9TH MIDDLE EUROPEAN WORKSHOP ON PAEDIATRIC ENDOCRINOLOGY

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TOPICS:

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GHRELIN CIRCADIAN SECRETION PATTERN FROM 24-H FASTING SUBJECTS

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Introduction. Ghrelin, an endogenous ligand for the growth hormone (GH) secretagogues receptor first isolated from rat and later from human stomach, strongly stimulates GH release and also causes weight gain through an increased food intake and reduced fat utilisation. As human ghrelin levels have been shown to vary in a diurnal pattern, rising in the pre- and falling in the postprandial periods, it has been hypothesized that this peptide could play a role in meal initiation. Although ghrelin levels are known to be significantly increased after fasting, its secretion pattern during a 24-h fasting period has not been reported to date.

Objective. To investigate the 24-h fasting ghrelin profile.

Patients and methods. 6 healthy volunteers accostumed to eating 3 meals/d (3 females, 25,4 yrs, range 18-30 yrs; BMI 22,6 kg/m2, range 20,0-26,6 kg/m2), were asked to fast from 0000h of day 1 until 0900h of the following day (day 2). Water was allowed ad libitum during this period. Peripheral blood samples were collected every 20 min from 0800h day 1 until 0900h day 2. At 0800h day 2 an unexpected meal was served. During the sampling period the subjects serially rated their hunger on a 0-10 score scale every hour. Ghrelin levels were measured using a commercially available RIA (Peninsula Lab., Inc, Belmont, CA, USA) that uses a polyclonal rabbit antibody, according to manufacturers‘ instructions.

Results and conclusions. Despite of important intra- and interindividual variations between the 6 ghrelin profiles, we could identify following common tendencies: Highest ghrelin levels were measured during the morning, from the beginning of the sampling until the early afternoon, and in the evening, with elevated levels at the accostumed meal periods (around 0900h, from 1100h to 1400h, and from 1800h to 2200h). Lowest concentrations were found in the afternoon and at night. Surprisingly, no constant overall increase of the ghrelin levels was observed. In addition, we noted no correlation between ghrelin levels and hunger ratings, which is in sharp contrast with previous findings.

VALIDATION OF GROWTH PREDICTING MODELS FOR PREPUBERTAL CHILDREN WITH IDIOPATHIC GROWTH HORMONE DEFICIENCY

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Objective. A prospective validation of mathematical models established to predict the growth response during the first to sixth year of GH replacement therapy in prepubertal children with idiopathic GHD (M. Ranke).

Patients and methods. A cohort of 38 prepubertal patients (13 girls and 25 boys) with idiopathic GHD were studied. All data required for the growth prediction within the models (i.e. maximum GH response to testing, age at the onset of therapy, height, weight, birth weight, midparental height and GH dose) for the first, second, third, fourth, fifth and sixth year were available from 38, 35, 27, 21, 15 and 10 patients respectively. Some characteristics of our cohort differed from those of the cohort from which the models were derived - our patients were younger, smaller, lighter and had a lower maximum GH response to testing.

Two mathematical models (one including and one excluding the maximum GH response to testing) were used to calculate the expected growth response during the first year and corresponding models were used for prediction from the second to the sixth year of therapy. The obtained values of predicted growth response for every year were then statistically compared with observed height velocities.

Results. Using the model for the first year including maximum GH response to testing, and the model for the sixth year, the growth response in our cohort was not different from that predicted. Differences between observed and predicted height velocities were found, using the second model for the first year, and models for the second, third, fourth and sixth year – in all cases the observed growth response exceeded the predicted one.

Conclusions. The model including maximum GH response to testing showed good ability to predict growth response and should be preferred to the one excluding maximum GH response. The models for following years, except the sixth year, underpredicted the growth response. The more severe GHD in our group compared to the original group may be an explanation for the observed differences.

TW3 METHOD IN OUR CLINICAL PRACTICE

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Introduction. For many years we have been using the TW2 method (*„point scoring system", Tanner et al., 1975)* and the GP method ("*atlas matching", Greulich and Pyle, 1959)* in assessment of skeletal maturity. Immediately after the release of the TW3 method (*Tanner et al., 2001*) we introduced this innovated version of TW2 into our routine clinical practice.

Objective. To compare results obtained by TW3 method with TW2 and GP methods.

Material and methods. 85 radiographs of the left hand and wrist of 31 early or late maturing boys and 39 girls with anorexia nervosa were assessed by three currently most accurate methods of assessment of skeletal maturity i.e. the GP, TW2 and TW3 methods. None of the individuals was undergoing any drug therapy. Two evaluators (KI and KH) read all scans independently (used all three methods). The results of the three methods were compared using the paired t-test.

Results. (1) We found a very good accordance of values of bone age assessed by GP and TW3 methods (average difference 0.01 year, SD=0.45, p=0.971), (2) The difference between TW2 and TW3 values of bone age (in the RUS compartment) is in average 1.04 one year (SD=0.23, p=0.00002). The magnitude of the difference is given by the construction of the two methods, but also proves, that our readings are correct. (According to Tanner "it is approximately 1 year").

Conclusions. From the clinical point of view (multicentric studies, therapy monitoring etc.) is one-year difference between TW2 a TW3 very significant and reflects the secular advance in RUS skeletal maturity of used reference populations. We consider that is necessary to abandon the TW2 in clinical practice. Based on our findings we recommend the GP method for common practice where accurate evaluation is not required. For exact evaluation (for ossification rate assessment or for treatment control) we prefer the TW3 method (scoring of multiple parameters gives results accurate to tenths of year).

FINAL HEIGHT IN TURNER SYNDROME: TEN YEARS AFTER

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Aim. Following a short-term clinical trial in 1991, GH therapy became routine in Turner syndrome (TS) in the Czech Republic since 1992. We are analysing final height in 50 subjects with TS who completed a course of GH treatment in a single centre between 1993-2002.

Patients and methods. GH therapy (0.05 mg/kg/day; 1 IU/kg/week) was started at 11.5 years of age (median; range 6.2-17.5) and lasted for 5.3 years (median; range 1.0-9.8). Eight subjects developed puberty spontaneously; in the remaining 42, estrogens were administered since 13.5 years of age (median; range 9.0-17.5), 2.4 years after the first GH dose (range: 3.8 years before up to 7.5 years after). Until 1996, estrogens were prescribed by a gynaecologist according to the vaginal smear, since 1997 all patients followed a standard protocol of estrogen replacement.

