Two boys with 47,XY,XXY 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. 47,XXY 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, malacolusion, and long, thin fingers. Genitalia were prepuberal 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 adenoma 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 XYY karyotype.

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 all 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.

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 development of patients with CAH, as to their 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.
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), whereas 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%)/47XY, and pathologic analysis revealed on the ovaries the presence of testicular structures like tubules and epididyma, coexisting with ovary-like fasciculate cortex. Karyotype on skin fibroblast culture confirmed the mosaic 45 X (32%)/47 XY. 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 completely Mullerian 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.

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**R-61 Read by Title**

### Intersexuality and culture - an interdisciplinary, cross-cultural study

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Intersexuality is non-existent in our society and individuals with intersex disorders are non-visible. Malformations of the external genitalia are covered with taboos and shame and patients and their families suffer from social non-existence rather than from their medical disorder. While in the Western world it is widely accepted as natural - and seen almost as a law of nature - that mankind is divided into two sexes or genders, there are many cultures and societies, however, which recognize more than two sex and/or gender categories. In some instances sex and/or gender refer to the biological sex, in others to gender role and social status. In the following we have reviewed the medical and anthropological literature describing individuals who live neither as men nor women. Only in rare exceptions these individuals are intersexuals - individuals with a disordered sexual differentiation - in the modern medical or biological definition: in many if not all societies the existence of individuals who are not covered by the gender category male or female could be demonstrated. Therefore there appears to exist a cultural need for people with a special neither-male-nor-female status, which we classified as gender variance.

It is of interest to note that many of these previously accepted and institutionalized third or fourth sex/gender categories have disappeared or were transformed as a result of the influences of Western culture. Retrospective anthropological studies may thus attempt to interpret the function of these third gender roles, and explain them within their cultural context. Furthermore, such studies may illuminate the meaning and function of intersexuality in non-Western cultures. These include the thesis that medical treatment of disorders of sexual development must be seen in a particular cultural context, as it is predicated on modern, Western concepts of gender dimorphism, of sex as the basis of gender and of social and societal definitions of what is normal and deviant.

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**R-62 Read by Title**

### Gonadotropin and testosterone levels with semen quality in patients operated upon for unilateral cryptorchidism

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**Background:** The study of fertility and endocrinological findings in men with a history of orchiectomy for surgical correction of unilateral cryptorchidism is important. The study was financed of the grant of Russian President MD -8267.2006.7.

**Methods:** The clinical series included 60 men from 16 to 34 (the mean age 21,7 s = 3.8) who were operated from 1988 to 1994. The mean age of surgery – 6.5 years (S=1.39). On the left side the orchiectomy was realized in 39 cases (65%), on the right side in 21 (35%). Physical examination, collection of complaints, the serum level of testosterone, the prolactin, the follicle-stimulating hormone (FSH) and the luteinizing (LH) was investigated by the immunoenzyme analysis, the level of sperm antibodies (ELISA-test), and sperm quality was investigated.

**Results:** The erectile dysfunction recognized in one case. Two patients had lower serum level of testosterone. A serum level of the prolactin, FSH, LH was normal in all. The oligospermia was found in two (the hypoandrogenemia was found at him); aspermina in one; oligozoospermia in 40; true azoospermia in two; asthenozoospermia in 15; oligoasthenozoospermia in 11. The leukospermia was found in 9. The level of sperm antibodies was normal in all.

**Conclusions:** 1. The level of gonadotropin was normal in all patients; 2. The hypoandrogenemia was found in tow; 3. The patosperma was found in 2/3 cases; 4. The level of sperm antibodies was normal in all.
Hyperthyroidism in children: experience with propylthiouracil (PTU)

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Hyperthyroidism is rare in children and its treatment remains controversial. In this late decade, propylthiouracil (PTU) has become the treatment of choice in our hospital, because methimazole was no longer available in Serbia. The objective of this study was to review our recent clinical experience in the management of hyperthyroidism. We reviewed the charts of 37 patients (31F/6M) with hyperthyroidism treated at University Children's Hospital in Belgrade from 1995 to present. The mean age at diagnosis was 11.4 ± 3.6 years (range 4-16.8) and 27% of them were prepubertal (half of them < 6 years). The main cause of hyperthyroidism was Graves disease (89%), Hashimoto thyroiditis (8%) and thyroid adenoma (3%). Family history for autoimmune disease was positive in 45%. Majority of patients were treated with PTU (84%, the mean dose 4.7mg/kg/day), methimazole (13%) and carbimazole (3%). Minor side effects (neutropenia - carbimazole, arthralgia and elevation of liver enzymes - PTU) were seen in 11 % of patients during the first 4 months of treatment and resolved either spontaneously or with switching to other antithyroid drug (ATD). Fifty-one percent of patients were treated longer than 2 years and half of them achieved remission after 3.8 ± 1.8 years.

