1. GROWTH AND ENDOCRINE DATA IN CHILDREN AFTER BRAIN TUMOR AND IRRADIATION

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Due to advances in therapeutic regimes of malignant brain tumors in childhood the survival rates have significantly improve over the last decades. Besides neurological problems, long-term survivors of child brain tumors are at high risk of developing irradiation induced hypothalamic-pituitary dysfunction, primary hypothyroidism and severe growth retardation due to diminished growth of the spine after craniospinal irradiation and additional hormonal deficiency. In several patients the first clinical sign of endocrine disturbance is the precocious or early puberty. Thus, the growth velocity may be normal even in spite of the presence of growth hormone deficiency which results in late diagnosis and treatment and further results in severely affected body height in adulthood.

In numerous previous investigations, the frequency of endocrine defects, the relation to irradiation dose and time after the end of treatment have been documented, indicating that the growth impairment of the spine and hypothalamic deficiencies may still develop after 5-10 years or more, while in several cases the thyroid function noramlizes. These studies retrospectively analyzed the data of patients after various treatment protocols with a wide range of irradiation doses and time after the end of treatment.

We recently started an endocrine and auxiological analysis of patients treated for brain tumors in our department and so far treated 18 of such patients. The aim of this study was to define the frequency and time course of growth- and endocrine deficiencies in this homogenous groups of patients as defined by the rather high irradiation dose combined with chemotherapy. On the basis of these data we further aim to define a prospective protocol for auxiological and endocrine investigations. It is essential that these patients are seen by an pediatric endocrinologist from the very beginning, since our experinece showed that the correct interpretation of the growth curve requires sufficient frequency of the data on body proportions and pubertal development as a basis for the timing of endocrine testing and eventual hormonal replacement.

2. FINAL HEIGHT AND BODY MASS INDEX AFTER TREATMENT FOR CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA

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Objective. The growth and weight expressed as body mass index (BMI) of 48 patients (28 girls, 20 boys) long-term survivors of childhood lymphoblastic leukemia was retrospectively analyzed.

Methods. Height standard deviation score (HSDS) according to Tanner and body mass index standard deviation score (BMISDS) before the treatment and at follow-up were calculated. At the time of analysis all patients remained in the first remission. Twenty nine patients had cranial radiation with 1200-1800 cGy and 15 with 2000-3000 cGy. Four patients had no radiotherapy. All patients were treated with standard chemotherapy including intrathecal Methotrexat. Mean age (±S.D.) at the diagnosis was 6.1 (±3.60), range 1.1-13.8 years and that at the time of evaluation was 17.9 (±3.71), range 13.8-31.5 years. Statistical comparisons were made by Student's paired and unpaired t-test.

Results. We observed significant decrease in HSDS from diagnosis to the final geight in both radiation groups ($P<0.01$), but the decrement in final height was similar with both radiation dose regimens. The decrement in final height SDS was greater in the patients treated at young age ($P<0.01$). Girls treated with higher radiation dose (2000-3000 cGy) were more severely affected than boys ($P<0.01$). In both groups treated with different radiation doses significant increase of BMISDS was found between the height at diagnosis and at the end of treatment ($P<0.001$) with no significant difference between the treatment groups. In the treated girls the menarche occurred significantly earlier in comparison with normal girls according to Tanner with no significant difference between both radiation regimens used.

Conclusions. Significant deterioration of HSDS and increament of BMISDS was observed regardless to the radiation dose. The relative roles of cranial radiation and chemotherapy in the disturbance of growth, puberty and body composition, as observed in the survivors of childhood ALL, is most liely a multifactorial cumulative role of radiation induced growth hormone failure, early puberty, steroids and chemotherapy all having the role.

3. ENDOCRINOPATHIES IN PATIENTS AFTER TREATMENT FOR HODGKIN'S DISEASE AND SARCOMAS IN CHILDHOOD

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Background. In patients treated for Hodgkin's disease (HD) and soft tissue or bone sarcomas (SA in childhood by surgery, chemotherapy and radiotherapy, late sequelae including endocrine dysfunction are common.

Patients and methods. Standard endocrinological tests were used to determine endocrine function in 23 patients, among them 14 (10 males and 4 females) being treated for HD and 9 (7 males and 2 females) for SA.In this group, 8 patients were suffering from sarcoma of the soft tissue and one from oestrogenic sarcoma. At diagnosis the mean age of the patients with HD was 10.4 years (range 5.0 to 14.0), while that of the patients with SA was 9.5 years (range 5.0 to 13.2).

At the time of the follow-up examination the mean age of HD patients was 22.2 years (range 17.3 to 30.0) and that of SA patients was 18.8 years (range 16 to 22).

The evaluation was performed at least 5 years after the treatment, the mean interval being 11.7 years (range 5-21) for the patients with HD and 9.3 (range 6-12) for the patients with SA.

Results. Endocrine dysfunction was found in over 80 % of all treated, and it was clinically evident only in 26 %. We detected a high prevalence of hypotha-

lamic-pituitary-gonadal dysfunction due to gonadal lesion comprising 11 (78.6%) patients with HD and 7 (77.8%) patients with SA.

Thyroid dysfunction was found in 7 (30.4%) patients examined, primary latent hypothyroidism in 3 patients with HD and in 2 with SA, secondary hypothyroidism in one patient with HD and in one with SA. There were 2 cases of adrenal dysfunction, one in a patient with HD and one in a patient with SA.

Pituitary dwarfism with diminished levels of growth hormone and IGF-I was found in one patient treated for SA.

Conclusions. According to the results of our study, for the patients for HD and SA in childhood the function of the hypothalamic-pituitary-gonadal axis and of the thyroid gland should be assessed at frequent intervals in order to detect endocrinological abnormalities and to introduce a replacement therapy when necessary.

