

ORIGINAL ARTICLE

Prevalence and long-term follow-up outcomes of testicular adrenal rest tumours in children and adolescent males with congenital adrenal hyperplasia

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Abstract

Objective There are a few studies regarding the prevalence of testicular adrenal rest tumours (TARTs) in boys and adolescent males with congenital adrenal hyperplasia (CAH), and there is little information regarding the treatment outcomes in patients with TARTs. The aim of this study was to determine the long-term treatment outcomes in boys and adolescent males with CAH.

Patients and methods Sixty boys and adolescent males with CAH, who were between 2 and 18 years of age, were included in the study. Fifty-five patients had 21-hydroxylase deficiency (21-OHD), and five patients had 11- β hydroxylase deficiency (11 β -OHD). All patients were screened for TARTs by scrotal ultrasonography (US) performed by an experienced radiologist.

Results TART prevalence was 18.3% in 2–18 years' of age; eight patients had 21-OHD, and three had 11 β -OHD. The youngest patient with TART was 4 years old, whereas eight patients with RTs were at puberty. Only two patients had tight metabolic control: eight patients had stage 2, one had stage 4, and two had stage five rest tumours. In four patients with stage 2 TARTs, tumours disappeared after high-dose steroid treatment and did not recur. Shrinkage of tumour was observed in two patients. Testis-sparing surgery was performed in one patient with stage five tumour. Gonadal functions were normal in patients with partially regressed tumours. Two patients became fathers of healthy male off-springs.

Conclusions Detection and treatment for TARTs in children with CAH at younger ages, earlier stages, may prevent infertility in adulthood. Therefore, we recommend that scrotal US screening should be performed in every 1–2 years starting from early childhood.

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Introduction

One of the most important and frequently detected complications in males with congenital adrenal hyperplasia (CAH) is the development of testicular adrenal rest tumours (TARTs). TARTs were first reported in 1940.¹ Since that time, testicular tumours have been described in several publications (mainly case reports). However, several complications can develop in adult patients with CAH, and in the recent years, it became clear that some of patients could have been diagnosed in childhood.

Testicular adrenal rest tumours are frequently detected in adult males with CAH, with the prevalence up to 94%.² TARTs in children have mostly been presented as case reports in the literature,^{3–5} and only a limited number of studies have described the prevalence of TARTs in large populations of children and adults.^{6–11} Avila *et al.* reported that the prevalence of TARTs in male patients with CAH between 6 and 31 years of age was 21%, with the youngest case being 6.2 years of age. Vanzulli *et al.* reported the prevalence of TARTs in 30 male patients with CAH, ageing between 9 and 32 years, was 27%, and the prevalence of TARTs in patients with CAH < 18 years of age was 29%. Importantly, these studies did not focus on children. Prevalence of TARTs was reported as 24% among CAH patients between 2 and 18 years of age in the most comprehensive study conducted on children, and inhibin-assessed gonadal function was normal in children with TARTs.¹¹ Preservation of gonadal functions is associated with tumour size; however, gonadal function of patients with TARTs might deteriorate during adulthood. Moreover, tumour sizes might be increased during the follow-ups, and the increase might subsequently lead to impairment of gonadal function. Therefore, long-term follow-ups are important in patients who were diagnosed during the childhood.

To the best of our knowledge, there have been no studies reporting long-term outcomes in TART cases diagnosed and

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treated during the childhood. The aims of our study were (i) to determine the prevalence of TART by scrotal ultrasonography (US) in boys and adolescent males after CAH diagnosis; (ii) to determine the most common age at which TART was diagnosed in children under regular follow-ups; (iii) to assess treatment modalities and treatment outcomes in children with TART; and (iv) to report potential complications that might occur after treatment and during long-term follow-up (recurrence of TART and impairment of gonadal functions).

