JCEM Case Reports, 2024, **2**, luae191
https://doi.org/10.1210/jcemcr/luae191
Advance access publication 18 October 2024
Case Report

5α Reductase Deficiency—a Rare Cause of Ambiguous Genitalia and Gender Dysphoria

Ellen Wall[1] **and Veena Jayadev**[2]

[1]Department of Endocrinology, Prince of Wales Hospital, Randwick 2031, NSW, Australia
[2]Department of Andrology, Concord Repatriation General Hospital, Hospital Road, Concord 2139, NSW, Australia

Correspondence: Ellen Wall, Bachelor of Medicine, Department of Endocrinology, Prince of Wales Hospital, 320-346 Barker St, Randwick 2031 NSW, Australia. Email: ewal1393@gmail.com.

Abstract

We present a case of pseudovaginal perineoscrotal hypospadias, secondary to 5α-reductase deficiency presenting as gender dysphoria. This particular enzyme deficiency accounts for only a small number of disorders of sexual development cases worldwide. A feature of this disorder is the presence of ambiguous genitalia at birth followed by the development of male secondary sexual characteristics during puberty when testicular production of testosterone can compensate for previous low circulating levels of 5-dihydrotestosterone (DHT). Our described patient, raised female, presented with gender dysphoria with no male secondary sexual features given a bilateral orchidectomy in infancy.

Initial testing showed biochemical primary hypogonadism and whole-genomic sequencing demonstrated pathogenic compound heterozygous variants in the *SRD5A2* gene. Treatment was commenced with injectable testosterone undecanoate leading to development of desired male secondary sexual characteristics.

Key Words: 5α-reductase deficiency, disorder of sexual development, gender dysphoria

Abbreviations: 17-OHP, 17-hydroxyprogesterone; DHT, 5-dihydrotestosterone; FSH, follicle-stimulating hormone; IM, intramuscular; LH, luteinizing hormone.

Introduction

Five α-reductase deficiency is an exceedingly rare cause of disorder of sex development in males (46, XY karyotype). Aside from identified familial clusters among groups where consanguineous relationships are common, the worldwide prevalence has yet to be quantified.

The 5α-reductase enzyme is responsible for conversion of testosterone to the more physiologically potent androgen receptor agonist, 5α-dihydrotestosterone (DHT). In its absence, there is impaired virilization during embryogenesis, and hence infants can present as phenotypically ambiguous or female.

There are 2 isoenzyme forms (1 and 2), and it is deficiency in the type 2 5α-reductase enzyme that affects urogenital development. Notably, these patients can still have detectable (often low) levels of serum DHT due to either residual impaired type 2 enzyme function or nonimpaired type 1 enzyme activity (found predominantly in the liver).

Classically, patients present with ambiguous genitalia at birth and are often raised as female [1]. Characteristics include neonatal undervirilization of external genitalia, including a clitoral-like phallus, bifid scrotum, and pseudovaginal perineoscrotal hypospadias. Testes are usually extra-abdominal, including within the scrotum, labia majora, or within the inguinal canals.

An increase in testicular production of testosterone during puberty typically results in development of male secondary sexual characteristics at that time. In cases where there has been testicular removal, patients do not experience the classic clinical course.

Case Presentation

Our patient is a 36-year-old man who was initially referred seeking treatment for female-to-male transition. Of Thai origin, they were an only child who was born with ambiguous genitalia, micropenis, hypospadias, and bilateral cryptorchidism. Testicles were located in the inguinal canal and they were believed to have undergone bilateral orchidectomy at age 12 months. As far as our patient was aware, there was no formal early testing to confirm chromosomal sex. There was no relevant family history.

She was raised as female during childhood and went away to boarding school at age 10 years. As a teenager at age 15 years, she noted easy fatiguability and was found to not have gone through puberty after medical review. Notably, she had never had a period. She was asked at that time if she wanted to be a boy or a girl ongoing; as she had been raised a girl until that point, she elected to commence estrogen-replacement therapy following biochemical testing, which detected low serum estradiol levels (based on the female reference range). She developed pubic hair and breasts only following initiation of estrogen therapy.

Around age 18 years, our patient realized that she felt male and it was at this point she was switched to testosterone replacement therapy. She commenced a low (subtherapeutic) oral dose of testosterone (testosterone undecanoate 40 mg daily) and did not develop secondary male sex characteristics. She would continue on this treatment for many years, traveling back to Thailand to obtain testosterone until travel restrictions during the COVID-19 pandemic prevented this.

Received: 18 June 2024. **Editorial Decision:** 2 October 2024. **Corrected and Typeset:** 18 October 2024

They presented for our review at age 36 years. Currently in a relationship with a female partner (who had a child from a previous relationship), our patient continues to identify as male.

Diagnostic Assessment

On initial examination, there was the appearance of female genitalia with no palpable undescended testes. There was scrotal fusion, no vagina, and a perineal urethra with normal-size clitoris. There was bilateral enlarged breast tissue and presence of axillary and pubic hair.

