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CASE REPORT

Late Gender Re-Assignment in 46XY 17 Beta-Hydroxysteroid Dehydrogenase (Type 3) Deficiency: A Case Report Highlighting Challenges of Diagnosis and Management

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Summary

A 12-year-old child, previously raised as a female, presented with phallic enlargement at puberty. The sexual maturity ratings were Stage 2 and 4 for breast and pubic hair, respectively, with a stretched phallic length of 3.2cm. The patient re-presented at 16 years with progressive masculinisation and regression of breast buds. A pelvic ultrasound scan, magnetic resonant imaging and laparoscopic examination showed intrabdominal left testis, intracanalicular right testis, vas deferens, and bilateral pampiniform plexus with no uterus or ovaries. Histology of gonadal biopsy showed germ cell aplasia, and the karyotype was 46XY. The surgeons fixed the gonads in the scrotal sacs after biopsy. The human chorionic gonadotrophin stimulation test showed low basal and stimulated testosterone/androstenedione ratios (0.22 and 0.17, respectively) which were strongly suggestive of 17 beta-hydroxysteroid dehydrogenase-3 (17β-HSD3) deficiency. The patient was evaluated by the mental health team and after sessions of therapy, the patient requested for gender reassignment, which necessitated orthoplasty and urethroplasty. It is to be noted that 17β-HSD3 deficiency is a frequent cause of gender change at puberty.

Keywords: *17β-Hydroxysteroid Dehydrogenase-3 Deficiency, 46XY, Disorder of Sexual Differentiation, Gender Reassignment, Puberty.*

Introduction

17-Beta-hydroxysteroid dehydrogenase-3 (17β-HSD3) deficiency is a rare autosomal recessive disorder of sex development. [1,2] The enzyme 17β-HSD3 (also called 17-ketosteroid reductase) is required for the conversion of androstenedione (A) to testosterone (T) in the testis. Testosterone is subsequently converted to dihydrotestosterone (DHT), which facilitates the development of male external genitalia. [1-3] The HSD17B3 gene, which encodes the 17β-HSD3 enzyme, is expressed in the Leydig cells of the testes, and the loss-of-function mutations result in testosterone deficiency and under-virilisation of 46XY foetuses. The most severe forms of 17β-HSD3 deficiency in 46XY individuals are assigned female gender at birth. [2-5] Different degrees of enzyme deficiency in affected 46XY individuals may result in the external genital phenotype ranging from a completely female appearance with a blind-ending vaginal pouch to variable degrees of genital ambiguity with gonads palpable in the labio-scrotal folds, labio-scrotal fusion, and hypospadias. [6,7]

The worldwide incidence of this disorder is about 1 in 147,000 live births. [8] However, the incidence is reported to be as high as 1 in 100 to 300 people among the Arab Population along the Gaza Strip, with high rates of consanguineous marriages. [9,10]

At puberty, increased secretion of luteinising hormone (LH) and follicle-stimulating hormone (FSH) results in increased androgen levels from the action of unaffected 17β-HSD isoenzymes in the testis, liver, and adrenals, resulting in masculinisation of patients who have previously been assigned a female gender at birth. [2,5,11] Marked virilisation with phallic enlargement, male pattern body hair and muscle development may prompt clinical presentation and requests for gender reassignment. [5] Gender role changes were reported in 39–64% of 46XY cases with 17β-HSD-3 deficiency, previously raised as girls. [11] The process of gender re-assignment is not usually an easy one, and this case is reported to highlight the challenges encountered in the diagnosis and management of the disorder and create awareness about this rare cause of 46XY disorder of sex development (DSD).

Case Description

The patient first presented at the age of 12 years, with phallic enlargement at puberty, having been raised as a female. The parents reported that the external genitalia were clearly female at birth but described the complaints at presentation as a "protrusion" from the private part. The pregnancy was reportedly uneventful, except for a post-term delivery. The neonatal period was uneventful, and the family history did not suggest DSD. The patient's parents are not related. On examination, the Tanner stages were 2 and 4 for breasts and pubic hair, respectively, with a stretched phallic length (SPL) of 3.2cm and no palpable gonads. (Prader 3 genitalia). Unfortunately, a clinical photograph was not obtained at the first presentation. The anthropometry plotted on a female chart was a weight of 38.5kg (between the 3rd and 10th centile) and a height of 1.465m (25th centile). The patient had a normal pulse rate of 88 beats per minute and a blood pressure of 96/70 mmHg (systolic below 50th centile and diastolic between 50th and 90th centile).