Results. The patients reached a mean adult height of 154.0 ± 6.7 cm (mean ± SD), 5.8 ± 5.2 cm above the projected value. The final height has been gradually increasing from 137.1 cm (mean) in those who completed therapy in 1993, to 146.9 cm in 1995, 153.1-154.2 cm (yearly means) in 1996-1999 and to 158.6–158.8 cm in 2000-2002 ($p<0.0001$, ANOVA). The young women with TS lost 5.5 cm (mean) compared to predicted final height in 1993, but gained 0.6-3.9 cm (yearly means) in 1995-1998 and 7.1-10.1 cm in 1999-2002 ($p<0.0001$, ANOVA).

The two most important predictors of height gain included duration of estrogen-free interval of GH therapy ($r=0.64$; $p<0.0001$) and the total period of GH administration ($r=0.62$; $p<0.0001$).

Conclusions. Our data suggest that the „historical" women with TS were in fact losing their height due to an early and inappropriate estrogen administration. GH therapy may lead to a consistent height gain of up to ~10 cm, if accompanied by a sophisticated schedule of estrogen replacement. The introduction of GH in TS improved height outcome not only thanks to its pharmacological action but also thanks to a new complex therapeutic approach.

THYROID DISORDERS IN GHD PATIENTS ON RGH TREATMENT

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Aim. Continual therapy with recombinant growth hormone (rGH) was started in Slovak children with growth hormone deficiency (GHD) in October 1992. It is known that TSH deficiency is often "unmasked" during the initial phase of hGH therapy, but also other thyroid disorders may be found. Presence of thyreopathy was therefore retrospectively evaluated from the data of large group of Slovak patients treated with hGH.

Patients. T4 or fT4, TSH levels were examined in a group of 287 children in Slovakia, who were treated with hGH for GHD. Authors evaluated hormonal levels at the start of the hGH therapy and in 3 to 6 months intervals thereafter.

Results. Authors have found thyreopathy in 55 children at the start of hGH therapy; none of them had congenital hypothyroidism. Elevated TSH levels were found in 24 children during the therapy. Decreased fT4, T4 levels during hGH therapy were present in 20 children. All these patients were substituted by such doses of thyroxine which normalised the hormonal levels.

Conclusions. Our data suggest that attention to different thyroid disorders should be paid to GHD patients, especially at the first year of hGH therapy. Regular clinical and laboratory evaluation is necessary . Thyroxine substitution supports normal growth in this subgroup of GHD children.

TRICHO-RHINO-PHALANGEAL SYNDROME II (TRPS II OR LANGER-GIEDION SYNDROME) ASSOCIATED WITH GROWTH HORMONE DEFICIENCY: CASE REPORT

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Introduction: The Langer-Giedion syndrome (LGS) is characterized by craniofacial and skeletal abnormalities. Most of the affected patients are mentally retarded. In contrast to TRPS I and TRPS III which are caused by mutation of a single gene (TRPS1 gene), LGS is a contiguous gene syndrome caused by the deletion of at least TRPS1 and EXT1 genes on the long arm of chromosome 8. Patients with small deletions affecting TRPS1 and EXT1 genes only can be of normal intelligence. This means that the genes involved in mental retardation map outside of these two genes. We describe a girl with Langer-Giedion syndrome associated with complete GH deficiency.

Case report. The girl was born after an uncomplicated pregnancy as second child of nonconsanguineous healthy parents. Because of multiple craniofacial abnormalities chromosomes were examined and a terminal 8q-deletion was detected. When we saw her the first time she was ten years old. She was 112,4 cm tall (-4,76 SD), had a bulbous nose, a long, flat philtrum with thin upper vermillion border, large protruding ears, sparse hair and abnormally positioned teeth. Furthermore she had delayed speech development and mild mental retardation. She had severe brachyphalangy with cone-shaped epiphyses and multiple exostoses. Her bone age was retarded.

Growth hormone provocation tests (Arginine and L-Dopa) showed GH deficiency (maximal increase to 3,1 ng/ml and 6,8 ng/ml).

Conclusion. This is the first case of a patient with LGS and GH deficiency. GH treatment was initiated. Molecular genetic studies of the affected girl and her parents are done to determine the breakpoints and the exact extension of the deletion on chromosome 8.

GROWTH HORMONE EXCESS IN A MALE ADOLESCENT WITH MC CUNE ALBRIGHT SYNDROME - A CASE REPORT

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McCune Albright syndrome is part of a spectrum of disorders including isolated endocrine lesions, simple monostotic fibrous dysplasia, polyostotic fibrous dysplasia, and all combinations up to the full syndrome. It has been shown recently that all these different expressions are caused by somatic activating GNAS1 gene mutations in a random mosaic state so affecting the alpha subunit of the stimulatory G protein.

We present an individual **case report** of a 15 year old male adolescent who was known as having polyostotic fibrous dysplasia for years and then by detailed procedures was diagnosed as having growth hormone

excess. Ongoing growth was completely depressed only by somatostatin analogues, but complete remission in terms of acromegaly treatment was not achieved by now, following one year in the course of treatment.

For future therapeutical options one has to discuss surgery, irradiation and the new growth hormone receptor antagonist (pegvisomant). Surgery would be a very difficult issue in this case because of the massive osseous lesions of the skull base.

In **conclusion** we are able to present clinical data before and following therapy of a rare complication of the McCune Albright syndrome complex. It seems wise in cases of any fibrous dysplasias to look for any endocrine abnormality very carefully.

THYROID HORMONE AND RETINOIC ACID NUCLEAR RECEPTORS: SPECIFIC LIGAND-INDUCIBLE TRANSCRIPTION FACTORS

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Transcriptional regulation by both the thyroid hormone and the vitamin A-derived biologically active compounds is a critical component in controlling many aspects of higher vertebrate development and metabolism. The functions of 3,5,3´-L-triiodothyronine (T_3), the thyromimetically active metabolite, of L-thyroxine as well as *all-trans* retinoic acid (RA) the biologically active vitamin A metabolite are mediated by nuclear receptor proteins – members of the steroid/thyroid/retinoid receptor superfamily. It has been established that both thyroid hormone receptors (TR) and *all-trans* retinoic acid receptors (RAR) function as ligand inducible transcription factors via formation of heterodimeric complexes with *9-cis* retinoic acid receptors (RXR). Both TR and RAR are capable to function as transcriptional repressors in the absence of specific ligands and potent activators upon binding of T_3 or RA. The TRs, RARs or RXRs are classified into a and b subtypes based on mapping to human chromosome and on sequence homology. The ligand-nuclear receptor complexes regulate target gene expression through the binding to short *cis*-acting DNA sequences, hormone responsive elements (HREs). The ability to recognize target genes is a particularly important aspect of nuclear receptor function. In addition, SMRT (silencing mediator of retinoic acid and thyroid hormone receptor) and N-CoR (nuclear receptor corepressor) and a variety of other specific proteins – transcriptional corepressors play an important role in repressing basal transcription.