Patients and methods

Sixty boys and adolescent males (2–18 years of age) with CAH who were regularly follow-up our paediatric endocrinology clinic were included in this study and underwent scrotal US examination. The first US was performed at 2 years of age. US screening was performed at every 1–2 years in most of patients. Fifty-five patients had 21-hydroxylase deficiency (21-OHD; 37 patients had the simple virilizing [SV] type, and 18 patients had the salt wasting [SW] type), and five patients had 11 β -hydroxylase deficiency (11 β -OHD). CAH due to 21-OHD was diagnosed based on virilization findings (ambiguous genitalia, pubarche and precocious puberty) at the time of admission, accelerated growth velocity and elevated basal and adrenocorticotrophic hormone (ACTH)-stimulated concentrations of 17-hydroxyprogesterone (17-OHP), cortisol and dehydroepiandrosterone sulfate (DHEAS). ACTH (Synacthen Depot, Novartis [36 mcg/kg, maximum, 250 mcg]) was administered intramuscularly, and blood samples for 17-OHP, cortisol and DHEAS were obtained at 0, 30 and 60 min. Levels of basal and ACTH-stimulated 17-OHP were interpreted differently in the newborn and childhood periods.^{12,13}

Congenital adrenal hyperplasia due to 11 β -OHD was diagnosed based on high plasma ACTH, deoxycorticosterone and testosterone levels. The 17-OHP and serum sodium (Na⁺) levels were normal, and activity plasma renin activity (PRA), and aldosterone and potassium levels (K⁺) were low.

All patients were treated with hydrocortisone three times a day, and in patients with SW, fludrocortisone was added to the treatment regimen. Follow-up appointments were conducted every 3 months during infancy and childhood and every 6 months thereafter. Standard anthropometric measurements (height and weight) were performed at each visit. Growth velocity and body mass index were assessed. Glucocorticoid dose was monitored by determination of ACTH, 17-OHP, testosterone, and deoxycorticosterone levels, and PRA in peripheral blood collected in the morning before the use of glucocorticoids. Patients, who had a growth rate over 25th percentile and with low hormone levels (ACTH, 17 OHP and testosterone), were accepted as patients with good metabolic control in the phase when growth was continuing. Evaluations were performed in patients with closed epiphysis by hormonal levels.^{14,15} Hydrocortisone doses were decreased in cases with low growth rate, obesity/overweight and much suppressed levels of hormones. For evaluation of pubertal status, the Tanner stages were used.¹⁶ Bone maturation was determined according to Greulich and Pyle.¹⁷

All US evaluations were performed in our hospital by paediatric radiologists with extensive experience in scrotal US. At least three transverse and axial images of each testicle were obtained. Doppler images of the lesion(s) were obtained. Testicular tumours within the mediastinum of the testicle can be detected by US when at least 2 mm in size.¹⁸ TARTs are classified in five different stages.¹⁹

Stage 1. Presence of adrenal rest cells within the rete testis, not detectable by scrotal ultrasound.

Stage 2. The adrenal rest cells might be visible in ultrasonography.

Stage 3. Further growth of the adrenal rest cells has compressed the rete testis.

Stage 4. Further hypertrophy and hyperplasia of the adrenal rest cells with progressive obstruction of the rete testis. Induction of fibrosis and focal lymphocytic infiltrates.

Stage 5. Chronic obstruction and irreversible damage of testicular parenchyma.

In the molecular analysis of patients with 21 OHD, the most commonly encountered eight mutations (P30L in exon 1, IVS2-13C>G in intron 2, 8-bp deletion in exon 3, p.I172N in exon 4, cluster mutation in exon 6, p.V281L in exon 7, p.Q318X and p.R356W in exon 8) in Turkey were analysed in DNA samples obtained from patients' peripheral blood. PCR, RFLP, agarose gel electrophoresis techniques were employed for molecular studies. DNA region, which contained the before mentioned mutations were replicated using appropriate primers. Then, PCR product was sliced with specific restriction enzymes for the mutations, and sliced products were imagined after the agarose gel electrophoresis.²⁰

The study was approved by the Local Ethics Committee of our hospital, and informed consents were provided from all participants and/or their parents and/or legally responsible persons. All study procedures were performed in accordance with the Helsinki Declaration of 1975, as revised in 2008.

Results

Among 60 patients included in this study, 11 (18.3%) were diagnosed with TARTs by scrotal US. The age at time of initial US examination ranged from 2 to 18 years, and all patients were followed up in our clinic. Among patients diagnosed with TARTs, eight had 21-OHD (four had the SV type and four had the SW type), and three had 11-OHD. Patients with the SW type 21-OHD were diagnosed during the neonatal period, and other patients were diagnosed between 1 and 3 years of age. Two patients with TARTs were under tight metabolic control, seven were under poor metabolic control, and 2 (cases 5 and 6) were initially under tight metabolic control, but subsequently the control was deteriorated. The youngest patient with TART was 4 years old. Three patients with TARTs were in the prepubertal period, and eight patients were in the pubertal period. TARTs were bilateral in the majority of patients ($n = 9$), and eight patients had stage two tumours. With the exception of one patient (case 4), all patients were started on high-dose hydrocortisone treatment (30 mg/m² per day). Tumours disappeared

with medical treatment in four patients (cases 1, 2, 7 and 8) and did not recur during the follow-ups. Hydrocortisone dose was reduced after the tumour disappeared. Tumour sizes were decreased with medical treatment in two patients (cases 3 and 5), and they continued to receive high-dose steroid treatment. One patient (case 4) who was followed for 11β -OHD and diagnosed with TART at the age of 17 years had the stage five tumour. Testis-sparing surgery was performed in this patient because the tumour did not respond to medical treatment.²¹

