

## 5. MIDDLE EUROPEAN WORKSHOP ON PEDIATRIC ENDOCRINOLOGY (MEWPE 1998)

*Szépalma (Zirc), Hungary, November 13-15, 1998*

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Growing interest in pediatric endocrinology together with improving possibilities of international cooperation stimulated the effort to organize Middle European Workshops in pediatric endocrinology. This series of meetings was established to stimulate close personal communications among pediatric endocrinologists from several neighbouring countries of Central Europe. Discussions on unresolved problems and the presentation of some interesting and complicated cases have been proposed to be main topics of these events.

The short history shows that so far following meetings were organized:

1994 – Saint Oswald (Austria)

1995 – Třeboň (Czech Republic)

1996 – Bled (Slovenia)

1997 – Smolenice Castle near Bratislava (Slovakia)

## IDDM ASSOCIATED TURNER SYNDROME: TREAT OR NOT TO TREAT WITH hGH?

*L. BARKAI, L. SAGODI, A. LUCZAI, L. MADACSY*

*II. Department of Paediatrics, Imre Haynal University of Health Sciences, Miskolc and I. Department of Paediatrics, Semmelweis Medical University, Budapest, Hungary*

A case of a six year old girl is presented in whom Turner syndrome has been confirmed at her age of 6 months. Human recombinant GH therapy was started at the age of 3 years with a dose of 0.6 IU/kg/week and it has been increased up to 1.0 IU/kg/week. After 2 years of such treatment, gastroenteritis and dehydration were observed with frank hyperglycaemia.

Type 1 (insulin-dependent) diabetes mellitus was confirmed by ICA and GAD positivity showing that hGH treatment could not have been involved as a primary cause of the development of diabetes. While GH treatment was discontinued, insulin replacement resulted in a rapid metabolic compensation and a nearly normal long-term control of gly-

chemia has been attained with a multiple administration of short and intermediate acting insulin (total daily dose: 0.6 IU/kg). Although hGH treatment is widely used in Turner syndrome, justification of the continuing administration of hGH in this patient is

questionable. As no literary data and recommendations can be found regarding hGH treatment in Turner syndrome associated with IDDM, advices and proposals would be appreciated from those professionals who have experience with similar cases.

## **AUTOIMMUNE POLYGLANDULAR SYNDROME TYPE 1**

*Z. HALASZ, E. TOMSITS, J. SOLYOM*

*2nd Department of Pediatrics, Semmelweis University Medical School, Budapest, Hungary*

Autoimmune polyglandular syndrome type 1 is featured by progressive loss of function of multiple endocrine organs, most frequently of the parathyroids, thyroid, adrenal glands as well as of the endocrine pancreas. These endocrine manifestations frequently associate with functional derangements of non-endocrine organs such as gastrointestinal tract, liver, skin, etc.

We report the case history of a 7-year-old girl. She was repeatedly hospitalized due to relapsing abdominal cramps and vomiting leading to severe fluid and electrolyte disturbances. Five months after the first clinical symptoms, the patient was admitted to our clinic because of severe fatigue and exsiccosis. Laboratory investigations revealed severe hyponatremia and moderate hyperkalemia (serum sodium: 103 mmol/l; serum potassium: 5.6 mmol/l). Hormone measurements confirmed the diagnosis of primary

hypoadrenia (serum basal cortisol: 3.6 mg/dl; post-ACTH serum cortisol: 3.9 mg/dl; basal plasma ACTH: > 1500 pg/ml). The presence of anti-adrenal autoantibodies was demonstrated by immunofluorescent method. Rapid improvement was observed after initiating the replacement therapy (18 mg cortisone acetate and 0.1 mg fludrocortisone/day). Two months later, hypocalcemic tetany developed (serum calcium: 1.3 mmol/l; serum phosphorous: 3.37 mmol/l; serum parathormone: 0.1 pmol/l) which was treated with 0.5 mg calcitriol/day and increased calcium intake. The subsequent disease manifestation was buccal and perioral candidiasis cured by the administration of local antimycotic drug.

The interesting and infrequently reported feature of this case history is the primary hypoadrenia as the first sign of autoimmune polyglandular syndrome type 1.