Biochemical analysis was suggestive of primary hypogonadism (Table 1). Karyotyping was performed that confirmed a 46, XY karyotype on cytogenetic analysis, and presence of *SRY* mutation on quantitative fluorescent polymerase chain reaction. There was no uterus, ovaries, or vagina visualized on transabdominal ultrasonography. There was no visible prostate gland.

Whole-exome sequencing was performed that demonstrated pathogenic compound heterozygous variants in the *SRD5A2* gene (c.383_384delinsGA and c.607G > A).

Treatment

Our patient commenced intramuscular (IM) testosterone undecanoate (Reandron 1000 mg IM) replacement (0, 6, and 12 weeks) with subsequent normalization of serum testosterone, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) levels to the male reference range (Fig. 1).

Outcome and Follow-up

After 7 months of 6-weekly testosterone undecanoate 1000 mg IM therapy, there was phallus development, increasing pubic and axillary hair growth, increased muscle strength, and loss of adipose tissue. On examination, the patient's phallus was 6 cm long and 2 cm in diameter. Given this response to testosterone replacement, a previous differential diagnosis of partial androgen insensitivity syndrome seemed less likely.

Discussion

Pathogenic variants in the *SRD5A2* gene, located on chromosome 2p23, are known to be associated with autosomal recessive pseudovaginal perineoscrotal hypospadias in 46, XY patients. Five α-reductase deficiency is a known cause. There is wide phenotypic variability in patients with this condition, and a review of the literature suggests inconsistent genotype-phenotype correlation.

There have been scattered clusters of cases worldwide, including within consanguineous families in the Dominican Republic and a subset of African-Brazilian patient cases; there is no clear ethnic preponderance for 5α-reductase deficiency [1]. A Thai patient cohort review of 104 children born with ambiguous genitalia from Siriraj Hospital described only 4 cases of the condition [2].

In our patient's case, a premature termination codon (with substitution of a tyrosine amino acid) and a missense mutation were detected on gene sequencing; however, there have been more than 100 mutations described in the literature previously [3]. Classically, the use of molecular genetic sequencing has been limited by cost, access, and feasibility. However, it offers an efficient and accurate alternative to standard biochemical testing (eg, serum testosterone:DHT analysis, human chorionic gonadotropin stimulation test) and is comparatively easier to perform than other molecular genetic sequence targets given the small size of the *SRD5A2* gene. Given that an accurate diagnosis is crucial to ensure timely, appropriate management for these patients (in whom the underlying diagnosis is often uncertain), the benefit of expedited genetic sequencing can allow for genetic counseling and informed treatment decisions, thus minimizing psychosocial complications.

Currently, there are no guidelines to direct management of children with 5α-reductase deficiency. Given the presence of frequently ambiguous genitalia, the majority of patients were historically raised as female, with gender assignment at birth—however, data suggest that more than 60% of affected children raised female subsequently transitioned to male during puberty [4]. Often difficult to distinguish clinically from androgen insensitivity syndrome in early infancy, the testosterone:DHT ratio can be unreliable (eg, equivocal results in patients with only partial enzyme deficiency) and hence consideration of definitive genetic analysis is essential to allow early decision-making. Despite the presence of external genital undervirilization, fetal brain exposure to androgens is not affected—this is thought to contribute to higher rates of gender dysphoria in this group [5]. It has been shown that increased volume of specific regions of brain gray matter

Table 1. Initial biochemistry results, prior to commencement of testosterone replacement

Test	Result	Female reference range	Male reference range
Estradiol	23.9 pg/mL (88 pmol/L)	Early follicular phase 28.85-57.7 pg/mL (100-200 pmol/L) Preovulatory phase 144.25-490.45 pg/mL (500-1700 pmol/L) Luteal phase 144.25-259.65 pg/mL (500-900 pmol/L)	10-50 pg/mL (36.71-183.55 pmol/L)
Testosterone	**34.62 ng/dL (1.2 nmol/L)**	15-70 ng/dL (0.5-2.4 nmol/L)	300.04-721.25 ng/dL (10.4-25 nmol/L)
FSH	**27.8 mIU/L (27.8 IU/L)**	1-8 mIU/mL (1-8 IU/L)	1.5-12.4 mIU/mL (1.5.12.4 IU/L)
LH	**21.1 mIU/L (21.1 IU/L)**	2-15 mIU/mL (2-15 IU/L)	1.7-8.6 mIU/mL (1.7-8.6 IU/L)
Sex hormone–binding globulin	**1.49 ug/mL (15.7 nmol/L)**	1.805-13.78 ug/mL (19-145 nmol/L)	2.06-6.16 ug/mL (18.3-54.8 nmol/L)
17-OHP	0.33 ng/mL (1.0 nmol/L)	Follicular <0.8 ng/mL (<24 nmol/L) Luteal <2.85 ng/mL (<85.5 nmol/L)	<2.2 ng/mL (<0.726 nmol/L)

Abnormal values are indicated in bold, based on male reference ranges. Values in parenthesis are International System of Units (SI).
Abbreviations: 17-OHP, 17-hydroxyprogesterone; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