4. ENDOCRINE FUNCTIONS AFTER ANTILEUKEMIC TREATMENT

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Objective. The aim of this study was to reveal potential disturbances in endocrine functions in adults who were treated with antileukemic therapy during childhood.

Patients and methods. We evaluated 59 adolescents and young adults (28 males and 31 females) aged 15-25 years (mean 18 years) who underwent intensive chemotherapy and cranial irradiation (24 Gy or 18 Gy) because of acute leukemia, and were disease free for a minimum of three years (3-12 years, mean 7 years) after the completion of treatment. The following parameters were evaluated: basal auxologic data (H=final height, W=weight, BMI=body mass index, MPTH=difference to midparental target height), TSH=thyrotropin, T4=thyroxine, USG=thyroid ultrasound, sexual development staging, age of menarche.

Results. As shown in the Table, there was no statisticaly important difference in auxologic parameters between those with higher (24 Gy) and lower (18 Gy) dose of cranial irradiation. Hypothyroidism was diagnosed in 1 female and 3 males, smaller thyroid volume by USG in 3 males and 1 female. Sexual development was appropriate to the age in all except of two male subjects with primary hypogonadism after irradiation to testes because of testicular leukemic infiltration. The age of menarche was 9.5 to 14 years (mean 12 years).

Auxologic data	Females (N=31)	Males (N=28)
H	145-170 cm (m 160 cm)	164-191 cm (m 175 cm)
MPHT	+5.5 to -12.0 cm (m -5.5 cm)	+9.0 to -6.0 cm (m -3.5 cm)
W	35-84 kg (m 60 kg)	54-197 kg (m 68 kg)
BMI	14/32 (m 24)	17-36 (m 22)

Conclusions. Median height was lower than the average height of general population. Apparently short were 2 males (164 and 165 cm) and 1 female (145 cm). The majority of study subjects did not attain their midparental target height. A strong tendency to overweight was apparent both in the male and female subjects. Evidenmtly obese were 5 females and 3 males. No signs of central hypogonadism were found, but two male subjects suffered from primary hypogonadism after the irradiation of gonads. In the majority of females menarche started earlier than the average in our general population. One male and 4 females were already parents and had a total of 6 healthy children. Regular evaluation of thyroid functions revealed hypothyroidism in 4 subjects which were then treated by hormonal substitution. The results of this study call for a regular evaluation of endocrine functions in the subjects who underwent antileukemic treatment.

5. SERIOUS OBESITY AND MENTAL REGRESSION AFTER SURGERY DUE TO CNS-MIDLINE TUMOURS IN TWO ADOLESCENT GIRLS

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Patients with tumours affecting the hypothalamic-hypophyseal area are at high risk of developing multiple pituitary deficiencies due to surgery and radiation. Supplemetation of hormonal deficiency often fails to be effective and well tolerated, especially in respect to corticoids. Moreover, obesity can be a long lasting disastrous handicap even in carefully treated patients.

We report on 2 adolescent girls, who were diagnosed with craniopharyngeoma (CP; aged 14) and with astrocytoma I (AC; aged 16), respectively. The patient with CP underwent surgery and irradiation with a total of 55 Gy, whereas the girl with AC only was subjected only to the radical surgery. Each of them was treated with rhGH, estradiol, thyroxine and hydrocortisol at a very low dose. GH treatment was succesfull only in the AC patients. Unfortunately, the CP patient died 4 years after diagnosis due to anaplastic astrocytoma III which was most likely induced by irradiation. Both patients became cushingoid and showed overweight as early as during the first months after treatment. Most alarmingly, they suffered from mental regression. Their behaviour turned to an introverted, childish fashion and perseverating nonsense actions (e.g. washing procedures). The pathogenesis of these quite worrying features are yet unknown. We would like to discuss this in the context of the hormonal and auxological data of our patients.

6. PARTIAL GROWTH HORMONE SENSITIVITY – CLINICAL AND BIOCHEMICAL ASPECTS

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Introduction. During the last years the growth hormone (GH) insensitivity (GHI) has been frequently discussed in the literature. Although the clinical and biochemical indicators are very typical in the case of the homozygous mutation of GH receptor (Laron syndrome), they are not as well defined in the cases of heterogenous GH receptor (GHR) defects. Although some of these GHR mutations may result in relative insensitivity to GH in some studies, obligate heterozygotes did not present any obvious clinical manifestations. In contrast, biochemical parameters of partial GHI have been described: elevated GH binding protein levels, lower levels of insulin-like growth factor I (IGF I) and IGF binding protein 3 (IGF BP3). Whether the sensitivity of this screening approach can be increased by administering pharmacological doses of GH for a few days and measuring the resultant increase in serum IGF I concentrations (IGF generation test) remains to be determined by studies.

Aim and methods. We have investigated the clinical and biochemical indicators of partial GHI in a group of children with idiopathic short stature (ISS). We have tried to find the parameters which

differentiate the children with partial GHI in a group of ISS. IGF-I and IGF BP3 increments in IGF-I generation test (serum levels after the stimulation with rhGH (2 IU/m^2/day for 4 days) were used as the markers of partial GHI in children.

Patients. 44 children with ISS (height about -2SD) who were rearranged in different groups regarding parental height, bone age, basal and stimulated serum levels of GH.

