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 objective was to estimate the prevalence of TART in a group of 50 male CAH patients and assess their impact on testicular function.

PATIENTS AND METHODS

A total of 50 male CAH patients aged 1.8-40 years. Twenty-four 21-OHD patients had SW, 14 had SV and 8 NC form of disease, four patients had 11-OHD. SW patients were treated with hydrocortisone 12-15mg/m2/day and fludrocortisone; SV and 11-OHD patients with hydrocortisone 10-12 mg/m2/day and four NC patients with hydrocortisone 6-8 mg/m2/day. The patients nos. 10, 12, 14 and 29 were on therapy with GnRHa.

Luteinizing hormone (LH), 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 6-30 nmol/L. Overtreatment: suppressed androgen and normalized 17-OHP concentrations.

Molecular genetic analysis of of CYP21A2 gene (categorized in group null, A, B and C) and CYP11B1 gene was performed.

Testicular ultrasound (US) was performed using GE Healthcare LOGIO S8 and E9
ultrasound systems Aloka scanner. Volumes calculation: V (ml)=length (cm) X width (cm) X (depth (cm) X 0.52).

According to Claashen-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 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 during US screening, bilaterally in 11 and unilaterally in three patients. TARTs were staged as 2/- in three, 2/2 in three, 2/3 in one, 3/3 in two and 4/4 in five patients.

The volume of both testes in group of seven adults with and group of 10 adults without TART was similar: 26.9 mL (range 19.7-33.0) and 27.1 mL (range 19.7-33) respectively, as well as in five 13.3 to 15.5 years old pubertal patients with and eight pubertal patients without TART aged 13.1-16.0 years: 22.7 mL (range 17.3-28.5) and 23.8 mL (15.5-30.3), respectively.

Clinical evaluation

TART was found in 13 SW 21-OHD and one 11-OHD patient. Patient no.1 had Tanner stage 1, patient no. 16 had Tanner stage 3, five patients (nos.29-33) had Tanner stage 4 and seven were adults (nos. 44-50).

No TART was found in 36 patients (11 of the 24 SW, 3 of 4 the 11-OHD, 14 SV and 8 NC patients). There was not statistically significant difference in FH and TH between adults with and without TART. The mean BA-CA in group of five pubertal patients with TART aged 13.3-15.5 years was 20.4 months (range 0-48) and 12 months (range 0-24) in eight 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 treated 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 to 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 null and A, one of the detected mutations was deletion or conversion in 10 of 13 of them.

Fertility

Four of 14 patients with TART had low inhibin-B and high of FSH levels (nos. 33, 48-50), one had low inhibin-B and normal FSH 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 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. 8, 16, 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 FSH level (no.49).

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

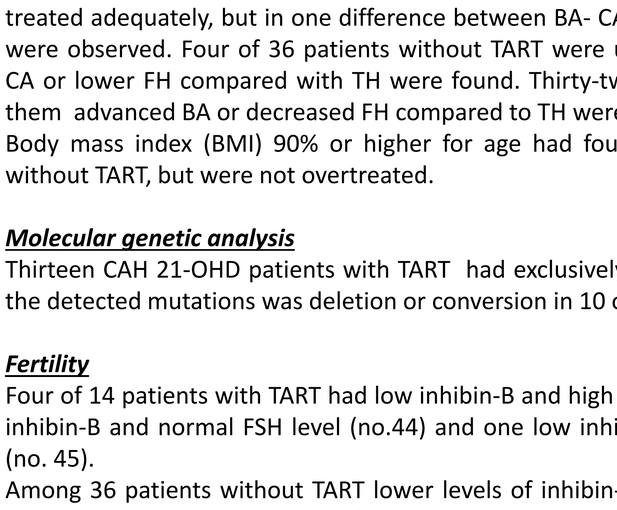

Figure 1. Longitudinal testicular ultrasound and color Doppler images of a 1.8 years old boy with salt wasting form of congenital adrenal hyperplasia. Arrows indicate bilaterally slightly lobulated well defined hypoechoic masses with central hyperechoic part in the area of rete testes measuring 1.1 X 0.6 X 0.4 cm =0.13 ml (1a right testis) and 1.0 X 0.6 X 0.4 cm = 0.12ml (2a left testis). The masses identified as testicular adrenal rest tumors are hypervascular (1b right testis and 2b left testis).

