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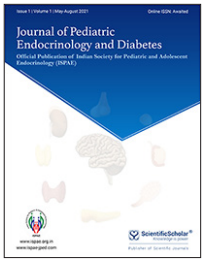

*Case Series*

# 17Beta-hydroxysteroid dehydrogenase type 3 deficiency: A single-center case series experience

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## ABSTRACT

17Beta-hydroxysteroid dehydrogenase type 3 (17β-HSD3) deficiency is a rare cause of disorders of sex development. It leads to an external female phenotype or varying degrees of undervirilization in XY patients. We report four cases with 17β-HSD3 deficiency, who presented at different ages with different complaints. The aim of this case series is to review the clinical, biochemical, and genetic characteristics of individuals diagnosed with 17β-HSD3 deficiency in a single tertiary center.

**Keywords:** 17Beta-hydroxysteroid dehydrogenase type 3, Male disorders of sex development, XY disorders of sex development

## INTRODUCTION

17Beta-hydroxysteroid dehydrogenase type 3 (17β-HSD3) deficiency is an autosomal recessive condition causing 46,XY disorder of sex development (DSD).

Due to rarity of this condition, the exact incidence has not been accurately estimated. The incidence of 17β-HSD3 deficiency in Netherland was estimated at 1:1,47,000. Higher incidence was described in populations in certain areas of the Middle East, Mediterranean regions and in other regions with a high consanguinity rate reaching up to 1:200 and 1:300.[1,2]

The condition can lead to an external female genitalia phenotype or varying degrees of undervirilization in XY patients. This case series reflects the wide variability of presentations in different age group of patients. Moreover, this study provides a step by step diagnostic workup and the outcome in each case.

## CASE SERIES

We present four cases with 17β-HSD3 deficiency, which presented at different ages with different complaints. This case series aim to review the clinical, biochemical, and genetic characteristics of individuals diagnosed with 17β-HSD3 deficiency in a single tertiary center.

### Case 1

The first case was 16-year-old female who presented initially with primary amenorrhea. Clinical assessment showed a female with husky voice and underdeveloped breast B2, normal external

female genitalia, with slightly enlarged clitoris. She had pelvic ultrasound scan (USS), examination under anesthesia (EUA), and further blood tests arranged. She had absence of internal female organs, an inguinal structure representing gonads and vaginal length about 2 cm. Blood tests confirmed karyotype 46,XY. She had human chorionic gonadotropin (hCG) stimulation test using a dose of 5000 units with samples obtained at baseline followed by day 4 of the test. The results showed initial luteinizing hormone (LH) 51 IU/L, follicle stimulating hormone (FSH) 43.6 IU/L, and low testosterone/androstenedione (TA) ratio of 0.23.

Based on these findings, she was diagnosed with 17β-HSD3 deficiency which was later confirmed on genetic testing. She received extensive multidisciplinary team (MDT) input throughout. With decision to continue as female, the patient was started on puberty blockers in the form of gonadotropin releasing hormone (GnRH) agonist and estrogen supplement followed by gonadectomy.

### Case 2

The second case was a 8-years-old who was referred to endocrine clinic with incidental finding of clitoromegaly. Examination in clinic showed prominent skin folds not typical for labia majora or minora and no signs of puberty. Examination otherwise was unremarkable. USS revealed absence of internal female organs and inguinal testes. Karyotype was confirmed as 46,XY. Further tests included standard hCG stimulation test with a dose of 5000 units, which showed FSH 2.4 IU/L, LH <0.3 IU/L, low baseline testosterone of 0.3 nmol/L, and 1.4 nmol/L on day 4 post-stimulation. The sample was insufficient for androstenedione test. Diagnosis was confirmed by genetics. With MDT support, the patient later underwent gonadectomy and was started on estrogen supplement.