Results and discussion. The diagnostic increment in IGF generation test for Laron syndrome is less than 15 mmmg/l for IGF-I and less than 0.4 ng/l for IGF BP3. None of the tested children has reached these criteria. An increase of IGF-I level bellow 25 % was suggested as an arbitrary cut off level for partial GHI (Thalange 1996). Four patients from the total number of the children have fulfilled this criteria (9 %), three of them with height >-2.6 SDS. This proportion is in agreement with the data about the frequency of the heterozygous mutations of GHR gene in the group of ISS (Goddard 1977).

The groups which were selected on a basis of clinical features (midparental height, bone age), were ot significantly different in any tested parameters. The patiets of a group selected for a high basal and stimulated GH levels had a signifificantly reduced IGF-I response to stimulation compared to the patients with normal levels (median percent incremenet in IGF-I was 57 % versus 167 %).

Suggestions. Our present work could be a good pilot approach for the multicenter study. Regarding our results we propose a following protocol:

– aim: phenotype/genotype in partial ISS and the usefulness of the IGF-I generation test
– including criteria: height about -3 SDS (ISS), age 3 to 8 years, prepubertal stage, IUGR may be present
– methods: IGF generation test, GH binding protein, genetic analysis of GHR genee and may be some other genetic analysis (as SHOX genes or dopamine receptor gene), bone mineral density
– number of patiemts: 50 children
– duration of the study: 2 to 3 years

7. GnRH ANALOGUE AND rhGR THERAPY IN CONSTITUTIONAL ADVANCE OF PUBERTY (CAP)

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The aim of this study is to demonstrate the real efficiency of GnRHa and rhGH treatment in girls who enter the puberty earlier regarding their height and bone age. Twelwe girls were diagnosed as CAP (CA: 8-10 yrs; statural age <-2 SD; bone age >+1-5 yrs according to Tanner et al.; mother's height <155 cm; puberty II-III Tanner stages; the projected adult height (PAH) for BA <150 cm) and treated with GnRHa alone (6 girls; 75 mmmg/kg/4 weeks) or with a combination of GnRHa plus rhGH (6 girls; 0.5/1.0 U/kg/week) for 30 months in average. The final height became 152 cm (5 cases) using combined therapy. The mean PAH in this group was 152.5 cm which was by 5.2 cm more than before the treatment. The gain proved to be 2.8 cm only in the group treated with GnRH alone. Negative correlation was found between the BA before therapy and the change of PAH during therapy (r=0.372).

Conclusions. 1. The GnRHa plus rhGH combination is more succesful than the GnRHa alone. 2. This form of hGH treatment – in contrast to some literary data – seems to be more effective in girls with CAP (who enter puberty early for BA) than in other special entities. 3. The late start of the therapy in relation to the BA stunts the good growth result.

8. GROWTH HORMONE THERAPY AFTER COMBINED TREATMENT OF CRANIOPHARYNGEOMA – A CASE REPORT WITH QUESTIONS

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Introduction. Craniopharyngeoma (C) is a congenital tumour derived from embryonic tissue presenting either endocrine or neurological symptoms. Its treatment consists of surgical resection, cyst aspiration, with or without radiotherapy and often a consecutive hormone replacement required. Question was raised whether recurrence rate of C is increased after growth hormone (GH) treatment or not. Statistical analysis does not support the view that GH increases the risk of relapse, though in all cases of C the decision should be done individualy.

Case report. The authors present the case of a boy subjected to surgery for C in which the recommendation of GH administration would be either confirmed or ruled out. Valid retrospective height data were available retrospectively to the birth length (33 measurements) and intracranial examinations were carefully repeated since the date when C was revealed (2 MRI + 20 CT scans as indicated by the neurosugeon). The boy showed neurological symptoms for several weeks prior to obtaining the diagnosis at the age of 6.5 yrs. Surgical removal of the tumour by subtotal resection was performed via craniotomy, and recraniotomy succeeded after 16 months. The yttrium capsule has been implanted three times after 6-6-5 months intervals. Since the progression of cyst formation seemed to be terminated after 6 months, GH treatmnet was initiated to improve the poor height velocity, beside the previously introduced thyroxine and ADH replacement. GH administration (0.5 IU/bw/week) has been continued for 12 months at half time with a control CT scan. Discontinuation of GH treatment was indicated due to recurrence of C. Subtotal resection was carried out repeatedly according to the control MRI scan verifying a tumour residuum. Four years elapsed after the last surgery and the decision on GH treatment would be done because of the poor height velocity. Growth rate of the 15 yrs old prepubertal short boy (140 cm) was the following: before the diagnosis 3.5 cm/yr, after the first surgery 7 cm/yr. At the time of radiotherapy followed by the second craniotomy 4 and 3 cm/yr, during the GH treatment 9.3 cm/yr, after the third surgical removal 2/2.5/1.5/2.7 cm/yr, respectively.

9. HYPOGLYCEMIA IN INFANCY: GENERAL ASPECTS AND WHEN TO CONSIDER INBORN ERRORS OF METABOLISM

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The central organ for maintenance of glucose homeostais is the liver with its gluconeogenetic and glycogenolytic pathways. In the regulation of these pathways various hormones (insulin, STH, glucagon, cortisol, adrenalin) are involved. By these mechanisms, in the fasting state, blood glucose levels are maintained for 6-12 hours in infants, and up to 30 hours in elder children.

Differential diagnosis of hypoglycemia is based on the presence/absence of ketosis, hepatomegaly and excretion of organic acids. The most frequent cause of hypoketotic hypoglycemia due to reduced availability of gluconeogenetic substrates is most frequently observed in infants at 1-6 years. In patients with hypoglycemia and hepatomegaly disorders of glycogenolysis and gluconeogenesis should be considered. Fatty acid oxidation defects are characterised by non (hypo) ketotic hypoglycemia, hepatopathy and acute progressive encephalopathy.

