and Initial Data

Ignacio Diez-Lopez^a, Ainhoa Sarasua-Miranda^a, Marta Hoyo-Moracho^a, Isabel Lorente-Blazquez^a, Raquel Gomez de Segura Lorente^a, Dorleta Pérez Campos^a, Victor Manuel Rodriguez-Rivera^b, Maria Teresa Macarulla-Arenaza^b

^aUniversity Hospital of Alava, Vitoria, Research Group of the Child PEG, Vitoria/Basque Country, Spain; ^bNutrition and Obesity if Basque Country University, Vitoria/Basque Country, Spain

Background: Up to 50% SGA did not do a proper catch up (for over/under) and may have implications in size, metabolic, cardiovascular. Arises: epiSGA – PreMeb Project. Global approach to study. **Objective:** Create clinical cohort of SGA for monitoring, assessment catch-up, use GHRH requirements, environmental/social factors and variables influence on clinical, laboratory and metabolic profiles in order to progress in the knowledge of natural history. Processing graph anthropometric and biochemical normalcy tables in each branch. **Material and methods:** Study and classification newborn singletons live our hospital (years 2012–2014) as age and weight/height tables regarding the Spanish (2008) (balance accuracy and standardized stadiometer) *n* estimated 110 cases. Visits to regulated 0, 3, 6, 9, 12, 15, 18, and 24 months. **Initial results:** SGA recruited in 6 months (20 ♂, 58%). Average age 30.5 years mother SDS 2.6 (22–41), first pregnant 24/34 (70%), Basque origin 30/34 (88%), and previous children SGA 5/34 (14%). Mean BMI 22.5 kg/m² SDS2.8 (19–26), mean height 162.5 cm stem. SDS 3.8 (156–186). Gestation habitual smoker in 15/34 (45%), middle eight cigarettes/day SDS 4 (3–15). Levels of primary studies (10%), FP (45%), diploma (30%), and graduate (15%). Working during pregnancy 24/34 (70%), with over 3 h of walking per week 80%. Taking drugs during pregnancy 11/34 (32%), 75% for asthma (inhaled B2/budesonida), 15% (l-thyroxine) 10% other. Pathologies associated with pregnancy 18/34 (53%) (gestosis, pre-eclampsia, DM, thyroiditis, and psychogenic stress). Term delivery 23/34 (67%), vaginal delivery in 30/34 (88%). 2.6 SDS medium weight (–3.5 to 2) 2.5 SDS medium size (–3.2 to 2.1) sex and corresponding EG. EBF 23/34 (68%) at 1 month of life. Income or pathology RN on first month of life 10/34 (29%). **Results:** The current lifestyle of pregnant women (age, snuff, stress, and work), taking regular medication (asthma) leads to a higher rate of SGA. Children born SGA seems requiring greater use of artificial feeding and is a population risk of disease in the first month of life.

P3-D1-883

Iodine Status in Pregnant, Lactating Mothers and their Infants and Effects of Iodine Supplementation

Natalya Zelinskaya^a, Marina Mamenko^b, Natalya Belykh^c

^aUkrainian Scientific Center of Endocrine Surgery MOH of Ukraine, Kiev, Ukraine; ^bLuhansk State Medical University, Luhansk, Ukraine; ^cLuhansk State Medical University, Luhansk, Ukraine

Background: Iodine deficiency has multiple adverse effects in humans, termed iodine deficiency disorders, due to inadequate thyroid hormone production. Iodine deficiency during pregnancy and infancy may impair growth and neurodevelopment of the offspring and increase infant mortality. **Objectives:** To evaluate

effects of iodine supplementation in pregnant, lactating women and their infants at the East of Ukraine. **Methods:** Target groups: epidemiological survey – pregnant ($n=1052$); dynamic observation – lactating women; and their infants ($n=183$). Dietary iodine intake in population: urinary iodine concentration (UIC) and breast milk iodine concentration (BMIC) by Sandell-Kolthoff reaction. Thyroid size: by ultrasonography. Iodine supplementation: by drugs potassium iodide 200 $\mu\text{g}/\text{day}$. Epidemiological criteria (WHO, 2001 and 2007). **Results:** The median UIC (MUIC) in pregnant was 78.2 $\mu\text{g}/\text{l}$ (range 17.0–510.7 $\mu\text{g}/\text{l}$). MUIC in pregnant with iodine supplementation was significantly higher than in those without iodine prophylaxis: 146.9 vs 67.3 $\mu\text{g}/\text{l}$ respectively ($P=0.001$). MUIC in lactating mothers was 91.2 $\mu\text{g}/\text{l}$ (range 16.8–302.3 $\mu\text{g}/\text{l}$). MUIC in mothers with iodine supplementation was higher (112.2 vs 68.8 $\mu\text{g}/\text{l}$ respectively, $P=0.001$). Median BMIC was 101.4 $\mu\text{g}/\text{l}$ in mothers with iodine supplementation vs 56.1 $\mu\text{g}/\text{l}$ in lactating women without it ($P=0.001$). MUIC in breast-feed infants was 81.2 vs 282.0 $\mu\text{g}/\text{l}$ in formula-feeding infants. MUIC in breast-feeding infants of mothers with iodine supplementation was 177.1 vs 81.5 $\mu\text{g}/\text{l}$ in infants of mothers without iodine prophylaxis ($P<0.001$). Median BMIC was 101.4 $\mu\text{g}/\text{l}$ in mothers taking iodine supplements vs women without it (56.1 $\mu\text{g}/\text{l}$, $P<0.001$). **Conclusions:** The MUIC in pregnant, lactating mothers and their breast-feeding infants demonstrated their insufficient iodine status. Iodine supplementation in pregnant and lactating mothers improves their own iodine status and iodine status in breast-fed infants.

P3-D1-884

Gender Differences in Sex Steroids and IGF1 at Birth and at 5 Years of Age

Kerstin Allvin, Ann-Katrine Karlsson, Carina Ankarberg-Lindgren, Jovanna Dahlgren

Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

Background: Gender differences in sex steroids and IGF1 are well known from pubertal years into adulthood. Few studies report data from pre-school years. **Objective and hypotheses:** To study gender specific changes in sex steroids and IGF1 at birth and at 5 years of age and correlate these with auxological measurements. There are gender differences in IGF1 levels due to differences in sex steroids already at birth and during pre-school years. **Method:** Eighty prepubertal children (35 females and 45 males) born moderately preterm (gestational age 32–37 weeks) were examined with blood sampling and auxological measurements at birth and 5 years of age. Estradiol, testosterone, and IGF1 were measured with RIAs. **Results:** At birth, IGF1 levels for boys were significantly lower; median (range) 38 (7–93) $\mu\text{g}/\text{l}$ than for girls 54 (8–96) $\mu\text{g}/\text{l}$, $P<0.05$. Testosterone levels were higher for boys 3.8 (1.7–8.8) vs 3.0 (1.2–5.1) nmol/l for girls, $P<0.01$. There was no statistical difference in gestational age; boys 35.8 (33.0–36.9) weeks vs girls 35.6 (32.0–36.7) weeks, nor in birth

weight or birth length. At 5 years of age, boys still had lower IGF1 levels; 89 (45–177) vs 105 (45–221) $\mu\text{g}/\text{l}$ in girls, $P<0.01$. Testosterone levels were significantly lower in boys; 0.14 (<0.03–0.34) vs 0.20 (<0.03–0.36) nmol/l in girls, $P<0.05$. **Conclusion:** Gender differences in testosterone and IGF1 were found both at birth and at 5 years of age. Boys had lower levels of IGF1 at both time points. However, there was a shift in gender differences concerning testosterone with higher levels at birth and lower levels at 5 years in boys. The higher testosterone levels seen in girls at 5 years of age may be due to a non-detected earlier adrenarche in girls.

P3-D1-885

Neonatal Seizures Neonatal due to Hypocalcemia Secondary to Maternal Vitamin D Deficiency

Ariadna Campos-Martorell, Karla Narvaez, Maria Clemente, Diego Yeste, Eduard Mogas, Laura Gerones, Antonio Carrascosa

Hospital Vall Hebron, Barcelona, Spain.

Background: Vitamin D is an essential hormone in the homeostasis of calcium. Its main source is sun exposure. Changes in lifestyle and migratory movements have favored the reappearance of vitamin deficiency in our country. **Method:** We present three cases of newborn with hypocalcemic seizures, secondary to maternal vitamin D deficiency. Mother's origin was North Africa. **Results:** Case 1: 7 days old male brought for several episodes of generalized seizures. Afebrile and without infectious signs. In laboratory test, calcemia 5.4 mg/dl with ionic fraction 0.73 mmol/l, phosphate 7.7 mg/dl, 25-hydroxy vitamin D 8.3 ng/ml, and parathormone 29.9 pg/ml. I.v. calcium gluconate was administered. He recovered well. Screening of infectious disease was negative. Maternal levels of 25-OH-VitD were 4.9 ng/ml. It was oriented as hypovitaminosis D with transient hypoparathyroidism. Case 2: 40 days old male referred for generalized seizures in the last 10 days. He was Afebrile. Laboratory test showed calcium 5.7 mg/dl, phosphate 7.1 mg/dl, 25-hydroxyvitamin D 4 ng/dl, and parathormone 221 pg/ml. Screening for infection disease were normal. Vitamin D levels in his mother were undetectable. Case 3: 34 days old female, admitted for diarrhea. She presented two episodes of generalized seizures. In laboratory test, calcemia 6.1 mg/dl with ionic fraction 0.67 mmol/l, 25-hydroxyvitamin D 7.1 ng/dl and parathormone 69 pg/ml. She required i.v. calcium gluconate, recovering well. Screening for infectious disease was negative. Maternal levels of vitamin D3 were 5.4 ng/ml. She was oriented as hypovitaminosis D with transient hypoparathyroidism. **Conclusions:** Vitamin D deficiency in the neonatal period can cause hypocalcemia, which can be manifested acutely compromising patient's life. Transient neonatal hypoparathyroidism could be associated and may worsen the symptoms and make the diagnosis more difficult. To avoid such complications in newborns is essential the determination of vitamin D levels in risky pregnancies.

P3-D1-886

3-Ketothiolase Deficiency Induced by ACAT1 Gene Mutation

Li Li, Zhu Min, Mao Huiying, Xiong Feng

The Children's Hospital of Chongqing Medical University, Chongqing, China

Background: 3-Ketothiolase deficiency (3KTD) is an inherited error of metabolism affecting isoleucine catabolism and ketone body utilization. This disorder is clinically characterized by intermittent ketoacidotic episodes with no clinical symptoms. **Objective and hypotheses:** To research the gene mutation of 3 acetoacetyl-CoA thiolase in non-diabetic ketoacidosis and provide a basis for diagnosis of 3KTD. To reveal the role of 3 acetoacetyl-CoA thiolase in isoleucine metabolism, and explore potential mechanisms of 3KTD by gene mutations. **Method:** DNA was extracted from blood of a Chinese patient, his family members and healthy children. The entire coding regions of ACAT1 gene with flanking intronic regions were amplified by PCR and directly sequenced, detected the mutation sites. Detected 3 - ketothiolase activity by enzyme assay using fibroblasts. **Results:** A127V missense mutation in exon 5 was identified in this patient, no mutation was observed in other tests. Some single nucleotide polymorphisms (SNPs) of ACAT1 gene were detected. A127V mutation activated a cryptic splice-acceptor site and occurred aberrant splicing, leading to 17-amino acids deletion, including the active-site 126Cys. 3-ketothiolase did not retain activity by enzyme assay using fibroblasts. **Conclusion:** These results confirmed that c.456C>T caused exon 5 aberrant splicing and may be a potential pathogenesis of 3KTD.

P3-D2-887

Permanent Neonatal Diabetes Mellitus in China

Ke Huang^a, Li Liang^b, Junfen Fu^a, Guanpin Dong^a

^aChildren's Hospital of Zhejiang University School of Medicine, Hangzhou, China; ^bNo. 1 Hospital of Zhejiang University School of Medicine, Hangzhou, China

Introduction: Permanent neonatal diabetes mellitus (PNDM) is a rare disease which is defined as the onset of diabetes before the age of 6 months with persistence through life. Patients with KCNJ11 or ABCC8 gene mutations have the opportunity to switch to oral sulfonylurea therapy. There were limited studies about the genetic analysis and long-term follow-up of PNDM. **Case report:** We report four cases of this kind of PNDM, including their genetic mutations, treatments and long-time follow-ups. All of the patients and their parents got gene analysis include INS, KCNJ11, or ABCC8 gene. All of the patients and their parents were not suffered from any genetic mutations of these three common genes. One of the children got continuous subcutaneous insulin infusion (CSII) and the others got multiple injections of

insulin (MII). The PNDM patients had persisted after 35–60 months of follow-up, three patients maintained almost stable blood sugar level, and one patient had poor sugar control. **Conclusion:** We suggested all of PNDM patients should undergo genetic evaluation. For patients without KCNJ11 and ABCC8 gene mutation, oral sulfonylurea might not be considered. CSII is a useful tool for overcoming the difficulties of diabetes, and it is also advantageous to the life quality improvement.

P3-D2-888

Neonatal Neurogenic Diabetes Insipidus: a Case Report

Inês Alves^{a,d}, Fátima Clemente^{a,d}, Cíntia Castro-Correia^{b,d}, Helena Pinto^{c,d}, Hercília Guimarães^{a,d}, Manuel Fontoura^{b,d}

^aServiço de Neonatologia do Hospital Pediátrico Integrado do Centro Hospitalar São João, Porto, Portugal; ^bUnidade de Endocrinologia Pediátrica do Hospital Pediátrico Integrado do Centro Hospitalar São João, Porto, Portugal; ^cUnidade de Nefrologia Pediátrica do Hospital Pediátrico Integrado do Centro Hospitalar São João, Porto, Portugal; ^dFaculdade de Medicina da Universidade do Porto, Porto, Portugal

Background: Neurogenic diabetes insipidus (NDI) is extremely rare in the neonatal period. In most cases, it's secondary to CNS injury. The clinical presentation in this group (particularly in preterm) is unspecific and a high degree of suspicion for the diagnosis is necessary. **Objective and hypotheses:** Diagnose NDI in a neonate with sodium and diuresis instability. **Method:** We present a case report. **Results:** Male, born at 25 weeks and 3 days of gestation. Eutocic birth delivery complicated by feet appearance, Apgar Index 1'/5'/10': 1/3/7. Difficult intubation caused by facial anomalies consistent with Pierre-Robin sequence (microretrognathia and posterior midline cleft palate). Transfontanelar ultrasound at D10 of life reveals bilateral grade III intraventricular hemorrhage with hemorrhagic infarction associated with hydrocephalus. Initially natriemic instability, after D11 he expresses a persistent hypernatremia (max 166 mEq/l) associated with increased diuresis (max 11.3 ml/kg per h), plasma osmolality increased and urinary osmolality decreased. The hypothesis of NDI was made, and the newborn started nasal desmopressin, with reduced sodium levels and urine output. In the beginning there was instability of both parameters, therefore the need of constant therapeutic setting. At 4 months of chronological age, he still needs desmopressin to maintain both parameters in a normal range. **Conclusion:** The main risk factors for neonatal NDI are asphyxia, severe infections, CNS anomalies, and intraventricular hemorrhage. Hypernatremia may occur in neonates, especially in preterm with severe disease, yet if it persists despite increased fluid's intake, it should be seen as an alarm signal. Treatment with desmopressin is effective but its dosage is variable and should be adapted individually. The aim is to keep sodium levels, diuresis and urine osmolality within the normal range, allowing a better metabolic balance and limiting aggression injured CNS.

P3-D2-889

Evolution and Epidemiological Assessment of the Influence of Sociological Variables of Children Born SGA in the Last Decade in Basque Country

Ignacio Diez-Lopez^a, Marta Hoyo-Moracho^a,
Ainhoa Sarasua-Miranda^a, Isabel Lorente-Blazquez^a, Victor
Manuel Rodriguez-Rivera^b, Maria Teresa Macarulla-Arenaza^b,
Raquel Gomez de Segura Lorente^a, Dorleta Pérez Campos^a

^aAraba University Hospital, Vitoria/Basque Contry, Spain;

^bNutrition and Obesity Group of Basque Country University,
Vitoria/Basque Contry, Spain

Background: Although the theoretical impact of small in weight and/or size at birth (<2 SDS for EG) is 3–5% (3.5% in the Basque Country (source: Local Government) the socio-economic situation in our country has conditioned a change in its although 50% at 2 years did not do a proper catch up (by excess or defect) with potential impact on future size and metabolic complications, cardiovascular require specific monitoring. **Objective:** To assess socio-epidemiological changes of the new born in our country in the past 10 years and its influence on the SGA pathology. **Material and methods:** Study and classification of 4934 cases (♂ 2485) live and single pregnant in our hospital (years 2004–2005) (G1) and weight/height tables regarding Spanish reference (2008) according to age, sex, and weight/height compared to 5942 cases (♂ 3066) live singletons in our hospital (years 2011–2012) (G2). SGA if <2 SDS weight and/or size (balance accuracy and normalized stadiometer). Student's *t* study bilateral IBM SPSS 18.0. Total: 10 876 cases studied. **Results:** G1 total SGA 319 (6.4% of total) (♂ 140, 43%). G2 total SGA 438 (7.4% of total) (194 ♂, 44%) increased 2.7% *P*: 0.01. In G1 ♂ 5.6% are SGA and 7.3% from G2 ♀ ♂ 6.3% is 8.6% SGA and ♀ Δ *P*: 0.02. Regarding maternal age distribution of RN is almost similar in both groups: G1 parity 25–29a (14%), 30–34a (38%), 35–39a (33%) average 31.8 years vs G2 parity 25–29a (15%), 30–34a (40%), 35–39a (31%) average 32.5 years Δ*P*: 0.06. PEG proporcional are distributed. About groups: G1 preterm newborns (<37s) represent 493 (10%), with 30 SGA (6%). G2 preterm infants (<37s) account 416 (7%), with 20 PEG (5%). Δ*P*: 0.01. Regarding parity: primiparous assume G1 2220 (45%) with SGA 255 (8.7%) (80% f total). G2 represent primiparous 2495 (42%), SGA 261 (10.5%) (60% of total). Δ*P*: 0.01. Regards, on 222 G1 mothers were foreign (4.5%) compared to 1366 G2 mothers were foreign (23%) Δ*P*: 0.001. Facing the Spanish their mean age was 26.2 vs lower 34th, the most parity 2.8 vs 1.6% and the lower the PEG (4.8 vs 8.2). **Conclusions:** Our media has seen an increasing number of children born SGA, especially in Spanish, primiparous and more elderly women. Global strategy is necessary.

P3-D2-890

A Novel Mutation Causing Pseudohypoaldosteronism

Emmeline Heffernan^a, Noina Abid^a, Shane McKee^b

^aRoyal Belfast Hospital for Sick Children, Belfast, UK; ^bBelfast City Hospital, Belfast, UK

Background: We present a case of a neonate with life threatening hyponatraemia and hyperkalaemia, due pseudo-hypoaldosteronism, found to be caused by a novel mutation. **Objective and hypotheses:** An 8-day-old girl presented with a short history of poor feeding and vomiting. She was born at term, to consanguineous parents. She was severely shocked and required fluid resuscitation. She had profound hyponatraemia and hyperkalaemia. She was admitted to PICU with continuous cardiac monitoring. Electrolyte abnormalities improved over 48 h. **Method:** We discuss a diagnostic algorithm; differentials considered included salt-wasting congenital adrenal hyperplasia, aldosterone synthase deficiency and adrenal hypoplasia congenita; resulting in aldosterone deficiency. **Results:** Blood testing revealed a markedly elevated aldosterone (45 200 pmol/l) and renin (> 34 ng/ml per h), leading to a diagnosis of pseudohypoaldosteronism. Pseudohypoaldosteronism is a rare syndrome of resistance to aldosterone, caused by decreased function of ENaC (epithelial sodium channel) and manifested by salt wasting, which can lead to shock and death. Genetic testing in this case has found a novel mutation in SCNN1A gene, which has autosomal recessive inheritance and is characterized by a permanent defect of ENaC, affecting all aldosterone target organs (kidney, salivary and sweat glands, respiratory tract, and colon). **Conclusion:** This is the first case of pseudohypoaldosteronism with this mutation, in Northern Ireland and illustrates the pertinent investigations and important differential diagnoses to consider in infants with severe hyponatraemia and hyperkalaemia.

P3-D2-891

A Novel Mutation in the NR3C2 Gene Causing Pseudohypoaldosteronism Type 1

Amalia Sertedaki, Christina Kanaka-Gantenbein, George P Chrousos

Division of Endocrinology, Metabolism and Diabetes, First
Department of Pediatrics, University of Athens Medical School,
Athens, Greece

Background: Pseudohypoaldosteronism type 1 (PHA1) is a rare inherited disease characterized by mineralocorticoid resistance with subsequent salt wasting, hyperkalemia, metabolic acidosis, and elevated plasma renin and aldosterone levels. **Patients and methods:** We report a male newborn that presented with failure to thrive and sustained hyponatremia during his early postnatal period. He was conceived after IVF (twin pregnancy) and prematurely born by cesarean section at the 34th gestational week. His birth weight was 1920 g, length 45 cm and head circumference 31 cm. His Apgar score was 5 at 1 min and 7 at 5 min. His twin brother had a birth weight of 2140 g. The patient presented with poor weight gain soon after birth; from the seventh day onwards he had significant hyponatremia (124–127 mEq/l) and hyperkalemia (5.6–6.2 mEq/l). Laboratory

investigations revealed normal circulating ACTH, 17-OH-progesterone and cortisol levels and significantly high plasma renin and aldosterone concentrations. With the diagnosis of pseudohypoaldosteronism, substitution of NaCl was initiated. The boy responded with a significant weight gain and normal psychomotor development on NaCl substitution. NaCl was gradually discontinued after the age of 22 months. Genomic DNA was isolated from peripheral blood lymphocytes of the patient and his mother and the coding region of *NR3C2* gene was PCR-amplified and sequenced. **Results:** A heterozygous four nucleotide duplication was detected in exon 7 of the *NR3C2* gene in the patient and his mother, namely c.2525_2526insATCA; p.A844Vfs*5. This mutation changes codon 844 from alanine to valine, causes a frameshift and a premature stop codon five amino acids downstream. Thus, a receptor protein 137 amino acids shorter than the WT and lacking the C-terminal ligand-binding domain of the receptor might be produced. **Conclusions:** We report a new mutation, p.A844Vfs*5, of the *NR3C2* gene causing autosomal dominant PAHI detected in a neonate and his mother.

P3-D2-892

Subcutaneous Fat Necrosis Causing Prolonged Hypercalcaemia in a Neonate: an Unusual Case

Usha Niranjana, Vivek Desai^b, Nigel Brooke^b, Anuja Natarajan^b

^aSheffield Children's Hospital, Sheffield, UK; ^bDoncaster Royal Infirmary, Doncaster, UK

Introduction: Subcutaneous fat necrosis (SCFN) is an uncommon inflammatory disorder of the adipose tissue. Though hypercalcaemia secondary to SCFN is a well-recognised entity, reported cases with persistence of symptoms requiring prolonged treatment as in our case are rare. There are also limited reports about the severity and duration of hypercalcaemia secondary to SCFN with possible correlation of the severity to the extensity of the skin lesions. We present a neonate who developed severe hypercalcaemia secondary to subcutaneous fat necrosis at 2 weeks of age which proved difficult to manage until 7 months of age. **Case report:** The term baby (4.3 kg) had significant hypoxia (pH 6.8) at birth requiring intensive care treatment. On day 10 she was noted to have firm palpable subcutaneous erythematous plaques all over her back suggestive of SCFN. Her bloods revealed hypercalcaemia (~3.05 mmol/l) requiring fluids, diuretics, and low calcium milk. The investigations for other causes of hypercalcaemia were inconclusive. She was treated with prednisolone (2 mg/kg per day) due to persistent hypercalcaemia (~3.53 mmol/l) with good effect. Attempts to wean her from prednisolone resulted in recurrence of hypercalcaemia. The reason for differing the use of bisphosphonates in this case was the exquisite steroid sensitivity which our patient demonstrated. She required close monitoring of her calcium levels, renal ultrasound scans, and parent education to return for early assessment if she was symptomatic. Eventually at 7 months she weaned from the prednisolone and low calcium feed (latest ~2.83 mmol/l). She is

currently thriving with normal development. The skin lesions have almost resolved now at 7 months of age. **Conclusion:** Hypercalcaemia though rare, is a serious complication of subcutaneous fat necrosis which can be fatal if not treated appropriately. Prolonged follow up with diligent management is essential.

P3-D2-893

Severe Vitamin D Deficiency Among Pregnant Women and Their Newborns in Turkey

Mesut Parlak^a, Zuhale Kalay^b, Ahmed Kirecci^c, Ozgur Guney^d, Esad Koklu^e, Salih Kalay^b

^aDepartment of Pediatric Endocrinology, Kahramanmaraş Necip Fazil City Hospital, Kahramanmaraş, Turkey; ^bDepartment of Pediatrics, Kahramanmaraş Necip Fazil City Hospital, Kahramanmaraş, Turkey; ^cDepartment of Obstetrics and Gynecology, Kahramanmaraş Necip Fazil City Hospital, Kahramanmaraş, Turkey; ^dDepartment of Biochemistry, Kahramanmaraş Necip Fazil City Hospital, Kahramanmaraş, Turkey; ^eKahramanmaraş Megapark Hospital, Kahramanmaraş, Turkey

Objectives: Vitamin D deficiency is an important health problem in pregnant women and their infants in sunny countries. The present study evaluated serum 25-hydroxyvitamin D3 (25(OH)D3) concentrations in pregnant women and in their newborns and determined the risk factors in LSES cities in Turkey. **Methods:** Ninety-seven pregnant women and their newborns were included in the study between December 2012 and February 2013. All of the pregnant women had irregular follow up or had received no antenatal care, were pregnant during summer, had presented to the hospital after 37 weeks of gestation (WG) and had received no vitamin D supplementation. A detailed history was obtained, which included mothers' age, number of births and dressing style. Maternal and cord blood samples were taken to measure 25(OH)D3 levels. **Results:** All of the pregnant women were predominantly LSES, had covered dressing style and none of them had received vitamin D3 supplementation during pregnancy. The mean serum 25(OH)D3 level and mean cord blood level of 97 mothers were 4.97 ± 3.27 and 4.29 ± 2.44 ng/ml respectively. There was a strong positive correlation between maternal serum and umbilical cord 25(OH)D3 levels ($r: 0.735, P < 0.05$). Ninety-five mothers had serum 25(OH)D3 below 20 ng/ml and all cord blood serum 25(OH)D3 levels were below 20 ng/ml. Level of 25(OH)D3 was not correlated with mother age, WG or newborn weight. Serum 25(OH)D3 concentrations in primigravida and multigravida were 3.71 ± 1.88 and 5.2 ± 3.4 ng/ml respectively, with a significant difference between them ($P < 0.05$). **Conclusion:** Dressing style, not having received vitamin D supplementation and LSES were identified as major risk factors. Vitamin D supplementation campaigns which should cover pregnant women and the newborn to prevent maternal and perinatal vitamin D deficiency should be implemented especially in risk areas.

P3-D2-894

Relationship of Birth Gestational Age with IGF Binding Protein 3 Beyond Influences of Gender, Small-For-Gestational-Age Status, Caesarean Section, Caloric Intake, Parenteral Nutrition, and Predominant Breast Milk Feeding in the Not-Life Threatened Newborn: Relevance of Not-Brain-Related Birth Body Weight

Cesare Terzi^a, Werner F Blum^b, Sergio Zani^c, Marco Riani^c, Gabriele Tridenti^d, Andrea Cerioli^c, Lidia Garavelli^d, Sergio Bernasconi^a, Raffaele Virdis^a, Giacomo Banchini^d

^aDepartment of Pediatrics – Dipartimento di medicina Clinica e Sperimentale – University of Parma, Parma, Emilia-Romagna, Italy;

^bFriedrich-Stengel-Str. 14, Usingen, Hessen, Germany; ^cDepartment of Economics, University of Parma, Parma, Emilia-Romagna, Italy;

^dDepartment of Obstetrics, Gynecology and Pediatrics, S. Maria Nuova Hospital, Reggio Emilia, Emilia-Romagna, Italy

Background/objective and hypotheses: Not-brain-related birth body weight (NBBW) relevance to known relationships of birth gestational age (GA) with blood serum IGF binding protein 3 (IB3) was studied in the not-life threatened newborn (NWB). **Method:** SEX, GA (unit:complete week), postnatal age (PNA; unit:day), birth body weight (BW; unit:g), birth head circumference (HC; unit:cm), BW < 10th centile for GA (SGA), caesarean section (CS), predominant oral/enteral breast milk feeding (BM), and parenteral nutrition (KIVD) were recorded in each NWB. IB3 RIA measurements in $\mu\text{M}/\text{dl}$ were performed in each NWB at one of the first 5 postnatal days (x), 5 days after x (y) and 10 days after x (z), caloric intake (KT) was calculated as total postnatal kcal intake before x in presence of PNA at x (PNA_x) < 24 h. In all other cases KT was calculated as total kcal intake over 24 h periods immediately preceding x , y and z . The presence of any among i) total KIVD, ii) KIVD calories deriving from substances other than dextrose, iii) life-threatening disease, iv) diabetes mellitus (DM), or v) mother with DM led to NWB exclusion. 78 NWBs with complete data were included in the study (males, $n=43$; CS, $n=52$; SGA, $n=20$; BM, $n, x=16, y=43, z=54$; KIVD, $n, x=46, y=34, z=17$; GA range=28–42; BW range=1200–4150; $\text{GA} \leq 36, n=46$; KT, 25th/75th percentile, $x=6.0/44.8, y=60.9/89.3, z=85.9/109.2$). Natural log-transformed IB3 (IB3-LN) resulted near-normally distributed. BRW (unit:g) was calculated as $0.037 \times \text{HC}^{2.57}$ according to McLennan–Lindley. NBBW (unit:g) was calculated as BW minus BRW. Multiple linear regression (MLR) was used (computations; male SEX, SGA, CS, BM and KIVD; condition present=1, condition absent=0). **Results:** MLR models with IB3-LN $_{x-y-z}$ as outcome showed 1) a significant partial correlation (r) of GA with IB3-LN $_x$ ($r: -0.409$; $P: 0.000359$), IB3-LN $_y$ ($r: -0.353$; $P: 0.002346$) and IB3-LN $_z$ ($r: -0.383$; $P: 0.000885$) adopting GA + SEX + PNA_x + SGA + BRW + CS + BM + KT + KIVD as predictors, but 2) no significant r of GA with IB3-LN at x, y or z adopting i) GA + SEX + PNA_x + BWR + CS + BM + KT + KIVD + NBBW or ii) GA + SEX + PNA_x + BWR + CS + SGA + BM + KT + KIVD + NBBW as predictors (in all MLR models BM, KT and KIVD corresponded chronologically to the outcome and R^2 was significant).

Conclusion: NBBW could be relevant to GA-IB3 relationships in not-life-threatened NWBs even considering effect of SEX + PNA_x + SGA + BRW + CS + LM + KT + KIVD.

P3-D2-895

Relationship of Birth Gestational Age with the Ratio between IGF2 and IGF Binding Protein 3 in Blood Serum Beyond Influences of Gender, Small-For-Gestational-Age Status, Caesarean Section, Caloric Intake, and Predominant Breast Milk Feeding in the Not-Life-Threatened Newborn: Relevance of Parenteral Nutrition

Cesare Terzi^a, Raffaele Virdis^a, Werner F Blum^b, Sergio Zani^c, Marco Riani^c, Gabriele Tridenti^d, Andrea Cerioli^c, Elena Chesid^d, Sergio Bernasconi^a, Giacomo Banchini^d

^aDepartment of Pediatrics, Dipartimento di Medicina Clinica e Sperimentale, University of Parma, Parma, Emilia-Romagna, Italy;

^bFriedrich-Stengel-Str. 14, Usingen, Hessen, Germany; ^cDepartment of Economics, University of Parma, Parma, Emilia-Romagna, Italy;

^dDepartment of Obstetrics, Gynecology and Pediatrics, S. Maria Nuova Hospital, Reggio Emilia, Emilia-Romagna, Italy

Background/objective and hypotheses: Parenteral nutrition (KIVD) relevance to known birth gestational age (GA) relations to the blood serum IG2/blood serum IGF binding protein 3 (IB3) ratio (IG2 through chronologically corresponding IB3, IG2/IB3) was studied in the not-life-threatened newborn (NWB). **Method:** SEX, GA (unit, complete week), postnatal age (PNA; unit, day), birth body weight (BW; unit, g), birth head circumference (HC; unit, cm), $\text{GA} \leq 36$ (PTB), BW < 10th centile for GA (SGA), caesarean section (CS), predominant oral/enteral breast milk feeding (BM), and KIVD were recorded in each NWB. IG2 and IB3 R.I.A. measurements in $\mu\text{M}/\text{dl}$ were performed in each NWB at one of the first 5 postnatal days (x), 5 days after x (y), and 10 days after x (z). Caloric intake (KT) was calculated as total postnatal kcal intake before x in presence of PNA at x (PNA_x) < 24 h. In all other cases KT was calculated as total Kcal intake over the 24 h immediately preceding x, y , and z . The presence of any among i) total KIVD, ii) KIVD calories deriving from substances other than dextrose, iii) life-threatening disease, iv) diabetes mellitus (DM), or v) mother with DM led to NWB exclusion. 78 NWBs with complete data were included in the study (males, $n=43$; CS, $n=52$; PTB, $n=46$; SGA, $n=20$; BM, $n, x=16, y=43, z=54$; KIVD, $n, x=46, y=34, z=17$; GA range=28–42; BW range=1200–4150; KT, 25th/75th percentile, $x=6.0/44.8, y=60.9/89.3, z=85.9/109.2$). IG2/IB3 standardized according to Van der Waerden (IG2/IB3-S), resulted near-normally distributed. Multiple linear regression (MLR) was used (computations; male SEX, SGA, CS, BM, and KIVD; condition present=1, condition absent=0). **Results:** MLR models with IG2/IB3-S as outcome showed i) a significant partial correlation (r) of GA with IG2/IB3-S $_x$ ($r: -0.409$; $P=0.000359$), IG2/IB3-S $_y$ ($r: -0.353$; $P=0.002346$) and IG2/IB3-S $_z$ ($r: -0.383$; $P=0.000885$) adopting GA + SEX + PNA_x + SGA + CS + BM + KT as predictors, but

ii) no significant r of GA with IG2/IB3-Sx, IG2/IB3-Sy, or IG2/IB3-Sz adopting GA + SEX + PNAx + SGA + CS + BM + KT + KIVD as predictors (in all MLR models BM, KT, and KIVD corresponded chronologically to the outcome and R^2 was significant). **Conclusion:** KIVD could have been involved in GA relations to IG2/IB3 in not-life-threatened NWBs beyond possible influences of SEX + PNAx + SGA + CS + BM + KT.

P3-D2-896

Cord Blood Vitamin D Concentrations in Native and Immigrant Population from a Mediterranean Area in Spain

Miguel Angel Guagnelli, Diego Yeste, Roser Ferrer, Inmaculada Comás, Antonio Carrascosa

Hospital Universitario Vall d'Hebron, Barcelona, Spain

Background: Recent studies have found a widespread deficiency of vitamin D during pregnancy. Its significance is still not fully understood, although low Vit-D levels have been associated to increased risk for conditions such as preeclampsia, bacterial vaginosis, neonatal sepsis, and early respiratory infections in the child. Supplementation to the pregnant mother is still a matter of debate, therefore it is important to understand better the causes, risk factors, and possible consequences of such deficiency.

Objective and hypotheses: Our aim was to obtain information about vit-D levels and some of the potential risk factors in a coastal area with mediterranean weather. **Method:** The study was conducted between May 2012 and May 2013 in the Baix Penedes County Hospital (El Vendrell). We collected statistical data of the mothers and measured the Vit-D levels of 358 cord blood samples. Forty-seven percent of the children born during the study period. The mothers were 57% from Spanish origin, 25% moroccan, 10% latinamerican, and 8% from other European countries. **Results:** The levels in all groups followed closely the solar radiation pattern during the year, being higher on august and lower during January, in average below deficiency threshold. Mothers of Maghrebi ethnicity had the lowest levels on average (9.26 ng/dl) and consistently during the year, down to undetectable on winter months. The average Vit-D levels had a positive relationship to the ingestion of Vit-D containing supplements, and negative relationship to the weight gain during pregnancy and heavy tobacco consumption. We found a significant association between low Vit-D levels and third trimester strep-B positive cultures, but were unable to find other relationships. **Conclusion:** There are significant differences between seasons among ethnic groups, winter being worse for all but, particularly for women of Maghrebi origin.