Spermograms to evaluate fertility status were performed in six patients with TARTs; the spermogram findings were normal in three patients (cases 1, 2 and 8), and three patients (cases 3, 4 and 5) had azoospermia (Table 1). Case 1 got married and had a child. Patients with normal spermogram findings had stage two tumours, which disappeared after medical treatment for 6–12 months without recurrence during the follow-ups. Among patients with azoospermia, case 3 had the stage 4 tumour at the time of diagnosis, and the tumour was still stage 3–4 despite a mild reduction in size with the medical treatment. Case 3 did not consent for the surgery, and therefore, medical treatment was continued. This patient got married and had a healthy baby girl. Case 4 also had the stage five tumour at the time of TART diagnosis, and surgical treatment was performed. Tumour was diagnosed as stage 2 in case 5, but did not disappear after 5 years of medical treatment. However, we noted that the patient occasionally did not comply with the recommended dose.

As the results of molecular studies performed on six patients with adrenal rest tumour and 21 OH deficiency, case 1 was shown to be homozygote for I172N mutation; case 9 was shown to be homozygote for Q318 mutation; case 3 was shown to be heterozygote for IVS2-13C>G mutation; and case 5 and 11 were shown to be homozygote mutant for IVS2-13C>G mutation. There was no mutation in case 6. The clinical characteristics and follow-up results of patients with TARTs are summarized in Table 2.

Discussion

The prevalence of TARTs in boys and adolescent males with CAH was 18.3% in the current study. Our youngest patient was 4 years of age, and he was also the youngest patient, who was reported with TART in the literature. Most of the reported patients with TART in the literature were in the pubertal period and under poor metabolic control. It was observed that stage two tumours disappeared and did not recur during follow-up in patients receiving regular, high-dose hydrocortisone and that these patients had normal gonadal function.

Although the prevalence of TARTs ranged between 24% and 29% in studies performed on children,^{6–12} our study results have indicated a lower prevalence (18.3%). These results may vary in line with the screened age range. The frequency of TARTs increases with age; namely it increases in the pubertal and post-pubertal periods and reaches up to 94% in the adulthood. The lower prevalence, which is reported in our study, may be due to the lower age range screened. The important point is the early detection of tumours with US screening, which have been performed at younger ages.

Until now, the aetiology and functional features of TARTs are not completely understood. TARTs are suppressed if serum ACTH is suppressed by the higher-dose glucocorticoid treatment, which acts on ACTH receptors.^{22,23} Recently, studies have shown the presence of adrenal-specific enzymes (CYP11B1 and CYP11B2) as well as ACTH and angiotensin II (AII) receptors, as measured by mRNA expression with quantitative polymerase chain reaction.²⁴ Therefore, it can be suggested that tumour growth in patients with CAH may not only be stimulated by elevated ACTH concentrations, but also by elevated AII levels, as present in SW CAH patients under poor hormonal control. Moreover, Benveniste *et al.*²⁵ had shown LH receptor presence on TART. Therefore, increased LH secretion may be responsible for increased TART frequency in the pubertal period.²⁵ In agreement with the previous reports, the majority of our patients

Table 1. Results of semen analysis, according to 2010 WHO guidelines in 6 male patients with testicular adrenal rest tumours

Patient no.	Semen volume (ml)*	Sperm concentration (10^6 /ml)*	Motile spermatozoa (%)**†	Normal spermatozoa (%)**‡	Classification§
1	3.1	40	44	28	N
2	4	82	62	40	N
3	1				A¶
4	0.9				A¶
5	1.1				A¶
8	3.7	68	58	34	N

*According to 2010 WHO guidelines (World Health organization: Laboratory manual for the examination and processing of human semen, 5th edn. Geneva: WHO Press, 2010).