10. PERSISTENT HYPERINSULINEMIC HYPOGLYCEMIA OF INFANCY (PHHI): CLINICAL AND MOLECULAR HETEROGENEITY (REVIEW)

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Persistent or recurrent hypoglycemia during the neonatal period and in infancy is a potential life-threatening condition and can lead to permanent brain damage. Hyperinsulinisn is the most common cause of hypoglycemia in early childhood. PHHI is relatively easily diagnosed by demonstrating (during hypoglycemia) inappropriately elevated levels of insulin and/or C-peptide, hypofattyacidemia and hypoketonaemia. The exogenous glucose requirement to maintain normoglyucemia is also inappropriately high (>10 mg/kg/min),

Transient hyperinsulinemic hypoglycemia is observed in infants of poorly controlled mothers, in infants with asphyxia, and in small for gestational age neonates.

PHHI can be caused by insulinoma of the pancreas and recently several genetic forms have been described. These include mutations of the sulfonylurea receptor (SURI), the potassium pore (KIR6.2), glucokinase, and glutamate dehydrogenase (hypoglycemia is associated with hyperammonaemia) genes and focal hyperinsulinism with somatic loss of maternal chromosome 11p15.1.

Medical therapy involves drugs such as diazoxide and somatostatin which inhibit insulin secretion. Recently, calcium channel blockers have been used with success in some cases. Failure of medical therapy is an indication for pancreatectomy. Before surgery is considered, the possibility of focal hyperinsulinism should also be explored, since partial pancreatectomy may be curative in these cases.

11. HYPOGLYCEMIA IN CHILDREN: FOUR SAD CASE STORIES

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Aim. To document medical hazards of childhood hypoglycemia on the background of case histories.

Case history 1. At the age of 2.5 months, Susan suddenly developed unconsciousness and seizures after an overnight fasting. Lumbal puncture was done because of the suspicion of meningitis and revealed a low glucose level in CSF (0.7 mmol/l). The corresponding blood glucose level was 1.1 mmol/l. Even

after glucose infusion, glycemia remained low (1.9-3.4 mmol/l), but symptoms disappeared. Insulin at the glycemia of 1.9 mmol/l was high (26 mU/l). Nesidioma was not found. Subtotal pancreatectomy was done and histology revealed diffuse ß-cell hyperplasia typical for PHHI (nesidioblastosis). Susan suddenly died at home some months later.

Case history 2. Lucy suffered from transitory total alopecia at 2 years, from hypothyroidism starting at 4 years, from "nail dysplasia" and from frequent infections. At 5 years, she vomited repeatedly and got high fever during a gastrointestinal infection. She got seizures when sleeping and could not be waken up. Her glycemia was 1.0 mmol/l and cortisol only 6 nmo/l (normal: 140-700 nmol/l). She developed Addison disease within APS-I. Her "nail dysplasia" in fact was a sign of candidiasis. This story happened 5 years ago, but Lucy is remaining in a vigil coma.

Case history 3. Mary, a full-term baby, had hypoglycemia (1.2 mmol/l) with tonic seizures and apnoea at 2nd day of life. At 8 months, she got seizures and a transitory unconsciousness in the morning. Blood glucose was not measured. She was treated for "refractory epilepsy" bacause of frequent seizures, mostly during intercurrent illnesses. Much later, her parents noted that Mary is not growing well. At 7 7/12 years, her height was 106.5 cm (-3.4 SD). After initial vomiting, she had asymptomatic hypoglycemia of 1.8 mmol/l with GH <1.5 mmmg/l and normal cortisol. Central hypothyroidism was supported by fT4 and TSH levels. Mary suffers from GH deficiency. She has serious school problems and her IQ is 74 – probabluy due to frequent hypoglycemia.

Case history 4. Jane presented with unconsciousness and seizures at 7.30 a.m. after an overnight fast at the age of 3.5 years. Her blood glucose was 0.8 mmol/l. Her brother died suddenly 5 years earlier at his 3rd day of life. The autopsy revealed diffuse myocardial and liver steatosis. The other day, Jane had asymptomatic hypoglycemia (1.5 mmol/l) with only slightly positive ketones in urine. Insulin and C-peptide were low, cortisol and GH were high. Glucagon testing gave normal results. Jane was found to suffer from medium chain acyl-CoA dehydrogenase (MCAD) deficiency, a ß-oxidation defect. Her brother was ubdoubtedly also affected. One year later, Jane dies suddenly at home.

Conclusions. 1. Pediatricians should be aware of hazards of hypoglycemia and should be trained to recognise affected individuals; 2. In infants/children with "epileptiformic" symptoms, hypoglycemia should be excluded; 3. Blood and urine sampling at hypoglycemia is a clue to a quick and efficient diagnosis; 4. Children with polyglandular autoimmunity should be examined for silent Addison disease; 5. Infants/children with a history of hypoglycemia have to get immediate glucose infusion at intercurrent illnesses with reduced food intake and/or vomiting.

12. EXOCRINE PANCREATIC INSUFFICIENCY AFTER SUBTOTAL PANCREATECTOMY DUE TO PHHI (CASE REPORT)

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Introduction. Persistent hyperinsulinemic hypoglycemia of infancy (PHHI) may be a life-threatening condition leading to cerebral damage. In severe cases with failure of medical therapy surgical treatment is indicated.

