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Prevalence of Testicular Adrenal Rest Tumor and Factors Associated with its Development in 6 Months to 18 Years-old Patients with Congenital Adrenal Hyperplasia

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Abstract

Background: Congenital adrenal hyperplasia (CAH) is a potentially life-threatening form of primary adrenal insufficiency characterized by cortisol, aldosterone, and epinephrine deficiencies, as well as overproduction of androgens. Infertility is one of the most important complications in male patients with CAH, and testicular adrenal rest tumors (TARTs) are known to be the most important cause of infertility in these patients. The prevalence of TART is considered to be high in patients with classic type of CAH, and poor hormonal control is known as a factor associated with tumor development. In the present study, the prevalence of TART and factors associated with its development were evaluated in pediatric patients with CAH.

Methods: This is a descriptive cross-sectional study evaluating 30 males (6 month -18 years) with the classical 21-hydroxylase deficiency (21-OHD) through testicular ultrasonography. Data including age, bone age, puberty status, 21-OHD phenotype (salt wasting (SW) or simple virilizing (SV)) and serum levels of 17- hydroxyprogesterone (17-OHP), androstenedione and adrenocorticotropic hormone (ACTH) were recorded.

Results: The prevalence of TART was determined as 56.7%, which increased with age with a higher prevalence in children >12 years old (52.9%). The mean age in patients with TART was 12.4 ± 4.18 years. No association was found between TART and 21-OHD phenotype, androstenedione, or 17OHP levels, but an association was found between TART and elevated levels of ACTH (p= 0.049), advanced bone age (p= 0.030) and puberty (p= 0.003).

Conclusion: According to the results, TART is very common and can occur in pre-pubertal and young patients, and the disease control could be a factor associated with its development. Therefore, it is suggested to investigate the TART development early in childhood, mainly in poorly controlled 21-OHD patients.

Key Words: Adrenocorticotropic hormone, Congenital adrenal hyperplasia, Testicular adrenal rest tumor.

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1- INTRODUCTION

Congenital adrenal hyperplasia (CAH) is a potentially life-threatening form of adrenal insufficiency characterized by a deficiency of cortisol, aldosterone, and epinephrine and overproduction of androgens (1). It is one of the most common endocrine diseases with an estimated incidence of 1 10,000 -20,000 in birth and autosomal recessive inheritance pattern. This type of genetic disorder is commonly caused by mutations in the cyp21A2 gene; it inactivates the 21-α-hydroxylase enzyme, leads to a decrease in cortisol and aldosterone levels, increases adrenocorticotropic hormone (ACTH), adrenal hyperplasia, accumulation of steroid precursors and excess androgen production (3). Infertility is one of the most important complications of CAH in men (4).

Many explanations for the infertility have been suggested; however, testicular adrenal rest tumors (TARTs) are known to be the most important cause of infertility in these patients (5).

TART was first reported in 1940 and called tumor rest because of the morphological and functional resemblance with adrenal tissue. The prevalence of TARTs in CAH patients has not been clearly established yet. According to previous studies, the prevalence of TART varies from 0 to 94% depending on the age and hormonal factors of patients as well as the method of determining the tumor (by touch or ultrasonography)(6).

The etiology and functional characteristics of TART have not been fully understood. However, clinical observations have shown that high doses of corticosteroids can reduce tumor size, suggesting the presence of an ACTH receptor on tumor cells (7). A recent study has shown the presence of specific adrenal enzymes such as cyp11B1 and cyp11B2, ACTH receptor and angiotensin II in testicular tumors (8). Therefore, it can be concluded that tumor growth in this disease may not only be stimulated by increased ACTH but also by the angiotensin II level. Also, adrenal rest cells may have originated from a different population of similar adrenal cells (9). The TART does not have malignant features and even need to be removed in the early stages, but due to the location of tumors near the mediastinum of the testicles and pressure on the nephrotic ducts, it may lead to obstructive azoospermia and irreversible damage to the surrounding testicular tissue (10).

CAH, as a common disease in men and some of them, may be diagnosed in childhood (6). The tumor may cause a compressive effect with tubular obstruction, or azoospermia. In some cases, large TART can compress normal tissue and affect spermatogenesis and testosterone production, leading to infertility in men with congenital adrenal hyperplasia (11). Proper management of the disease, including early diagnosis, adequate and timely treatment and regular follow-up is essential to reduce the adverse complications of the disease. Due to the high prevalence of CAH and its consequences, inclusion of TART screening in the child care program and determining a certain age to start the screening and determining the best screening method in these patients can inform the parents and physicians in preventing, intervening and treating this complication, which promotes community health. In the present study, the prevalence of TART and its associated factors in children with CAH was studied in Mashhad Children's Hospital in 2020.