In conclusion, the recent findings indicate that the molecular biology of thyroid hormones or other biologically active ligands that act within the cell nucleus will be even more complicated than ever imagined.

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ANALYSIS OF RET GENE MUTATION ASSOCIATED WITH MULTIPLE ENDOCRINE NEOPLASIA TYPE 2A, SPORADIC MEDULLARY THYROID CARCINOMA AND PHEOCHROMOCYTOMA

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Multiple endocrine neoplasia type 2 (MEN2) is an inherited cancer disease, which comprises three syndromes: MEN2A, MEN2B and familial medullary thyroid carcinoma (FMTC). The common and most fatal clinical manifestation of MEN2 is the medullary carcinoma of the thyroid gland (MTC) connected with the incidence of pheochromocytomas and hyperplasia/or adenomas of the parathyroid glands. *RET* gene mutations are associated with MEN2 syndromes. The penetrance of the mutated gene with MEN2A is 100%.

The aim of our study is to detect *RET* gene mutations in order to identify mutated gene carriers in families with predisposition to MEN2A and/or patients with MTC and pheochromocytomas.

DNA from peripheral blood mononuclear cells, tumors or paraffin embedded tissues was tested. To detect mutations the DNA fragment of interest, amplified by polymerase chain reaction, was analyzed by direct sequencing, restriction enzyme digestion and SSCP.

Several members of Slovak MEN2A families and patients with medullary thyroid carcinoma or pheochromocytoma were investigated for *RET* gene mutations. In addition polymorphisms of *RET* gene as a possible genetic modifiers of MEN2A were analyzed. Until now three different mutations of the *RET* gene have been found including exon 11 and 16, and two polymorphisms in exon 13 and 14 were detected. The mutations in exon 11 of *RET* gene with the change of TGC (cysteine) to CGC (arginine) or TGC (cysteine) to TAC (tyrosine) were detected to be of germ-line origin. Based on the fact that the *RET* gene mutation in exon 16 leading to the change of ATG (methionine) to ACG (threonine) was found in tumor tissue only, this medullary thyroid carcinoma was classified as sporadic form.

In conclusion molecular genetic analyses might be considered as an early diagnostic tool in identifying or excluding patient at risk for an inherited predisposition for cancer. Prophylactic thyroidectomy in mutated *RET* gene carriers is recommended early in the life as the most reliable way to cure the patient. Members of the family with predisposition to MEN2A but without the *RET* gene mutations are no more at the risk of MTC.

CONGENITAL HYPOTHYROIDISM IN SLOVAKIA – RESULTS OF THE LONG-TERM MONITORING OF PATIENTS DETECTED BY MASS NATIONAL SCREENING

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Background. The authors submit the results of 16 years of mass neonatal screening, diagnosis and therapy of congenital hypothyreosis (CH) in 90 patients from the region of Bratislava and Western Slovakia.

Mass screening of CH has been routinely performed in Slovakia since 1985. In 1994 simplification of the screening of CH and hyperphenylalaninemia (HPA) was done . Screening of CH and HPA in Slovakia is

organized by The Methodical Direction of The Ministry of Health of The Slovak Republic, all neonates born in evidence of health care centers of SR were examined and suspect cases were solved in 7 – 14 days.

Patients and methods: Total number of patients with CH was 90, 38 girls and 26 boys. Distribution according to the diagnose: athyreosis 16, ectopy 36, dyshormonogenesis12, TBG deficiency 26. Incidence of CH in Slovak Republic in 2001 only was 1 : 2540, while that for 16 year period was 1 : 5343.

Surveyed data: monitoring of fT4 and TSH levels (laboratory estimation); bone maturity (X-ray evaluation); anthropometric evaluation; somatic development; psychological evaluation; mental development; selected hemathological and biochemical parameters.

Results. Psychological evaluation: (mental degree): average (92.6 %): over-average (5.2 %), under-average (2.2 %). Anthropometric evaluation: all measured somatic parameters were in the range of ±2 SD, body height to midparent´s body height ratio was –1 SD.

Conclusions. (1) Dependence of substitution therapy efficacy on time factor; (2) necessity of fT4 and TSH estimation, as well as monitoring with the use of other selected biochemical and hemathological parameters; (3) longitudinal monitoring of somatic and mental development.

The reasons for mass screening of CH are: possibility of early treatment, complex and long-time care in diagnostic and therapeutic centers.

THE USE OF POVIDONE-IODINE AND THYROID FUNCTION IN PEDIATRIC CARDIOSURGICAL PATIENTS

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Objective. To examine whether povidone-iodine used in pediatric cardiosurgical patients compromises thyroid function.

Patients and methods. Thyroid hormones and urinary iodine excretion were examined in 53 infants with delayed sternal closure after open heart surgery in whom povidone-iodine was used for sternal wound protection and in 18 children in whom continuous povidone-iodine mediastinal irrigation was used for the treatment of mediastinitis.

Results. In patients with delayed sternal closure low total triiodothyronine, total thyroxine, thyroxine-binding globulin levels, high reverse triiodothyronine levels and normal free triiodothyronine, free thyroxine, and thyroid-stimulating hormone levels were recorded in the immediate postoperative period. Two weeks after sternal closure, the levels of total triiodothyronine, total thyroxine, and thyroxine-binding globulin increased significantly, and the levels of reverse triiodothyronine decreased, but not significantly. Thyroid-stimulating hormone levels increased significantly, being above normal in 15 patients. Further check-up in 2 weeks showed markedly increased thyroid-stimulating hormone levels in 4 infants. These patients were deemed to be hypothyroid and were started on thyroxine replacement therapy. Urinary iodine concentration on the last day of povidone-iodine exposure was significantly higher than in the control group of infants, who had primary sternal closure following cardiopulmonary bypass.

In patients with mediastinitis TT3 and TT4 levels were below normal prior to the mediastinal reexploration, then increased significantly being after discontinuation of povidone-iodine irrigation within the normal range. No patient showed laboratory signs of iodine-induced hypothyroidism although urinary iodine concentration was high in all patients.

Conclusions. Transient hypothyroidism occurred in infants with delayed sternal closure after cardiac surgery who were exposed to high amount of povidone-iodine for sternal wound protection. The use of continuous povidone-iodine irrigation for the treatment of mediastinitis has not lead to any significant thyroid dysfunction.

VOLUMES OF THE THYROID GLAND IN CHILDREN IN CZECH REPUBLIC

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Objective. To determine our own normative values of the thyroid gland in children of the age 1 – 18 years in Czech Republic and to compare these results with thyroid volume reference data recommended by the WHO / ICCIDD from 1997.

