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ORIGINAL ARTICLE

Frequency of testicular adrenal rest tumor in male congenital adrenal hyperplasia.

Sadia Mehak[1], Mohsina Noor Ibrahim[2], Maira Riaz[3]

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ABSTRACT… Objective: To determine the frequency of testicular adrenal rest tumour (TART) in male children suffering from congenital adrenal hyperplasia (CAH). **Study Design:** Cross-sectional study. **Setting:** Department of Endocrinology, National Institute of Child Health (NICH), Karachi, Pakistan. **Period:** January 2024 to August 2024. **Methods:** Male children aged 2 to 16 years, and diagnosed cases of CAH were analyzed. Among children fulfilling the eligibility criteria, demographic and clinical characteristics were noted. TART was diagnosed on clinical evaluation, ultrasound, or biochemical analysis of hormones. **Results:** In a total of 121 children, the mean age was 7.34±3.69 years. The mean duration of CAH was 6.73±3.49 years, respectively. The most common presenting complaints were vomiting, dehydration, diarrhea, and abdominal pain, reported in 75 (62.0%), 41 (33.9%), 35 (28.9%), and 31 (25.6%), respectively, TART was identified in 33 (27.3%) children with CAH. The frequency of TART was significantly associated with relatively higher age ($p<0.001$), weight ($p<0.001$), and height ($p<0.001$). The duration of CAH was significantly higher among children with TART ($p<0.001$). It was noted that 17-OHP ($p<0.001$), and ACTH ($p<0.001$) were significantly higher among children with TART. **Conclusion:** The prevalence of TART in male children with CAH was high, with significant associations between TART and older age, prolonged CAH duration, higher weight, height, and elevated levels of 17-OHP and ACTH.

Key words: Abdominal Pain, Congenital Adrenal Hyperplasia, Dehydration, Diarrhea, Testicular Adrenal Rest Tumor, Vomiting.

INTRODUCTION

Congenital adrenal hyperplasia (CAH) describes a group of disorders caused by defective steroidogenesis. The most common and potentially life-threatening form of CAH is classical CAH, which is the leading cause of primary adrenal insufficiency in childhood. CAH occurs in approximately 1 in 13000 to 15000 live-births.[1,2] The most frequency cause behind CAH is "21-hydroxylase enzyme deficiency (21-OHD)", which contributes to increased adrenocorticotropic hormone (ACTH) levels accounting around 90% of all CAH cases.[1,2]

Testicular adrenal rest tumors (TARTs) are well-known complication in CAH. The overall proportion of TART in CAH ranges between 14-89%, depending on age, genotype, and diagnostic methods, with an average prevalence of around 40%.[3] These benign tumors may cause azoospermia, gonadal dysfunction, and infertility.[4] TARTs are present from childhood but become more common during puberty and adulthood.[5]

During embryonic development, cells that are intended to form the adrenal glands may migrate into the rete testis, resulting in residual adrenal cells. These testicular adrenal rest cells arise from these residual cells that travel with the primitive gonadal cells from the urogenital ridge around the eighth week of fetal development. High levels of ACTH stimulate these cells to proliferate and form masses.[6,7] Consequently, early detection and treatment of TARTs are crucial. Both ultrasound and MRI are effective imaging techniques for detecting and monitoring TART, particularly when the tumors are not palpable during physical examination.[8,9]

1. MBBS, Post-graudate Trainee Pediatrics Unit-II, National Institute of Child Health, Karachi, Pakistan.
2. MBBS, FCPS (Pediatric Medicine), Professor Pediatrics Unit-II, National Institute of Child Health, Karachi, Pakistan.
3. MBBS, FCPS (Pediatric Medicine), Assistant Professor Pediatrics Unit-II, National Institute of Child Health, Karachi, Pakistan.

