R-57 Read by Title

**Morphological pituitary abnormalities and hormonal assessment in two patients with 47,XYX karyotype**

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Two boys with 47,XYX karyotype, were referred to our department for mental retardation and morphological pituitary abnormalities as detected by MRI. Their hypothalamic-pituitary function was then duly investigated. 47XYX is one of the most common chromosome abnormalities. The clinical features of these patients are variable and can be subtle. Patients are usually tall and thin and may have delayed speech, decreased IQ, hyperactivity, learning disabilities and central nervous system alterations including morphological abnormalities of the ventricles, corpus callosum and cerebellum. However, abnormalities of the pituitary gland have never before been described as being part of this syndrome. Patient 1 was referred to us at the age of 12.3 yrs. His stature (155 cm) was normal for his age while his BMI (26) was slightly elevated. Physical examination revealed convergent strabismus of the left eye, malocclusion, and long, thin fingers. Genitalia were prepubertal in accordance with chronological age. Patient 2, referred to our department at 16 yrs of age, was tall (180 cm) and obese (BMI 29). Physical examination did not reveal any features of the syndrome. He had nearly completed puberty. A MRI of the brain revealed pituitary hypoplasia and horizontal clivus in Patient 1 and a micro adena of the pituitary gland with left deviation of the pituitary stalk in Patient 2. Endocrinological investigation before and after pharmacological stimulation tests showed normal pituitary function in both patients. In both patients global IQ was low (51 and 63 respectively), with greater impairment in verbal abilities and attention span. Neither demonstrated inappropriate behavior or temper tantrums. Although the presence of morphological pituitary abnormalities in these 2 patients might merely be a coincidence, we suggest that MRI of the pituitary gland be included in the assessment of brain abnormalities of males with XYX karyotype.

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R-58 Read by Title

**A unique association of AR mutation and 5 alpha reductase heterozygosity in an Indian male with disorder of sexual differentiation**

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It is well known that manifestations of one endocrine syndrome can alter in the presence of another endocrine abnormality. Little is known however, of phenotypic expressions of an individual presenting with the simultaneous occurrence of two defined hypogonadal syndromes. The situation becomes more complex with syndromes such as PAIS where there is no defined phenotype. We report here a family where affected men with PAIS had hypospadias and variable degrees of virilisation. The details of the phenotype and the hormonal parameters of the family are given in the table below.

The genetic analysis for these revealed mutations in the third exon of the androgen receptor gene Ala596Thr. The one who was strikingly dissimilar in comparison to others in terms of a more virilised phenotype was also found to have a heterozygous mutation in the fourth exon of the 5 alpha reductase gene Gly596Ser. We tried to correlate the phenotype of this patient with the known molecular characteristics of the two mutations and our present understanding of androgen metabolism in situations of enzyme deficiencies and androgen receptor defects. A decrease in the 5 alpha reductase activity (due to a heterozygous defect in the 5 alpha reductase gene) would have resulted in increased concentrations of androgen precursors(Androstenedione in particular) and a hypothetical increase in intranuclear precursor bound AR. Given the ability of the Ala596Thr mutant to dimerise with DNA promoters with multiple androgen response elements, it is possible that interaction of androgen precursor bound AR with its response element in a promoter could have stabilised the dimeric interaction of AR 596 mutant to DNA in the same promoter.

In conclusion, this was a rare case of an association of Androgen Resistance and a heterozygous 5 alpha reductase deficiency. The unexpected virilisation in this patient possibly gives new dimensions to the role of steroid precursors and their interaction with Androgen Receptor in sex differentiation and virilisation.

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R-59 Read by Title

**Psychosexual alterations in patients with congenital adrenal hyperplasia**

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Congenital adrenal hyperplasia (CAH) is a disease that causes increased androgenic hormone levels during the fetal period. This exposition has raised the hypothesis of a possible influence of such hormones on the subject’s identity and the corresponding behavior of the individual regarding sexual orientation. The objective of the present study is to analyze if there are changes in the development of those patients and the way such changes can interfere with their life. This is a qualitative study re-garding possible changes in the behavior, identity and sexual orientation. A half-structured interview was carried with two different groups of participants (patients with and without CAH). Differences in certain aspects have been identified concerning the patients’ behavior, their aggressiveness, sexual identity and orientation, their social interaction, considering that in certain situations the differences have been more easily identified than others, especially when the two groups have been compared. The psychological changes observed in the CAH patients have a great impact on the future of these patients and the therapeutic approach must take this into account.