Case report. We report on a case with PHHI who presented postpartally with recurrent severe hypoglycemic episodes (BG <20 mg/dl, insulin 90 mmmU/ml) despite treatment with diazoxide and intravenous glucose (>10 mg/kg/min). Subtotal (95 %) pancreatectomy was performed at the age of three weeks. During a short period postoperatively the patient required insulin substitution because of hyperglycemia. Stable normoglycemia was achieved three weeks after pan-

creatic surgery. At the age of two and a half year the child showed polydipsia and despite polyphagia failure to thrive. Glucose tolerance was normal, but fecal elastase levels were subnormal in accordance with the diagnosis of exocrine pancreatic insufficiency. Oral enzyme substitution was initiated and then the weight gain of the patient increased, but the height and weight are still bellow the third percentile. Psychomotoric developpment of the child showed a slight retardation.

Conclusion. The follow up of PHHI patients after pancreatic surgery should regularly include an investigation of the endocrine and exocrine pancreatic function as the development of diabetes and/or exocrine failure remain an ongoing risk for these children.

13. HYPOGLYCEMIA DUE TO HYPERACTIVE INSULIN METABOLISM

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Objective. To investigate whether the cause of symptomatic hypoglycemia in children with ideal body composition is the hyperinsulinism per se or there are any different determinable components in the background.

Methods. In 15 nondiabetic children with symptomatic hypoglycemia (age 1.8-9.6 years) the serum levels of glucose, C-peptide and immunoreactive insulin (IRI) were measured and the C-peptide/IRI ratio was calculated at various time intervals during the i.v. (n=4) and oral (n=11) glucose tolerance test. The results were compared with the data of 5 healthy children of the same age with ideal body weight.

Results. In 5 cases C-peptide detected insulin hypersecretion was found with high IRI levels. In 10 children, together with high or normal C-peptide secretion markedly low or undetectable IRI levels were found in the last period of tolerance tests, and the C-peptide/IRI ratio was significantly higher than that in healthy children.

Conclusions. Hypersecretion of insulin can be the cause of hypoglycemia. However, in the cases of high or normal C-peptide detected ß-cell function and with low IRI levels and high C-peptide/IRI ratio, an increased receptor function (or number?) may be supposed in the background. Knowledge of IRI level in serum per se does not give any exact information about its origin. In the cases of hypoglycemia the C-peptide determination parallel with IRI can give more information and is necessary for the correct diagnosis.

14. METABOLIC STUDY IN 11 CHILDREN WITH MCAD AND LCHAD DEFICIENCIES

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Introduction. Both inherited and acquired disturbances of mitochondrial energy generating system predominently affect the tissues with high energetic demands and often manifest with hypoglycemia. Animal studies and the scarcy data available from human tissues indicate a maturation process of mitochondrial metabolism during the gestation and early postnatal period. However, especially in the neonates it may be difficult to ascertain the cause of the disease without biochemical and molecular analyses.

Methods. We present the results of clinical, biochemical and molecular analyses in seven children with medium-chain acyl-CoA dehydrogenase deficiency (MCAD) and four children with long chain 3-OH-acyl-CoA dehydrogenase deficiency (LCHAD).

Results. The first symptoms in most children were episodes of Rey-like syndrome, hepatomegaly, convulsions, hypoketotic hypoglycemia, low blood level of free and total carnitine and dicarboxylic aciduria in those with LCHAD deficiency. All children with MCAD deficiency had point mutation A985G, three of them in homozygous form, the others were compound heterozygotes for mutation A985G and G346 or deletion T474 or T475. All children with LCHAD deficiency had mutation G1528C, three of them in homozygous form. Three children died during the first attack of Rey-like syndrome, while one girl died later. Seven children are in good clinical condition. They are receiving frequent meals and low-fat diet and those with LCHAD deficiency are supplemented with MCT oil.

Conclusion. Early diagnosis and simple dietary regime can prevent the development of acute metabolic disturbances and may improve the prognosis in children with MCAD and LCHAD deficiencies.

15. GROWTH HORMONE TREATMENT IN A PATIENT WITH HEPATIC GLYCOGEN SYNTHASE DEFICIENCY (CASE REPORT)

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In a 7 year old boy presenting with growth retardation and fasting hypoglycemia with ketosis the deficiency of glycogen synthase was suspected on account of the characteristic metabolic profile. The diagnosis was confirmed by liver biopsy. An associated growth hormone deficiency was diagnosed on account of low GH levels during hypoglycemia, a low GH increase after stimulation tests and reduced IGF and IGF-BIII levels. After four years of growth hormone therapy the height has increased from -4.9 SDS to -2.05 SDS which is near the target height. However, the GH treatment did not prevent the fasting hypoglycemia. Blood glucose levels could only be normalized by avoiding the fasting intervals of more than five hours and by the frequent feeding of protein rich meals.

16. CONSEQUENCES OF PRESENT DIAGNOSTIC PRACTICE ON THE SEX RATIO IN CONGENITAL ADRENAL HYPERPLASIA (CAH) IN 5 MIDDLE-EUROPEAN COUNTRIES

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"MEWPE-CAH" Study group: [1]Hungary, [2]Austria, [3]Czech Republic, [4]Slovakia and [5]Slovenia

Objective. As a part of multi-center CAH-study organized by the "Middle European Workshop for Pediatric Endocrinology (MEWPE)" the clinical and personal data of 460 patients from Austria (A), Czech Republic (CZ), Hungary (H), Slovakia (SK) and Slovenia (SLO) were analyzed using the international MEWPE-

CAH data bank. The aim of the present study was to evaluate the gender difference in diagnosed patients.

Methods. Male/female ratio was analyzed by sophisticated statistical methods: 1. in individual countries, 2. in two time periods within last 30 years (e.g. 1970-84 and 1985-99), 3. in different forms of the disease.