## **PROLONGED EXPERIENCE WITH HYDROCHLOROTHIAZIDE AND AMILORIDE IN CHILDREN WITH NEPHROGENIC DIABETES INSIPIDUS**

*V. KIRCHLECHNER, D. KOLLER, M. VOLGGER, R. SEIDL, F. WALDHÄUSER*

*Department of Pediatrics, University of Vienna, Währinger Gürtel 18-20, A-1090 Vienna, Austria*

Nephrogenic diabetes insipidus (NDI) is due to a receptor or postreceptor defect of the arginine<sub>8</sub>-vasopressin receptor located in the collecting tubules

of the kidney. The ensuing inability of arginine<sub>8</sub>-vasopressin to concentrate urine results in severe polyuria and polydipsia. Associated dehydration and elec-

trolyte imbalances, particularly observed at infancy, may cause intracerebral calcifications, seizures, psychomotor and somatic retardation. In addition, hydronephrosis and hydroureters may be the sequel of polyuria. To date there is no causal or definitive treatment for NDI. However, reports on short-term usage of hydrochlorothiazide/amiloride indicate a fifty percent urine reduction and few side-effects.

We treated 4 children suffering from NDI, diagnosed by endocrine and genetic methods, with 3 mg/kg BW hydrochlorothiazide and 0.3 mg/kg BW amiloride per day po. tid. up to 5 years. Treatment was initiated at the age of 2 months to 2 <sup>9</sup>/<sub>12</sub> years.

While on treatment none of the patients had signs of dehydration or electrolyte imbalances, all showed

normal body growth and there was no indication for cerebral calcification or seizures. All but one had normal psychomotor development. Normal fluid balance, however, was not attainable (fluid intake: 3.8 – 7.7 liters/m<sup>2</sup>/day; urine output: 2.2 – 7.4 liters/m<sup>2</sup>/day) and the patient with the highest urine output displayed hydronephrosis grade I after 4.5 years of therapy. The treatment was well accepted and tolerated by the children and we were unable to detect any side-effects.

Prolonged treatment with hydrochlorothiazide/amiloride seems to be more potent and better tolerated than hydrochlorothiazide only. Its efficacy appears to be similar to hydrochlorothiazide/indomethacin without the severe side-effects reported with this combination.

## HOW THE ENDOGENOUS SERUM CONCENTRATION OF MELATONIN IN HUMAN BEINGS IS REPRESENTED BY URINARY EXCRETION OF MELATONIN AND 6-HYDROXY-MELATONIN SULFATE ?

<sup>1,2</sup>J. KOVACS, <sup>2</sup>M. LANGER, <sup>3</sup>W. BRODNER, <sup>2</sup>F. WALDHÄUSER

*Departments of <sup>1,2</sup>Pediatrics and <sup>3</sup>Orthopedics <sup>1</sup>Medical University School of Szeged, Hungary and <sup>2,3</sup>University of Vienna, Austria*

**Introduction:** In healthy humans the hormone melatonin (MLT) is reportedly involved in certain physiological functions and it is secreted primarily by the pineal gland in a circadian fashion. The endogenous plasma concentration of MLT is low during the day and high at night. There are age-related changes in MLT levels, but the diurnal amplitude of secreted MLT exhibits day to day consistency in the same person. Thus, among the individuals the amount of secreted MLT may vary considerably. The blood half-time of the hormone is short, ranging from 40 – 60 minutes. Some 85 % of circulating melatonin are inactivated by the liver where it is converted to 6-hydroxy-melatonin. After conjugation with sulfate it is excreted in urine in a water-soluble form as 6-hydroxy-melatonin sulfate (6-OH-MLT-S). Approximately 1 % of blood melatonin is excreted with the urine without being metabolized.

**Aim:** The aim of the present study was to examine the correlations among serum melatonin, urinary excreted melatonin (uMLT) and 6-OH-MLT-S.

**Methods:** 14 adolescents (age: 12 – 16.5 years) were involved in the study. During a 16 hours observation period (16 p.m. – 10 a.m.) blood samples were taken at 2-hour intervals through an indwelling intravenous catheter for measuring actual serum levels of MLT. From these values the area under the curve (AUC<sub>MLT</sub>) was calculated. Over the same period the patients' urine was collected for the determination of uMLT and 6-OH-MLT-S. All measurements were performed with highly specific and sensitive RIA methods.

