Case Report

Phenotype variation among siblings with 5-alpha reductase deficiency: A case series

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ABSTRACT

Steroid 5α-reductase deficiency (5ARD) is a rare autosomal recessive disorder caused by mutation in the 5α-reductase type 2 gene (*SRD5A2*). 5ARD results in the impaired conversion of testosterone (T) to dihydrotestosterone (DHT) and is characterized by undervirilization in 46XY individuals. We report a case series of three siblings presenting with ambiguous genitalia and different phenotypes. They did not meet the widely accepted biochemical criteria for 5ARD. In view of strong clinical suspicion, genetic analysis was performed which revealed pathogenic mutation in *SRD5A2*. This report highlights the importance of definitive diagnosis with molecular methods as the treatment and prognosis differs greatly among the close differential diagnoses. Reliance on the biochemical criteria alone may lead to misdiagnosis.

INTRODUCTION

5ARD is a rare autosomal recessive disorder, caused by mutation in the gene *SRD5A2*.[1] The familial incidence of the disease is about 50%.[2] Steroid 5α-reductase is a microsomal enzyme that converts testosterone to the more potent androgen dihydrotestosterone, which is the major virilizing agent. It has three isoenzymes,[3] of which, the predominant isoenzyme, Type 2 is encoded by the gene *SRD5A2* and is responsible for normal virilization during the development in males. It is detectable in fetal genital skin, seminal vesicles, epididymis, and the prostate. It has a higher affinity for testosterone (T) than the type 1. Isoenzyme type 1 is absent in the fetus but is expressed in the newborn liver and skin transiently and in the skin permanently after puberty. Isoenzyme 3 has been described in castrate-resistant prostate carcinoma. 5ARD is characterized by undervirilization of 46, XY individuals. Affected individuals may present with micropenis, varying degrees of hypospadias, and ambiguous genitalia with pubertal virilization. The varying degrees of virilization are attributed to the residual enzymatic activity, ethnicity, and the action of steroid 5α-reductase type 1.[1]

We illustrate a case series of three siblings with 5ARD with varied phenotype and biochemical profiles.

CASE REPORTS

Three siblings presented with complaints of small-sized penis. Clinical features and biochemical parameters are summarized in Table 1.

Index case

A 25-year-old male presented with micropenis and penoscrotal hypospadias. He was assigned female sex at birth. At 4 years of age, he presented to a pediatrician with genital swellings and was diagnosed to have bifid scrotum, penoscrotal hypospadias, and right cryptorchidism [Figure 1] and the sex was reassigned as male. Right orchidopexy and chordee correction surgery were performed. No further evaluation was performed at this point. In the childhood, he identified himself as male and

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Table 1: Clinical and biochemical parameters

Parameter	Case 1	Case 2	Case 3
Age in years at presentation	25	20	18
Gynecomastia	Absent	Absent	Absent
SMR	P5G4A3	P5G5A3	P5G5A3
SPL	3 cm	4.5 cm	2.5 cm
Hypospadias	Penoscrotal	Penoscrotal	Penoscrotal
Scrotum	Bifid	Normal	Bifid
Testes			
Right	3 ml, at superficial inguinal ring	20 ml	18 ml
Left	15 ml in scrotal sac	20 ml	18 ml
Both		Scrotal sac	Scrotal sac
External masculinization score	5.5	6	6
Investigations			
Serum FSH (miu/ml)	13.5	6.2	12.4
Serum LH (miu/ml)	8.4	9.5	9.6
Basal testosterone (ng/dl)	510	620	570
Basal DHT (ng/dl)	71.2	59	78
T/DHT ratio (basal)	7.16	10.5	7.3
Post-hCG stimulation test			
Testosterone (ng/dl)	620.5	820.3	684.2
DHT (ng/dl)	79.7	72.5	91.5
Testosterone: DHT ratio	7.78	11.3	7.47
USG for prostate volume	3 cc (small for age)	5 cc (small for age)	2.4 cc (small for age)

‖Testosterone, FSH, and LH were assessed by chemiluminescent immunoassay and dihydrotestosterone by radioimmunoassay, ‡‡Age-based hCG test protocol consisting of three intramuscular injections of hCG 1500 IU on successive days was used.[4] Blood sample was taken 24 h after the last dose and T: DHT ratio was calculated. FSH=Follicular-stimulating hormone, LH=Luteinizing hormone, HCG=Human chorionic gonadotropin, USG=Ultrasonography, SMR=Sexual maturity rating, SPL=Stretched penile length, DHT=Dihydrotestosterone

played with boys, but he used to urinate in sitting position. At about 15 years of age, he started noticing testicular enlargement, marginal increase in penile length, pubic and axillary hair development, and change in voice. There was no gynecomastia and he did not receive exogenous testosterone.

Case 2

The sibling of the index case, a 20-year-old-male, presented with micropenis and penoscrotal hypospadias. He was assigned female sex at birth, later reassigned as male at 2 years of age. Both gonads were descended. He underwent chordee correction at the age of 6 years and was reared as a boy, and he identified himself as a male. He noticed testicular enlargement, pubic and axillary hair development, and voice change at about 12 years of age. There was no gynecomastia.

Case 3

The youngest sibling, an 18-year-old male, presented with similar complaints as his brothers. He was assigned male sex at birth. He identified himself as male. Both the gonads were descended. He had bifid scrotum, with testicular enlargement, pubic and axillary hair development, and voice change at the age of 14 years. No corrective surgeries were performed.

A detailed psychiatric assessment revealed that all three had male gender role and identity from the early childhood. Orientation to the female sex was present.

Family history

They were born of third-degree consanguinity. Three out of the four siblings had ambiguous genitalia. One sibling had normal male phenotype. There was no other relevant family history.