### Case 3

The third case was a 3-days-old baby born preterm with normal looking external female genitalia and inguinal swelling containing palpable gonads. USS confirmed the presence of normal size and appearance of testes in addition to absence of female internal organs. Systemic examination was otherwise unremarkable. The karyotype was 46,XY and further blood tests carried out with standard hCG stimulation test using a dose of 1500 units. Initial results showed LH value of 50 IU/L, FSH of 1.3 IU/L, and low T/A ratio 0.08. Considering the above, the biochemical diagnosis

**Table 1:** Summarizes the characteristics, test results and outcome for each case.

| | Presentation | Ultrasound scan (USS) | Pre-and post-hCG stimulation (MS) | Genetic mutation | Outcome | Testicular biopsy |
|---|---|---|---|---|---|---|
| Case 1<br>16 years | Primary amenorrhea | No Müllerian structures<br>Inguinal testes | T 3.58→3.98 nmol/L<br>A15.3→16.7 nmol/L<br>T/A: 0.23 | Homozygous mutation c. 277+4A>T<br>In 17β-HSD3 gene | - Female<br>- GnRH analog and estrogen<br>- Gonadectomy (malignancy risk) | Atrophic Seminiferous tubules reduced in size and numbers with no evidence of neoplasia |
| Case 2<br>8 years | Clitoromegaly | No Müllerian structures<br>Inguinal testes | T: 0.3→1.4 nmol/L<br>A: N/A<br>T/A: N/A | Heterozygous mutation c. 614T>A p.(val205Glu) and C.645A>T p. (Glu215ASP) in 17β-HSD3 gene | - Female<br>- Estrogen<br>- Gonadectomy | Atrophic with occasional residual germ cells present<br>No spermatogenesis or Leydig cells seen<br>No evidence of neoplasia |
| Case 3<br>3 days | Normal female external genitalia and palpable gonads in groins | No Müllerian structures<br>Inguinal testes | T: 0.6→1.5 nmol/L<br>A: 10.9→18.9 nmol/L<br>T/A: 0.08 | Homozygous mutation [C.210delA, *P* (lys70fs] in 17β-HSD3 gene | - Male<br>- Testosterone IM<br>- Orchiopexy and reconstructive surgeries | |
| Case 4<br>16 years | Primary amenorrhea | No Müllerian structures<br>Abdominal testes on MRI | T: 4.2→7.2 nmol/L<br>A: 11.8→34.1 nmol/L<br>T/A: 0.21 | Homozygous mutation [c. 524G>C p. (Arg175Th] in 17β-HSD3 gene | - Female<br>- GnRH analog and estrogen<br>- Gonadectomy | Seminiferous tubules containing Sertoli cells<br>No spermatogenesis or atypia |

hCG: Human chorionic gonadotropin, MS: Mass-spectrometry, T: Testosterone, A: Androstenedione, T/A: Testosterone/Androstenedione ratio, IM: Intramuscular, MRI: Magnetic resonance imaging

of 17β-HSD3 deficiency was made. Following extensive MDT discussion with parents and considering their choice; the baby was started on testosterone injections followed by EUA which showed micropenis, high bifid scrotum, severe chordee, and penoscrotal hypospadias. Baby underwent multi-stage reconstruction surgeries.

**Case 4**

This was another 16-year-old female who presented with primary amenorrhea. Clinical assessment revealed underdeveloped breast B2, normal external genitalia, and body hair mainly on the face. EUA confirmed vaginal pouch with no cervix. USS confirmed the absence of internal female organs; but was unable to identify gonads in inguinal regions. She later had magnetic resonance imaging (MRI) scan which showed small abdominal testes. Standard dose of 5000 units hCG stimulation test showed: FSH 8.5 IU/L, LH 15.3 IU/L and T/A ratio 0.21. Diagnosis was further confirmed with genetic studies. Like the other patients, this child also received puberty blockers and estrogen followed by gonadectomy.

All four cases had karyotype which was 46,XY consistent with undervirilized males. Each case had initial hormonal tests followed by standard dose hCG stimulation test. Except for one case (due to insufficient sample), all other three cases had extremely low T/A ratio of <0.3 which, in the context of clinical suspicion, provided a biochemical diagnosis of 17β-HSD3 deficiency. The four cases described had genetic confirmation with different mutations identified, all were missense mutations [Table 1].

