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Review Article

Approach to testicular adrenal rest tumors in children and adolescents with congenital adrenal hyperplasia

Sirmen Kizilcan Cetin[1,*], Zehra Aycan[1]

[1]Department of Pediatric Endocrinology, School of Medicine, Ankara University, Ankara, Turkey

*Author for correspondence:
Email: drsrmnkzlcn@gmail.com

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Abstract

Testicular adrenal rest tumor (TART) is a long-standing, significant complication of congenital adrenal hyperplasia (CAH). Although it is the main reason for infertility in adult patients with CAH, little is known about the development mechanism, genotype-phenotype features, and exact treatment options of TART. However, in the literature, there are mainly case reports and only a few studies in the pediatric period on this subject. The critical point is the early detection of tumors to prevent infertility in adulthood. This paper reviews the embryological, clinical, diagnostic, genetic features, and treatment alternative of TART and discusses the early screening options.

Keywords: Testicular adrenal rest tumor, TART, Congenital adrenal hyperplasia, Infertility, Genotype-phenotype correlation

Abbreviations: ACTH: Adrenocorticotropic Hormone; CAH: Congenital Adrenal Hyperplasia; MR: Magnetic Resonance Imaging; NC: Nonclassic Form; SW: Salt Wasting; SV: Simple Virilizing; TART: Testicular Adrenal Rest Tumor; US: Ultrasonography

Introduction

Congenital adrenal hyperplasia (CAH) is a disorder affecting cortisol biosynthesis in the adrenal cortex [1]. 21-hydroxylase deficiency is the most frequent reason for CAH, with an incidence between 1:10.000 and 1:20.000 [2]. Due to the lack of enzyme function, patients with any enzyme deficiency cannot synthesize cortisol effectively. A low cortisol level decreases the negative feedback on adrenocorticotropic hormone (ACTH), causing an increase in ACTH production. High ACTH results in hyperplasia of the gland. Due to the overstimulation of the gland, cortisol precursors convert to sex hormones. As a result, androgen excess and aldosterone deficiency can cause serious problems. These include ambiguous genitalia, salt wasting, failure to thrive, hypovolemia, shock, and death. Disease severity varies depending on residual enzyme activity [1-3]. 11-B-hydroxylase deficiency is the second reason for CAH, with 5–8% incidence. Both patients with 21-hydroxylase deficiency and 11-B-hydroxylase deficiency may present classic or nonclassic forms (NC) [4]. 21-hydroxylase deficiency is categorized into four mutation groups based on enzyme activity as follows: Salt wasting (SW) in group null and group A, simple virilizing (SV) form in group B and nonclassic form in group C [5]. Testicular adrenal rest tumor (TART) is one of the significant complications of CAH with 21-hydroxylase deficiency and 11-B-hydroxylase deficiency [5]. Wilkins et al. first reported TART in males with 21- hydroxylase deficiency in 1940 [6]. TART is a well-known long-term complication of CAH and a reason for infertility in adult male patients. The frequency of TARTs increases with age. The important point is the early detection of tumors with US screening, which have been performed at a younger age. Treatment for TARTs in children with CAH at younger ages, earlier stages, may prevent infertility in adulthood.

Embryological Development and Characteristics of TART

In the embryological period, steroidogenic cells arise from areas adjacent to the coelomic mesoderm of the urogenital ridge. The primitive adrenal cortex develops close to the gonads. At the 8th week of pregnancy, the primitive adrenal cortex separates from the gonads. Adrenal cortical tissue may adhere to the gonad and descend with the testis. TART develops in the aberrant adrenal tissue descending with the testicles. The development of these cells is ACTH-dependent [7]. TARTs are situated in the testicular mediastinum. This location causes infertility by clogging the seminiferous tubes over time [8]. We can speculate that adrenal rest cells in the testes present at a very early time of life in boys with CAH. We may realize them when they reach detectable size (>2 mm) by ultrasonography (US) under the effect of stimulant factors such as ACTH, angiotensin II, and LH [9,10]. Leydig cell tumors and TART are histologically similar. In a pathological examination, it is challenging to distinguish between TART and Leydig cells. Malign degeneration has never been described in patients with Leydig cell tumors (10%). However, TARTs are benign tumors. Although the presence of crystalloids of Reinke is a sign of Leydig cell tumors (25-40%), it does not always accompany them. TART is mostly bilaterally located (80%), whereas Leydig cell tumors are unilateral [7,11,12].

