20TH MIDDLE EUROPEAN WORKSHOP OF PAEDIATRIC ENDOCRINOLOGY (MEWPE)

November 7th-9th, 2014
Győr, Hungary

WELCOME NOTE

Dear Friends And Colleagues!

It gives us great pleasure to invite you to come together from the 7th of November to the 9th of November in Győr, Hungary for the 20th Anniversary MEWPE meeting!

In the past twenty years MEWPE gave an excellent opportunity for the participating countries to get to know each others research and clinical practice. Several joint projects were successfully conducted, papers were published and efforts were united to provide a better patient care. This year we celebrate twenty years of cooperative effort.

The congress is themed obesity, diabetes and environmental diseases. We also focus on translational new prospectives in pediatric endocrinology. Dr. Attila Patócs is invited to give lectures on the topics of pediatric phaechoromocytoma and vitamin D metabolism

Aside from the scientific program we have also prepared an exciting social program in Pannonhalma.

Andrea Luczay, MD, PhD and Dóra Török, MD, PhD

MAIN TOPICS

– obesity
– diabetes
– environmental diseases
– translational new prospectives in pediatric endocrinology

CONGRESS VENUE

HOTEL KLASTROM GYŐR
Address: H-9021 Győr, Zechmeister u. 1.
Phone: (+36 96) 516 910; Fax: (+36 96) 327 030
E-mail: klastrom@klastrom.hu
Web: www.klastrom.hu

REGISTRATION

Friday, 7th of November 11.00 – 19.00
Saturday, 8th of November 08.00 – 12.00

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REGISTRATION FEE

Registration fee 115 EUR
Registration fee includes: name badge, congress bag, access to scientific programs of Congress, program and abstract book, lunch and dinner on Friday, lunch and dinner on Saturday, coffeebreaks and a guided sight seeing tour

ACCREDITATION

FOR HUNGARIAN PARTICIPANTS ONLY

A továbbképzést a Semmelweis Egyetem a SE-TK/2014.II/00277 kódszámon szabadon választható továbbképző tanfolyamként akkreditálta. A részvételért 12 kreditpont adható.

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Program

FRIDAY – NOVEMBER 7TH

13:00	**LUNCH**
15:00	**WELCOME ADDRESS**
15:15–15:45	**INVITED LECTURE**

Chair: *Dóra Török*

Pheochromocytoma in children; genetics and behind
Attila Patócs Budapest, Hungary

15:45–17:00 SESSION I.

Chair: *Miriam Čiljaková, Éva Erhardt*

1. **Depressive and Anxiety Symptoms in Children and Adolescents with Suboptimally Controlled Type 1 Diabetes Mellitus**
Jančinová M., Čiljaková M., Chromá O., Vojtková J., Bánovčin P.
Department of Pediatrics, Jessenius Faculty of Medicine, Comenius University, Martin, Slovakia

2. **A rare cause of early proteinuria in a type 1 diabetic child**
Bokor Sz.[1], Nyikuly K.[1], Degrell P.[2], Kozári A.[1], Györke Zs.[1], Soltész Gy.[1], Erhardt É.[1]
[1]Department of Paediatrics ,University of Pécs, Pécs, Hungary
[2]2nd Department of Internal Medicine and Nephrology Centre, University of Pécs, Pécs, Hungary

3. **A spoonful of sugar helps the medicine go down – parental health literacy and children with type 2 diabetes**
Gács Zs.
2nd Department of Pediatrics, Semmelweis University, Budapest, Hungary

4. **Sleep architecture in children with type 1 diabetes mellitus**
Ďurdík P.[1,2], Šujanská A.[1,2], Vojtková J.[1], Čiljaková M.[1,2]
[1]Pediatric department, Jessenius Faculty of Medicine, Comenius University, Martin, Slovakia
[2]Centre of experimental and clinical respirology, Jessenius Faculty of Medicine, Comenius University, Martin, Slovakia

5. **Is insulin resistance more frequent in children born SGA?**
Bizerea T.[1], Stroescu R.[1,2], Chiru D.[1,2], Olariu L.[1,2], Craciun A.[1,2], Marcovici T.[1,2], Mărăzan M.[1], Mărginean O.[1,2]
[1]Louis Țurcanu Emergency Hospital for Children Timişoara
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17:00–17:15 **COFFE BREAK**

15:45–17:00 **SESSION II.**

Chair: *Ivana Čermáková, Zita Halász*

1. **Priming the diagnosis of growth hormone secretion stimulated by dynamic tests (GHST)**
Cirmanová V.
Institute of Endocrinology, Prague, Czech Republic

2. **Endocrine assessment in children with Neurofibromatosis type I – how much is enough?**
Pysova Z., Bolcekova A., Nemethova A., Hlavata A., Pribilincova Z.
2nd Department of Paediatrics, Children´s University Hospital, Comenius University Medical Faculty Bratislava, Slovakia

3. **Familial isolated pituitary adenoma causing Cushing's disease in a 11-year-girl**
Halász Z.[1], Czirják S.[2], Korbonits M.[3], Tóth M.[4]
[1]1st Department of Pediatrics,Semmelweis University, Budapest
[2]National Institute of Neurosurgery, Budapest
[3]Department of Endocrinology, St. Bartholomews Hospital, London
[4]2nd Department of Medicine, Semmelweis University, Budapest

4. **Typically pediatric diagnosis of panhypopituitarism revealed and treated in adulthood – case report of a PROP1 gene mutation**

Čermáková I.[1,2], Kalvachová B.[1], Brunerová L.[2,3], Sedlak P.[4]
[1]Institute of Endocrinology, Prague, Czech Republic
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[4]Department of Anthropology and Human Genetics, Faculty of Science, Charles University in Prague, Czech Republic

19:00	**DINNER**

SATURDAY – NOVEMBER 8TH

09:00–10:15 SESSION III.