**Results:** After analysing the data we have found a strong positive correlation ( $r = 0.78$ ;  $P < 0.001$ ) between AUC<sub>MLT</sub> and 6-OH-MLT-S in the urine. A weaker but also significant correlation ( $r = 0.52$ ;  $P < 0.05$ ) was observed between MLT concentration

in serum ( $AUC_{MLT}$ ) and urinary melatonin. The correlation between both substances in urine, namely uMLT and 6-OH-MLT-S was unequivocal ( $r=0.79$ ;  $P<0.001$ ).

**Conclusion:** We conclude that both urinary 6-OH-MLT-S and uMLT represent endogenous serum

concentrations of melatonin. 6-OH-MLT-S, however, appears to reflect serum MLT more accurate than uMLT. These non-invasive methods can be used for rough estimation of the human pineal MLT production in different physiological and pathological conditions.

## CONGENITAL ADRENAL HYPERPLASIA IN 5 MIDDLE-EUROPEAN COUNTRIES: FIRST REPORT ON THE “MEWPE-CAH” DATABANK

<sup>1</sup>J. KOVACS, <sup>2</sup>H. FRISCH, <sup>2</sup>F. WALDHÄUSER, <sup>1</sup>J. SOLYOM, <sup>3</sup>J. LEBL, <sup>4</sup>Z. MISIKOVA, <sup>4</sup>Z. PRIBILINCOVA,  
<sup>5</sup>C. KRZISNIK, <sup>5</sup>T. BATTELINO, AND ALL MEMBERS OF THE “MEWPE-CAH” STUDY-GROUP

<sup>1</sup>Hungary, <sup>2</sup>Austria, <sup>3</sup>Czech Republic, <sup>4</sup>Slovakia, <sup>5</sup>Slovenia

The *Middle-European Workshop for Pediatric Endocrinology* (MEWPE) was founded in 1994 and it assembles pediatric endocrinologists from Hungary, Slovenia, Slovakia, Czech Republic and Austria. Last year at the annual meeting it was decided to establish a network for research and treatment of patients with congenital adrenal hyperplasia (CAH) in these countries. The main goal of the multi-center study is to optimize the diagnostic procedures and treatment modalities of CAH-patients under 18 years of age in Central Europe. The first step for this purpose is to collect all the existing data and create an international databank on children and adolescents with CAH in the Central European region. The financial support for the study is provided by foundations (ÖAD, AÖU) and international programs (CEEPUS) for improving health care in these countries.

A preformed questionnaire (Case Report Form) was sent to the participants to collect data on as many CAH-patients as possible. These forms were distributed to all colleagues involved in CAH treatment. After collecting auxological, hormonal, clinical and pharmacological data of patients with CAH from the time of diagnosis until the late adolescence, the forms were sent to Vienna to summarize them in

a data-analyzing computer program (MS-Excel). Until September 1998 the data from a total of 467 patients were worked up.

This databank contains the information not only on the past and present procedures in diagnostics, but also on previous and still existing treatment and follow-up regimens on CAH. The complete register will provide data for further investigators to evaluate different aspects of the disease based on the largest CAH-patient database so far. The following projects are scheduled:

- to analyse the relationship between physical growth and hormonal status or treatment protocols (dosage, method of substitution), respectively, in a retrospective way;
- to measure insulin-like growth factors (IGF) and their binding proteins (IGFBPs), plasma renin activity (PRA), bone mineral density (BMD) in different groups of CAH-patients in prospective studies;
- to correlate genotype vs. phenotype by performing molecular diagnosis for all patients;
- epidemiologic analysis, incidence.

The large databank and the results of these studies will allow to create “Guidelines” for optimal diagnostic and therapeutic handling of CAH-patients.