Table 1. Clinical, molecular, hormonal and testicular ultrasound features in 50 patients with congenital adrenal hyperplasia (14 with and 36 without testicular adrenal rest tumors)

Patient No.	Age (yrs)	Phenotype	Genotype	FHSDS –THSDS (SDS)	BA – CA Months	BMI (kg/m²) percentile (%)	Tanner stage G/P	FSH (U/l)[1]	LH (U/l)[2]	Testosterone (nmol/l)[3]	17OHP (nmol/l)[4]	Androstenedi-one (nmol/l)[5]	PRA (ug/ml/h)[6]	Inhibin B (pg/mL)[7]	Hormonal control	Testis volume (ml) L/R[8]	TART stage[9] L/R	Echogenicity L/R
0 yrs – 6 yrs and 11 mo																		
1.	3.1	SV	I2G/p.I173N		+ 6 mo	16.0 (50%)	1/1	<0.1	1.0	<0.1	23.3	0.5	1.2	60.4	Good	0.7/0.6		
2.	3.4	SW	del/del		0	16 (50%)	1/1	1.5	0.1	0.2	3.9	0.2	1.8	74.5	Good	0.8/0.9		
3.	4.2	SV	p.G110fs/ p.I173N		+ 12 mo	17.0 (50-75%)	2/2	1.5	0.4	0.2	28.0	0.8	2.1	74.1	Good	0.5/0.5		
4.	4.4	SW	I2G/I2G		+ 6 mo	16.2 (50-75%)	1/1	1.3	1.8	0.3	0.5	1.3	0.2	71.6	Good	0.7/0.8		
5.	4.6	SW	I2G/I2G		+ 18 mo	17.8 (85%)	2/2	2.4	0.9	1.3	189.0	0.3	3.5	62.4	Poor	1.0/1.0		
6.	5.0	SV	p.G110fs/ p.I173N		+ 12 mo	16.9 (85%)	2/2	1.2	0.3	1.1	20.3	7.6	1.7	56.8	Poor	0.5/0.6		
7.	5.7	SW	del/del		+ 6 mo	15.9 (50-75%)	1/1	<0.1	0.2	<0.1	3.6	1.1	4.2	95.9	Good	0.4/0.5		
8.	**1.8**	**SW**	**del/del**		**0**	**16.2 (25-50%)**	**1/1**	**<0.1**	**0.2**	**<0.1**	**3.6**	**<0.7**	**3.2**	**95.9**	**Good**	**0.5/0.5**	**2/2**	**hypo-hyper/ hypo-hyper**
7 yrs – 11 yrs and 11 mo																		
9.	7.6	NC	p.V282L/ p.V282L		+ 18 mo	17.0 (75-85%)	2/2	0.8	0.2	1.3	7.1	1.2	2.1	54.1	Good-B	0.8/0.8		
10.	9.2	SV	I2G/p.I173N		+ 24 mo	20.0 (90-95%)	2/2	<0.1	<0.1	0.6	12.7	0.1	1.0	43.0	Good-B	1.2/1.0		
11.	9.3	SV	I2G/p.I173N		+ 18 mo	17.0 (75%)	2/2	1.1	2.0	1.3	46.0	1.8	1.4	72.0	Good	0.8/0.7		
12.	10.4	11OH	R448H/IVS 8DS+4A>G		+ 24 mo	22.0 (90-95%)	3/3	1.8	<0.1	<0.1	3.1	2.1	0.1	82.0	Good-B	2.4/2.9		
13.	10.6	NC	p.V282L/ p.V282L		+ 6 mo	17.2 (50%)	1/1	2.1	2.4	1.4	9.7	3.1	2.1	85.0	Good	1.7/1.3		
14.	11.3	SV	p.I173N/ p.I173N		+ 24 mo	22.1 (90%)	2/3	<0.7	0.3	0.2	12.2	1.9	1.8	95.5	Good-B	2.6/3.0		
15.	11.7	SW	del/del		+ 6 mo	16.0 (25%)	2/2	3.6	2.1	1.3	28	2.2	1.1	95.7	Good	1.2/1.3		
16.	**10.2**	**SW**	**I2G/del**		**+ 18 mo**	**23.2 (90%)**	**3/3**	**3.1**	**2.2**	**2.6**	**43.7**	**2.7**	**3.6**	**226.8**	**Good-B**	**3.0/3.5**	**2/3**	**hypo /hyper**
12 yrs – 17 yrs and 11 mo																		
17.	13.1	NC	p.V282L/ p.V282L		+ 18 mo	19.0 (50-75%)	¾	5.4	2.7	8.8	17.9	3.4	2.7	92.8	Good-B	8.0/7.5		
18.	14.4	NC	p.R357W /p.P31L		+ 6 mo	18.2 (25%)	4/4	3.6	2.7	9.3	13.0	5.3	2.6	145.3	Good	9.5/10.6		
19.	15	SW	p.Q319X /p.P31L		+ 18 mo	19.3 (25-50%)	4/4	4.1	3.7	6.2	16.0	12.5	0.8	137.8	Poor	12.2/12.4		
20.	15.2	SV	p.R357W /p.P31L		+ 18 mo	20.2 (25-50%)	4/4	2.9	3.6	6.8	34.6	3.3	2.1	278.2	Good-B	15.3/14.4		
21.	15.3	SV	p.Q319X /p.P31L		+ 24 mo	23.3 (75-85%)	5/5	2.0	2.2	4.1	44.0	3.9	1.7	98.8	Good-B	15.2/15.1		
22.	15.4	SW	p.Q319X/ p.Q319X		0	19.2 (25-50%)	3/3	1.3	1.8	3.3	1.4	0.7	2.3	76.7	Good	9.0/8.0		
23.	16.0	SW	I2G/I2G		0	20.3 (25-50%)	4/4	2.1	2.7	4.1	29.0	2.4	1.0	96.4	Good	12.1/12.0		
24.	16.0	NC	p.V282L/ p.V282L		+ 12 mo	19.5 (25-50%)	5/5	2.9	3.1	9.9	24.1	2.2	1.8	107.2	Good	14.4/15.1		
25.	17.2	NC	p.R357W/ p.P31L	-0.5		20.1 (25-50%)	5/5	3.3	2.5	14.5	6.6	7.2	2.9	133.4	Good	14.3/14.7		
26.	17.3	NC	I2G/p.V282L	-0.2		20.3 (25-50%)	5/5	1.9	3.7	26	149.0	5.1	0.9	245.2	Good	21.1/22.9		