†Motile spermatozoa: the percentage of rapidly and slowly moving spermatozoa (grades a and b) to the total number of spermatozoa counted, normal value 40% or more.

‡Normal spermatozoa: the percentage of morphologically normal spermatozoa to the total number of spermatozoa counted, normal value. 15% or more.

§Classification: A, azoospermia; N, normozoospermia.

¶Confirmed with minimal two analyses.

Table 2. Diagnostic, clinical, sonographic features of cases with testicular adrenal rest tumours and treatment outcomes in these cases

Case	Type of CAH	Age of Dx	Metabolic control	Age at TART Dx (years)	Tanner stage	Maximum diameter at baseline (cm)	Tumour stage	Treatment/duration	Maximum diameter at follow-up (cm)	Follow-up duration after TART Dx	Recurrence
1	21-OHD (SV)	2 years	Tight	16.5	5	R: 1.5; L: <1	2	Medical/8 months	R: -, L: -	10 years	No
2	21-OHD (SW)	25 days	Tight	17	5	R: 0.8; L: 1	2	Medical/7 months	R: -, L: -	3 years	No
3	21-OHD (SW)	10 days	Poor	18	5	R: 2.2; L: 1.2	4	Medical/4 years	R: 1.5; L: 1	7 years	-
4	11 β -OHD	1.3 years	Poor	17	5	R: 4.5; L: 4	5	Medical + surgery/6 months	-	7 years	No
5	21-OHD (SV)	1 year	Tight $\rightarrow$ prepub Poor $\rightarrow$ pub	15	4	R: 0.8; L: 0.7	2	Medical/5 years	R: 0.6; L: 0.4	6 years	-
6	21-OHD (SV)	1.2 years	Tight $\rightarrow$ 1-7 years Poor $\rightarrow$ 7-10 years	8	1	R: -; L: 1	2	Medical/2 years	R: -, L: -	3 years	-
7	11 β -OHD	3 years	Poor	13.9	5	R: -; L: 1	2	Medical/2 years	R: -, L: -	3 years	No
8	21-OHD (SW)	28 days	Poor	13	1	R: 1; L: 0.7	2	Medical/1 year	R: -, L: -	7 years	No
9	21-OHD (SW)	25 days	Poor	15.5	4	R: 0.8; L: 1	2	Medical/1 year	R: -, L: -	1 year	-
10	11 β -OHD	?	Poor	16	5	R: 5; L: 4.5	5	Medical/1 year	R: 2.5; L: 2	1 year	-
11	21-OHD (SV)	8 month	Poor	4	1	R: 0.4; L: 0.5	2	Medical/1 year	R: -, L: -	1 year	-

CAH, congenital adrenal hyperplasia; 11 β -OHD, 11 β -hydroxylase deficiency; 21-OHD, 21-hydroxylase deficiency; SV, simple virilizing; SW, salt wasting; TART, testicular adrenal rest tumour; R, right; L, left; -, no tumour present; prepub: prepubertal; pub, pubertal; Dx, diagnosis; ?, initial time treatment is unknown.

*If more than one tumour was found, the maximal diameter of all tumours is given.

with TARTs were in the pubertal period. However, tumours in patients who were diagnosed with TARTs in later stages might be diagnosed earlier or detected when the tumour size was small with earlier screening for TARTs. Thus, because TARTs have been more common in the pubertal and postpubertal periods, screening during these periods might lead to delayed diagnosis and could be related to the increased infertility risk. Our observation that TARTs could already be detected in early childhood, even in adequately treated patients, suggested that when adrenal rests cells have been observed within testicles, even mildly increased ACTH and AII concentrations might induce proliferation of these cells within the testicles. Poor hormonal control with high ACTH levels and high pubertal LH levels might accelerate the process.^{8,9,24} As it has been difficult to detect the tumour on physical examination before it has reached 2 cm in size, we recommend that TART screening by US should be performed in boys with CAH, starting from the childhood period. Disappearance of the tumours after 7–8 months of high-dose hydrocortisone treatment in two of our cases (cases 1 and 2), in which tumours have been detected early at very small in sizes, was a great chance for these patients. In contrast, our patient with a large tumour did not respond to medical treatment and required surgery (case 4). The age of screening for TARTs in children with CAH was controversial because there has been limited clinical experience of this issue at the childhood.

