Testicular Adrenal Rest Tumors in Patients with Congenital Adrenal Hyperplasia: A Case Series

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ABSTRACT

Objective: *Testicular adrenal rest tumors (TARTs) are the main etiology of infertility in congenital adrenal hyperplasia (CAH). The aim of this study is to determine the patients diagnosed with TART and to evaluate the risk factors associated with the development of the disease.*
Methods: *Clinical characteristics of 31 patients with CAH including 19 male, and 12 female patients who were followed up in our clinic were retrospectively reviewed regarding the presence of TART. Differences between clinical and laboratory findings of patients with and without TART were examined. Six male patients with TART were included in the study. Clinical characteristics such as pubertal stage, treatment doses, laboratory findings were evaluated. Changes in size of TARTs were examined with ultrasound follow-ups at six month- intervals.*
Results: *The prevalence of TARTs was 31.5 % (6/19 male). Precocious puberty was higher in patients with TART than without TART. The mean age of the patients was 9.1±2.4 (range: 5.2-12.4) years at the time of diagnosis with TART. Five patients with TART were inadequately controlled. Four patients had a history of precocious puberty. Tumor progression was detected in 4 of 6 patients. In three patients with tumor progression, serum 17-hydroxy progesterone (17-OHP) values increased during follow-up, probably due to non-compliance with treatment.*
Conclusion: *Scrotal ultrasound monitoring should be performed in all male patients with CAH in early childhood irrespective of disease control.*

INTRODUCTION

Congenital adrenal hyperplasia (CAH) belongs to a group of autosomal recessive disorders caused by the deficiency of one of the enzymes involved in adrenal steroidogenesis. More than 90% of the cases have 21-hydroxylase enzyme deficiency caused by CYP21A2 mutation.[1,2]

One of the most serious long- term complications of 21-hydroxylase enzyme deficiency is benign testicular tumors, called TART.[1] The etiology and pathogenesis of TARTs are not fully elucidated. Common adrenogenital primordium-derived undifferentiated adrenal cells are thought to remain in the testicular parenchyma and lead to tumor formation by chronic ACTH stimulation.[3,4]

Poor hormonal control seems to be associated with TART. Decreasing ACTH levels with high-dose glucocorticoid therapy causes shrinkage in testicular adrenal rest tumors. However, in some cases, high dose steroid therapy does not reduce tumor size. Moreover, TARTs can also be seen in well-controlled patients with CAH. These findings suggest that, factors other than hormonal control may cause tumor formation and growth.[5-7] Adrenal-specific enzymes (CYP11B1 and CYP11B2), ACTH, angiotensin 2 and LH receptors were detected in tumor tissue. Increase in pubertal LH has been reported to contribute to tumor growth through LH receptors in tumor tissue. Increase in the frequency of TART in well-controlled patients after puberty is attributed to this condition.[1]

The frequency of TARTs was reported to range between 14% and 86% in different studies.[1,8] Most cases in the literature are detected in the pubertal period and in generally poorly controlled patients.[5]

Tumors with a size of <2 cm are usually not noticed by palpation. Ultrasonography (USG) is the gold standard method of detection. Additional methods such as magnetic resonance imaging (MRI) should be used in smaller and suspicious lesions.

The aim of this study is to determine the patients diagnosed with TART by testicular ultrasound in our clinic and to evaluate the factors associated with the development of the disease such as its clinical manifestations, disease control and presence of puberty.

MATERIAL and METHODS

The study was conducted in pediatric endocrinology outpatient clinic of the university. Medical records of the patients followed with the diagnosis of CAH between January 2012 and September 2020 were retrospectively reviewed. In our clinic, anthropometric measurements, physical examination, and hormone assays of patients with CAH are performed every three months during the follow-up period.

Adequate control of CAH was defined as having a mean serum level of 17-hydroxyprogesterone (17-OHP) ≤10 ng/mL and age appropriate growth during the follow-up period.

Serum ACTH, renin and androstenedione levels were measured by chemiluminescence immunoassay (CLIA). Serum 17-OHP and aldosterone levels were measured using radioimmunoassay (RIA).

Pubertal development was evaluated according to Tanner staging. Bone age assessment was reported by a pediatric endocrinologist according to the Greulich and Pyle method.

TART investigation was performed by scrotal ultrasonography obtained in a Siemens Acuson Antares (5–13 MHz) at six- month intervals during follow-up period.

The statistical analysis was conducted with IBM SPSS Statistics 20 (IBM Corp., New York, USA). Descriptive analysis was performed and data were further analyzed using Mann-Whitney U and chi-square tests. For all tests, the level of significance was set at $p < 0.05$.

RESULTS

Nineteen male patients with CAH who were followed up in our clinic were included in the study. One patient was followed up with 11-hydroxylase deficiency, two with simple virilizing type, and 16 with classical salt-wasting type 21-hydroxylase deficiency. TART was diagnosed in 6 (31.5%) of the patients screened by ultrasound. All six patients with TART had salt -wasting type 21-hydroxylase deficiency.