## IGF-I IN TURNER SYNDROME DURING GROWTH HORMONE THERAPY: OVERCOMING THEIR IGF-RESISTANCE ?

J. LEBL, <sup>1</sup>I. HORKA, M. PECHOVA

Department of Paediatrics, 3rd Faculty of Medicine, Prague, Czech Republic; <sup>1</sup>Department of Nuclear Medicine, 2nd Faculty of Medicine, Prague, Czech Republic

Although the growth failure is a well recognized feature in girls with Turner syndrome, the pathogenesis of this phenomenon remains obscure. None of the known circulating hormones is probably primarily involved. The reports indicate that their growth hormone (GH) secretion and plasma IGF-I levels are normal and that their estrogen deficiency plays no significant role until mid-childhood. Several studies showed that the growth promoting effect of growth hormone therapy is accompanied by the increments in circulating IGF-I levels. Two recent studies showed a reduced autocrine/paracrine action of IGF-I or a decreased sensitivity to IGF-I in distinct cell lines in Turner syndrome. Therefore a concept of an “IGF-resistance” or of an “equivalent of bone dysplasia”

was accepted. A role of a novel SHOX gene within the pseudoautosomal region (PAR1) of the sex chromosomes was suggested but it was not explained until now.

The actual growth promoting therapy in Turner girls may be characterized as a permanent overcoming of their IGF-I resistance. In order to evaluate the effects of GH or GH plus estradiol (E<sub>2</sub>) treatment on their circulating IGF-I, we prospectively measured IGF-I levels in 56 Turner girls at 138 occasions during a standardized long-term (0.3 – 6.8 years) GH (1 IU/kg/week) or GH+E<sub>2</sub> therapy and compared them with previously published local IGF-I standards. IGF-I levels expressed as SDS according to age are given in the table.

s)	5	6	7	8	9	10	11	12	13	14	15	16	17	18
n	7	5	12	4	10	8	14	19	17	1	3	-	2	-
IGF-I (SEM)	1.48 0.82	4.00 0.69	2.58 0.46	4.09 1.32	6.62 1.00	5.61 1.03	3.60 0.36	3.39 0.24	2.15 0.25	4.01 -	4.80 1.53	-	3.98 0.41	-
GH+E <sub>2</sub> n	-	-	-	-	-	-	-	2	4	7	2	8	7	6
IGF- (SEM)	-	-	-	-	-	-	-	2.31 0.50	3.88 0.20	1.29 0.32	4.45 1.06	3.80 0.74	3.23 0.60	3.91 1.05

### Conclusions:

1. In Turner girls on long-term GH therapy, circulating IGF-I levels are consistently markedly elevated compared to age-specific standards.

2. The age-dependent pattern of IGF-I levels is conserved in Turner girls during GH therapy in spite of their lack of estrogens but the onset of pubertal increase tends to appear earlier. It might be contributed to adrenarche. With respect to clinical experience, there is no correlate in an increasing growth rate.

3. Later on, the estrogen substitution does not lead to any further increase of IGF-I levels in spite of its known modest growth promoting effect.

4. Supraphysiological IGF-I levels are apparently essential mediators of the growth promoting effect of GH but IGF-I-independent factors may contribute to the regulation of growth.

5. Possible long term risks of the markedly elevated IGF-I levels remain unknown.

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## ISOHORMONAL TREATMENT OF AUTOIMMUNE THYROIDITIS IN CHILDHOOD

J. MICHALEK, G. FODOR, F. MESZAROS, E. KLENCOVA, <sup>1</sup>V. SANDRIKOVA

*Institute of Endocrinology, Lubochna, Slovakia; <sup>1</sup>Regional Hospital, Prievidza, Slovakia*

**Aim of study:** to detect the effect of treatment with thyroxine (T4) on the course of Hashimoto thyroiditis (HT) in childhood.

**Patients and methods:** during the period of 1993-98 91 children were treated (81 girls, 10 boys, average age in time of diagnosis 13.37 years). The diagnosis of HT was estimated by simultaneous incidence of positive USG findings and of antiperoxidase and antithyroglobulin antibodies. The levels of antibodies were estimated each 6 months, USG examination was repeated not earlier than after 12 months. The majority of children was treated with thyroxine drugs (L-Thyroxin Berlin Chemie, Euthyrox Merck).

