Testicular adrenal rest tumors in 50 boys, adolescents and adult male with congenital adrenal hyperplasia

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INTRODUCTION
One of the long term complications of congenital adrenal hyperplasia (CAH) is the development of testicular adrenal rest tumors (TART) associated with the risk of infertility in adult male patients. The volume of tumors is in proportion to the severity of CAH and]{what was extracted: Testicular adrenal rest tumors in 50 boys, adolescents and adult male with congenital adrenal hyperplasia

PATIENTS AND METHODS
A total of 50 male CAH patients aged 1.8-80 years. Twenty-four 21-OHD patients had SW, 14 had 5A and 8 N Cushing syndrome, four had 11-OHD. SW patients were treated with hydrocortisone 12-15mg/m²/day and fluocortolone, 5A and 11-OHD patients with hydrocortisone 10-12 mg/m²/day and four NC patients with hydrocortisone 6-8 mg/m²/day. The patients no. 12, 14 and 29 were on therapy with GnRHa.

Leukocytosis (4X), follicle-stimulating hormone (FSH), testosterone (T), 17-hydroxyprogesterone (17-OHP), androstenedione (A), inhibin B and plasma renin activity (PRA) were measured about 9.00 h (2 h after morning medication). Adequate hormonal control: normal androgen levels and 17-OHP concentration < 6 nmol/L. Overtreatment: suppressed androgen and normalized 17-OHP concentrations.

Molecular genetic analysis of CYP21A2 gene (categorized in group a, b and c) and CYP11B1 gene was performed.

Testicular ultrasound (US) was performed using GE Healthcare LOGIQ 9i and E9 ultrasound systems Aloka scanner. Volumes calculation: V (ml)=length (cm) X width (cm) X (depth (cm) X 0.52).

According to Claasen- van der Grinten TARTs are classified in five different stages. Final height (FH) and target height (TH) values were compared with t test. The study was approved by the Ethics Committee of University Hospital Centre Zagreb.

RESULTS
Radiological evaluation
TART was detected in 14 of 50 patients (28%) in patient no. 32 during US examination due to torsion of testis, in patient no. 29 by palpation, in remaining 12 patients US screening, bilaterally in 11 and unilaterally in three patients. TARTs were staged as 2/ in three, 2/3 in two, 2/3 in one, 3/3 in two and 4/5 in four patients. The volume of testes in comparison of seven adults with and group of 10 adults without TART was similar: 26.9 mL (range 19.7-36.7) and 27.1 mL (range 19.7-37.3) respectively as well as in five patients with normal adult years and 15.5 years old paternal hypertrophic with and eight pubertal patients without TART aged 13.1-16.0 years: 22.7 mL (range 17.3-28.5) and 28.3 mL (15.3-30.3), respectively.

Clinical evaluation
TART was found in 36 patients (11 of the 24 SW, 3 of the 4 11-OHD, 14 5A and 8 NC patients).

There was not statistically significant difference in FH and TH between patients with and without TART. The mean BA in four group of pubertal patients with TART aged 13.3-15.5 years was 20.4 months (range 14.8) and 12 months (range 0.4-28) in patients without TART aged 13.1-16.0 years.

Parameters of short term and long term hormonal regulation
Five of 14 patients with TART were undertreated and showed significant difference between bone age (BA)-chronological age (CA) or lower FH compared with TH. Nine of patients with TART were undertreated adequately, but in one difference between BA CA and lower FH compared with TH in other were observed. Four of 36 patients without TART were undertreated, and difference between BA CA or lower FH compared with TH were found. Thirty-two were treated adequately but in nine of them advanced BA or decreased FH compared with TH were noted.

Body mass index (BMI) 90% or higher for age had four patients with TART and three patients without TART, but were not overtreated.

Molecular genetic analysis
Thirteen CAH 21-OHD patients with TART had exclusively mutations from group A and A1, one of seven patients with non-inherited mutations was deletion or conversion in 10 of 13 of them.

Fertility
Four of 14 patients with TART had low inhibin B and high FH levels (nos. 33, 48), one had low inhibin B and normal FH level (no.44) and one low inhibin B level and suppressed gonadotropins (no. 45).

Among 36 patients without TART lower levels of inhibin B but normal FH levels of FSH were found in one poor regulated patient (no.6), three adequately regulated patients (nos. 22, 28 and 43) and two patients with significantly advanced BA (nos. 9 and 10).

Two married patients with TART (nos. 48 and 50) were azoospermic. Among remaining 12 patients, five adults (nos. 44-47 and 49) reported no cohabitation with female partner, and seven are children or adolescents (nos. 6, 8, 29-33). One adolescent has low inhibin B and high FSH level (no. 33), one adult has low inhibin B-level and suppressed gonadotropins (no.45) and other has low inhibin B and high FH level (no.49).

Seven of 36 patients with no TART married and fathered at least one child naturally, 29 patients are under aged or are not living with female partner.

DISCUSSION
Prevalence of TART found exclusively in SW 21-OHD and 11-OHD patients was 28%. Except in 1.8 year old patient (no. 3) the youngest patient, reported with TART detected by US and a 10.2 years old patient (no. 16), TART was discovered only during puberty and adulthood. Since in three of the paternal patients (nos. 29, 30 and 33) TART were stage 0 to 3, it is likely that the onset of tumor growth was earlier.

Regulation of TART is not the only factor that has influencing tumor development (we found considerable number of inadequately regulated patients without TART and adequately regulated with TART).

Low fertility rates in male CAH patients can be hyponadotropic or hypergonadotropic hypogonadism. The most common cause of hypergonadotropic hypogonadism is TART. It may be reversible in early stages when intensification of treatment might decrease tumor size but further growth leads to irreversible damage of testis.

Two patients with TART had attempted to father a child, but never succeeded and presumed cause of their azoospermia is TART (they have normal inhibin B levels and high FSH levels). Among other 12 patients with TART two had low inhibin B and high FSH levels, and one had low inhibin B-level and suppressed gonadotropins, but they declined sperm analysis.

Among 36 patients without TART lower levels of inhibin B were found in six , but without elevated FSH levels. Five of them were children or adolescents and one adult (no.43) fathered one child. As both of our azoospermic patients are adequate regulated, treatment option could be testicular sperm extraction and intracytoplasmic sperm injection.

In conclusion, we recommend optimization of glucocorticoid treatment and TART screening by testicular US from early childhood especially in patients with severe forms of CAH.

All authors declare no conflict of interest.

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Figure 1. Longitudinal testicular ultrasound and color Doppler images of 1.8 years old boy with well defined TART with moderate sized hydrocele, in 7.8 cm diameter right testis and 4.7 cm diameter left testis. Notice that the right testis is slightly elevated with thin echogenic, hypoechoic, with some hyperechoic structures, solid part 1.2 cm in diameter (right testis) and 1.3 cm x 0.6 cm x 0.4 cm (left testis). The lesion identified as testicular adrenal rest tumors are hypoechoic (color Doppler) right testis and left testis.