

Brief Report
Patient and parent perspectives on testicular adrenal rest tumors in congenital adrenal hyperplasia

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Short Title: Parent/patient perspectives on TARTs

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Abstract

Background: Testicular adrenal rest tumors (TARTs) increase the risk of infertility in males with classic congenital adrenal hyperplasia (CAH). There is no consensus regarding at what age screening testicular ultrasounds should begin and how often they should be repeated. Furthermore, it is unknown whether patients and parents are aware of the significance of TARTs.

Objective: To investigate awareness, concern, and screening rates for TARTs in males with classic CAH.

Methods: Males with CAH and parents completed an online questionnaire from 2019-2020. Responses to questions about TARTs were analyzed. Fisher's exact test was used to determine statistical significance.

Results: Of 123 responders, 14 were males with CAH (range 16-54 years) and 109 were parents of males with CAH (son's age range infancy to 37 years). Of all responders, 74% were concerned about the possibility of TARTs, 48% had discussions about TARTs with their endocrinologist, and 42% were aware of possible infertility in males with CAH. There was no difference between responses provided by affected males and parents for these topics ($p \geq 0.08$). Among male responders with CAH, 93% had at least one testicular ultrasound, and 77% had undergone more than one. Among parent responders, 30% of their sons had at least one testicular ultrasound, and 61% had more than one. The frequency, total number, and age when the first testicular ultrasound was obtained was inconsistent in both groups. Fifty percent of male responders with CAH and 11% of sons were referred to a urologist for evaluation.

Conclusions: Although most responders were concerned about TARTs, less than half recalled discussing this issue with their endocrinologist, and less than half were aware of the possibility of infertility. Although TARTs are most often treated medically, several responders were referred to a urologist. Standardized patient education and consensus guidelines are needed for the surveillance and management of TARTs in males with classic CAH.

Introduction

Males with classic congenital adrenal hyperplasia (CAH) are at risk for reduced fertility [1]. Testicular adrenal rest tumors (TARTs) can result in irreversible testicular damage and are a common cause of infertility in these patients [2]. The frequency of TARTs increases with age and is thought to be related to disease severity and biochemical control of CAH. There is no clear consensus regarding when screening testicular ultrasounds should begin and how often they should be performed [3-5]. Furthermore, it is unknown whether parents and patients with classic CAH are aware of the significance of TARTs. The aim of this study was to investigate patient and parent awareness and screening rates for TARTs in males with classic CAH.

Materials and Methods

The Life with CAH Study Group explores patient- and family-centered CAH research topics, including TARTs [6]. An anonymous, online international questionnaire was conducted. The survey was serially distributed at comprehensive CAH centers as well as through the Congenital Adrenal hyperplasia Research, Education & Support (CARES) Foundation. Country of residence, age of male patient responder with classic CAH, and age of affected child whose parent filled out the survey were recorded. A series of questions about TARTs was asked of male patients and parents of an affected son. Answer options were typically: yes, no, and prefer not to answer. Fisher's exact test was used to compare responses between patient and parent groups using Stata (StataCorp, College Station, TX, USA). $P \geq 0.05$ was considered significant for analyses.

Results

The survey was sent to 1,339 individuals, some of whom were parents and some were patients who self-identified as having CAH. The overall response rate for the survey was 34.9%. The total number of responses was 123, including 14 male patients with classic CAH and 109 parents. Median age of the patient responders was 29 years (16 to 54 years). Median age of the son-of-parent responders (91% mothers; median age 44 years) was 10 years (infancy to 37 years). Most responders ($n=119$) were from the United States. Other countries included Canada ($n=2$), South Africa ($n=1$), and Thailand ($n=1$).