Results. (1) We have found significantly less genetic males (n=173, 37.6 %) than females (n=287, 62.4 %) among CAH patients diagnosed from 1970 in all 5 countries investigated (A: 40%, CZ: 28.1%, H: 35.2%, SK:45.9 %, SLO:32.3% males). This male/female ratio statisticaly differs from that of general population (51.3/48.7%) as based on the numbers of live births published by the appropriate National Institutes of Health.

(2) The male/female ratio was 39.2%/60.8% between 1070-84 and 37.5%/62.5% between 1985-99. Thus means that the percentage of diagnosed boys did not increase within the last 15 years.

(3) Salt wasting (SW) form of CAH was diagnosed in 282 cases (61.3% of all patients), while milder forms of the disease (simple virilizing + late onset = NSW) was found in 178 patients (38.7%). The percentage of diagnosed SW form was less in males than in females (44.0%/56.0%). In milder forms the sex ratio was 27.5/72.5% thus showing that significantly less males with NSW forms are diagnosed as compared to SW form.

Conclusion. It was found that the diagnostics of CAH in these 5 countries is apparently insufficient, at least in males. We suppose that neonatal mass screening would improve the efficiency of our diagnostics.

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17. BODY GROWTH IN CONGENITAL ADRENAL HYPERPLASIA DUE TO CLASSICAL 21-HYDROXYLASE DEFICIENCY: RESULTS OF MULTICENTER STUDY

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Objective. To analyse bone age advancement, detect possible factors influencing the final height, describe growth patterns of the patients especially in pubertal period and to introduce disease specific centile charts for body height and growth velocity in CAH.

Methods. The retrospective data on 450 Middle European patients (0-18 year old) with the salt-wasting and simple virilizing clinical forms were evaluated. Bone age was assessed according to the methods of Greulich and Pyle or TW2-20, 1975. Body height and velocity centiles of CAH patients were constructed by the LMS method and were compared to those by Prader. In this longitudinal study the data were analysed by Preece Baines model.

Results and conclusions. Bone age was advanced in both clinical forms and genders. The growth of patients with the salt wasting clinical form of the disease was impaired in infancy and early childhood (bellow 3 years of age), but followed the normal patterns in childhood. In contrast, the children with the simple virilizing clinical type had normal growth pattern during the infancy and early childhood (bellow 3 year of age) and were considerably taller than healthy referents during childhood. Our longitudinal study showed that the reason of either lacking or reduced pubertal spurt is not biological, but rather methodological. Thus, the peaks of individual spurts of CAH patients are varying considerably in time, causing reduced cross sectional mean values and masking the pubertal growth spurt. The mean values of adult height achieved by patients with CAH were bellow the mean adult values of reference popula-

tion – e.g. 166.47 cm (-1.55 SDS) for boys and 156.93 cm (-1.25 SDS) for girls – and also bellow the individual target height based on midparental height. The final height of those patients was not influenced by the age at diagnosis. It is suggested that such findings on suppressed growth may result from the use of larger than replacement doses of glucocortisocids in the first year of life.

18. SALT-LOSING SYNDROME DUE TO CORTICOSTERONE METHYLOXIDASE DEFICIENCY TYPE I

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Introduction. Isolated deficiencies in aldosterone biosynthesis are caused by mutations in the CYP11B2 gene. Aldosterone synthase deficiency has two biochemical forms characterized by low or high secretion of 18-hydroxycorticosterone (corticosterone methyl-oxidase deficiency type I and type II, resp.).

Patients. We have studied three patients (two girls and one boy) who presented by failure to thrive, dehydration, hyponatriemia and hyperkaliemia during early infancy. Both of them had normal level of cortisol and its precursors, elevated plasma renin activity and low aldosterone concentration. Serum level of corticosterone and excretion of corticosterone metabolites in urine were elevated, while 18-hydroxycorticosterone metabolites in urine were not detectable by gas chromatography/mass spectrometry. Sequence analysis of CYP11B2 gene which was performed in one of the patients revealed a compound heterozygosity (Gins84/E198D). Mineralocorticoid replacement therapy resulted in the normalization of serum electrolytes and somatic development in all three patients.

19. CLINICAL, HORMONAL AND MOLECULAR GENETIC CRITERIA FOR THE DIAGNOSIS OF NON-CLASSICAL 21-HYDROXYLASE DEFICIENCY (21-OHD)

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Objective. To compare the frequency of heterogenous clinical forms of 21-OHD in various ethnic groups the consensus is needed for the definition and diagnostic criteria of different CAH types.

Patients. Post-ACTH serum 17-hydroxyprogesterone concentrations were measured in 285 patients with clinical signs of inappropriate peripubertal virilization. Nine patientss had the values between 10 and 20 ng/ml. Based on analysis of urinary steroid profiles and mutations in the CYP21 gene 5 out of 9 patients proved to have non-classical 21-OHD.

Conclusions. We suggest to use a stimulated 17-OHP level of 15 ng/ml for cut-off value to distinguish between the patients with or without mild 21-OHD. Only molecular genetic investigations can separate homozygous affected patients with mild dele-

terious mutations from heterogenous patients carrying one severe mutation.

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20. MISSENSE MUTATION OF THE WT1 SEQUENCE RESULTED IN INTERSEX GENITALIA, DYSGENETIC TESTIS AND WILM'S TUMOUR WUTHOUT DENYS-DRASH SYNDROME IN AN 11 YEAR OLD BOY

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Introduction. The Denys-Drash syndrome (DDS) is characterized by the association of nephropathy, disorders of gonadal and genital differentiation and Wilm's tumour (WT).