2- METHODS

This descriptive-analytical cross-sectional study was performed in 2020 in the pediatric endocrinology and metabolism clinic of Akbar Hospital in Mashhad. There was no intervention in

this study. Scrotal ultrasound with a high frequency linear transducer (5-21 MHz) was performed to evaluate TART, and the largest axial diameter of the tumor was measured in the radiology department of Akbar Hospital. Hormonal tests including 17-hydroxyprogesterone (17-OHP) (Diametra- immunodiagnostic reagents and test kits), androstenedione, and ACTH (Siemens, Germany) were performed prior to ultrasonography. Skeletal age was determined based on the Greulich-Pyle method and accordingly, the patients were divided into two groups of advanced and non-advanced skeletal age. The diagnosis of 21-hydroxylase deficiency was confirmed by cyp21A2 genetic analysis, or based on clinical observations. Patients were classified according to clinical presentation into two forms of salt wasting (SW) or simple virilizing (SV).

2-1. Inclusion and exclusion criteria

Inclusion criteria in this study were age between 6 months to 18 years, and male patients with classic CAH. The patients were excluded in lack of cooperation of the child, and incomplete tests of androstenedione and ACTH and 17-OHP.

2-2. Ethical considerations

This research was approved by the Organizational Ethics Committee of Mashhad University of Medical Sciences with the code IR.MUMS.MEDICAL.REC.1398.829. In this study, all the information and the results of data analysis as well as demographic information of the participants were confidential and were used for reporting without the name and personal information of the patients. After the patient's visit, the necessary explanations about the research plan were given to the parents and the written informed consent was received from the participants and ultrasound was then performed.

2-3. Statistical Analysis

Demographic and clinical data of patients were analyzed by using SPSS software version 22. Descriptive statistics methods were used to describe the data. Chi-square test was used to investigate the relationship between qualitative variables, while independent t-test and ANOVA as its non-parametric equivalent were used to evaluate the relationship between quantitative variables in the two groups or more than two groups, respectively. A p-value less than 0.05 (typically ≤ 0.05) was considered as statistically significant. It indicates strong evidence against the null hypothesis. The sample size was calculated (by $\alpha= 0.05$, $\beta= 0.2$, 0.64 prevalence of TART and the prevalence error of 0.3) as 25 people using the ratio estimation formula in the community described by Kang et al. (12); however, sample size was increased to 30 participants.

3- RESULTS

In this study, 30 boys with classic congenital adrenal hyperplasia were studied. The mean age of the participants was 9.5 ± 5.16 years (ranging from 8 months to 18 years). Out of 30 patients, 17 (56.7%) had TART. The mean age in the TART and non-TART groups was 12.41 ± 4.18, and 5.9 ± 3.89 years, respectively, indicating a significant difference between the groups ($p <0.001$). There was only one patient with TART in the age group under 5 years, but 52.9% were over 12 years old, and all patients over 12 years (100%) had TART. Overall, 16 patients had increased bone age among patients with (n=12) and without (4 patients) TART. In addition, 14 patients with (n=5) and without (n=9) TART had no advanced skeletal age, which was statistically significant ($p= 0.030$). Similarly, there were significant differences in the ACTH levels between the patients with and without TART ($p= 0.049$).

Depending on CAH type, the patients were categorized into two groups of SW and SV. The frequency of SV CAH type was 2 and 0 in patients with and without TART, while SW type was more frequent among the patients with (n=15) and without (n=13) TART indicating no significant difference between the groups (0.492). Likewise, no significant difference in 17-OHP level was observed between the patients with and without TART (p= 0.454). Moreover, androstenedione levels were quite similar in both patients with and without TART, indicating no significant difference between the groups (p= 0.057) (**Table 1**).

Table-1: Frequency of TART and the associated factors

Variables		Skeletal age		ACTH		Androstenedione		17-OHP		CAH type	
		Advanced	Non-advanced	Normal	High	Normal	High	>10	≤10	SW	SV
Frequency	TART	12	5	2	15	8	9	12	5	15	2
	Without TART	4	9	6	7	11	2	7	6	13	0
	Overall	14	16	8	22	19	11	19	11	28	2
% total frequency		46.7	53.3	26.7	73.3	63.3	36.7	63.3	36.7	93.3	6.7

4- DISCUSSION

CAH is a potentially life-threatening form of primary adrenal insufficiency, which is characterized by deficiency of cortisol, aldosterone, and epinephrine, and excessive production of androgen. Infertility is the most important side effect of CAH and TART is recognized as the most important cause of infertility in these patients. In the present research, the prevalence of TART was investigated among 30 patients aged 6 months to 18 years with classic CAH referred to the endocrinology clinic. Also, the frequencies of skeletal age, ACTH, androstenedione, 17-OHP, and CAH type were studied in patients with and without TART.