Methods. During 10 years / 1991 – 2000/ more than 2000 randomly selected children were investigated in 10 areas of Czech Republic . A subgroup of 1127 children (608 boys and 519 girls) had their urinary iodine levels above the recommended value of 100 µg/l. Ultrasonography is a precise method for the assessment of thyroid volume. We have used the Brunn´s formula ”length x depth x width x 0,479” which is suitable for the thyroid volume measurement .Results were related to the body surface of examined boys and girls since the thyroid volume correlates better to total body surface area.

Results. In both groups - boys and girls - the upper limits of the normal range of thyroid volume related to body surface were found lower in comparison to the Thyromobil study of 1997. Our normative values of the thyroid gland are the first ones in Czech Republic and as such they contribute to an exact evaluation of the thyroid volume .

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EXPERIENCE WITH THE FIRST (PORCINE TSH RECEPTORS) AND SECOND (RECOMBINANT HUMAN TSH RECEPTORS) GENERATION METHODS FOR TRAB DETERMINATION IN GRAVES' DISEASE

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More than two thousand determinations were carried out with the assays based on porcine TSH receptors (two thousands) and human TSH receptors (two hundreds) in children and adolescents (560 cases). Round two hundreds proved to be Graves' (GD) patients.

The aim of these studies was to confirm the diagnosis of GD in the last quarter of the previous century and the comparison of the first generation test with the species specific one recently.

Results. the number of positive test-results increased (between 1985 and 1995 9,3 ± 3,0; since 1996: 12,3 ± 3,9 / year). The results were negative by the first generation test (porcine) in 10 of 173 cases at the first (in

7 cases at the second-times) study, but increased the antibody-level till the subsequent test (in 8 cases). This elevation in the first phase of the disease was characteristic in 20 other cases in higher ranges. All of the 73 samples gave positive results (> 1,5 IU/L) with the second generation (human) test, which samples proved to be positive (> 9 U/L) with traditional (porcine) method. In 21 samples we received positivity by the 2nd generation test despite the normal results in the first generation test.

Conclusions. The new method seems to be much more sensitive than the older one but in the clinical and biochemical remission could remain moderately elevated. Because of its high sensitivity this new test is excellent for the early diagnosis of GD but we are convinced that the optimization of the reference range during therapy and remission need much more observations. The activity and course of GD is so individual that the changes of the anti-TSH-receptor antibody-level could be helpful not only for the diagnosis but also during the therapy.

MANAGEMENT OF HYPERTHYROIDISM IN CHILDREN AND ADOLESCENTS – THE USE OF RADIOIODINE THERAPY

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Graves' disease is the most common cause of hyperthyroidism in children and adolescents. The optimal treatment of children with Graves' disease remains controversial. Three major treatment options, e.g. antithyroid drugs (ATD), surgical resection, and radio-iodine ablation are currently available, but controversy still surrounds the optimal treatment.

Subjects and methods. We have conducted a retrospective review of the medical records of 45 patients (41 girls) seen at the University Childrens Hospital Ljubljana between 1991 and 2000 to determine management practice and outcome of therapeutic interventions.

All patients were initially treated with ATD. After an euthyroid state was achieved thyroxine was introduced, followed by definitive treatment with either surgery or radio-iodine if stable remission with ATD could not be achieved.

Results. Fourteen (31.1 %) patients achieved sustained long-term remission without a elapse with ATD alone. Of the 31 (68.9 %) patients with one or more relapses 3 (6.7 %) remained in remission without therapy, 15 (33.3 %) are remaining in remission currently on ATD treatment, one (2.2 %) did not reach any remission yet.

Twelve (26.7%) patients needed further therapy following failure of ATD treatment to induce sustained remission, because of recurrent relapses and side effects of medical treatment (agranulocytosis). Surgery was carried out in 6 (50 %), ablation therapy with ^{131}I was successfully used in other 6 (50 %) patients. Four patients underwent total and 2 subtotal thyroidectomy. Transient hypocalcemia was noted in 3 patients. One patient developed permanent hypoparathyroidism. All patients treated with radio-iodine received a fixed dose of radioactive iodine (15 mCi), one of the patients required a second dose of radioactive iodine. Transitory hyperthyroidism was noted in 4 patients. Permanent hypothyroidism developed in 5 patients. The average time to hypothyroidism was, 60 ± 31 days (range from 33 to 120 days).

Conclusion. Radioiodine offers a simple, effective and inexpensive method of treatment for Graves' disease in young patients. There are no immediate adverse effects and, although some theoretical concerns remain, to date the long-term safety record of thyroid ablation is excellent and the potential risks seem to be outweight by the advantages.

FOLLICULAR ADENOMA OF THYROID

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Benign thyroid neoplasms are called adenomas. Thyroid nodules are infrequently encountered and follicular adenoma is a frequent cause of a solitary thyroid nodule in children. In spite of the fact that the great majority of solitary thyroid nodules are benign, the treatment strategy is completely dominated by the risk for malignancy.

Case report. We present a 15 year old girl with palpable solitary nodule in the left thyroid lobe without any clinical signs or symptoms. Laboratory data: TSH 1.18 μIU/ml, FT4 1.27 ng/dl, T3 1.27 ng/ml, anti-TPO 125 IU/ml, TSI 5.9 %. Ultrasonography showed 31x17x14 mm nodule, with a 5 mm diameter cystic lesion in the middle. Otherwise, lobes were larger as compared to the age-matched controls with no hypoechogenicity but with slightly inhomogeneous structure. On scintiscan (^{99m}TC- pertechnetate) the lesion was cold. Fine needle aspiration (FNA) biopsy identified moderately packed follicular epithelial cells sometimes with clear cytoplasm, and a few epithelioid cells and lymphocytes. No neoplasia was diagnosed by FNA cytopathology. After six months of thyroid suppression therapy the size of the nodule was unchanged, and surgical intervention was decided. Enucleation was performed and histopathology on the sample found thyroid tissue, encapsulation by thick fibrous capsule. Within the capsule there were narrow follicles partly filled with colloid without sign of malignancy. There was no need for postoperative thyroxine substitution therapy.

Although most solitary thyroid nodules are benign, there is a definite risk of malignancy (about 20 %). Follicular adenoma is a benign neoplasm of follicular cells, showing a distinctive histology, clearly different from the surrounding thyroid, and well encapsulated. The microscopic differentiation (simple, micro-, macrofollicular, fetal, embrional, trabecular adenoma), as usually performed in the past, has no clinical significance. However, cytologically it is difficult to distinguish between follicular adenoma and well-differentiated follicular adenocarcinoma.

In the presented case the surgical intervention was indicated as based on the clinical presentation, no response to thyroid suppression as well as on sonography and scintiscan results. FNA did not support the diagnosis of follicular adenoma. The girl is under observation, as the mean recurrence rate after benign lesion of the thyroid is reported to be 5%.