Blood investigations showed normal serum electrolytes, urea and creatinine. Serum testosterone was 11.20nmol/L (reference ranges: female 0.17-1.7, male 0.34-19.0) and serum 8.00 am cortisol level was 210 nmol/L (240-618). The initial pelvic ultrasound scan (USS) report indicated the presence of the uterus and ovaries. The patient could not afford serum 17-hydroxyprogesterone (17OHP) assay and karyotype at the time. Based on available investigations, a presumptive diagnosis of simple virilising congenital adrenal hyperplasia was made, and oral hydrocortisone was commenced while awaiting other investigations. However, the patient defaulted from follow-up care for four years and then re-presented at 16 years of age, with absent female sexual characteristics and progressive masculinisation, as shown in Figures 1 and 2.

The breast buds had regressed (Tanner breast stage 1), and the external genitalia was graded at Sinnecker stage 3b. At that point, the karyotype revealed 46XY pattern. A repeat pelvic USS reported an absence of uterine and ovarian structures. Magnetic resonant imaging (MRI) showed bilateral inguinal testes, a left para-testicular cyst and a blind-ending vaginal pouch with the absence of ovaries and a uterus. The hormonal profile showed testosterone level 13.12nmol/L (Tanner V Female: 0.11-0.60nmol/L, Male: 0.67-9.42nmo/L), oestradiol 122pmol/L, (female 90-2000pmol/L, male: 75-175pmol/L).

Figure 1: Masculine build on re-presentation at 16years

Serum 8.00 am cortisol level was 319.06nmol/L, and gonadotropin levels were elevated. (LH: 37.95 IU/L (0-9) and FSH: 26.94 IU/L (0-19). Laparoscopic findings included intra-abdominal left testis, intracanalicular right testis with normal vas deferens and pampiniform plexus bilaterally. The surgeons fixed the gonads in the scrotal sacs after biopsy.

Figure 2: External genitalia showing penoscrotal hypospadias and a blind-ending vagina.

The histological examination of biopsied gonadal tissue revealed germ cell aplasia (Sertoli cell-only syndrome).
The results of the human chorionic gonadotropin (hCG) stimulation test were strongly suggestive of 17β-HSD3 deficiency (Table I). However, genetic mutation analysis could not be done to confirm the diagnosis.

Table I: Results of HCG stimulation tests

Serum analyte (nmol/L)	*Day 1(Pre- hCG)*	*Day 4 (Post- hCG)*
Testosterone (T)	8.05	8.36
Dihydrotestosterone (DHT)	1.62	0.68
Androstenedione (A)	36.75	48.54
T/DHT ratio (ref <20)	4.95	12.3
T/A ratio (ref >0.8)	0.22	0.17

The psychiatrist did a mental health assessment with a clinical interview and observation. These were followed with supportive psychotherapy. The pros and cons of gender reassignment were explored, and options for coping were identified. Strategies to address identified psychosocial concerns were investigated. Without coercion, the patient requested for gender reassignment to male. Psychotherapy follow-up sessions continued. The patient had surgery five years after re-presentation. The delay was caused by financial constraints and social issues surrounding gender reassignment in school. The patient had orthoplasty with urethroplasty six months later (Figures 3 to 5). He was also commenced on testosterone injections 250mg (given every two weeks), and care is currently being transitioned to the adult endocrinology team as he is presently 22 years of age.

Figure 3: Penile elongation following testosterone therapy

Discussion

17-Beta-hydroxysteroid dehydrogenase-3 deficiency was first characterised by Saez *et al*. [12] in the mid-1970s, but some cases were probably published before this time. [13] It is the most common cause of 46XY DSD among testosterone biosynthetic defects. [5,13] The condition is rare in the Western population and even rarer in individuals of African ethnicity. [5,13] The largest 46XY DSD due to 17β-HSD3 deficiency cohort was diagnosed in 57 out of 85 subjects from a largely consanguineous Arab population in Israel and followed over 25 years. [10] Six out of the 14 families reported in literature were from the Mediterranean or Middle East. [5] Three affected families of African descent were also reported. [5] There has not been any reported case of 17β-HSD3 deficiency in Nigeria from literature search. It is also possible that misdiagnosis and lack of diagnostic facilities may have affected case findings and reporting in Nigeria. However, it is still noteworthy that ethnic origin and the history of consanguinity are essential in evaluating this condition.