27.	17.3	SV	I2G/p.I173N	-1.6		19.6 (25%)	5/5	6.2	1.7	9.4	36.0	3.1	2.3	121.9	Good	8.3/8.6		
28.	17.4	SV	I2G/p.I173N	-0.7		21.2 (50%)	5/5	3.7	4.9	8.9	19.7	4.2	0.8	71.6	Good	15.2/17.3		
29.	**13.3**	**SW**	**p.G110fs/**		**+ 48 mo**	**24.2 (90-95%)**	**4/4**	**4.2**	**2.7**	**8.9**	**35.5**	**2.4**	**2.1**	**104.1**	**Good-B**	**11.2/10.4**	**4/4**	**hyper/ hypo**
30.	**15.2**	**SW**	**Ex6 cluster/del**		**+ 24 mo**	**21.1 (50-75%)**	**4/4**	**1.7**	**3.7**	**7.3**	**170.1**	**12.9**	**17.9**	**213**	**Poor**	**8.1/9.2**	**3/3**	**hypo/ hypo**
31.	**15.3**	**SW**	**del/I2G**		**0**	**19.6 (25-50%)**	**4/4**	**9.8**	**11.4**	**13.2**	**3.7**	**1.5**	**4.8**	**126.6**	**Good**	**12.3/11.2**	**-/2**	**hypo/ -**
32.	**15.3**	**SW**	**conv/I2G**		**+ 12 mo**	**22.3 (75%)**	**4/4**	**6.2**	**3.7**	**9.4**	**17.4**	**3.2**	**0.6**	**88.5**	**Good**	**15.8/12.8**	**-/2**	**hypo/ -**
33.	**15.5**	**SW**	**I2G/conv**		**+ 18 mo**	**20.4 (50%)**	**4/4**	**15.2**	**2.8**	**8.2**	**370.6**	**17.3**	**11.2**	**48.2**	**Poor**	**12.2/10.8**	**4/4**	**hypo/ hypo**
18 yrs – 40 yrs																		
34.	22	SW	p.R357W/ p.R357W	-2.1		21.5 (25%)	5/5	1.3	1.0	5.8	312.0	21.4	0.2	99.8	Poor	11.3/11.4		
35.	22	11OH	T318R/R141Q	-1.5		24.1 (50-75%)	5/5	2.9	3.0	24.4	2.4	3.7	0.8	316.2	Good-B	12.2/11.8		
36.	27	SW	del/del	-2.4		24.5 (50-75%)	5/5	3.7	2.7	22.6	4.7	0.4	1.8	167.3	Good-B	13.3/12.4		
37.	32	SV	I2G/p.I173N	-0.5		23.0 (50%)	5/5	2.8	4.2	18.1	24.2	4.6	1.9	136.1	Good	17.5/15.7		
38.	33	SV	p.R357W/ I2G	-1.7		24.6 (50-75%)	5/5	3.2	1.6	18.0	34.0	7.4	3.1	184.5	Good-B	14.7/15.2		
39.	34	SV	I2G/I2G	-0.9		22.7 (50%)	5/5	3.2	2.1	24.5	4.4	1.0	1.9	119.2	Good	15.1/13.9		
40.	34	SV	I2G/p.I173N	-0.6		23.5 (50%)	5/5	5.1	4.0	9.2	13.1	4.2	2.1	109.9	Good	15.2/15.6		
41.	34	11OH	L66fs/R448H	-1.2		23.2 (50%)	5/5	2.3	1.8	19.4	4.1	2.9	0.2	205.9	Good	11.5/12.5		
42.	40	NC	p.P31L/ p.V282L	-0.3		28.1 (85-90%)	5/5	4.1	3.4	17.9	18.0	3.2	3.1	212.4	Good	12.3/12.5		
43.	40	SW	I2G/I2G	-0.4		22.3 (50%)	5/5	4.7	1.9	9.7	9.3	6.3	1.2	89.1	Good	13.3/13.5		
44.	**19**	**SW**	**I2G/I2G**	**-2.3**		**22..5 (50%)**	**5/5**	**4.3**	**5.1**	**13.3**	**42.7**	**7.2**	**1.9**	**85.5**	**Good**	**12.9/13.6**	**4/4**	**hypo/ hypo**
45.	**20**	**SW**	**p.R357W/ del**	**-1.9**		**31.0 (95-97%)**	**5/5**	**<0.7**	**0.4**	**27.3**	**988.3**	**31.1**	**41.3**	**41.5**	**Poor**	**14.8/15.2**	**2/2**	**hypo/ hypo**
46.	**22**	**SW**	**p.Q319X /del**	**-0.1**		**22.2 (25-50%)**	**5/5**	**3.8**	**2.3**	**18.8**	**60.6**	**4.6**	**4.1**	**255.4**	**Good**	**10.6/11.9**	**2/2**	**hypo/ hypo**
47.	**27**	**SW**	**p.R357W/ I2G**	**-3.2**		**26.2 (75-85%)**	**5/5**	**0.1**	**0.1**	**7.9**	**188.0**	**9.6**	**13.7**	**144.2**	**Poor**	**9.7/10.0**	**-/2**	**hypo/-**
48.	**32**	**SW**	**p.R357W /conv**	**-0.8**		**26.4 (75%)**	**5/5**	**14.8**	**4.5**	**12.9**	**10.2**	**4.2**	**5.6**	**30.7**	**Good**	**15.3/14.6**	**4/4**	**hypo/ hypo**
49.	**35**	**SW**	**I2G/del**	**-2.8**		**29.2 (90-95%)**	**5/5**	**16**	**5.2**	**13.8**	**230.5**	**17.2**	**8.2**	**39.5**	**Poor**	**16.2/16.8**	**4/4**	**hypo/ hypo**
50.	**36**	**11OH**	**L66fs/R448H**	**-0.6**		**27.5 (85%)**	**5/5**	**10.7**	**2.3**	**14.2**	**3.6**	**4.7**	**0.5**	**70.7**	**Good**	**14.1/12.8**	**3/3**	**hypo-hyper/ hypo-hyper**