THYROID AUTOIMMUNITY AND TYPE 1 DIABETES IN CHILDREN: THE EFFECT OF HLA-DQ POLYMORPHISMS

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Background and objectives. Type 1 diabetes mellitus is frequently accompanied by thyroid autoimmunity (TAI). The aims of the present study were to estimate the prevalence of TAI and to determine the contribution of HLA-DQA1 and DQB1 polymorphisms to TAI susceptibility among children with Type 1 diabetes.

Patients and methods. Two hundred and eighty five diabetic children (158 boys and 127 girls) aged 0 to 18 years were screened for thyroid autoimmunity using autoantibodies against thyroid peroxidase (anti-TPO)

and thyroglobulin (anti-Tg). The HLA-DQA1, -DQB1 were genotyped using polymerase chain reaction with sequence-specific primers (PCR-SSP). The levels of risk were calculated as odds ratios (OR) and their confidence intervals were expressed according to Woolf´s formula.

Results. Repeated positivity of TPO and/or Tg autoantibodies was found in 45/285 diabetic children (15.8 %). The prevalence rate was significantly higher in girls than in boys (27% vs. 7%, $p<10^{-4}$). The HLA-DQB1*0302 allele conferred susceptibility to TAI in children with Type 1 diabetes (OR 2.6, CI 95% 1.1-6.2, p=0.03), while the DQB1*05 alleles acted protectively (OR=0.24, CI 95 % 0.08 - 0.70, p=0.01).

Conclusions. The high prevalence of thyroid autoimmunity found in our group of Type 1 diabetic children emphasises the need for their regular screening. The present study indicates that the HLA-DQ polymorphisms significantly modify the risk of TAI in children with Type 1 diabetes.

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ENDOCRINOLOGICAL APPROACH TO CHILDREN AFTER CEREBRAL MIDLINE SURGERY

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Objective. To demonstrate the pitfalls in hormonal replacement therapy in diffuse or unsharply demarcated hypothalamic lesions.

Case report. We report on a 7 year old girl with a gigantic suprasellar brain tumor. She underwent surgical removal after a several months lasting shunting of the ventricular system. Immediately after the operation appeared mineral dysbalance (natremia up to 163 nmol/l, natriuria down to 2 nmol/l) necessitating a DDAVP therapy. It showed that the Adiuretin medication couldn‘t later be withdrawn. The central hypocorticalism first required continuous dexamethasone and hydrocortisone therapy, which however, could be stopped from the 9th day on. Six months later it had to be reestablished again. Also a permanent thyroxine replacement from the 6^{th} day after the operation has been initiated. Surprisingly this girl did not require any growth hormone treatment. Her growth rate even increased during two following years – in spite of corticotherapy.

Conclusions. In general, the endocrinological morbidity associated with CNS midline tumors is high, but usually managable with the aid of appropriate hormone replacement. In contrast to pituitary resections, the decrease of the whole hormonal production in midline hypothalamic lesions does not need to be complete. The often unpredictable postoperative development demands individually adapted hormonal therapeutic protocol.

Our case confirms this individuality in regard to the preserved activity of the adrenal axis starting from the subacute stage for the whole half a year and the preserved growth hormone secretion.

ENDOCRINE FUNCTIONS IN CHILDREN AFTER BONE MARROW TRANSPLANTATION - FOLLOW UP OF PATIENTS IN SLOVAK BMT CENTRE

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Since 1995 the Slovak bone marrow transplantation (BMT) unit has been established which was associated to the 2nd Department of Pediatrics, Children´s University Hospital in Bratislava. According to the increasing number of long-term survivors and potential endocrine complications after BMT we prospectively follow up growth, puberty, gonadal, thyroid and adrenal functions.

We have evaluated data from 26 patients (11 girls) after alogenic BMT and 6 boys after autologous BMT. Patients suffered from aplastic anaemia (7), AML or CML (6), ALL (9), lymphoma (2), solid tumors (3) and others (4). Age at the BMT ranges from 3 to 17 years. Time of follow up ranges from 1 to 6,5 years. Only chemotherapeutic preparatory regimen was used. Height, puberty Tanner stage and testicular volume, basal serum levels of TSH, fT4, LH, FSH, testosterone and cortisol were assesed and checked 6 months and than once yearly after BMT.

Preliminary results showed development of primary hypothyroidism in 3 of 26 patients, testicular failure in 3 of 6 pubertal boys, and ovarian failure in 6 of 8 pubertal girls. Gonadal failure developed earlier in boys (0,5 to 2 years after BMT) than in girls (2 to 5 years after BMT). We have not recognized significant changes in basal cortisol values.

Despite of a very heterogenic group of patients and relatively short period of follow-up we can conclude that endocrine functions are often disturbed in patients after BMT and that complications might occur in a long time period after BMT. Endocrine surveillance of BMT survivors belongs to basic follow-up regimen and adequate treatment of endocrine disorders in these patients increases their quality of life.

COHEN SYNDROME - IS AN ENDOCRINOLOGICAL FOLLOW-UP NECESSARY?

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Introduction. Cohen syndrome is an autosomal recessive disease. Its clinical picture is characterized especially by: psychomotor retardation, typical craniofacial features and body appearance, granulocytopenia and ophthalmologic symptoms. All phenotypical features develop and change with age. Some of children are of short stature or obese, delayed puberty is also frequent. Various endocrine abnormalities have been described in these patients so far.

Aims: Aims of this study are to describe clinical features and natural history of Cohen syndrome with a special focus on haematological, ophthalmologic, endocrine, cardiac, psychological and radiological characteristics.

Patients. 9 patients (6 males, 3 females) at the age of 2 - 20 years are followed-up. Cohen syndrome diagnosis was suggested in all patients by ophthalmologists first, according to typical ophthalmologic symptoms.

Methods. The examination programme includes general clinical evaluation (personal and family history, evaluation of morphological features), basic haematological examination, evaluation of endocrine function (clinical examination, hormone profile- IGF-I, IGFBP-3, fT_4, TSH, PRL, ACTH, cortisol, LH, FSH, estradiol, testoteron), heart ultrasound, hand X-ray, ophthalmologic examination, examination of the central nervous system (psychological examination, brain MRI and spectroscopy).

Results. Phenotypes of our patients are quite homogenous - facial features 9/9, myopia 9/9, retinochoroidal dystrophy 9/9, psychomotor retardation 8/9, granulocytopenia 5/9, short stature 5/9, truncal obesity 4/9, microcephaly 4/9. We observed abnormalities of hormone profile in 5/9 patients, mostly unspecific (4/5), most interesting is low level of IGF-I and IGFBP-3 in an asymptomatic girl of normal stature but with insufficient response in GH stimulation test.