Prevalence of TART

In the literature, there are mainly case reports about TART in childhood [13-17]. Follow-up and prevalence studies have been shared in the last ten years. However, there are only a few studies in the pediatric period on this subject [9,18-20]. Although TART is rare in childhood, it has a high rate of infertility in adulthood, with an incidence of up to 94% [21].

The prevalence of TART has been reported in limited pediatric studies: Claahsen-van der Grinten et al. [18] 24%, Martinez-Aguayo et al. [22] 24%, Cakir et al. [23] 14.3%, Aycan et al. [9] 18.3%, Aycan et al. [24] 17.4%. TART was mostly detected in patients with CYP11B1 deficiency up to 35.7%- 40% [19,24,25]. The prevalence of TART has varied. It may be related to the screened age. The frequency of TART increases with puberty and is most common in adulthood. The prevalence might have been higher in childhood if the subjects had been screened earlier [10,18,24]. However, it is recommended to perform the US earlier to detect TART [9,24]. Another significant point that may affect the frequency of TART is the genotype of the disease. Unfortunately, limited studies exist to understand the genotype-phenotype relationship [20,24-27]. TART is mainly detected in patients with CAH in groups null and A and rare in group C [24,26]. Our previous study showed 82.7% of patients with SW type CYP21A2 deficiency had TART [24].

Age at Diagnosis of TART

The youngest case with TART shared in the literature was defined as <8 weeks in autopsy studies [28]. To our knowledge, Dumic et al. described the youngest child with TART at the age of 1.8 years. This patient had an 11-B-hydroxylase deficiency [29]. In a previous study, we reported that almost half of the patients with 11-B-hydroxylase deficiency had been diagnosed with TART before the age of 10 years, and the youngest was two years old [24]. To our knowledge, the youngest patient with 21-hydroxylase deficiency was reported as four years [24]. It was recommended that children with CAH should be screened every two years in childhood and annually at puberty for TART [9]. We suggest that boys with an 11-B-hydroxylase deficiency should be screened very closely since it can be detected in the first year of childhood.

Diagnostic Imaging

Clinicians should follow boys diagnosed with CAH closely for the development of TART from childhood. There is no certain laboratory test to show TART. A-fetoprotein, and α-human chronic gonadotropin are not high in patients with TART [19]. A study shared that 11-oxygenated-C19 steroids and pregnenolone sulfate might effectively check whether TART is under control [30]. Unfortunately, it is challenging to use mass-spectrometry panel routinely since it is expensive and unavailable in every center. Although the physical examination is the first step for diagnosis, the mass is located within the rete testis and is not always palpable. TART tissue, usually >2 cm, can be detected on physical examination [9,10,12,24]. Infertility is a significant morbidity reason in adulthood, and treatment costs increase. Therefore, diagnostic imaging is needed to determine the small lesions TARTs. There is no gold standard method to show TART. Changes in size should be evaluated by US or magnetic resonance imaging (MR). Although MR and US display almost coequally, the US is more accessible, wieldy, and cost-effective [9,11,12,31].

"TART is evaluated in five stages according to histological and clinical features [12]:

Stage 1. The presence of adrenal rest cells within the rete test is not detectable on the US.

Stage 2. The US might detect the adrenal rest cells due to hypertrophy/hyperplasia.

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

Stage 4. Further compression of the rete testis with fibrosis and focal lymphocytic infiltrates

Stage 5. Irreversible damage of testicular parenchyma [9,12].