P3-D2-897

Transient Neonatal Diabetes Mellitus: New Case

Suna Hancilli^a, Ayla Güven^a, Ilke Mungan Akin^b, Ayse Nurcan Cebeci^c, Sian Edwards^d

^aGöztepe Education and Research Hospital, Pediatric Endocrinology Clinic, Istanbul, Turkey; ^bGöztepe Education and Research Hospital, Neonatology Clinic, Istanbul, Turkey; ^cDerince Education and Research Hospital, Pediatric Endocrinology Clinic, Kocaeli, Turkey; ^dWessex Regional Genetics Laboratory, Faculty of Medicine, University of Southampton, Southampton, UK

Introduction: Neonatal diabetes mellitus (NDM) is a monogenic form of diabetes that occurs in the first 6 months of age. It is a rare condition occurring in only one in 100 000–300 000 live births. Clinically, NDM subgroups include transient (TNDM) and permanent NDM (PNDM). TNDM is most frequently caused by abnormalities in the imprinted region of chromosome 6q24.

Case Report: A 18-day-old male was referred from another clinic due to diabetic ketoacidosis (DKA). The patient was born to healthy first-degree cousins at 38 weeks of gestation with a birth weight of 2500 g and birth length of 42 cm. Physical examination did not reveal any dysmorphic features. He was appeared extremely dehydrated, tachypneic, and lethargic. Laboratory investigations revealed ketonuria, acidosis (pH: 7.02, HCO₃: 2.9 mmol/l) and hyperglycemia (plasma glucose 828 mg/dl). The patient was then hydrated with i.v. fluids and treated with an insulin and sodium bicarbonate. His serum C-peptide was 0.15 ng/dL (normal range, 0.9–7.1), HbA1c was 6.7% (normal range, 4–6%). Anti-GAD and anti-insulin antibodies were negative. Abdominal ultrasonography demonstrated a normal pancreas anatomy. After hydration therapy i.v. insulin infusion changed to s.c. neutral protamine Hagedorn (NPH). At the age of 5 months, the patient entered remission at which stage insulin treatment was withdrawn. The patient is currently 11 months of age. His HbA1c is 4.7% and his growth and physical development are normal. *ABCC8*, *KCNJ11*, *INS*, and *EIF2AK3* genes were sequenced and no mutations were detected. In addition to these, a novel mutation determined on chromosome 6q24 due to paternally duplication, confirming a diagnosis of TNDM.

Conclusion: A total 70% of TNDM is caused by defects causing overexpression of paternally expressed genes in the imprinted region of chromosome 6q24. Correctly identifying monogenic NDM is important for facilitating accurate diagnosis, appropriate therapy and genetic testing for at risk family members.

P3-D2-898

Marfan Neonatal Syndrome: a Case Report

Magdalena Hawkins^a, Ana Alcalde^a, Julia Yebra^a, Maria Royo^a, Beatriz Perez-Seoane^a, Maria de la Serna^a, Teresa Raga^a, Ana Barrios^a, Sixto García-Miñaur^b

^aHospital Infanta Sofia, Madrid, Spain; ^bHospital Infantil La Paz, Madrid, Spain

Background: Marfan syndrome is an autosomal dominant genetic disorder with skeletal, cardiac, and ocular involvement. Mutations in the fibrillin-1 gene on chromosome 15 are responsible for the development of the syndrome. **Objective:** To present one case of neonatal Marfan syndrome. **Case:** The

patient was a 1-day-old female neonate who was born at 36 weeks gestation via normal delivery. Her body weight was 2900 g and height 48 cm. Ultrasonographic examinations reported megacysterna magna. Several bizarre appearances of the neonate were noted: dolicocephaly, arachnodactyly, pigeon chest, rigidity, and contracture of bilateral elbows and knees. Large ear lobes, enophthalmos, micrognathia, and high palate were evident. Forehead skin was redundant. The abdomen was soft. Her cariotype was normal 46,XY. Also, grade II/VI systolic murmur over left lower sterna border was found. Chest X-ray showed cardiomegaly. Echocardiography revealed interauricular communication Ostium Secundum and dysplastic mitral valve with mild mitral and aortic regurgitation. Brain sonographic examination confirms megacysterna magna. She needs continuous enteral nutrition from 10 months of age. We treated the patient with diuretics and ACE inhibitor due to the detection of congestive heart failure. Digoxin was prescribed to prevent the state becoming worse. However dilatation of aorta, mitral regurgitation, tricuspid regurgitation, aortic regurgitation, and congestive heart failure got worse progressively. In two different occasions she needs hospital admission for respiratory infections. Unfortunately the patient expired due to severe congestive heart failure at 14 months of age due to a rotaviruses gastroenteritis. **Results:** After consulting geneticist, neonatal Marfan syndrome was impressed, molecular studies detected the presence of the heterozygote mutation c.3203G (p.Cys 1068Tyr) in the 25 exons, that confirmed the diagnosis. Familiar molecular study confirmed *de novo* mutation. **Conclusions:** Marfan syndrome is rarely presented in the neonatal period, is the worst phenotype of this disease and has a poor prognosis. The estimated life expectancy is about 12 months.

P3-D2-899

Iodine Status in the Neonate and the Effect on Thyroid Function

Jeesuk Yu, Seung Ho Lee, Young Pyo Chang

Dankook University Hospital, Cheonan, Republic of Korea

Background: Sufficient iodine intake is required for the synthesis of thyroid hormone. Thyroid hormone is very important for normal growth and development, especially in newborn period. It is also well known that excess iodine intake may cause adverse effect in thyroid function. **Objectives and hypotheses:** This study was designed to find the iodine status of the newborn with normal thyroid function confirmed by newborn screening of thyroid function test (TFT) and to compare the values with those obtained from the neonates with thyroid dysfunction using random spot urine. **Methods:** Newborns in euthyroid were classified as group 1, and the neonates referred for the elevated TSH were classified as group 2. Total 197 urinary samples were collected for the assay of the iodide concentrations in group 1 and 25 urinary samples were obtained from group 2. A *P* value < 0.05 was considered statistically significant using the KESS Software program. **Results:** The mean value of urinary iodide was 110.4 ± 165.2 $\mu\text{mol/g Cr}$ in group 1 and 271.0 ± 320.7 $\mu\text{mol/g Cr}$ in group 2

(*P* < 0.05). The free T_4 and TSH levels were also significantly different between two groups (1.59 ± 0.54 vs 1.03 ± 0.52 ng/dl, *P* < 0.001 for free T_4 ; 1.36 ± 1.10 vs 93.0 ± 145.9 mIU/l, *P* < 0.01 for TSH). The TSH levels showed statistically significant correlation with urinary iodide concentrations in group 2 (*r* = 0.58, *P* < 0.01). **Conclusion:** The neonates with thyroid dysfunction showed higher urinary iodide concentrations compared to the neonates with normal thyroid function, suggesting that excess iodine exposure in neonate can contribute to the thyroid dysfunction. It will be worthwhile to check the iodine status as well as TFT for the evaluation of thyroid function in neonates.

P3-D1-900

Effect of Pubertal Status, Age and Gender on Cortisol Response to Insulin Induced Hypoglycaemia in Children and Adolescents

Dinesh Giri, Ian Robert Mulvey, Arundoss Gangadharan, K Saravanan-Prabu, Jo Blair, Poonam Dharmaraj, Urmi Das, Senthil Senniappan, Mohammed Didi

Department of Paediatric Endocrinology, Alder Hey Children's Hospital, Liverpool, UK

Background: There is evidence that baseline and peak cortisol response to the low dose short Synacthen test (LDSST) varies with pubertal status and gender in children with asthma on inhaled corticosteroids. There are no published data reporting effects of puberty on cortisol response to the insulin tolerance test (ITT) in childhood and adolescence. **Objective and hypotheses:** To determine whether pubertal status, age or gender influence basal and peak cortisol concentrations to insulin induced hypoglycaemia in childhood and adolescence. **Method:** The basal and peak cortisol concentrations in children and adolescents undergoing ITT for the investigation of short stature at a single centre were analysed retrospectively. The basal cortisol concentration was obtained at 0900 h after an overnight fast. Insulin, 0.15 units/kg (Actrapid) was administered i.v. to induce adequate hypoglycaemia and samples were collected at 20, 30, 45, 60, 90 and 120 min. Age, gender, Tanner pubertal stage, and peak cortisol were determined. The relationships between age, gender, pubertal status, basal and peak cortisol values were examined using ANOVA. **Results:** 101 patients (79M, age 5–21 years) underwent an ITT. Forty eight patients (32M, range 7–21 years, median age 15 years) who were GH and cortisol sufficient (peak GH response ≥ 6.4 $\mu\text{g/l}$ and peak cortisol responses ≥ 500 nmol/l)

Table 1.

	Pre-pubertal (n = 13)	Pubertal (n = 35)	<i>P</i> value
Baseline cortisol (nmol/l)	221.31 ± 73.075	278.89 ± 117.53	0.107
Peak cortisol (nmol/l)	632.69 ± 66.86	610.43 ± 82.34	0.432

were studied. The age, sex and puberty did not have a significant relationship to cortisol concentration. The cortisol concentrations in the pubertal and pre-pubertal groups are summarised in Table 1. **Conclusion:** Age, gender or pubertal status did not influence the baseline or peak cortisol responses to insulin induced hypoglycaemia. Caution is appropriate since pre-pubertal children are underrepresented in this study.

P3-D1-901

Music Benefits on Postoperative Distress and Pain in Pediatric Day Care Surgery

Valeria Calcaterra^a, Daniela Larizza^a, Ghassan Nakib^b, Selene Ostuni^b, Irene Bonomelli^a, Simonetta Mencherini^c, Elisa Zambaiti^b, Savina Mannarino^a, Riccardo Albertini^d, Carmine Tinelli^e, Gloria Pelizzo^b

^aPediatric Unit, Department of the Mother and Child Health, IRCCS Policlinico San Matteo Foundation, Pavia, Italy; ^bPediatric Surgery Unit, Department of the Mother and Child Health, IRCCS Policlinico San Matteo Foundation, Pavia, Italy; ^cDepartment of Anaesthesiology and Intensive Care, IRCCS Policlinico San Matteo Foundation, Pavia, Italy; ^dLaboratory of Clinical Chemistry, IRCCS Policlinico San Matteo Foundation, Pavia, Italy; ^eBiometry & Clinical Epidemiology, Scientific Direction, IRCCS Policlinico San Matteo Foundation, Pavia, Italy

Background: Postoperative effect of music listening has not been established in pediatric age. **Objective and hypotheses:** The purpose of this study is to better understand the benefits of music on postoperative distress and pain in Pediatric Day Care Surgery. **Methods:** Forty-two children admitted for minor or intermediate surgery, were enrolled in this study. Patients were randomly assigned to the 'music-group' (music intervention during awakening period) or to the 'non-music group' (standard postoperative medical care). Slow and fast classical music and pauses were recorded and played via ambient speakers. Heart rate (HR), blood pressure (BP), oxygen saturation (SpO₂), glucose and cortisol levels, faces pain scale and Face, Legs, Activity, Cry, Consolability (FLACC) Pain Scale were considered as indicators of physiological response to stress and pain experience. **Results:** 40 boys and two girls (6.7 ± 4.1 years) were evaluated. No differences were found between 'music' group (*n*=21) or 'no-music' group (*n*=21) with respect to age, sex, weight, BMI. Music during awakening induced low increase of systolic and diastolic BP levels (*P*=0.09 and *P*=0.003 respectively). Preoperative cortisol levels were lower than at the end of surgical procedure (*P*=0.01) and at the awakening (*P*=0.06). A significant decrease at the awakening respect to the end of surgical procedure was found (*P*=0.02), without difference between the two groups (*P*=0.6). The 'non-music' group showed progressive increasing values of glycemia; in 'music' group the curve of glycemia presented a plateau pattern (*P*<0.001). Positive impact on reactions to pain was noted using the behavioural FLACC scale. **Conclusions:** Music improves cardiovascular parameters, stress-induced hyperglycemia and perception of pain immediately after surgery in children.

The relaxing effect seems to be achieved by the alternation of fast, slow rhythms and pauses even in paediatric age.

P3-D1-902

A Case of Congenital Isolated ACTH Deficiency due to *tbx19* Gene Mutation

Natalya Kazachenko^a, Anatoly Tiulpakov^b, Yulia Skorodok^c, Dmitry Ivanov^d, Zukhra Mullakhmetova^e

^aSt-Petersburg Pediatric Medical University, St-Petersburg, Russia; ^bDepartment and Laboratory of Inherited Endocrine Disorders Endocrinology Research Center, Moscow, Russia; ^cSt-Petersburg Pediatric Medical University, St-Petersburg, Russia; ^dSt-Petersburg Children Hospital 1, St-Petersburg, Russia; ^eSt-Petersburg Pediatric Medical University, St-Petersburg, Russia

Objective: To characterise clinical presentation of congenital isolated ACTH deficiency. **Methods and results:** Clinical and anthropometric data were obtained. Biochemical liver function parameters, blood glucose, insulin, TSH, free thyroxin (FT₄), GH, cortisol, and ACTH levels were analyzed. POMC and TBX19 genes were analysed by Sanger sequencing. The girl was born at full-term with normal weight and length. The parents are cousins. At birth craniofacial dysmorphisms and left-side clubfoot were present. At the age of 2 months hepatitis was diagnosed on the basis of elevated bilirubin and liver enzymes levels. At the age of 7 months the patient presented with severe hypoglycemia (blood glucose 10.9 mg/dl). Serum cortisol and ACTH levels were low: 15.9 nmol/l (reference 138–635) and below 1.1 IU/ml (reference 1.8–10.2) respectively. Insulin, TSH, FT₄, and GH levels were normal. Homozygous p.Q28X mutation in TBX19 gene was found in the child. The girl's mother is healthy heterozygous carrier. After initiation of replacement therapy with hydrocortisone (10 mg/m² daily) hypoglycemia and signs of hepatitis were resolved. **Conclusion:** In the case of severe hypoglycemia associated with neonatal liver dysfunction the diagnosis of congenital isolated ACTH-deficiency should be considered.

P3-D1-903

Xanthogranulomatous Hypophysitis: a Rare but Mistaken Pituitary Lesion

Jaya Sujatha Gopal Kothandapani^a, Veejay Bagga^b, Stephen Wharton^c, Saurabh Sinha^b, Paul Dimitrid^d

^aDepartment of Human Metabolism, University of Sheffield, Sheffield, UK; ^bDepartment of Neurosurgery, Royal Hallamshire Hospital, Sheffield, UK; ^cDepartment of Histopathology, Royal Hallamshire Hospital, Sheffield, UK; ^dDepartment of Paediatric Endocrinology, Sheffield Children's Hospital, Sheffield, UK

Introduction: Xanthogranulomatous hypophysitis (XGH) is a very rare form of pituitary hypophysitis that may present both clinically and radiologically as a neoplastic lesion or

craniopharyngioma. Our case series compares the paediatric and adult presentations of XGH and the differential diagnoses considered. **Case series:** *Patient 1:* A 15-year-old female presented with refractory headache, lethargy, short stature, delayed growth (weight (-3.36) SDS, height (-1.73) SDS, and BMI 14 kg/m²), primary amenorrhoea and pubertal arrest over 18 months. Visual examination showed bitemporal quadrantanopia.

Patient 2: A 21-year-old female presented with lethargy, frontal headaches and secondary amenorrhoea, 3 years after delivery. *Postpartum* she had initial galactorrhoea and irregular periods, which stopped after a year. Visual examination was normal.

Patient 3: A 64-year-old female presented with multiple syncopal attacks over 7 years. A MRI scan performed for suspected vertebrobasilar insufficiency revealed a pituitary mass. There was a previous history of hypothyroidism for 20 years and hysterectomy at 39 years of age for irregular periods. Eye assessment revealed left temporal quadrantanopia. Endocrine investigations suggested panhypopituitarism in all three patients and were commenced on treatment. Patient 2 had high prolactin levels requiring Cabergoline. Pituitary MRI revealed a suprasellar mass compressing the optic chiasm suggestive of craniopharyngioma or Rathke's cleft cyst in patient 1; non-functioning pituitary macroadenoma in patients 2 and 3. MRI appearance was of mixed signal intensities on T1- and T2-weighted sequences. All three patients underwent an endoscopic trans-sphenoidal surgery. Histology revealed areas with cholesterol cleft formation associated with multinucleate giant cells and numerous macrophages. **Conclusion:** XGH presents with a variation of symptoms in children and adults. It is regularly mistaken for other pituitary lesions but must be considered as part of the differential diagnosis when a pituitary mass is identified through cranial imaging demonstrating mixed signal intensities on both T1- and T2-weighted images.

P3-D1-904

Long-Term Endocrinological Follow-Up in Diencephalic Syndrome

Maria Parpagnoli, Salvatore Seminara, Giulia Anzilotti

AOU Meyer, Florence, Italy

Background: Diencephalic syndrome (DS), diencephalic cachexia or Russell syndrome, is a rare, rapidly fatal condition, usually occurring during the first year of life, as a result of a hypothalamic dysfunction due to hypothalamic/chiasmatic tumors. Clinical features of DS are weight loss leading to cachexia despite a normal caloric intake and growth rate, hyperalertness, hyperkinesia, and euphoria. Treatment is related to treatment of the hypothalamic lesion. The role of cytokines, tumor-derived compounds, peptides and/or neuropeptides, neurotransmitters and hormones is still debated. **Objective and hypotheses:** The aim of the authors is to evaluate if a longer endocrinological follow-up is necessary after treatment. **Method:** We describe eight pediatric patients, 4 m and 4 f (median age at diagnosis of 6.5 months, range 4–60) followed at Meyer Children Hospital for DS as a result of an hypothalamic tumor. Surgical treatment was based on tumor location and extent. Patients received 10 monthly courses of cisplatin and etoposide and nutritional support. Weight,

length, head circumference, and baseline endocrine function (IGF1, TSH, T₄, cortisol, prolactin, ACTH, and ADH) was evaluated before and after therapy. **Results:** Despite different baseline endocrine values, at standard follow-up (2 years after therapy) we did not find any clinic endocrinological abnormality. Prolonging follow-up, endocrine dysfunction developed in 2/8 patients. One had diabetes insipidus and precocious puberty and the other had a short stature due to GH deficit. **Conclusion:** As previously reported, our endocrinological data did not reveal any significant trend or correlation with the therapy immediately after treatment. But a longer follow-up revealed endocrinological diseases. We conclude that a longer follow-up is necessary not only to better define long-term effectiveness of this low-dose cisplatin–etoposide regimen in the recovery of DS patients with hypothalamic tumors, but also to be able to recognise endocrine deficits.

P3-D1-905

Key-Role of TSH Deficiency in Disclosing Craniopharyngioma Diagnosis in a Short Girl with Hashimoto's Thyroiditis

Tommaso Aversa, Mariella Valenzise, Giuseppina Zirilli, Mariaausilia Catena, Filippo De Luca, Malgorzata Wasniewska

Department of Pediatrics, Gynecology, Microbiology and Biomedical Sciences, University of Messina, Messina, Italy

Background: Hashimoto's thyroiditis (HT) in childhood may present with either euthyroidism (52.1% of cases), or primary overt hypothyroidism (22.2%), subclinical hypothyroidism (19.2%), overt hyperthyroidism (3.5%), or subclinical hyperthyroidism (3%). In a large series of 608 children and adolescents with presenting HT, we found in no cases a biochemical picture with low free thyroxine (FT₄) and normal or low-normal TSH serum levels, i.e. a thyroid pattern that is consistent with central hypothyroidism (CH), but is not compatible with HT. Therefore, the finding of such a biochemical pattern in a child with HT should direct work-up towards seeking an associated central cause of hypothyroidism. **Aim:** The aim of the present case report is to reinforce the above view. **Case report:** In a short girl with celiac disease and HT, the suspect of an associated pituitary lesion was suggested, despite the lack of neuro-ophthalmic symptoms, by the finding of a thyroid function pattern that was not compatible with HT (low FT₄ with normal TSH). This case report reinforces the view that the finding of a normal TSH in presence of a low FT₄ should always alert pediatricians and raise the suspect of central hypothyroidism, even when a primary thyroid disease has been already identified. In this case TSH deficiency played a critical role in disclosing diagnosis of craniopharyngioma (CP). **Conclusions:** Among the endocrinological manifestations of CP, TSH deficiency is observed in only 25% of children, whereas GH deficiency (100% of cases) and ACTH deficiency (68%) are distinctly more frequent. In this case report TSH deficiency was present and played a critical role in disclosing diagnosis of CP. If it had been absent, it might be hypothesized that diagnosis of CP would have been furtherly delayed.

P3-D1-906

Pituitary Dysfunction with Associated Lesions in the Hypothalamo-Pituitary Region: Histiocytosis or Dysgerminoma?

Elpis Vlachopapadopoulou^a, Vassilios Papadakis^b,
Panagiotis Nomikos^c, Stefanos Michalacos^a,
Sophia Polychronopoulou^b

^aChildren's Hospital P & A, Athens, Greece; ^bChildren's Hospital Agia Sophia, Athens, Greece; ^cYgeia Hospital, Athens, Greece

Background: Patients who present with clinical and laboratory findings of pituitary dysfunction and whose MRI findings reveal increased pituitary size or thickening of pituitary stalk, pose a diagnostic challenge. The differential diagnosis mainly includes dysgerminoma, histiocytosis, and hypophysitis. A non-invasive approach is often non-diagnostic. **Objective and hypotheses:** To present two patients with similar clinical picture and positive MRI findings, in whom transphenoidal biopsy of the pituitary lesion, led to prompt accurate diagnosis and further therapeutic management. **Method:** *Patient 1:* Prepubertal girl 8 years of age, presented with the main complaint of slow growth rate. Detailed history revealed polydipsia and polyuria. Growth curve evaluation revealed a change of percentile from the 50th to the 15th percentile in the previous 3 years. Physical exam was unremarkable and she was prepubertal. MRI of the hypothalamo-pituitary region revealed enlargement of the anterior pituitary lobe and thickening of the pituitary stalk, enhancing with gadolinium. Displacement of the optic chiasma was appreciated. Skeletal survey, chest X-ray and abdominal US were normal, HCG blood and CSF levels were low as well as CSF cell count/protein. A transphenoidal biopsy of the lesion revealed dysgerminoma. *Patient 2:* Adolescent girl 15.5 years old, presented with a history of diabetes insipidus, of 2 years duration, and irregular menses. Physical exam was unremarkable and she was fully pubertal. MRI revealed thickening of the pituitary stalk 3.8 mm. Follow-up MRI revealed further enlargement up to 5.4 mm. Skeletal survey, chest X-ray, and abdominal US were normal, HCG blood and CSF levels were low as well as CSF cell count. Transphenoidal biopsy revealed dysgerminoma. **Conclusions:** Tissue biopsy provides the definitive diagnosis and the transphenoidal approach appears to be optimal for certain patients. Inconclusive imaging appearance, negative markers, and slow progression cannot exclude the diagnosis of germinoma.

P3-D1-907

A Case of Combined Pituitary Hormone Deficiency in a Patient Affected by Osteogenesis Imperfecta

Evelina Maines, Grazia Morandi, Diego Ramaroli, Claudia Anita Piona, Paolo Cavarzere, Rossella Gaudino, Franco Antoniazzi

Department of Life Sciences and Reproduction Sciences, Pediatric Clinic, 'Giambattista Rossi' Hospital, University of Verona, Verona, Italy

Background: Combined pituitary hormone deficiency (CPHD) is a condition that causes deficiency of several hormones produced by the pituitary gland. The first signs of this condition include a failure to grow at the expected rate and short stature that usually becomes apparent in early childhood. Other features of CPHD include hypothyroidism, delayed puberty, and deficiency of the hormonal cortisol. Some conditions may exacerbate the growth failure of CPHD. Osteogenesis imperfecta (OI) is a congenital bone disorder characterized by bone fragility and short stature caused by mutations in the genes that codify for type 1 procollagen (COL1A1 or COL1A2). Severity of OI varies widely, ranging from intrauterine fractures and perinatal lethality to very mild forms without fractures. **Case report:** We report the case of a 4-year-6-month-old boy, who was brought to our Pediatric Clinic to evaluate severe short stature. His height was between -4 and -5 s.d. below the mean. In the first month of life he had a femur fracture. To evaluate short stature we performed two GH provocative tests that revealed peak stimulated GH levels below 10 µg/l (arginine stimulation test 2.56 µg/l, and glucagon stimulation test 2.3 µg/l). Nuclear magnetic resonance (NMR) imaging revealed an ectopic neurohypophysis thyroid function test detected also a secondary hypothyroidism (TSH 2.43 mU/l and fT₄ 5.9 ng/l). The patient started recombinant human GH (rhGH) and l-thyroxine therapy. The clinical examination of the patient was normal with the exception of light blue sclera suggesting OI. The patient was a heterozygote for a missense mutation in the COL1A1 gene (exon 48 g.14865 G > A), leading to a structural abnormality of collagen 1. At 16 years old, GnRH agonist (GnRH_a) stimulation test revealed a hypogonadotropic hypogonadism and we diagnosed CPHD. **Conclusion:** Our case suggests that severe short stature in patient with CPHD could be exacerbated by other conditions such as OI. Blue sclera and a history of fractures in children with short stature may suggest investigation into OI.

P3-D1-908

Macroprolactinoma in Adolescence: a Case Report

Amanda Scott^a, Valli Velayutham^a, Robert Campbell^b, Ross Cuneo^b,
Andrew Cotterill^a

^aChildren's Services Queensland, Brisbane, Queensland, Australia;

^bMater Hospitals, Brisbane, Queensland, Australia

Background: Prolactinomas are relatively rare during childhood, with an incidence of 0.1 per million. Children with hyperprolactinaemia have widely varied presentations depending on age, sex, and tumour size. Whilst adults typically present with galactorrhoea or hypogonadism, children tend to present with pubertal delay and growth issues. **Objective and hypotheses:** Poorer surgical outcomes have been reported in children with macroprolactinomas compared to adults, leading to uncertainty regarding optimal treatment. The following outlines a case of macroprolactinoma in an adolescent. **Method:** A 15.5-year-old male presented with concerns of slow pubertal progression. Examination showed 15 ml testes and early secondary sex characteristics. Baseline bloods showed measurable gonadotrophin

levels and low testosterone. Clinical review following 6 months observation, showed interval growth deceleration and progression of testes to 20 ml without further secondary sex characteristic development. Repeat investigations revealed unchanged gonadotrophin and testosterone levels and markedly elevated serum prolactin (48 061 mU/l, reference range 100–420). The patient was otherwise asymptomatic of hyperprolactinaemia. Magnetic resonance imaging showed a large pituitary mass measuring 23×22×14 mm, with features consistent with macroprolactinoma. Extrasellar extension was present (optic nerve compression, cavernous sinus invasion, internal carotid artery displacement, and left posterior clinoid process erosion). Impressively there was no visual field defect on ophthalmological assessment. Dynamic endocrine testing revealed GH insufficiency and partial ACTH and gonadotrophin insufficiencies. **Results:** Cabergoline was commenced and dose intermittently increased over 6 months. The prolactin level gradually decreased to 700 mU/l by 9 months post diagnosis. Additional management included testosterone and GH therapy and emergency glucocorticoids. Surgical intervention was deferred at presentation, in the absence of neurological signs. **Conclusion:** This case demonstrates a cabergoline-responsive macroprolactinoma presenting with growth deceleration and an unusual pattern of pubertal arrest. It raises the controversial question of surgical intervention indications. In Australia it also raises the dilemma of GH access in the context of a pituitary tumour.

P3-D1-909

Idiopathic Central Diabetes Insipidus: a Case of Pediatric Xanthogranuloma

Gabriella Pozzobon, Chiara Damia, Andrea Voto, Maria Piera Ferrarello, Gisella Garbetta, Sara Osimani, Giulia Pruccoli, Cristina Partenope, Giuseppe Chiumello

Department of Pediatrics, San Raffaele Scientific Institute, Milan, Italy

Background: Xanthogranuloma of the sellar region (XG) is a very rare brain tumor and is clinically and pathologically distinct from classical adamantinomatous craniopharyngioma, but the differential diagnosis is difficult because there are no typical neuroradiological signs. The characteristic and the outcome of XG in children remain still unclear. **Objective and hypotheses:** We aimed to describe a case report of XG and multiple pituitary hormone deficiency. **Method:** A 12-year-old boy presented with polyuria, polydipsia and nocturia with episodes of morning headaches and vomiting. No visual disturbances. The physical exam was normal, with adequate auxological parameters. **Results:** The water balance documented polyuria (67 ml/kg per day) and polydipsia (54 ml/kg per day). Laboratory exams showed diabetes insipidus (diagnosed through fluid deprivation test) associated with central hypothyroidism and secondary adrenal insufficiency. Brain MRI evidenced a small hyperintense expansive sellar and suprasellar lesion with cystic aspect, without vascular abnormalities; no calcifications at TC control were found. The lesion was

surgically removed with a transphenoidal approach. The histological examination showed a xanthogranulomatous hypophysitis with giant cell reaction, cholesterol crystal, and necrotic inflammatory material. A multiple pituitary hormone replacement therapy (hydrocortisone, desmopressin, and L-thyroxine) was started with good response. **Conclusion:** XG of the sellar region is a very rare tumor and only few pediatric cases have been described in literature, moreover the nature and clinical course remains unclear. When a lesion of the sellar region is associated with a multiple pituitary hormone deficiency XG should be included in the differential diagnosis. Further studies are needed to understand the prognosis and the long-term outcomes of this tumor.

P3-D1-910

Central Diabetes Insipidus Caused by Congenital Cytomegalovirus: a Rare Association?

Tiago Jeronimo dos Santos, Caroline Passone, Leandra Steinmetz, Louise Cominato, Hilton Kuperman, Thaís Della Manna, Hamilton Menezes Filho, Vaê Dichtchekenian, Joyce Pupo, Nuvarte Setian, Durval Damiani

Instituto da Criança, HCFMUSP, São Paulo, São Paulo, Brazil

Introduction: Central diabetes insipidus (CDI) is a condition in which large volumes of diluted urine are excreted due to vasopressin deficiency. In most patients, DI is caused by the destruction of neurons in the hypothalamus and the known causes include local inflammation or autoimmune aggression, vascular and infiltrative diseases, as well as compressive masses, trauma or midline cranial malformations. CDI caused by cytomegalovirus (CMV) infection is a very rare condition. **Case Report:** A Brazilian 5-month-old boy, with failure to thrive, was referred due to intermittent fever, polyuria, and hypotonia. His mother was infected by cmv in the first trimester of pregnancy. Neither the mother nor the child was treated. A cranium CT was performed showing scattered intracranial calcifications, mainly in white matter and periventricular region. CMV serum PCR was positive (162 virus samples/ml). Abdominal ultrasound showed mild hepatosplenomegaly. Fundoscopy was normal, and, in auditory evoked potential, a sensorial loss in the left ear was found. Lab work-up: serum Na 155 mEq/l (135–145), serum osmolality 307 mOsm/kg (285–310), and urinary osmolality 82 mOsm/kg (50–1400). Other hypothalamic–pituitary hormone dysfunctions have been excluded. A brain MRI showed loss of hypersignal (T1-weighted) in the posterior lobe of pituitary gland; and high intensity signal (T2) on perivascular space and caudate nucleus, corresponding to calcifications. Desmopressin treatment was started. One month later, neurodevelopment and ponderal improvement, as well as adequate serum and urinary osmolality, without polyuria, were achieved. **Conclusion:** CMV infection is a rare association with CDI in infants. Therefore, in infants with failure to thrive, associated to maternal infectious diseases during the pregnancy, attention about their osmolality should be given due to the difficulties to notice DI symptomatology in these patients.

P3-D1-911

Primary Polydipsia in a Family with Mutation in the AVP Gene and Proven Central Diabetes Insipidus

Ruth Casey, Anne Marie Hannon, Caroline Joyce, Domhnall O'Halloran, Susan O'Connell

Cork University Hospital, Cork, Ireland

Background: Diabetes insipidus (DI) is characterised clinically by the inappropriate production of large volumes of dilute urine even in the presence of clinical dehydration or deprivation of water. DI occurs either due to a deficiency or insufficiency of arginine vasopressin (AVP) hormone production. Hereditary DI accounts for <10% of the DI cases. As hyponatraemic seizures secondary to inappropriate use of desmopressin can occur, caution is required before a diagnosis of DI is made. On the other hand, primary polydipsia does not exclude the patient from possibly later developing DI and genetic testing within families may be indicated. The gold standard diagnostic test remains the water deprivation test. **Method:** Case report. **Results:** This is the case of a family with a known heterozygous pathogenic missense mutation, c.232>A (GLU78LYS) in the AVP gene. The mother and her eldest daughter have biochemically confirmed central DI and are symptomatically well controlled on desmopressin. The youngest daughter, aged 8, who is symptomatic has passed a water deprivation test on three occasions, mutation. A son, now 16, who had primary polydipsia as a toddler, is negative for the mutation. MRI in the mother and youngest daughter show normal posterior pituitary bright spot, but this is absent in the eldest daughter. **Conclusion:** These cases illustrate that primary polydipsia can co-exist in families where a diagnosis of central DI has already been established in other family members. This can be challenging especially where there is a different perception of what normal fluid intake is. A child who exhibits water-seeking behaviour and who has a sibling or parent with known central DI can mistakenly be assumed to have the same condition. Complex diagnostic and management issues may be faced when a genetic mutation is found in the context of symptoms but negative biochemical confirmation.

P3-D3-912

Screening for SOX2 Mutations in Bulgarian Patients with Congenital Hyposomatotropism: First Results

Ani Aroyo^a, Iva Stoeva^a, Daniela Dacheva^b, Radka Kaneva^b, Atanaska Mitkova^b, Alexander Oscar^c, Vassil Haikin^c, Vanio Mitev^b

^aUniversity Pediatric Hospital, 'Screening and Functional Endocrine Diagnostics' Medical University, Sofia, Bulgaria; ^bCentre for Molecular Medicine, Medical University, Sofia, Bulgaria; ^cClinic of Ophthalmology, University Hospital 'Alexandrovska', Medical University, Sofia, Bulgaria

Background: The transcription factor (TF) SOX2 is expressed early in the embryological development and is essential for the development of many structures like neural system, pituitary

gland, eyes, ears, esophagus, and gonads. The most common clinical manifestations of mutations in the SOX2 gene are eye abnormalities (anophthalmia/microphthalmia, coloboma, nystagm, and refractive errors) and hypopituitarism (deficiency of gonadotropic, GH, TSH, and ACTH). Molecular genetic studies in children with combined pituitary hormone deficiency (CPHD) started in Bulgaria in 2001 by screening of PROP1 using the candidate gene approach. An allele frequency of PROP1 mutations was found for 12.2% of the preselected patients, mostly 150delA, followed by 301-302delAG. The mutational screening panel was extended by POU1F1, HESX1, SOX3 between 2011 and 2013. **Objective and hypotheses:** To extend further the TF mutational screen by implementation of screening for SOX2 as a diagnostic tool in congenital CPHD. **Method:** Study population: 22 patients, aged ($x \pm s.d.$) 8.5 ± 4.0 , median 8.3 years, 13 females (8.1 ± 4.2 , median 7.6 years), nine males (8.5 ± 4.0 , median 8.3 years). Inclusion criteria: obligate congenital GH deficiency; additional criteria: CPHD, ophthalmologic abnormalities; pathologic findings on hypothalamo-pituitary region MRI; phenotype characterization based on: auxology, bone age, hormonal tests (GH, TSH, fT₄, Prl, LH, FSH, T, E₂ by Delfia, IGF1 and BP3, cortisol by ELISA); molecular genetic analysis by direct sequencing of the single exon of the SOX2 gene. **Results:** No mutations of SOX2 in the selected patients could be verified. **Conclusion:** Mutations in SOX2 are a rare cause of hypopituitarism in Bulgarian patients. Therefore, PROP1 mutational screening should be the first to be performed in children with congenital CPHD. Changes in the mutational screening strategy (next generation sequencing instead of single gene candidate approach) could help in revealing the complex etiology of congenital hypopituitarism.

P3-D3-913

Follow Up for Adult Height of Girl with the Onset of Puberty at 6 or 7 Years Old

Zhuang-Jian Xu, Ya-Ping Ma, Jin-Ling Zhao, Jian-Mei Zhang, Bing-Yang Xia

Affiliated Hospital of Jiangnan University, Wuxi 4th People's Hospital, Wuxi City, Jiangsu, China

Background: It is not yet clear whether the adult height (AH) is affected by the onset of puberty at 6 or 7 years old in girl in China. **Objective and hypotheses:** To evaluate AH in girl with the onset of puberty at 6 or 7 years old. **Method:** The standard of AH in girl was considered that their bone ages were equal to (or greater than) 15 years old or they were at least 3 years post-menarche. Eighty-two girls with the onset of puberty at 6 years old (A group, $n=32$) and 7 years old (B group, $n=50$) met the standard of AH, who received no treatment. AH of 69 girls with normal puberty were assigned to normal control group (C group). And above-mentioned girls were from Wuxi City, Jiangsu Province, China. **Results:** The chronological ages in A and B group were (6.46 ± 0.35) years and (7.59 ± 0.25) years respectively. And the target heights were (158.66 ± 3.83) cm and (159.33 ± 3.93) cm respectively. And the AH were (161.73 ± 5.60) cm and (161.24 ± 4.99) cm respectively. The target heights and AH in C group were (158.33 ± 4.02) cm and (161.43 ± 4.51) cm

respectively. There was no difference ($P > 0.05$) for AH or target heights between C group and A group, or C group and B group. **Conclusion:** AH is not affected by the onset of puberty at 6 or 7 years old in girl in Wuxi City, Jiangsu Province, China.