Conclusions. Cohen syndrome should be suspected in children who born at term and healthy but by the age of 6 moths to 1 year show hypotony, microcephaly, delayed developmental milestones, and later non progressive psychomotor retardation, in addition to typical facial features, granulocytopenia, myopia and retinochoroidal dystrophy. It is difficult to judge whether endocrine abnormalities belong to this syndrome as true but rather uncommon features or whether they are just coincidental or express heterogeneity of this hereditary disease.

"MESPE" MULTICENTER STUDY ON SEPTO-OPTIC DYSPLASIA (SOD): FOLLOW-UP NOTES

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Objectives. The MESPE ongoing study on septo-optic dysplasia is still in the period of patient recruitment. The aim is to evaluate as many patients as possible according to a detailed investigation protocol. Uniform analysis of MRI films by one investigator and coordinated ophthalmological, endocrinological and neurological evaluation shall lead to creation of a diagnostic scoring system.

Patients and methods. So far, 25 patients from Austria and 11 Czech patients have been enrolled. Another 30-40 patients are expected from the other MESPE countries. Patients are followed with respect to ophthalmological, endocrinological, neurological, and MRI data. Ophthalmological investigations comprise exact evaluation of fundus pictures, ophthalmological symptoms like strabism or nystagm, and visual development. Base-line endocrine investigations are performed first, followed by provocative testing according to base-line results. Neurological data are obtained by motor, developmental, behavioural, and performance tests, adapted to the respective age of the individual patient. Additionally, EEG, VEP, and BAEP investigations are done. Olfactory testing is performed from age 10 years on if feasible. MRI films are evaluated centrally in Vienna by one investigator.

Results. Mean age at diagnosis was 5 years with a broad range from 0 to 24 years, ophthalmological symptoms being the most frequent leading to suspicion of SOD. Pituitary insufficiency was observed in nearly half of the patients, multiple deficiency occuring in about half of them. AVP and ACTH deficiency

were relatively frequent observations, while gonadotrophic function was preserved in most patients. MRI showed typical features like optic nerve hypoplasia, absent septum pellucidum and/or corpus callosum, and abnormities of the pituitary gland but also a malrotated or malshaped hippocampus, a feature so far unknown in SOD. Neurological and/or behavioural disorders were noticed in the majority of patients. As the recruitment phase is still going on, there are no definitive data so far.

Conclusions. The MESPE multicenter study will provide the biggest data base on SOD as compared to literature. Detailed analysis of data of each subspeciality can add new pathognomonic and nosologic features to this heterogeneous disorder.

ESTIMATION OF THE FALSE NEGATIVE RATE IN THE NEWBORN SCREENING FOR CONGENITAL ADRENAL HYPERPLASIA

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Background. An effective tool for early, preclinical diagnosis of congenital adrenal hyperplasia due to 21-hydroxylase deficiency (CAH) is the newborn screening (NS) based on measurement of 17-α hydroxyprogesterone (17-OHP) in a dried blood spot on the filter paper. The prevention of a life-threatening salt wasting (SW) crisis is the most important rational of this screening, while in patients with the simple virilizing (SV) form early diagnosis may avoid the disadvantages of excess androgen production. The possible inability to detect all cases (false negative rate) by the NS for CAH is discussed since its introduction. We intended to answer the question which percentage of our clinically ascertained CAH patients would have been detectable by the NS, in order to estimate its false negative rate.

Patients and methods. NS cards (dried blood spots on filter paper) of 110 patients with the classical type of CAH (77 SW and 33 SV) and cards of 920 random healthy newborn controls have been located and analysed. The patients originated from the Middle European CAH data bank (Austria, Czech Republic, Hungary, Slovakia and Slovenia). The diagnosis was based on the typical clinical symptoms and on elevation of basal serum 17-OHP and in most cases on CYP21 mutations analysis. The years of origin of the NS cards range between 1988 - 2000. All 17-OHP measurements in the dried blood spots were carried out using a time-resolved fluoroimmunoassay kit (DELFIA neonatal 17α-OH-progesterone kit, Wallac Oy, Turku, Finland).

Results. In patients with the SW form of CAH the median of 17-OHP levels in the NS blood spot was 561 nM/L (range 91 – 1404 nM/L), in patients with the SV form the median was 40 nM/L (range 4 – 247 nM/L). All 77 SW patients would have been detected by the NS using the cut-off limits recommended by ESPE (30 nM/L). However, 10 of 33 SV patients had 17-OHP levels below this cut-off and would have been missed. 17-OHP levels of all controls were below the cut-off.

Conclusions. NS for CAH is an efficient tool to diagnose SW form of the disease, but it is inappropriate to identify all patients with the SV form using the current cut-off values. It appears that the false negative rate in SV is at least one third.

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XY FEMALE INFANT WITH PROGRESSIVE BULBAR PALSY

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Testicular feminisation (XY genotype with female phenotype) is a rare clinical syndrome usually without any neurological disorder. We present an XY female baby with rapidly progressive bulbar palsy. The serum testosterone level after HCG stimulation was low, the androgen receptor structure was normal, and the histology revealed a dysgenetic gonad. The early onset of Kennedy-Alter-Sung syndrome was excluded. This type of presentation, which may be termed complete gonad dysgenesis with progressive bulbar palsy is a rare clinical condition. This case is being reported to call attention to determine the karyotype in the progressive neurological disorders of unknown origin.

METASTATIC ADRENOCORTICAL CARCINOMA: HISTORY OF THE FIRST YEAR OF LIFE (CASE REPORT)

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We present the medical history of a girl who showed the typical clinical picture of Cushing syndrome. Diagnosis was made when she was about 10 weeks old. Laboratory findings showed extremely adrenocortical hypersecretion (serum cortisol: 120 μg/dl, urinary free cortisol: >10000 μg/g creatinine, serum DHEAS: 980 μg/dl), while plasma ACTH level was not fully depressed. Severe hypertrophic cardiomypathy was diagnosed. Abdominal sonography revealed a well circumscribed mass in the right part of the abdomen. Chest computed tomography scan detected diffuse pulmonary metastases. Right adrenalectomy was done and the mass was completely resected. Left adrenal region was without any lesion. Histopathological examination of the tumorous mass defined adrenocortical carcinoma.

After complete resection of the primary tumor chemotherapy was given repeatedly (Cisplatin, VP/16) with combination of continuous o,p-DDD administration (1000 mg/day). During the time of this treatment no severe side effect was detected. Last control showed acceptable somatic development of the one year old child, without clinical signs of hypercortisolism and with partial regression of metastatic lesions.

IDENTIFICATION AND TREATMENT OF SALT-WASTING PATIENTS WITH CONGENITAL ADRENAL HYPERPLASIA

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Aim. To construct guidelines for starting mineralocorticoid replacement therapy in classic CAH patients, clinical and laboratory data of newborns and infants with 21-hydroxylase deficiency (21-OHD) have been studied.

