

A rare case report of ambiguous genitalia

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ABSTRACT

An ambiguous genitalia is a commonly referred clinical scenario to endocrinology outpatient department. Accurate diagnosis is paramount to prevent associated salt-wasting crisis, direct the gender of rearing in the short-term, and monitoring for the development of malignancy in the gonads in the long-term. 17 beta-hydroxysteroid dehydrogenase 3 deficiency (17 β HSD 3) is one of the causes of defective testosterone biosynthesis. 17 β -HSD3 deficiency should be suspected in children with female external genitalia with inguinal hernias or mild clitoromegaly; as well as males with ambiguous genitalia who develop virilization and gynecomastia at puberty. A hormonal evaluation may not always be diagnostic which makes genetic confirmation essential.

Key words: Ambiguous genitalia, 17 beta HSD-3, Congenital adrenal hyperplasia

Deficiency of 17 β hydroxysteroid dehydrogenase 3 (17 β -HSD3), also known as 17-ketosteroid reductase deficiency, is a rare autosomal recessive cause of disorder of sexual development that results from a defect in the final reversible step in testosterone synthesis in the testes, specifically, the conversion of androstenedione to testosterone. It may be confused with other enzyme deficiencies such as 5-alpha reductase or partial androgen insensitivity syndrome.

In resource limited setting and poor social awareness of the clinical problem, diagnosis may not always be straightforward. Here, we describe rare case of ambiguous genitalia who presented to our OPD at 10 years.


CLINICAL DESCRIPTION

A 10-year-old boy presented to our endocrinology outpatient department with complaints of enlargement of both breasts past 7 months, which was gradually progressive. There was no pain or asymmetry of the breast. There was no history suggestive of any raised intracranial tension or head trauma. There was no history of any drug intake or recent weight gain or recent increase in height velocity.

The child was born out of non-consanguineous marriage and pre-term delivery by lower segment cesarean section in view of premature rupture of membranes. The baby was initially identified as a female child with no gonads seen externally and

well-formed scrotum or penis. There was no history suggestive of salt wasting crisis after birth. On day 20 of life, the parents noticed a phallic swelling which did not increase which did not vary in size with position or on coughing. The parents described the phallus had a single opening, appeared short, and did not notice any hyperpigmentation. Later at 5 months of age, parents noticed that the phallic swelling increased and hence was evaluated. After evaluation by an endocrinologist, it was found that it was a male child with 46 XY karyotype and gonads the present at the high inguinal region. Investigations done at that time are tabulated in Table 1. HCG stimulation test was suggestive of testosterone biosynthetic defect. The child underwent orchidopexy and penile reconstruction in a staged procedure. The left testis was left *in situ* as it was said to be atrophic. There was no urinary disturbance after the complete procedure. There were no complaints thereafter till this presentation. There was no family history of ambiguous genitalia.

On examination, his height was 153 cm (90–97th centile) and his mid-parental height was 168 cm (10–25th centile). His weight was 52.2 kg (90–97th centile). His blood pressure was 102/51 (50–75th centile). There were no midline defects or malformations. Genital examination revealed a right-side testicular volume of 5 cc and left-side testis 2 cc situated at the left inguinal region. Stretched penile length was 4 cm. A single urethral opening was present and was the tip of the glans penis. The scrotum was well formed with posterior labioscrotal fusion present. Pubic hair staging was P3. The external masculinization score was 5.5 No axillary hair was present. There was

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gynecomastia on both sides with a glandular tissue disc diameter of 3 cm. Systemic examination was normal.

Management and Outcome

Laboratory investigations were done and are summarized in Table 1. Investigations done showed an androstenedione to testosterone ratio of 0.55 suggestive of 17 β HSD3 deficiency. Clinical whole exome sequencing was done and found a pathogenic variant in the 17 beta HSD gene (Fig. 1).