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R-60 Read by Title

**A case of gonadal dysgenesis with an uncommon gonosomal karyotype**

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A girl was examined for the first time at 13 years of age for a 3.8 SDS growth delay. She was born with normal dimensions. She suffered from a cardiac inter-aурicular communication. Her neck and shoulders were widened and the interpinnal distance was increased , with no other dysmorphic feature nor mental delay. External genitalia presented a perfectly female aspect. Her bone age was 9 years. Investigations evidenced primary gonadal insufficiency with elevated FSH (65.1 IU/L), undetectable Anti Mullerian Hormone, inhibit

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B, estradiol and testosterone levels. Ultrasound exam showed a normal prepubertal uterus but ovaries were not visualized. Pelvis MRI showed a little mass (10x4 mm) at the right side of the uterus. Lymphocyte karyotype was 47 XXY, with a SRY gene present at in situ hybridization (FISH), whose sequencing revealed normal. The karyotype of both parents was normal. At surgery, gonads appeared as streak ones and were removed. Karyotype on these streaks showed a mosaic 45X (82%) 47XXY, and pathologic analysis revealed on the ovaries the presence of testicular structures like tubules and epideridyma coexisting with ovary-like fasciculate cortex. Karyotype on skin fibroblast culture confirmed the mosaic 45 X (32%) / 47 XXY. On the basis of a Turner-like syndrome, the patient was administered growth hormone treatment since December 2006. In conclusion, this patient, bearing a normal SRY gene including in the gonads, in the frame of a double Y karyotype, presents with a completelyullerian and external female phenotype. Short stature, cardiac malformations and some dysmorphic features may be imputable to the coexistence of 45X monosomic somatic cells and streak gonads to the local presence of cells with the same karyotype.
A part of the Georgian population lives in the iodine-deficient Caucasian mountain region of Kachetia, where the use of iodized table salt was introduced in 1997. We examined frequency and extent of enlargement of the thyroid gland in school children and adolescents in this region, as well as their growth and pubertal development.

In a total of five villages 451 school children and adolescents (199 boys and 252 girls) aged 8-16 years were examined. The thyroid gland was examined by palpation and its size categorized according to the WHO goiter classification. Body height and weight were recorded. Height SDS, weight SDS and BMI were calculated, pubertal development assessed according to Tanner stages, and in girls age at menarche, when present, was recorded.

Thyroid enlargement grade 0 was found in 133 (29%) children, boys: 56 (28%), girls 77 (31%). Grade I was found in 131 children (29%), boys: 62 (31%), girls: 69 (27%), grade II in 148 children (32%), boys: 61 (31%), girls: 87 (34%), and grade III in 39 children (9%), boys: 20 (10%), girls: 19 (8%). There was no diagnosis of grade III (0%). Frequency of grade IB and grade II increased with the age of the children. The children from this region were smaller than their normal peers. Girls’ height SDS was -0.28±0.84, and weight SDS -0.14±0.79. In boys, height SDS was -0.31±0.79 and weight SDS -0.3±0.80. Height deficit was most pronounced in the age group 13-16 years.

The mean age for reaching testicle volume 4 ml was 11.08±1.09 years (range 9.35-13.78). Mean age for genital development G2 was 11.77±0.99 years (range 9.63-13.16). Mean age for breast development B2 was 10.84±1.03 years (range 9.08-13.23).

Mean age of menarche was 12.67±1.15 years (range 9.63-16.7). The main cause of hyperthyroidism was: Graves disease (89%), Hashimoto thyroiditis in children and adolescents (28%), autoimmune disease (10%); other autoimmune disease was positive in 4 patients (9.3%). No parasitic diseases were diagnosed. Other complaints leading to referral were goiter, accounting for significantly more referrals in females. A positive family history of autoimmune thyroid disease is associated with a higher risk of hypothyroidism. Hypothyroid patients may occur in higher percentage of children and adolescents than previously reported.
dose than it is currently recommended. Obesity may be the consequence of long duration of ATD therapy. Surgery was successful, but radioactive iodine may become more convenient definitive treatment in near future.

**R-68 Read by Title**

**Pituitary dysfunction due to an adenoma secondary to chronic unrecognized hypothyroidism**

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Chronic hypothyroidism develops pituitary TSH adenoma, compressing surrounding cells. After l-thyroxine, regression of adenoma avoids neurosurgery, but pituitary function can remain impaired.