P3-D3-914

The Influence of Specimen pH on Urinary LH and FSH by Immunochemiluminometric Assays

Ya-Ping Ma, Zhuang-Jian Xu, Yu Hu, Wen-Ying Zhu, Qing Wang

Affiliated Hospital of Jiangnan University, Wuxi 4th People's Hospital, Wuxi City, Jiangsu, China

Background: It remains unclear whether specimen pH can influence urinary LH and FSH assayed by immunochemiluminometric assays (ICMA). **Objective and hypotheses:** To investigate the effect of specimen pH on urinary LH and FSH assayed by ICMA. **Method:** The first morning-voided urine were collected and divided into 11 samples (each 100 ml). The urine pH was determined with a pH meter. Hydrochloric acid and sodium hydroxide were added to aliquots of urine as needed to achieve pH of 2.5, 3.5, 4.5, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, and 10.5 respectively. Each sample was then assayed for urinary LH and FSH respectively. **Results:** Urinary LH at various pH as a percentage of urinary specimen at pH 7.5 (as same as pH in standard solution of LH or FSH) were as follows: 104% at pH 2.5, 109% at pH 3.5, 108% at pH 4.5, 105% at pH 5.5, 103% at pH 6.0, 100% at pH 6.5, 99% at pH 7.0, 99% at pH 8.0, 99% at pH 8.5, and 99% at pH 10.5; and for urinary FSH 14, 89, 95, 101, 102, 102, 99, 100, 99, and 95% respectively. Urinary LH were unaffected by changes of pH from 2.5 to 10.5, as well as urinary FSH from pH 3.5 to 10.5. But urinary FSH at pH 2.5 was lower than that at pH 7.5 ($P = 0.000$). **Conclusion:** ICMA can accurately measure urinary LH and FSH at a urinary physiological range of pH.

P3-D3-915

Thickened Pituitary Stalk with Central Diabetes Insipidus: What Diagnosis?

Amel Merazka, Achir Samia, Baz Ouidad, Foudil Dalila, Semrouni Mourad

Pierre and Marie Curie Center, Algiers, Algeria

Background: Central diabetes insipidus (DIC) is usually the final result of lesions affecting the hypothalamic–neurohypophyseal system, for the children, germinoma is the main reason. The MRI aspect is often limited to thickness pituitary stalk with loss of hyperintensity of the neurohypophysis. **Objective and hypotheses:** Thickening of pituitary stalk is suggestive of germinoma, the clinical picture is dominated by a DIC (90%), associated to hypopituitarism (60%), his natural history is unpredictable, he should always be considered. The diagnosis is easy if the β hCG rate is high, or if there is a pineal localization,

but in most cases, these tests are normal and the MRI does not differentiate germinoma from other causes thickening pituitary stalk (histiocytosis, sarcoidosis or lymphocytic hypophysitis). **Method:** A 15-year-old boy, referred to our clinic for his growing delay and polyuria–polydipsia syndrome appeared 6 months earlier (estimated 5 l/day). Physical exam: weight = P3, size < P3, Tanner step 1. He shows signs of GH and corticotropin deficiencies. No intracranial tumor syndrome. **Results:** (i) Hormonal test: DIC with hypocortisolism, hypogonadism and GH deficiency. (ii) Pituitary MRI: pituitary stalk enlargement (6 mm), loss of T1 hyperintensity of the posterior pituitary. (iii) Biologic and morphologic analysis discards a secreting germinoma, histiocytosis X and sarcoidosis assumption. **Conclusion:** MRI report is the diagnosis key of isolated large pituitary stalk, with other clinical clues; but still a long monitoring each 3–6 months, without histological evidence, can be suggested; checking for germinoma or histiocytosis existence, especially in child case. There are no good imaging predictors for hypopituitarism, making clinical and hormonal evaluation of all patients with pituitary stalk lesion crucial.

P3-D3-916

Polyuria Syndrome Associated with Visual Disorders in Children: Discuss at First Craniopharyngioma, the Primary Polydipsia is an Exclusion Diagnosis

Rahem Yacine, Belacel Merouane, Achir Samia

Pierre et Marie Center, Algiers, Algeria

Background: True diabetes insipidus (DI) is a rare disease in children, defined as the excretion of hypotonic urine and polydipsia, secondary to an absolute or relative deficiency of antidiuretic hormone arginine vasopressin (central DI) or a resistance to the action of this hormone (nephrogenic DI). To differentiate from primary polydipsia. **Objective and hypotheses:** We report the case of AM a 13 years old girl, with personal history of cholecystectomy at age 8 years, who present polyuria and polydipsia syndrome evolving for 4 years without identifiable precipitating factor, amounted to 5.5 l/24 h, associated with visual disturbances which evoke craniopharyngioma nevertheless without symptoms of intracranial hypertension. **Method:** Cerebral MRI, the water deprivation test and ophthalmologic examination were performed. **Results:** Cerebral MRI does not find evocative mass and shows a persistent hyper posterior pituitary signal in T1, without thickening or infiltration of the pituitary stalk. The water deprivation test showed a concentration of urine after 3 h, in favor of the diagnostic of primary polydipsia. Ophthalmologic examination found a bilateral decrease in visual acuity associated with astigmatism and amblyopia. **Conclusion:** Association of visual impairment and a polyuria syndrome in children must suggest first a craniopharyngioma, pituitary MRI permit to invalidate this diagnosis, primary polydipsia is retained only as diagnosis of exclusion as this is the case for our patient.

P3-D3-917

Multiple Pituitary Hormone Deficiency with Transitory Pituitary Enlargement due to Prop1 Mutation (Case Presentation)

Lavinia La Grasta Sabolic, Gordana Stipancic, Marija Požgaj Šepec
University Hospital Centre Sestre Milosrdnice, Zagreb, Croatia

Background: In pediatric patients multiple pituitary hormone deficiency (MPHD) can be caused by mutations in pituitary-specific transcription factors. Among those, mutations in PROP1 gene account for ~50% of genetically determined cases of CPHD. Regarding morphology, the anterior pituitary can be normal, hypo-/aplastic or enlarged. **Results:** We present two unrelated patients referred for evaluation of growth retardation. Both had profound growth retardation at the age of 5.6 and 4.1 years, accompanied by significant retardation of bone age. They had insufficient GH response to provocation tests. Their initial MRI scan revealed enlarged anterior pituitary. GH therapy was instituted, along with L-thyroxine substitution due to secondary hypothyroidism. Basal prolactin levels diminished with time. Both children required sex steroid substitution for secondary hypogonadism and so far had no overt symptoms of adrenal insufficiency. Control MRI detected hypoplastic/normal anterior pituitary. **Conclusion:** Clinical presentation, results of endocrine work-up and pituitary morphology of both patients are in line with MPHD caused by PROP1 mutation which was subsequently proven by genetic analysis. This was the first time that gene mutation responsible for MPHD was identified in Croatian population. A marked phenotypic variability with delayed appearance of the different hormone deficiencies can be expected in patients with PROP1 mutations and the possibility of corticotroph deficiency should not be overlooked.

P3-D3-918

MRI in Children with GH Deficiency

Ouidad Baza^a, Mourad Semrouni^a, Samia Sakher^a, Nadia Chouikrat^b, Mourad Benallegue^b

^aEndocrinology Department, Pierre and Marie Curie Center, Algiers, Algeria; ^bRadiology Department Nafissa, Hamoud Hospital, Algiers, Algeria

Background: Magnetic resonance imaging (MRI) is advisable in all patients with GH deficiency (GHD). MRI pituitary morphology has important clinical implications, both in terms of diagnostic accuracy and long-term prognosis; indeed, when MRI findings are appropriately interpreted, they clearly represent a gold standard to investigate the etiology of GHD. **Objective and hypotheses:** To evaluate frequency and type of MRI anomalies in children with GHD, after diagnosis was established. **Method:** These is retrospective and analytical study about 124 children follow in our consultation between 2009 and 2013, which diagnosis of GHD was establish with two stimulation tests. All these children were examined by MRI; The presence, size, location,

and morphologic characteristics of the stalk, the neurohypophysis, and the adenohypophysis were recorded in each case. The age ranged between 2 and 16 years. The mean age was 11 ± 5 years, we collect 32 girls and 92 boys with sex ratio 2.8 boy/one girl. **Results:** We objective 45% children with normal MRI, whose was identified idiopathic GHD. 55% of our population had anomalies the most important was pituitary hypoplasia in 30% of cases, the association of two or three anomalies was found in ~16% of MRI. The truncated stalk syndrome which is defined as an association of three anomalies was found in eight cases. Tumors was found in six cases with craniopharyngioma, germinome, and astrocytoma. The location of the neurohypophysis was ectopic in 8% of cases. **Conclusion:** MRI is the technique of choice in the diagnosis of children with hypopituitarism. Marked differences in MR pituitary gland morphology suggest different etiologies of GHD and different prognoses.

P3-D3-919

Dynamic Stimulation Testing in Pediatric Endocrinology: Experience of a Pediatric Endocrine Unit in a Developing Country

Janani Sundaram, Hemchand Krishna Prasad, Gnanabalan Murugesan, Ravisekar Vasudevan, Thangavelu Sangaralingam

Mehta Children's Hospital, Chennai, India

Background: Basal or unstimulated hormone levels frequently do not provide sufficient diagnostic information in the investigation of endocrine disorders. A range of dynamic or provocative tests are available to assess the dynamic responses of hormones and make necessary diagnoses. **Objective and hypotheses:** To describe the experiences with dynamic stimulation testing of a Paediatric Endocrine Unit in a developing country. **Method:** Retrospective review of case records of children who underwent dynamic stimulation testing in a Pediatric Endocrine Unit in a 1 year period (March 2013–February 2014). **Results:** During the study period, 35 children warranted dynamic testing, of whom 29 underwent testing, reasons for not testing include: costs (50%) and risk explained (17%) and unknown (33%). GH stimulation testing done: stimulant: glucagon ($n=4$) and clonidine ($n=7$). Interpretations: GH deficiency; GH sufficiency; GH insensitivity; and neurosecretory dysfunction. Synacthen stimulation testing; indications – low basal cortisol levels ($n=3$) and abnormal neonatal congenital adrenal hyperplasia screening test ($n=1$): adequate cortisol reserve established. GnRH analogue test ($n=4$); diagnosis of thelarche variant ($n=2$); central precocious puberty ($n=1$); and hypothalamic amenorrhea ($n=1$). Other tests done water deprivation test, dexamethasone suppression test practical modifications include: combining two tests to share stimulant costs; reducing the number of blood samples; using analogues and avoiding i v cannulation. Three minor complications encountered during the study: minor anaphylactic reaction (Synacthen), hypotension (clonidine) and symptomatic hypoglycaemia (glucagon); no deaths. The average cost Indian rupees 6500 ± 840 (€77); laboratory expenditure 76.3%. Other difficulties include

discrepancy between dosage of stimulant calculated by body weight and surface area, difficulty in fasting infants, and inadvertent collection of sample in inappropriate container. **Conclusion:** Dynamic stimulation tests are feasible in resource scarce settings of developing countries. They must be done in day care settings with all necessary precautions.

P3-D3-920

A Case of Hypopituitarism Caused by Traumatic Brain Injury in Infancy

Shinji Higuchi, Noriko Nishina, Masaki Takagi, Yukihiro Hasegawa
Tokyo Metropolitan Children's Medical Center, Tokyo, Japan

Background: While reports of hypopituitarism resulting from traumatic brain injury are increasingly common in European countries, long-term clinical courses are scarcely documented. We here present Japanese 31-year-old case with hypopituitarism caused by traumatic brain injury at the age of 5 months. **Objective and hypotheses:** To clarify the evolution of clinical and endocrinological data for 30 years in this patient. We hypothesize that the evolution progressed gradually. **Method:** Retrospective analysis of the chart. **Results:** He was born uneventfully by spontaneous cephalic delivery. He had no hypoglycemia or polyuria. Micropenis was not observed. Height velocity began to decrease around the age of 3 years, which was the initial symptom. Height was 107 cm (-3.4 S.D.), and he did not have micropenis at the age of 7 years. Endocrinological tests at this time were as follows: TSH 1.38 μ U/ml, T_4 3.91 μ g/dl, LH <0.1 mIU/ml, FSH <0.1 mIU/ml, GH response to arginine 1.8 ng/ml, and cortisol peak to insulin 12.53 μ g/dl. We diagnosed him as having GH, TSH, ACTH, and GN deficiencies. The pituitary stalk could not be identified on MRI, and ectopic posterior pituitary bright spot was noted. ACTH deficiency deteriorated with age. Cortisol peak to insulin was 3.0 μ g/dl at the age of 10 years, when hydrocortisone therapy was started. Testosterone enanthate therapy was needed to induce pubertal development at the age of 14 years, when hypogonadotropic hypogonadism was confirmed (LH, FSH, testosterone; all below the detection limit). After starting GH injection, growth rate improved with his final height being 0.4 S.D. at the age of 31 years. The mutations for congenital hypopituitarism were not detected, such as *POU1F1*, *LHX4*, *KALI*. **Conclusion:** After the head trauma, GH, ACTH, and GN gradually worsened in this patient.

P3-D3-921

Severe Features of Central Hypothyroidism and Hypoadrenalism Effectively Resolved by Treatment with Somatropin in a Boy with Panhypopituitarism

Gunter Šimic-Schleicher

Klinik für Kinder- und Jugendmedizin und für Kinder, Bremen, Germany

Background: A case of hypopituitarism usually related to hypothyroidism and hypoadrenalism. The unexpected effect of somatropin treatment is reported presented with clinical signs. **Method and results:** A 4-year-old adynamic boy in a wheel chair with normal height (105 cm, -0.7 SDS) but low weight (13 kg) and reduced TSH and thyroid hormones was transferred for further endocrine evaluation. Born after twin pregnancy in 35 weeks (2780 g, 49 cm, and 34 cm) together with a healthy brother, he sucked slightly more weakly than his brother. Walking was weak and late (20 months). He could neither climb nor run. He received physiotherapy up from 6 months and further examinations for neuromuscular diseases were started without results. His health deteriorated. With 4 years, he was adynamic, could hardly walk and used a wheel chair. Hypomimic, he seldom reacted on questions and slept 18 h/day. There were no signs for paresis and the tendon reflexes were of low normal activity. He was obstipated since infancy. Basal TSH and the surge after TRH were reduced and no circadian TSH rhythm could be detected. Thyroxine treatment was introduced with only little improvement in 4 months. Pituitary examination revealed a partial hypoadrenalism with high total cortisol but reduced free saliva and urine cortisol due to high CBG. There was a complete somatropin deficiency. 5 mg/day Cortisol was introduced without further improvement in the following 2 months. Then, somatropin treatment was started. After 2 months the symptoms almost resolved and after 6 months the boy was clinically totally normal. **Conclusion:** Complete somatropin deficiency may present without growth retardation. Hypoadrenalism combined with severe hypothyroidism in panhypopituitarism requires determination of free cortisol for diagnosis due to increased CBG. Treatment with thyroxine and cortisol alone in panhypopituitarism may not resolve all typical symptoms but only in addition with somatropin. The metabolic effects of somatropin in children need more attention.

P3-D3-922

A Case of Combined Pituitary Hormone Deficiency (CPHD) due to Anterior Pituitary Hypoplasia

Ekaterine Kvaratskhelia^a, Maia Rekhviashvili^a, David Metreveli^{a,b}, Rolf Peter Willig^c

^aDavid Metreveli Medical Centre, Tbilisi, Georgia; ^bTbilisi State Medical University, Tbilisi, Georgia; ^cEndokrinologikum, Hamburg, Germany

Background: Multiple anterior pituitary hormone deficiency (MPHD) may present in the newborn period or in early infancy with hypoglycemia, prolonged cholestatic jaundice micropenis, undescended testes due to GH, ACTH, and LH deficiency. Central hypothyroidism is becoming manifest later, less severe than primary hypothyroidism, usually without intellectual impairment. A male patient was admitted to our clinic with severe short stature at the age of 2 years, born with normal length and weight, from the nonconsanguine healthy parents. The first gestation of his mother

was unremarkable, delivery by cesarean section due to breech presentation. Newborn had a small but not micropenis, the location of testis at that time is unknown. Prolonged jaundice, constipation, and failure to thrive were developed soon after birth. Hormonal and biochemical investigations indicated severe anemia and signs of central hypothyroidism. The neonate was treated with by blood transfusion and later by L-Thyroxine (L-T₄). Psychomotor development of the patient improved under the treatment, but linear growth decelerated progressively. **Objective:** Typical signs of GH- and IGF-deficiency: doll-like appearance, large neurocranium, frontal prominence, small mid-face, deep nasal bridge, high-pitched voice, undescended testes, small penis, and severe retardation of growth: height SDS (−5.13 SDS), retarded bone age, global developmental delay. Severe GH deficiency was confirmed with low basal IGF1 and IGFBP3 and low GH in arginine stimulation test. Head MRI confirmed anterior pituitary hypoplasia. Basal level of cortisol in blood and free cortisol in 24 h urine were normal, to perform ACTH test was not possible, ultrasound showed thyroid hypoplasia. Further genetic investigation is planned. Treatment with GH (in addition to L-T₄) was initiated. Height SDS was increased from −6.94 to −4.51 SDS during the first year of treatment. Surgery (orchidopexy) was done after unsuccessful treatment of cryptorchidism with hGH. **Conclusion:** Clinical signs and severity of congenital hypopituitarism depends on the number and on the quality of hormonal failure. Early recognition is important for correction of auxological and mental retardation.

P3-D3-923

Think Histiocytosis X Facing Insipidus Diabetes with Thickened Pituitary Stalk

Lydia Lichtenberger-Geslin^a, Antoine Gourmel^b, Christian Sainte-Rose^c, H el ene Trifunovic-Bony^a, Karine Braun^a, Bernard Boudailliez^a, Catherine Devoldere^b

^aDepartement of Pediatric Endocrinology, Amiens Hospital, Amiens 80054, France; ^bDepartment of Pediatric Hematology, Amiens Hospital, Amiens 80054, France; ^cDepartment of Neurosurgery, Necker Hospital, Paris 75743, France

Background: Insipidus diabetes is a rare disease in pediatric endocrinology. **Objective and hypotheses:** Facing a thickened pituitary stalk on MRI pituitary, the main diagnosis to mention are: dysgerminoma, histiocytosis, sarcoidosis, and autoimmune hypophysitis. Histiocytosis is a rare and often underdiagnosed cause. **Method:** We report the case of a teenage girl who presented polyuria–polydipsia syndrome at the age of 14 years consequent full central insipidus diabetes confirmed by water restriction test. **Results:** MRI showed pituitary stalk thickened measured at 2.9 mm with a loss signal of post-pituitary. The initial analysis were negative (blood and cerebrospinal fluid markers of dysgerminoma, body skeletal radiographies, bone scintigraphy, ear scan, lung scan, and auto-immune research). The patient was treated with desmopressin. Later, the pituitary stalk has grown to

5 mm with apparition of an asthenia, a weight gain, and several anterior pituitary deficits in gonadal and somatotrophic axis. The GHD could not be supplemented until the diagnosis of dysgerminoma had not been dismissed. A stalk biopsy was performed at the age of 15.5 showing nonspecific inflammatory tissue and CD1a+ marker for a histiocytosis X. Complementary analysis showed bone defects and lung nodules which were not present during the initial radiographies. **Conclusion:** Histiocytosis X is a difficult and late diagnosis. Annual repetitions skeletal radiographies in search of bone's lesion, skin biopsy and repeat pituitary MRI before placing the indication of tige biopsy must be part of the key elements of diagnosis.

P3-D1-924

Leptin Levels in Boys with Pubertal Gynecomastia

Atilla Buyukgebiz^a, Bumin Dundar^b, Nihal Dundar^b, Ece Bober^c

^aFlorence Nightingale Hospital, Istanbul, Turkey; ^bKatip  elebi Univeristy, Izmir, Turkey; ^cDokuz Eylul University, Izmir, Turkey

Background: It has been reported that there is a relationship between circulating leptin and sex steroid hormones and leptin is able to stimulate estrogen secretion by increasing aromatase activity in adipose stromal cells and breast tissue. Leptin receptors have been also shown in mammary epithelial cells and it has been suggested that leptin is involved in the control of the proliferation of both normal and malignant breast cells. **Objective and hypotheses:** To investigate circulating leptin levels in boys with pubertal gynecomastia. **Method:** 20 boys with pubertal gynecomastia who were in early puberty and had no obesity and 20 healthy individuals matched for age, pubertal stage, and BMI with the study group were enrolled in the study. Body weight, height and left mid arm circumference (MAC) and left arm triceps skinfold thickness (TSF) were measured and BMI was calculated. A fasting blood sample was collected and routine hormonal parameters including prolactin, beta human chorionic gonadotrophin, total and free testosterone, estradiol, LH, FSH, and retestosterone (AS) and DHEAS levels were studied. Serum leptin levels were analyzed. **Results:** The mean ages of the study and control group were not different (13.9 ± 0.89 and 14.2 ± 0.66 respectively). No significant difference were detected for BMI, MAC, TSF, and hormonal levels except leptin. Leptin levels were found significantly higher in the study group compared with the healthy controls (5.58 ± 0.82 and 2.39 ± 0.29 , $P < 0.001$). No correlation could be determined between serum leptin levels and hormonal parameters. **Conclusion:** The presence of higher leptin levels in boys with pubertal gynecomastia indicates that leptin maybe involved in the pathogenesis of pubertal gynecomastia. The role of circulating leptin in pubertal gynecomastia is probably related to increase in estrogen and/or estrogen/androgen ratio by stimulating effect of leptin on aromatase enzyme activity in both adipose and breast tissues, or a direct stimulating effect of leptin on mammary epithelial cells or increase in sensitivity of breast epithelial cells to estrogen with inducing functional activation of estrogen receptors by leptin in breast tissue.

P3-D1-925

The Timing and Evolution of Puberty in a Sample of School-Aged Children in a Brazilian City

Taciana Carla Maia Feibelmann, Adriana Paula da Silva, Daniela Cristina Silva, Elisabete Aparecida Mantovani Rodrigues de Resende, Lúcia Marina Scatena, Maria de Fátima Borges

Universidade Federal do Triângulo Mineiro, Uberlândia, Minas Gerais, Brazil

Background: The beginning and evolution of physiological puberty may be occurring earlier, resulting in change in the age at which clinical investigation on precocious puberty must be conducted, as well as concerns regarding the possible deleterious effects of hormone exposure in a later stage of life. **Objective and hypotheses:** Assess age of beginning and evolution of puberty in boys and girls acknowledging the age of thelarche (T), menarche (M), period between thelarche and menarche (PTM) among girls, Tanner staging in boys and pubarche (P) in both. **Method:** A random sample of 1095 students from the city of Uberaba aged 5–18 years comprised 665 (60.7%) girls and 430 (39.3%) boys were assessed. Characteristics associated with puberty were answered by the participants and parents through questionnaires and pictures representing stages of development according to Tanner. **Results:** Among girls the mean age of T, P, M, and PTM occurred respectively at 9.8 ± 1.4 ; 10.2 ± 1.4 ; 11.7 ± 1.3 ; and 1.7 ± 1.3 years. Considering the third percentile, the cut-off age for precocious puberty (PP) would be <7 years old. For this value, the prevalence of PP among girls was 0.6% compared with 2.7% for the classical value <8 years old. The mean age among the boys at Tanner's stage 2 of genital development and pubic hair onset was 11.3 ± 1.7 and 11.1 ± 1.5 years respectively. **Conclusion:** In girls, puberty occurred earlier than expected if we consider the third percentile and longitudinal follow-up of them as well as investigation to rule out any precocious puberty eventually present in this studied population is mandatory. In clinical practice, it would be premature to change the age limit for investigation of PP.

P3-D1-926

The Significance of GnRH Stimulation Test, Leptin, and Pelvic Ultrasound Findings for Differentiating Idiopathic Central Precocious Puberty from Premature Telarche

Betül Ersoy^a, Pinar Yazici^a, Ece Onur^b, Mine Ozkol^c

^aDivision of Pediatric Endocrinology and Metabolism, School of Medicine, Celal Bayar University School of Medicine, Manisa, Turkey; ^bDivision of Biochemistry, School of Medicine, Celal Bayar University School of Medicine, Manisa, Turkey; ^cDivision of Radiology, School of Medicine, Celal Bayar University School of Medicine, Manisa, Turkey

Background: We aimed to investigate the differences of serum leptin, gonadotropin hormones levels on GnRH stimulation test,

and pelvic ultrasound (US) findings between girls with idiopathic central precocious puberty (ICPP) and premature telarche (PT). Additionally, we aimed to determine correlations between leptin and other parameters. **Method:** Thirty-nine girls who had the breast budding before the age of 8 years and 19 healthy age-matched pre-pubertal girls who served as controls were included in this study. GnRH stimulation test was performed for diagnosis of ICPP to girls with breast budding. All participants underwent anthropometric and bone age assessment, and pelvic US. Basal gonadotropin and leptin levels were evaluated in all participants. **Results:** No significant difference was found in leptin levels among girls with ICPP, premature telarche and prepubertal healthy peers ($P > 0.05$). Although significant greater ovarian volumes in girls with ICPP and PT were found compared to prepubertal girls, there was no significant difference in ovarian volumes between girls with ICPP and PT. Girls with ICPP revealed a significantly greater endometrial thickness than other groups. There was positive correlation between leptin levels and body weight in all subjects. Leptin was strongly correlated with estradiol in girls with ICPP ($r: 0.725, P < 0.01$). **Conclusion:** Our results indicate that leptin level does not change in girls at the same age according to onset of puberty. In pubertal girls, leptin is correlated with estradiol level and body weight. Ovarian volume assessment is a useful examination. However, it seems not to differentiate ICPP from PT. Endometrial thickness may be useful a parameter for the diagnosis of central precocious puberty.

P3-D1-927

Basal LH Combined with the Tanner Stage of Breast Development can Predict the Gonadotropin Response Following GnRH Stimulation Test

Osnat Admoni^a, Naama Schwartz^b, Yardena Tenenbaum-Rakover^a

^aPediatric Endocrine Unit, Ha' Emek Medical Center, Afula, Israel; ^bClinical Research Unit, Afula, Israel

Background: The GnRH stimulation test is widely used in the evaluation of precocious puberty but it requires repeated blood sampling, time-consuming and uncomfortable for the patients. **Objective and hypotheses:** To identify which parameters can be used to predict pubertal response in GnRH stimulating test for the diagnosis of central precocious puberty (CPP) in girls. **Method:** Included in the study 123 girls aged 3–9 years that underwent GnRH stimulating test due to early pubertal development. Clinical parameters were collected from the medical files. The results of GnRH tests were retrieved retrospectively. Stepwise logistic regression was used to identify which variables can predict the probability for GnRH pubertal response (peak LH ≥ 6 IU/l). **Results:** Included in the final model the following variables; age, Tanner breast stage (B1–5) and basal LH with cut of point of LH > 0.3 IU/l ($P < 0.0001$, C-statistic 84.3%). In girls aged 3–6 years that presented with Tanner B2 and in girls aged 7–9 years that presented with Tanner B1, when basal LH was ≤ 0.3 IU/l, the predictive probability for pubertal response in GnRH test

was <9%. In girls aged 3–9 years that presented with Tanner B3 and with basal LH higher than 0.3 IU/l, the probability for pubertal response was more than 72%. BMI and advanced bone age were not significantly associated with GnRH pubertal response. **Conclusion:** Basal LH combined with age and Tanner breast stage can predict the response to GnRH test, therefore GnRH test is unnecessary in the majority of the cases for the diagnosis of CPP in girls.

P3-D1-928

Characteristics of Children Treated with Leuprolide Acetate

Gulcan Seymen Karabulut^a, Ayşegül Yüksel^a, Elif Özsu^a, Gül Yeşiltepe Mutlu^b, Filiz Mine Çizmecioglu^a, Şükrü Hatun^a

^aPediatric Endocrinology, Kocaeli University, Kocaeli, Turkey;

^bZeynep Kamil Gynecologic and Pediatric Training and Research Hospital, Istanbul, Turkey

Objective: This study aims to reveal clinical, hormonal and ultrasound imaging features of patients treated with leuprolide acetate for diagnosis of precocious puberty. **Design:** Retrospective analysis of patients with a diagnosis of central precocious puberty and treated with leuprolide acetate between January 2008 and January 2013. **Patients:** 81 girls and two boys with early signs of puberty. **Results:** There was a positive correlation between basal LH and peak LH/FSH values. An organic etiology was revealed in 14.8% of girl patients (hydrocephaly (7), meningomyelocele (2), hypophyseal tumor (2), rathke cleft cyst (1), and 50% of boys hamartoma (1)). The 50% of girls with organic etiology was >6 years. Majority of the patients were between 6 and 8 years old and idiopathic cases. Organic etiologies also can be seen in children older than 6 years old age, so kranial MR imaging may be indicated for selective cases >6 years old children (Table 1).

P3-D1-929

Long-Term Consequences of Indirect Topical Exposure to Testosterone Gel in Young Children

Inge Gies^a, Jesse Vanbesien^a, Yannick De Brucker^b, Caroline Ernst^b, Ellen Anckaert^c, Jean De Schepper^a

^aUZ Brussel, Pediatric Department, Brussels, Belgium; ^bRadiology Department, UZ Brussel, Brussels, Belgium; ^cClinical Chemistry Department, UZ Brussel, Brussels, Belgium

Background: Virilization of young children after topical androgen use by their fathers through skin contact is well-known. The long-term consequences of such exposure at very young age are not well known. **Objective and hypotheses:** The aim is to report the occurrence of spermarche in a young boy and central precocious puberty in a young girl as late consequences of interpersonal transfer of testosterone gel. **Method:** Testosterone contamination was evidenced in a 4-year-old boy presenting with penile enlargement and pubic hair development (serum testosterone: 1.07 µg/l) and in a 3.5-year-old girl presenting with pubic hair development and acne (serum T: 1.66 µg/l). Bone age was accelerated with respectively 14 and 27 months. A suppressed LH response to GnRH was documented. In both children testosterone levels were unmeasurable after discontinuation of the exposure. **Results:** Regular semen staining in the underpants was observed in the boy at the age of 8 years (4 years after testosterone exposure). Genital examination showed a penis size of 8 cm and testes of 5 ml. Hormonal testing showed normal prepubertal values of gonadotropins (basal and after GnRH) and testosterone. Bone age was 11 years. Ultrasound evidenced an enlarged prostate and seminal vesicles. Breast development was seen in the girl at the age of 6.2 years (3 years after exposure). Pubertal staging was A2P3M3. Genital examination showed a clitoral size of 1 cm. LH increased up to 22.1 U/l after GnRH. Bone age was 9.5 years. Ultrasound evidenced an

Table 1. (abstract for P3-D1-928)

Patient number	83
Mean age of first sign of puberty (years)	6.66 ± 1.87
Mean age of initiation of leuprolide acetate (years)	7.78 ± 1.82
Time to treatment (months)	13.80 ± 11.5
Height (s.d.)	0.96 ± 1.39
Weight (s.d.)	1.29 ± 1.16
Midparental height	−0.82 ± 0.95
Predicted adult height	−0.86 ± 1.46
Bone age	9.78 ± 2.22
Tanner stage at the initiation of treatment	stage 2: 6 (7.3%); stage 3: 32 (39%); stage 4: 37 (45.1%); stage 5: 7(8.5%)
Mean uterine length on USG (mm)	37.02 ± 11.07
Mean ovary volume (ml)	2.89 ± 2.22
Mean basal LH (mIU/ml)	1.61 ± 1.9
Mean peak LH on LHRH analog test (mIU/ml)	12.46 (72% > 5 mIU/ml)
Pubertal LH/FSH (>0.66) (%)	42%
Mean bone age (years)	9.78 ± 2.22

enlarged uterus. **Conclusion:** Penile and clitoral enlargement as well as bone age advancement can persist, while early spermatogenesis and pubertal development can develop some years after testosterone exposure in children at a young age. Attentive clinical surveillance of these children is thus needed for several years.

the height benefit with treatment. This modest effect is without detrimental effect on BMI.

P3-D1-930

Final Height in Girls with Idiopathic Central Precocious Puberty Treated with GnRH Analog: Comparison with Untreated Controls

Zeynep Atay, Saygin Abali, Tulay Guran, Belma Haliloglu, Serpil Bas, Serap Turan, Abdullah Bereket

Department of Pediatric Endocrinology, Marmara University, Istanbul/Pendik, Turkey

Background: Studies evaluating the gain in final height in patients with idiopathic central precocious puberty (ICPP) report variable outcomes and mostly lack comparison with untreated controls. **Objective and hypotheses:** To compare the final height of ICPP patients treated with GnRH analog with and untreated control group. **Method:** 48 girls with ICPP treated with GnRH analog and 52 untreated girls with ICCP (due to late referral or refusal of treatment) formed study groups and followed to adult height (min. 2 years after menarche). **Results:** The mean age at referral and treatment was 7.76 ± 1.24 and 8.08 ± 0.85 years respectively. The difference between chronological age and bone age at the start of treatment was 1.9 ± 1.18 years. Mean PAH at the beginning of treatment was 154.6 cm. There was a 5.6 cm gain at final height with respect to PAH at the beginning of treatment. Treatment group exceeded MPH by 1.6 cm whereas control group remained 1.9 cm below MPH. (total difference is 3.5 cm). Treatment duration was 2.7 ± 0.89 years. The time interval from the end of treatment to the menarche was 1.3 ± 0.74 years. Height gain from the end of treatment to final height was 12.2 ± 3.3 cm. Height gain from the beginning of treatment to final height was 26.9 ± 6.8 cm. BMI SDS at the beginning and end of treatment was 0.99 ± 0.90 and 0.90 ± 0.75 respectively (P : NS) (Table 1). **Conclusion:** Treated patients exceeded their MPH by 1.05 cm whereas untreated patients remained -2.01 cm below their MPH which corresponds to a total gain of 3.06 cm. This means a gain of 1.13 cm/treatment year. Thus the younger the patient, the more is

P3-D1-931

X-Linked Recessive Form of Nephrogenic Diabetes Insipidus in a 7-Year-Old Boy

Aleksandra Janchevska^a, Velibor Tasic^a, Marina Krstevska-Konstantinova^a, Hae Il Cheong^b

^aMedical Faculty, University Children's Hospital, Skopje, Macedonia; ^bChildren's Hospital, Seoul National University, Seoul, Republic of Korea

Background: Nephrogenic diabetes insipidus (NDI) is caused by inability of renal collecting duct cells to respond to arginine vasopressin (AVP)/antidiuretic hormone (ADH). **Objective and hypotheses:** The majority of patients (about 90%) have type 1, X-linked recessive form, of NDI caused by mutation in gene encoding the vasopressin V2 receptor. Type 2, autosomal NDI, have the rest 10% of patients. This type is caused by the aquaporin-2 water channel (AQP2) gene mutations. **Method:** We present a 7-year-old boy with a history of excretion of a large amount of dilute urine, thirst, and polydipsia since infancy. The boy had several vomiting episodes with mild dehydration during the first 3 years of life. No evidence of headaches, dizziness, or visual problems. He drinks between 2 and 3 l/day and has 24 h diuresis of 2 l. He has normal prepubertal appearance with appropriate weight ($+0.85$ SDS) and height ($+0.15$ SDS) for his age. Boy's intelligence is normal, too. Diagnostic assessment was achieved according to clinical findings, kidney ultrasound, a water deprivation test and molecular analysis. **Results:** Kidney ultrasound was uneventful. Water deprivation test showed urine osmolality 26 mOsm/kg after 8 h of dehydration. After desmopressin administration urine osmolality was 22.1 mOsm/kg. Serum osmolality was in normal range for the sex and age before and after desmopressin administration. This implicates nephrogenic form of diabetes insipidus. Molecular analyses showed a hemizygous c.317G>A mutation in exon 2 of AVPR2 (p.Arg(CGT)106His(CAT)), which was inherited from his mother. The treatment includes high liquids and low salt intake in addition to hydrochlorothiazide. **Conclusions:** This patient is the first case with confirmed X-linked recessive form of NDI in Macedonia. Molecular analysis confirmed the clinical diagnosis and enabled genetic advice in this family.