Figure 4: Genital structures post-orthoplasty

Figure 5: Patient commenced growth of beard.

The clinical presentation of individuals with 17β-HSD3 deficiency has been documented to vary greatly. [3,6] Most affected males usually present with female external genitalia, a fusion of the labia and blind-ending vagina, with or without clitoromegaly and will usually present at puberty because of progressive virilisation. [3-6] This sequence was observed in our patient. Less frequently, affected infants can present with ambiguous external genitalia [6, 7] or are mainly male with hypospadias and micropenis. [8] Additionally, phenotypes vary even in families with the same homozygous mutation, suggesting that the specific mutation is not likely to predict the phenotype. [3,8] Affected individuals have Wolffian derivatives, including the epididymis, vas deferens, seminal vesicles, and ejaculatory ducts, as seen in our patient, making it probable that a low amount of testosterone is enough to develop male internal genitalia or that testosterone is produced in these tissues by alternative 17β-HSD isoenzymes. [5]

Other causes of DSD need to be differentiated from the rare condition of 17β-HSD3 deficiency. As the most common cause of genital ambiguity and virilisation is likely to be congenital adrenal hyperplasia (CAH), it is essential to exclude possible adrenal disease by measuring early morning serum cortisol, if necessary, post-ACTH stimulation levels. [3] Unfortunately, in our patient, the initial reported low cortisol, high female range serum testosterone level, an initial erroneous USS report of female internal organs [14], and the unavailability of karyotype and serum 17OHP made CAH likely. Imaging plays a vital role in evaluating the internal organs and urogenital anatomy in children with DSD. [15] Ultrasonography is a primary modality for evaluating the internal reproductive organs [15] but it is also operator-dependent. Magnetic resonance imaging (MRI) serves to clarify internal anatomy and search for internal gonads, as it is more sensitive in detecting gonads than USS. [15]

Basal (puberty) or pre-pubertal hCG stimulated androgens [androstenedione (A), testosterone (T) and dihydrotestosterone (DHT)] ratios are usually discriminatory and can reliably diagnose 17β-HSD3 deficiency [5,8] though pitfalls have been documented. [1,6] The endocrine hallmarks of 17β-HSD3 deficiency are increased concentrations of androstenedione and reduced testosterone levels, leading to a low T/A ratio. A T/A ratio below 0.8 has a sensitivity of 100%. [3,5,7,13] The index case had basal and hCG-stimulated T/A of 0.22 and 0.17, respectively. Controls typically have a T/A ratio >1.0. In a large series of 19 patients, hCG-stimulated serum ratios T/A in 17β-HSD3-deficient patients were discriminative in all cases. They did not overlap with ratios in normal controls, and all investigated patients had mutations in both HSD17B3 alleles. [8] Serum androstenedione concentrations may be as high as 35 nmol/L post-puberty, [3] as was seen in the index case with a 36.75 nmol/L level. Pitfalls in the hormonal diagnosis of 17β-HSD3 deficiency have been reported in some cases and confirmed later by mutations in the HSD17B3 gene with a T/A ratio > 0.8. [1,6] The possible explanation for the normal T/A ratio in these affected children is the individual and temporal variability in the HSD17B isoenzymes activity. [1,5] Therefore, it may be safer to speculate that when the T/A ratio is low, there is a strong possibility of the diagnosis of 17β-HSD3 deficiency. Still, a normal T/A ratio does not rule out the diagnosis. Molecular genetic mutation analysis is the gold standard for diagnosing 17β-HSD3 deficiency because low T/A ratios have also been documented in some patients with 46XY DSD other than 17β-HSD3 deficiency. [16]

There are other differential diagnoses which cause pubertal masculinisation in 46XY DSD previously raised as females. [1,3,5,8] The closest condition which shares the same phenotype is 5-alpha reductase two deficiency. The enzyme 5α-reductase type 2 converts testosterone to DHT, the hormone responsible for the virilisation of the external genitalia. Serum testosterone levels may be elevated, whereas DHT levels are typically low. Elevated basal or hCG-stimulated testosterone-to-DHT and normal T/A ratios are consistent with the diagnosis. [2,3] This condition is unlikely in the index who had normal T/DHT ratios.