Although adrenal rest tumours have been reported to be more common during puberty and the postpubertal period, this might also be associated with late US screening. Based on our experience, we have recommended that adrenal rest screening should be initiated at an earlier age to detect the tumour at stage 2. This is clinically important as early stage tumours can disappear with medical treatment. Compression on the rete testis can be avoided, and progression to fibrosis can be stopped by preventing tumour growth. Thus, it would be possible to prevent infertility. As only patients in whom aberrant adrenal cells have been nestled in the testicle during the embryologic period are at risk for developing TARTs, it is very important to identify these patients as early as possible. However, there is currently no consensus about the timing of the initiation of TART screening. In some centres, TART screening by annual US examination has been recommended in patients with CAH after 8 years of age.^{19,24} Until now, the youngest patient with TART ever reported was 6.2 years.⁶ On the other hand, we diagnosed TART in a 4-year-old boy under poor metabolic control (case 11). To the best of our knowledge, this case has been the youngest TART case reported in the literature by far. As TARTs may occur at very young ages, especially in patients with CAH under poor metabolic control, we recommend that TART screening should be performed at younger ages, especially in patients with poor hormonal control.

Patients with TARTs are at risk for infertility. Semen analysis can be performed in postpubertal and adult patients. Inhibin B is the best marker for the evaluation of Sertoli cell function in prepubertal patients.^{2,9} When our six patients with TARTs were evaluated with respect to the fertility status; cases 1, 2 and 8 had normal spermograms. Case 1 was married and had a healthy

baby boy. There has been no previously reported case with TART who had a child. In contrast, there were no functional sperm cells on the spermograms of cases 3, 4 and 5. In TARTs of stage 3 and greater, fibrous strands were visible as a hyperechogenic reflection similarly case 3. The tumour did not disappear in this patient despite long-term high-dose steroid therapy (6 years). In case of long-standing tumours in infertile CAH patients, a testicular biopsy might be helpful to evaluate the quality of residual testicular parenchyma.^{19,24} A testicular biopsy was recommended for this patient; however, he did not consent and medical treatment was continued. Case 3 got married 2 years ago, and his wife got pregnant this present year, and she experienced no problem in her 7 months of gestation. This was a quite surprising outcome for us, too. Case 4 could not provide a sample for spermogram 7 years after testis-sparing surgery, but the AMH level was very low (<0.1 pmol/l). Azoospermia was noted on the preoperative spermogram of this patient. In this case with stage 5 TART, infertility developed despite testis-sparing surgery. Increasing the dose of glucocorticoids in patients with stage 4 TARTs was not likely effective in decreasing tumour size, but tumour removal might prevent further testicular damage. Testis-sparing surgery has been recommended for the treatment due to the benign nature of tumours. Our patient (case 4) was also treated by testis-sparing surgery.²¹ Although TART was detected at stage 2 in case 5, the tumour did not disappear despite 5 years of high-dose steroid therapy due to patient's noncompliance. The tumour was occasionally observed to become even larger during follow-up, and his semen analysis showed azoospermia.

Until now, intensifying glucocorticoid treatment has been the treatment of choice in patients with TARTs. Intensifying glucocorticoid therapy might lead to a reduction in tumour size by suppression of ACTH secretion, thereby improving testicular function in stages 2 and 3.^{19,24} On the other hand, several problems might occur during long-term high-dose steroid therapy, such that patients might not fully comply with the long-term treatment. Inadequate treatment may lead to tumour recurrence and treatment prolongation. One of our previously published cases (case 7) had an increase in TART size during the follow-up, because he was not compliant with regular, high-dose steroid therapy. The patient began to use regular high-dose dexamethasone, and the tumour disappeared 2 years later, only when the patient was told about the treatment importance and complications.³ Therefore, we consider that patient persuasion is an important issue to provide treatment compliance. Optimizing glucocorticoid treatment, especially in patients with poor hormonal control, is important to determine whether or not tumour growth is reversible.

While tumour sizes in rest tumour cases have been observed to decrease, and even disappeared, with the early treatment, there was no difference between mutations and treatment responses of patients with mutations.

In conclusion, TART screening by scrotal US beginning from early childhood is important in male patients with CAH to prevent the development of future complications, especially with respect to infertility. It should be kept in mind that TARTs

originate from adrenal rests occurring during the intrauterine period, and high TART prevalence in adult patients is due to failure of detection during childhood. Based on our experience, we recommend that boys with CAH should be screened for TART by scrotal US every 2 years in early childhood and annually in the peripubertal period.

Conflict of interest

Authors declare that they have no conflict of interest, and the study is performed without any financial support.

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