Chair: *Michael Meyer, Rita Bertalan*

1. **Epigenetic marks in childhood obesity**
Ács O.D.[1,4], Péterfia B.[2], Hollósi P.[2], Lehotkai N.[1], Luczay A.[1], Kovalszky I.[2], Patócs A.[3], Török D.[1], Szabó A.[1]
[1]Semmelweis University 2nd Department of Pediatrics
[2]Semmelweis University 1st Department of Pathology and Experimental Cancer Research
[3]Semmelweis University 2nd Department of Internal Medicine
[4]Semmelweis University School of Ph.D. Studies

2. **Body mass index (BMI): current data for Austrian boys and girls aged 4 to 18 years**
Mayer M.[1,2], Gleiss A.[3], Häusler G.[4], Borkenstein M.[5], Kapelari K.[6], Köstl G.[7], Lassi M.[8], Schemper M.[3], Schmitt K.[2], Blümel P.[9]
[1]Department of Paediatrics, General Hospital 'Barmherzige Schwestern', Ried im Innkreis, Austria
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[8]Department of Paediatrics, Landesklinikum Mödling, Austria
[9]Department of Paediatrics, Gottfied von Preyer'sches Kinderspital, Vienna, Austria

3. **Carotid intima media thickness in obese children born SGA versus AGA-is SGA status associated with an increased risk of atherogenesis?**
Stroescu R.[1,2], Micle I.[1], Bizerea T.[1,2], Mărăzan M.[1], Puiu M.[1,2], Marcovici T.[1,2], Crăciun A.[1,2], Mărginean O.[1,2]
[1]Louis Ţurcanu" Emergency Hospital for Children Timişoara
[2]Victor Babeş" University of Medicine and Pharmacy Timişoara

4. **Evaluation of Liver Involvement in Obese Children**
Brad G.[1,2], Belei O.[1,2], Marcovici T.[1,2], Bizerea T.[1,2], Gradinaru T.O.[3], Marginean O.[1,2]
[1]"Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania
[2]"Louis Turcanu" Children Hospital, Timisoara, Romania
[3]Country Emergency Hospital Timisoara, Romania

5. **Potential role of glucocorticoid receptor polymorphisms in pediatric ALL**
Eipel O., Csordás K., Hegyi M., Németh K., Török D., Ponyi A., Csoka M., Kovács G.
2nd Department of Pediatrics, Semmelweis University, Budapest

10:15–10:30 COFFE BREAK

10:30–11:45 SESSION IV.

Chair: *Magdalena Avbelj Stefanija, Attila Tar*

1. **Difficult diagnosis: a case of Prader-Willi syndrome**
Liptovszky J., Török D., Luczay A., Fekete Gy.
2nd Department of Pediatrics, Semmelweis University, Budapest, Hungary

2. **Unusual case of rickets**
Vitariusova E., Kostalova L.
2nd Department of Pediatrics, Comenius University Medical Faculty, Children's University Hospital, Bratislava, Slovak Republic

3. **Fifteen years follow-up of a patient with APS I**
Tar A.[1], Sarkadi A.K.[2], Maródi L.[2]
[1]Railway Health Hospital, Budapest, Hungary
[2]Department of Infectious Diseases and Pediatric Immunology, Faculty of Medicine, University of Debrecen, Debrecen, Hungary

4. **Kallmann syndrome in a patient with familiar hypocalciuric hypercalcemia due to CASR mutation**
Avbelj M.S.[1], Bratanič N.[1], Trebušak P.K[2], Bertok S.[1], Debeljak M.[2], Battelino T.[1]
[1]Department of Pediatric Endocrinology, Diabetes and Metabolic Diseases, University Children's Hospital, UMC, Ljubljana, Slovenia
[2]Unit of Special Laboratory Diagnostics, Centre for Medical Genetics, University Medical Centre, Ljubljana, Slovenia

5. **Current state of our project on Noonan syndrome**
Ilencikova D.
2nd Department of Pediatrics, Comenius University Medical Faculty, Children's University Hospital, Bratislava, Slovak Republic

11:45–12:15	**MEWPE PROSPECTIVES AND CLOSING REMARKS**
12:30	**LUNCH**
15:00	**DEPARTING TO PANNONHALMA MONASTERY**
	Meeting at 14:45 – Hotel Klastrom's reception
15:30–17:00	**ENGLISH SPEEKING GUIDED SIGHT SEEING PANNONHALMA MONASTERY**
18:00	**Back to the Hotel Klastrom**
19:00	**DINNER IN GYŐR**
	Meeting at 18:45 – Hotel Klastrom's reception

Depressive and Anxiety Symptoms in Children and Adolescents with Suboptimally Controlled Type 1 Diabetes Mellitus

Jančinová M., Čiljaková M., Chromá O., Vojtková J., Bánovčin P.
Department of Pediatrics, Jessenius Faculty of Medicine, Comenius University, Martin, Slovakia

Background: Children and adolescents with type 1 diabetes (especially those with poorly controlled diabetes) are at increased risk of developing depression and anxiety disorders when compared to the healthy population. Symptoms of depression and anxiety, as well as personality traits, affect adherence to treatment and lifestyle management, metabolic control and quality of life in patients with type 1 diabetes. Comorbid psychiatric disorders represent substantial health risks and burden for the patient and can be a serious complication in the treatment of type 1 diabetes. Objectives The aim of our research is to investigate the incidence and severity of depressive and anxiety symptoms in the sample of children and adolescents with poorly controlled type 1 diabetes compared to a group of healthy children without chronic illness and to patients with well-controlled type 1 diabetes. Possible relationships between personality traits, anxiety-depressive symptomatology, demographic indicators, HbA1c level and other biochemical and anthropometric parameters were also evaluated.

Methods: Depressive and anxiety symptoms in youth were assessed with self-report questionnaires CDI (Children's Depression Inventory) and CMAS (Manifest Anxiety Scale for Children). Personality traits (neuroticism, psychoticism, extroversion) were measured by personality questionnaires B-JEPI/DOPEN. Study participants were 27 children and adolescents (age range: 8-18 years; mean age: 14, SD = 2,68) who received care at pediatric clinic from a multidisciplinary diabetes care team.

Results and Conclusions: Partial results from our pilot study were subjected to qualitative analysis and will be further processed quantitatively after the enlargement of the reference sample. Results of the study will serve to enhance the knowledge of the possible psychological causes of poor metabolic control and for possible application of psychotherapeutic interventions.