Correspondence Address:
Dr. Sadia Mehak
Department of Pediatrics Unit-II
National Institute of Child Health, Karachi, Pakistan.
drsadiamehak@gmail.com

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Different studies reported the different prevalence of TART in children such as a study by Kocova et al. reported that 25 children suffering from CAH were evaluated, among which 8 (32%) children were diagnosed with TART.[10] Wang Z, et al. reported the 79 children with CAH, among which TART was diagnosed in 15 (19%) children.[11] Aycan Z, et al. reported the 60 children and adolescents with CAH, among which TART was diagnosed in 18.3% children and adolescents.[12] There is a significant lack of studies on adrenal rest tumor in children in Pakistan. This study was aimed to determine the frequency of TART in male children suffering from CAH.

METHODS

This descriptive cross-sectional study was conducted at the department of endocrinology, National Institute of Child Health (NICH), Karachi, Pakistan from January 2024 to August 2024. A sample size of 121 was calculated taking the proportion of TART in CAH as 19%[11], by taking a confidence level of 95% and margin of error as 5%. Non-probability consecutive sampling technique was adopted. Inclusion criteria were male children aged 2 to 16 years, and diagnosed cases of CAH. Exclusion criteria were children with congenital heart defects, or those with nephrotic syndrome (as per medical record and history). Parents of children not willing to take part in the study were also excluded.

This study was performed after the permission of "Institutional Ethical Review Board" of NICH (letter number: IERB-47/2023, dated: 18-12-2023). Written and informed consents were obtained from parents/guardians. Among children fulfilling the eligibility criteria, demographic and clinical characteristics were noted. Each CAH patient was clinically evaluated for the presence of palpation on the testis. Blood samples of each child was collected in aseptic conditions in sterilized containers and sent to the laboratory of the hospital for hormonal screening, including 17-OHP, ACTH, renin activity, and testosterone. Ultrasound of each child was also be performed by experienced radiologists for identification of the size of the lesion, shape of the lesion, hypervascularity, and other key findings of TART. TART was diagnosed on clinical evaluation, ultrasound, or biochemical analysis of hormones. Clinical evaluation included the presence of palpation on testis, when the lesion has a diameter of at least 2 cm. Ultrasound evaluation included the presence of small or large lesions even of a few millimeters, heterogeneous, hypoechogenic areas surrounding the echogenic testis mediastinum with well-defined margins and hypervascularity. Serum hormonal screening evaluated hormones including 17-OHP, ACTH, renin activity, and testosterone.

Data was analyzed using "IBM-SPSS Statistics, version 27.0". Mean and standard deviation were calculated for quantitative variables. Frequency and percentages were calculated for qualitative variables. Effect modifiers like age in groups, duration of CAH in groups, and presenting complaints were controlled by stratification by applying chi-square test and taking p-value < 0.05 as significant.

RESULTS

In a total of 121 children, the mean age, weight, and height were 7.34±3.69 years, 25.64±12.39 kg, and 119.57±25.94 cm, respectively. The mean CAH duration was 6.73±3.49 years. The most common presenting complaints were vomiting, dehydration, diarrhea, and abdominal pain, reported in 75 (62.0%), 41 (33.9%), 35 (28.9%), and 31 (25.6%), respectively (Figure-1).

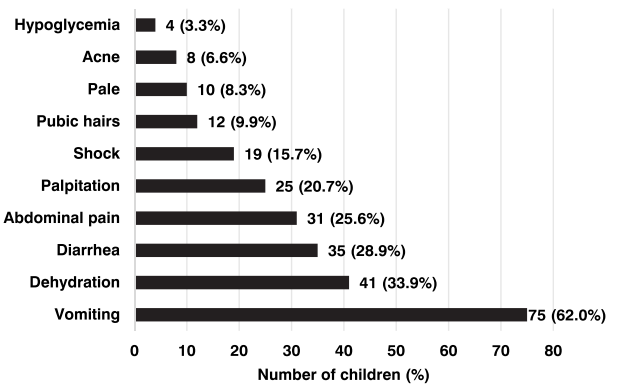

Figure-1. Frequency of presenting complaints in children with congenital adrenal hyperplasia

TART was identified in 33 (27.3%) children with CAH. The frequency of TART was significantly associated with relatively higher age ($p<0.001$),

weight (p<0.001), and height (p<0.001). The duration of CAH was significantly higher among children with TART (p<0.001). It was noted that 17-OHP (p<0.001), and ACTH (p<0.001) were significantly higher among children with TART (Table-I).