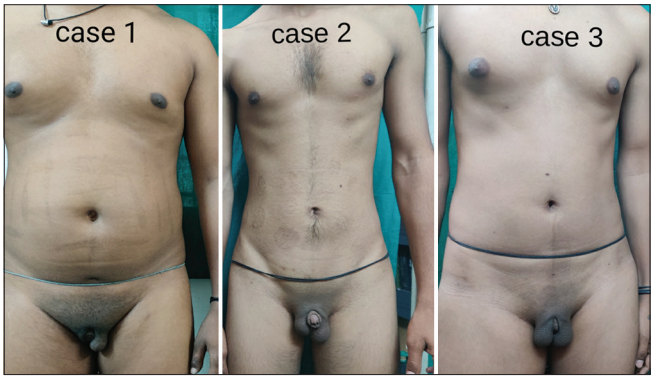

Figure 1: Clinical image depicting ambiguous genitalia

Based on the clinical and biochemical findings, the diagnosis of 5ARD versus partial androgen insensitivity syndrome (PAIS) was considered. In view of the pubertal virilization without gynecomastia, 5ARD was more probable. The biochemical evaluation, however, did not support it. T/DHT ratio was lower than the standard cutoff of 10 in two cases. In view of strong clinical suspicion and implications on the management, genetic analysis was obtained for a definitive diagnosis.

Genetic analysis

Genetic analysis was performed for the index case by next generation sequencing, which revealed a homozygous pathogenic missense variant in SRD5A2 gene at Exon 5,

c. 737G>A (protein change: P. Arg246Gln). This variant is described as pathogenic for pseudovaginal perineoscrotal hypospadias in multiple databases such as the Exac, gnomAD, and 1000 Genomes. It has been previously reported as a pathogenic variant in multiple studies.[1,5] Sanger sequencing of the same gene was done in the other two siblings, which revealed the same mutation, thus confirming the diagnosis of 5ARD in all the three siblings.

For fertility prospects, semen analysis of the index case was obtained which showed oligospermia. Semen analysis in the other two cases was advised but could not be obtained as there was no ejaculation. The need for sperm extraction and fertility issues were explained to the index case. They are currently awaiting genital reconstruction.

DISCUSSION

We report a case series of three siblings presenting with ambiguous genitalia and undervirilization. Despite having the same mutation of SRD5A2, they had different phenotypes. The eldest sibling had unilateral cryptorchidism with bifid scrotum. The second sibling had fused scrotum with descended testes, whereas the youngest sibling had descended testes and bifid scrotum. These findings are consistent with previous studies which showed that the phenotypic variation is a possibility even with the same mutation.[1] Factors other than the residual activity of 5α-reductase enzyme may account for this variation.[1] The classical description of hormonal profile in 5ARD is an elevated or normal testosterone with low levels of DHT. A universally accepted cutoff for T: DHT ratio for the diagnosis of 5ARD is lacking. A ratio of >30 has good specificity of 99% but poor sensitivity of 11%. A cutoff of 10 has reasonably good sensitivity of 78% and specificity of 72%.[6] Thus, a cutoff of 10 was employed in the present study as used in the earlier studies.[1]

We performed postpubertal HCG stimulation test in all the three cases for better sensitivity. One patient had poststimulation T/DHT ratio of >10, whereas the other two had ratio <10. Using biochemical profile alone with T/DHT cutoff of >10, the diagnosis would have been missed in these patients. In addition, T/DHT ratio may be elevated in some cases of PAIS, hence it can be misdiagnosed as 5ARD. SHBG suppression test using stanazol can be of help in supporting the diagnosis of androgen insensitivity syndrome. However, the reports regarding the test and the threshold cutoffs are scarce.[6] Genetic analysis plays an important role in avoiding such missed diagnosis and misdiagnosis.

The distinction is important because of major clinical implications in treatment and prognosis. In 5ARD, local application of DHT can be used in the treatment. However, despite the best efforts, the patient could not procure the drug. The risk of germ cell tumors is lower in 5ARD[7] compared to the PAIS. Gender reassignment and genitoplasty are recommended based on the clinical aspects. Sex of rearing is based upon multiple factors such as the adult psychosexual and psychosocial functions. Studies suggest a male gender identity in the majority of the patients with 5ARD. Thus, it is reasonable to raise most of these patients as males. Modern molecular diagnostic techniques permit an early and accurate diagnosis of these patients helping in gender assignment. Semen analysis of the index case was obtained which showed oligospermia. Most of the affected individuals are oligospermic or azoospermic and are infertile. This is mainly attributed to the deficient DHT action on spermatogonia maturation, rudimentary prostate glands, and seminal vesicles.[4] The decision of the type and the timing of surgery must be made after a detailed discussion with the family about the options available and their implications. Early correction of cryptorchidism is crucial to prevent damage to the seminiferous tubules and to preserve the spermatogenesis and future fertility.[8] Surgical reconstruction of the hypospadias is typically performed between 6 and 15 months of age. Early genitoplasty can also alleviate the undue psychological stress of the atypical genitalia in children.[9] For those raised as males, the surgery consists of orthophaloplasty, scrotoplasty with obliteration of the vagina, proximal and distal urethroplasty, and orchidopexy when necessary.[10] When the sex of rearing is female, laparoscopic gonadectomy and resection of the internal organs, if appropriate, should be considered.

This case series also highlights an important aspect of delay in the diagnosis. Ambiguous genitalia was not noticed at birth and was not addressed appropriately in childhood. Lack of awareness among the parents and clinicians needs to be addressed to avoid such unfortunate occurrences. More number of such case descriptions may help address the issue to some extent.

CONCLUSION

T/DHT ratio can be misleading and is not always diagnostic of 5ARD. Molecular testing is crucial in differentiating 5ARD from PAIS conclusively.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published, and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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