**Results:** at the initial examination an increased volume of thyroid gland was found in 37 children

(40.6 %), normal volume in 44 children (48.35 %), decreased volume 11 children (12.08 %). Repeated USG examination showed increased volume in 19 children (31 %), not changed volume in 38 children (63.3 %), decreased volume in 3 children (5 %) 31 children were examined by USG only once. The children were chronically treated with following doses of T4 drugs: daily dose 25 µg: 25 children (27.47 %), 50 mg: 33 children (26.26 %), 75 mg: 13 children (14.28 mg), 100 mg and more: 8 children (8.79 %).

**Conclusions:** our experience verifies that long term treatment of HT using T4 drugs can decelerate the autoimmune damage. Higher doses of T4 drugs are also well tolerated.

## CATCH UP DEVELOPMENT OF SLOWLY GROWING CHILDREN TREATED WITH ANABOLIC STEROID

A. MUZSNAI, F. PETER

*Buda Children Hospital, Budapest, Hungary*

Anabolic steroid hastens growth and bone maturation in children thus it has therapeutic effect in selected slowly growing children. Authors present the somatic development of short stature patients treated transiently with Oxandrolone. Fifty four children (46 boys, 8 girls) received Oxandrolone for the average period of  $1.0 \pm 0.6$  years. Eighty percent of them (n=43) were tested and gave response to growth hormone stimulation ( $\text{GH} > 7 \text{ ng/ml}$ ), while 11 children did not consent the provocation test. The chronological age of these patients was around 10 years ( $9.9 \pm 3.2$  years), the growth retardation being about 2.5 years (mean height corresponded to the age of

$7.4 \pm 2.6$  years), while the average bone age retardation was  $3.0 \pm 1.1$  years). Eight of them (aged  $14.2 \pm 1.0$  years) presented starting puberty.

The effective treatment increased significantly the body height ( $P < 0.001$ ) by increasing the body growth rate to  $3.3 \pm 1.7 \text{ cm/year}$  which resulted in a significantly ( $P < 0.001$ ) better percentile in height. Since the bone maturation was accelerated, even the bone age retardation decreased to  $2.2 \pm 1.2$  years as compared to the chronological age. By the end of treatment 41 percent of prepubertal patients have turned to develop puberty, although their chronological age was significantly lower ( $P < 0.05$ ) than that

of 8 those patients with starting puberty at the beginning of the therapy ( $12.8 \pm 1.4$  vs.  $14.2 \pm 1.0$  years) and met the time of onset of normal puberty. The average age of still prepubertal children was  $9.4 \pm 2.4$  years.

We conclude that anabolic steroid can control not only the growth velocity and bone maturation, but can correct the delay of puberty. It appears to be the choice of therapy in well selected non growth hormone deficient short and delayed puberty.

## **LIFE-THREATENING INCIDENTS AND LATER ON SPONTANEOUS NORMAL GROWTH IN A GH-DEFICIENT PATIENT WITH CRANIOPHARYNGIOMA : THE IMPACT OF CORTICOID SUBSTITUTION IN MULTIPLE PITUITARY HORMONAL DEFICIENCY (MPHD)**

*O. RITTINGER*

*Clinical Genetics, Children's Hospital, Salzburg*

Craniopharyngioma is the most common tumor affecting the hypothalamo-pituitary region. However, about 70 % of patients develop MPHD resulting from the treatment. Hypoadrenal crises associated with intercurrent infections or other stress situations are hazardous due to inappropriate release of adrenal steroids. Moreover, even the treatment of growth failure with rhGH can be dangerous, if there is insufficient cortisol substitution.

We report on a boy 13 year old with craniopharyngioma who has been subjected to the surgical procedure followed by irradiation with a total dose of 55 Gy at the age of 5 years. Apart from unilateral amaurosis due to tumour pressure the patient was well with normal growth over 3 1/2 years after operation without hormonal support, in spite of biochemically proven hypocortisolism. Later on the growth rate decreased and the height declined to the 3<sup>rd</sup> centile. Endocrine evaluation revealed MPHD and rhGH-therapy was initiated after proven response of IGF1 in short GH-generation test from 31 to 273 ng/ml. However, as early as one week after the onset of treatment the patient complained about headache and after 1 month from the onset of treatment he developed a life-threatening crisis with convulsions, intensive headache, apnoe and hyperpyrexia. Comprehensive investigation could not reveal any infectious