Table 1. (abstract for P3-D1-930)

	Treatment group (n: 48)	Control group (n: 52)	P
Final height cm (SDS)	160.6 (0.10)	158.1 (0.33)	0.026 (0.042)
MPH, cm (SDS)	159 (-0.23)	160 (0.00)	0.239 (0.226)
Final-MPH, cm (SDS)	1.05 (0.17)	-2.01 (-0.34)	0.026 (0.03)
Age at menarche (years)	12.1 ± 0.9	10.0 ± 0.6	<0.001
Maternal age of menarche (years)	13.0 ± 1.4	12.6 ± 1.7	0.182

P3-D1-932

Idiopathic Hypogonadotropic Hypogonadism due to a *GNRH1* Mutation

Eda Mengen Ucakturk^a, Leman Damla Kotan^b, Fatih Gurbuz^a, Bilgin Yuksele^a, Ali Kemal Topaloglu^{a,b}

^aDepartment of Pediatric Endocrinology, Faculty of Medicine, Cukurova University, Adana, Turkey; ^bDepartment of Biotechnology, Institute of Sciences, Cukurova University, Adana, Turkey

Background: Idiopathic hypogonadotropic hypogonadism may be normosmic (nIHH) or it may be associated with anosmia, which is known as Kallmann syndrome (KS). First mutation *GNRH1* was described in 2009 in patients with nIHH. Mutations of the human *GNRH1* gene are a very rare cause of nIHH, with only six mutations so far described. **Case:** The proband is a 11.3-year-old boy who first presented at age 1 with micropenis and cryptorchidism. His past medical history is unremarkable except for a bilateral orchidopexy surgery at the age of 2 years. His parents are healthy cousins. The proband's height and weight are 149 cm (50th–75th percentile) and 84.5 kg (>95 percentile) respectively. His pubic and axillary hair are at Tanner stages 4 and 2 respectively. His testes are 1 ml bilaterally in the scrotum. His stretched penile length was 3.6 cm. Chromosome analysis revealed a 46,XY karyotype. Pelvic ultrasonography confirmed the absence of müllerian structures and the presence of both gonads with features of normal testes in the scrotum. His bone age is 11 years. **Results:** Genetic analysis of this patient identified a homozygous deletion (c.87delA) leading to a frameshift mutation (p.G29GfsX12) in *GNRH1*. **Conclusion:** We here described a frameshift *GNRH1* mutation which is produced to lead a total failure of GnRH synthesis. This mutation was previously reported by Chan *et al.* Comparison of phenotypes show no were difference. *GNRH1* mutation in IHH are indeed very rare as we found only one mutation among 30 families with identified causative mutations. These rare patients offer a unique opportunity to study the effects of human GnRH deficiency.

P3-D1-933

Effect on BMI of GnRH Analogue Treatment in Central Precocious Puberty or Early and Fast Puberty Girls

Chen Qiuli, Su Zhe, Li Yanhong, Ma Huamei, Chen Hongshan, Zhang Jun, Du Minlian

The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China

Objective: We assessed in a retrospective unicenter study the effect on BMI of treatment with GnRH analogs (GnRHa) in central precocious puberty (CPP) or early and fast puberty (EFP) girls. **Methods:** The BMI of 318 girls (227 CPP and 91 EFP) who treated with GnRHa alone were analyzed. Among them 89 were

followed up to their final adult height (FAH). **Results:** Before GnRHa treatment started, the girls with CPP and EFP had a mean BMI SDS for chronological age (CA) of 0.39 ± 0.84 and for bone age (BA) of -0.11 ± 0.69 . At the end of treatment, the mean BMI SDS was 0.59 ± 1.00 for CA and 0.24 ± 0.85 for BA, which both were significantly higher than initiation. The increment of BMI SDS for BA (0.38 ± 0.56) was larger than for CA (0.21 ± 0.59). Moreover, the ratio of overweight (BMI > 85%) was significantly elevated. BMI SDS for CA of 89 girls who were visited at their FAH were 0.17 ± 1.73 , which were similar with BMI SDS at initiation and normal population. **Conclusion:** The mean BMI SDS for CA of CPP and EFP was significantly higher than population, while for BA was significantly lower. During GnRHa treatment, there was an obese tendency and which was reversible. At FAH, the mean BMI SDS was back to normal.

P3-D1-934

An Unusual Combination of Premature Ovarian Failure and a History of GnRH Treatment for Idiopathic Precocious Puberty

Maria Parpagnoli, Salvatore Seminara, Giulia Anzilotti

AOU Meyer, Florence, Italy

Background: The normal recovery of the hypothalamic-pituitary-gonadal axis after discontinuation of therapy with GnRH analogue for precocious puberty has been proven and documented in the last decades. There has been no report in the literature of patients in which a history of GnRH treatment of precocious puberty is correlated with premature ovarian failure. **Objective and hypotheses:** The aim of the authors is to evaluate the possibility of a correlation between the development of premature ovarian failure and the previous therapy with GnRH analogue. **Method:** We describe the case of a patient followed for precocious puberty treated with GnRH analogue until the age of 11 years. After menarche, which occurred 9 months after the discontinuation of treatment the menstrual cycle has come back only the following months. The patient then developed secondary amenorrhea of 9 months duration for which she came to our attention. She carried GnRH test, complete blood count, TSH, fT₄, fT₃, prolactin, total testosterone, SHBG, DEAS, 17 β estradiol, glucose, insulin, tumor markers, karyotype, array cgh, organ- and nonorgan-specific autoimmunity, brain MRI with contrast and pelvic ultrasound. **Results:** All tests performed were normal with the exception of the GnRH test that showed values of FSH and LH indicative of ovarian failure (>di 90 mUI/ml basal e> di150 mUI/ml after stimulation) and a prepubertal value of 17 β-estradiol. Pelvic ultrasound has always shown uterus and ovaries of prepubertal size and morphology. **Conclusion:** Owing to the normality of all the hormonal tests performed, the absence of autoimmune diseases, and the exclusion of genetic causes predisposing the patient to early menopause, we have to consider the possibility of an association between treatment with GnRH analogue and the development of premature ovarian failure.

P3-D1-935

An Unusual Case of Early and Accelerated Puberty

Perla Scalini, Stefano Stagi, Paola Pelosi, Franco Ricci,
Giulia Anzillotti, Paolo Del Greco, Salvatore Seminara,
Maurizio de Martino

Health Science Department, Anna Meyer Children's University
Hospital, University of Florence, Florence, Italy

Background: Unlike precocious puberty, early and/or fast puberty have been less studied, despite the fact that this disorder may be associated to an organic lesion at CNS level. **Objective and hypotheses:** We illustrate a case of early and fast puberty in a girl with an occult intra-cranial tumor. **Method:** The girl was the first child of non-consanguineous, Italian parents. The family had a positive history of early puberty. Target height was 0.1 SDS. Pregnancy and neonatal period passed uneventfully. The proposita grew on the 10th centile during infancy and childhood. At the age of 8 years 11 months, she showed the first signs of an early puberty (height 125.5 cm, -1.17 SDS), but at 9.6 years old her height was 136 cm (0.01 SDS), BMI was 15.14 (-1.20 SDS), pubertal staging was B3-4PH3AH2. The height velocity was very high (16.01 SDS). So, she was referred to our unit. **Results:** Neurological and ophthalmologic examinations were normal, such as biochemical and metabolic examinations. Thyroid and adrenal hormones were in the normal range. The LHRH test highlighted a very high LH (82.4 IU/l) and FSH peaks (29.6 IU/l). The α -fetoprotein, β HCG, and CEA were in the normal range. Pelvic ultrasonography showed a transitional uterus and enlarged ovaries with a normal echostructure. Bone age corresponded to the chronological age. The nuclear magnetic resonance imaging of the brain showed an impaired signal zone, 1 cm diameter with a rounded aspect, at a level of the left cerebral peduncle. The position of the tumor did not consent surgical therapy and biopsy of the mass; therefore, the patient began chemotherapy and radiotherapy. **Conclusion:** Our case report confirms that LH and FSH values and also an accelerated development of puberty may be important in hypothesizing the presence of an endocranic tumor.

P3-D1-936

Association of Van Wyk Grumbach and Debre Semelaigne Syndromes in Two Cases with Severe Hypothyroidism

Fatma Demirel^a, Alkim Oden^b, Meltem Tayfun^a, Ahmet Ucakturk^a,
Ali Gungor^b

^aDepartment of Pediatric Endocrinology, Ankara Children's
Hematology and Oncology Training Hospital, Ankara, Turkey;

^bDepartment of General Pediatrics, Ankara Children's Hematology
and Oncology Training Hospital, Ankara, Turkey

Background: Van Wyk Grumbach (VWG) and Kocher Debre Semelaigne (KDS) syndromes are rare syndromes with clinical manifestation of hypothyroidism associated with precocious pseudo puberty and myopathic pseudomuscular hypertrophy. We present

two cases that have the characteristic of both VWGS and KDSS syndromes developed in association with a long-term untreated hypothyroidism. **Case 1:** Seventeen years old girl was referred to our hospital due to menstrual irregularities and multicystic ovaries. In her medical history, she was assessed for vaginal bleeding, and diagnosed congenital hypothyroidism when she was 5. But she was noncompliant with her treatment. At the age of 11, her menstrual cycle started again, but she complains oligomenorrhea. On her physical examination, she had coarse facial appearance and marked hypertrophy of both calves. Her pubertal development was in stage 4, and she had all the clinical and laboratory signs of severe hypothyroidism such as mental retardation, short stature, high TSH and low free T₄ levels. Bone age was consistent with the age of 17. In laboratory evaluation also blood creatinine and creatinine kinase (CK) levels were 1.21 mg/dl and 254 U/l respectively. **Case 2:** Thirteen years old boy was referred to our clinic because of severe muscle pain, hypothyroidism, and goiter. His physical examination showed that his weight was 45 kg (10-25 p), and his height was 149 cm (3-10 p). He had dry skin, coarse facial features, grade 2 goiter and muscular pseudohypertrophy. Both testes were 25 ml in size. Laboratory investigations showed TSH 100 mIU/ml, fT₄ 0.2 ng/dl, thyroid peroxidase antibody >1072 IU/ml, LH 0.67 μ IU/ml, FSH 3.22 mIU/ml, testosterone 2.01 ng/ml, CPK 2537 U/l, and serum creatinin level was 1.15 mg/dl. **Conclusion:** Both patients were diagnosed with VWGS and KDSS. Therefore, long-term untreated hypothyroid patients should be evaluated for these syndromes.

P3-D1-937

Van Wyk Grumbach Syndrome: Case Report from Georgia

Irakli Paghava

I. Tsitsishvili New Pediatric Hospital, Tbilisi, Georgia

Background: Association of hypothyroidism, isosexual precocious puberty and macrogonadism was first described by Van Wyk Grumbach in 1960. Van Wyk Grumbach syndrome (VWGS) was reported predominantly in females, precocious puberty and clinical picture of hypothyroidism being the clinical hallmarks. **Objective and hypotheses:** Publishing additional data on clinical and hormonal spectrum of VWGS, providing for better understanding of its pathology and primary diagnostics optimization. **Method:** Describing our case (follow-up included). Comparing our data with available information. **Results:** A 10 years 5 months old girl presented with short stature (113 cm), MaII, PubI, AxI, no menstruation. Constipation, hair loss, poor academic performance, fatigue, growth delay 'for years'; thelarche at 9 years 9 months. Suspicion for Turner syndrome prompted additional studies: gynecological ultrasound, LH, FSH, and estradiol. Results: multicystic enlarged ovaries (20 and 22 ml), enlarged uterus (15 ml); thyroid ultrasound: 2.1 ml, normal structure, fT₄ 0.23 ng/dl, TSH 147.23, TPO-Abs 57.93, TG-Abs 86.93; estradiol 5.24 pg/ml (prepubertal), FSH 5.53 and LH 2.01 (both adequate for Tanner 2 stage); bone age: 5 years (height age

5–5.5 years). VWGS diagnosed and L-thyroxine prescribed (50 µg/day). In 10 weeks: fT4, TSH levels normalized, ovaries shrunk to 6.7 ml, catch-up growth of 2.5 cms. **Conclusion:** Highly elevated level of TSH with ‘quasi-normal’ (inappropriate to bone age) level of FSH (and LH) support the Anasti *et al.* (1995) hypothesis (direct impact of TSH upon the FSH-receptors). Macrogonadism precedes the clinical signs of precocious puberty – ‘quasi-normal’ (appropriate to chronological age, inappropriate to delayed bone age) puberty development may be erroneously considered ‘normal’ if taking into account only chronological age. Our data confirm the workup significance of X-ray in case of pediatric patients with hypothyroidism. Gynecological ultrasound is a valuable and highly recommended imaging study for female children with severe hypothyroidism.

P3-D3-938

Hyperandrogenism Doesn't Increase the Insulin Resistance in Overweight and Obese Adolescent Girls with Polycystic Ovary Syndrome

Natalija Smetanina^a, Audrone Seibokaite^a, Raimondas Valickas^b, Rasa Verkauskiene^a

^aInstitute of Endocrinology, Lithuanian University of Health Sciences, Kaunas, Lithuania; ^bDepartment of Radiology, Hospital of Lithuanian University of Health Sciences, Kaunas, Lithuania

Background: Polycystic ovary syndrome (PCOS) is associated with metabolic abnormalities and increased insulin resistance (IR), which is closely associated with abdominal obesity and hyperandrogenism in adults. Some studies indicate that hyperandrogenism influences insulin resistance development in PCOS patients. Data on PCOS association with risks of metabolic disorders in adolescence are scarce. **Objectives:** In this study we aimed to investigate androgen profiles and its association with IR in overweight/obese adolescent girls. **Methods:** Study included 60 overweight (OW) (BMI >1.0 SDS) and obese (OB) (BMI >2.0 SDS) girls (mean age 15.4 ± 1.3 years) at least 2 years post menarche. Mean BMI–SDS was 2.37 ± 0.9 (58.7% were obese). BMI was evaluated according to International Obesity Task Force (IOTF) criteria for children. PCOS was diagnosed according to Rotterdam criteria. **Results:** 31.1% of OW/OB girls were diagnosed with PCOS. BMI–SDS and waist circumference SDS in girls with PCOS were significantly lower compared to girls without PCOS (1.85 ± 0.7 vs 2.55 ± 0.9, *P* = 0.005 and 0.85 ± 0.6 vs 1.49 ± 0.8, *P* = 0.003 respectively). Testosterone, LH, and FSH levels were significantly higher in girls with PCOS compared to those without PCOS (mean 4.12 ± 1.9 vs 2.52 ± 1.3 nmol/l, *P* < 0.001; 7.72 ± 4.9 vs 5.12 ± 4.3 IU/l, *P* = 0.009; and 4.34 ± 2.1 vs 3.36 ± 2.0 IU/l, *P* = 0.027 respectively). DHEAS and free androgen index (FAI) were also significantly higher in girls with PCOS (mean 8.18 ± 2.9 vs 5.76 ± 2.7 µmol/l, *P* < 0.001 and 25.37 ± 17.3 vs 13.34 ± 8.0, *P* < 0.001 respectively). Neither fasting insulin nor homeostasis assessment model index (HOMA-IR) were not significantly different in both groups. In both groups combined, androgen levels were not associated with neither fasting insulin nor HOMA-IR. **Conclusions:** Every third OW/OB

adolescent girl over 2 years post menarche has PCOS. OW/OB girls with PCOS were leaner and had lower waist circumference compared to girls without PCOS. OW/OB girls with PCOS were not more IR than girls without PCOS.

P3-D3-939

Precocious Puberty due to Duplication of the Pituitary Gland

Carla Minutti^{a,b}, Deborah Goldstein^a

^aJohn H Stroger Jr Hospital of Cook County, Chicago, Illinois, USA;

^bRUSH University School of Medicine, Chicago, Illinois, USA

Case Report: A 7 years 5-month-old female presented in our clinic for evaluation of early pubertal development. Parents reported telarche occurring at age 6 years and menarche at age 7 years and 3 months. No history of development of pubic or axillary hair, adult body odor, or acne. Mother had menarche at 13 years of age. Physical examination revealed a height of 138 cm (>95th centile). Mid-parental height was calculated at 157 cm (20th centile). She was found to be Tanner 3 for breasts and Tanner 1 for pubic hair. Rest of examination was unremarkable. A leuprolide stimulation test confirmed a diagnosis of central precocious puberty, with a peak LH of 37 IU/l and a stimulated estradiol of 118 pg/ml. Bone age was read at 12 years of age at a chronological age of 7 years and 5 months. CT and MRI of the brain revealed a duplication of the sella turcica and two sets of pituitary glands each with its own pituitary stalk and two posterior pituitary bright spots. Started on leuprolide acetate, (Lupron Depot) 300 µg/kg per monthly. She had good suppression chemically and clinically of pubertal progression. Eight months after starting leuprolide therapy, at a chronological age of 8 years and 3 months, her bone age was read at 13 years and 6 months. Parents decided to stop treatment after 10 months, against medical advice, due to pain during injections. Her last height was 144.6 cm with a bone age of 13 years and 6 months. **Discussion:** Duplication of the pituitary gland is a rare finding that results from an earlier developmental anomaly. It can be associated with central precocious puberty or delayed puberty, as well as other facial and CNS abnormalities. **Method: Result: Conclusion:**

P3-D3-940

Inhibin B in the Boys with Constitutional Delay of Puberty: Relationship with Gonadotropins, Testosterone, and Anti-Müllerian Factor

Oleg Latyshev, Elena Kiseleva, Goar Okmynyan, Lubov Samsonova

Russian Medical Academy of Postgraduated Education, Moscow, Russia

Objective: The aim of this study were to investigate the level of inhibin B and its relationship with testosterone, anti-Müllerian factor, basal, and GnRH-stimulated gonadotropin hormones

(LH and FSH) concentration in boys with constitutional delay of puberty. **Material and methods:** In the study were included 15 boys (mean age 14.5 ± 1.6 years) in Tanner stages 1–2. The investigation consists of genital examination with prader orchidometer, definition pubertal stage, ultrasound examination of the testis, analyzing basal level testosterone, LH, SSH; and GnRH agonist test. **Results:** In the boys with constitutional delay of puberty the mean level of inhibin B was 155.6 ± 69.72 pg/ml; LH 1.23 ± 0.77 mIU/ml; FSH 2.36 ± 2.0 mIU/ml; and testosterone 5.28 ± 5.9 nmol/l. Inhibin B correlated positively with GnRH-stimulated FSH concentration ($P=0.05$) and correlated negatively with anti-Müllerian factor ($P=0.017$). Inhibin B did not correlated with basal level FSH, LH, testosterone, and stimulated LH. **Conclusion:** It has been revealed positively relationship between inhibin B and stimulated FSH and negatively correlation with anti-Müllerian factor in the boys with constitutional delay of puberty.

P3-D3-941

A Rare Cause of Peripheral Precocious Puberty: Adrenocortical Tumor

Erkan Sari^a, Erman Atas^b, Ahmet Guven^c, Ediz Yesilkaya^a

^aPediatric Endocrinology, Gülhane Military Medical Academy, Ankara, Turkey; ^bPediatric Oncology, Gülhane Military Medical Academy, Ankara, Turkey; ^cPediatric Surgery, Gülhane Military Medical Academy, Ankara, Turkey

Background: Adrenocortical tumor is very rare in the pediatric age group. These tumors may cause peripheral precocious puberty, Cushing's syndrome or both. It is seen most commonly in children under 5 years of age and fourth decade. p53 mutation and other pathologies that may accompany should be investigated especially in young children. **Objective and hypotheses:** A 18-month-old boy was brought with pubarche and phallic enlargement, and was noticed 6 months ago for the first time by parents. Parents defined growth spurt and erections. His medical records and family history were unremarkable. Chronological age 1.6 years, height: 86 cm (78 p + 0.80 SDS), weight 14.5 kg (95 p), target height SDS -1.65, testicular volume 2 ml/2 ml, stretched penil length 6 cm (90–97 p), and pubarche grade 2. There was no other findings of hyperandrogenism. Laboratory results were consistent with peripheral precocious puberty FSH: <0.3 U/l, LH: 0.05 U/l, total testosterone: 473 ng/dl, 17-OH P: 0.5 ng/dl, DHEA-SO4: 206 µg/dl, and androstenedione: 3.35 ng/ml. Thyroid functions, α -fetoprotein ve β HCG were normal. A mass with 22×17 mm was detected ultrasonographically in right adrenal gland and being 35 Hounsfield Unit, the mass was considered as nonadenomatosis. Tumor weighted 50 g with intact capsula after adrenalectomy. Pathological diagnosis was adrenocortical carcinoma and no metastasis was detected with PET-CT scanning. p53 mutation analysis is being tested. Androgen hormones decreased to prepubertal levels in second day post-operatively. Mass originated from soft tissue was detected third month after adrenalectomy and resected material was consistent

with rhabdomyosarcoma histopathologically. **Conclusion:** Simple radiologic methods should be selected in peripheral precocious puberty before further complicated investigations. Besides it is noteworthy to be careful for comorbidities such as other malignancy especially in young children.

P3-D3-942

A Severe LHRH-Independent Precocious Puberty in a 26-Month-Old Girl with a Clinical Diagnosis of McCune–Albright Syndrome

Maciej Flader^a, Anna Latos-Bielenska^b, Karina Kapczuk^c, Przemyslaw Mankowski^d, Elzbieta Malecka^a, Marek Niedziela^a

^a2nd Chair of Pediatrics, Department of Pediatric Endocrinology and Rheumatology, Poznan University of Medical Sciences, Poznan, Poland; ^bDepartment of Medical Genetics, Poznan University of Medical Sciences, Poznan, Poland; ^cChair of Perinatology and Gynecology, Department of Gynecology, Poznan, Poznan University of Medical Sciences, Poznan, Poland; ^dChair and Department of Pediatric Surgery, Traumatology and Urology, Poznan University of Medical Sciences, Poznan, Poland

Background: Gonadal hyperfunction is the most frequent endocrine dysfunction in females with McCune–Albright syndrome (MAS), and precocious puberty (PP) is usually the first manifestation of MAS in children. **Objective and hypotheses:** The optimal pharmacologic treatment of PP in girls with MAS has not been yet identified and new therapeutic options like anti-estrogen should be taken under consideration especially in patients with extreme high estradiol levels. **Results:** We present a case report of a 2-year-old girl suffering from PP. She experienced her first episode of PP at the age of 26 months by the signs of estrogenisation, such as bilateral breast development with strongly pigmented nipples (Tanner 3), swelling of the labia minora and vaginal bleeding. Laboratory tests showed elevated estradiol levels (85 pg/ml) with a suppressed gonadotropin response after LHRH-stimulation (peak LH <0.5 mIU/ml; and peak FSH <0.37 mIU/ml). Bone age was appropriate for chronological age and pelvic ultrasound revealed cysts (predominant 17 mm Ø) in the right ovary, pubertal uterus and numerous small cysts in the left ovary. After 4 weeks the predominant cyst had regressed spontaneously and estradiol level decreased <20 pg/ml. Four months later, the girl experienced the first relapse of the PP. Large ovarian cyst was detected in the left ovary (32 mm Ø). Estradiol levels reached rarely recorded concentrations of 4487 pg/ml. The PCR analysis from ovarian tissue obtained during laparoscopy does not revealed the most common *GNAS1* gene mutations (pR201C and pR201H). No other signs and symptoms associated with MAS were seen nevertheless, and atypical form of MAS cannot be excluded in our patient – further genetic analyses are ongoing and the remaining regions of *GNAS1* gene are being analysed. The fulvestrant in a dose of 2 mg/kg per month was initiated. **Conclusion:** Effective and safe therapy of PP caused by MAS syndrome is needed and we do hope that fulvestrant may be such an option.

P3-D3-943

Triptorelin Test in the Diagnosis of Precocious Puberty

Saida Kabour^a, Soumeia Fedala^a, Fetta Amel Yaker^a, Ali el Mahdi Haddam^b, Lila Rabhi^a, Farida Chentli^a, Djamila Meskine^b

^aBab-El-Oued hospital, Algiers, Algeria; ^bBologhine Hospital, Algiers, Algeria

Background: Central precocious puberty (CPP) in girls is characterized by an activation of the hypothalamic–pituitary–ovarian (HPO) axis before 8 years of age. Given the gradual awakening of the GnRH pulse generator, a spectrum of presentations has been found among girls with premature sexual development. CPP are not easily distinguished from idiopathic precocious thelarche (PT) or other intermediate positions along this spectrum. The GnRH test is the gold standard to confirm the diagnosis of CPP. However, this test is not available in our department. **Objective and hypotheses:** To evaluate the diagnostic accuracy of Triptorelin test in girls with suspicion of CPP. **Method:** A prospective randomized clinical trial about 14 girls with premature breast development was performed. All patients underwent s.c. Triptorelin acetate test (0.1 mg/m², to a maximum of 0.1 mg) with blood sampling at 0, 3, and 24 h for LH, FSH, and estradiol ascertainment. CPP or PT was diagnosed according to maximal LH response to Triptorelin test and clinical characteristics during follow-up. **Results:** Clinical features were similar between CPP (*n*=8) and PT (*n*=6) groups. Maximal LH response (LH, 3 h) under Triptorelin test ≥ 8 IU/l by ECLIA confirmed the diagnosis of CPP in all cases. **Conclusion:** Triptorelin acetate is a therapeutic regimen to suppress the gonadotrophic axis. It has an acute stimulatory effect on the gonadotrophs when given as single dose, with gonadotrophins reaching maximum levels 3 h after administration. Owing to its longer half-life, this effect lasts at least 24 h, making possible to additionally evaluate the sex-hormone secretion by the gonads. The Triptorelin test had high accuracy for the differential diagnosis of CPP vs PT providing a valid alternative to the classical GnRH test.

P3-D3-944

Central Precocious Puberty and Autism: Three Cases Report

Daniela Amaral, Lurdes Lopes

Pediatric Endocrinology Unit, CHLC- Hospital de Dona Estefânia, Lisbon, Portugal

Background: Central precocious puberty (CPP) is a rare disorder that occurs five times more often in girls. Patients are mostly healthy children whose pubertal maturation begins at an early age: girls <8 years; and boys <9 years. Imaging usually reveals no abnormalities in girls while in boys abnormal MRI findings are more frequent. **Objective and hypotheses:** We describe three cases of CPP in children with autism, a rarely

reported association. **Method:** Complete revision of three cases. **Results:** Case 1 is a 3.4-year-old boy with autistic spectrum disorder. He started pubarche at the age of 2 years. On first endocrinology consultation with bilateral testicular volume = 6 ml, pubic hair Tanner 2, and bone age (BA) of 4.5 years. LHRH stimulation test had a pubertal response. MRI revealed an hypothalamic sessile hamartoma. Case 2 is a 15-month-old girl evaluated for thelarche, pubarche and increased growth velocity; bone age: 3 years. LHRH stimulation test had a pubertal response. Pelvic ultrasound (US) showed a pubertal uterus with visible endometrium and MRI revealed an hamartoma in the tuber cinerium. Around 3 years of age, parents noticed a regression in development milestones and changes in behavior and by the age of 4 she was diagnosed with autistic spectrum disorder. Case 3 is a 7.9 years old girl diagnosed with autism at the age of 2 years. She was evaluated for bilateral telarche and pubarche during the previous 6 months; bone age: 10 years. LHRH stimulation test showed a pubertal response; pelvic US revealed a pubertal uterus with a thick endometrium. **Conclusion:** All patients started triptorelin with good clinical results in the second and third cases. In the first case, although there was a good central response (LH and FSH non-responsive on LHRH stimulation test), some behavior changes associated with puberty remained. Neurophysiologic mechanisms involved in autism are not well known and changes in these pathways maybe related to CPP. This unreported association may open new avenues for further research in this area.

P3-D3-945

Precipitated Puberty: Correlations with Embarrassed Ovarian Function

Eduard Circo

Ovidius University, Constanta, CT, Romania

Scope: The assessment of the functional ovarian maturity in a group of girls with precipitated puberty. **Method:** Ovarian function was assessed in a group of girls with puberty precipitated (77 – group 1) compared with a group of girls with normal puberty (59 – group 2) according to development criteria accepted by the population of Romania. They calculated the incidence of menstrual disorders, changes in menstrual flow, presence of dysmenorrhoea or premenstrual syndrome, breast development, serum levels of ovarian hormones, the incidence of ovarian cysts. **Results:** The existence of menstrual disturbances (66.1% – group 1 and 34% – group 2), duration of the menses (66.6% – group 1 and 33.3% – group 2); the quantity of the menstrual flux – altered (61.3% – group 1 and 36.8% – group 2), the presence of dysmenorrhea and/or premenstrual syndrome (60.4% – group 1 and 39.6% – group 2), end-stage of breast development (24.7% – group 1 and 75.3% – group 2), the presence of low blood levels of ovarian hormone (81.4% – group 1 and 18.6% – group 2), presence of ovarian cysts (64% – group 1 and 36% – group 2). **Conclusions:** These observations reveal disorders of the sexualization process on girls with precipitate puberty on the grounds of a delayed functional ovarian maturity ($P < 0.001$) compared with girls with normal puberty.

P3-D3-946

Impact of Bisphenol-A on the Puberty of Female Rats

Chen Linqi, Yang Fan, Jin Meifang, Wu Haiying

Soochow Children's Hospital, Soochow, Jiangsu, China

Background: It is now widely accepted that chemical pollutants in the environment can interfere with the endocrine system. The impact of endocrine disrupting chemicals on puberty disorders is concerned. bisphenol-A (BPA) has been measured in fetal plasma. There are different toxic effects with different doses of BPA. **Objective and hypotheses:** To observe vaginal opening day (VOD) hypothalamic kiss-1 gene and ovarian estrogen receptors (ER) gene expression level changes in neonatal rats exposure to different doses of BPA. **Method:** Neonatal female SD rats were randomly divided into six groups: control group, vehicle group, 17 β -estradiol group (17 β -estradiol (E₂), 10 μ g/day), low-dose BPA group (25 μ g/kg per day), medium-dose BPA group (50 μ g/kg per day), and high-dose BPA group (250 μ g/kg per day). The rats got seven s.c. injections over postnatal day (PND) 0–6 and were sacrificed on the VOD and weighed. The VOD was recorded. The hypothalamus and ovaries were removed, weighed and calculated the organ/body weight ratio. Real-time PCR were used to observe the mRNA level changes of hypothalamic kiss-1 gene and ovarian ER gene. **Results:** Data suggests that neonatal 50 and 250 μ g/kg per day BPA exposure induced premature puberty of rat, but it may not result from the expression level changes of hypothalamic kiss-1 mRNA; neonatal 25 μ g/kg per day BPA exposure did not induce premature puberty of rat. **Conclusion:** Neonatal 50 and 250 μ g/kg per day BPA exposure induced premature puberty of rat. The premature puberty above mentioned was not caused by the changes of the hypothalamic kiss-1 mRNA and its protein expression. Neonatal 25 μ g/kg per day BPA exposure did not induce premature puberty of rat.

P3-D3-947

The Etiology of Central Precocious Puberty and Effect of GnRH Agonist for 2 years in Korean Boys

Young Suk Shim^a, Hwal Rim Jeong^a, Hae Sang Lee^a, Jung Sub Lim^b, Jin Soon Hwang^a

^aDepartment of Pediatrics, Ajou University Hospital, Ajou University School of Medicine, Suwon/Gyeonggi-do, Republic of Korea; ^bDepartment of Pediatrics, Korea Cancer Center Hospital, Seoul/Seoul, Republic of Korea

Background: GnRH agonist (GnRHa) are able to modify natural course of Central Precocious Puberty (CPP) in girls. **Objective and hypotheses:** We evaluated the etiology and the effect of GnRHa in Korean CPP boys. **Method:** Total 29 boys diagnosed for CPP from 2007 to 2012 were included in Ajou University Medical Center. Sellar MRI was performed in 26 of 29 patients (89.7%). CPP was diagnosed on the basis of i) onset evidence of testicular enlargement (≥ 4 ml) before the age of 10 years in boys, ii) bone age ≥ 2 s.d. above the mean value for age,

and iii) pubertal LH peak after GnRH stimulation test (> 5.0 UI/l). **Results:** i) Mean age was 9.45 ± 0.81 years, mean height 142.20 ± 8.27 cm (SDS 1.42 ± 1.20), mean bone age 12.09 ± 1.16 years before treatment. ii) 26 boys who were evaluated for organic brain lesion were identified no abnormality in sellar MRI (0%). iii) The mean duration of treatment was 2.28 ± 1.15 years. iv) Mean age was 11.29 ± 0.99 years, mean height 153.53 ± 6.60 cm (SDS 1.36 ± 1.00), mean bone age 13.18 ± 0.79 years after 24 months of treatment. v) There was significant increase in PAH from 172.57 ± 9.57 cm (SDS -0.17 ± 1.73) before treatment to 178.33 ± 7.45 cm (0.86 ± 1.32) after treatment of 2 years ($P=0.002$). vi) PAH after 24 months of treatment was associated with bone age, PAH and PAH SDS before treatment ($P<0.05$). **Conclusion:** There was no organic brain lesion as etiology of precocious puberty in Korean boys in this study. There was an significant increase of PAH in boys who treated with GnRHa for 2 years.

P3-D3-948

Hypothalamic Hamartoma as a Cause of Central Precocious Puberty in 4.5-Year-Old Girl: Case Report

Ewa Jakubowska, Beata Sawicka, Hanna Borysewicz-Sanczyk, Aneta Zasim, Artur Bossowski

Department of Pediatrics, Endocrinology, Diabetology with Cardiology Division, Medical University of Białystok, Białystok, Poland

Background: Hamartoma is a benign, focal malformation, which is composed of tissue elements normally found at that site which are arranged chaotically within the mass. It may occur in many different parts of the body and often is undetected. Hypothalamic hamartoma, unlike most such growths, is symptomatic. It may cause gelastic seizures, visual problems, rage disorders and early onset of puberty. **Objective and hypotheses:** A 4.5-year-old girl was hospitalised for the first time in 2004 because of accelerated growth (height – 97th centile) and thelarche (Tanner stage 3). Bone age was evaluated at 8 years and 10 months. Dynamic profile of LH and FSH – after stimulation with LHRh – showed values typical for puberty. PRL, DHEAS, TSH, and α -fetoprotein levels were within the range. Abdominal ultrasonography showed no abnormalities. MRI scan showed tumorous mass (20 \times 18 \times 15 mm) in the hypothalamic region, modelling the bottom of ventricle III and dislocating the cerebral lacuna and optic chiasm. **Method:** Girl was referred to Neurosurgery Ward (The Children's Memorial Health Institute in Warsaw), where a decision was taken to postpone the surgical intervention and start treatment with GnRH analogue. **Results:** Girl has been treated with LHRH analogue in the years 2004–2009. Patient has been regularly evaluated – undergoing hormonal tests and diagnostic imaging procedures. Subsequent MRI scans showed no progression in the size of tumour. Treatment was terminated at the age of 9 years and 7 months as the patient reached the adequate height and growth velocity of 6 cm/year with bone age evaluated at 12 years. Menarche occurred at the age of 11 years and 8 months. Currently- at the age of 13 years and 8 months – girl menstruates regularly, bone age is equal to chronological age. **Conclusion:** Hypothalamic hamartoma may be a rare cause of central precocious puberty in children.

P3-D3-949

The Perception of Body Image and Self-Esteem in Girls with Precocious Puberty, Being Treatment with GnRH Analogue

Eun Young Kim^a, Min Sun Choi^a, Se Young Kim^b, Il Tae Hwang^c

^aDepartment of Pediatrics, Chosun University Medical School, Gwangju, Republic of Korea; ^bDepartment of Pediatrics, Bundang Jesaeng General Hospital, Kwandong University College of Medicine, Seongnam, Republic of Korea; ^cDepartment of Paediatrics, Hallym University College of Medicine, 150, Seongan-ro, Gangdong-gu, Seoul, Republic of Korea

Background: Precocious puberty (PP) is associated with psychological and behavioral problems. However, little is known about body image and psychological features in girls with PP, being treatment with GnRH analogues. **Objective and hypotheses:** This study aimed to evaluate the perception of body image and self-esteem in girls with PP, were receiving GnRH analogue therapy. **Method:** From March to August 2013, 82 girls with PP with GnRH analogue therapy were enrolled. Participants completed a battery of questionnaires asking about the perception of body image, pubertal self-assessment, and self-esteem. The degree of depression was calculated using Korean Kovasc's Children's Depression Inventory (CDI). **Results:** The mean duration of GnRH analogue treatment in PP was 13.22 ± 8.27 months. Pubertal status of all patients was Tanner stage 1 on physical examination and laboratory test. The mean depression score were not different between patients and normal control. There were classified as Tanner stages by self assessment of patients; Tanner stage 1 (32.9%), Tanner stage 2 (43.9%), Tanner stage 3 (20.7%), and Tanner stages 4 and 5 (each 1.2%). The mean depression scores according to Tanner stage (1, 2, and 3-5) by self assessment were 4.92 ± 0.11 , 5.56 ± 0.09 , and 9.76 ± 0.45 ($P < 0.05$). The perception of overall body build and Figure (%) and the mean depression scores in patients were dissatisfied (25.6%, 10.86 ± 0.39), neutral (37.8%, 4.86 ± 0.09), and satisfied (36.6%, 4.96 ± 0.10) ($P < 0.05$). No significant difference of depression score was found between overweight/obese and normal weight patients. However 42 patients were dissatisfied with body weight and 22 patients among them were normal body weight. The depression score in the patients of those dissatisfied with their weight was significantly high ($P < 0.05$). **Conclusion:** The perception of pubertal status and overall body build and figures is unrelated to objectively physical findings. The wrong perception of body image seems to contribute to negative self-esteem.