Comparison of the frequency of TART revealed significant association with palpitation (p<0.001), and pubic hairs (p=0.003), as shown in Table-II. Vomiting was found to have significant association with children without TART (p=0.035).

DISCUSSION

Our study reported a TART prevalence of 27.3%. Engels et al., in their review described a variable TART prevalence, ranging from 14% to 89%, with an overall average of 40% in patients with classical CAH. The wide range in prevalence rates is likely attributable to differences in the method of detection (e.g., clinical examination vs. ultrasound) and the population studied (children vs. adults).[13] Our study's relatively lower prevalence might be explained by the younger age of our cohort (mean age 7.34 ± 3.69 years), as TARTs are more frequently detected in older CAH patients due to their progressive nature. This trend was supported by Corcioni et al., who found a higher prevalence (31%) in adults compared to children, with nearly all TART cases identified in the salt-wasting (SW) subtype of CAH.[14] Schorder et al.,[15] conducted a large multicenter study and reported a prevalence of 38%, which aligns with our findings but highlights the variability of detection rates. Their study also underscored the importance of early diagnosis, noting that delayed diagnosis of CAH beyond the first year of life was associated with a 2.6-fold increased risk of developing TART.

This observation underscores the need for early and effective glucocorticoid treatment in preventing TART development, a point that resonates with the lower TART prevalence in our younger cohort, where early intervention may have mitigated tumor development.

Variables	Testicular adrenal rest tumour		P-Value
	Yes (n=33)	No (n=88)	
Age (years)	9.39±3.33	6.57±3.54	<0.001
Weight (kg)	32.73±10.66	22.98±11.99	<0.001
Height (cm)	135.82±18.44	113.47±25.79	<0.001
Duration of congenital adrenal hyperplasia (years)	8.42±3.34	6.10±3.34	<0.001
17-OHP (ng/ml)	197.52±120.62	133.84±115.5	<0.001
ACTH (pg/ml)	442.45±129.46	285.02±259.44	<0.001
Renin activity (ng/ml/hr)	2.61±1.18	2.95±0.91	0.095
Testosterone (ng/dl)	514.24±202.61	455.82±117.67	0.051

Table-I. Comparison of demographics, and relevant laboratory parameters with respect to the frequency of testicular adrenal rest tumor (N=121)

Presenting Complaints	Testicular Adrenal Rest Tumor		P-Value
	Yes (n=33)	No (n=88)	
Vomiting	15 (45.5%)	60 (68.2%)	0.035
Dehydration	16 (48.5%)	25 (28.4%)	0.052
Diarrhea	9 (27.3%)	26 (29.5%)	1
Abdominal pain	13 (39.4%)	18 (20.5%)	0.060
Palpitation	25 (75.8%)	-	<0.001
Shock	4 (12.1%)	15 (17.0%)	0.587
Pubic hairs	8 (24.2%)	4 (4.5%)	0.003
Pale	-	10 (11.4%)	0.060
Acne	4 (12.1%)	4 (4.5%)	0.212
Hypoglycemia	-	4 (4.5%)	0.574

Table-II. Comparison of presenting complaints with respect to the frequency of testicular adrenal rest tumor (N=121)