A rare cause of early proteinuria in a type 1 diabetic child

Bokor Sz.[1], Nyikuly K.[1], Degrell P.[2], Kozári A.[1], Györke Zs.[1], Soltész Gy.[1], Erhardt É.[1]
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University of Pécs, Pécs, Hungary

Aim: To present a rare disease in the background of a developing nephrotic syndrome in a 12-year-old girl suffering from type 1 diabetes.

Case report: A 12-year-old girl was acutely admitted to our Department with a nephrotic-range proteinuria (3.2 g- 4.3 g/day). Type 1 diabetes was diagnosed in a county hospital 3 months earlier. She presented ahypoproteinemia (44.8 g/l), hypoalbuminemia (23 g/l), hypercholesterolinemia (9.02 mmol/l) and moderate periorbital oedema reflectingto nephrotic syndrome. A very wide range of glucose levels and glucosuria were measured during self control (6.1-23.7 mmol/l), so her insulin therapy had to be modified. Because of the short history of diabetes and nephrotic syndrome, a renal biopsy was performed which revealed a membranosus glomerulonephritis (MGN). In the background of MGN we could detect neither secondary causes nor phospholipase A2 receptor (PLA2R) autoantibodies that have recently been implicated as a causative agent in most cases of adult primary MGN. Cyclophosphamide (2 mg/bodyweight/day) treatment was started because of her diabetes instead of the first line recommended high doses of steroid. Two months later her laboratory parameters were normalised, proteinuria could not be detected. Cyclophospamide treatment was finished after 12 weeks; the girl had no symptoms or complaints.

Presently (after 1.5 years) her MGN is in remission, her diabetes is well controlled (HbA1c: 5.7%), no microalbuminuria can be found and we can not detect any complications or co-morbidity of diabetes.

Discussion: MGN is a rare histological entity in children, representing 1-2 % of nephrotic syndrome. Neither finding of secondary cause nor detection of PLA2R autoantibodies in the background of MGN could not be detected in this case. We would like to emphasise that proteinuria, especially occurring in a short period after the onset of diabetes, is probably not due to diabetic nephropathy. It is necessary to think on other primary renal diseases. This case presents a coexistence of two rare diseases in children: type 1 diabetes and MGN.

A spoonful of sugar helps the medicine go down – parental health literacy and children with type 2 diabetes

Gács Zs.
2nd Department of Pediatrics, Semmelweis University, Budapest, Hungary/

There is a rapidly increasing trend in the prevalence of type 2 diabetes mellitus in pediatric population. In order to lower its long-time medical burdens it's inevitable to understand not only the risk factors, but also the self-care approaches of this population. It being a chronic disease, which requires an active involvement from the patient, in the case of a diabetic child the parent performs not only as a caregiver but as a teacher of health-, lifestyle-, and health-specific lessons.

Parental health literacy is a useful concept for studying the antecedents of this active involvement as well as its effects on the child's disease-career.

Although there is an increasing amount of data on the correlation between health literacy and disease characteristics in type 2 diabetes on adult population, less is known about the pediatric population.

The lecture gives a review of the literature on type 2 diabetes and parental health literacy, and proposes a possible collaboration to study the question in the pediatric population of the MEWPE-countries.

Sleep architecture in children with type 1 diabetes mellitus

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Sleep is the basic active physiologic process associated with the restitution of somatic nervous structures and metabolic changes that promote the formation of reserves. Recent published works describe the high incidence of insufficient sleep, anomalies in sleep architecture and sleep related breathing disorders in patients with type 2 diabetes mellitus. In aspect of type 1 diabetes mellitus, the data are significantly less frequent. Disorders of sleep in diabetic patients lead to lower insulin sensitivity of peripheral tissues, more frequent hyperglycemia and higher HbA1c can be associated with sleep disorders. Diabetic patients spent significantly more time of sleep in the stage NREM2 compared to NREM3. The lower percentage of deep sleep stages can be associated with sub-optimal metabolic control, problems of behaviour, mood, worsening life quality and school results. The authors present a pilot study of patients with type 1 diabetes mellitus, night videopolysomnography and continuous glucose monitoring were performed during 8 hours of night. The parameters of sleep micro- and macro-architecture (total sleep time, sleep latency, arousal index, wake during the sleep, percentage of sleep stages, respiratory events) were described and statistically correlated with onset, duration and compensation of type 1 diabetes mellitus and severity of night glucose variability.

This work was supported by the Grant VEGA 1/0262/14.

Is insulin resistance more frequent in children born SGA?

Bizerea T.[1], Stroescu R.[1,2], Chiru D.[1,2], Olariu L.[1,2], Craciun A.[1,2], Marcovici T.[1,2], Mărăzan M.[1], Mărginean O.[1,2]
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Introduction: Study of the risk factors for the increased incidence of the metabolic syndrome and its components (type II diabetes, obesity, hypertension, dyslipidemia), characteristic pathology of the end of the twentieth century, led to the discovery of the importance of endocrine and metabolic programming early in the perinatal period. Insulin resistance occurred in the prenatal period has a protective role, that of intrauterine survival in conditions of malnutrition. In the postnatal period, early onset insulin resistance becomes a risk factor for metabolic syndrome and its components correlated with normal (or excessive) nutritional intake. Understanding the role of insulin resistance in the onset of the metabolic syndrome and its components enables an early prophylactic approach thereof.

Material & methods: A retrospective observational study was carried out on long-term metabolic complications in children born SGA, which were admitted to our hospital over a 5 year period from 2007 to 2013. 541 patients (mean age 12 years±0.6, aged between 6 - 18 years) were divided in two study groups, following the statistical processing of data sheets, as follows: 379 obese patients that were born AGA (79,30 %) and 162 obese patients that were born SGA (29,69 %). Glucose and insulin levels of the patients were measured and the insulin resistance index (IR) was assessed by homeostasis model assessment (HOMA). A cut-off HOMA level of >2.5 in the prepubertal period and of > 3.5 for adolescents was used to identify an insulin-resistance status.