Case report. We present an 11 year old 46,XY male pseudohermaphrodite with dysgenetic testis who was operated for Wilms tumour at the age of 10 months. Later he had normal kidney functions but hypertension was not observed. Amplification of exons 8 and 9 of WT1 gene by PCR and subcloning of PCR products (Stratagene) followed by DNA sequencing from 8 subclones by the dideoxy-chain termination method using the 17 Sequencing Kit, revealed constitutional heterozygous missense mutations in exon 8 (C to T transition) converted a CGA-362Arg codon to TGA-stop codon. Constitutional heterozygote mutations in WT1 gene are known in patients with DDS, in boys with cryptorchism/hypospadias combined with Wilm's tumour and patients presenting uni/bilateral WT. The patient did not fulfill the criteria of DDS or WAGR syndrome, respectively. However, he is comparable to such cases where WT1 mutations led to both abnormal genitalia system development and WT. The same mutation was found in cases with WT combined either with or without hypospadias, in DDS and in carrier father who never developed WT.

Conclusion. We suppose that our patient has yet not presented symptoms of nephropathy or presents only incomplete penetrance of WTI gene mutation in the urogenital system.

21. TRIPLE X SYNDROME PLUS TRANSLOCATION BETWEEN Xp AND 6p ASSOCIATED WITH X-LINKED HYPOPHOSPHATEMIC RICKETS: IDENTIFICATION OF BREAKPOINT WITHIN THE PHEX-GENE

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Introduction. X-linked hypophatemic rickets (HYP) have been attributed to the mutations of a recently analysed gene on the short arm of the X-chromosome (PHEX, **P**hosphate-regulating gene with **H**omologies to **E**ndopeptidases on the **X**-chromosome), presumably acting indirectly by altering the activity of a humoral phosphate-regulating factor.

Case report. We report a girl with triple X syndrome who also had a balanced translocation between chromosomes Xp and 6p, leading to HYP.

Prenatal diagnosis by cord blood sampling was made because of severe dystrophy and revealed a 47,XXX,t(X;6)(p22.3;p22) karyotype. Gestation time was 38 weeks and forceps delivery had to be performed, birth weight 1870 g, length 45 cm. At presentation with 16 months because of short stature, gonadal dysgenesis and presumed vitamin D deficient rickets were diagnosed and vitamin D supplementation was started. As further decrese of growth velocity was observed, GH treatment was initiated. At the age of 3 years, HYP were diagnosed and phosphate and calcitriol substitution was started. Laboratory values showed low serum phosphate (1.0 mmol/l) and moderately elevated alkaline phosphatase (977 U/l) in the presence of low normal 1,25-OH-Vit-D_3, normal calcium and PTH and hyperphosphaturia. Hypergonadotropic hypogonadism was proven by GnRH-testing, no ovaries were detectable by ultrasound. DNA analysis showed the location of Xp-breakpoint within 24 kB fragment containing exons 17-20 of the PHEX-gene. After 4 years of combined therapy with phosphate, calcitriol and HG, growth is within the normal range (50th Pz) and the initially elevated sitting-height/leg/length ratio tended towards normalization.

Conclusion. The combination of polysomy X and HYP has not been described so far.

22. ANALYSIS OF SIX 46,XX MALES

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The XX male syndrome characterized by a male phenotype and an XX karyotype was found in three infertile adults, in one adolescent suspicious for Klinefelter syndrome, and in two infants, one of themwith genital ambiguity. All six patients have Y-chromosomal DNA including SRY as it has been demonstrated in the majority of males with the 46,XX karyotype. Cytogenetic analysis (PCR) was apllied to analyse the Y-chromosomal breakpoints. Three of these patients show a breakpoint within a protein kinase gene, PRKY, previously described as a hotpot of ectopic recombination between homologous regions on X and Y chromosomes during male meiosis. The different clinical phenotyoes of the patients cannot be correlated with the localization of the breakpoints, but would be partially explained by the different degrees of inactivation of translocated Y-chromosome.

23. SEVERE MUSCULAR HYPOTONIA IN A NEWBORN INFANT (CASE REPORT)

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The differential diagnosis of neonatal hypotonia include a broad spectrum of disorders.

A 4 month old infant is presented who was born at 34 gestational week with birtweight of 1450 g.

She was refered at four hours of age because of tachypnea and dyspnea and was noted to have diffuse muscular hypotonia, clinodactyly and almond shaped eyes. She had a normal karyotype by mid-metaphase chromosome analysis. At four months of age she was readmitted because of severely impaired psychomotor development and markedly diminished muscle tone. At this time small hands and feet were recognized, so a fluorescent in situ hybridization (FISH) was done. The probes (Oncor) used were from the 15(q11-13) region and comprised DNA specific for the loci D15S11 for Prader-Willi syndrome (PWS). The diagnosis of PWS was confirmed by FISH, which demonstrated a deletion in the proximal part of chromosome 15.

Conclusion. In all neonates with undiagnosed central hypotonia, despite the absence of the classical neonatal features of PWS, specific genetic testing for this syndrome should be considered. The early diagnosis of PWS in newborns allows the correct assignment of the underlying etiology, thereby avoiding needless invasive diagnostic testing. Furthermore, the early diagnosis of PWS has important genetic implications and offers therapeutic options for the prevention and treatment of obesity.

24. LONG-TERM EFFECTS OF ORAL MELATONIN ON HORMONAL SECRETION AND SLEEP/WAKE ACTIVITY IN NEUROLOGICALLY MULTIPLY DISABLED CHILDREN

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Objective. Children with multiple neurological deficits often experience disturbances of the circadian system with chronic sleep-wake difficulties which poorly respond to traditional sleep medication. The pineal hormone melatonin (MLT) is presently discussed as an endogenous natural sleeping substance, which definitely has sleep promoting properties if orally administered.