We studied two severe hypothyroid patients: a male (M) 13 yrs, a female (F) 12yrs, before and after l-thyroxine treatment during a prolonged follow-up. M: impaired growth, weight increase and -2 years bone age, tests volume >4 ml. F: severe growth retardation, -5 years bone age.

M+F: Low T4T and FT3, elevated TSH, impaired GH growth (peak M=2.2 F=4 ng/ml) low IGF-1 M: 59.1 F=59.2 (ng/ml) normal ACTH, FSH and LH, increased PRL. Large adenoma compressing also optic chiasma.

After six months of l-thyroxine: normal thyroid hormones, TSH and PRL completely normalized, GH secretion almost normal in M, slightly reduced GH and IGF-1 in F.

M: slow catch-up growth and pubertal progression, so we repeated pituitary NMR without adenoma evidence. Puberty and catch-up growth were completed six years later, not in accordance with parents development.

F: improvement of stature for one year, then poor therapy compliance and reduction of growth velocity. No evidence of adenoma recurrence after NMR. Treatment optimization without growth increase, in spite of the pubertal progression in the following two years. GH secretion restored, confirmed the defect 9.25 ng/ml, low IGF-1 (273 ng/ml v.n. 288-756) After rhGH therapy, growth velocity rapidly increased.

The adenoma secondary to prolonged hypothyroidism affects pituitary secretion, GH, and Gn. The damage, transitory or persistent, depends on the prolonged pituitary compression, severity and duration of the hypothyroidism.

After a chronic hypothyroidism we recommend a pituitary NMR, if positive for adenoma, it is necessary to test pituitary function, especially GH secretion, and to repeat the evaluation if the growth or the pubertal progression are not satisfactory, also after adenoma regression.

**R-69 Read by Title**

**Evaluation of Hashimoto thyroiditis in children and adolescents**

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**Background:** Hashimoto thyroiditis ( HT ) is common cause of goiter and hypothyroidism in children and adolescents. Spontaneous remission may occur in 50% patients, but development of hypothyroidism is possible.

**Objective:** To investigate the clinical manifestations and presentations, clinical course and long-term outcome of HT in children, patients of Endocrinology departments.

**Subjects and methods:** We rewied charts of 43 HT children ( F=36, M=7 ), diagnosed at present two or more criteria, with mean age 12.3 years, mean follow-up duration 4.6 years.

**Results:** HT is common in females than males (5F / 1M). The common complaints leading to referral were goiter, in 19 children ( 44.3%), either isolated in 15 (34.4%) or associated with other complaints in 4 children. Other complaints HT is: anaemia in 8 ( 18.5%), fatigue in 5 ( 11.8%) increased appetite in 4 ( 9.7%) weight gain in 3 ( 7.0%) growth retardation in 2 children, ( 4.7%) & irregular menses in 3 pubertal girl. The prevalence of goiter it accounted for significantly more referrals in females ( 14F = 73.7% and 5 M= 26.3%, t test; p=0.005 ). Hypothyroidism had 18 HT patients ( 41.1%), for ( 7 38.8%) in initial admission, and 11 ( 61.8%) mean follow up duration was 4.6 years. Euthyroid HT patients was 22 ( 59.9%), 2 children with initial hyperthyroid, mean follow up duration 4.6 months, and 1 child remained euthyroid for least 23 month. The family history of thyroid disease positive at 16 children ( 37.5%), 12 of them - hypothyroid, ( 71.4%). Associated with other autoimmune disease had a 4 patients ( 9.3 % ). No parasites diseases, or alopecia found.

**Conclusions:** HT is fifth times common in females than males. The common complaints leading to referral were goiter, it accounted for significantly more referrals in females. A positive family history of autoimmune thyroid disease is associated with a higher risk of hypothyroidism. Hypothyroid patients may occur in higher percentage of children and adolescents than previously reported.