TARTs are commonly bilateral, multifocal, and hypoechoic on the US. Normal adrenal glands and TART have similar MR features; they are both isointense to muscle on T1-weighted and T2-weighted images. TART can be hyperintense on T1-weighted images relative to testicle tissue. Children have tiny lesions, mostly unpalpable and undetectable. They should be evaluated by experienced radiologists [7,10-12]. Microlithiasis might be a warning sign for TART during the follow-up of patients with CAH [19,23].

In the literature, the age of onset of TART screening is variable (1-8 years), and there is no guideline about the screening time of TART. It is significant to diagnose before stage 3 to prevent infertility with medical treatment. If it cannot be detected, the rete testis progress to fibrosis constricted. In this stage, it is hard to prevent infertility [9,12,24]. Based on our experience, we suggest that boys with CAH should be evaluated for two years in early childhood and every year in the pubertal period by the US [9].

Etiology and Clinical Features of TART

The etiology and clinical heterogeneity of TART are still poorly understood. Steroidogenesis is hormonally regulated in adrenals by ACTH through the melanocortin 2 receptor (MC2R) and in gonads

by LH through the LH receptor [32]. TART cells express *Cyp11b1, Cyp11b2, Cyp21, Cyp17, MCR2*, and *LHCGR* (encoding the LH/human chorionic gonadotropin [hCG] receptor) [32]. Contrary to what is known, recent studies have shown that it also expresses the Leydig cell markers *INSL3* and *HSD17B3* [32,33]. TART might be under the hormonal control of ACTH and LH. Engels et al. thought that dysregulation of transcription factors plays a role in the etiology of TARTs. GATA1, GATA3, GATA4, and GATA6 gene expression levels were measured in healthy and TART adrenal and testicular tissues. GATA3 and GATA6 were expressed in both fetal and adult adrenal. GATA4 was demonstrated in both fetal and adult testis. GATA3, GATA4, and GATA6 gene expressions were all detected in TART [34]. These studies show that TART tissue resembles adrenal and testicular tissue with embryological and genetic features.

One of the most popular hypotheses for the development of TART is elevated ACTH levels. As a CAH complication, TART is shared in incompatible patients with treatment. Researchers reported poor metabolic in 58% to 75% of patients with TART [24,25]. Under the higher dose glucocorticoid treatment, ACTH decreases. When the stimulation disappears, TART is taken under control, or the size of TART is reduced or even completely disappears [13,21,35,36]. A patient with NC form of CAH was reported to have TART, too [24]. Although TART is a long-term complication of CAH, it has not only been described in CAH cases. TART developed 12 years later in a patient with Cushing Syndrome after bilateral adrenalectomy [37]. Those approve that ACTH is a significant factor in tumor growth in poor hormonal control. It can be speculated that elevated ACTH levels in utero may cause the development of TART. However, all CAH boys in poor hormone control do not have TART in follow-up [10,24,25,38]. To our knowledge, despite exposure to high ACTH levels in high intervals predisposes factors to TART, the presence of TART in NC cases with tight control shows that elevated ACTH is not an absolute necessity for TART [15,20,35]. Very low levels or short-term elevation of ACTH also cause tumor growth. Patients with CAH in healthy hormone control had TART, too [10,25]. Besides, no relevancy could be demonstrated between TART volume and final height, body mass index, adrenarche, testicular volume, bone age, glucocorticoid dose, pregnanetriol excretion, plasma renin, and ACTH levels [26,38]. More than poor metabolic control, various factors might influence TART development.

The mechanism of TART formation is complex and cannot be attributed to a single factor. Angiotensin II (AII) receptors were shown in TART. After inhibition of AII, adrenal gland volume decreased. This situation means TART growth depends not only on ACTH, but AII is also an essential factor in SW CAH patients [39].

The other hypothesis on TART development is LH stimulation. It has been noted in the studies/case reports reported so far that TART is detected in puberty/postpuberty [9,12,39,40]. While the presence of LH receptors could not be shown in some reports, the increase in the frequency of TART in puberty and the postpuberty period did not exclude the effect of LH [41]. Finally, Benvenga et al. supported LH receptor existence on TART [40]. LH may stimulate tumor growth. On the other hand, most patients have been screened at puberty. LH may be a stimulant factor, or TART, which is less than 2 cm in diameter in childhood and was not scanned by the US, may be newly diagnosed. Longitudinal studies are needed to understand its precise effect.