P3-D3-950

Leydig Cell Hyperplasia Mimicking Tumor: a Rare Cause of Isosexual Precocious Puberty

Gülcan Seymen Karabulut^a, Şükür Hatun^a, Ayşegül Yüksel^a, Funda Özer Çorapçioğlu^b, Yonca Anık^c, Gülşen Ekingen^d, Yeşim Gürbüz^e

^aPediatric Endocrinology Department, Kocaeli University, Kocaeli, Turkey; ^bPediatric Oncology, Kocaeli University, Kocaeli, Turkey; ^cRadiology Department, Kocaeli University, Kocaeli, Turkey; ^dPediatric Surgery, Kocaeli University, Kocaeli, Turkey; ^ePathology, Kocaeli University, Kocaeli, Turkey

Background: A 5 years and 10 months boy presented with pubic hair, recent penile growth, aggressive behaviour and rapid growth of height. Antenatal, perinatal, and developmental history was unremarkable. There was no family history of precocious puberty. His height and weight were 128 cm (2.24 s.d.) and 25 kg (1.55 s.d.) respectively. Vital signs were normal. He was Tanner 2 for pubic hair and his stretched penis length was 11 cm, right testis volume was 5 cc and left testis volume was 3 cc. His bone age was advanced to 8.5 years. Serum total testosterone level was elevated (150 ng/dl) with prepubertal LH level (< 0.2 IU/l), other laboratory results were DHEAS: 66 µg/dl, androstenedione: 2.10 ng/ml, ACTH: 16.2 pg/ml, kortizol: 6.7 µg/dl, 17-OH progesterone: 0.9 ng/ml, TSH: 1.42 mIU/l, and fT4: 0.79 ng/dl. On LHRH analog test, peak LH was 1.35 IU/l. Cranial MRI was normal and a prediagnosis of peripheric isosexual precocious puberty was made. Abdominal MRI was normal to exclude adrenal tumors. A scrotal ultrasonographic scan showed a heterogeneous mass lesion with heterogenous vascularisation on doppler, in the right testis measuring $23 \times 12 \times 8.5$ mm. Left testis was normal. Pelvic MR showed a mass lesion in right testis. Tumor markers including β-HCG and AFP were negative. A diagnosis of isosexual precocity due to testosterone-secreting testis tumor (Leydig cell tumor?) was made. **Objective and hypotheses:** To attract attention to Leydig cell hyperplasia which should be kept in mind in the differential diagnosis of testicular tumors. **Method:** Case report. **Results:** High inguinal orchiectomy was done. As a result of histologic examination, a final diagnosis of Leydig cell hyperplasia was established. **Conclusion:** Nodular Leydig cell hyperplasias are very rare during childhood and may present with peripheric precocious puberty. It should also be considered as differential diagnosis of testicular masses.

P3-D3-951

Impact of Different Doses of Bisphenol-A on the Puberty of Female Rats

Chen Linqi, Yang Fan, Jin Meifang

Soochow Children's Hospital, Soochow, Jiangsu, China

Objective: To observe vaginal opening day (VOD), hypothalamic kiss-1 gene and ovarian estrogen receptors (ER) gene expression level changes in neonatal rats exposure to different doses of bisphenol-A (BPA). **Methods:** Neonatal female SD rats were randomly divided into six groups: control group, vehicle group, 17β-estradiol group (17β-estradiol, E2, 10 µg/kg per day), low-dose BPA group (25 µg/kg per day), medium-dose BPA group (50 µg/kg per day) and high-dose BPA group (250 µg/kg per day). The rats got seven s.c. injections over postnatal day (PND) 0-6

and were sacrificed on the VOD and weighed. The VOD was recorded. The hypothalamus and ovaries were removed, weighed and calculated the organ/body weight ratio. Real-time PCR were used to observe the mRNA level changes of hypothalamic kiss-1 gene and ovarian ER gene. **Results: Conclusions:** Data suggests that neonatal 50 and 250 µg/kg per day BPA exposure induced premature puberty of rat, but it may not result from the expression level changes of hypothalamic kiss-1 mRNA; neonatal 25 µg/kg per day BPA exposure did not induce premature puberty of rat.

P3-D1-952

Discordant Genotypic Sex and Concordant Phenotypes in Two Spanish Siblings with 17 α -Hydroxylase/17, 20-Lyase Deficiency Carrying the Most Prevalent Mutated Alleles in Brazilian Patients

Laura Audí^a, Mónica Fernández-Cancio^a, Marta Melón-Pardo^b, Emilio García-García^b

^aPaediatric Endocrinology Unit, Vall d'Hebron Research Institute and Hospital, CIBERER, Autonomous University, Barcelona, Spain;

^bPaediatric Service, Hospital Virgen del Rocío, Sevilla, Spain

Background: 17 α -Hydroxylase/17,20-lyase deficiency is a rare form of congenital adrenal hyperplasia caused by mutations in *CYP17A1*, characterized by reduction of androgens, estrogens and cortisol production and mineralocorticoid excess. **Objective and hypotheses:** To describe the clinical and molecular characteristics of two sisters with 17 α -hydroxylase/17, 20-lyase deficiency. **Method:** Two sisters, phenotypic females, aged 17 and 15, the oldest with 46,XY and the youngest with 46,XX karyotypes, presented with primary amenorrhea and absent secondary sexual characteristics; the eldest presented elevated blood pressure. Both had elevated levels of ACTH, gonadotropins, progesterone, corticosterone and deoxycorticosterone, and reduced estradiol, testosterone, androstendione, 17-OH-P, DHEA-S, cortisol, aldosterone and renin activity. **Results:** Mutational analysis identified compound heterozygous mutations (p.Arg362Cys/Trp406Arg) in *CYP17A1* gene, previously described as the most prevalent mutations in Brazilian families of Spanish (p.Trp406Arg) or Portuguese (p.Arg362Cys) descent. The present siblings were born from parents with origins near Sevilla. They may represent the combination of the ancestral alleles for the most prevalent homozygous mutations in Brazil. The clinical and biochemical phenotypes agree with a complete lack of combined 17 α -hydroxylase/17,20-lyase activities. Estrogen therapy and hydrocortisone were given in both cases and gonadectomy will be performed in the oldest. **Conclusion:** Mutations in *CYP17A1* should be investigated in patients with mineralocorticoid excess and deficiency of cortisol, androgens and estrogens. Regardless of genotypic sex, patients with combined 17 α -hydroxylase/17,20-lyase deficiency are treated with glucocorticoids and estradiol.

P3-D1-953

The Development of Gonadoblastoma in a 3-Year-Old Girl with 46,Xdel(Y)p11.3, Gonadal Dysgenesis and Associated Congenital Anomalies

Zofia Kolesinska^a, Aleksandra Rojek^b, Helena Kedzia^c, Michal Blaszczyński^d, Anna Latos-Bielenska^e, Karina Kapczuk^f, Marek Niedziela^{a,b}

^aDepartment of Pediatric Endocrinology and Rheumatology, Poznan University of Medical Sciences, 2nd Chair of Pediatrics, Poznan, Poland; ^bMolecular Endocrinology Laboratory, Department of Pediatric Endocrinology and Rheumatology, Poznan University of Medical Sciences, Poznan, Poland;

^cDepartment of Pathomorphology, Gynecology and Obstetrics, Clinical Hospital, Poznan, Poland; ^dChair and Department of Pediatric Surgery, Traumatology and Urology, Poznan University of Medical Sciences, Poznan, Poland; ^eDepartment of Medical Genetics, Center for Medical Genetics GENESIS, Poznan University of Medical Sciences, Poznan, Poland; ^fDepartment of Gynecology, Poznan University of Medical Sciences, Chair of Perinatology and Gynecology, Poznan, Poland

Background: One of the crucial aspects of the management of disorders of sex development is the assessment of the risk of malignant transformation of a dysgenetic gonad. **Objective and hypotheses:** The PCR analysis of germ-cell risk factors as the presence of the *TSPY* gene may be helpful in decision making of an early gonadectomy. **Results:** We report a 46,Xdel(Y)p11.3 girl with gonadal dysgenesis, that was referred to the Department of Pediatric Endocrinology because of discordance between the karyotype assessed by amniocentesis and the postnatal phenotype. The prenatal diagnosis was performed because of the presence of generalized fetal oedema, multiple pulmonary cysts, agenesis of nasal bone on the ultrasound, and revealed 46,XY karyotype. After birth the diagnosis of congenital cystic adenomatoid malformation was established. A girl presented with dysmorphic features (lymphoedema of the feet, epicanthus, micrognathia, and skin malformation on the head) and female external genitalia. The laboratory tests revealed high plasma concentration of FSH (39.1 mIU/ml), normal of LH (4.4 mIU/ml), low of estradiol (8 pg/ml), and testosterone (0.71 nmol/l). The ultrasound visualized the prepubertal uterus, but no ovaries were found. The postnatal karyotype confirmed the deletion of the part of the short arm of Y chromosome – 46,Xdel(Y)p11.3. The PCR analysis confirmed the presence of the deletion encompassing *SRY* and *ZFY1* genes located in short arm of Y chromosome. Moreover, it enabled detection of four genetic markers including *TSPY* gene located in *GBY* locus (gonadoblastoma region on Y chromosome). The follow-up was discontinued until the time the patient was 3 years old, when she underwent bilateral adnexectomy. The histopathological examination revealed gonadoblastoma. **Conclusion:** We confirmed the association between the presence of the *TSPY* gene and the development of the pre-malignant lesion as carcinoma *in situ*– gonadoblastoma in a girl with gonadal dysgenesis at an early age.

P3-D1-954

46,XX DSD: Bilateral Ovotestis with SOX9

Alessandra di Lascio^a, Silvia Laura Carla Meroni^a,
Moira Gianninoto^a, Orsetta Zuffardi^b, Gianni Russo^a

^aSan Raffaele Scientific Institute, Milan, Italy; ^bUniversity of Pavia, Pavia, Italy

Background: Disorders of sex development (DSD) are congenital conditions in which chromosomal, and gonadal or anatomical sex is atypical. **Objective and hypotheses:** We describe the case of a 46,XX newborn with ambiguous genitalia. 46,XX DSD set in differential diagnosis disorders of gonadal development (ovotesticular DSD, testicular DSD, gonadal dysgenesis), androgen excess of fetal (mainly congenital adrenal hyperplasia due to deficiency of 21-hydroxylase, 11-hydroxylase, and 3 β -hydroxysteroid dehydrogenase), fetoplacental (aromatase deficiency) or maternal origin (luteoma and virilizing tumors) and malformations. **Results:** Hormonal tests showed testosterone above normal and cortisol at the lower limit; steroid replacement therapy was started. Search for SRY was negative. Ultrasound revealed two gonads at the external genitalia. The patient was given the female sex. The absence of maternal virilization excluded tumors and aromatase deficiency. The following hormonal investigations documented normal values of gonadotropins, androgens, and cortisol adjusted for age. The absence of adrenal insufficiency excluded forms of congenital adrenal hyperplasia, so glucocorticoid replacement therapy was discontinued. The HCG test showed a poor response of androgens. The patient was subjected to gonadal biopsy with histological diagnosis of bilateral ovotestis. **Conclusion:** The ovotesticular DSD is a rare disorder defined by the presence of both ovarian and testicular tissue in the same individual. The structure of the ovary is usually normal, while testicular tissue is immature and histologically abnormal. The development of müllerian and Wolffian derivatives is variable. The external genitalia are ambiguous with various degrees of virilization. The SRY gene in 46,XX ovotesticular patients is present in ~1/3 of the cases. Array-CGH analysis of our patient showed duplication 17q24, which contains SOX9 gene. In embryos XY SRY interacts with SOX9 in the differentiation of the testis. In subjects XX duplication of SOX9 has been described as a cause of 46,XX DSD. The same duplication was present in the father.

P3-D1-955

Severe Undervirilisation in a 46,XY Case due to a Novel Mutation in HSD17B3 Gene

Ayfer Alikasifoglu^a, Dogus Vuralli^a, Olaf Hiort^b, E Nazli Gonc^a,
Z Alev Ozon^a, Nurgun Kandemir^a

^aDepartment of Pediatric Endocrinology, Hacettepe University, Ankara, Turkey; ^bDivision of Pediatric Endocrinology and Diabetes, University of Lübeck, Lübeck, Germany

Background: 17- β -hydroxysteroid dehydrogenase 3 (17- β -HSD3) deficiency is a rare disorder of sex development due to impaired conversion of androstenedione to testosterone. Children with 46,XY karyotype often have female appearing external or ambiguous genitalia at birth. At the time of puberty, virilisation can occur. Therefore 46,XY patients with HSD17B3 gene defects should be raised as male. **Objective and hypotheses:** When a child with 46,XY karyotype present with female appearing external or ambiguous genitalia and there is impaired conversion of androstenedione to testosterone, 17- β -HSD3 deficiency must be kept in mind. **Method:** A case with 17- β -HSD3 deficiency with a novel mutation is presented. **Results:** One year old girl was referred with the complaint of swelling in the right inguinal area. The parents were first cousins. In physical examination bilateral gonads were palpable in inguinal regions. She had a fallus of 1.5 cm and vaginal and urethral orifices were separate. The karyotype was 46 XY. On ultrasonography no Mullerian structures could be seen and gonads were in the inguinal canal. Following injection of 1500 U/m² hCG for 3 days testosterone, dihydrotestosterone and androstenedione levels were 29.9 ng/dl, 82.4 pg/ml and 2.78 ng/ml respectively. Testosterone/dihydrotestosterone ratio was 3.6 which was normal. Testosterone/androstenedione ratio was found to be 0.107 ($n > 0.8$) suggesting 17- β -HSD3 deficiency. Molecular analysis of the HSD17B3 gene showed a homozygous mutation c.761_762delAG corresponding to p.E254VfsX10 in the patient and both parents were heterozygous. A deletion of two nucleotides in exon 10 was found, which lead to a frameshift and subsequently to premature termination within the protein. This deleterious mutation caused 17- β -HSD-3 deficiency in this patient. The parents did not accept sex reassignment into male and bilateral gonadectomy was performed. The histopathology of gonads were consistent with testis and spermatic cord. **Conclusion:** A novel mutation p.E254VfsX10 in HSD17B3 gene caused severe undervirilisation in a 46,XY patient. Early diagnosis is crucial for appropriate sex of rearing.

P3-D1-956

Gonadoblastoma and Papillary Tubal Hyperplasia in Ovotesticular Syndrome

Enver Simsek, Cigdem Binay, Baran Tokar, Sare Kabukcuoglu,
Melek Ustun

Eskisehir Osmangazi University School of Medicine, Eskisehir,
Turkey

Background: Ovotesticular disorder of sexual development (DSD) is a rare form of DSD in which both testicular and ovarian tissues are present in the same individual either in a single gonad (ovotestis) or in opposite gonads with a testis and an ovary on each side. **Objective and hypotheses:** To discuss rare cases of ovotesticular DSD and one of the novel findings of these cases. **Methods and patients:** Case 1 is the first child of unrelated parents and was referred on the third day after birth due to ambiguous genitalia. Upon physical examination, the patient had ambiguous genital including a phallus with a length of 2.3 cm,

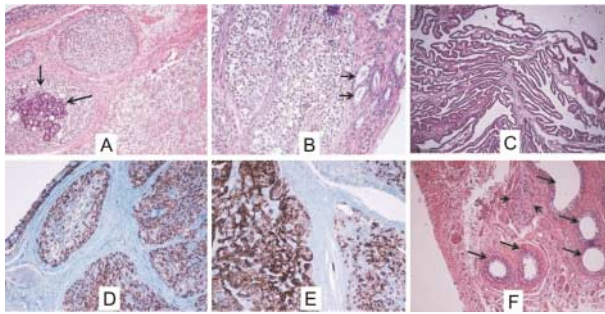


Figure 1 Histological examination of gonadoblastoma with superimposed dysgerminoma in the left gonad (A, B, C and D) and streak right gonad (E and F). (B) Sertoli cells (arrows) and dysgerminoma nests progressing to gonadoblastoma. The right streak gonad showed polypoid and papillary hyperplasia of the tubular epithelium. (F) Leydig cell remnants (arrowheads) and epididymis (arrows).

bifid labioscrotal folds, incomplete labioscrotal fusion, ventral opening of the urethra, chordea, and non-palpable gonads. Case 2 was a 15-year-old female presented with lack of pubertal development and primary amenorrhea. Physical examination revealed short stature (-2.1 SDS), Tanner stage I breast development, normal female external genitalia phenotype.

Results: Hormonal investigations of case 1 excluded congenital adrenal hyperplasia, leydig hypoplasia, 5α -reductase deficiency and androgen insensitivity syndrome. Chromosomal analysis and fluorescence *in situ* hybridisation of SRY revealed a SRY-positive 46,XX. Laparoscopic examination of case 1 revealed Mullerian remnants. Histopathological examination of bilateral gonadal biopsies showed ovotestes. Karyotype analysis and FISH of SRY of case 2 showed an SRY (+) 46,XY karyotype. Laparoscopic examination of case 2 revealed rudimentary Müllerian structures. **Conclusions:** Laparoscopic examination and gonadal biopsy for histopathological diagnosis remain the cornerstones for a diagnosis of ovotesticular DSD.

P3-D1-957

5α -Steroid Reductase 2 Deficiency in a Large Family

Eda Mengen Ucakturk^a, Yılmaz Kor^b, Fatih Gurbuz^a, Ali Kemal Topaloglu^a, Bilgin Yukse^a

^aPediatric Endocrinology, Cukurova University, Adana, Turkey; ^bDepartment of Pediatric Endocrinology, Adana Numune Training Hospital, Adana, Turkey

Background: 5α -Reductase is an enzyme that converts testosterone to dihydrotestosterone (DHT) in peripheral tissues. DHT is responsible for the differentiation of male external genitalia. Mutations in the 5α -steroid reductase type 2 gene (*SRD5A2*) result in incomplete masculinisation of the external genitalia in subjects with a 46,XY karyotype. The clinical spectrum of a 46,XY individual with 5α -reductase deficiency at birth can range from complete female appearance of the external genitalia to

nearly complete male phenotype. **Aim:** Our aim is to report the molecular and clinical characteristics of a Turkish family with 5α -reductase deficiency who had a homozygote mutation of *SRD5A2* gene. **Patients and methods:** A 14-year-old girl presented with primary amenorrhea and lack of breast development. She had a history of inguinal hernia surgery. Her parents are healthy cousins. Physical examination of the patient identified a predominantly female phenotype except clitoris-like phallus (2 cm) and bilateral inguinal masses. Genital ambiguity was stage 4b according to Sinnecker's classification. Her breast, pubic hair and axillary hair were at Tanner stage 1, 4 and 1 respectively. A chromosome analysis revealed a 46,XY karyotype. Pelvic ultrasonography confirmed absence of müllerian structures and the presence of both gonads with features of normal testes in the inguinal canal. A testosterone:DHT ratio was 9.7 and further increased to 14.5 after stimulation with hCG. **Result:** A previously reported homozygous missense mutation (p.A65P) was detected in the *SRD5A2* gene. After the diagnosis, her eight sisters were screened. Three of her sister were also found to be homozygous for the same mutation. **Conclusion:** Although rare, *SRD5A2* gene defect should be suspected in any girl presenting with primary amenorrhea and virilisation at puberty. It is important that siblings of the diagnosed cases be screened with genital system examination, as well as chromosomal and, if necessary mutational analysis.

P3-D1-958

17 β HSD-3 Enzyme Deficiency in Newborn Due to a Novel Mutation in HSD17B3 Gene

Elif Sagsak^a, Zehra Aycan^a, Senay Savas Erdeve^a, Melikah Keskin^a, Semra Cetinkaya^a, Kadri Karaer^b

^aPediatric Endocrinology Clinic, Dr. Sami Ulus Obstetrics and Gynecology, Children's Health and Diseases Training and Research Hospital, Ankara, Turkey; ^bIntergen Genetic Disease Diagnostic Center, Ankara, Turkey

Background: 17 β -Hydroxysteroid dehydrogenase type 3 (17 β HSD-3) deficiency is an autosomal recessive form of 46,XY disorder of sex development (DSD). 17 β HSD-3 is present almost exclusively in the testes and converts androstenedione to testosterone. The diagnosis can be easily missed in early childhood as the clinical presentation may be subtle. The most frequent presentation of 17 β HSD-3 deficiency is a 46,XY individual with female external genitalia, labial fusion and a blind ending vagina, with or without clitoromegaly. In these patients, the diagnosis may be missed until adolescence. At the time of puberty, patients present with primary amenorrhea, varying degrees of virilization including development of male body habitus, increased body hair and deepening of the voice. A low T/A ratio on baseline or human chorionic gonadotropin stimulated testing is suggestive of 17 β HSD-3 deficiency. The diagnosis can be confirmed with molecular genetic studies. **Objective and hypotheses:** 17 β HSD-3 deficiency, a rare cause of 46,XY sexual development disorder can be diagnosed with a careful physical examination.

Method: A 12-day patient was referred to our hospital because of palpable gonad in labia majora. On physical examination, she has female external genitalia, without clitoromegaly. The karyotype was 46,XY. **Results:** T/A ratio was 0,128 and diagnosed 17 β HSD-3 deficiency. We detected compound heterozygous novel frameshift mutations in exon 9 and 10 of HSD17B3 gene. **Conclusion:** The external genitalia of our case was totally female in appearance, but it was the first case that could be diagnosed in the newborn period as a gonad was seen in the labium major. The patient is now 1.5 years old and the decision regarding final gender will be made eventually.

P3-D1-959

Partial Androgen Insensitivity Syndrome in a Boy with Inactivating Androgen Receptor Mutation and Somatic Mosaicism

Johanna Tommiska^{a,c}, Päivi Keskinen^b, Taneli Raivio^{a,c}

^aInstitute of Biomedicine/Physiology, Helsinki, Finland; ^bChildren's Hospital, Tampere University Central Hospital, Tampere, Finland; ^cChildren's Hospital, Helsinki University Central Hospital, Helsinki, Finland

Background: Mutations in the X-chromosomal androgen receptor (AR) gene, rendering the AR protein completely or partially inactive, cause complete or partial (PAIS) androgen insensitivity syndrome. **Case report:** The proband was born at term following uneventful pregnancy. His phallus length was 28 mm, he had palpable gonads in the lower portion of the inguinal canal, and he had a severe penoscrotal hypospadias. His karyotype was 46,XY, and molecular karyotype (defined by array comparative genomic hybridization) was normal. At 7 days of age, his serum testosterone was 0.7 nM and increased to 20 nM in human chorionic gonadotropin stimulation test. Sequencing of the AR gene revealed a 148 bp deletion in exon 1. This mutation, c.108_255del (p.Pro37Serfs*89), leads to premature stop codon truncating over 90% of the 920 amino acid receptor. However, the PCR amplification and sequencing of the genomic DNA from the proband's peripheral blood leukocytes showed also the existence of the normal allele without the deletion, implying somatic mosaicism and *de novo* origin of the mutation. His mother only displayed one PCR band consistent with normal AR. **Conclusions:** Mutations in AR that completely inactivate the receptor may manifest as PAIS due to somatic mosaicism.

P3-D1-960

Clinical Characteristics of 30 Patients with 45,X/46,XY Mosaicism

Sukran Poyrazoglu, Nurcin Saka, Firdevs Bas, Ruveyde Bundak, Feyza Darendeliler

Pediatric Endocrinology Unit, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey

Background: 45,X/46,XY mosaicism is associated with a broad spectrum of phenotypes, ranging from ambiguous genitalia at birth to patients with a completely male or female phenotype. Turner syndrome stigmata and associated anomalies could be found in these patients. **Objective and hypotheses:** To evaluate clinical presenting symptom and follow-up data of 30 patients with 45,X/46,XY karyotype. **Method:** Thirty patients with 45,X/46,XY mosaicism diagnosed between 1989 and 2014 in Pediatric Endocrinology Unit were reviewed retrospectively. **Results:** The mean age at diagnosis was 5.7 ± 6.3 years (range: 0.03–16.7). Their presenting symptoms were ambiguous genitalia ($n=16$), bilateral undescended testis ($n=3$), hirsutism and amenorrhea ($n=1$), amenorrhea ($n=2$), and short stature ($n=7$). One patient was diagnosed by prenatal amniocentesis; karyotype was confirmed after birth. Turner stigmata were found in eight patients. Müllerian structures were identified in 28 patients on ultrasound. Sixteen children were reared as female, 13 as male and 1-year-old patient was undefined. Four patients (10%) had cardiac anomalies, two (5%) renal anomalies, two celiac disease (5%), two Hashimoto thyroiditis (5%) and one patient bilateral conductive hearing loss. Three patients had gonadoblastoma. GH treatment was initiated six patients (five female, one male) at a mean age of 12.9 ± 0.8 years (range: 12.0–14.1). Mean height SDS at the initiation of GH treatment of six patients was -4.3 ± 1.7 . Four patients reached a mean adult height of -3.4 ± 2.6 on GH treatment. **Conclusion:** Although main presenting symptom of 45,X/46,XY mosaicism is ambiguous genitalia in early ages, a significant number of patients could be diagnosed with different symptoms in older ages. Besides follow-up for gonadal tumors, patients with 45,X/46,XY mosaicism require a clinical evaluation similar to that performed in Turner syndrome and growth velocity must be routinely followed up.

P3-D1-961

Three Siblings Extremely Androgen Insensitivity Syndrome Due to an AR Mutation with Differing Phenotypes

Bilgin Yuksel, Eda Mengen Ucakturk, Fatih Gurbuz, Ali Kemal Topaloglu

Pediatric Endocrinology, Cukurova University, Adana, Turkey

Background: Androgen insensitivity syndrome (AIS) is the most common cause of 46,XY sexual differentiation disorders. Clinical presentation is variable among cases with a range from a complete female to male external genitalia. There is a weak correlation between genotype and phenotype. **Aim:** Our aim is to report clinical and molecular characteristics of siblings with AIS. **Patients and methods:** Two siblings newborns with ambiguous genitalia were examined. The parents were second-degree cousins. Both patients had a genital ambiguity Stage 3a according to Sinnecker's classification. Chromosome analysis revealed a 46,XY karyotype. Pelvic ultrasonography confirmed absence of müllerian structures and the presence of both gonads with features of normal testes in the inguinal canal. Patient 3, who was reared as a girl, their

12 years and 6 months old sibling, who was reared as a girl, invited for screening. The physical examination revealed female phenotype, and bilateral inguinal masses. Genital ambiguity was Stage 5 according to Sinnecker's classification. A chromosome analysis revealed a 46,XY karyotype. Pelvic ultrasonography confirmed absence of müllerian structures and the presence of both gonads with features of normal testes in the inguinal canal. **Results:** All three patients were found to have a hemizygotus mutation of p.R856H (c.2567g>A) in *AR* gene. This mutation was previously defined to cause the disease. **Conclusion:** Androgen insensitivity syndrome has a wide range of clinical spectrum. Even members of the same family may have different clinical pictures. Therefore, siblings of diagnosed cases should have genital system examination, chromosomal analysis, and mutation screenings. It is important that families should be informed about prenatal diagnosis and preimplantation genetic diagnosis.

P3-D1-962

46,XY Female with Turner Syndrome, Crohn's Disease and Low Level Mosaicism for Monosomy X

Emir Tas^a, Svetlana Yatsenko^{b,c}, Jadranka Popovic^a

^aDepartment of Pediatric Endocrinology, Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania, USA; ^bDepartment of Obstetrics, Gynecology & Reproductive Sciences, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA;

^cDepartment of Pathology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA

Introduction: Turner syndrome (TS) is characterized by short stature and premature ovarian failure. Genetic component of TS patients with diagnosis of inflammatory bowel disease has not been largely studied. **Case Report:** A 9⁴/₁₂-year-old girl with history of Crohn's disease was evaluated for short stature. Her disease was well controlled with medications, however she continued with linear growth failure. Medical history included frequent ear infections, speech delay, ADHD and learning and emotional support. She was short (height <2SD), had hypertelorism, micrognathia, overcrowding of teeth, high arched palate, low posterior hairline, dysplastic nails, cubita valga and widely spaced nipples. She was pre-pubertal with normal female external genitalia without clitoromegaly. Karyotype from peripheral blood showed mosaicism for a 45,X cell line in ~11% of the cells and 46,XY male chromosome complement in ~89% of metaphase cells. Fluorescence *in situ* hybridisation ISH analysis using the X chromosome centromere specific and the SRY probes showed that ~80% of the interphase cells had both X and Y chromosomes with the intact SRY gene. FISH analysis on a urine sample demonstrated monosomy X in ~44% of the cells, while 56% of cells showed signals for both X and Y chromosomes. Pelvic US showed presence of uterus. No gonads were identified. She had low testosterone (<0.1 ng/dl), LH (0.46 mIU/ml), anti-Müllerian hormone (<0.03 ng/ml) and inhibin (<10 pg/ml). FSH was

elevated (29.8 mIU/ml). **Conclusion:** Approximately 5–10% of the TS patients have 46,XY cell line. Phenotype is variable depending on the type and function of the gonadal tissue. Our patient is a phenotypic female despite a predominant male chromosome complement in the peripheral blood, however the level of cells with monosomy X in the urine is significantly higher. Our data indicate the necessity of studying more than one tissue from each patient to reveal a tissue-specific differences in the proportion of cells with different chromosome complement.

P3-D2-963

Hypospadias in a Male Patient with 21-Hydroxylase Deficiency and Atypical Clinical Course: Presentation of Two Brothers

Ayla Güven^a, Suna Hancili^a, Wiebke Arlt^b

^aGöztepe Education and Research Hospital, Pediatric Endocrinology Clinic, Istanbul, Turkey; ^bSchool of Clinical and Experimental Medicine, Centre for Endocrinology, Diabetes and Metabolism, University of Birmingham, Birmingham, UK

Introduction: 21-Hydroxylase deficiency (21OHD) is the most common form of congenital adrenal hyperplasia (CAH). Clinical and laboratory findings vary depending on the enzyme activity. **Case Report 1:** A 2-month-old male infant referred as hypospadias. He was born at term from consanguineous parents with intrauterine growth retardation. The mother had no problem during pregnancy. The external genitalia had penoscrotal hypospadias with chordee and both testes were normally sized within the scrotum. No other dysmorphic signs, skeletal malformations were observed. The karyotype analysis was 46,XY. Biochemical and baseline hormonal findings were normal except for slightly high 17-OHP (9.3 ng/ml). ACTH stimulation test revealed similar to non-classical CAH with no clinically compatible. When he was 33 months old there was signs of salt loss (hyperkalemia and hyponatremia), so performed Synacthen test again. Basal ACTH was at the upper limit of the normal range, with elevated 17-OHP and progesterone levels, while androgen levels were low; basal cortisol was normal (8.56 µg/dl) but stimulated was low (8.75 µg/dl). POR deficiency was considered. But any mutation of POR was not detected. **Case report 2:** The siblings of Case 1, because of this the patient brought to our clinic postnatally. His physical examination was completely normal. Biochemical and baseline hormonal findings were normal except for slightly high 17-OHP like his brother. Also adrenal insufficiency demonstrated with repeated ACTH tests. However 24-h urinary steroid hormone profiles of patients were compatible with 21OHD. Genetic analysis established a homozygous V281L mutation in the CYP21A2 gene in both cases. **Conclusion:** These patients don't exhibit the typical clinical and laboratory findings of 21OHD. Case 1 is a rare male patient with 21OHD accompanied by hypospadias. In the literature, there is only two 46,XY cases that presented with insufficient virilization in 21OHD.

P3-D2-964

An Ovulating Testis

Jaya Sujatha Gopal Kothandapani^a, Pooja Sachdev^a, Neil Wright^b

^aDepartment of Human Metabolism, University of Sheffield, Sheffield, UK; ^bDepartment of Paediatric Endocrinology, Sheffield Children's Hospital NHS Foundation Trust, Sheffield, UK

Background: Ovotesticular disorders of sexual development (DSD) are a rare form of DSD with co-existence of both ovarian and testicular tissue in one or both gonads. **Case report:** A term infant (weight +1.38 SDS) presented at birth with severe penoscrotal hypospadias, a small phallus and a right hemiscrotum with descended gonad (external masculinization score 1.5). Pelvic ultrasound revealed no Mullerian structures, a small right gonad with probable epididymis, and no gonad on the left. Karyotype showed 46 XX with no mosaicism. A 3-day HCG test demonstrated functioning testicular tissue with a testosterone rise (7.9–13.4 nmol/l). Laparoscopy showed a vestigial uterus and a left gonad associated with fallopian tube which was removed. Histology confirmed ovotestes on both sides. Gonadal karyotype was 46,XX. A diagnosis of 46,XX ovotesticular DSD was made and a male gender was assigned with parental concurrence. He underwent hypospadias repair with good results. Family were keen to preserve gonad hence right ovotestis was left in the scrotum with a view to monitoring carefully at puberty. From age 13 there was evidence of virilisation. His testosterone was 4.4 nmol/l, oestradiol 88 nmol/l, LH 10.3 nmol/l and, FSH 23 nmol/l, indicating a failing gonad producing predominantly testosterone. Subsequently he developed progressive gynaecomastia. Repeat blood tests showed a fall in testosterone (0.8 nmol/l) but detectable oestradiol (34 nmol/l) levels. Hence a 3-day HCG test was undertaken (testosterone 1 14 nmol/l; oestradiol 168 → 83 nmol/l); shortly afterwards he presented with acute right scrotal pain. Intra-operatively he was found to be bleeding from the ovarian tissue within the testicular capsule. In view of progressive gynaecomastia and future malignant risk, his right ovo-testis was removed after extensive discussions with the family. Sperm counts prior to surgery had shown azoospermia and sperm harvesting was also unsuccessful. He had bilateral prosthesis sited and testosterone replacement commenced. **Conclusion:** This case emphasises the complexity involved in the management of such rare conditions and the importance of systematic patient and family centred approach.

P3-D2-965

Mosaicism Ratios of 45,X to 46,X IdicY Explained a Phenotype in a Case with Mixed Gonadal Dysgenesis

Megumi Hatano, Ryuji Fukuzawa, Yukihiko Hasegawa

Tokyo Metropolitan Children's Medical Center, Tokyo, Japan

Background: Patients with mixed gonadal dysgenesis (MGD), whose prototypical karyotype is 45,X/46,XY may manifest complications characteristic of Turner's syndrome. We here

present a 10-year-old male with MGD who had coarctation of aorta. At birth, he was found to have hypospadias, bifid scrotum and cryptorchidism. Chromosomal analysis of lymphocytes revealed a karyotype of 46,X idic Y (23)/45,X (7). Left gonadectomy was performed in infancy and the removed gonad showed streak gonad with a region of testicular tissue, compatible with MGD. At the age of 10 years, coarctation of the aorta was pointed out by chance. **Objective and hypotheses:** The objective of this study was to see mosaicism ratios of the removed gonad and aortic tissue. We hypothesize that mosaicism ratios of 45,X/46,XY varies among tissues, and tissues with a higher ratio of 45,X to 46,XY are more likely to exhibit phenotypes of Turner's syndrome. **Method:** The mosaicism ratios of the removed gonad and aortic tissue were estimated by fluorescent immunostaining with probes to identify X centromere-specific repeat sequence and Yp11.2. **Results:** The percentages of Yp11.2 negative cells in the left gonad and aortic tissue were 80 and 90% respectively. In contrast, the percentages of Yp11.2 negative cells in the aortic tissue from 46,XX and 46,XY individuals were more than 95% and <5%, respectively. **Conclusion:** Mosaicism ratios in tissues may explain phenotypes in MGD, and further studies to prove this should be conducted in a larger number of cases.

P3-D2-966

A Rare Case of Swyer Syndrome with Spontaneous Breast Development and Menstruation

Bumin Nuri Dundar^{a,b}, P Sule Can^a, Caner Alparlan^c, Sinem Akbay^c, Gonul Catli^a, Sefa Kelekci^d

^aPediatric Endocrinology Unit, Tepecik Training and Research Hospital, Izmir, Turkey; ^bDepartment of Pediatric Endocrinology, Katip Celebi University, Izmir, Turkey; ^cDepartment of Pediatrics, Tepecik Training and Research Hospital, Izmir, Turkey; ^dDepartment of Obstetrics and Gynecology, Katip Celebi University, Izmir, Turkey

Background: Swyer syndrome (46,XY pure gonadal dysgenesis) is a rare disorder, which is characterized by female phenotype, female internal genitalia and fibrotic and primitive gonads. Classically, breast development and menstruation are absent due to hypergonadotropic hypogonadism. **Objective and hypotheses:** To our knowledge, three cases of Swyer syndrome with spontaneous breast development have been reported so far. In these reports, breast development was suggested to be due to estrogen secretion from the neoplastic tissue, limited ovarian functions, and aromatization of androgens to estrogen or increased sensitivity to estrogen in breast tissue. Additionally, one patient with regular menstrual cycles linked to estrogen secretion from gonadoblastoma was also reported. **Methods:** A 15-year-old girl presented to our clinic with the complaint of amenorrhea. Thelarche and pubarche have occurred at the ages of 10 and 11 years respectively. Her weight was 55.2 kg (0.25 s.d.), height was 165.5 cm (0.95 s.d.), with a BMI of 20.1 kg/m² (0.10 s.d.). Her external genitalia was completely female with a breast development and pubic hair compatible with Tanner stage V. The rest of the physical examination was unremarkable.