**R-70 Read by Title**

**Effects of growth hormone replacement therapy on hypothalamic-hypophyseal-thyroid axis in growth hormone deficient children**

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Changes in thyroid hormones levels may occur during growth hormone (GH) replacement therapy, even in those children considered euthyroid at baseline. Our goal was to evaluate effects of GH therapy on thyroid function in GH deficient patients. 40 GH deficient children, 9/40 (22.5%) secondary to abnormalities in hypothalamic-hypophyseal region, mean age 10.3 ± 2.8 y, comprising 30 boys and 9 pubertal. FT4 and TSH levels were determined at baseline and after a mean of 1.1 ± 0.5 yr of GH replacement therapy at a mean dose of 0.1 IU/kg/day. TSH levels < 6.0 IU/L and FT4 > 0.46 ng/dL were considered within the normal range. 33/40 subjects (82.5% — group A) were euthyroidian at baseline and 7/40 (17.5% — group B) were previously diagnosed as central hypothyroidism, had taken sodium levothyroxine and 6/7 (86%) kept plasma levels of thyroid hormones within the normal range.

There was a decrease in FT4 levels after GH replacement in group A (1.1 ± 0.3 vs 0.9 ± 0.3 [ng/dL], p=0.008) and in group B (1.5 ± 0.9 vs 0.9 ± 1.7 [ng/dL]) p=0.4), but only in the former group the difference was significant. 43/33 (12%) subjects previously euthyroidian (group A) were put under sodium levotyroxine because, of FT4 levels. Only the patient who presented with FT4 levels above the normal range at baseline (group B) required medication adjustments during therapy. There were no changes in TSH levels in both groups during follow-up. Thyroid antibodies were negative in all patients. GH replacement therapy may decrease FT4 levels with no apparent changes in TSH levels. Few patients previously euthyroidian required sodium levotyroxine therapy during GH replacement. Futhermore, exogenous GH did not exacerbate central hypothyroidism previously diagnosed in our study population. In conclusion, GH might influence thyroid function, but the mechanisms are not quite clear yet. Patients under GH replacement must be monitored closely in order to diagnose and treat thyroid dysfunction.

**R-71 Read by Title**

**Resistance to thyroid hormone (RTH) detected by TSH at neonatal screening**

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RTH is an inherited disorder of reduced responsiveness of the target tissues to thyroid hormone (TH), usually suspected when elevated TH are associated with non suppressed TSH. Basal TSH levels are normal or slightly increased, and, because routine screening programs are based on the determination of TSH, are not appropriate for identified RTH (Refetoff, 2004). We present a newborn with RTH detected by TSH screening and the most likely mechanism to explain the early detection. A 12-day-old boy delivery by caesarean section at term after an uneventful pregnancy was referred due to borderline 72hs blood spot TSH level at screening (9.2 µIU/ml). He was breast fed and the
mother was disinfected daily with povidone iodine. On physical examination no signs of hypothyroidism were found. Serum TSH value was elevated (101 μIU/ml), FT4 was normal (1.31 ng/dl) and Tg was markedly elevated (2.00 ng/ml) at 12 days of age. Both knee epiphyses were visualized on X-Ray. Thyroid ultrasound revealed a diffuse enlargement of the gland and a 99Tc scintigraphy confirmed this finding. Treatment with 25 μg of L-T4 was initiated but discontinued after three months, owing to significantly elevated FT4. After one month without treatment, FT4 was elevated (4.2 µg/dl) with no suppressed TSH (6.6 µIU/ml). TRH/TSH test was still high and higher respondent (33.7 µU/ml) despite high FT4 levels. RTH was confirmed by detection of a heterozygous mutation (P453T) in the thyroid hormone receptor-β (TR-β) gene.

We conclude that in this infant the increased iodine load during the neonatal period impaired the ability of the thyroid gland to supply adequate amounts of TH allowing the early unusually detection of RTH at screening.

**R-72 Read by Title**

**Influence of problems related to body perception on self-esteem (S.E.) development in girls affected by Turner syndrome (TS)**

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Self-esteem and body perception are significantly related during the puberal age. According to our clinical approach these issues can be altered in girls affected by TS.

The aim of the study was to investigate in TS young patients’ self-esteem, to verify its relationship with body perception and if it changes according to their growth.

**Sample:** 10 girls affected by TS (aged 10 - 18 years, mean 13.9) Questionnaire TMA was given to patients regularly followed up in our out-patients Centre. TMA valuates self-esteem collecting scorings in fields, such as body perception, emotions, school achievement, relationships in family and external environment, personal skills.

Data were gathered taking into consideration subgroups A: 5 pts aged 10-14 and B: 5 pts aged 15-18, besides, scorings of body perception were regrouped (C: 5 pts having lower scorings, D: 5 pts higher).