Results: Insulin resistance was found in 20% of obese AGA children and 25,3% of obese SGA. Rate of insulin resistance in patients born SGA was greater compared to obese children born AGA and had a significant statistical difference (P = 0.03, mean 2,95229 AGA versus 3,72778 SGA group and SD 1,7 versus 2,6).

Conclusion: Increased prevalence of IR patients born SGA compared to AGA indicates that being born SGA appears to be an additional risk factor in the developement of IR. IR met in a high percentage among obese patients born SGA, allows us to affirm that the cardiovascular risk in these patients as well as the risk of developing type 2 diabetes is higher. Monitoring, periodic evaluation and appropriate dietary therapy in the case of obese children born SGA is crucial in preventing early onset cardiovascular disease.

Key words: SGA, Obesity, IR

Priming the diagnosis of growth hormone secretion stimulated by dynamic tests (GHST)

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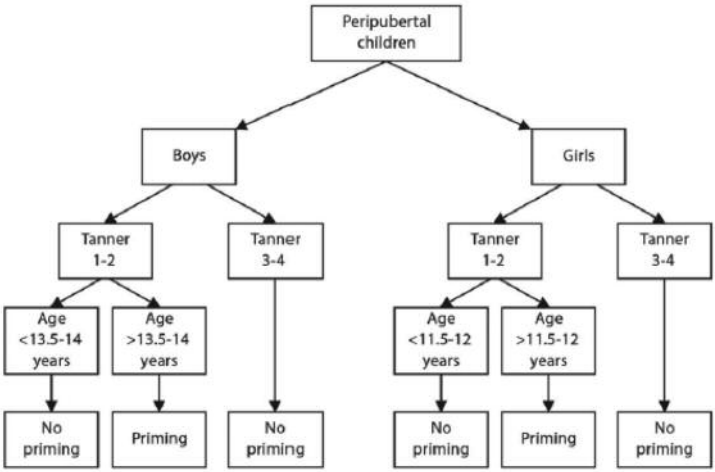
Diagnosis of growth hormone deficiency (GHD) in children and adolescents remains a challenge. The administration of steroid sex hormones before the test is still under discussion. Our paper summarizes the use of existing data on priming the diagnosis of GHD.

We studied the available literature devoted to priming when tested stimulated the secretion of growth hormone (GH) and proposed recommendations we have used practically in our department.

Paediatric endocrinologists preferring priming claims that priming during pre-and peri-pubertal period increases the specificity of GH stimulation tests, reduces the percentage of false-positive diagnoses and allows differentiation between genuine GHD and constitutional delay of growth and puberty. Non steroid priming studies suggest the possibility of insufficient and incomplete diagnosis of GHD standardization procedures priming.

Recent guidelines recommend that routine priming has been used automatically for all peripubertálních children undergoing examination provoked GH secretion. Does have the requisite adolescent girls (aged 11.5 - 12 years) and boys (aged 13 - 13.5 years) with retarded bone age and puberty.

So far there is no consensus on the use of steroid priming before dynamic tests in the evaluation of GH deficiency. A more focused approach to the use of priming steroid sex hormones is certainly reasonable and should remain the responsibility of a paediatric endocrinologist.



Flow chart for sex steroid priming prior to growth hormone stimulation test (GHST) in peripubertal children.

Endocrine assessment in children with Neurofibromatosis type I – how much is enough

Pysova Z., Bolcekova A., Nemethova A., Hlavata A., Pribilincova Z.
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Background: Neurofibromatosis type1 (NF1)is an autosomal dominant disorder with incidence of 1: 3500. NF1 represents a multisystem disease affecting predominantly the skin and the nervous system. In childhood there is also evidence of increased endocrine disorders involving mainly hypothalamic-hypophyseal axis. They may be caused by 1. hypothalamic and hypophyseal lesions of NF1, 2. consequence of their treatment (chemotherapy, radiotherapy, surgery) or 3. by disturbing signaling pathway regulating hypothalamic-pituitary axis resulting in growth hormone (GH) deficiency. Patients followed at the NF clinic of the 2. Department of Paediatrics, University Children's Hospital, Bratislava have MRI examination of CNS performed on yearly basis, together with thyroid function testing and height measurement.

Aim: To revise our approach to the screening of endocrine disorders in children with NF1.

Subjects and methods: Retrospectively we have evaluated linear growth and thyroid function in 91 (43 girls) patients with genetically confirmed NF1. The age at assessment was 1,5 to 19 years (median 6,58 years). MRI or CT scan of CNS was performed in 82 (79/3) patients and there were pathological changes in 76: hamartomas 74, optic nerve changes and gliomas 56, astrocytomas 3, multicystic glioma 1, neuroepithelial blastoma 1. Eleven patients underwent chemotherapy (CHT) and/or radiotherapy (RAT). One patient carried karyotype 47 XYY. Three patients were diagnosed as NF1- Noonan syndrome. Four patients had pseudoarthrosis of tibia and one had spine surgery for severe scoliosis. Height and puberty data from the most recent visit were evaluated according to National growth charts. TSH and fT4 were assessed during follow up, in case of increased TSH, ultrasound of thyroid gland and antibodies were performed. Statistical analysis was performed by 2 tail T-test.

Results: Average height SDS was -0,48 (median -0,33), comprising 11 children below -2 SDS (12,08%). Height SDS in 70 patients with supratentorial lesions seemed to be lower -0,48 compared to those without supratentorial lesion (9) -0,19 SDS, but the difference showed no significance. Children who inherited the NF1 gene mutation from one of their parents (36), had average SDS -0,91, compared to 55 children with de novo mutation of NF1 gene with an average height SDS -0,27 (p 0,0026). Patients with positive NF1 inherited from the father (average SDS -1,12) were not significantly shorter (p 0,17) than those with positive mother (average SDS -0,79). Out of 11 patients with height less than 2 SDS, 3 patients had NF 1-Noonan syndrome and 1 had hypopituitarism after CHT and RAT of suprasellar astrocytoma. Prepubertal patients: 38 girls with average SDS -0,55 and 37 boys with average SDS - 0,50 weren´t significantly (p 0,2) shorter than 5 girls with average SDS

-0,58 and 11 boys with average SDS -0,40 during or after puberty. Eight patients have reached final height of average -0,8 SDS. Patients with skeletal lesions (n=5) were prepubertal and showed an average SDS of - 0,62. Thyroid function was impaired in 9/91 patients (9,8%), 3 of whom underwent oncologic treatment. In 6/9 patients there was primary hypothyroidism, 2/9 had secondary and 1/9 had hyperfunction of thyroid gland. Three patients had thyroid dysfunction based on Hashimoto´s thyroiditis (3,2% of studied group).