Results: Her laboratory findings were as follows; FSH: 45 mIU/ml, LH: 13 mIU/ml, E₂: 66 pg/ml, total testosterone: <20 ng/dl, progesterone: <0.2 ng/dl, 17-OH progesterone: 1.5 ng/dl, DHEA-S: 121 µg/dl, prolactin: 5.3 ng/ml, and β-HCG: 0 mIU/ml. A pelvic ultrasound revealed small ovaries (1.4 and 2.4 cm³) and a uterus of 6×2.5×2.3 cm in size. Her karyotype was 46,XY and SRY (+). A clomiphene citrate challenge test showed an insufficient ovarian reserve. Thereafter, for nine months, the patient had regular, spontaneous menstrual cycles. On follow-up, the patient underwent diagnostic laparoscopy. After bilateral salpingo-oophorectomy histopathological examination of the specimen revealed gonadoblastoma. **Conclusion:** In this rare case of 46,XY pure gonadal dysgenesis breast development and menstrual cycles were considered to be due to the active hormone secretion from the gonadoblastoma.

P3-D2-967

Phenotypic and Genotypic Variability of Patients with 5-α Reductase Type 2 Deficiency

Kun Hu, Nils Krone, Jeremy Kirk

Birmingham Children's Hospital NHS Foundation Trust, Birmingham, UK

Background: Steroid 5-α reductase type 2 (SRD5A2) deficiency is a rare inherited disorder resulting from mutations in the SRD5A2 gene, causing 46,XY DSD (Disorder of Sex Development). The mutated SRD5A2 enzyme can no longer convert testosterone to dihydrotestosterone, which is needed for virilisation of external genitalia. **Objective and hypotheses:** To describe the phenotype, investigations and management of SRD5A2 deficiency. **Method:** Retrospective data was collected from the medical records of SRD5A2 deficiency patients seen at a regional paediatric endocrine centre over the last 20 years. **Results:** Full medical records were available in eight patients. The median age of patients presenting at birth (*n*=5) and at puberty (*n*=3) were 1 year 1 month and 13 years 6 months respectively. Male patients (*n*=6) presenting at birth and puberty had symptoms including micropenis (*n*=6), hypospadias (*n*=5), undescended testes (*n*=4), penoscrotal transposition (*n*=2) and bifid scrotum (*n*=1). Female patients (*n*=2) who presented during puberty had symptoms including primary amenorrhea, absent breast development, palpable testes (*n*=1) and voice change (*n*=1). Pelvic ultrasound showed absent uterus and ovaries, and detectable testicular tissue. Rapid molecular genetic analysis confirmed homozygous recessive mutations in exon 4 of the SRD5A2 gene (c.598G>A; c.574G>A; c.586G>A) as well as compound heterozygous mutations in other exons of SRD5A2 gene (g.237_250dup and g.264C>G; c.586G>A and c.737G>A). After diagnosis, one of the female patients underwent a change in gender. Management included hypospadias repair, dihydrotestosterone 2.5% gel or orchidopexy. **Conclusion:** SRD5A2 deficiency is a heterogeneous condition both in terms of age at diagnosis and presentation, and can be caused by several different mutations in the SRD5A2 gene. Better understanding of these phenotypic features can facilitate timely diagnosis, management and relevant counselling for patients and their families.

P3-D2-968

The Novel Mutation in the Steroidogenic Acute Regulatory Protein in 46,XY Case with Adrenal Insufficiency and Complete Sex Reversal

Fatih Gurbuz^a, L Damla Kotan^b, Eda Mengen^a, Ali Kemal Topaloglu^a, Bilgin Yuksele^b

^aPediatric Endocrinology, Cukurova University, Adana, Turkey;

^bBiotechnology, Cukurova University, Adana, Turkey

Background: The steroidogenic acute regulatory protein (StAR) has been shown to be essential for steroidogenesis by mediating cholesterol transfer into mitochondria. Inactivating StAR mutations cause the typical clinical picture of congenital lipoid adrenal hyperplasia. **Objective and hypotheses:** We aimed to identify causative mutations in cases presenting with adrenal failure during early infancy. **Method:** Consecutive cases with adrenal failure during early infancy were studied. The coding regions of the StAR gene (uc003xkv.1) is PCR-amplified and automatically sequenced. **Results:** A homozygous state consisting of p.S13P was detected in a patient. Functional studies of the new mutations are ongoing. **Conclusion:** The novel mutation of p.S13P cause early infancy adrenal insufficiency and complete sex reversal in the 46,XY case.

P3-D2-969

A Challenging Diagnosis in Three 46,XY Females from Two Related Families

Raffaella Di Mase^a, Nicola Improda^a, Manuela Cerbone^a, Lucia De Martino^a, Donatella Capalbo^a, Lilia Baldazzi^b, Mariacarolina Salerno^a

^aDepartment of Medical Translational Sciences, Federico II University, Naples, Italy; ^bDepartment of Gynaecologic, Obstetric and Paediatric Sciences, S.Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy

Background: Mutations in the 17β-hydroxysteroid dehydrogenase (17βHSD 3) result in 46,XY disorder of sex development (DSD). Biochemical hallmark of 17βHSD 3 deficiency is a Testosterone/Androstenedione ratio (T/A ratio) <0.8. 17βHSD 3 mutations have been associated with a wide spectrum of phenotypes, ranging from under-virilized male to a female appearance of genitalia at birth. Indeed, 17βHSD 3 deficiency in prepubertal patients is often clinically indistinguishable from androgen insensitivity syndrome (AIS) and its diagnosis can be extremely challenging. **Objective and hypotheses:** Three females from the same pedigree (two siblings and their first cousin) were suspected to be affected by 46,XY DSD because of clitoromegaly and inguinal masses. **Method:** Basal and dynamic hormonal assessment as well as genetic tests have been performed in all subjects. **Results:** The two sisters were admitted at the age of 2 and 6 years respectively, their cousin at the age of 10 years. Their

karyotype was 46,XY. They were suspected to be affected by androgen insensitivity and thus they underwent gonadectomy. Molecular analysis of androgen receptor gene did not reveal any mutation. A low T/A ratio (<0.8) in one of the patient raised the suspicion of 17 β HSD 3 deficiency. Molecular analysis of the HSD17B3 gene (which encodes for the 17 β HSD 3 enzyme) revealed a compound heterozygous mutation in all three girls. The two sisters inherited a novel mutation IVS3+1 G<T from the mother and the rare mutation IVS3-1 G<C from their father. Their cousin inherited the RW80 mutation from the father and IVS3-1 G<C from the mother. **Conclusion:** Our cases suggest that 17 β HSD 3 deficiency should be considered in 46,XY DSD cases with female appearance of external genitalia. Moreover, we reported a novel mutation of 17 β HSD 3, causing 46,XY DSD in two out of three related subjects.

P3-D2-970

A Familial Case of Complete Androgen Insensitivity Syndrome

Evelina Maines^a, Claudia Piona^a, Grazia Morandi^a, Fulvia Baldinotti^b, Franco Antoniazzi^a, Rossella Gaudino^a

^aDepartment of Life and Reproduction Sciences, Pediatric Clinic, University of Verona, Verona, Italy; ^bLaboratory of Cytogenetics and Molecular Genetics, University of Pisa, Pisa, Italy

Background: Complete androgen insensitivity syndrome (CAIS) is a condition that results in the complete inability of the cell to respond to androgens and falls within the category of 46,XY disorder of sex development (DSD). CAIS is characterized by female external genitalia in a 46,XY karyotype individual with normal testis development but undescended testes and unresponsiveness to age-appropriate level of androgens. The typical presentation is primary amenorrhea in an adolescent female, but CAIS can also present in infancy with an inguinal hernia or labial swelling containing a testis. CAIS is inherited in an X-linked recessive pattern and the diagnosis can be confirmed by androgen receptor (AR) gene sequencing. About two-thirds of all cases of CAIS are inherited from mothers; the remaining cases result from *de novo* mutations. **Case report:** We report the case of a 12-year-old girl, who we diagnosed as affected by CAIS when she was 1 year old, because of bilateral inguinal hernia containing testis, complete female phenotype and XY karyotype. Her parents chose early bilateral gonadectomy because of the fear of cancer risk, when she was 2 years old. At 12-year-old, on physical examination, the patient was a complete female girl without signs of puberty (Tanner 1 breasts and Tanner 1 pubic hair). She began hormonal replacement therapy (HRT) with estradiol transdermal patch, to induce development of secondary sex characteristics. Molecular analysis of AR gene revealed a nucleotide deletion in exon 1 (c.1112delT) leading to a premature stop codon after 108 amino acids (p.Leu371Argfs*108). This new mutation was not yet reported in the Androgen Receptor Gene Mutations Database and is predicted to produce a shorter AR (protein). AR gene

analysis revealed that her mother and her sister (karyotype 46,XX) are carriers of the same mutation. An in-depth medical family history allowed us to identify three sisters of the mother, all married but childless. Genetic counseling was performed. All the three sisters of the mother have 46,XY karyotype. **Conclusion:** Our case confirms that CAIS affected families should be offered genetic counseling in order to be informed of the risk of recurrence and to identify other potential carriers or affected relatives in the family.

P3-D2-971

A Case of 46,Y,dup(x)(p21.2p22.2) DSD Caused by Overexpressed DAX1

Sasaki Takako^a, Izumi Youko^b, Fukami Maki^b, Yatsuga Shuichi^a, Koga Yasutoshi^a

^aDepartment of Pediatrics and Child Health, Kurume University School of Medicine, Kurume, Fukuoka, Japan; ^bDepartment of Molecular Endocrinology, National Research Institute for Child Health and Development, Setagaya, Tokyo, Japan

Introduction: DAX1 (dosage-sensitive sex reversal, adrenal hypoplasia critical region, on chromosome X, gene 1) plays an important role in developing the adrenal gland and testis during embryonic stage. On the other hand, overexpressed DAX1 causes 46,XY disorders of sex development (DSD), in which patients often have short stature, mental retardation, and telecanthus. Here we report a case of 46,Y,dup(X)(p21.2p22.2) DSD caused by overexpressed DAX1. **Case report:** Patient was a 3-year-old girl, referred to our hospital for short stature (-2.2 s.d.). Physical examination was as follows; complete female genitalia, low set ears, telecanthus, and cleft palate. Motor and mental development was severely delayed. Chromosome was 46,Y,add(X)(p22.1) and sex-determining region Y (SRY) gene was positive. Diagnosis of DSD was made, and endocrine tests were performed. Serum cortisol level was 7.80 μ g/dl (reference range: 5–23), ACTH level was 31.0 pg/ml (reference range: 25–100), 17-OH-progesterone level was 0.33 ng/ml (reference range: 0.3–8.2), LH level was 0.26 mIU/ml (reference range: 0.02–0.3), FSH was 13.26 mIU/ml (reference range: <3.0), serum estradiol level was 19 pg/ml (reference range: 5–11), testosterone level was <0.03 ng/ml (reference range: <0.1), TSH level was 11.8 μ IU/ml (reference range: 0.7–6.4), and free T₄ level was 1.15 ng/dl (reference range: 0.8–2.2). In hCG stimulating test, testosterone level did not increase. In TSH stimulating test, TSH level was 315 μ U/ml at 30 min, indicating that she had subclinical hypothyroidism. Pelvic MRI did not show ovary, testis, and uterus. Array CGH was performed (Agilent Technology, USA), and duplication was located from p21.1 to p22.2 on X chromosome including DAX1 region. No duplication or deletion existed in any other chromosomes. **Conclusion:** This is the first report of overexpressed DAX1 with subclinical hypothyroidism. Although thyroid dysfunction may be coincidental, TSH stimulating test is recommended in such patients in the future.

P3-D2-972

Disorders of Sexual Differentiation Observed in Endocrinology

Ali el Mahdi Haddam^a, Soumeiya Fedala^b, Djamila Meskine^a, Farida Chentli^b, Leylaahmed Ali^b, Naziha Fedala^b

^aBologhine Hospital, Algiers, Algeria; ^bBab El Oued Hospital, Algiers, Algeria

Background: Disorders of sexual differentiation (DSD) at birth is a serious defect often seen in endocrinology. Diagnosis must be early to ask an etiologic diagnosis, choose the sex of rearing and effectively treat the disease. **Objective and hypotheses:** Search etiologies of sexual ambiguities and clarify the phenotypic characteristics. **Method:** This is a retrospective study of 180 sexual ambiguities hospitalized. All patients underwent a clinical examination, radiological, cytogenetic exploration, and hormonal investigation guided by the clinical presentation. **Results:** There was a predominance of DSD for girls (126 vs 54). The mean age of patients at diagnosis is 8 years (3 months–19 years old). The ambiguity was observed at birth in 68% of XX TDS cases and 24% TDS XY ambiguity was observed at birth in 68.1%. Nonetheless children have been oriented endocrinology since the first year of life in 37.5% of cases. Parental consanguinity was found in 45% of cases with a family form in 10% congenital adrenal hyperplasia. Phenotypically sexual ambiguity in DSD, XY was at stage 3, 66.6 and 4: 25% (Quigly), whereas in stage 3, 30% and stage 4, 40% for DSD, XX (Prader) Exploration etiological found: TDS XY: gonadal dysgenesis (25%), an enzyme block (16.6%), an androgen resistance (16.6%), an syndrome polymalformative. No recognized etiology (41.6%). TDS XX: HCS: 88%; Turner syndrome with material Y (12%). **Conclusion:** DSD cover a broad spectrum of clinical pictures. Their causes are varied and affect all stages of sex determination. They require taking rational and rapid charge within a multidisciplinary team.

P3-D2-973

Incidents of Sex Differentiation Disorder: 46,XY

Shakhrizada Sultanova^a, Rano Yakupova^b

^aThe Centre of Scientific and Clinical Study of Endocrinology in Republic of Uzbekistan, Tashkent, Uzbekistan; ^bThe Centre of Scientific and Clinical Study of Endocrinology in Republic of Uzbekistan, Tashkent, Uzbekistan

Background: Disorder in forming the sex is a condition associated with the clinical and biochemical manifestation of the discrepancy between genetic, gonadal and phenotypic sex of a child. **Clinical case:** A girl of 15 years old with complaints about the menses lack. **History of the case:** Parents are closely related marriage. They are first cousins. There are three children in the family, two of them being healthy. At 13 years of age, the operation

took place on the occasion of herniotomy (possibly testicle was removed). From the words of mother and girl; she gives preference to male games, clothes and communication with adolescent boys. **Objectively:** The body build is male type. Milk glands are absent. Labia are like scrotum type, clitoris is like a penis (3 sm.). On the left there is a palpable formation resembling V testis = 8 ml - Tanner II. **Results:** Karyotype – 46,XU. Estradiol – 139.7 pg/ml (norm of a male – 15–71, that of female – 57–277). Free testosterone – 3.1 pg/ml (norm 8.69–21.71). Testosterone – 3.5 nmol/l (norm is 10.4–41.6). Sex thyroid connecting globulin SSG – 30.8 nmol/l FSH 5.1 IU/l (norm of a male is 1.3–11.5; that of a female 2.6–15.0 – pre-ovulatory phase. LH 4.3 IU/l (norm of a male is 1.8–10.0). According to the data of ultrasonography of organs of contracted pelvis – uterus, cervix of uterus, epididymises are not seen. Parents (knowing about the genetic male sex) and the girl insisted on changing the passport sex to male one. **Conclusions:** The experience of such rare observations is necessary because further stages of examination and treatment is based on the genetic sex of the child. However, taking into account their late seeing a doctor, removal of the testicles is recommended to the patient, to avoid malignization at the puberty period and parents continue to bring up the child as a female.

P3-D1-974

Increasing Incidence of Congenital Hypothyroidism in Neonatal Screening Program in Central Serbia: 30 Years of Experience

Tatjana Milenkovic, Branka Opancina, Katarina Mitrovic, Sladjana Todorovic, Rade Vukovic

Institute of Mother and Child Health Care Institute of Serbia, Belgrade, Serbia

Background: Neonatal TSH screening program for congenital hypothyroidism (CH) in Central Serbia was introduced in 1983. Over the past three decades, increasing overall incidence rate of children with both permanent and transient forms of CH has been observed. **Objective and hypotheses:** The aim of the study was to compare incidence of CH in the first 16 years of screening (period 1) with the last 15 years of screening (period 2). We also investigated the impact of the TSH cutoff change on incidence of CH. **Method:** From 1983 to 1998 TSH cutoff measured by IFMA was 15 mU/l. From 1999, TSH was measured by DELFIA: from 1999 to 2006 cutoff was 10 mU/l and from 2007 was 9 mU/l. Overall incidences were calculated, and period 1 and period 2 were compared. **Results:** In the period 1, a total number of 131 newborns with CH have been detected resulting in incidence of 1:5655. During this period, frequency of transient CH was 0.8%. In the period 2, CH was detected in 285 newborns (incidence 1:2829) with frequency of transient forms of 8.0%. This increase in number of transient CH in period 2 compared to period 1 was statistically highly significant ($P < 0.01$). **Conclusion:** The results of our study revealed significant increase in incidence of both permanent and transient forms of CH related to lower cutoff. Further investigations are needed to reveal other contributory factors important for increasing incidence of CH in Serbia.

P3-D1-975

Prevalence of Additional Autoimmune Diseases in Autoimmune's Thyroiditis Children and Their First- and Second-Degree Relatives: Results from a Large, Single-Center Study

Lucia De Martino, Iolanda Di Donato, Sara Alfano, Ida D'Acunzo, Rosita Di Pinto, Donatella Capalbo, Mariacarolina Salerno

Department of Translational Medical Sciences, University of Naples 'Federico II', Napoli, Campania, Italy

Background: Autoimmune's thyroiditis (AT) is the most common cause of thyroid diseases in children and adolescents with a peak in early to mid-puberty (prevalence of 0.3–1.2%). Previous studies showed a high rates of familiarity for autoimmune disease (AD) and co-existing autoimmunity in AT subjects. **Objective and hypotheses:** Aim of our study is to investigate familiarity for AD and co-existing autoimmunity in a large cohort of pediatric AT patients. **Method:** A cohort of 91 pediatric patients with AT from a single center was retrospective evaluated for the age at onset of AT, presence of additional autoimmune diseases at diagnosis or during the follow-up and history of autoimmunity within first and second degrees' line. **Results:** Mean age at diagnosis of AT was 9.74 ± 2.65 . Presence of additional AD occurred in 21 of the 91 AT patients (23.1%). The most common AD in our subjects were psoriasis (PS) (28.6%) and rheumatoid arthritis (RA) (28.6%), followed by mucocutaneous candidiasis (MC) (23.8%), vitiligo (VT) (14.3%), celiac disease (CD) (9.5%), autoimmune hepatitis (AH) (4.8%). Forty-nine patients (53.8%) had first- and/or second-degree relatives affected with AD, in particular 26/49 children (53%) had a familial history of AT, 16 (32.6%) of PS, eight (16.3%) of RA, six (12.2%) of VT, five (10.2%) of alopecia areata, four (8.2%) of Graves disease, four (8.2%) of AH, three (6.1%) of MC, three (6.1%) of CD and two (4.1%) of onicodystrophy (OD). The latter is not an AD but is frequently associated with autoimmunity. **Conclusion:** Our study documented a high rate of additional AD in children with AT and an increased prevalence of AD in first- and second-degree relatives. Therefore, an accurate follow-up for a prompt diagnosis of any additional AD is recommended in children with AT. Moreover, screening of autoimmunity in relatives should also be suggested.

P3-D1-976

Adiposity and Pubertal Status Effects on Thyroid Function in Overweight Children and Adolescents

Aristeidis Giannakopoulos, Panagiota Pervanidou, Natalia Lazopoulou, George Chrousos, Christina Kanaka-Gantenbein

Obesity Clinic, Division of Endocrinology, Diabetes and Metabolism, First Department of Pediatrics, Agia Sophia Children's Hospital, University of Athens Medical School, Athens, Greece

Background: In recent years, studies have consistently demonstrated higher TSH concentrations in overweight/obese

children and adults compared with normal weight individuals, whereas the levels of thyroid hormones in peripheral blood remain within normal range. This euthyroid hyperthyrotropinemia on the background of a worldwide increase in childhood obesity raises the question of whether subjects with this elevated TSH should be treated. **Objective and hypotheses:** In this study, we compared a group of overweight/obese children and adolescents to a normal weight age-matched group in order to characterize the thyroid function in correlation with BMI and pubertal status in both males and females. **Method:** The study groups included 389 overweight/obese children (BMI z-score > 2) and 158 healthy normal-weight children, who served as controls. Mean BMI z-score in pre-pubertal and pubertal subgroups of the overweight/obese children was not significantly different. TSH, T₄ and T₃ were assessed. **Results:** Mean serum TSH value of overweight/obese group was higher ($2.95 \text{ mU/l} \pm 1.2$) compared to that ($2.42 \text{ mU/l} \pm 1.43$) of normal weight group ($P < 0.0001$). In females of both overweight and control groups, serum TSH, T₄ and T₃ concentrations were all lower during puberty compared to the pre-pubertal period. On the contrary, males showed no statistically significant variation in TSH and peripheral thyroid hormone concentrations after initiation of puberty in both overweight and control groups. In overweight/obese pre-pubertal girls and boys, a statistically significant correlation between TSH and BMI was found (coefficients $r = 0.32$, $P = 0.012$ and $r = 0.47$, $P < 0.001$ respectively). This correlation between TSH and BMI was not sustained after initiation of puberty. **Conclusion:** Our results confirm the TSH elevation observed in overweight/obese children and furthermore, imply that puberty has an impact on thyroid axis function and may negatively affect the relation between TSH and BMI in overweight/obese children.

P3-D1-977

Neonatal Thyrotoxicosis in Maternal Grave's Disease: a Case Series and Review of the Literature

Niall Johnston, Meenal Mavinjurve, Nuala Murphy, Ciara McDonnell, Sinead Moloney, Declan Cody, Colm Costigan

Temple Street Childrens University Hospital, Dublin, Ireland

Background: Neonatal thyrotoxicosis, a rare and life-threatening condition, is caused by transplacental transfer of thyroid stimulating immunoglobulins from mother to infant. While clinical features may include goitre, prominent eyes and poor weight gain, these may be absent in some cases. Early diagnosis and treatment of affected infants is critical. **Objective:** We report a case series of infants with neonatal thyrotoxicosis from two tertiary paediatric hospitals. **Methods:** Case notes of four infants with neonatal thyrotoxicosis were reviewed. Details of maternal thyroid disease, perinatal course, clinical features, diagnostic tests and management of infants were recorded. **Results:** All infants were born to mothers with known Graves' disease. Three of four mothers had positive thyroid receptor antibodies during the third trimester of pregnancy. In two of four cases, isolated tachycardia was the only clinical finding. Mean age at diagnosis was 6 days (range 2–10 days). Three infants were treated with carbimazole alone and one infant receive a

combination of carbimazole, iodine and propranolol. Mean duration of therapy was 11 weeks (range 6–24 weeks). One infant became biochemically hypothyroid during treatment and required thyroxine replacement. All infants were thriving, developmentally normal and euthyroid at follow-up. **Conclusion:** This case series illustrates the importance of antenatal risk assessment, early recognition, prompt treatment and close follow-up of infants with neonatal thyrotoxicosis. Maternal thyroid receptor antibodies should be measured in the third trimester. Isolated tachycardia may be the only clinical feature. In infants taking anti-thyroid medications, weekly thyroid function testing and dose titration is important to avoid late-onset hypothyroidism.

P3-D1-978

Treatment the Resistance to Thyroid Hormones in Girl

Elzbieta Budzynska^a, Iwona Ben-Skowronek^a, Elzbieta Korobowicz^b, Maria Klatka^a

^aMedical University Dept. Paediatric Endocrinology and Diabetology, Lublin, Poland; ^bMedical University Dept. Pathomorphology, Lublin, Poland

Background: The cardinal feature of the resistance to thyroid hormone (RTH) is reduced responsiveness of target tissues to thyroid hormone action caused by thyroid hormone receptor β gene (*THRB*) mutations impairing hormone binding in the majority (90%) of cases. It results in elevated serum levels of free thyroxine (FT₄) and triiodothyronine (FT₃) associated with unsuppressed thyroid SH. **Objective and hypotheses:** The aim of the study is presentation of rare syndrome resistance to hormones. **Results:** A 11-year old female with Marfan-like phenotype was referred with clinical suspicion of hyperthyroidism. She appeared hyperkinetic, complained of palpitation persisted on beta adrenergic blocking agent, which was administered by her cardiologist. The current examination revealed a goiter, exophthalmos and tachycardia. The elevated serum levels of FT₄ and FT₃ coexisted with unsuppressed TSH. Well responsive TRH test excluded TSH secreting adenoma. A magnetic resonance imaging (MRI) study of the pituitary did not reveal any pathologic mass. In the presence of thyrotoxic signs her treatment with thiamazole was initiated before the final diagnosis of RTH. During the treatment the patient's clinical state significantly improved, while the goiter was increasing in size. The final estimated gland volume based on ultrasonography was 40 ml. Ultrasonography revealed the hypoechoic foci up to 8 mm in diameter. The thyroid scintigraphy with Tc-99m showed excessive uptake with the total suppression of the background activity. The thyroid foci was biopsy-verified (FNAB), and classified in second category by the Bethesda System. Now patient was ordered bromocriptine with cardioselective beta-blocker. **Conclusion:** The presented patient develops nodular goiter, which is the background to the thyroid cancer under the condition chronic overstimulation by TSH. The elevated cardiovascular risk in RTH, connected to the high levels of FT₃ and its influence on isoform THR alpha predominated in the heart. i) Primary and secondary hypothyroidism is more prevalent in patients who have received oncologic treatment than in healthy

individuals. ii) The cytostatics, especially anthracycline and XRT have an effect on the development of primary hypothyroidism. iii) BMT in children has significant effect of development of hypothyroidism in course of AITD. iv) Cytostatic treatment and XRT contribute to development of potentially neoplastic thyroid nodules.

P3-D1-979

Free T₃/free T₄ Ratios in Children with Hypothyroidism Treated with Levothyroxine Monotherapy

Tsutomu Takahashi, Yuki Konno, Ikuko Takahashi

Akita University Graduate School of Medicine, Akita-shi, Japan

Background: Levothyroxine monotherapy is the treatment of choice for congenital hypothyroidism (CH). Recently, it was reported that levothyroxine monotherapy cannot guarantee euthyroidism in all athyreotic adult patients. A more physiological treatment than levothyroxine monotherapy was suggested to be required in some patients with hypothyroidism. **Objective and hypotheses:** To elucidate whether levothyroxine monotherapy is appropriate for all children with hypothyroidism. Levothyroxine monotherapy may not sustain physiological condition of thyroid hormones in some children with hypothyroidism. **Method:** Serum thyroid hormones, free T₃ (pg/ml), free T₄ (pmol/l), TSH (mU/l), and free T₃:free T₄ ratio (pg/ml per pmol/l), were determined in a control group ($n=54$), a severe CH group ($n=5$), a mild CH group ($n=18$), and a pan-hypopituitarism (PHP) group ($n=4$). Free T₃:free T₄ ratios were also analysed with dosages of levothyroxine. A control group was hormonally examined only once, but each of the patients with hypothyroidism was frequently examined. **Results:** Serum thyroid hormones were determined as; i) control: fT₃ 3.51 ± 0.51 , fT₄ 1.29 ± 0.20 , TSH 2.31 ± 0.98 , fT₃/fT₄ 2.78 ± 0.56 , ii) severe CH: fT₃ 3.78 ± 0.60 , fT₄ 1.64 ± 0.32 , TSH 2.52 ± 2.02 , fT₃:fT₄ 2.35 ± 0.46 , iii) mild CH: fT₃ 3.48 ± 0.42 , fT₄ 1.69 ± 0.26 , TSH 2.45 ± 1.69 , fT₃/fT₄ 2.11 ± 0.38 , iv) PHP: fT₃ 2.56 ± 0.68 , fT₄ 0.95 ± 0.24 , TSH 0.03 ± 0.05 , fT₃/fT₄ 2.86 ± 1.06 . Free T₄ levels of two CH groups were significantly higher than those of a control group. Free T₃:free T₄ ratios of two CH groups were significantly lower than that of a control group. Free T₃:free T₄ ratios of two CH groups were negatively correlated with dosages of levothyroxine. **Conclusion:** This study suggested that levothyroxine monotherapy might maintain different conditions of peripheral thyroid hormones from physiological state in CH patients.

P3-D1-980

Diagnostic challenges of thyroid dysfunction in eating disorders

Priyha Santhanam, Louise Denvir, Pooja Sachdev, Tabitha Randell

Queen's Medical centre, Nottingham University Hospitals NHS trust, Nottingham, UK

Background: Anorexia nervosa is usually associated with lower levels of thyroid hormones especially suppressed TSH and T₃ with normal T₄ levels due to the effects of starvation on metabolism. We present two cases where the underlying eating disorder masked the thyroid dysfunction. **Patient 1:** 15-year-old girl with anorexia nervosa and BMI of 15.6 was noted to have suppressed TSH < 0.1 mU/l, high normal T₃–7.0 pmol/l and normal T₄–17.4 pmol/l suggesting subclinical hyperthyroidism within one month after starting on re-feeding regimen. On examination she had right thyroid nodule. Thyroid peroxidase antibodies were mildly raised at 72.6. Radio-Isotope scan showed good uptake in the right lobe with no uptake in the left lobe. Ultrasound thyroid showed multinodular goitre. She was started on carbimazole. Three months after her initial presentation her thyroid function had normalised with normal thyroid antibody level. Hence carbimazole was stopped and subsequent thyroid function tests have been normal. Hence, the thyroid dysfunction was attributed to her eating disorder. She presented after 2 years with biochemical evidence of hyperthyroidism following relapse of her eating disorder and was restarted on carbimazole. **Patient 2:** 16-year-old girl with anorexia nervosa and BMI-15 was noted to have biochemical evidence of autoimmune hypothyroidism on presentation. Her TSH was raised at 44 mU/l, with markedly suppressed T₄–4.9 pmol/ and T₃–2.7 pmol/l. Her thyroid function tests had normalised after starting on thyroxine. **Conclusion:** Anorexia nervosa may mask thyroid dysfunction making it difficult to interpret the thyroid function tests.

P3-D1-981

Kocher–Debré–Semelaigne Syndrome with Rhabdomyolysis and Increased Creatinine: a Case Report

Emine Ayca Cimbeç, Yasar Sen, Sevil Ari Yuca, Demet Kivanc, Celal Gur, Harun Peru

Selçuk University Medical School, Konya, Turkey

Background: Hypothyroidism is frequently associated with muscular disorders and sometimes with moderately elevated levels of muscle enzymes. On the other hand, neuromuscular manifestations are rarely the only symptoms/signs present. Kocher–Debré–Semelaigne syndrome is a myopathy of hypothyroidism in childhood characterized by muscular hypertrophy. Rhabdomyolysis due to hypothyroidism is very rare. A very high creatinine kinase level in the range seen with inflammatory myopathy is a rare finding also. **Objective and hypotheses:** We present a case of Kocher–Debré–Semelaigne syndrome with rhabdomyolysis secondary to Hashimoto's thyroiditis. **Method:** A 15-year-old boy was admitted to our clinic complaining of lethargy, dry coarse skin, swelling of hands and feet, and muscular symptoms simulating poly/dermatomyositis. His calf muscles were hypertrophied with minimal proximal muscle weakness in the lower limbs. He had massively elevated creatine kinase levels and high creatinine levels. Hypothyroidism was suspected and confirmed with thyroid function tests. **Results:** The patient was treated with

intravenous fluids and was commenced on thyroxine replacement therapy. All clinical and laboratory findings reversed on treatment of hypothyroidism. The response to the therapy strongly suggested that Kocher–Debré–Semelaigne syndrome was the underlying etiology. **Conclusion:** Serum TSH levels should be routinely determined in all patients with muscular symptoms and/or elevation of creatine kinase and creatinine, keeping Kocher–Debré–Semelaigne syndrome in mind.

P3-D1-982

Preliminary Result and Normative TSH Values for Healthy Nigerian Newborn Children

Iroko Yarhere^a, Abiola Oduwale^b, Salma Suwaid^c, Alkali Yahaya^d, Maryanne Ibekwe^e, Kayode Adeniran^f, Bolanle Fetuga^g, Jerome Elusiyan^h, Hafsat W Idrisⁱ, Tamunopriye Jaja^j, Omotayo Adesiyun^k, O O Jarrett^l

^aUniversity of Port Harcourt Teaching Hospital, Port Harcourt, Nigeria; ^bLagos University Teaching Hospital, Lagos, Nigeria; ^cAminu Kano Teaching Hospital, Kano, Nigeria; ^dFederal Medical Center, Gombe, Nigeria; ^eUniversity of Nigeria Teaching Hospital, Enugu, Nigeria; ^fFederal Medical Center, Asaba, Nigeria; ^gOlabisi Onabanjo University Teaching Hospital, Sagamu, Nigeria; ^hObafemi Awolowo University Teaching Hospital, Ile-Ife, Nigeria; ⁱAhmadu Bello University Teaching Hospital, Zaria, Nigeria; ^jUniversity of Port Harcourt Teaching Hospital, Port Harcourt, Nigeria; ^kUniversity of Ilorin Teaching Hospital, Ilorin, Nigeria; ^lUniversity College Hospital, Ibadan, Nigeria

Background: Congenital hypothyroidism (CH) is the commonest congenital endocrine disorder in the world and also the commonest most preventable cause of mental retardation. Screening is mandatory in developed countries, but none exists in sub-Saharan country. We present a preliminary report of the first Nigerian screening for CH. **Objective and hypotheses:** To screen normal newborn babies in different regions in Nigeria and to determine the normal range of TSH in Nigerian babies. **Method:** A cross-sectional study was carried out between January 1, 2013 and December 31, 2013 in six different tertiary hospitals in Nigeria. Cord and heel prick blood were dropped in four circles on a Whartman filter paper. Samples were transferred to Charité Universitätmedizin Berlin, Germany via courier in batches within 1 week of collection and were analysed for TSH using 1235AutoDelfia Perkin/Elmer immunoassay machine. Normal TSH level was set between 0.3 and 5.5 µIU/ml and levels > 50 µIU/ml were considered positive for CH. SPSS 20 was used to analyse mean TSH (\pm s.d.) for sex, birth weights, socioeconomic class, and birth city. Pearson's correlation was used to determine association between TSH and birth weight, SEC, and birth city. P value < 0.05 was considered significant. **Results:** A total of 214 subjects were recruited during the study period. Female:male ratio was 1.07:1. The mean TSH was 1.86 µIU/ml (s.d. 2.25). 1543 (76.6%) of subjects had TSH levels within normal range with regards to international reference values. Twenty-two (1.1%)

subjects had elevated TSH values but none had CH. There was no significant difference between sex ($P=0.309$) or birth weight ($P=0.316$). **Conclusion:** The mean TSH level of our subjects is similar to those obtained in the countries doing newborn screening. Though no CH was picked, we advocate immediate mandatory newborn screening for all newborns in Nigeria.

P3-D1-983

Resistance to Thyroid Hormone Syndrome from Childhood to Adulthood: Variation in Symptoms and Thyroid Function

Aoife Garrahy^a, Mariana Grace^b, Mary Stapleton^c, Carla Moran^d, Krishna Chatterjee^d, Matthew Murphy^a, Susan O'Connell^e

^aDepartment of Endocrinology and Diabetes, South Infirmity Victoria University Hospital, Cork, Ireland; ^bDepartment of Paediatrics and Child Health, University College Cork, Cork, Ireland; ^cDepartment of Clinical Biochemistry, Cork University Hospital, Cork, Ireland; ^dInstitute of Metabolic Science, University of Cambridge, Cambridge, UK; ^eDepartment of Paediatrics and Child Health, Cork University Hospital, Cork, Ireland

Introduction: Resistance to thyroid hormone (RTH) is a rare autosomal dominant condition characterised by tissue-specific insensitivity to thyroid hormone. In 85% of cases the disorder is associated with thyroid hormone receptor β (TR β) gene mutations. **Case report:** A 2.6-year-old boy was referred to the Paediatric service with abnormal thyroid function tests (TFTs) (fT₄ 30.4 pmol/l; RR 12–26, fT₃ 10.2 pmol/l; RR 3.7–8.5, TSH 2.34 μ IU/l; RR 0.73–8.4) and is currently being assessed for behavioural problems. Review of family history revealed the index case's mother had undergone thyroidectomy. He and two of his three older brothers have subsequently been diagnosed with RTH based on TFTs and genetic testing has confirmed a mutation in the TR β gene. They have learning problems but are growing normally. The mother was diagnosed with RTH at age 3 (I431T mutation), with abnormal TFTs (fT₄ 29.7 pmol/L; RR 7.7–21, TSH 1.8 μ IU/L; RR 0.6–4.3) and goitre. She was clinically hyperthyroid with tachycardia, diarrhoea and poor concentration. Symptoms improved following beta-blocker and 3,3,5-tri-iodothyroacetic acid treatment. She achieved a final height on the 75 centile, and weight below the 10. Symptoms of hyperthyroidism off treatment abated in her late teens and she was then lost to follow-up. She was re-referred age 28 years with a thyroid nodule and underwent surgery which showed a 22 mm papillary thyroid cancer, follicular variant (pT2(m)). **Conclusions:** This family describes the spectrum of RTH presenting across two generations. Clinical features result from tissue-specific resistance to thyroid hormone, with effects on learning and behaviour in childhood, and apparent spontaneous improvement in hyperthyroid symptoms and thyroid function beyond the second decade. In the mother's case, the condition was complicated by development of papillary thyroid cancer, with congruence of the latter with RTH being extremely rare.