Three patients underwent thyroidectomy because of an uncontrolled course. In follow up, 5 euthyroid girls in remission (>5 years) continued to gain weight, despite diet counseling (mean BMI SDS was 2.38). We report no prepubertal (especially those < 6 years old) patients compared to the other published reports. Treatment with PTU was safe, although with smaller mean

7 (38.8%) in initial admission, and 11 (61.8%) mean follow up duration was 4.6 years. Euthyroid HT patients were 22 (59.9%), 2 children with initial hyperthyroid, mean follow up duration 4.6 months, and 1 child remained euthyroid for least 23 months. The family history of thyroid disease positive at 16 children (37.1%), 12 of them - hypothyroidism. (71.4%). Associated with other autoimmune disease had a 4 patients (9.3%). No parasites desesses, or alopecia found.

Conclusions: HT is five times common in females than males. The common complaints leading to referral were goiter, accounted for significantly more referrals in females. A positive family history of autoimmune thyroid disease is associated with a higher risk of hyperthyroidism. Hyperthyroid patients may occur in higher percentage of children and adolescents than previously reported.
R-68 Read by Title
 Pituitary dysfunction due to an adenoma secondary to chronic unrecognized hypothyroidism
 Elenita Paeschini; Laura Travai; Stefania Bassanese; Giorgio Tonini
 Burgo Garofoli Trieste, Dept. of Pediatric, Trieste, Italy

Chronical 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 tT4 and fT3, elevated GH secretion (GH peak M=2,2²F= 4 (ng/ml) low IGF-1 M: 59,1 F=52,9 (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 normalised, 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 retested, confirmed the defect 9,25 ng/ml, low IGF-1 (273 ng/ml) v.a. 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.

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 reman euthyroid for least 23 mouth. The family history of thyroid disease positive at 16 children (37,1%), 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-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 to 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 revided 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: anemia 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

R-70 Read by Title
 Effects of growth hormone replacement therapy on hypothalamic-hypophyseal-thyroid axis in growth hormone deficient children
 Adriana Sávio-Machado1; Angela Spinola-Castro2; Erika Kitahara2; Patricia Tosta-Hernandez2; Fabiola Garcia2; Marcia Pereira2
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Changes in thyroid hormone levels may occur during growth hormone (GH) replacement therapy, even in those children considered euthyroidian 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 yrs, 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 > 0.6 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 levoythroxine 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. 433 (12%) subjects previously euthyroidian (group A) were put under sodium levoythroxine therapy, 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 levoythroxine 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
 Mirta Silver1; Carina Rivolta2; Adriana Onetto3; Gustavo Maccallini3
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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 cesarean section at term after an uneventful pregnancy was referred due to borderline 72hs blood spot TSH level at screening (9.2 µU/mL). He was breast fed and the
Turner Syndrome (TS) and Neoplasms: Three New Cases

Rosaith Bergamaschi; Laura Mazzanti; Emanuela Scarrano; Laura Castiglioni; Federica Tamburro; Milva Bai; Alessandra Cassio; Davide Tassinari; Alessandro Cicognani

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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. 3 pts developed neoplasms.

Case 1: 46,XXp+46,XX(Xq)47,X(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: neuroblastoma S100+, focal neurofibrilament 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. GH 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.

P3 3 developed neoplasm 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.
Hirsutism is a common disorder in girls at pubertal age, manifestation of disorders such as nonclassical congenital adrenal hyperplasia and follow-up, because in a number of cases hirsutism represents the first sometimes starting from its early stages. It necessitates thorough investigations.

Conclusions: Only three of them [6.6%] were with uncompleted pubertal maturation still needs to do a lot of study.

Results: In 35% the pubertal development was in 2-4 stage.

Bone age in 33 children

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Ultrasound-based bone age (y)</th>
<th>X-ray-based bone age (y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.2+/−2.3</td>
<td>9.9+/−3.3</td>
<td>9.9+/−3.4*</td>
</tr>
</tbody>
</table>

* Compare with first time, P>0.05

Ultrasound-based bone age (y) 10.4+/−3.1**

**Compare with X-ray-based bone age, P<0.01

Conclusions: Repeatability of ultrasound-based bone age was well, but ultrasound-based bone age was significant difference with X-ray-based bone age. Ultrasound-based bone age as a method to estimate child growth and maturation still needs to do a lot of study.