Conclusions: In concordance with literature the average height of the studied group was below the average height of general childhood Slovak population. Children of affected parents are significantly shorter than those with de novo mutation of NF 1 gene. We have found short stature below - 2 SDS in 12,08% of the patients with NF 1: 1.) 1/11 with hypopituitarism due to suprasellar tumor, 2.) 7/11 patients had inherited mutation of NF1 gene, 3.) 1/11 had isolated GH deficiency without suprasellar solid expansion. Localisation of hamartomas didn't have significant impact on height. We didn't find significant difference in height neither between patients before and after puberty, nor in patients with skeletal dysplasia. We suggest evaluation of hypathalamic- pituitary axis in NF1 patients with SDS below -2, despite absence of supratentorial lesion. Screening of thyroid functions in our patients with NF1 didn´t show clear benefit, except of those who underwent oncologic treatment.

Familial isolated pituitary adenoma causing Cushing's disease in a 11-year-girl

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A 11 year old girl was referred to our Department because of short stature and extensive weight gain. Previous results proved isolated growth hormone deficiency and celiac desease. She was on gluten-free diet and treated with growth hormone for two years without effect. At the age of 11 year her weight was 46 kg (+1SDS), height: 124 cm (-2,27 SDS), BMI: 30.0 kg/m^2. Family history showed that her grandmother was operated because of non-functioning pituitary chromophob adenoma and her mother also has a small inactive pituitary adenoma.

Our investigations confirmed ACTH-dependent hypercortisolism caused by a pituitary macroadenoma. Following two unsuccessful pituitary surgery, the third neurosurgical intervention resulted in cure of Cushing's disease, however complete anterior and porterior pituitary deficiency developed. Molecular genetic examination was done to detect mutation of the tumor suppressor aryl hydrocarbon receptor interacting protein (AIP) gene.

Typically pediatric diagnosis of panhypopituitarism revealed and treated in adulthoodth – case report of a PROP1 gene mutation

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Introduction: Mutation of the PROP1 (Prophet of Pit1) gene is connected to combined deficiency of pituitary hormones. Although panhypopituitarism caused by PROP1 mutation is typically diagnosed in childhood, we present a case of a female patient diagnosed and treated in adulthood.

Case report: Ms. Svitlana was born in 1985 in Ukraine and since her young age suffered of growth retardation. The only known data is the treatment with growth hormone which had not started until the age of 16 and lasted for 1,5 year.

After she moved to the Czech Republic, she was referred by her GP to the endocrinologist for a suspicion of hypopituitarism. At the age of 28 the examination presented her with an infantile and hypothyroid appearance without axillary and pubic hair. She was only 149 cm tall and weighed 43 kg, with no menstrual period so far.

Laboratory evaluation confirmed central hypothyroidism (fT4 3.1 pmol/l; fT3 2.2 pmol/l, TSH 1.3 mIU/l), central hypogonadism (LH < 0.2 U/l; FSH 0.7 U/l, estradiol < 0.03 nmol/l), adrenocortical – pituitary axis was within normal limits (S-cortisol 323 nmol/l, ACTH 27.7 g/l), abnormally low IGF-I (under detection limit) and prolactin was at the lower limit of normal range (6.4 ug/l). While TRH (thyreoliberin) test confirmed central hypothyroidism (TSH 1.3-1.7-2.44 mUJ/l), LHRH (LH-releasing hormone) test confirmed central hypogonadism (FSH 0.2-1.3-0.3 U/l; LH abnormally low-0.2-0.1U/l, estradiol 0.4 nmol/l - abnormally low). Two dynamic tests confirmed the growth hormone deficiency (Arginine test: peak GH 0.05 and Insulin test: peak GH 0.08 ug/l). Furthermore, Insulin test revealed low adrenocortical reserve (S-cortisol: 453-294-394-273 nmol/l with glycemia from 1.13-1.5 mmol/l). Karyotype was normal female (46,XX). Gynaecologic examination described small ovaries (cca 15x5mm) and infantile uterus (38x9x13 mm). DXA showed significantly decreased BMD related to age (L-spine Z- score - 3,7 and Total Hip Mean - 2,1 respectively). MR of pituitary showed small pituitary gland. Carpal X-ray and following anthropologic examination evaluated the bone age as to be 10.6 years by TW3-CARP method. Molecular biologic examination confirmed homozygous mutation c.150delA in PROP1 gene.

At the beginning the therapy with levothyroxine was introduced and continuously titrated in order to achieve euthyroid status, afterwards hydrocortisone 15 mg daily,

calcium + vitamin D and growth hormone started being administered. After three months of therapy with growth hormone (Humatrope 12, initial dose 1.35 mg had to be decrease to 0.6 mg daily due to massive swelling) she grew by 2.8 cm, whereas in 6 months by 5.3 cm. At the same time therapy with low-dose estrogen was initiated. Currently the patient continues with substitution of all the pituitary hormones including growth hormone and sexual hormones, which will be slowly up-titrated in accordance with gynaecologic findings.

Conclusion: We present a unique case report of an adult female patient with panhypopituitarism due to PROP1 mutation who has successfully started to be treated with growth hormone in indication of growth.

Epigenetic marks in childhood obesity

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Introduction: Obesity incidence is rapidly growing worldwide, prevention is especially important in children. However, some people are more prone to gain weight than others. Several mechanisms seem to contribute to excess weight gain. There is emerging evidence that certain epigenetic marks might contribute to obesity predisposition. Among other metabolic anomalies vitamin D deficiency is especially frequent in overweight individuals. Vitamin D as an epigenetic regulator might be a player in the epigenetic disturbances in obesity.

Hypothesis: Low vitamin D level that is present in obesity and insuline resistance is associated with hypermethylation of CYP27B1 gene, which leads to lower production of active vitamin D.