Genetic Variant Description

A homozygous missense variation in exon 10 of the HSD17B3 gene (*chr9:g.96240885G>A; Depth:85x*) that results in the amino acid substitution of Leucine for Serine at codon 232 (*p.Ser232Leu; ENST00000375263.8*) was detected (Table 2). The

observed variation lies in the short chain dehydrogenase domain of the HSD17B3 protein [1].

The variant has previously been reported in unrelated patients from different ethnic regions, affected with 17 β -hydroxysteroid dehydrogenase 3 deficiency [2,3]. The *p.Ser232Leu* variant has not been reported in the 1000 genomes database and has a minor allele frequency of 0.002% and 0.007% in the gnomAD.

OMIM phenotype: Male pseudohermaphroditism or polycystic ovary disease (OMIM#264300) is caused by homozygous or compound heterozygous mutations in the HSD17B3 gene (OMIM*605573). This disorder is characterized by hypoplastic-to-normal internal genitalia (epididymis, vas deferens, seminal vesicles, and ejaculatory ducts) but female external genitalia and the absence of a prostate. This phenotype is caused by inadequate testicular synthesis of testosterone, which, in turn, results in insufficient formation of dihydrotestosterone in the anlage of the external genitalia and prostate during fetal development. At the

Table 1: Hormonal analysis of the patient

Hormone	At age of 5 months	At age of 10.5 years	Remarks
TSH (mIU/L)	2.1		
Free T4 (ng/dL)	1.6		
FSH (mIU/mL)	2.5	16.03	
LH (mIU/mL)	9.8	7.07	
Testosterone (ng/mL)	Pre HCG- 1.5 Post HCG- 2.6		Ratio T/DHT: 21.4
Dihydrotestosterone (pg/mL)	Pre-HCG- 77 Post-HCG- 128		
AMH (ng/mL)		4.57	Low
Androstenedione (ng/mL)		2.76	T/A ratio: 0.55
Inhibin B (pg/mL)		92.8	Low
Karyotype	46 XY		

Table 2: Varied clinical phenotype, investigations, and outcome in cases with similar mutation

Case report	Chirag <i>et al.</i>	Galli-Tsinopoulou <i>et al.</i>	Mains <i>et al.</i>
Clinical features	Gonads – Right scrotum and Left Inguinal canal	Bilateral inguinal gonads	Primary Amenorrhea Gonads – visualized on MRI
Geographical area/country	South India	Greece	North America
Age at diagnosis	Ambiguous genitalia at birth; final diagnosis at 10 years	Birth	16 years
Investigation	Low T/ Δ 4 ratio after a human chorionic gonadotropin stimulation test androstenedione not measured at birth	low T/ Δ 4 ratio after a human chorionic gonadotropin stimulation test (<0.55)	low T/ Δ 4 ratio after a human chorionic gonadotropin stimulation test (<0.55)
Treatment/ Outcome	Reared as male testosterone replacement	Reared as male testosterone therapy	Reared as female Gonadectomy done

Gene (Transcript) *	Location	Variant	Zygoty	Disease (OMIM)	Inheritance	Classification
HSD17B3 (-) (ENST00000375263.8)	Exon 10	c.695C>T (p.Ser232Leu)	Homozygous	Male pseudohermaphroditism or polycystic ovary disease	Autosomal recessive	Pathogenic

*Genetic test results are reported based on the recommendations of American College of Medical Genetics [1].

Figure 1: Pathogenic variant causative of the reported phenotype was detected. [§]Genetic test results are reported based on the recommendations of American college of medical genetics

expected time of puberty, there is a marked increase in plasma luteinizing hormone and, consequently, in testicular secretion of androstenedione. Hence, a diagnostic hallmark of this disorder is a decreased plasma testosterone-to-androstenedione ratio. Significant amounts of the circulating androstenedione are, however, converted to testosterone, in peripheral tissues, thereby causing virilization [4].