Genotype of CAH Patients with TART

There have been significant advances in genetics over the years. The genomic background of development TART has begun to be understood with increasing genetic studies [19,23,24,42]. However, these studies are still not sufficient. It is hard to assess the genotype-phenotype correlation. In a study, the most frequent mutation in patients with 21 hydroxylase deficiency was c.293-13C>G (IVS-2) (22.0%), followed by large conversion (14.3%), p. Ile173Asn (9.9%) p. Arg357Trp (8.8%), and large deletion (6.6%). The most common mutation in SW type was IVS-2 (11.5%), and in SV was IVS-2 (20%) [43]. In this study, no patients with TART shared. TART is mainly identified in patients with SW and SV forms of 21-hydroxylase deficiency [24,26,27]. In the literature, a recent study with the most extensive number of TART patients showed that 82.7% of patients with TART had SW type of 21 hydroxylase deficiency with the frequent mutations: c.293-13C>G (32.8%) and c.955C>T (p.Gln319Ter) (27.6%) [24]. Claahsen-van der Grinten et al. shared the first study of the evaluation of TART in childhood. The most common mutation related to TART with CYP21A2 deletion/large conversion, followed by c.518T>A (p.Ile173Asn), c.1069C>T (p.Arg357Trp), c.293-13C>G, and c.955C>T (p.Gln319Ter) [10]. These two studies were reported from different countries, far from each other. The variability of mutations could be due to the founder effect.

Although the genetic background of 21-hydroxylase deficiency has been mostly clarified, there is still little known about 11β-hydroxylase deficiency. The presence of TART with 11-B-hydroxylase deficiency is lower than TART with 21-hydroxylase deficiency. On the other hand, it is more frequent in the Turkey [42]. A few case reports of TART patients with 11-B-hydroxylase deficiency have been reported so far. Unfortunately, the specific location of the mutation in the codon is not shared in most [13,44-48]. Most of the mutations identified in CYP11B1 are located in exons 6, 7, and 8 [23].

Khattab et al. evaluated 108 CAH patients with 11β-hydroxylase deficiency from 11 countries, including Turkey. They shared that the severe form of CYP11B1 mutations affected the heme-binding region and enzyme stability. R448P mutation presented very moderately, with the lowest point of Prader score. R374, R448C, R448H, G267S, R141X, and W260X were linked to severe virilization (Prader score 4-5). R374 and R448C were associated with severe hypertension [49]. This study has been one of the most comprehensive studies; in contrast, no patient with TART was mentioned. Kandemir et al. reported that the c.954G>A (p.Thr318Thr) in CYP11B1 was the most prevalent mutation. 75% were located in exons 3, 5, and 7[42]. There were no TART patients in this study too.

In a case report, a boy with classical 11-B-hydroxylase deficiency had a complete loss-of-function mutation (p.Leu463_Leu464dup). He was diagnosed with premature pubarche. TART was noticed on the right testis at 27 years of age with 70 times higher ACTH levels. He had testis-sparing surgery and high-dose prednisolone therapy and had children [46].

Limited studies sharing TART genetics are as follows: The most curious question about TART is whether cases with genetic mutations have the same clinical features. In one of the studies seeking an answer to this question, Bas et al. showed that the c.896T>C (p.Leu299Pro) was the most frequent mutation in TART patients with 11-B-hydroxylase deficiency. c.421C>T