agent; but there was cortical enhancement in MRI suggesting meningoencephalitis. Aside from antiinfectious agents and anticonvulsive treatment with carbamacepin a hormonal substitution with hydrocortone (HC) and L-thyroxine was started, GH-was withdrawn and the patient's condition improved visibly. Afterwards, spontaneous growth increased and HC switched to a standby therapy. 18 months later a similar crisis occurred due to acute tonsillitis with hyperpyrexia, convulsions and salt loosing hypotension. Endocrine reexamination revealed low ACTH (5 pg/ml), and unmeasurable cortisol, which could not be stimulated at all in ITT. Likewise, the level of hGH was 0.1 ng/ml without any increase after insulin. Therefore, a low-dose HC treatment (10 mg daily) was initiated and L-thyroxin continued. Flucortisol could be discontinued after some months. Afterwards, the patient showed stable recovery. Interestingly, the height improved spontaneously and reached almost the 50<sup>th</sup> percentile for age. Bone age was still retarded for 1.5 years, the weight for height was in the +1SD range; no pubertal signs were visible.

In conclusion, our patient showed normal growth despite total unresponsiveness in ITT and without developing obesity for 8 years after diagnosis. We would like to stress the crucial role of HC in this topic.

## GASTROINTESTINAL DISEASE AND DELAYED GROWTH AND/OR PUBERTY

K. SCHMITT, R. SCHWARTZ, G. EBETSBERGER

*Children's Hospital Linz, Linz, Austria*

Chronic gastrointestinal diseases may cause delay of growth and/or puberty. We want to present three case reports where the time lag between the first symptom and the correct diagnose was at least one year.

**Case 1 :** A 16 year old boy presented with short stature. Maximum stimulated growth hormone (GH) was 6.9 ng/ml. IGF I 75 was ng/ml (144-672). GH treatment was started without any significant improvement of the growth rate. One year later during a gastrointestinal infection the boy complained about anal discomfort. An anal fissure was found and Crohn disease diagnosed. Remission was induced with cortisone and salazopyrine. GH stimulation was repeated with a peak GH value of 42.5 ng/ml.

**Case 2:** A girl was admitted with two year history of recurrent abdominal pain, weight loss and growth delay. The arrested development was contrasting to her twin sister. Serum protein was 5.2 g/dl, ferritin 6

ng/ml, bone age 12.5 yrs. Celiac disease was excluded. LHRH test: Max. LH 0.5 mU/ml, FSH 4.7 mU/ml. Double contrast X-ray imaging of her small bowel revealed diffuse Crohn disease. Catch up growth was observed after induction of therapy.

**Case 3:** A 11 year old girl was admitted with a height of 21 cm below the 3<sup>rd</sup> percentile. She had a history of undigested loose stools for many years and an extensive distended abdomen. Beside gluten IgA antibodies (274 AU) and endomysium antibodies (1:2560 U), increased levels of amylase and lipase were found. Hemoglobin was 5.5 g percent and ferritin 1 ng/ml. Celiac disease was confirmed biotically.

Despite awareness the diagnoses of gastrointestinal diseases in children with growth retardation and pubertal delay are often missed for months or even years. The hypotheses of the growth failure in gastrointestinal disease are discussed.

## MOLECULAR DIAGNOSIS OF PRADER-WILLI SYNDROME

A. TAR, ZS. SZEVEK, <sup>1</sup>G. ROYER-LEGRAIN, <sup>1</sup>J.P. BONNEFONT

*Madarász Children's Hospital, Budapest, Hungary, <sup>1</sup>Service de Génétique Médicale, Hôpital Necker-Enfants Malades, Paris, France<sup>2</sup>*

Prader-Willi syndrome (PWS) is a neurogenetic syndrome caused by the loss of function of distinct but closely linked genes on chromosome 15. The lack of normally active paternal genes in 15q11-q13, as an outcome of either a paternal deletion or maternal disomy, accounts for >95 % of all patients with PWS. Within 15q11-q13 four genes including small nuclear ribonucleoprotein polypeptide

N (SNRPN) have been found to be expressed only from the paternally inherited chromosome. The product of the SNRPN gene is active in RNA splicing in neurons.