Objective: To investigate the correlation among obesity, metabolic parameters, vitamin D levels, and methylation of certain loci.

Materilas and methods: We selected a total of 83 (41 boys and 42 girls) healthy, obese (BMI pc 95<) children, age between 3 and 18 years, who were examined and followed up at the 2nd Department of Pediatrics, Semmelweis University. Anthropometric data, metabolic parameters were recorded, 24-hour blood pressure monitoring was carried out. We collected anamnestic data focusing on perinatal issues, development and lifestyle. DNA was isolated from peripherial blood samples and treated with bisulfite. After bisulfite polimerase chain reaction (BS-PCR) the methyl ation pattern of VDR, CYP27A1, CYP27B1, CYP2R1 and CYP24A1 genes was examined with Methylation Specific High Resolution Melting Analysis (MS-HRM) in 83 cases.

Results: 63 of the 83 investigated children had at least one abnormality associated with metabolic syndrome, hypertension being the most frequent (68 %). Serum vitamin D levels did not correlate with the methylation status of the investigated vitamin D related loci. However, methylation of the VDR gene was slightly different between patients with no metabolic abnormalities at all and patients with impaired glucose tolerance.

Conclusions: Metabolic abnormalities and low vitamin D are extremely common in obese children. Certain epigenetic marks might predispose to excess weight gain and obesity related metabolic disorders.

Body mass index (BMI): current data for Austrian boys and girls aged 4 to 18 years

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Background: BMI reference charts are widely used to diagnose overweight, obesity and underweight in children and adolescents.

Aim: To provide up-to-date national reference values for Austria.

Methods: A cross-sectional sample of over 14 500 children and adolescents (4-19 years) stratified by provinces according to age- and sex-specific population proportions was drawn via schooling institutions (kindergartens, schools and vocational colleges). The generalized additive models for location, scale and shape were used for a flexible estimation of percentile curves.

Results: Austrian boys and girls have higher average weight compared with previous prevalence data. BMI centiles matching BMI values at age 18 years, which are used for defining thinness, overweight and obesity in adults, were calculated (Table 1).

In Austria, using our reference values as thresholds, about 18% of boys and 12% of girls are overweight (with thresholds passing through BMI 25.00-29.99 kg/m² in adults) and 5% of boys and 3% of girls are obese (with thresholds passing through BMI ≥30.00 kg/m² in adults).

Conclusion: Overweight and obesity are common in Austria and their prevalence is increasing (using the same IOTF reference for international comparison). Up-to-date national BMI reference values are provided to classify children and adolescents according to our proposed overweight and obesity thresholds.

Table 1: BMI for girls and boys (4 to 18 years) - BMI equicurves corresponding to BMI 16.00 kg/m², 17.00 kg/m², 18.50 kg/m², 25.00 kg/m², 30.00 kg/m² and 35.00 kg/m² at the age of 18 years; equicurve's percentile value as indicated for each BMI equicurves.

age (years)	girls						boys					
	BMI equicurves						BMI equicurves					
	16.00	17.00	18.50	25.00	30.00	35.00	16.00	17.00	18.50	25.00	30.00	35.00
	P0.225	P1.35	P9.35	P85.52	P97.27	P99.27	P0.18	P0.824	P5.45	P77.2	P94.85	P98.46
4.00	12.635	13.179	14.009	16.996	19.171	21.293	12.619	13.249	14.099	16.704	18.361	19.834
4.50	12.528	13.087	13.946	17.134	19.439	21.666	12.553	13.121	13.906	16.555	18.283	19.830
5.00	12.322	12.892	13.778	17.159	19.599	21.945	12.514	13.043	13.792	16.553	18.411	20.100
5.50	12.156	12.742	13.662	17.281	19.900	22.420	12.471	12.978	13.710	16.653	18.709	20.620
6.00	12.065	12.668	13.625	17.540	20.376	23.096	12.449	12.945	13.676	16.880	19.214	21.443
6.50	12.033	12.647	13.636	17.890	20.943	23.830	12.462	12.952	13.691	17.228	19.913	22.546
7.00	12.073	12.691	13.707	18.328	21.576	24.567	12.509	12.997	13.746	17.656	20.725	23.784
7.50	12.163	12.786	13.826	18.836	22.273	25.346	12.564	13.052	13.814	18.091	21.506	24.912
8.00	12.266	12.897	13.968	19.387	23.038	26.226	12.622	13.115	13.894	18.519	22.221	25.857
8.50	12.361	13.006	14.113	19.951	23.850	27.205	12.705	13.206	14.006	18.969	22.906	26.672
9.00	12.448	13.111	14.259	20.505	24.670	28.230	12.801	13.316	14.143	19.429	23.542	27.341
9.50	12.533	13.216	14.408	21.026	25.457	29.241	12.892	13.426	14.290	19.870	24.096	27.848
10.00	12.622	13.327	14.561	21.500	26.179	30.189	12.967	13.529	14.436	20.274	24.562	28.227
10.50	12.728	13.454	14.727	21.917	26.808	31.026	13.034	13.627	14.583	20.634	24.945	28.511
11.00	12.854	13.601	14.910	22.271	27.327	31.726	13.102	13.729	14.736	20.949	25.259	28.741
11.50	13.014	13.782	15.123	22.578	27.750	32.297	13.184	13.845	14.901	21.235	25.545	28.982
12.00	13.226	14.015	15.385	22.868	28.106	32.758	13.293	13.988	15.091	21.518	25.844	29.280
12.50	13.486	14.295	15.691	23.151	28.408	33.124	13.435	14.163	15.311	21.811	26.173	29.654
13.00	13.777	14.605	16.022	23.421	28.663	33.407	13.616	14.376	15.568	22.121	26.539	30.109
13.50	14.085	14.929	16.364	23.674	28.879	33.627	13.835	14.627	15.861	22.451	26.943	30.642
14.00	14.397	15.255	16.703	23.909	29.067	33.815	14.086	14.908	16.181	22.795	27.373	31.234
14.50	14.699	15.570	17.029	24.124	29.238	33.994	14.353	15.203	16.512	23.140	27.809	31.852
15.00	14.981	15.862	17.330	24.315	29.393	34.169	14.620	15.497	16.839	23.472	28.230	32.462
15.50	15.234	16.124	17.597	24.478	29.528	34.338	14.877	15.779	17.153	23.783	28.621	33.035
16.00	15.453	16.350	17.827	24.615	29.647	34.503	15.123	16.049	17.452	24.070	28.972	33.551
16.50	15.645	16.547	18.026	24.732	29.753	34.657	15.356	16.304	17.734	24.333	29.285	34.006
17.00	15.819	16.724	18.202	24.834	29.844	34.793	15.578	16.546	18.001	24.575	29.559	34.399
17.50	15.977	16.885	18.363	24.926	29.928	34.921	15.792	16.780	18.256	24.797	29.796	34.723
18.00	16.123	17.033	18.500	25.000	30.000	35.040	16.001	17.006	18.500	25.000	30.000	34.983