Patients and methods. Serial blood sampling for measurement of serum sodium and potassium levels was performed in 116 patients with classic 21-OHD (180 samples derived from 107 salt-waster patients, SW; 21 samples from 9 simple virilizers, SV) during the first weeks of life before starting mineralocorticoid and glucocorticoid replacement therapy.

Results. In SW patients mean serum K level increased to 6.3 mmol/l at age of 9 days (5.1-7.5 mmol/l, -1 to +1 SD, resp.) accompanied by a body weight below birth weight. Serum K reached summit (8 mmol/l) at age of 15 days. Mean serum Na level decreased below 130 mmol/l at age of 12 days, and below 120 mmol/l at age of 21 days, resp. Patients with normal increase of body weight and normal serum sodium levels during the first two weeks of life have been defined as simple virilizers. However, these patients had serum potassium levels between 5.6 and 6.6 mmol/l at age of 6 to 29 days of life, but normalization of electrolytes occured without mineralocorticoid replacement therapy during the second month of life.

Conclusions. There is no clear-cut differentiation of patients with and without salt-wasting state. Therefore all classic patients with CAH should be treated by mineralocorticoid replacement therapy from the 10th day of life on to prevent life-threatening salt-losing crisis. Reevaluation of salt-wasting state is suggested at age of 6 to 12 months of life by PRA measurements after withdrawal of mineralocorticoid replacement.

THE RESULTS OF THE SCREENING FOR HYPERCHOLESTEROLEMIA IN 5 YEAR OLD CHILDREN IN SLOVENIA

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Background: The developed countries are reporting the increased incidence of cardiovascular disease which is the most frequent cause of morbidity and mortality. Dyslipidemia is one of the important cardiovascular risk factors. Elevated cholesterol levels (especially LDL cholesterol) and increased triglyceride levels contribute to the progression of atherosclerosis. The increased lipid levels predict the subsequent cardiovascular disease already in the young age. Many developed countries have started programs for the early detection of hypercholesterolemia. In Slovenia we have screened the cholesterol levels in children at the age of five for the last 5 years. The data of total cholesterol concentrations obtained from a group of 5-year old children were analyzed in the present study.

Methods. 17 pediatric primary care facilities from Slovenia were taking part in the study. Values of total cholesterol concentration of 2742 children born 1995 or 1996 were collected. The values of body mass index (BMI) were included in the analysis. The study was approved by the State committee for medical ethics.

Results. Total average cholesterol concentration was significantly higher in girls (4.46 ± 0.78 mmol/L) compared to boys (4.33 ± 0.76 mmol/L)(p<0,0001). Twenty-one percent of values were above 5 mmol/L, 15 % above 5.2 mmol/L, and 2.8 % above 6 mmol/L. Values of total cholesterol concentration were not distributed according to the normal distribution.

LDL cholesterol level and total cholesterol concentration did not correlate with the BMI. A significantly higher proportion (p<0,002) of the girls with BMI above 90-percentile of the standard had a total cholesterol concentration above 5 mmol/L. No such difference was observed in boys with BMI above the 90-percentile of the standard.

Conclusions. The screening for hyperlipidemia in childhood has been started in many countries and the results of the present study are in accordance with other similar published studies. Hyperlipidemia is one of the determinants of atherosclerosis in the youth and general screening for hypercholesterolemia in childhood is cost effective. Twenty-one percent of Slovenia population has total cholesterol concentration above 5 mmol/L. The long-term follow-up of these children is planed in the future. The medical care will be structured and rationally planed. The dietary modifications and behavioral therapy in the childhood are easier to perform and more successful if started early. The preventive change of the life-style can be the main advantage of early detection of hypercholesterolemia.

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TYPE 2 DIABETES MELLITUS IS RARE BUT NOT ABSENT IN CHILDREN <15 YEARS IN AUSTRIA

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Background. Until recently most children with diabetes mellitus (DM) had type 1 diabetes. The prevalence of type 2 DM is on the rise in North America especially in risk populations as the American Indians and as well as in Japan. Few epidemiological data on the incidence of the disease exist in Europe.

Aim. To evaluate the incidence of type 2 diabetes mellitus in Austria in children younger than 15 years of age between 1999 and 2001.

Methods. Population-based epidemiological study. Newly diagnosed cases of diabetes mellitus <15 years were registered prospectively nation-wide since 1989. In 1999 the different types of diabetes according to the ADA diagnostic criteria were registered separately in the same network. Differential diagnosis was based on clinical case definition.

Results. During the three years of the study period 537 cases of DM <15 years were documented. 510 were clinically assigned to type 1 DM (271 boys, 239 girls) resulting in a incidence of 11,97 –13,07/ 100 000. In the same network nine cases were diagnosed as type 2 DM (2 boys, 7 girls) and three cases with an atypical form of type 2 DM (Prader Willi syndrome etc, 1 boy, 2 girls). Together representing 2,3% of the total diabetic cohort diagnosed during the same period. The age of onset of type 2 DM was 12-15 years and all patients were overweight (BMI >90 percentile).

The calculated incidence for type 2 DM <15 years in Austria was 0,22/ 100 000 (0,07 –0,38/ 100 000).

Conclusion. At the moment type 2 DM is rare but not absent in children <15 years in Austria. Follow up of this registration will help to describe the secular trend.

GENETIC EVIDENCE THAT HNF-1A REGULATES HNF-4A EXPRESSION IN HUMAN PANCREAS: EXPERIENCE FROM A CZECH MODY FAMILY

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Mutations in the genes encoding hepatocyte nuclear factor-4α (HNF-4α)/MODY1 and HNF-1α/MODY3 impair insulin secretion and cause Maturity Onset Diabetes of the Young (MODY). HNF-4α is known to be an essential positive regulator of HNF-1a in the liver. More recent data demonstrate that HNF-4α expression is dependent on HNF-1α in mouse pancreatic islets and exocrine cells. This effect is mediated by binding of HNF-1α to a tissue specific promoter (P2) located 45.6 kb upstream from the previously characterised HNF-4α promoter (P1).

We have identified a MODY family where the proband is a 23-year-old girl diagnosed with diabetes 9 years of age. She is treated with insulin and has no signs of diabetic complications. Her mother started with insulin therapy at the age of 19. Mother's brother and sister have both diabetes too. Screening for mutation in the HNF-4α, HNF-1α, GCK, IPF-1 and NeuroD1 genes did not reveal any mutations. After suggestive linkage to the MODY1 locus was obtained by multipoint linkage studies, we sequenced 1kb of the HNF-4α P2 promoter in the proband, and a G to A nucleotide substitution was found in a conserved nucleotide position of the HNF-1α binding site of the P2 promoter. This mutation co-segregated with diabetes in the family.