(p.Arg141Ter), c.1398 + 2T> A (IVS8+2T>A), and c.954G>A (p. Thr318Thr) were the other mutations associated with TART in exon 3, 5, and intron 8. Patients had a variable presentation with the same mutation. No clinical and genetic correlation could be shown [19]. The most recent study is done by Aycan et al. They shared seven mutations in 11 patients with TART with classical pathogenic variants with 11-B-hydroxylase deficiency. c.896T>C (p.Leu299Pro) was the most frequent (31.8%) pathogenic variant. It is followed by c.1120C>G (p.Arg374Gly). Five patients with TART had associated mutations: c.421C>T (p.Arg141Ter), c.896T>C (p.Leu299Pro), c.1398 + 2T> A (IVS8+2T>A), and c.954G>A (p. Thr318Thr) [24]. It was noted that there were similar mutations: c.954G>A (p.Thr318Thr), c.896T>C p.Leu299Pro, c.421C>T (p.Arg141Ter), c.1398 + 2T> A (IVS8+2T>A) in these studies. These mutations were in Turkish patients, possibly related to the founder effect. We also shared different variants with low frequency in the same study: c.1120C>G (p.Arg374Gly), c.372delG (p.His125ThrfsTer8), c.1179_1180dupGA (p.Asn394ArgfsTer37), c.896T>C (p.Leu299Pro)/c.1398 + 2T>A (24). More cases are needed to say whether it is indeed directly related to the development of TART. Kocova et al. shared that there was no variation in genetic mutations in patients with and without TART [20]. To our knowledge, no study compares TART patients and no TART patients with the same mutation. Poor hormonal control might contribute to the development of TART, too. Functional analysis studies are needed to give a definitive answer to the questions of whether these mutations are directly related to TART development or whether TART was incidentally detected.

Treatment

In patients with CAH, TART presents with unilateral or bilateral testicular mass. Infertility related to TART is a well-known long-term complication. As the size of the tumor enlarges, it occludes seminiferous tubules. Screening and early diagnosis are essential to prevent infertility. Spermiogram can be evaluated in postpubertal patients. Inhibin B and AMH can be performed to assess Sertoli cell function in children [9].

Since the development mechanisms of TART are not still precise, its treatment is also controversial and still limited. When TART is detected, the first-line treatment is to use a supraphysiological dosage of glucocorticoid therapy. It is crucial to advance glucocorticoid treatment in poorly metabolic controlled patients [9,10,24]. The treatment dosage has been reported as 30 mg/m2/day hydrocortisone [9,13]. Long-acting steroids such as prednisolone or dexamethasone (1.5 mg/day) can be administered in patients who reach final height [10,50]. However, no consensus exists on medical therapy dosage and treatment duration, and no specific therapy option to prevent the development of TART [10,25]. Some have responded well to the treatment with a reduction in size or complete regression [8,13,21,22,51]. Generally, it is shared that the size of TART decreases in 4 to 8 months, which might be considered an early response [9,10,13]. In our recent study, 20% of patients with TART on supraphysiological treatment dosage recovered, whereas high-dose glucocorticoid treatment did not affect 22.5% [24].

Augmenting steroid therapy might be effective on stages 2 and 3 TART [9,39]. On the other hand, there were cases who could not be continued the high-dose treatment due to the complications such as hypertension, weight gain, striae, and hypertension or its effect on final height in childhood [9,10,50]. Even though some cases were on high-dosage steroid treatment for an extended interval (6 years), the tumor persisted [9]. Since elevated ACTH is not the only reason for TART, it is acceptable that every patient could not respond well to ACTH suppression treatment [17,50,52].

No difference in response to treatment was noted between the diagnosis of 21 hydroxylase deficiency and 11-B-hydroxylase treatment [9,50,52]. As the diameter of the mass gets more excessive, it is hard to cure with medical treatment [9]. If the testicular size is not diminished despite suppression treatment or persistent azoospermia is detected, testicular-sparing tumor enucleation should be considered. Testis-sparing surgery recovers fertility [17,50], but it is shared that it does not improve infertility [25].

In conclusion, today's knowledge about TART is smaller than a grain of sand in the desert. Many points are still inexplicable in the evolution mechanisms of TART, extending from the embryological period to the adult period. Further longitudinal studies in childhood and adolescence are needed to reveal the development of TART, genotype-phenotype correlation, and exact treatment options.

Statements

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