P3-D1-984

Thyroid Disorders After Oncologic Treatment in Children

Iwona Ben-Skowronek^b, Elzbieta Sadurska^a, Agnieszka Prazmo-Zauchac, Robert Piekarski^b, Jerzy Kowalczyk^c

^aMedical University, Department of Paediatric Cardiology, Lublin, Poland; ^bMedical University, Department of Paediatric Endocrinology and Diabetology, Lublin, Poland; ^cMedical University, Department of Paediatric Oncology-Hematology, Lublin, Poland

Background: The length of patient survival after cancer treatment is increasing and in some cases does not differ from the average life span in healthy individuals. **Objective and hypotheses:** The aim of the study is evaluation of thyroid function after oncologic treatment in children. **Method:** A group of 158 patients aged 16–25 who underwent oncologic treatment in childhood and the control group — 66 children and young adults were examined. The prospective study was conducted in the period between 4 and 19 years after the diagnosis. After physical examination, were assayed the levels of TSH, fT₄, and fT₃ (Abbott). TPO Ab and Tg Ab (DAKO, Denmark); in patients with hyperthyroidism the TSI Ab (BRAHMS Germany). The ultrasound of the thyroid gland was done using a Siemens-2000 device. **Results:** The prevalence of hypothyroidism in the group of patients was statistically significantly higher than in the control group (27.2% vs 6.1%. $P=0.001$). The occurrence of primary hypothyroidism was correlated with the total anthracycline dose and with the total X-irradiation (XRT) dose. The incidence of autoimmune thyroid diseases was statistically significantly higher in children after BMT. There was a statistically significantly higher prevalence of thyroid nodules in children undergone oncologic treatment. The nodules developed more frequently after XRT anticancer therapy and their prevalence was correlated with the total XRT dose. **Conclusion:** i) Primary and secondary hypothyroidism is more prevalent in patients who have received oncologic treatment than in healthy individuals. ii) The cytostatics, especially anthracycline and XRT have an effect on the development of primary hypothyroidism. iii) BMT in children has significant effect of development of hypothyroidism in course of AITD. iv) Cytostatic treatment and XRT contribute to development of potentially neoplastic thyroid nodules.

P3-D1-985

Trends in Incidence of Permanent and Transient Congenital Hypothyroidism in Shanghai China

Xin Fan^{a,b}, Xuefan Gu^a, Jingsi Luo^b, Wenjuan Qiu^a, Jun Ye^a, Shaoke Chen^b, Jianfeng Xu^c

^aXinhua Hospital, Shanghai Jiaotong University School of Medicine, Shanghai Institute for Pediatric Research, Shanghai, China;

^bMaternal and Child Health Hospital of Guangxi Zhuang Autonomous Region, Nanning/Guangxi, China; ^cSchool of Public Health, Fudan University, Shanghai, China

Background: Congenital hypothyroidism (CH) is a major target of new born screening. It has two major forms (permanent and transient) that have different prognoses. **Objective and hypotheses:** The purposes of this study were to assess the trends in incidence of permanent and transient CH in China, and to identify clinical variables that may help to distinguish these two forms of CH. **Method:** Newborns were screened for CH at Xinhua Hospital of Shanghai Jiaotong University, Shanghai, China, from December 1983 to December 2012. Newborns diagnosed with CH were treated and followed. **Results:** Among 1 187 906 newborns screened, 417 were diagnosed with CH. The overall incidence of CH was 1:2 849 newborns. The incidence more than doubled during the 30-year study period, $P_{\text{trend}} = 5.8 \times 10^{-10}$. The increasing incidence was observed for transient CH ($P_{\text{trend}} = 0.006$) but not for permanent CH ($P_{\text{trend}} = 0.64$). The ratio of transient to permanent CH was 0.52 overall and increased significantly during the study period ($P_{\text{trend}} = 0.01$); from 0.21 prior to 1997 to 0.71 between 2008 and 2012. Compared to transient CH patients, permanent CH patients with normal thyroids had a significantly lower birth weight (3.4 vs 3.2 kg) and higher thyrotrophic (TSH) levels at the time of screening (29.4 vs 41.6 $\mu\text{IU/ml}$). The AUC for discriminating these two types of CH was 0.63, and 0.64 for birth weight and TSH levels at the time of screening, respectively. **Conclusion:** The incidence of CH increased in Shanghai, China, during the last three decades, and was attributable to the increase of transient CH.

P3-D1-986

Klippel-Feil Syndrome and Thyroiditis: a Case Report

Elisa Guidoni, Renato Scarinci, Giovanna Municchi

University of Siena, Siena, Italy

Background: Klippel-Feil syndrome (KFS) is characterized by congenital fusion of cervical vertebrae and has a prevalence of 1:50 000. The phenotypic expression is variable, sometimes presenting with extraskeletal symptoms. **Case report:** A girl was referred at the chronological age (CA) of 10.3 years with a suspected diagnosis of Turner syndrome, due to the presence of webbed neck and progressive deceleration of growth velocity. The girl, born in Russia, was adopted by an Italian family at the CA of 14 months. Clinical examination showed short neck, bilateral thelarche Tanner stage II, pubarche Tanner stage II, hyperlordosis and valgus elbow. The height was 134 cm (10° – 25° ct), weight 28 kg (10° ct) and head circumference 55 cm. Pelvic ultrasound showed the presence of normal uterus and ovaries. Due to the presence of pubertal development and normal uterus and ovaries, karyotype was not performed. Surprisingly, investigations showed markedly elevated TSH values ($>75 \mu\text{U/ml}$, range 0.4–4.0) and low values of FT_3 (2.5 pg/ml, range 2.5–3.9) and FT_4 (4.1 pg/ml, range 5.8–16.4). Serum antitreoglobulin and antiperoxidase antibodies were both elevated: ATG $>3000 \text{ U/ml}$ (range <45), ATPO 298 U/ml (range <35). Thyroid ultrasound showed increased thyroid size

with markedly heterogeneous echogenicity, hypervascularization and slightly thickened isthmus. The patient was started on thyroid replacement therapy (Eutirox). Due to the presence of short neck, cervical X-ray was also performed: the images showed fusion of the cervical vertebrae C2 and C3, confirming the suspect of a Klippel-Feil syndrome. **Conclusion:** To our knowledge, association of KFS with Hashimoto's thyroiditis has not been reported in the literature. We believe that the coexistence of thyroiditis and KFS in our patient represents a random association, since there are no data to support the hypothesis of an increased incidence of autoimmune disorders in these patients.

P3-D2-987

The Association of Thyroid Dysfunction and Blood Pressure in Korean Children

Hae Soon Kim^a, Hye Sook Park^b, Sujin Cho^a, Sun Jung Baik^b, Bo Hyun Park^b, Hye Ah Lee^b

^aDepartment of Pediatrics, School of Medicine, Ewha Womans University, Seoul, Republic of Korea; ^bDepartment of Preventive Medicine, School of Medicine, Ewha Womans University, Seoul, Republic of Korea

Background: Hypertension is the leading cause of cardiovascular disease worldwide and both high and low blood pressures are associated with various chronic disease. Thyroid hormones have profound effects on cardiovascular function, including effects on blood pressure. **Objective and hypotheses:** Recent studies suggest that early life high blood pressure could be attributed to hypertension in late adulthood. Therefore, we aimed to investigate the association between thyroid hormones and blood pressure in children. **Method:** In the birth cohort at Ewha Womans University Hospital, 181 children are participated in the subsequent 7–9 year check-up program. We compared the level of serum TSH and blood pressure status in children aged 7–9 years. Serum TSH levels were measured with the electro-chemiluminescence immunoassay (ECLIA). Hypertension was defined according to the Korea centers for disease control and prevention guideline of hypertension. **Results:** In this study, the means of serum TSH was higher in children who had hypertension compared with the normal group (2.9 $\mu\text{IU/ml}$ (95% CI: 2.7–3.2) vs 3.3 $\mu\text{IU/ml}$ (95% CI: 2.6–4.0) adjusted for sex, age, birth weight, current BMI, breast-feeding, parents age and income status. The higher levels of TSH (≥ 75 percentile) were related to a higher risk of hypertension (odds ratio = 1.04, 95% CI: 0.64–1.69). In contrast, the levels of TSH were associated with reduced risk of hypertension in the control group (TSH: 25–75 percentiles). **Conclusion:** These findings suggest that there may be a positive association between serum TSH concentrations and hypertension within the reference range.

P3-D2-988

Thyrotoxicosis in Childhood and Adolescents

Ana Hreniuc, Letitia Leustean, Ioana Bodescu, Ioana Hristov, Simona Gherasim, Cristina Preda, Carmen Vulpoi, Voichita Mogos, Christina Ungureanu

Department of Endocrinology, Iasi, Romania

Background: There are many aspects of the child thyrotoxicosis similar as in adult but there are also particular characteristics. Thyrotoxicosis is rare in childhood and in majority is about Grave's Disease. **Study Group:** 61 patients with ages between 9 and 19 years that were admitted for hyperthyroidism in our department for 19 years. The diagnosis was sustained by clinical signs, hormonal profile, and ultrasound and scintigraphy exam. **Results:** The hyperthyroidism has higher incidence at girls 83.6% and at puberty 21.56% at age group 10–14, 74.5% for 15–19 and only 5.8% cases between 5 and 9 years old. The great majority has Graves's disease. Thyrotoxicosis in childhood and adolescence is a relatively rare disease, it is mostly due to Graves' disease 75.4%, followed by toxic multinodular goiter 19.6% and toxic adenoma 4.91%. Clinical signs were in majority: weight lost, swatting, palpitations with tachycardia, emotional liability, irritability. Psychological and psychiatric exam was performed at 52% patients and revealed a great impact of the disease over the personality, possible to compartmental disorder: memories troubles, low scholar performance, anxiety, and psychical asthenia going to paranoid tendencies. The treatment was with antithyroid drugs 67.13% or surgery 32.7%. Radioiodine therapy was not performed because the law experience in our country with radioactive substances at children and due to no unit for radioiodine therapy in our centre. **Conclusion:** The Grave's disease is the most frequent form of thyrotoxicosis at children; A late diagnosis may deter growth and psychological disturbances. In our department oral therapy with antithyroid drugs is the first line treatment.

P3-D2-989

Aetiology and Different Clinical Conditions of Hyperthyroidism in Children and Adolescents

Bouferoua Fadila, Zeroual Zoulikha, Tari Saliha, Bouterfas Nabila, Khiari Mohamed El Mokhtar, Boukelal Houria

CHU Beni Messous, Algiers, Algeria

Background: Hyperthyroidism is considered to be rare in children; it's clinical profile is different and the most cause is Grave's disease (GD). **Objective and hypotheses:** To evaluate clinical features and evolution of childhood hyperthyroidism. **Method:** Longitudinal retrospective study of patients diagnosed with hyperthyroidism. **Results:** 8 cases were identified between 2006 and 2013: 6F/2M, the patient's average age at diagnosis was 12.8 (range 10–15) years in seven patients and one at 2 days of live, diagnosis delay was 6 days of live in a neonate, and at median 3 (range 1–8) months in seven patients, appearing symptoms were

thyrotoxicosis signs and goiter in seven cases, ophthalmological signs in four cases; in the laboratory evaluation, we highlight: TSH suppression in all patients, raised free T₄ in all patients; Trab were elevated in six cases, elevated title of antiperoxidase were found in seven patients. There were six cases with GD, one case with Hashimoto's thyroiditis who presented type 1 DM, and one case with neonatal thyrotoxicosis who is severely affected. All patients received Carbimazol (CM); four patients have been treated for more than 2 years, one patient was treated surgically after one year of treatment with CM, the reasons for alternative treatment were very large goiter and poor compliance. Relapse was observed in two cases in which treatment was stopped at 24 months. We observed healing at 3 months of age for neonatal thyrotoxicosis and remission in two cases. **Conclusion:** Rather high rate of relapse is observed in GD; stop antithyroid medication after 24 months is usually unsui is usually unsuccessful particularly in prepubertal children. Poor compliance with treatment and drug side and drug side effects may also lead to consideration of radioiodine treatment or surgery; the maisurgery; the main advantage of surgery is the rapid cure of the thyrotoxicosis. Radioiodine therapy still controversial in children before 10 years of age.

P3-D2-990

Bmi and Auxological Follow Up in Children with Hashimoto Thyroiditis: Utility of a Physical Activity Program

Giovanni Corsello, Marilena Maltese, Mariagrazia Irene Mineo, Maria Cristina Maggio

Universitary Department Pro.Sa.M.I. 'G. D'Alessandro', University of Palermo, Palermo, Italy

Background: Hashimoto thyroiditis (HT) is the most frequent acquired thyroid disease in childhood and adolescence. However it can evolve silently also for a long period, without signs and/or symptoms evocative of the diagnosis. **Objective and hypotheses:** A late diagnosis can reduce growth velocity, increase weight and particularly BMI, with an increased risk of obesity in pubertal age. **Method:** We analyzed 39 patients (age: 11.3 ± 3.8 years; ten males; 29 females) with HT. All the patients during the follow up were euthyroid, with or without L-thyroxine treatment. **Results:** At the first control only two patients had a BMI > 2 SDS; only two had BMI < -2 SDS. During the follow up only one patient had a BMI < -2 SDS and only one had a BMI > 2 SDS. TSH was 7.52 ± 12.75 at the first visit, fT₃ was 5.2 ± 2.64 , fT₄ was 3.21 ± 4.80 . TSH was directly correlated with SDS BMI, SDS weight. At the following visits (from the second to the seventh) TSH levels ranged between 3.03 ± 2.44 and 2.28 ± 1.60 , with an adequate compliance to the treatment. SDS of stature and weight were inversely correlated to the age at the diagnosis, even without a statistically significant correlation. SDS of stature, weight and BMI at the first visit were directly and significantly correlated to the same measurements relieved at the following controls, without a

worsening during the follow up, excluding any negative influences from the course of HT. **Conclusion:** All the families received an adequate nutritional education, and the patients were trained to a program of physical activity 3–4 times/week, suitable with age and sex of the patients. We obtained an 80% of adherence and the maintenance of a SDS BMI adequate to age.

P3-D2-991

Missed Cases of Congenital Hypothyroidism Detected By Screening Program in Central Serbia (1983–2014)

Sladjana Todorovic, Tatjana Milenkovic, Dragan Zdravkovic, Katarina Mitrovic, Rade Vukovic

Institute for Mother and Child Health Care of Serbia 'Dr Vukan Cupic', Belgrade, Serbia

Background: There are a lot of reasons for missing the diagnosis in neonatal screening for congenital hypothyroidism (CH), but errors in processing samples and reporting results are the most frequent! In Central Serbia screening for CH was instituted in 1983 by determination of the TSH level in dried filter-paper blood spots. All samples are analyzed at one central laboratory. The average number of specimens that are annually screened is 50 000. The screening process was divided into: specimen collection, laboratory procedures, follow-up phase. A missed case was defined as one not identified through the standard protocol of a neonatal screening. **Objective and hypotheses:** The aim of the study is to determine the extent of the problem of missed cases. **Method:** To gather data on missed cases of congenital hypothyroidism, in 2013. we did the retrospective study that included: investigation of case notes of all patients with congenital hypothyroidism who were treated and followed up in our hospital, questionnaires that were sent to the pediatricians in the primary health care and to pediatric endocrinologists in Central Serbia. **Results:** During 30 years of screening program in Central Serbia over 1 500 000 newborns are screened. The diagnosis of CH was confirmed in 415 newborns and missed in 12 cases. According to our knowledge, there was one missed case of congenital hypothyroidism for every 35 detected. For eight children specimens were not received in the laboratory, for one patient there was an exchange of samples done in maternity ward, and for three patients false negative result has been observed. **Conclusion:** For the great majority of infants, neonatal screening program for CH has been successful. Because standard screening procedures may not detect every case of CH, physicians should be clinically vigilant with regard to signs and symptoms of CH.

P3-D2-992

Thyroid Pathology Among 14-Year-Old Adolescents

Anastasia Statova

Federal State Budgetary Educational Institution of Higher Professional Education 'Kuban State Medical University' of Ministry of Health of the Russian Federation, Krasnodar, Russia

Background: Thyroid diseases rank first in endocrine pathology among children with the iodine deficiency disorder (IDD) being the significant part. **Objective and hypotheses:** To study the frequency of thyroid pathology in view of the results of the profound preventive medical check-up of 14-year-old teenagers of Krasnodar. **Method:** We examined 578 adolescents (301 boys and 277 girls). All adolescents were examined by an endocrinologist with the screening by ultrasound of the thyroid gland and research on thyroid hormones in cases of medical necessity. **Results:** Thyroid gland was examined by touch among 53 adolescents (9.2%), more often among girls (15.5%), than boys (3%). According to ultrasonic research of thyroid gland structural infringements are registered roughly in one in five patients (22.4% – boys 23.5%, girls 21.3%). The most frequent result of thyroid ultrasonography is diffuse thyroid changes in its structure (60.6% – with an equal frequency among girls and boys) followed by cystic tissue changes (25.7%). In this case changes are by 2.5 times oftener among boys than among girls (35.6 and 14% respectively). The symptoms of mass lesion are detected in 6.4% cases (by 1.5 times oftener among girls than among boys). The specific ultrasonographic pattern, estimated as immunologic thyroiditis is diagnosed in 3.7% cases, by 3.5 times oftener (6%) among girls in comparison to boys (1.7%). The diagnosis of all patients immunologic thyroiditis was confirmed on the ground of increased thyroid peroxidase antibodies titer. In 38.8% cases immunologic thyroiditis results in thyroid insufficiency. According to ultrasonic research hyperplasia of thyroid gland is registered in 1.8% cases only among girls. **Conclusion:** Roughly one in five adolescents in Krasnodar has a palpable thyroid gland, structural tissue changes are registered in one in four cases. The profound preventive medical check-up is a significant method of symptomless diagnosis of thyroid pathology.

P3-D2-993

Raised Free Thyroxine Levels in a Boy with Hypertension

Sharon Lim

Broomfield Hospital, Chelmsford, UK

Background: Raised free thyroxine levels in blood results are not unusual in adults. This may be due to protein or drug interference with laboratory assays. However this phenomenon can occur in children depending on the assay method used. **Case:** An 8-year-old boy with a strong family history of essential hypertension and raised BMI was admitted for fixation of a fracture of his right forearm after falling off a roundabout. Routine blood pressure monitoring pre-operatively revealed hypertension of BP 152/64. His height was on the 75th centile and weight on the 98th centile. The 95th centile BP for his height and age was 118/78. His pain was well-controlled, he was not symptomatic from his hypertension, his resting pulse ranged between 80 and 100/min, he had no palpable goitre. Thyroid function tests showed fT_4 23.6 pmol/l (Roche 6.3–14), fT_3 6.4 pmol/l (Roche 2.5–5–7),

TSH 1.74 mU/l (Roche 0.3–5.6), TPO and TSHr antibodies were negative. **Management:** 24-h BP monitoring confirmed persistent hypertension with normal nocturnal dip (mean daytime BP 126/76, night BP 113/74). More than 50% of his systolic recording was above the 95th centile. An echocardiogram showed normal left ventricular size and function. Based on his inpatient and 24 h ambulatory BP recording, he was started on Atenolol 20 mg once daily. At review in clinic 3 months later, his BP was 118/57 and because he complained of dizzy spells, his Atenolol was reduced. Thyroid function tests sent to a Thyroid research laboratory for further studies confirmed that his initial raised thyroxine levels were due to assay interference. Repeat thyroid function tests locally continued to show raised fT_3 6.9 pmol/l (no local results for TSH or fT_4) paired with the research laboratory results of fT_4 17.5 pmol/l (Centaur 10–19.8), fT_3 7.4 pmol/l (Centaur 4.05–7.5), TSH 3.8 mU/l (Centaur 0.35–5.5). **Conclusion:** The local hospital used a Roche assay for all routine thyroid function tests. Centaur assays were used in the research laboratory. The interesting feature here is a coincidental finding of hypertension in an overweight boy possibly due to stress from his fracture. Added to this is a positive family history of hypertension. It is important to be aware of other reasons for a raised thyroxine result and arrange for the appropriate confirmatory tests and the correct management.

P3-D2-994

The Evaluation of Transient Hypothyroidism in Patients Diagnosed with Congenital Hypothyroidism

Havva Nur Peltek Kendirci, Zehra Aycan, Elif Sagsak, Meliksah Keskin, Semra Çetinkaya

Dr Sami Ulus Maternity, Children's Health and Diseases Training and Research Hospital, Ankara, Turkey

Background: Congenital hypothyroidism (CH) is divided into two main groups as 'permanent' and 'transient'. Diagnosis of transient hypothyroidism is important to avoid lifelong unnecessary therapy with its possible side effects. **Objective and hypotheses:** We aimed to determine the rate of transient and permanent congenital hypothyroidism of the newborns referred to our clinic from the neonatal screening program in this study. **Method:** Of the newborns who were referred to our clinic due to TSH elevation from the neonatal screening program, those who were diagnosed with CH and started to be treated were included in the study. The treatments of the patients whose treatment dose required was reduced to under 1 µg/kg per day were terminated and those who were followed up monthly and whose fT_4 and TSH levels were normal at least three times without treatment were considered to have transient hypothyroidism. The clinical and laboratory findings of the patients with transient and permanent hypothyroidism in the admission and follow up were compared. **Results:** 114 of the 256 (44.5%) newborns referred to our clinic from neonatal screening program were diagnosed with congenital hypothyroidism. Of the CH patients, 70% ($n=58$) were evaluated

to have permanent and 30% ($n=25$) transient hypothyroidism. There was no difference between the sex distribution, days of screening and application, serum T_4 levels and treatment start date for the permanent and transient hypothyroidism cases, but the neonatal and serum TSH levels, and treatment doses were found to be significantly lower in the transient hypothyroidism patients. **Conclusion:** Initial measurements of the serum TSH level, and the required doses of L-thyroxine therapy for maintaining normal thyroid hormone levels, growth and development may have a predictive role for differentiating permanent forms of CH from the transient forms. Diagnosis of transient hypothyroidism is important to avoid lifelong unnecessary therapy.

P3-D2-995

Optimizing Treatment in Congenital Hypothyroidism

Joana Serra-Caetano, Joana Miguéis, Rita Cardoso, Isabel Dinis, Alice Mirante

Pediatric Endocrinology and Diabetology Unit, Coimbra Pediatric Hospital, Centro Hospitalar Universitário de Coimbra, Coimbra, Portugal

Background: Congenital hypothyroidism (CH) is an important and preventable cause of growth retardation and neurological deficit. Early treatment is crucial to minimize long term effects and today regimens tend to be more aggressive targeting hormonal control. **Objective:** To correlate CH severity at diagnosis with levothyroxine (LT) dosage and time needed to control TSH levels. **Methods:** Retrospective study including children with CH at least 1 year of follow up (2005-2012). Variables included: age and severity at diagnosis, age at onset of treatment, TSH levels and LT dosage along time. CH was defined as mild (TSH: 20–40 mU/l) and severe (TSH > 40 mU/l) and hormonal control was considered at date of TSH levels' normalization. Statistical analysis: SPSS 21. **Results:** We included 39 children, 27 females (69.2%). Mean TSH at screening was 164 ± 125 mU/l: 33 (84.6%) had severe CH (SCH), 6 (15.4%) had mild CH (MCH) ($P < 0.001$). Comparing CH groups, age at the first visit was 18 days in SCH and 31 in MCH, ($P = 0.01$); mean total LT dosage during the first year of treatment was 6.1 ± 3.6 mcg/kg per day in MCH and 9.81 ± 2.46 mcg/kg per day in SCH, ($P = 0.003$). There was no significant difference in initial LT dosage between groups (7.9 ± 2.6 mcg/kg per day in MCH, 9.3 ± 3.0 mcg/kg per day in SCH; $P = NS$). LT was started at a median age of 36 days in MCH and 17 days in SCH ($P < 0.001$). Hormonal control occurred at the mean age of 2.7 ± 1.8 months in MCH and 4.2 ± 3.6 months in SCH ($P = NS$). At 1 year of age we found a significant difference in LT dosage between groups (3.5 ± 1.3 mcg/kg per day in MCH, 4.6 ± 1.1 mcg/kg per day in SCH; $P = 0.03$). **Conclusion:** Babies with severe CH at diagnosis started treatment earlier, needed higher LT dosage and hormonal control occurred later than those with mild disease. This supports that LT initial dose should be higher in severe CH.

P3-D2-996

Report of a Hurthle Cell Neoplasm in a Boy

Zerrin Orbak, Atilla Cayir, Hakan Doneray, Akgün Oral, Nesrin Gursan

Ataturk University Medical Faculty, Erzurum, Turkey

Background: Thyroid nodules are rare in children compared to adults. Although most thyroid nodules are benign, the risk of malignancy is greater in pediatric patients. **Case:** We described a 10-year-old boy who presented with a right sided thyroid nodule that was 12×8 mm. He had not cervical lymphadenopathy. His fine needle aspiration biopsy cytology was benign. It was subsequently diagnosed as a Hurthle cell adenoma after thyroidectomy. In histopathological evaluation, there was no vascular and capsular invasion. **Conclusion:** Hurthle cell adenoma is very rare during childhood. We suggest that follow-up of thyroid nodule is very important.

P3-D2-997

Delayed Diagnosis of Congenital Hypothyroidism and Consequences: a Case Series

Tamunopriye Jaja^{a,b}, Irore Yarhere^b, Calistus Chuku^a

^aUniversity of Port Harcourt Teaching Hospital, Port Harcourt, Rivers State, Nigeria; ^bCollege of Health Science, University of Port Harcourt, Port Harcourt, Rivers State, Nigeria

Background: Screening for congenital hypothyroidism (CH) in newborns and early treatment of the condition is a cost effective way of preventing mental retardation and growth retardation worldwide. **Objective and hypotheses:** To highlight consequences of delayed diagnosis and treatment of four children with congenital hypothyroidism in our centre. **Method:** We present four cases of children with congenital hypothyroidism seen at our centre. Information was retrieved from endocrine register and case files of the patients. Details on clinical history, examination, investigations, treatment and outcome retrieved. **Result:** The children reported included four males and a female with age range between 12 months and 13 years. Age at diagnosis ranged between 8 months and 4 years. Commonest reason for presentation was mental apathy, dull look, delayed milestones. All patients had nonspecific features of CH within the first 3 months of life. Confirmatory diagnosis using thyroid function was done in all patients and l-thyroxin commenced. There was an improvement in general condition in all the children, but delayed developmental milestones, mental apathy and inability to cope with formal education was noted in those of school age. **Conclusion:** No child was diagnosed in new-born period despite presence of some nonspecific features of CH. New-born screening is therefore advocated to prevent the cumulative increase in children with mental retardation.

P3-D2-998

Importance of Early Indemnification of Hashimoto Thyroiditis at Pregnant Women in Conditions of Iodine Deficiency in Republic of Uzbekistan

Sakhlo Muratova

Republican Scientifically – Practical Medical Centre of Endocrinology, Tashkent, Uzbekistan

Aims: Comparison of perinatal outcomes and thyroid status of newborns from women with Hashimoto thyroiditis (HT) in depending on indemnification of hypothyroidism in 1st trimester of pregnancy. **Methods:** 43 newborns have been divided into two groups where 1st group was newborns from mothers with non-compensated HT in 1st trimester of pregnancy, $n=27$; 2nd group – newborns from mothers, compensated in 1st trimester, $n=16$. The health estimation was spent on a scale of Apgar. TTG, T₃, T₄, Ab-TPO was defined in blood serum by radioimmune methods. **Results:** In 1st group authentically smaller number of children were born in time ($P<0.05$), and 4 (14.8%) – functionally unripe. In 1st group of an estimation of newborns on scale Apgar on 1st and 5th minutes (6.19 ± 0.15 and 7.15 ± 0.15) were low, than in 2nd group (6.81 ± 0.14 and 7.69 ± 0.12 ($P<0.01$)). At newborns of 1st group it was more often observed easy intrauterine asphyxia (63%), and only in this group 1 child was born with average asphyxia. Only in this group at 9 (33.33%) newborns are diagnosed cases of a long current of the icteric period. At newborns of 1st group levels of TTG and Ab-TPO were authentically above, T₃ and T₄ – more low, than in 2nd group ($P<0.001$). Newborns from mothers with late compensated HT with high level Ab-TPO in 3.6 times is more often were born, 44.4%(12) had neonatal transitory hypothyroidism, 7.41%(2) – congenital hypothyroidism. **Conclusions:** Adequate indemnification of HT in early pregnancy is very important.

P3-D2-999

Improvement of Hematological Values with Stabilization of STH

Claudio Marcelo José Malem

Asociación Bioquímica of General Alvear, General Alvear, Province of Mendoza, Argentina

Background: 125 patients between the ages of 6 and 12 years old were studied, 100 of them were girls and 25 were boys. All of them were on medication with TSH. They were all residents in urban areas belonging to middle/upper strata of society. **Objective and hypotheses:** Changing it for the ingestion of nutriments. Physical exercise during at least 5 days a week. Medical treatment consisting of ferrous fumarat and folic acid. **Method:** During the first 60 days they were treated with ferrous fumarat and folic acid to raise the hemoglobin level whose value was between 8 at 9g/dl for the boys and 7 at 7.5 for the girls,

accompanied with the diet and physical activity. At the next blood control the value of STH was within 0.49 to 4.67 μ UI/ml (in average) and all the hematological values, specially the hemoglobin value between 9.5 and 11.70 g/dl (average). That's why it was decided to suspend the ferrous fumarat and folic acid continue with physical activities, the new diet and to check the weight of children and pubescents from then on. **Results:** After 90 days when the corresponding blood control was done, the patients had got normal analytical values in STH, hemoglobin between 11 and 12.5 g/dl for the boys and 11 g/dl for the girls, accompanied with normocitic elements and value of count of thrombocytes between 220 to 400 \times 10⁹/l and the homocystein value diminished remarkably, to minor value to those stimated as reference value. **Conclusion:** All these boys and girls because of the diet and the period in which they were treated with ferrous fumarat and folic acid recovered their health and vitality. Basically it was achieved to diminish the plasmatic homocystein values to normal manageable values to prevent future thrombotic event. Besides, the hormone STH returned to normal.

P3-D2-1000

Changes of Laboratory Findings Before and After Thyroid Hormone Replacement in a Naïve 19.24 Year-Old Female Case of Ectopic Thyroid

Phil Soo Oh, Joong Wan Choi

Hallym Univ. Med. Ctr., Chuncheon, Republic of Korea

Background: Hypothyroidsism is known to be associated with liver function, cholesterol and some hormone levels including GH. But, there are fewer reports about the gonadotropin levels in thyroid dysfunction. **Objectives and hypotheses:** We report here some interesting laboratory findings in a 19.24-year-old

severe short stature female case of ectopic thyroid. **Methods:** Laboratory investigations including the combined anterior pituitary function (Cocktail) study were done before and after thyroid hormone replacement. **Results:** A 19.24-year-old female presented with short stature; height 141 cm (mid-parental height, 167 cm), weight 52 kg and bone age 13 years. Since 15 years of age, she had periods every 3 months until last year, but this year every 2 months. Laboratory investigations showed free T₄ < 0.40 ng/dl, TSH > 100 IU/ml, ALT/AST 92/63 IU/l, cholesterol 459 mg/dl, total protein/albumin 7.7/5.1 g/dl, and prolactin 94.4 ng/ml. In the 1st day of GH stimulation, successive l-dopa and clonidine tests resulted in 1.4 and 1.5 ng/ml of GH peaks, respectively. In the 2nd day of Cocktail study, insulin stimulation test (Humalog 0.1 u/kg, 52 units) resulted in 3.5 ng/ml of GH peak with the lowest blood glucose of 59mg/dl. And, LH basal/peak were 0.5/6.4 mIU/ml and FSH basal/peak were 7.8/11.7 mIU/ml, respectively. Thyroid scan showed ectopic thyroid. In abdominal ultrasonography, fatty liver was suspected and 2 cm-sized echogenic mass was found in uterine cervix. After 6 weeks of thyroxine replacement, her thyroid function was 1.84 ng/dl of free T₄ and 0.281 IU/ml of TSH. She lost 6 kg and menstruation was normalized. Laboratory findings of ALT/AST, cholesterol, and prolactin were also normalized; 22/23 IU/l, 140 mg/dl and 16.7 ng/ml, respectively. But, total protein/albumin decreased to 5.7/3.6 g/dl. In the rechecked 1st day of GH stimulation, l-dopa and clonidine tests showed 2.40 and 3.13 ng/ml of GH peaks, respectively. The 2nd day Cocktail test (Humalog 0.1 u/kg, 46 units) showed 7.31 ng/ml of GH peak with the lowest blood glucose of 33mg/dL. And, LH basal/peak were 25.6/43.7 mIU/ml and FSH basal/peak were 11.2/15.0 mIU/ml, respectively. In follow-up abdominal ultrasonography, the findings of suspicious fatty liver and echogenic mass in uterine cervix disappeared. **Conclusion:** In GH stimulation after thyroxine replacement, we found an interesting finding of about two-fold increases of GH peaks using the three stimulating agents of l-dopa, clonidine and insulin. In GnRH study, LH levels were markedly increased, but just with a little increase in FSH. And, levels of total protein/albumin decreased and the echogenic mass in uterine cervix disappeared after thyroid hormone replacement.

Late Breaking Posters

LBP-D3-1001

Histological Evaluation of Patients with Partial Gonadal Dysgenesis and *NR5A1* Mutations: Review in Leydig and Germ Cell Pattern

Juliana Gabriel Ribeiro de Andrade^a, Ralf Werner^b, Helena Campos Fabbri^a, Gil Guerra-Junior^a, Andrea Trevas Maciel-Guerra^a, Maricilda Palandi de Mello^a, Konstanze Holl-Ulrich^b, Olaf Hiort^b

^aUNICAMP (State University of Campinas), Campinas, São Paulo, Brazil; ^bUniversity of Lübeck, Lübeck, Germany

Background: Recent data describe that the gonads of patients with partial gonadal dysgenesis (PGD) and mutation in the *NR5A1* gene can present with a different histological pattern. **Objective and hypotheses:** To evaluate histological aspects of PGD caused by *NR5A1* mutations. **Method:** Five patients with PGD, a history of gonadal biopsy or gonadectomy and confirmed mutation on *NR5A1* gene were selected from a Brazilian Center for DSD. The histological aspects were evaluated with H&E standard staining. All patients presented with ambiguous genitalia and a hormonal analysis suggesting gonadal dysgenesis. Patient 1 (p.D293N) was gonadectomised at age 20 years old. Patient 2 (p.Lys38*) had gonadal biopsy at age 4 years. Patient 3 (p.L80Wfs*8) had left and right gonads biopsied with 2.5 and 4 years respectively. Patient 4 (c.1138+1G>T) had gonadectomy at age 1.5 years. Patient 5 (p.Lys396Argfs*34) had gonadal biopsy at age 8 years. **Results:** P1: Leydig cell (LC) hyperplasia with vacuolated cytoplasm (foamy aspect); Sertoli-cell-only-syndrome (SCOS) and wide tubules (bilaterally). P2: small primitive tubules within ovarian-type stroma; few germ cells and no definite LC (left gonad). P3: right gonad showing SCOS within small fibrosis areas. Left gonad: prepubertal testis. P4: SCOS, fibrosis and presence of enlarged LC with vacuolated cytoplasm (bilaterally). P5: atrophic tubules within a fibrotic stroma; few germ cells, some of them showing atypical nucleus (bilaterally). **Conclusion:** We found an unusual LC pattern in 2/5 patients – hyperplasia with vacuolated cytoplasm in the 20-year-old patient and the presence of LC (enlarged and vacuolated) in the 1.5-year-old patient, not expected in this age. We also found atypical germ cells that can be an early sign of tumour development in one patient. In conclusion, histological pattern can be useful to differentiate PGD caused by *NR5A1* mutations from others. Although it is believed that those patients have a lower tumour risk, more studies are necessary to assess such risk.