DISCUSSION

The presentation of 17 β -HSD3 deficiency is highly variable among patients and usually presents with female phenotype at birth, primary amenorrhea and peripubertal virilization at puberty in 46 XY individuals. In 46 XX individuals, they may be asymptomatic and are fertile [4]. The clinical presentations of 17 β -HSD3 deficiency, 5 α -reductase Type 2 deficiency and partial androgen insensitivity syndrome (PAIS) can be similar [3]. 17 β HSD-3 deficiency should be considered in a 46 XY child presenting phenotypically female [5]. In these individuals, the diagnosis can go unnoticed until the child is brought to medical attention after some degree of virilization or testes has been found on examination or during hernia repair [6]. Gynecomastia is present in most of the patients with 17 BSD 3 deficiency and PAIS, where it is very rare in 5 α reductase deficiency. Gynecomastia occurs at puberty because of estrogens derived from conversion of androstenedione to estrone by aromatase in extra glandular tissue and subsequent conversion of estrone to estradiol by the action of 17 beta HSD 1 and 2 isoenzymes. It is rare in 5 alpha reductase enzyme deficiency as there is no defect in testosterone synthesis and inadequate substrate for extra glandular estrogen compound production. When such patients present with peripubertal onset of gynecomastia which is progressive, the suspicion of 17 BHSD precedes the other differential diagnosis. Early diagnosis is critical for management which includes gender assignment and the decisions regarding orchidectomy [7]. Many individuals who were previously diagnosed with PAIS might have had a 17 β -HSD3 deficiency. The diagnosis should be considered in a severely undervirilized male infant with no abnormal adrenal steroid biosynthesis, absent Müllerian ducts, and normal Wolffian duct structures, or when an assigned female virilizes at puberty with or without gynecomastia [8]. A ratio <0.8 after the hCG stimulation test significantly suggested 17 β -HSD3 deficiency after excluding other diseases such as gonadal dysgenesis [9].

In this case, the child was diagnosed to have 5 α reductase 2 deficiency based on testosterone and DHT ratio after HCG stimulation. Androstenedione levels were not done, which mislead the diagnosis, which emphasizes its importance during the HCG stimulation test. The confirmation of the diagnosis is by genetic analysis. There is no approved treatment for 17BSD3 deficiency. If the patient is reared as female, gonadectomy can be considered, or else may lead to virilization at puberty. If reared as male, orchidopexy or orchidectomy can be done based on the age of presentation and considering the risk of malignancy. Our patient is being followed for spontaneous progression of puberty

as he was reared as a male.

Differentiation from 5 Alpha reductase and PAIS adds invaluable data to medical literature in terms of long-term outcomes about the development of malignancy in gonads and gender preference as these are very rare in the general population. Premature definitive diagnosis based on stimulation testing should be avoided.

17 β -HSD3 deficiency is a rare disorder and only 187 families (239 patients) have been reported along with their causative mutations. A total of 70 different *HSD17B3* mutations have been reported so far in the literature. In particular, the common p.Arg80Gln mutation has been found almost exclusively in patients originating from the Mediterranean and Middle East regions, and the common c.277+4A>T mutation has been found predominantly in patients originating from western Europe [10].

In the case series from India by Krishnappa *et al.* [11] on 17 Beta HSD deficiency, out of the 10 cases; six cases had novel mutation. The variant has been previously reported in multiple patients with HSD17B3-related 17 beta-hydroxysteroid dehydrogenase deficiency [2,12-14].

This variant has strong evidence for segregation with the disease. The variant has been shown to segregate with disease in one family [15] and has moderate functional evidence supporting the abnormal protein function. Site-directed mutagenesis study shows that this variable causes enzyme inactivation [12].

CONCLUSION

17 β HSD 3 deficiency is one of the differential diagnoses of ambiguous genitalia in a 46 XY individual. It may be confused with 5 α reductase deficiency and androgen insensitivity syndromes. This case highlights the importance of complete evaluation at presentation and avoiding over dependence on stimulation testing for diagnosis and emphasizes on genetic confirmation. A genetic confirmation has prognostic implications for the patient in terms of counseling regarding gonadectomy for increased risk of malignancy and future monitoring.

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