Carotid intima media thickness in obese children born SGA versus AGA-is SGA status associated with an increased risk of atherogenesis?

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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.

Aim: 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.

Material and methods: A prospective study was carried out over a 1 year period (March 2013-August 2014). We analyzed 162 obese patients, 126 patients appropriate for gestational age (AGA) and 36 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.

Key word: small for gestational age, common carotid intima media thickness, obesity

Evaluation of Liver Involvement in Obese Children

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Background: According to the WHO, the prevalence of children obesity is increasing in the last years. Some important complications of obesity are the metabolic syndrome and pediatric nonalcoholic fatty liver disease (NAFLD).

Aim: To evaluate the involvement of the liver in obese children.

Material and method: The study took place in the Endocrinology Department of Children's Hospital Timisoara, Romania between January 2013 and January 2014. We studied obese children with their BMI >97th percentiles for age and gender diagnosed with NAFLD based on the ESPGHAN guidelines. Every patient was evaluated anamnesistic (birth weight, birth height), anthropometrical (real height, real weight, height-for-age, weight-for-height, waist circumference, prehepatic diameter), clinical (blood pressure), and biological. For the metabolic complications insulin, glycosylated hemoglobin, OGTT, C-peptide, HOMA-IR, lipids, alanine aminotransferase, alkaline phosphates and gamma glutamyl transpeptidase were performed. The liver aspect and size were estimated clinical and echographic and the liver fibrosis was accessed using the M Fibroscan® probe (Echosens, Paris, France). Patients with other hepatic pathology overweight adolescents were excluded. We obtained the parents' informed consent before the start of this study.

Results: Out of 96 obese patients admitted in the hospital during the study period, 21 children (57.2% boys, 16.3 years mean age) were eligible. Hepatomegaly was detected in 47.61% of patients and acanthosis nigricans was observed in 28.57% of cases. Hypertension was presented in 23.80% and the mean waist circumference measured was 94.7 cm. Insulin resistance was encountered in 85.71% of cases, while the altered OGTT in 23.80% . Elevated triglycerides values were found in 61.90% of patients and abnormal values of C-peptide in 28.57%.The liver fibrosis was minimal in half of patients, and 14.28 % were with moderate fibrosis. One quarter of these were diagnosed with metabolic syndrome and received Metformim treatment.

Conclusions: 1.The prevalence of obesity is high. 2. The liver involvement is increasing. 3.FibroScan is a non-invasive method to assess the liver fibrosis.

Key words: adolescent, liver fibrosis, insulin resistance, metabolic syndrome

Potential role of glucocorticoid receptor polymorphisms in pediatric ALL

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Backround: Acute lymphoblastic leukemia is the most common malignancy in childhood. Glucocorticoids are key drugs in the treatment of ALL. Several studies has already investigated a variety of glucocorticoid receptor polymorphisms such as N363S, ER22/23EK, BclI polymorphisms as potential pharmacogenetic risk factors for the development or modifying of intensity of glucocorticoid related toxicity in ALL.

Our aim was to investigate whether the increased individual glucocorticoid sensitivity due to the N363S polymorphism of the glucocorticoid receptor increases susceptibility to steroid-related toxicities during ALL therapy.

Methods: We examined 346 pediatric ALL patients who underwent chemotherapy due to ALL. The 363S- carrier status was investigated by allele specific PCR. Clinical and laboratory signs of glucocorticoid related toxicities were analyzed and compared retrospectively. Event-Free Survival (EFS) were investigated by Kaplan-Meier analysis. Furthermore we investigated the 8. day prednisolone response as well.

Results: There were 32 heterozygous carriers of 346 patients (9.2%). Hepatotoxicity (31.3% vs 11.2%, p=0.004, carriers and non-carriers, resp.) and glucose metabolism abnormalities (18.8% vs 3.8%, p=0.001, carriers and non-carriers, resp.) were significantly more frequent among carriers. There was no difference in the incidence of hypertension and encephalopathy among carriers and non-carriers. Carriers were also more prone to have a combination of toxicities. EFS (71.8% vs 93.1%, p=0.0012) and good 8.day prednisolon response (100% vs. 89.17%) occured significant higher in the carrier-group as well.

Conclusion: Patients with 363S genotype of the glucocorticoid receptor gene were prone to have intesively reaction regarding both the developing of glucocorrticoid related toxicity and effectivity of the chemotherapy.

Difficult diagnosis: a case of Prader-Willi syndrome

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The early symptoms of Prader-Willi syndrome in babies are profoundly different from the symptoms of toddlers and might be misleading. Here we present a case when Prader-Willi syndrome was masquerading as a neuromuscular disorder and in addition the uniparental disomy was detectable only by methylation analysis and not by FISH.

His weight development was delayed in the last month of the pregnancy. The baby was delivered on the 41st week of gestation, the amniotic fluid was stained with meconium. His birth weight was 2700 g. After birth he required mask ventilation for 30 seconds. He had episodes of hypoglycemia in the first few hours. Perinatal infection was suspected and antibiotics were administered. He was hypotonic and had elevated serum lactate level (3.8 mmol/L) throughout the first few weeks of life. Therefore spinal muscular atrophy and mitochondrial muscular diseases were suspected but the genetic tests were negative for both.