All our patients received MDT input throughout. The MDT included psychologist, urologist/surgeon, geneticist, and pediatric endocrinologist. In only one case, the choice was to be raised as male. He underwent multiple stage surgeries. The other three cases chose to continue their lives as females and were started on hormonal treatment. Decapeptyl (GnRH analog) was started for our two adolescent patients to prevent testicular stimulation during puberty and hence avoiding further virilization while awaiting gonadectomy. Subsequently, gonadectomy was performed on the three female cases.

## DISCUSSION

The condition was first described in 1970s but with the recent advances in biochemical analysis combined with our understanding of steroidogenesis pathways, more cases have been described over the years. The enzyme 17β-HSD3 is responsible for converting Δ4-androstenedione (A) to testosterone (T) in testicles and both play key role in sex differentiation.

The presentation is variable, ranging from undervirilization of XY baby at birth (empty or bifid scrotum, perineoscrotal hypospadias or cltoromegaly) to normal female external genitalia which makes it difficult to recognize during infancy unless an inguinal or labial mass is identified and triggers further assessment. Majority of patients present in childhood or around puberty with virilization or primary amenorrhea. The initial differential diagnosis would include androgen insensitivity syndrome and 5-alpha reductase deficiency. Our four cases represent the variety in presentation at different ages.

**Diagnosis and workup**

The British Society for Paediatric Endocrinology and Diabetes (BSPED) document for DSD workup 2021 has highlighted the biochemical tests for various DSD conditions and differential diagnosis based on interpretation of stimulation tests.[3]

In addition to confirmation of the presence or absence of Mullerian structures, identifying the location of gonads is important. Gonads are usually detected during USS but, in some cases, MRI might be required.

Once karyotype, USS, and baseline hormonal tests are done, it is reasonable to perform stimulation test as the next step. This will allow better accuracy in measuring precursors and metabolites compared to random hormone levels. It can help in reaching a biochemical diagnosis based on the ratio between androstenedione (precursor) and testosterone (metabolite).

The T/A ratio in under-masculinized males was reviewed in some studies with the conclusion that 17β-HSD3 deficiency should be considered if T/A ratio is <0.8.[4,5] Although low T/A ratio would highly suggest the diagnosis, it may not be specific for the condition and can be seen in cases of abnormal testes. It was recommended to consider careful evaluation for testicular dysgenesis with prolonged hCG stimulation.[5]

It is important to mention that urine steroid profile has no role in diagnosing 17β-HSD3 deficiency, and the confirmation of definitive diagnosis requires genetic testing.

**Genetics**

In literature, a total of up to 70 different *HSD17B3* mutations have been reported. The condition can develop due to homozygous or compound heterozygous mutations. Out of all described mutations linked to 17β-HSD3 deficiency, missence mutations represent 55%, splice-site 29%, small deletions and insertions (7%), and less frequently nonsense mutations, multiple exon deletions, and/or duplications.[6,7]

**Management**

Early involvement of MDT is paramount to provide support particularly when it comes to decision about gender choice. Previous studies found out that more than 78% of patients

with 17β-HSD3 chose to continue as females.[8] This most likely was influenced by late presentation age when patients were already identified as females for many years and choose to continue the same.

For patients who choose to continue as females, gonadectomy is recommended due to risk of malignancy. For those who present later in adolescence, blocking puberty while awaiting surgical procedure is essential. Without blockers, the testes could be stimulated leading to further virilization. In addition, estrogen replacement should be initiated to enhance breast development and support bone health.

## CONCLUSION

17β-HSD3 deficiency can be diagnosed based on clinical suspicion and low T/A ratio, but the definite diagnosis is through genetic testing. It is a complex condition and requires extensive MDT input.

The endocrine team is the lead for these cases and responsible for liaison with other specialties in the MDT. After diagnosis, starting GnRH blockage and estrogen or testosterone is based on the discussion with parents/patient regarding expected outcome and choice. Psychology support should be started as soon as a DSD case is suspected and should continue throughout.

The surgical input from urologist includes (in some cases) details of surgeries needed to achieve near normal external genitalia and the implications on future sexual life. These types of surgeries are complex and can involve multiple-stage genital reconstruction. Management of the condition could be even more complex considering the social, cultural, religious, and psychological factors which all need careful consideration and continuous support.

### Ethical approval

Institutional Review Board approval is not required.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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### Conflicts of interest

There are no conflicts of interest.

### Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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