The characteristics of patients with and without TART are summarized in Table 1. The prevalence of precocious puberty was higher in patients with TART than patients without. Other laboratory and clinical

Table 1. Comparison of clinical and laboratory characteristics of the patients with and without TART

	TART (+)	TART (-)	p value
Age at the time of CAH diagnosis (year)	0.15 (0.10-0.20)	0.25 (0.10-4.6)	0.105
Weight (SDS) kg	1.8 (-0.2-2.3)	0.5 (-0.2-0.9)	0.302
Height (SDS)	1.4 (-0.18-2.8)	-0.82 (-1.8-0.7)	0.119
Height velocity (SDS)*	-0.7 (-0.1- -2.1)	-0.3 (-1.08-0.17)	1.000
BMI (SDS)*kg/m^2	1.4 (0.1-1.8)	1.4 (0.4-2)	1.000
17-OHP level (ng/ml)*	5 (2.7-19.1)	4.5 (3.8-9.5)	1.000
Renin (ng/ml/h)*	38.4 (12.8-124.9)	3.7 (0.94-6.9)	0.119
Aldosterone (ng/dl)*	92 (24.2-140.2)	5.5 (2.9-25.3)	0.242
Hydrocortisone dose (mg/m^2/day)*	14.4 (10.5-16.4)	11.7 (9.3-14.2)	0.608
Fludrocortisone dose (mg/day)*	0.1 (0.08-0.11)	0.08 (0.05-0.11)	1.000

** mean of the last 1 year*

Table 2. Clinical, laboratory and ultrasonography characteristics of the patients with TART

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Median (min-max)
Genotype	I2splice	I2splice+ V281L+P453S	NA	NA	NA	I2splice/ del8bpE3	
Age at the time of CAH diagnosis (day)	10	60	30	24	15	15	19.5 (10-60)
Age at the time of TART diagnosis (decimal year)	5.2	10.1	9.1	7.9	12.4	10.1	9.66 (5.25-12.41)
BA-CA *(years)	-0.75	2.84	4.84	6.09	-	2.34	2.84 (-0.75-6.09)
Age at the time of onset of puberty (years)	-	8.9	NA	6.6	NA	6	NA
Follow-up time with usg (years)	-	4.6	2	4.3	4.3	6	4.2 (2-6)
TART size (mm)**	NA/NA	-/3	NA/NA	12/14	13/12	4/5	
Tanner stage *	1	2	2	2	4	2	
Precocious puberty	-	+	+	+	-	+	
17-OHP level (ng/ml)***	3.5	5.26	32.4	4.75	0.33	19.6	5 (0.33-32.4)
ACTH level (pg/ml) ***	139	13.1	16.2	7.69	41.16	44.8	28.9 (7.69-139)
Androstenedione level (ng/ml)***	0.46	NA	6.65	NA	NA	1.9	1.9 (0.46-6.65)

** at the time of TART diagnosis, **at the first diagnosis, long diameter, right/left (mm) ***mean of the last 1 year before TART diagnosis NA: not available, BA: bone age, CA: chronological age, min: minimum, max: maksimum.*

Table 3. Comparison of follow-up ultrasound dimensions of TART with laboratory values

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
TART size at diagnosis (mm)	NA/NA	3	microlithiasis	14	13	5
TART size at last control (mm)	-	5	8	14	23	29
Follow-up time with US (years)	-	4.6	2	4.3	4.3	6
17-OHP level (ng/ml)*	1.3	16.9	19	0.87	37.3	37.2

**mean of the last 1 year before last USG, NA not available*

follow-up parameters were comparable between groups.

The characteristics of 6 patients are summarized in Table 2. TART was diagnosed after the onset of puberty in all patients expect one. Four patients (patients 2, 3, 4 and 6) received leuprolide acetate with the diagnosis of central precocious puberty before determination of TART.

While a unilateral lesion was detected in one of the patients, other patients had bilateral lesions. During the 4.5 year follow-up of the patient with unilateral TART, no lesion developed in the contralateral testicle.

MRI was performed in one patient (Case 6) to detect significant tumor growth, and to exclude malignancy. MRI showed hypointense lesions compatible with TART.

Mean follow-up time of the patients was 4.2±1.4 years. TART size increased during follow-up in four patients (Table 3).

DISCUSSION

The prevalence of TARTs in boys with CAH was 31.5% in the current study. Reported prevalence of TARTs varied between 14% to 86% in the literature.[1-11] This variation is related to age range of the patient

population, the severity of the disease and the method of detection. In studies included only children, the prevalence was reported between 10% to 70%.[8,10] TART prevalence was associated with the severity of the disease, and it was more common in patients with classic salt-wasting type CAH.[8,10] However, cases with simple virilising or non-classical forms of 21-hydroxylase or 11-hydroxylase deficiency have also been reported.[5,12-14] Most of the studies reported that, TART was associated with non-compliance to treatment or inadequate treatment.[5,8,12,15] However, TART was also described in well-controlled cases.[8,11,13,16,17] Therefore, metabolic control may not be the only factor contributing to the development of TART. In our case series, Case 1 had high ACTH levels, however other clinical and laboratory data were not suggestive of inadequate metabolic control. Cases 3 and 6 had high serum 17-OHP levels and precocious puberty suggestive of inadequate control. Cases 2 and 4 had normal mean ACTH and 17-OHP levels before diagnosis of TART, however both of them had a history of precocious puberty. Case 5 was well-controlled. As a conclusion, 4 of 6 TART patients had inadequate metabolic control.