LBP-D3-1002

Pseudoexon Activation in Nicotinamide Nucleotide Transhydrogenase in Two Siblings with Familial Glucocorticoid Deficiency

Li Chan^a, Tatiana Novoselova^a, Shoshana Rath^b, Karen Carpenter^b, H Atkinson^b, Jan Dickinson^b, Nick Pachter^b, G Price^b, Cathy Choong^b, Lou Metherell^a

^aQueen Mary University of London, London, UK; ^bUniversity of Western Australia, Crawley, Western Australia, Australia

Background: Two siblings of non-consanguineous parents presented with FGD, demonstrated by ACTH resistance with glucocorticoid but not mineralocorticoid deficiency. The proband presented at 21 months, unresponsive with hypoglycaemia (BGL 1.5 mmol/l). Endocrine evaluation subsequent to resuscitation indicated adrenal insufficiency with elevated ACTH. Hydrocortisone therapy was commenced. A sibling, 4 years younger than the proband had a short Synacthen test (SST) performed on day 4 of life: baseline cortisol 38 nmol/l, 60 min peak 380 nmol/l. The child was clinically well and remained under surveillance. Increased pigmentation was noted by her parents from 6 months and repeat SST was performed when she presented with gastrointestinal symptoms at 8 months: baseline 110 nmol/l, 60 min 130 nmol/l, consistent with FGD. Hydrocortisone therapy was commenced but no fludrocortisone was required for either child. **Objective and hypotheses:** To discover the genetic aetiology of the siblings disease. **Method:** Whole exome sequencing, cDNA analysis and sequencing of genomic DNA. **Results:** Whole exome sequencing identified a novel, heterozygous variant (R71X) in the antioxidant defence gene Nicotinamide Nucleotide Transhydrogenase (*NNT*), in both affected individuals. Follow-up cDNA analysis detected the pseudoexon inclusion (p.P998_D999ins23) and sequencing of genomic DNA identified a 4 bp duplication responsible for its activation. Both affected siblings were compound heterozygotes for the *NNT* mutations and an unaffected sibling had inherited only the R71X variant. Neither variant has been annotated in SNP/mutation databases. Both will lead to premature truncation and presumably result in an inactive protein. **Conclusion:** Aberrant pseudoexon inclusion is rarely recognised as a cause of human disease. Here, we report two novel, compound heterozygous mutations in *NNT*, including one which activates a pseudoexon, as the cause of FGD in two siblings. This case highlights the importance of cDNA analysis, particularly for recessive disorders where one defective allele has already been demonstrated, to investigate the possibility of non-coding variants contributing to disease.

LBP-D3-1003

Increasing Incidence of Infants Born Small and Large for Gestational Age Over 20 Years

Valentina Chiavaroli^a, Valeria Castorani^a, Paola Guidone^a, Ilaria Di Giovanni^a, Marco Liberati^a, Francesco Chiarelli^b, Angelika Mohn^a

Table 1. Annual number of AGA, SGA and LGA births. (for abstract LBP-D3-1003)

	1993 (n=857)	1998 (n=862)	2003 (n=1027)	2008 (n=1570)	2013 (n=1217)
AGA (%)	691 (80.6)	697 (80.9)	765 (74.5)	1151 (73.3)	887 (72.9)
SGA (%)	75 (8.8)	81 (9.4)	128 (12.5)	153 (9.8)	167 (13.7)
LGA (%)	91 (10.6)	84 (9.7)	134 (13.0)	266 (16.9)	163 (13.4)

^aDepartment of Paediatrics, University of Chieti, Chieti, Italy;

^bDepartment of Obstetrics and Gynecology, University of Chieti, Chieti, Italy

Background: Infants born small (SGA) and large (LGA) for gestational age have been identified at increased risk of perinatal morbidity and later cardio-metabolic alterations. Nevertheless, the progression over time in incidence of SGA and LGA births is yet to be determined. **Objective and hypotheses:** To investigate temporal trends in SGA and LGA infants compared to those born appropriate (AGA), and to identify factors potentially associated over a 20-year period. **Method:** A population-based cohort of Caucasian infants born between January 1993 and December 2013 was evaluated. Infants with birth weight and/or length <10th percentile were defined SGA, and those >90th percentile LGA. Incidence rates were compared at 5-year intervals (1993, 1998, 2003, 2008, 2013). Logistic regression was used to identify factors associated with SGA and LGA. **Results:** A total of 5533 infants were born in 5-year eras from 1993 to 2013. SGA and LGA incidence increased respectively from 87 and 106 per 1000 live births in 1993 to 137 and 134 per 1000 births in 2013 (Table 1). A temporal change was detected over 20 years in SGA ($P=0.003$) and LGA ($P=0.0003$) rates. Maternal height and gestational weight gain were associated with SGA birth, whereas maternal height, pre-pregnancy BMI and gestational weight gain with LGA birth. **Conclusion:** SGA and LGA births have substantially increased over the last 20 years, in association with and possibly as consequence of changes in maternal outcomes.

LBP-D3-1004

Methyl Donor Deficiency Impairs Pre-Osteoblast Differentiation Through PGC-1 α Hypomethylation and Increased ERR α

Eva Feigerlova^{a,b}, Essi Ewub, Georges Weryha^a, Brigitte Leininger^b, Jean-Louis Guéant^b

^aDepartment of Endocrinology, Centre Hospitalier Universitaire Nancy, Vandoeuvre lès Nancy, France; ^bInserm U-954, Faculté de Médecine, Vandoeuvre lès Nancy, France; ^cLaboratoire de Biochimie, Centre Hospitalier Universitaire Nancy, Vandoeuvre lès Nancy, France

Background and aims: Folate and vitamin B12 are methyl donors (MD) needed for the synthesis of methionine, which is the precursor of S-adenosylmethionine (SAM), the substrate of methylation in epigenetic, and epigenomic pathways. Low dietary

intakes of folate and vitamin B12 are frequent, especially in pregnant women and in the elderly, and deficiency constitutes a risk factor for various diseases. The MD deficiency (MDD) leads to a decrease in SAM:SAH (S-adenosylhomocysteine) ratio and hyperhomocysteinemia, which has been related to osteoporosis and disruption of normal development of epiphyseal cartilage in rats by mechanisms that remain elusive. **Method:** We studied the consequences of MDD on proliferation and differentiation of pre-osteoblasts *in vitro* using the human osteosarcoma cells, MG-63. **Results:** The deprived cells showed a decreased expression of SIRT1 and PRMT1, PGC-1 α and decreased SAM:SAH ratio, and increased expression of ERR α . Moreover, the MDD cells had an impaired response to treatment by 1,25(OH)₂ vitamin D with a decrease in alkaline phosphatase activity and a strong expression of adipocyte markers FABP4 and PPAR- λ indicating a disrupted osteoblast differentiation. These changes were explained by an imbalanced activation of PGC-1 α , leading to its hypomethylation and hyperacetylation, through decreased expression of SIRT1 and PRMT1 and decreased SAM:SAH ratio, and by increased expression of ERR α . **Conclusion:** Our data suggest that down-regulation of PGC-1 α would be a key factor in the deleterious effects of MDD on bone development. This link between methyl donor deficiency and epigenomic deregulations opens new insights into the pathogenesis of bone disease, in particular, in relation to the fetal programming hypothesis.

LBP-D3-1005

A 2-Year Multi-Centre, Open Label, Randomized Two Arm Study of Genotropin Treatment in Very Young Children Born Small for Gestational Age: Early Growth and Neurodevelopment

Jean De Schepper^{a,b}, Johan Vanderfaellie^b, Primus-E Mullis^c, Raoul Rooman^d, Lisa Matthews^e, Maria Dilleen^f, Richard Browning^f, Roy Gomez^g, Hartmut Wollmann^f

^aUZ Brussel, Brussels, Belgium; ^bVrije Universiteit Brussel, Brussels, Belgium; ^cUniversity Children's Hospital, Bern, Switzerland; ^dUniversiteit Antwerpen, Antwerpen, Belgium; ^eQuanticate, Hitchin, UK; ^fPfizer, Sandwich, UK; ^gPfizer, Brussels, Belgium

Background: There are limited data available on the efficacy and safety of GH treatment in very young (<30 months) short children, born small for gestational age (SGA). **Objectives:** To determine the effect of 24 months of GH treatment on body height, BMI, and head growth as well as overall psychomotor development (using the Bayley Scale of Infant Development (BSID-II)) and demonstrate its safety in young (aged between 19 and 29 months) short SGA children. **Methods:** Sixteen centers

from eight European countries participated in the study; 21 short (height < -2.5 s.d.) SGA subjects were treated with GH (Genotropin®) at a dose of 0.035 mg/kg per day for 24 months, with 22 controls untreated. An ANCOVA model was performed on the change from baseline endpoint with appropriate covariates. **Results:** GH treatment significantly increased height SDS compared to untreated controls at both month 12 (LS mean (s.e.): 1.03 (0.12) vs 0.14 (0.12)) and month 24 (LS mean (s.e.): 1.63 (0.13) vs 0.43 (0.13)) ($P < 0.001$). Greater changes from baseline in the GH group compared to the control group were observed for head circumference, body weight and BMI. At month 12, there was no significant difference in the BSID-II MDI score and PDI score ($P = 0.738$; $P = 0.301$, respectively). At month 24, the mean change in bone age was >18 months in both groups. The observed AEs reflected the background occurrence of common childhood infections in this age group. Treatment-related SAEs (adenoidal and tonsillar hypertrophy) were reported in 1 (4.8%) subject in the GH group. **Conclusion:** GH therapy initiated between the ages of 19 and 29 months in short SGA children, who failed to show early catch-up growth, was well tolerated and promoted rapid growth recovery without improving neurodevelopment. AEs were consistent with the safety profile of GH therapy.

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Abstract withdrawn.

LBP-D3-1007

Hepatic NAD Metabolism is Dysregulated by an Excessive Supply of Lipids

Wieland Kiess^a, Melanie Penke^a, Jonas T Treebak^b, Susanne Schuster^a, Theresa Gorski^a, Antje Garten^a

^aCenter for Pediatric Research Leipzig, University Hospital for Children & Adolescents, University of Leipzig, Leipzig, Germany;

^bFaculty of Health and Medical Sciences, The Novo Nordisk Foundation Center for Basic Metabolic Research, University of Copenhagen, Copenhagen, Denmark

Background: Animal and human studies have shown that nicotinamide phosphoribosyltransferase (NAMPT), the key enzyme of mammalian NAD biosynthesis from nicotinamide, is modified in non-alcoholic fatty liver disease. Here, we investigated the effect of a high fat diet on hepatic NAD metabolism in mice. **Objective and hypotheses:** A dysregulation of NAD metabolism is a pathogenic factor for the development of steatohepatitis (NASH). **Method:** C57BL/6 mice were either fed a standard chow diet ($n = 12$) or a high fat diet (HFD) ($n = 12$) for 11 weeks. NAD levels were determined by HPLC. NAMPT activity was assessed by measuring the conversion rate of ¹⁴C-Nam to ¹⁴C-NMN. Protein and mRNA levels were analysed by western blot and qPCR, respectively. **Results:** Mice fed a HFD significantly gained weight (39.0 ± 4.2 g vs 29.9 ± 2.5), stored more hepatic triglycerides

compared to chow fed animals (2.2-fold) and showed a significantly impaired glucose tolerance. Acetylation status of p53, a Sirt1 target, and phosphorylation status of eIF2 α was significantly decreased (-67.4 and -27.9%, respectively) as well as total protein levels of Bax and Caspase3 (-63.1 and -43.0%, respectively), indicating a reduction in proapoptosis signaling in mice fed a HFD compared to control mice. NAMPT mRNA (2.0-fold) and protein levels (2.2-fold), NAMPT activity (1.6-fold) and intracellular NAD concentration (1.6-fold) were significantly higher in HFD compared with control mice, as well as protein levels of the NAD dependent deacetylase Sirt1 (1.4-fold). **Conclusion:** We found increased NAMPT activity, higher NAD levels, and higher Sirt1 activity in HFD mice. This may be an early compensatory mechanism to protect against the excessive supply of lipids.

LBP-D3-1008

Long-Term Impact of Childhood-Onset Type 1 Diabetes: Social Insertion, Quality of Life, Sexuality

Hélène Mellerio^{a,b}, Sophie Guilmin-Crépon^{a,b}, Paul Jacquins, Corinne Alberti^{a,b}, Claire Levy-Marchal^d

^aUniv Paris Diderot, Sorbonne Paris Cité, ECEVE, UMRS 1123, Paris, France; ^bInserm, ECEVE U1123 et CIC-EC 1426, Paris, France; ^cAssistance Publique-Hôpitaux de Paris, Hôpital R. Debré, Médecine de l'adolescent, Paris, France; ^dInserm, CIC-EC, CIC 1426, Paris, France

Background: Little is known about the long-term social outcome of diabetic children. **Objective and hypotheses:** This study aimed to describe social and professional life, quality of life (QOL) and sexuality at adult age of children and adolescents with type 1 diabetes (T1D). **Method:** Participants ($n = 388$, age = 28.5 ± 3.1 years; duration of diabetes = 17.0 ± 2.7 years, recruited from a French national register) completed a questionnaire (198 items). Data were compared to French general population (FGP) using indirect standardized ratios (SIR) or Z-scores matched for age, gender and period +/- educational level, familial life. Linear regression was used to investigate correlates of Physical (PCS) and Mental (MCS) SF36 Composite Scores. **Results:** Educational level was similar to FGP (68.6% \geq high school degree, SIR = 1.06 (CI 95%: 0.93; 1.20)), as well as familial life pattern. Unemployment was increased in women (15.3%, SIR = 1.50(1.00; 2.10)) but not in men (8.6%, SIR = 0.96(0.51; 1.57)). Social discrimination was more common (SIR = 5.64(4.64; 6.62)). Only 25.7% of participants were homeowner (SIR = 0.72(0.57; 0.89)). Frequency of daily alcohol consumption was increased (SIR: men = 3.34(2.38; 4.54); women = 6.53(4.57; 12.99)); 7.2% (12/166) of men consumed more than recommended (2 glasses/day), 5.0% (11/220) of women (1 glass/day). Overall, 7.1% were very dissatisfied with sexual life (SIR = 1.90(1.18; 2.75)). Prevalence of sexual problems was higher in women (SIR: dysorgasmia = 1.91(1.21; 2.88); decrease/loss of desire = 2.11(1.35; 3.08)), but similar in men. PCS and MCS were moderately (mean = 52.0 ± 7.5 ; mean Z-score = -0.2(CI 95%: -0.3; -0.1)) and substantially (42.1 ± 12.4 ; -0.7(-0.8; -0.6)) decreased respectively. Fatigue and abandoning sport were

predictive of decreased QOL. Participants with complication(s) had preserved social outcomes but altered QOL. Young adults with T1D have a satisfying social well-being but lower MCS, frequent dissatisfaction with sexuality and uncommon alcohol consumption suggest the high impact of disease on morale, especially in women. Improve the screening of sexual problems and alcohol consumption, as well as optimize the patients' psychological support to cope with the T1D burden must be high priorities for health caregivers.

LBP-D3-1009

Family Studies of CYP21A2 Gene Identify Different Haplotypes for Nonclassical 21-Hydroxylase Deficiency in Brazilian Population

Débora de Paula Michelatto^a, Larissa Magalhães Grimaldi^a, Marcel Costa Alpiste^a, Maria Tereza Matias Baptista^b, Gil Guerra-Júnior^c, Sofia Helena Valente de Lemos-Marini^c, Maricilda Palandi de Mello^a

^aCentro de Biologia Molecular e Engenharia Genética, Universidade Estadual de Campinas, Campinas, São Paulo, Brazil; ^bDepartamento de Clínica Médica, Faculdade de Ciências Médicas, Universidade Estadual de Campinas, Campinas, São Paulo, Brazil; ^cDepartamento de Pediatria, Faculdade de Ciências Médicas, Universidade Estadual de Campinas, Campinas, São Paulo, Brazil

Background: Congenital adrenal hyperplasia, one of the most frequent autosome recessive disorders, is caused by defects in steroidogenic enzymes involved in the cortisol biosynthesis. Approximately 95% of cases are caused by a deficiency of the 21-hydroxylase enzyme. Its deficiency leads to androgen excess, consequently, to virilization and rapid somatic growth with accelerated skeletal maturation. Mutations in CYP21A2 are responsible for different forms of 21-hydroxylase deficiency. **Objective and hypotheses:** The aim of this study was to investigate CYP21A2 mutations in nonclassical patients and evaluate haplotypes concerning novel or rare mutations. **Method:** Fifty-three patients and their families were investigated by CYP21A2 amplification and sequencing. **Results and Conclusion:** Genotypes identified in this study were divided in four groups: homozygous for p.Val281Leu (51%); compound heterozygous for p.Val281Leu and classical mutations (37%); compound heterozygous p.Val281Leu and other non-classical mutation (9%); and, compound heterozygous for different non-classical mutations (2%). Furthermore, ten haplotypes, defined by 13 SNVs in intron 2 and one in exon 3 of CYP21A2 gene, were identified. Although their functional roles have not been evaluated, *in silico* analysis for adrenal specific splicing enhancers and silencers using the algorithm *SpliceAid 2.0* (http://193.206.120.249/splicing_tissue.html) indicate that they might influence the rate of intron 2 splicing because they cause significant changes in the normal binding-protein pattern which is important for the splicing to occur correctly and in a proper rate. In addition, haplotypes defined by SNVs in 5' regulatory region outside the 126 pb defined as minimal promoter region have been identified in compound heterozygosity with p.Val281Leu. Due to the importance of the regulatory region for the gene expression the investigation on the

role of each haplotype might give clues to better understand cases where genotype shows only heterozygosity for nonclassical mutations.

LBP-D3-1010

Effect of Triptorelin 3.75 mg Subcutaneously Injection Every 6 Weeks on Adult Height in Girls with Idiopathic Central Precocious Puberty

Yan Liang, Hong Wei, Jie Li, Ling Hou, Jianling Zhang, Wei Wu, Yanqin Ying, Xiaoping Luo

Department of Pediatrics, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Objective and hypotheses: To evaluate the long-term efficacy of triptorelin 3.75 mg subcutaneously injection every 6 weeks on final height in girls with ICPP. **Method:** Forty females with ICPP received triptorelin 3.75 mg every 6 weeks subcutaneously injection and reached FAH were collected. These patients were divided into two groups. Group A: GnRHa alone, $n=17$; group B: triptorelin + rhGH, $n=23$. During the treatment, height, weight, annual GV, sexual development, PAH and adverse effects were observed. BA and height SDS were monitored yearly. After discontinuation of treatment, follow-up was continued for 4–9 years till final height was attained. **Results:** FAHs were 159.81 ± 4.95 and 161.01 ± 4.89 cm respectively in the two groups, exceed the genetic target height (THt), about the 50th percentile of normal female height. FAH increased by 1.51 ± 4.30 cm, 4.86 ± 4.49 cm from THt respectively. The values of (FAH-THt) and (FAH-PAH post-treatment) showed significant difference between the two groups ($P<0.05$). FAH was positively correlated with Ht SDS-BA at the end of treatment, THt, course of rhGH treatment and age of menarche ($R^2=0.66$). BMI increased after treatment, however, compared with healthy children at the same age, there was no significant tendency of increase. Ages of menarche were 11.74 ± 0.66 years and 12.18 ± 0.69 years respectively. Times of menarche from discontinuation were 17.41 ± 6.96 and 14.71 ± 4.77 months respectively. **Conclusion:** The FAH was improved effectively by GnRHa 3.75 mg subcutaneously injection every 6 weeks, and more height gain will be achieved when rhGH was used concomitantly to refrain from growth deceleration during the treatment. BMI maintained steadily and ovarian function restored quickly after discontinuation of the treatment with the age of menarche similar to that of normal children.

LBP-D3-1011

The Circulating miRNAs Expression in Simple Obese Children

Liyang Liang, Zhe Meng, Zulin Liu, Lele Hou, Lina Zhang, Wenqin Lao

Sun Yat-Sen Memorial Hospital of Sun Yat-Sen University, Guangzhou, China

Background: Childhood obesity is a major health concern worldwide which is associated with increased risk of chronic diseases such as metabolic syndrome (MS). MicroRNAs have been showed to play regulatory roles in several biological progresses such as adipocyte differentiation, glucose and lipid metabolism and insulin signaling pathway. The studies of the circulating miRNAs expressing involved in obesity and MS are of essential importance as it could lead to the identification of novel biomarkers and therapeutic targets. **Objective:** To explore the characteristics of circulating miRNAs in simple obese children and screen the miRNAs related to obesity in children. **Methods:** Screen of circulating miRNAs expression in six children (three in normal, three in obesity) by high-throughput microRNA microarray and verify the discrepant miRNAs in 30 children (15 in normal, 15 in obesity) by RT-PCR, and analyze the relationship between miRNA and clinical indexes. **Results:** i) We detected 1895 miRNAs and found 67 miRNAs in differences, including 48 down-regulated and 19 up; ii) miR-142-5p was up-regulated and miR-133b decreased in obese children and their levels affected by metabolic disorders. iii) The level of miR-142-5p was positive correlated with weight ($r=0.409$, $P=0.013$), waist circumference (WC) ($r=0.458$, $P=0.005$), waist circumference to height ratio (WHtR) ($r=0.510$, $P=0.002$), BMI ($r=0.500$, $P=0.002$), TG ($r=0.568$, $P=0.001$), CHOL ($r=0.422$, $P=0.010$), non-HDL ($r=0.367$, $P=0.023$), negative correlated with ISI ($r=-0.499$, $P=0.003$); and TG was the high-risk impact factors; iv) The level of miR-133b was negative correlated with weight ($r=-0.456$, $P=0.006$), WC ($r=-0.464$, $P=0.005$), WHtR ($r=-0.452$, $P=0.006$), BMI ($r=-0.467$, $P=0.005$), positive correlated with ISI ($r=0.489$, $P=0.003$); and ISI was the independent impact factor. **Conclusion:** miR-142-5p up-regulated and miR-133b down-regulated in simple obese children's circulating, may be involved in the occurrence and development of childhood obesity and MS pathological physiological process, might be an effective way to screen obesity and MS in children.

LBP-D3-1012

Total and Acylated Ghrelin Levels in Children and Adolescents with Growth Retardation

Mitra Nourbakhsh^{a,b}, Mona Latif^c, Davod Ilbeygi^d, Maryam Razzaghy Azar^{b,c}

^aDepartment of Biochemistry, School of Medicine, Iran University of Medical Sciences, Tehran, Iran; ^bMetabolic Disorders Research Center, Endocrinology and Metabolism Research Institute, Tehran, Iran; ^cH. Aliasghar Hospital, Iran University of Medical Sciences, Tehran, Iran; ^dDepartment of Biochemistry, School of medicine, Tehran University of Medical Sciences, Tehran, Iran

Background: Ghrelin is a somatotropic and orexigenic protein secreted primarily from stomach. **Objective and hypotheses:** Since both GH secretion and nutrition, two fundamental contributors in growth promotion, are enhanced by ghrelin, the aim of this study was to investigate the relationship of

ghrelin hormone with growth retardation in 3- to 16-year-old children and adolescents and determine whether ghrelin levels are different between normal subjects and those with delayed growth. **Method:** After thorough clinical examination, 60 subjects including 30 with normal weight and height and 30 with growth retardation were selected. All the endocrine, gastroenterological, genetic or mental disorders were ruled out. None of the subjects had any history of exposure to adverse conditions and inappropriate feeding practices. The subjects were evaluated for fasting total and acylated (active) ghrelin levels, GH, and IGF-1. Subjects with decline in growth were further divided into three groups based on the presence of low height (LH), low weight (LW) or both (LH-LW). Feeding behavior of the children was also assessed. **Results:** Total ghrelin levels were higher in LW and LH-LW subjects compared to that in other subjects but the difference was not significant. Acylated ghrelin levels were also not significantly different in the two groups but it showed a trend towards lower active ghrelin in children with poor growth. There was not any significant correlation between ghrelin and parameters of growth. Growth retardation was more prominent in children and adolescents with poor appetite and total ghrelin concentration was significantly higher in these subjects. **Conclusion:** The results of this study show that although ghrelin is not significantly altered in growth retardation, it is significantly higher in children with poor appetite than that in good eaters and inefficient ghrelin orexigenic function may be the indirect cause of poor growth in these children.

LBP-D3-1013

Copy Number Determination of CYP21A2 Gene Supplements the Molecular Biological Analysis of Hungarian Patients with 21-Hydroxylase Deficiency

Koncz Klara^a, Luczay Andrea^e, Doleschall Márton^b, Károly Rácz^{a,b}, Patócs Attila^{c,d}, Ágnes Sallai^a, Éva Hosszú^e, Zita Halász^f

^a2nd Department of Internal Medicine, Semmelweis University, Budapest, Hungary; ^bMolecular Medicine Research Group, Semmelweis University – Hungarian Academy of Sciences, Budapest, Hungary; ^cDepartment of Laboratory Medicine, Semmelweis University, Budapest, Hungary; ^dLendület Hereditary Endocrine Tumours Research Group, Hungarian Academy of Sciences, Budapest, Hungary; ^eSecond Department of Pediatrics, Semmelweis University, Budapest, Hungary; ^fFirst Department of Pediatrics, Semmelweis University, Budapest, Hungary

Background: Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder caused by 21-hydroxylase deficiency in 95% of all cases. This disorder is related to the mutation of CYP21A2 gene that is located in a multiallelic complex called RCCX module showing tandem copy number variation. Molecular genetic analysis of genes located in such region is frequently difficult but the accurate diagnosis of patients suspected with CAH requires a complex molecular analysis. **Objective and hypotheses:** Our aim was to analyze the most common mutations of the CYP21A2 gene together with copy number of

the CYP21A1P and A2 genes in patients diagnosed with CAH. **Method:** We studied 111 clinically diagnosed CAH patients (70 classical and 41 non-classical). For detecting the most frequent CYP21A2 mutations we used allele-specific PCR. The copy number of CYP21A2 and its pseudogene was measured by real-time quantitative PCR. **Results:** In the classical form among the examined 140 chromosomes we found deletions in 39.3%, the I2 splice in 27.8% and in 42.1% one of the most five frequent was detected. By using complex molecular biological analysis 58 of 70 (82.8%) cases were resolved. In the non-classical cases deletions in 20.7%, I2 splice mutation in 4.8% and in 64.6% cases one of the five most frequent mutations was detected. Totally in 31 of 41 patients (75, 6%) could the genotype correctly determined. **Conclusion:** Determination of copy number variations is an accurate and helpful method in molecular diagnosis of CAH. It may lead to a faster diagnosis for CAH suspected patients. The lacking mutations suggest that other methods including whole sequencing of the CYP21A2 gene and analysis of large deletions by MLPA should also be included into the molecular biological workup.

LBP-D3-1014

CpG Methylation Changes within the INS, HLA-G and PTPN-22 Promoters in Childhood Type 1 Diabetes

Ioannis Kyrgios^a, Konstantina Mouzaki^a, Theodoros Spandonidis^b, Aikaterini Fragou^b, Georgios Tzimagiorgis^b, Maria Eboriadou-Petikopoulou^a, Assimina Galli-Tsinopoulou^a

^a4th Department of Pediatrics, Faculty of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece; ^bLaboratory of Biological Chemistry, Faculty of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece

Background: Alterations in DNA methylation status of specific genetic loci may affect gene expression, thus leading to autoimmune pathologies. **Objective and hypotheses:** This study aimed to investigate possible differences in DNA methylation pattern between type 1 diabetes mellitus (T1DM) youngsters and healthy controls. **Method:** Ten T1DM participants and 10 age-/gender-matched controls were enrolled. DNA was extracted from white blood cells using the standard phenol chloroform technique. Genomic DNA (800 ng) was modified using the EZ DNA Methylation-Gold Kit. Treatment with sodium bisulfite converts unmethylated cytosines into uracils, whereas methylated cytosines remain unchanged. PCR reaction was performed in a total volume of 50 µl targeting a specific sequence of the 3 genes promoters HLA-G 441, INS 415, PTPN-22 418 bp sequence, respectively. The primers used to amplify the promoters sequences were: HLA-G forward 5'-GGGAGGTAGGGAGTTTGTGTTA3', reverse 5'-CCATAACCACCATCCTTAAC3', INS forward 5'-TTTGGGGATAGGGGTTTGGGGATAGTA3', reverse 5'-CC-TCTTCTAATACAACCTATCCTAAAAAACTAAAAACTAC3' and PTPN-22 forward 5'-TGATGGAATGGAATTTTAGTT-AAG3', reverse 5'-CACCAAAAATTCATTAACAACTCC3'. Amplicons were analyzed by electrophoresis (1% agarose gel stained with ethidium bromide) and visualized by ultraviolet

trans-illumination. PCR products were purified using Millipore Centrifugal Filters for DNA Purification and sequenced to identify any differences in DNA methylation. **Results:** Methylation profile of 16, 4 and 9 CpGs of the HLA-G, PTPN-22 and INS promoter respectively, was analyzed. No difference between T1DM cases and controls concerning the CpGs of all studied promoters was found, although a trend towards increased levels of methylation was observed in a number of CpGs of the INS promoter. **Conclusion:** These preliminary data suggest that a tendency for increased methylation in INS promoter already exists in T1DM in childhood. Studies with greater number of participants are needed to confirm these findings.

LBP-D3-1015

A Secular Trend for Pubertal Timing in Swedish Men Born 1946–1991: The BEST Cohort

Maria Bygdell, Liesbeth Vandenput, Claes Ohlsson, Jenny M Kindblom

Medicine, Gothenburg, Sweden

Background: A secular trend for the timing of menarche has been described in women, but for men, studies of pubertal timing are scarce. Both negative and positive associations between childhood obesity and pubertal timing in men have been reported. In Sweden, Child Health Care (CHC) centers follow all children regarding growth and general health. We have collected detailed CHC growth data (height and weight) from centrally archived records for all children born 1946 or later in Gothenburg and established a unique population-based cohort, the BMI Epidemiology Study (BEST; $n \approx 400\,000$). The overall aim of the well-powered BEST cohort is to determine the role of childhood obesity and pubertal timing for a variety of diseases later in life. **Objective and hypotheses:** The aim with the present BEST sub-study was to investigate if there is a secular trend for male pubertal timing and if childhood BMI influences pubertal timing. **Method:** Men born every 5 years from 1946 to 1991 were evaluated ($n = 200$ for each birth year, $n = 2000$ for the entire sub-cohort). The height measurements were curve-fitted according to the Infancy – Childhood – Puberty (ICP) model and age at Peak Height Velocity (PHV) was calculated. PHV is the maximum growth velocity and represents a method to objectively determine age at pubertal timing. **Results:** The mean age at PHV was 14.0 ± 1.1 years. Linear regression analyses revealed that age at PHV was 1.3 months earlier for every 10 year increase in birth year between 1946 and 1991 ($P = 5.3 \times 10^{-12}$). As expected, a secular trend of increased childhood BMI at 8 years of age was observed ($P = 1.2 \times 10^{-12}$). We next evaluated the impact of childhood BMI on age at PHV and found that age at PHV was 2.1 months earlier for every quintile increase in BMI at 8 years of age ($P = 1.1 \times 10^{-21}$). To determine the independent role of birth year and childhood BMI for age at PHV, both parameters were included in the same model, demonstrating that both birth year and childhood BMI were independently associated with age at PHV (standardized β ; birth year $\beta = -0.13$, $P = 8.2 \times 10^{-9}$; childhood

BMI $\beta = -0.21$, $P = 9.8 \times 10^{-21}$). **Conclusion:** In conclusion, we provide compelling statistical evidence of a secular trend for pubertal timing in Swedish men. The secular trend of earlier pubertal timing is partly explained by increased childhood BMI but also other factors, to be identified, contribute.

LBP-D3-1016

The Diverse Phenotype of Mutations in T₃ Receptor Alpha (TR α)

Anja van Gucht^a, Korcan Demir^b, Nitash Zwaveling^c, Hanneke Wennink^c, Muammer Büyükinan^d, Gönül Çatlı^d, Bumin Nuri Dündar^e, Marcel Meima^a, Edward Visser^a, Paul van Trotsenburg^c, Theo Visser^a, Robin Peeters^a

^aErasmus Medical Center, Rotterdam, The Netherlands; ^bDr Behcet Uz Children's Hospital, Izmir, Turkey; ^cAcademic Medical Center, Amsterdam, The Netherlands; ^dTepecik Education and Research Hospital, Izmir, Turkey; ^eKatip Celebi University, Izmir, Turkey

Background: Recently, the first patients with resistance to thyroid hormone (RTH α) due to inactivating mutations in TR α 1 have been identified. These patients are characterized by growth retardation, delayed bone development, mild cognitive defects, delayed motor development and abnormal thyroid function tests.

Objective and hypotheses: We hypothesized that the phenotype of a TR α mutation depends on its location, e.g. if it is present only in TR α 1 or in both TR α 1 and its non-T₃-binding splice variant TR α 2. Our objective was to characterize two patients (P1, P2) with such novel TR α mutations. **Method:** Patients were assessed clinically and biochemically before and during LT₄ treatment. In addition, we studied the influence of the mutations using cells co-transfected with WT and/or mutant TR α 1 and a TR-dependent promoter-reporter construct. **Results:** P1 was first seen at age 15 months and is now 21 months old. She presented with a mild phenotype comprising delayed motor development, hypotonia and growth retardation. P2 has been followed from age 2 and is now 12 years of age. She suffers from marked growth retardation and severe psychomotor retardation. Both patients showed low serum (F)T₄ and rT₃, increased T₃ and normal TSH levels. P1 has a D211G mutation in both TR α 1 and TR α 2, resulting in decreased transcriptional activity of TR α 1, overcome at higher T₃ levels. P2 has a 380fs387X mutation in TR α 1, known to completely inactivate TR α 1 with dominant-negative activity over WT TR α 1. **Conclusion:** These results suggest that a mutation affecting both TR α 1 and TR α 2 does not result in a more severe phenotype than a mutation in TR α 1 alone. The severity of the phenotype appears rather related to the location of the mutation in TR α 1 and its consequences for binding of T₃ and co-factors.

LBP-D3-1017

Exploring the Pathogenesis of Hypothalamic Obesity: the Interaction of Hormonal, Neuronal and Psychological Factors

Caroline Steele^a, Joanne Powell^{c,d}, Graham Kemp^c, Jason Halford^c, John Wilding^b, Joanne Harrold^b, Kumar Das^e, Daniel Cuthbertson^a, Mohsen Javadpour^f, Ian MacFarlane^a, Andrej Stancak^b, Christina Daousi^a

^aDepartment of Obesity and Endocrinology, University of Liverpool, Liverpool, UK; ^bDepartment of Psychological Sciences, University of Liverpool, Liverpool, UK; ^cMARIARC and Department of Musculoskeletal Biology, University of Liverpool, Liverpool, UK; ^dDepartment of Psychology, Edge Hill University, Liverpool, UK; ^eDepartment of Neuroradiology, The Walton Centre NHS Foundation Trust, Liverpool, UK; ^fDepartment of Neurosurgery, The Walton Centre NHS Foundation Trust, Liverpool, UK

Background: Acquired hypothalamic damage frequently causes obesity (BMI ≥ 30 kg/m²), often refractory to treatment. The interaction of hormonal, neuronal and psychological factors underlying hypothalamic obesity (HO) remains poorly understood. **Methods:** In fasted and fed states participants underwent blood sampling (GLP-1, insulin, PYY, ghrelin and glucose), fMRI scanning (viewing food/non-food photographs) and assessment of hunger and satiety (visual analogue scales). Standard biochemical analysis was undertaken. Interaction of ghrelin, PYY and insulin was analysed using ANOVA and post-prandial area under the curve (AUC) calculated. fMRI data was analysed using repeated-measures ANOVA. Analysis of covariance assessed neural activation while controlling for GLP-1, PYY, glucose and insulin. **Results:** We studied nine HO (mean BMI 37.7 kg/m²), seven hypothalamic-damage weight-stable (HWS) (BMI 26.9 kg/m²), ten non-obese controls (NOC) (BMI 26 kg/m²) and ten obese controls (OC) (BMI 38 kg/m²). Pituitary hormone deficiencies were replaced; age, gender and BMI of HO/OC and HWS/NOC were similar. Fasting and post-prandial AUC insulin was no different between HO and OC or HWS and NOC. Ghrelin was similar in HO and HWS ($P=0.5$) and HO and OC ($P=0.6$). Fasting PYY was similar in HO and HWS ($P=0.7$), HO and OC ($P=0.4$), HWS and NOC ($P=0.4$); none had post-prandial PYY increase. Fasting GLP-1 was similar between HO and HWS ($P=0.5$), HO and OC ($P=0.1$) and HWS and NOC ($P=0.7$); AUC post-prandial GLP-1 was similar in HO, HWS and OC. Viewing high-calorie food photographs resulted in significantly lower insula ($P=0.02$) and lingual gyrus activation ($P=0.025$) in HWS than all others and insulin was significantly negatively correlated with insula activation. Obese participants rated hunger and desire to eat higher at all timepoints, with no difference between patients and controls. **Conclusions:** Plasma insulin was strongly correlated with decreased insula activation, with PYY, GLP-1 and ghrelin unrelated. Decreased insula activation may 'protect' HWS individuals from the weight-gain in HO.

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