Methods. In a randomized double-blind cross-over design 3 mg MLT per 10 kg body weight or placebo was given orally to 9 neurologically multiply disabled children aged 2.5 to 12 yrs. The medication was administered one hour prior to habitual bedtime, each treatment being given for 42 days. Before and immediately after each treatment period the 24-hr MLT profile was determined. Similarly, all-night polysomnographic sleep recordings were taken both before and at the last day of each treatment block.

Results. Prior to and after both treatment periods all children but one displayed a normal circdian MLT profile. Prolonged MLT treatment, however, advanced the circadian hormone rhythm by 2 hours. Melatonin treatment resulted in reduced sleep latency (19 vs. 27 min; $P<0.06$). It also showed a tendency towards a reduction of the wake time within the sleep period (59 vs. 69 min) and an increase of the sleep efficiency (93.5 vs. 92 %), the sleep architecture being not affected.

Conclusions. This preliminary study indicates that in most cases of neurologically multiply disabled children the circadian system is preserved and responds to exogenous MLT by an expected phase shift. It further shows the signs of a positive long-term effect of exogenous MLT on sleep initiation and on sleep maintenance without any alterations of the sleep architecture.

25. AUTOIMMUNE POLYGLANDULAR SYNDROME TYPE 1 (APS 1) – MEWPE COLLABORATIVE PROJECT

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Introduction. APS 1 is a rare (expected incidence about 1:100 000) but perinatally life-threatening condition characterized by primary functional failure of endocrine glands as well as non-endocrine organs. The diagnosis is based on the presence of at least two of the three syumptoms: (1) chronic mucocutaneous candidiasis, (2) chronic hypoparathyroidism and (3) autommune adrenal insufficiency. Other symptoms may include hypergonadotropic hypogonadism, autoimmune thyroid disease, pituitary involvement, insulin dependent diabetes mellitus, pernicious anemia, atrophic gastritis, malabsorption, chronic active hepatitits, vitiligo, alopecia or extodermal dystrophy. APS 1 represents a unique entity among autoimmune disorders because of its monogenic inheritance, identification of the responsible gene (AIRE gene – **A**uto**I**mmune **RE**gulator) and known HLA association.

Methods. (1) Collection of patients' data from Central and East European countries, (2) evaluation of their clinical characteristics, (3) evaluation of their immune functions with special interest in Th1 and Th2 equilibrium, (4) estimation of organ-specific autoantibodies and (5) molecular analysis of the AIRE gene.

Results. So far the data from 13 patients (10 females) were obtained. The first clinical sign observed at the age of 0.2-16 yr (median 3.5 yr) was hypoparathyroidism (4 cases), mucocutaneous candidiasis (3), Addison disease (3), malabsorption (2) or chronic active hepatitis (1). Mucocutaneous candidiasis was present in 9/13 patients, Addison disease in 10/13 and hypoparathyroidism in 12/13 at the age of evaluation. Alopecia occurred in 5/13, hypothyroidism in 4/13 and keratoconjunctivitis in 3/13. The immune functions, organ specific autoantibodies and AIRE gene mutatiuons will be evaluated subsequently.

Conclusions. Recognition of the role of AIRE protein and of genotype-phenotype relationship in APS 1 patients might bring a clue to the understanding on the immunological autotolerance and on the pathogenesis of autoimmune disorders. Just the first steps have been made worldwide in this respect. The "Central and East European APS 1 Study" may bring new experience in this rare disease with a potential impact on patients with more common autoimmune conditions.

NEW BOOKS

NEUROSTEROIDS: A NEW REGULATORY FUNCTION IN THE NERVOUS SYSTERM

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"Steroids are remarkable molecules: basically they look almost alike, being derivatives of cholesterol, but the few slight chemical differences suffice to give them the extraordinary diverse biological specificities that are important in animal physiology and medical therapeutics" – these are words of the Editors of this comprehensive and delighting monograph.

It has been known for a long time that the brain is a target organ for peripheral steroid hormones. However, in 1981 E.E. Baulieu proposed a new term "neurosteroid" which applies to such steroids which accumulate in the central and peripheral nervous system independently of the supply of peripheral endocrine glands and which can be synthesized de novo in the nervous system.

This monographs brings up to date comprehensive review on the present state of art in this new and rapidly developing field. Twenty chapters written by selected experts and carefully edited cover most of major fields of actual interest from molecular biology, biosynthesis and metabolism, mechanisms of receptor transmission and interactions with the receptors of several other neurotransmitters. The distribution of neurosteroidogenic enzymes in the central and peripheral nervous system suggests that neurosteroidogensis appears to be developmentally regulated and that the initial steps of biosynthesis are common to all steroidogenic structures. Special chapters are dealing with cytochrome P450 in CNS, with the key role of steroidogenic factor 1 in adrenal and gonadal development and in endocrine function. Of special interest are several chapters on the distribution and function of individual steroid receptors in CNS, on the neurosteroid binding sites and modulations of the action of benzodiazepine, GABA-ergic, acetylcholine, glutamate and opioid receptors by neurosteroids including either their potentiation or inhibition. Similar modulatory effects of neurosteroids were found also on neuronal voltage-gated calcium channels. From these basal findings further generate the studies on the role of neurosteroids in brain functions starting with their effects on the synaptic plasticity in the brain which is closely related to the presence and distribution of steroid receptors in the brain. Finaly, there are several observations on the effects of steroids on the developing brain, on their memory-enhancing effects and even on several pathways to the future perspectives of promising psychopharmacological profile of neurosteroids and their analogues including the considerations on their membrane and genomic effects.

This monograph will be of great to endocrinologists, biochemists, pharmacologists, neurologists, psychiatrists and all those dealing with any functions of nervous system and its integrative role.

Pavel Langer