Here we present a case of a 17 months old girl with 46,XX karyotype and clinical symptoms of muscular hypotony, obesity whose clinical diagnosis was confirmed by DNA analysis.



**Methods:** DNA from peripheral blood was double digested with Hind III and the methylation-sensitive restriction enzyme Hha I, separated on agarose gel and analyzed by Southern blot hybridization with probe PW 71B (D15S63), situated very close to SNRPN. This technique is based on the differential methylation of Hha I restriction site, which is methylated on the maternally derived chromosome (6.6 kb band), but unmethylated on the paternally derived chromosome (3.4 kb band).

**Results:** The absence of 3.4 kb band indicates no paternal contribution at locus D15S63 in the child.

**Discussion:** The probe from the deletion region which can detect DNA methylation patterns specific for the parent of origin with the use of a methylation sensitive restriction enzyme such as Hha I, which cleaves DNA at a particular maternally imprinted locus provide a rapid and reliable diagnosis. The observation indicates that a combination of clinical experience and DNA methylation analysis offers the best diagnostic approach and ensures that PWS patients are diagnosed correctly so that unnecessary and potentially unpleasant investigations are avoided.

## A CASE OF SALT-WASTING SYNDROME IN 17 YEAR OLD BOY WITH MYELOMENINGOCELE

*F. VOTAVA, J. ZEŽULAK*

*Department of Paediatrics, 3<sup>rd</sup> Faculty of Medicine, Prague, Czech Republic*

Our patient J.S. was born with a covered lumbar myelomeningocele and operated during the newborn period. Hydrocephalus developed due to the type II Chiari defect and was resolved by a shunt. Unfortunately, numerous CNS complications developed during the first year of life. The boy had twice meningitis and the shunt was repeatedly blocked and replaced. Since the end of first year of age, his craniocaval shunt remained in a good function.

Currently the boy is paraplegic and incontinent and has a neurogenic bladder. His mother refused any palliative urologic surgery and she regularly catheterizes the boy to minimize residual urine volume and to prevent urinary tract infection. Despite repeatedly positive bacteriuria, the boy had only one clinically manifest pyelonephritis at the age of 16. Dynamic and static scintigraphy of kidneys was normal. Also the kidneys ultrasound structure is normal, but the pelves are bilaterally slightly enlarged. Cystography showed an unilateral active vesico-ureteral reflux of 1st degree. Glomerular filtration rate is normal and maximal urine concen-

tration only slightly decreased (max. 643 mOsm/kg H<sub>2</sub>O).

Hyponatremia developed (min. value 120 mmol/l) developed since his 15 years of age. Sodium and chloride are loosing by kidneys, urinary sodium excretion being about 6 mmol/kg/day and urinary sodium:potassium ratio about 8:1). Bicarbonate plasma levels are normal. The water and potassium households are normal. The patient is dependent on a supplementation of 150 mmol NaCl/day (3 mmol/kg/day) to maintain normal plasma sodium level. A withdrawal of his sodium supplementation resulted in hyponatremia (128 mmol/l) after 46 hours and the urinary losses of sodium during such hyponatremic status persisted.

Plasma aldosterone levels were low normal (0.1 – 0.2 nmol/l), plasma renin activity was in the upper normal range (1.8 ng/ml) and plasma levels of atrial natriuretic peptide (ANP) in the upper normal range (8.54 fmol/l). Is his salt-wasting syndrome of cerebral or of renal origin? Would you help to answer this question?

## CONGENITAL CHLORIDE DIARRHEA: DIAGNOSTIC AND THERAPEUTIC ISSUES

Z. PRIBILINCOVA, Z. MISIKOVA, D. BOLHOVA, <sup>1</sup> B. MILOSOVICOVA

*Department of Pediatrics, University Children's Hospital, Bratislava, Slovakia; <sup>1</sup>Department of Pediatrics, Ladislav Derer Hospital, Bratislava*

Congenital chloride diarrhea (CCD) is a rare autosomal recessive disorder of chloride transmembrane transport in the ileum and the colon, resulting in the loss of Na, K, HCl and HCO<sub>3</sub> via diarrhoic stools which finally results in hypovolemia. Compensatory mechanisms lead to metabolic alkalosis, achloruria, elevated PRA and aldosterone.