In our study the median age of the patients at the time of the diagnosis of TART was 9.6 (5.25-12.41) years and the youngest patient was 5.25 years old. TARTs are reported to be more common in adolescence and postpubertal period, the youngest patient described in the literature was 1.8 years old.[8,11] There is no consensus about time to start screening for TARTs. An expert opinion suggests screening by testicular ultrasound assessments should begin in adolescence.[18] However, regarding prepubertal cases reported with TART, screening should be started earlier, especially in poorly controlled patients.

Eighty percent of TARTs are reportedly bilateral, and rarely unilateral.[10] Similar to reported incidence rates five of our cases (%83) had bilateral TART. Bilateralism of the lesions should be linked with the origin of TART. The etiopathology of TARTs has been related to their embryological development. It has been speculated that, TARTs develop from the embriyogenic pluripotent steroidogenic cell types that are already present in utero. Gonadal and adrenal cells originate from a common adrenogenital primordium, and during differentiation and migration of gonadal cells, undifferentiated adrenal cells may remain within testicular tissue.[1,19] In poorly controlled patients with CAH, high ACTH levels cause proliferation of undifferentiated adrenal cells which induces the formation of TART in rete testis.[3] Optimization of steroid treatment is recommended to prevent disease progression. However, suppression of ACTH secretion is not always successful in reducing tumor size, and even well-controlled CAH patients with normal or suppressed plasma ACTH levels have testicular adrenal resting tumors.[1,6,8] The pubertal LH peak and its trophic effect are predicted to contribute to tumor growth.[6,10] In our study, TART was diagnosed after onset of puberty in our five cases (83.3%). Four of the patients had central precocious puberty suggestive of poor hormonal control of CAH. Thus, a conclusion suggesting that the trophic effect of LH or high ACTH due to poor control caused TART can not be regarded.

Differentiation of TARTs from adrenal tumors like testicular Leydig cell tumors (LCT), adrenocortical adenomas should be done in case of clinical or radiological suspicion.[6,8] More than 90% of the cases with LCT are unilateral[8] Additionally, The presence of Reinke crystalloids has never been reported in TARTs, but sometimes they are seen in LCT. However, differential diagnosis is very difficult as these tumors share the same steroidogenic cells origin.[20,21]

Treatment of TARTs depends on the stage of the tumor. According to Claashen-van der Grinten et al.[7], TARTs are classified in five different stages. In Stage 1, there are adrenal rest cells within the rete testis, not detectable by scrotal testicular ultrasound. In Stage 2, these cells become hyperplastic and hypertrophic. Further growth of these cells will lead to the development of multilobular lesions and compress the seminiferous tubules (Stage 3). Focal lymphocytic infiltrate and peritubular fibrosis are detected in TART at Stage 4 and, chronic obstruction, irreversible damage of testicular parenchyma is detected at Stage 5. Therefore, it is important to detect and treat the tumours before permanent damage of the testis has occurred. High-dose glucocorticoid therapy to suppress ACTH was recommended in cases with Stages 2 and 3, however

this treatment was not always successful in reducing the lesion size. Temporary increase in tumor size has also been reported in some patients.[5,13] Different steroid formulations (hydrocortisone, dexamethasone and prednisone) have been used as treatment of TARTs, and the superiority of one over others has not been reported so far.[5,8,13,22] Testis-sparing surgery has been also used as a treatment option in Stages 3 and 4.[1,6,15,23,24] Successful testicular sparing surgery has been described in small groups of patients with TARTs, but no significant improvement in gonadal function after surgery was seen.[15,23] TARTs might reappear after surgery.[15,23] In our clinic, the treatment plan after detection of TART varies according to the patient's clinic, but generally includes increasing the dose of hydrocortisone or adding dexamethasone to the treatment according to patient's age. Treatment dose was not increased after the detection of TART in Case 1 due to good laboratory and clinic control markers. High ACTH levels were attributed to variation of blood sampling time and we did not want to make dose adjustment based on a laboratory assessment. In rest of the patients, treatment doses were increased. In Cases 5 and 6, dexamethasone was added to therapy. However, serum 17-OH-P levels remained high suggestive of non-compliance to therapy.

There are some limitations of our study. Although, we performed non-parametric tests to compare medians, statistical results may not be reliable due to small sample size.

As a result, although TARTs are seen more frequently in pubertal period and in poorly controlled patients with CAH in the literature, well-controlled and prepubertal cases may be encountered as in our study. Therefore, routine scrotal ultrasound control should be performed intermittently in childhood and adolescence in male patients with CAH.

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