Survey responses from patients and parents are shown in the **Table**. Less than half (42%) of all responders were aware of the possibility of infertility in males with classic CAH. Although most (74%)

were concerned about TARTs, less than half (48%) recalled discussing this potential complication with their endocrinologist. However, 63% were aware that TARTs are a risk factor for infertility. There was no significant difference between responses provided by patients and parents. The age at the time of the first testicular ultrasound was variable (**Figure**). Half of the patient responders and 11% of sons with CAH were referred to a urologist for evaluation of TARTs. Patients, as compared to son-of-parent responders, were more likely to have been referred to a urologist ($p=0.003$) and to have had at least one testicular ultrasound ($p<0.001$).

Discussion/Conclusion

TARTs occur in up to 86% of males with classic CAH [3]. In children, the reported prevalence is 21-24% [7, 8] and though rare [9, 10], TARTs have been documented in boys as young as age 4 [11]. TARTs arise at the rete testis (stage 1) and are not palpable until stages 3 or 4 when fibrosis and lymphocytic infiltration are present [3]. As most TARTs are not palpable, testicular ultrasounds are necessary to make the diagnosis. Early detection and treatment are key to preventing long-term testicular dysfunction [2].

The Endocrine Society CAH Clinical Practice Guideline recommends an initial testicular ultrasound during adolescence and every 1 to 2 years thereafter with more frequent studies when TARTs are detected [4]. Other groups suggest yearly ultrasounds starting at 8 years and every 2 to 3 years in adulthood [3]. An initial testicular ultrasound upon completion of puberty with repeat studies every 2 to 5 years is also suggested [5].

In this study, we queried male patients with classic CAH and parents with an affected son about TARTs, including perceptions on infertility, testicular ultrasounds, and urology referral. Importantly, less than half were aware of the possibility of infertility. The age and timing of testicular ultrasounds were inconsistent, which was likely related to the lack of consistent guidelines for screening and surveillance.

We found that 93% of patient responders and 30% of the sons with CAH had at least one testicular ultrasound, with the majority initially obtained in adolescence or later. Interestingly, ultrasounds were also obtained in younger children, which suggests that some physicians are performing these studies prior to adolescence in boys with classic CAH.

If TARTs are detected, glucocorticoid treatment should be intensified with the goal of shrinking the adrenal rest tissue [4, 5]. Since surgical intervention has not been shown to improve testicular function [12], consultation with a urologist for a patient with TARTs is generally not indicated.

However, meeting with a urologist may be beneficial for fertility counseling and preservation if needed. Although most TARTs in our sample seem to have been managed medically, several survey responders were referred to a urologist.

Limitations of this study include self-reported information that may have been inaccurate. Discussions about TARTs or infertility may have occurred with an endocrinologist but not remembered by the parent or patient. The number of patient responses was low, which limited group comparisons. Responses to the survey may have potentially been from the same parent and patient, which could have resulted in redundancy of the data. Regardless, to our knowledge, this is the first study to query patients and parents about TARTs, which is an important aspect of medical care of classic CAH in boys and men.

In conclusion, most male patients and parents of males affected by classic CAH are aware of and concerned about TARTs, but more than half are not aware of the possibility of male infertility in CAH and have not discussed these implications with their endocrinologist. Our findings highlight the need for clear consensus guidelines with evidence-based recommendations for surveillance and management of TARTs in males with CAH in order to improve patient care and minimize healthcare costs.