We present a patient born from 3rd pregnancy (both previous were unsuccessful) who was premature and failed to thrive from the newborn period. During first months of life he developed loose stools, metabolic alkalosis, hypokalaemia, hypochloridaemia, **hypochloriduria and high levels of Cl<sup>-</sup> anions in the stool**. The levels of PRA and aldosterone were extremely elevated. Renal biopsy showed the evidence of juxtaglomerular hyperplasia. Thus, the child fulfilled the criteria of CCD and appropriate treatment with KCl/NaCl solutions was started. After clinical improvement still during the toddler period, the regular control examinations of this patient in the local hospital were discontinued

and the supplementation treatment was unsatisfactory.

We first saw the patient at the age of 16 years. At that time he was hypotrophic, with short stature -5 SDS and BA 12 years, distended abdomen, no signs of puberty, mentally subnormal. The average frequency of stools was 10 times a day, but this was not his major complaint, since he suffered much more from his low height (131 cm). The serum examination showed the levels of Na 138 mmol/l, K 2.68 mmol/l, Cl 96 mmol/l, pH 7.52. He had hypochloriuria, very low IGF 1 and sideropenic anaemia. Hormonal profile showed normal, but prepubertal values. After appropriate KCl/NaCl substitution at the hospital the frequency of stools remarkably diminished and chloriduria increased to acceptable values (i.e. above 10 mmol/l), so in case of good compliance at home we might support the boys catch up growth by some hormonal treatment (hCG, testosterone, GH).

Finally, the problems of differential diagnosis, treatment and prognosis of this rare congenital disease will be discussed.

## THYROID CARCINOMA IN 9 YEAR OLD GIRL (CASE REPORT)

J. ZIKMUND, <sup>1</sup>M. FINKOVA, <sup>2</sup>J. HORKA

*Department of Pediatrics, 3rd Medical Faculty, Charles University, Prague, Czech Republic <sup>1</sup>Department of Pathology, 3rd Medical Faculty, Charles University, Prague, Czech Republic*

Nine year old girl was referred to our department because of a thyroid nodule. Her asymmetric goitre was actually recognised first in a local hospital 18 months earlier. At that time her initial evaluation consisted only of the estimation of serum levels of thyroid hormonea (which were found within the normal range). Six months later an ultrasound examination was performed which showed irregular echo-

structure of the right thyroid lobe. At that time, neither scintigraphic examination nor fine needle aspiration biopsy (FNAB) were done. However, after one year a palpable nodule became apparent and the patient has been sent to our clinic.

Laboratory results at our department (ESR, FT<sub>4</sub>, TSH, Ab-TPO, Ab-hTG, S-TG) were found normal. Our ultrasound examination showed an asymmetric

goitre with enlarged right lobe. The total thyroid volume was 7,4 ml which is considered normal. There was a hypoechogenic unhomogenous nodule of 12 x 11 x 18 mm size located at the caudal part of the right lobe. Cervical lymph nodes were enlarged. Thyroid scintigraphy showed a cold nodule in the same localisation. A FNAB under ultrasound control was then performed and cytological examination was very suspicious of papillary carcinoma. Another ultrasound examination one month later showed, besides unchanged the nodule in the right lobe, also the dramatic extension of cervical lymphadenopathy with sonographic signs of its malignant nature.

Following these examinations, total thyroidectomy plus the extirpation of all cervical lymph nodes

was performed followed by radioiodine treatment. Histological examination of the nodule proved papillary carcinoma.

Thyroid carcinoma in childhood should not be considered as a rare finding, since it represents about 13 % of all thyroid cancers and is frequently associated with lymphadenopathy, but rarely with distant metastases. Female to male ratio is about 3:1. Nevertheless, the prognosis of thyroid carcinoma in childhood is fairly good especially in early recognised cases. In all children with an asymmetric goiter or with an apparent thyroid nodule, an extensive investigation including sonography, scintigraphy and FNAB is highly recommended.