Findings showed that the prevalence of TART in patients with the classic form of CAH was 56.7%. The prevalence of TART in other studies varied between 14% to more than 60% (6, 13). Mendes-Dos-Santos et al. demonstrated that the prevalence of TART in patients with classical CAH and mean age of 15.2 years was 23.7% among (14). Similar to our findings, Claahsen et al. reported a TART prevalence of 24% in patients aged between 2-18 years (8). The prevalence of TART in our study is significantly higher than similar studies, which may be due to poor patient control, although most of the patients have not been genetically evaluated for the patients' genotypes, these patients may have high-risk genotypes such as type A and N mutations. Furthermore, in the present study, the frequency of TART did not differ between patients with SW and SV types of CAH, which was consistent with other studies (14). Kim et al (13), in their study, observed all tumors in patients with SW form and not in SV type of CAH. The frequency of TART positively correlated with the patient's age demonstrating the high frequency of TART in patients over 12 year’s age, which was consistent with previous reports (8, 13). On the contrary, Mendes-Dos-Santos et al. reported that the youngest patient with TART in their study was 5.5 years old, emphasizing that TART is independent of age (14). Also, Shanklin et al. reported TART in 3 patients with CAH under eight weeks old (15).

Considering the above reports, it can be concluded that the lack of TART is probably due to the inability of ultrasound in detecting the tumor in the early stages due to the small size, and it is probable that ectopic adrenal tissue in the testes of patients with CAH be due to chronic elevated ACTH or other unknown growth factors enlarging gradually over time, and this may explain the increased accuracy of tumor diagnosis by ultrasound along with increasing the age. On the other hand, due to the higher prevalence of TART at older ages, in addition to the above hypothesis, high levels of hormones during puberty, such as luteinizing hormone (LH), may be an additional stimulant of tumor growth, and the presence of LH receptor in testicular tumor tissue supports this hypothesis (16).

In our study, there was a relationship between TART and ACTH and the prevalence of TART, as ACTH level in the TARTs group was significantly higher than in that in the non-TARTs group, which was also shown by several other studies (6, 17, 18), although no association was found between TART and ACTH in the study of Mendes-Dos-Santos et al (14). A limited number of studies have shown the presence of adrenal-specific 11-beta-hydroxylated steroids, such as 21-deoxycorticosterone and 21-deoxycortisol in the blood obtained from gonadal veins, which confirms the presence of adrenal-like tissue in the testes of these patients. The descending subtype is suggested to be present from the embryonic period along with the testes (16). Among the investigated parameters in our study, the prevalence of TART was positively associated with high ACTH, but there was not such association with androstenedione and 17 OHP. These results were similar to those of some other reports (13, 14). Unlike these findings, Mazilla et al. reported that the plasma level of 17 OHP was significantly higher in patients with TART compared to the control patients ($p < 0.01$) (17).

Our study also showed that the prevalence of TART was high in patients with advanced bone age, which was similar to some other studies (13). However, in the study of Claahsen et al., 6 out of 8 patients had normal bone age (8). Similarly, no association was found between TART and bone age in the study of Mendes-Dos-Santos et al (14).

Due to complications such as infertility and other consequences, and the high prevalence of CAH in the society, and TART among young children even those below 5 years of age, in our study, the need for screening patients and early diagnosis and treatment of this complication seems necessary. The major limitation of our study could not show the exact hormonal control required between visits. Due to the age group of patients, it was not possible to perform sperm analysis to assess fertility. Also, histological changes of these lesions are better identified in biopsy, which was not possible in our study. Also due to the limitations in our study, we could not evaluate the effect of corticosteroid dose modification and the markers of Sertoli cells such as inhibin B and gonadotropins for evaluation of gonadal dysfunction.

5- CONCLUSION

According to the findings of this study, the prevalence of TART in patients with classic type of CAH is high, and TART can be observed in pre-pubertal children even under the age of four years. We found that poor hormonal control is a factor associated with tumor development, and the prevalence of TART is higher at older ages.

5-1. Conflict of interest

None.

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