Statements

Acknowledgments

The Life with Congenital Adrenal Hyperplasia Study Group was formed in 2019 and consists of the following individuals. The Steering Committee includes Dix Poppas, MD, Institute for Pediatric Urology, Department of Urology, Komansky Children's Hospital, New York Presbyterian Hospital, Weill Cornell Medicine, New York, NY; Richard C. Rink, MD, Division of Pediatric Urology, Riley Hospital for Children at Indiana University Health, Indianapolis, IN; Jonathan C. Routh, MD MPH, Division of Urology, Duke University School of Medicine, Durham, NC; Phyllis W. Speiser, MD, Division of Pediatric Endocrinology, Cohen Children's Medical Center of New York and Zucker School of Medicine at Hofstra/Northwell, Lake Success, NY. Additional members of the group are Luis H. Braga, MD PhD, Division of Pediatric Urology, McMaster Children's Hospital, McMaster University, Hamilton, ON, Canada; Kelly L. Donahue, PhD, Division of Pediatric Endocrinology and Division of Adolescent Medicine, Department of Pediatrics, Indiana University School of Medicine and Riley Hospital for Children at Indiana University Health, Indianapolis, IN; Louise K. Fleming, PhD MSN-Ed RN, University of North Carolina Chapel Hill School of Nursing, Chapel Hill, NC; Heather M. Frady RN BSN, Division of Pediatric Urology, Riley Hospital for Children at Indiana University Health, Indianapolis, IN; John S. Fuqua, MD, Division of Pediatric Endocrinology, Department of Pediatrics, Indiana University School of Medicine and Riley Hospital for Children at Indiana University Health, Indianapolis, IN; Devon J. Hensel, MS PhD FASHM, Division of Adolescent Medicine, Department of Pediatrics, Indiana University School of Medicine and Department of Sociology, Indiana University Purdue University Indianapolis, Indianapolis, IN; Oksana Lekarev, DO, Division of Pediatric Endocrinology, Department of Pediatrics, Komansky Children's Hospital, New York Presbyterian Hospital, Weill Cornell Medicine, New York, NY; Brian D. Leland, MD, Division of Pediatric Critical Care Medicine, Department of Pediatrics, Indiana University School of Medicine, Riley Hospital for Children at Indiana University Health, Charles Warren Fairbanks Center for Medical Ethics, Indianapolis, IN; Karen Lin-Su, MD, Division of Endocrinology, Department of Pediatrics, Komansky Children's Hospital, New York Presbyterian Hospital, Weill Cornell Medicine, New York, NY; Heino F. L. Meyer-Bahlburg, PhD, New York State Psychiatric Institute and Vagelos College of Physicians and Surgeons of Columbia University, New York, NY; Rashida Talib, MBBS MPH, Division of Pediatric Endocrinology, Cohen Children's Medical Center of New York, Lake Success, NY; Benjamin Whittam, MD MSc, Division of Pediatric Urology, Riley Hospital for Children at Indiana University Health, Indianapolis, IN; Patrice M. Yasuda, PhD, Center for Endocrinology, Diabetes & Metabolism,

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Statement of Ethics

This study protocol was reviewed and approved by the Institutional Review Boards at Indiana University (protocol number 1903250601), Children’s Hospital Los Angeles (protocol number CHLA-19-00463), and Weill Cornell Medicine (protocol number 1706018326). As the anonymous survey presented minimal risk, written consent and assent were not required and exempted by the above Institutional Review Boards.

Conflict of Interest Statement

M.S.K. receives research support from Neurocrine Biosciences, Spruce Biosciences, and Adrenas Therapeutics. M.E.G. has a research contract with Novo Nordisk; is performing clinical trials with Adrenas Therapeutics, Diurnal, Neurocrine Biosciences, Novo Nordisk, and Spruce Biosciences; is a clinical trial adjudicator for Aeterna Zentaris; is a consultant or advisory board member for Adrenas Therapeutics, Eton Pharmaceuticals, Neurocrine Biosciences, Novo Nordisk, and Pfizer, Inc.; and receives royalties from McGraw-Hill and UpToDate.

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Author Contributions

T.D.N., M.S.K., P.J.K., K.M.S., M.E.G., and E.A.E. conceived the project and the questions for the survey. T.D.N. performed data analysis and wrote the initial draft of the manuscript. K.M.S. provided data and statistical analysis and interpretation. M.S.K., P.J.K., and M.E.G. provided expertise in the field and edited the manuscript. E.A.E. supervised the data collection and analysis, and edited the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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Figure Legend

Figure. Age at the time of the first testicular ultrasound as reported by parents who have sons with classic CAH, and male patient responders with classic CAH.

Figure.