Abbreviation: FHSDS-THSDS: final height SDS minus target height SDS; BA-CA: bone age minus chronological age; BMI: body mass index;
G/P: genital development according to Tanner stage/pubic hair according to Tanner stage
Normal ranges of our laboratories for hormones (except inhibin-B) according to age and Tanner stage (I-V): [1]FSH: Tanner I:0.1-2.1; Tanner II 0.7-3,1; Tanner III 0.9-7.6; Tanner IV=1.9-6.8; Tanner V=1.4-7.5; [2]LH: Tanner I: <0.1-0.9; Tanner II: Tanner III: 0.5-5.4; Tanner IV 1.1-5.8; Tanner V 1.5-6.3; [3]Testosterone: Tanner I <0.1-0.3; Tanner II 0.6-5.2, Tanner III 3.5-11.1; Tanner IV 6.9-21.5; Tanner V 12.1-28.5; [4]17-OHP (17-hydroxyprogesterone): 0.9-4.5; [5]Androstenedione: 2-6.9 y=0.2-0.6; 7-10 y= 0.3-1,7; Tanner II 0.4-2.5; Tanner III 1.7-5.9 ; Tanner IV 1.6-7.2; Tanner V 1.8-7.8; [6]Plasma renin activity (PRA): 0.2-2.8; [7]Inhibin B (32): Tanner I=35-182; Tanner II=62-338; Tanner III=78-323; Tanner IV=67-304; Tanner V=95-323; [8] L: left; R: right; [9]Classification of TART according H.L.Claahsen-van der Grinten et al. JPEM 1994

DISCUSSION

Prevalence of TART found exclusively in SW 21-OHD and 11-OHD patients was 28%. Except in 1.8 year old patient (no.1) 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 pubertal patients (nos. 29, 30 and 33) TARTs were stage 3 or 4, it is likely that the onset of tumor growth was earlier.

Regulation of the disease 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 hypogonadotrophic or hypergonadotrophic hypogonadism. The most common cause of hypergonadotrophic hypogonadism is TART. It may be reversible in early stages of 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 presumable cause of their azoospermia is TART (they have low inhibin B levels and high levels of FSH). 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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