In our study, the frequency of TART was significantly linked weight relatively older age ($p<0.001$), increased weight ($p<0.001$), and height ($p<0.001$). de Grinten et al.,[16] found that TART can manifest in children as young as five years old but more commonly affects older children, with 75% of cases identified after 10 years of age. Ma et al.,[8] reported that the mean age of TART detection as 20 years. Our results indicate that although TART can develop early, older children with CAH are at greater risk, suggesting a cumulative effect of prolonged disease and inadequate hormonal control. This trend is further supported by Norooziasi et al.,[17] who found that TART prevalence increased with age, particularly in children older than 12 years. They also noted that increased bone age, advanced puberty, and higher ACTH levels were associated with the development of TART. The strong linkage among prolonged CAH duration and TART in our study ($p<0.001$) highlights the chronic nature of CAH as a risk factor for TART development. In particular, inadequate metabolic control over time may predispose children to tumor formation due to elevated ACTH levels, as discussed in detail below.

In this study, TART was found to have significant link with higher levels of 17-OHP ($p<0.001$), and ACTH ($p<0.001$). Elevated 17-OHP and ACTH are indicative of poor hormonal control in CAH patients, and their association with TART has been well-documented. Mazzilli et al.,[18] found that TART patients had significantly higher levels of both 17-OHP and ACTH compared to patients without TART. In their study, an increase in ACTH was correlated with larger tumor size and a greater likelihood of bilateral TARTs, a finding that echoes our results. Yu et al.,[19] reported that higher ACTH levels were significantly associated with the development of TART, particularly in patients who exhibited poor adherence to glucocorticoid therapy. The persistence of elevated ACTH levels, despite treatment, may lead to hyperplasia of these adrenal-like cells, resulting in tumor formation. This hypothesis was suggested by Engels et al.,[13] who described TART as a testicular tumor with adrenal characteristics, likely due to pluripotent cell origin. Our study further substantiates this mechanism by demonstrating the association between elevated ACTH levels and TART development, reinforcing the need for strict hormonal control in CAH patients.

In terms of diagnostic modalities, our study utilized both clinical evaluation and ultrasound for TART detection. We found that TART was significantly associated with palpable testicular mass ($p<0.001$), and pubic hair ($p=0.003$), indicating early pubertal changes. Ultrasound was instrumental in identifying both palpable and non-palpable TARTs, highlighting its sensitivity in detecting tumors that might otherwise be missed on physical examination. As noted by de Grinten et al.,[16] TARTs can be detected by ultrasound long before they become palpable, particularly in younger children, where the tumors tend to be smaller and asymptomatic. Ma et al.,[8] described the characteristic sonographic features of TART, which include bilateral, hypoechoic lesions with clear boundaries, often located near the testicular mediastinum. Our study confirmed the utility of ultrasound in identifying small, non-palpable lesions, making it a valuable tool in the routine monitoring of CAH patients for early signs of TART.

As shown by Ortolano et al.,[20] patients with poor metabolic control had a significantly higher incidence of TART, and intensified glucocorticoid therapy led to a reduction in tumor size in some cases. This suggests that maintaining adequate hormonal control from an early age may not only prevent the development of TART but may also reverse tumor growth in some patients. The association between TART and impaired fertility, as documented by Engels et al.,[13] underscores the need for regular testicular ultrasound screening in male CAH patients, particularly those approaching puberty. Early detection of TART can help mitigate long-term complications, such as infertility, and guide decisions regarding fertility preservation, such as semen cryopreservation.

Relatively small sample size and a single study center were some of the inherent limitations of this study reducing the generalizability of our findings. We also did not assess the impact of

different CAH phenotypes (salt-wasting vs. simple virilizing) on TART development.

CONCLUSION

The prevalence of TART in male children with CAH was high, with significant associations between TART and older age, prolonged CAH duration, higher weight, height, and elevated levels of 17-OHP and ACTH.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

No.	Author(s) Full Name	Contribution to the paper	Author(s) Signature
1	Sadia Mehak	Data collection, Drafting, Responsible for data, Approval for publication.	
2	Mohsina Noor Ibrahim	Study concept, Methodology, Proof reading, Approval for publication.	
3	Maira Riaz	Critical revisions, Literature review, Discussion, Approval for publication.	