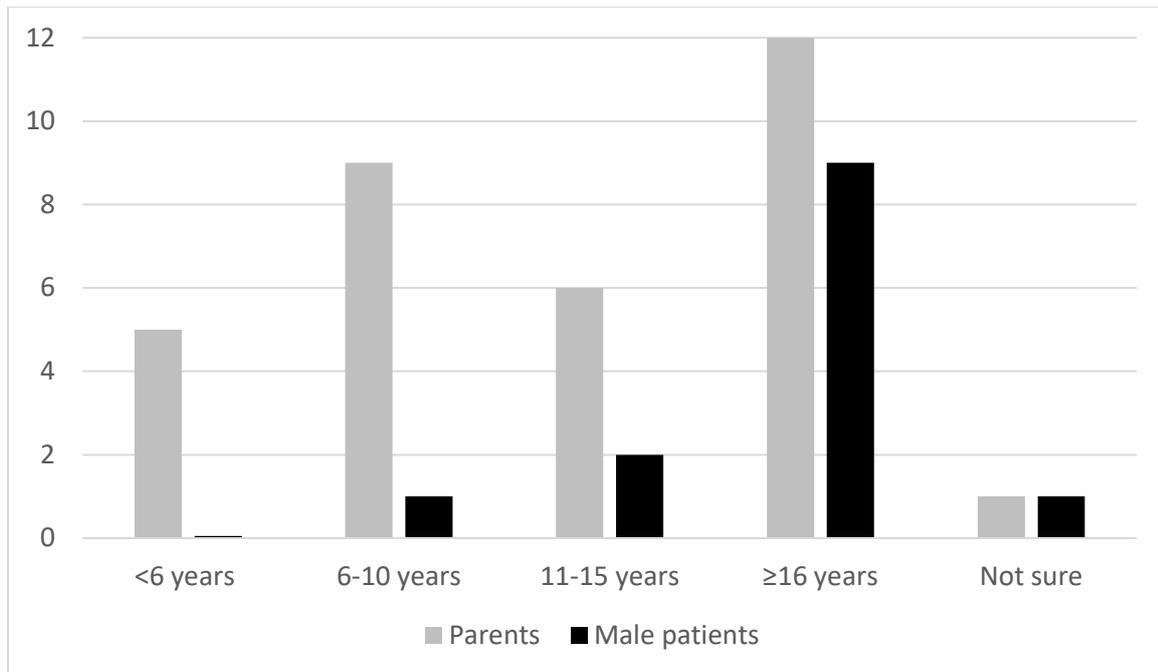


Table. Survey responses from parents and male patients with classic CAH about TARTs.

Question	Yes	No	Prefer not to answer	P-value
<i>Has your doctor talked to you about the possibility of infertility in males with CAH?</i>				
Parents	42	59	8	
Male patients	10	4	0	
Total	52 (42%)	63 (51%)	8 (7%)	P=0.08
<i>Has your doctor talked to you about TARTs?</i>				
Parents	49	54	6	
Male patients	10	4	0	
Total	59 (48%)	58 (47%)	6 (5%)	P=0.21
<i>Are TARTs a risk factor for infertility in males with CAH?</i>				
Parents	66	17	26	
Male patients	11	3	0	
Total	77 (63%)	20 (16%)	26 (21%)	P=0.08
<i>Are you concerned or worried about the possibility of TARTs?</i>				
Parents	81	17	11	
Male patients	10	4	0	
Total	91 (74%)	21 (17%)	11 (9%)	P=0.29
<i>Has your son/you ever been referred to a urologist for TARTs?</i>				
Parents	12	92	5	
Male patients	7	7	0	

Total	19 (15%)	99 (80%)	5 (4%)	P=0.003
<i>Has your son/you ever had a testicular ultrasound? *</i>				
Parents	33	71	5	
Male patients	13	1	0	
Total	46 (37%)	72 (59%)	5 (4%)	P<0.001
<i>Has your son/you had more than one testicular ultrasound?</i>				
Parents	20	13	0	
Male patients	10	3	0	
Total	30 (65%)	16 (35%)	0 (0%)	P=0.49

* Only those who answered yes to this question were asked the following question.