Here we report that the expression of HNF-4α in human islets and exocrine cells is primarily mediated by the P2 promoter. The mutation results in decreased affinity for HNF-1α, and consequently in reduced HNF-1α dependent transcription. These finding provide genetic evidence that HNF-1α serves as an upstream regulator of HNF-4α and interacts directly with the P2 promoter in human pancreatic cells. This regulation is essential to maintain normal pancreatic function.

METFORMIN TREATMENT IN OVARIAN HYPERANDROGENISM OF ADOLESCENT GIRLS

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Evidence suggest than insulin resistance (IR) and the resulting hyperinsulinemia (HI) are associated with ovarian hyperandrogenism (OHA) and menstrual irregularities in adolescent girls. Insulin resistance, impaired glucose tolerance (IGT) and HI are observed frequently in both obese and lean patients with OHA. Reduction of IR and HI may be considered as a treatment alternative of OHA and may lead to prevention of the later full development of PCOS, infertility and other complications.

Nineteen obese adolescent patients with OHA, HI, and IGT on a sugar-free diet were studied before and after one month, 6 months and 12 months of therapy with metformin 2x850 mg per day, an insulin sensitizing agent of the biguanide class. Average age of the patients was 17.65 years (17-19.07 years) with a BMI 30.8 (28.0-35.0), LH/FSH ratio 4.1 (0.4-9) plasma testosteron 1.08 ng/ml (0.2-2.61 ng/ml), plasma androstendione 288.5 ng/dl (110-613), pl. E2 52.29 pg/ml (2.4-137.7), fasting plasma glucose 4.8 mmol/l (4.3-8.5), fasting pl. insulin 23.83 μIU/ml (8.97-35.36), Ferriman-Gallwey score 16.8. Nine patients (47%) had a first degree relative with NIDDM, compared with baseline values the levels of LH/FSH ratio, plasma testosterone and androstendione decrease significantly. At the 12 months of treatment with metformin and sugar-free diet LH/FSH ratio was 1.1, plasma testosterone 0.59 ng/ml (0.23-1.1), androstendione 214.1 ng/dl (97-392), fasting IRI 10.9 uIU/ml. Fasting glucose values remained in normal range. No significant changes were recorded in body weight, so these effects appeared to be independent of weight loss. Ten subjects resumed normal menstruation and 9 patient after ovulation induction therapy with clomiphene citrate. Metformin was well tolerated, moderate side effects as flatulance, diarrhoea, nausea were observed at the beginning of the treatment. Later 4 subjects left the treatment because of headache, nausea and flatulance and fifth patient without any explanation.

Our results confirm that metformin treatment can lead to improvement in IR, HI and OHA and menstrual irregularities.

MATERNALY INHERITED DIABETES MELLITUS IN PATIENTS WITH MTDNA MUTATION A3243G

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Inherited disturbances of mitochondrial energy generating system represent heterogeneous group of disorders, which may affect together with the function of various tissues also the function of endocrine glands. Mutations in mitochondrial DNA (mtDNA) may be found in 1-1,5% of patients with diabetes mellitus (DM). This percentage is much higher in patients with maternal history of DM. The most common mtDNA mutation associated with maternally inherited diabetes mellitus (MDM) is heteroplasmic mtDNA mutation A3243G which is usually associated with clinical manifestation of syndrome MELAS. Some 70% of patients with MDM have also sensorineural hearing loss.

Patients and methods. Clinical and laboratory data of 25 patients in the age between 1 and 63 years from 11 families harbouring the heteroplasmic mtDNA mutation A3243G were analysed. In these patients, a broad spectrum of heteroplasmy was found in blood (3–65%), in hair folicules (2–70%) and in muscle tissue (26- 87%).

Results. Diabetes mellitus was found in 8 from 25 patients with mtDNA mutation A3243G (33%). In these patients, diabetes mellitus manifested between 13 and 46 years and their BMI was 12-28. Three patients have short stature (-2 SDS). Sensorineural hearing loss was found in 7 patients. Two patients have myopathy and two other cardiomyopathy, one boy has classic manifestation of MELAS. Six patients are treated with diet or oral hypoglycemic agent, two patients switched to insuline after several years of the disease. The level of B-lactate was significantly higher in patients with MDM (2,34 ± 0,7 mmol/l) in comparison with other family members with the same mutation (1,1 ± 0,2 mmol/l). In 6 from 9 families with more than one affected generations the percentage of mutated mtDNA was higher in maternal offsprings. The ratio of mutated mtDNA was highest in patient with neurologic manifestation (more than 60%) and lowest in patient, in which diabetes mellitus was the only manifestation.

Conclusion. Mitochondrial diabetes mellitus should be considered in noneobese patients with early onset of diabetes, especially if sensorineural hearing loss or short stature is present or if there is a positive family history of diabetes mellitus in maternal relatives.

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CSII TREATMENT IN CHILDREN AND ADOLESCENTS WITH T1D IMPROVES METABOLIC CONTROL AND QUALITY OF LIFE

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Aim. The ultimate goal of T1D treatment is to achieve sustained normoglycemia with the lowest incidence of hypoglycemia. Only a minority of patients accomplish the desired standard of glycemic control on treatment with multiple daily injections of insulin. CSII offers a more physiologic way to deliver insulin. The aim of the study was to compare glycemic control of children and adolescents with T1D before the beginning of CSII treatment and 6 to 24 months after it.

Patients and methods. Currently 100 patients with childhood-onset T1D participate in the CSII treatment program. Data on 62 patients (42 % female) who use the insulin pump for more than 6 months were analyzed. Mean duration of the use of CSII treatment, mean glycosilated hemoglobin (GlyHb) A1c pre and 6 to 24 months post CSII treatment were calculated. Quality of life was assessed by an interview.

Results. After a mean duration of CSII treatment of 1 year, mean GlyHbA1c decreased for 1.7 %, 2.2 % in females and 1.3 in males (Table). Patients expressed a significant improvement in quality of life with a reduction of hypoglycemic events.

	Duration of CSII (y)	GlyHbA1c – before (%)	GlyHbA1c – after (%)
Female	1.1 ± 0.3	10.1 ± 1.7	7.9 ± 1.0
Male	0.9 ± 0.4	8.9 ± 1.2	7.6 ± 0.8
All	1.0 ± 0.4	9.4 ± 1.6	7.7 ± 0.9

Conclusion. CSII treatment is a major advance for children and adolescents with T1D allowing individuals to be more in control of their condition. In our study, CSII treatment was associated with a significant improvement in glycemic control, a concomitant reduction of hypoglycemic events and a considerable improvement of quality of life.