Another differential of 17β-HSD3 deficiency is androgen insensitivity (AIS), which is an Xlinked recessive disorder caused by mutations in the androgen receptor (AR) gene. [2] Affected, 46XY children with complete AIS present in infancy with inguinal or labial gonads, inguinal herniae, but otherwise normal external female genitalia. Patients with partial AIS present with atypical genitalia in infancy. [2,7] Elevated serum testosterone levels are common in many patients with AIS. The testosterone level in our patient was not elevated, which makes AIS an unlikely diagnosis. A nationwide Netherlands study involving 19 patients with 17β-HSD3 deficiency (confirmed HSD17B3 gene mutation) showed that T/A ratios were discriminatory and did not overlap with patients with confirmed AR receptor mutations. [3] Recently, SF-1 (NR5A1) gene mutation has been added in the differential diagnoses of DSD cases that may show virilisation of females at puberty. [17,18] The phenotype ranges from a complete female appearance to an infertile male. Though the gonads are very dysgenetic in patients with SF-1 mutations, sufficient androgen synthesis in some affected cases can cause severe virilisation during puberty. [17,18] The low T/A ratio seen in our patient is not usual in NR5A1 gene mutations. The response of our patient to usual doses of testosterone therapy makes the diagnosis of 17β-HSD3 deficiency more likely. However, in view of the heterogeneity in the phenotype of these conditions, genetic mutation analysis remains the gold standard in diagnosis.

Factors contributing to gender change in affected patients with 17β-HSD3 deficiency include body image perception, religion, family, and culture. Previous perinatal androgen exposure may also play a role. [1,5,11] The cultural contribution to gender role adoption may be related to the fact that in many regions, including Africa, although the male-female ratio of infertility patients has increased recently, infertile women tend to experience a higher level of stigmatisation compared to men and are more psychologically distressed. [19] Most patients with 17 β-HSD3 deficiency who present in puberty will need hormonal replacement therapy irrespective of which gender they choose. In view of the germ cell aplasia and elevated gonadotrophins (reflecting primary gonadal failure) as seen in the index case, the chance of fertility is low. [3] He is likely to require assisted reproductive technology in the future.

For most patients presenting with genital ambiguity so severe that a multidisciplinary group is needed to consider male or female assignment, the Global DSD Update Consortium recommended male assignment for those with 17β-HSD3 deficiency, since greater than 50% of cases later switch to male. [20] Testosterone supplements (oral, injectable or transdermal patches) may be needed for incompletely virilised males. [3] In some cases, gonadectomy will have occurred in childhood, and oestrogen replacement treatment will be required at puberty for those raised as female. [3,4]

Limitation: This case report notes a limitation in the unavailability of molecular genetic studies to confirm mutations in the HSD17B3 gene.

Conclusion

17-Beta-hydroxysteroid dehydrogenase-3 deficiency is a rare recessive disorder and a significant cause of 46XY DSD. Affected individuals are frequently assigned female gender at birth, but masculinisation occurs at puberty. The DSD multidisciplinary team needs to support the patient through the transition process if the decision for gender change is made. Life-long care by the adult endocrinologist, surgeon and psychologist is essential. Early karyotyping and determination of internal genitalia by reliable imaging modalities are critical in evaluating individuals with DSD. Facilities for genetic studies are advocated in resource-constrained settings for confirmation of genetic mutations.

Ethical considerations: Informed consent was obtained from the patient for the use of the relevant data in this research.

Acknowledgement: The authors appreciate the patient and the parents for the consent and permission to use the patient's data, including photographs, for the purpose of this research.

Authors' Contributions: All the authors conceived the study after managing the case together. OEE did the literature review, and OEE, AMF, and OOY drafted the manuscript. All the authors revised the manuscript draft for sound intellectual content and approved the final version of the manuscript.

Conflicts of Interest: None.

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