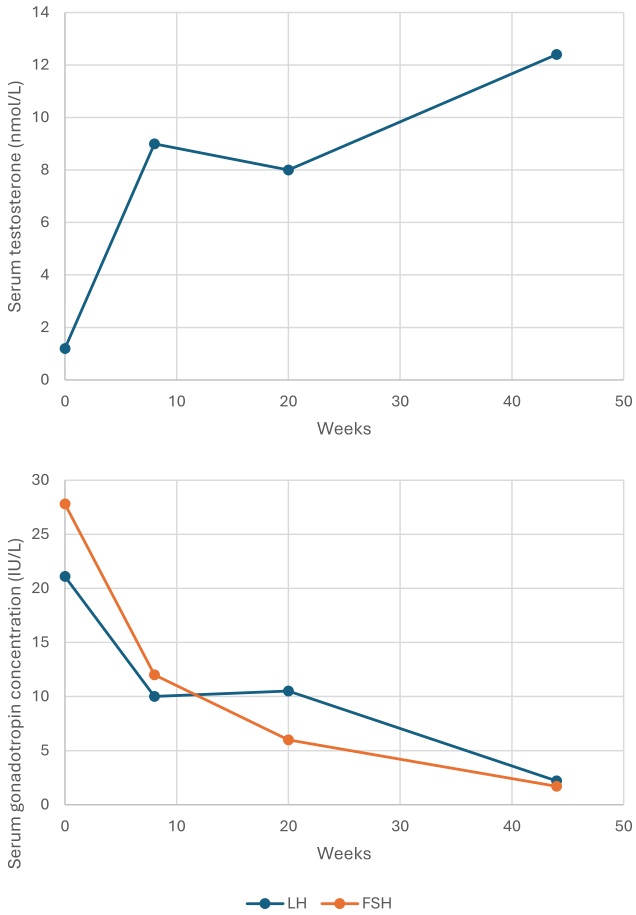

Figure 1. A, This graph demonstrates trend in serum testosterone following commencement of injectable testosterone undecanoate. B, Serum follicular-stimulating hormone (FSH) and luteinizing hormone (LH) are shown over the same 50-week time period.

classically associated with males can be positively predicted by fetal testosterone levels [6]. Permanent neural organizational changes occur via direct testosterone action during the prenatal period (at a different time from virilization of external genitalia due to DHT). Onset of testicular testosterone production during puberty is theorized to "activate" these circuits laid duration gestation and may explain the increased female-to-male gender transition at that age [7, 8].

As demonstrated in our case, patients may present for initial review well into adulthood. Management as part of a multidisciplinary team should occur, with focus on the individual patient's choice of gender and a combination of hormonal (and potentially surgical) interventions as desired.

Learning Points

- 5α-Reductase is a rare cause of disorder of sexual development that is phenotypically broad and may mimic more common conditions such as androgen insensitivity syndrome at birth.
- Molecular genetic testing offers an alternative accurate diagnostic test to routine hormonal investigations.
- Early diagnosis may help limit the medical and psychosexual complications related to gender dysphoria in patients with DSD.

Contributors

Both authors were involved in authorship. V.J. was involved in the diagnosis and management of the patient. E.W. was responsible for case write-up and manuscript submission. Both authors reviewed and approved the final draft.

Funding

No public or commercial funding.

Disclosures

The authors have no professional disclosures.

Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient.

Data Availability Statement

Some or all data sets generated during and/or analyzed during this study are not publicly available but are available from the corresponding author on reasonable request.

References

1. Avendaño A, Paradisi I, Cammarata-Scalisi F, Callea M. 5–reductase type 2 deficiency: is there a genotype-phenotype correlation? A review. *Hormones*. 2018;17(2):197-204.
2. Nimkarn S, Likitmaskul S, Sangacharoenkit P, *et al.* Ambiguous genitalia: an overview of 22 years experience and the diagnostic approach in the pediatric department Siriraj Hospital. *J Med Assoc Thai*. 2002;85(Suppl 2):S496-S505.
3. Imperato-McGinley J, Guerrero L, Gautier T, Peterson RE. Steroid 5-reductase deficiency in man: an inherited form of male pseudohermaphroditism. *Science*. 1974;186(4170):1213-1215.
4. McGee LM, Lin-Brande M, Woods K, Seidman CA. Pubertal suppression and surgical management of a patient with 5-alpha reductase deficiency. *Urology*. 2022;165:e29-e31.
5. Konishi A, Ida S, Matsui F, Etani Y, Kawai M. Male assignment in 5-reductase type 2 deficiency with female external genitalia. *Pediatr Int*. 2021;63(5):592-594.
6. Lombardo MV, Ashwin E, Auyeung B, *et al.* Fetal testosterone influences sexually dimorphic gray matter in the human brain. *J Neurosci*. 2012;32(2):674-680.
7. Wilson JD. Androgens androgen receptors and male gender role behaviour. *Horm Behav*. 2001;40(2):358-366.
8. Bao AM, Swaab DF. Sexual differentiation of the human brain: relation to gender identity sexual orientation and neuropsychiatric disorders. *Front Neuroendocrinol*. 2011;32(2):214-226.