At the age of 27 months orchidopexy was done.

His psychomotor development became normal due to intensive physiotherapy but speech development was delayed, he started to babble at the age of 14 months. The axial hypotonia persisted and he became obese at the age of 22 months. The dismorphic face became also evident at that age. Prader-Willi syndrome was suspected. Interestingly, the uniparental disomy was detected only by methylation analysis and not by FISH.

Thanks to the good parental compliance extreme obesity did not evolve but his growth was delayed. Growth hormone therapy was started at age of 4 years. GH treatment was well tolerated and his body composition is in the acceptable range. At the moment he is 7 years old, weight 28.6 kg (90-97 pc), height 119.8 cm (25-50 pc).

Early diagnosis is very important in Prader-Willi syndrome to prevent extreme obesity and maintain optimal development. In our case, although the diagnosis was not made until toddler age it was possible to prevent obesity and normalize growth. The overall outcome depends on the effective cooperation of the family and the physician to prevent obesity and related complications and provide optimal development.

Unsual case of rickets

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Introduction: The hormonally active form of vitamin D, 1,25-dihydroxy vitamin D3, is important for normal growth, psychomotoric development and bone mineralisation. Its renal synthesis is catalyzed by the 1α-hydroxylase. Vitamin D dependent rickets type 1 is a rare autosomal recessive disorder characterized by hypotonia, muscle weakness, growth failure, hypocalcemia and clinical and X ray findings of rickets.

Case report: Laura was born at 41st gestational week. Her birth weight and lenght were normal and there were no pathologies during her postnatal adaptation. In very early toddler age the delay of gross motor skills occured and later she suffered from fatigue and was prone to fall while walking. Blood tests done by general practitioner revealed hypocalcemia and elevated levels of alkaline phosphatase. The lack of vitamin D was suspected and the daily prophylactic dose of cholecalciferol was increased to 2000 units per day. Due to progression of symptoms despite the treatment she was sent to endocrine clinic. At the time of first endocrinological examination clinical features of severe rickets were observed. Laboratory examination confirmed previously seen pathologies and extremely low levels of 1,25-dihydroxy vitamin D3, while serum parathormone was increased. Severe signs of rickets were also seen on X ray scans. Finnaly we summarised all the data from history and the results of laboratory tests and suspected vitamin D dependent rickets type 1. This diagnosis was later proved by DNA analysis which revealed missense mutation in gene CYP27B1 for the 1α-hydroxylase. The patient responded to pharmacologic doses of 1,25-dihydroxy vitamin D3 and a normalization of calcemia, serum alkaline phosphatase and active form of vitamin D 3 was obtained. After six months the therapy was reduced with optimal metabolic control. Her clinical and biochemical features were normal, she started to walk stable with using braces, muscle tone and strenght increased and bone deformities diminished.

Fifteen years follow-up of a patient with APS I

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Objective: Autoimmune polyendocrine syndrome type I (APS I) is a rare primary immunodeficiency disorder characterized by chronic mucocutaneous candidiasis, multi-organ autoimmunity and ectodermal dysplasia. Autoantibodies to parathyroid and adrenal glands and type I interferons (IFN) are hallmarks of APS I, which results from mutations in the autoimmune regulator (AIRE) gene. We have studied clinical, immunological and genetic features of APS I in a Hungarian patient and his parents, and correlated anti-IFN-ω serum concentrations with APS I and other multi-organ autoimmune diseases.

Methods and Results: Mutational analysis of the proband and the parents was performed by bidirectional genomic sequencing of AIRE. Antibodies against IFN-ω that seem to appear very early in life and endocrine organ-specific autoantigens were studied with radioimmunoassay. RFLP was performed by digestion of DNA with Hin6I restriction enzyme. The sequence analysis revealed c.965_977del13bp/wt mutation in the proband's mother and c.769C>T/wt mutation in the proband's father. Biallelic AIRE mutation *(R257X and 967-979del13bp)* was found in the patient.

Clinical aspects: The nineteen-year old boy with mucocutaneous candidiasis was hospitalized because of suspected epilepsy at the age of one year. The low PTH value (0.18 pmol/l) confirmed hypoparathyroidism. Anti-adrenal antibodies were positive. No other abnormalities (GAD 25, ICA, insulin antibody) were found. Immunology examination showed slightly decreased absolute CD4 and CD8 T lymphocyte count.

Conclusion: The two common double allele mutations in the AIRE gene confirmed APS I in this Hungarian boy. Elevated anti-IFN-ω antibodies helped to differentiate APS I from other multi-organ autoimmune diseases. The fifteen years of follow-up of the patients continues in his good clinical condition. His only one new sign was the appearance of vitiligo.

Kallmann syndrome in a patient with familiar hypocalciuric hypercalcemia due to CASR mutation

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Background: Calcium-sensing receptor (CASR) is a plasma membrane G protein-coupled receptor expressed in the parathyroid cells and the kidney tubules. It senses small changes in circulating calcium concentration and modifies PTH secretion and renal cation handling. *CASR* mutations are implicated in various inherited disorders of calcium metabolism including familial hypocalciuric hypercalcemia type 1 (HHC1). CaR is also expressed in GnRH neurons in murine forebrain and in GnRH neuronal cell lines GT1-7 and GN11. Furthermore, calcium promotes chemotaxis and migration of GnRH neurons *in vitro* via CaR and CaR-null mice have reduced GnRH neuron population.

Case presentation: The proband, his father and sister carried a previously reported loss-of-function heterozygous *CASR* mutation p.Arg795Trp (c.2383C>T) and all of them displayed clinical picture of HHC1. The proband also had Kallmann syndrome with absent spontaneous puberty. The father, mother and sister reported normal pubertal development, but the father was anosmic. In the proband no mutation was identified by next generation sequencing in genes associated with hypogonadotropic hypogonadism.

Conclusion: This is the first report of a *CASR* mutation in a patient with KS. As in humans with *CASR* gene mutations pubertal disorders are not a recognized feature, we speculate that *CASR* mutation is likely not the main cause of KS in our patient. Nevertheless, according to the involvement of CaR in GnRH neuronal migration the question arises whether *CASR* mutation contributes to the KS phenotype.