**Results:** showed 1. global self-esteem : 91 (normal population range 85-115), 2. self-esteem improving in older girls TS (A 82.4 vs B 103.4), 3. a high connection between self-esteem and body perception (C 80.4 vs 83.2, D 105.4 vs 99.2).

**Conclusions and discussion:** Our data show that the patients’ self-esteem, placed on range of normal population, is mainly influenced by perception of the body and, accordingly, by the interpersonal relationships during the puberal age. It seems that a positive perception of the physical appearance could indirectly influence the coping of daily-life tasks of TS girls. These findings, resulting from a little sample, suggest the extention of this study so as to get more information.

**R-73 Read by Title**

**Turner syndrome (TS) and neoplasms: three new cases**

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TS pts have increased morbidity but the risk of cancer does not seem to be increased. 173 pts were followed for a mean of 6 yrs. GH therapy in 124 pts. 257 pts have increased morbidity but the risk of cancer does not seem to be increased. 173 pts were followed for a mean of 6 yrs. GH therapy in 124 pts. 3 pts developed neoplasms.

**Case 1:** 46,XXp-/46,Xi(Xq)/47,Xi(Xq)i(Xq). Horseshoe kidneys, not visible ovaries, no CHD. Amenorrhea treated with EP. At 35 yrs of age abdomen echography and CT scan showed mass in the left kidney. After surgical resection: chromophobe cell renal carcinoma confined to the kidney.

**Case 2:** 46,Xi(Xq). Horseshoe kidneys, not visible ovaries, no CHD. Amenorrhea treated with EP. At 22 yrs of age abdomen echography showed mass in retroperitoneal region, at MRI follow-up progressive increase. After laparoscopy: neurofibroma S100+, focal neurofilament positivity. At aortic angiography: dislocation of bowel, kidneys, aorta, cava. Surgical resection of 70% and confirmed diagnosis.

**Case 3:** 45,X. Normal kidneys, not visible ovaries, no CHD. GG for 7 yrs. At 21 yrs thyroid nodule. Needle aspiration biopsy: papillary thyroid carcinoma. Total thyroidectomy confirmed this diagnosis.

**Conclusion:** The risk of cancer in TS, except cancer of the bowel and gonadoblastoma in pts with Y sequences, does not seem to be increased. In our pts the prevalence of neoplasms is 1.7%. No family history of malignancies. No report of renal cancer in TS, although neural cell neoplasms have been noted in association with TS.

The long-term effects of GH in non-GH deficient pts are not fully known. Recent studies suggest a relationship between IGF-1 axis and neoplasms with an unclear mechanism.

Pts 1 and 2 developed neoplasms without GH therapy. Chromosomopathy, probably, determined cytogenetic and molecular abnormalities predisposing neoplasms.

Pt 3 developed neoplasms many years after GH treatment. A recent study reports 2 TS pts that developed papillary thyroid carcinoma after GH therapy. Long term follow-up is imperative to study the real risk of cancer in TS.
The prevalence of hirsutism among girls at pubertal age from Sofia
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The hirsutism in adolescent girls represents a serious problem because of the underlying heterogenic aetiology, the risk from concomitant metabolic and reproductive disturbances, and its underestimation by the public opinion. The aim of the present study is to establish the prevalence and the onset of clinical manifestation of hirsutism among girls at pubertal age.

Materials and methods: Six hundred and thirty girls from seven schools in Sofia were included in the study, from 11 to 18 years of age, mean age 14.82 ± 2.37 years. The stage of pubertal development according to Tanner and the score of hirsutism according to the Ferriman and Gallwey scale was assessed in all of them.

Results: The vast majority of the investigated girls [65%, n = 409] were with completed pubertal development [4-5 Tanner stage], and in the remaining 35% the pubertal development was in 2-4 stage.

In 45 from 630 girls [7.1%], mean age 15.25 ± 1.14 years, increased amount of hairs was established with a score above 8 according to Ferrimann and Gallwey. Only three of them [6.6 %] were with uncompleted pubertal development. In all girls the hirsutism was moderately expressed [<5].

Conclusions: Hirsutism is a common disorder in girls at pubertal age, sometimes starting from its early stages. It necessitates thorough investigations and follow-up, because in a number of cases hirsutism represents the first manifestation of disorders such as nonclassical congenital adrenal hyperplasia or polycystic ovary syndrome.