SEVERE UNDERVIRILISATION IN A 46,XY CASE DUE TO A NOVEL MUTATION IN HSD17B3GENE

Ayfer Alikasifoglu[1], Dogus Vuralli[1], Olaf Hiort[2], E Nazli Gonc[1], Z Alev Ozon[1], Nurgun Kandemir[1]
[1]Department of Pediatric Endocrinology, Hacettepe University, Ankara, Turkey; [2]Division of Pediatric Endocrinology and Diabetes,University of Lübeck, Lübeck, Germany

*Authors have nothing to disclose

BACKGROUND

17-ß-hydroxysteroid dehydrogenase type 3 (HSD17B3) isoenzyme is present almost exclusively in the testes and converts Δ4 androstenedione to testosterone. HSD17B3 deficiency is a rare autosomal recessive disorder of sex development due to impaired conversion of androstenedione to testosterone[1].

Children with 46,XY karyotype often have female appearing external genitalia at birth with or without clitoromegaly and/or labial fusion and a blind-ending vagina. Less often ambiguous genitalia, male genitalia with micropenis or hypospadias are reported. Affected patients often have testes and normal Wolffian duct derivatives[2].

At the time of puberty, marked virilisation can occur in children raised as females[3]. This pubertal changes are potentially due to peripheral conversion of androstenedion to testosterone by HSD17B isozymes. Therefore 46,XY patients with HSD17B3 gene defects should be raised as male if possible.

OBJECTIVES

When a child with 46,XY karyotype present with female appearing external or ambiguous genitalia and there is impaired conversion of androstenedione to testosterone, HSD17B3 deficiency must be kept in mind.

METHOD

A case with HSD17B3 deficiency with a novel mutation is presented.

CONCLUSION

- A novel mutation p.E254VfsX10 in HSD17B3 gene caused severe undervirilisation in a 46,XY patient.
- Early diagnosis is crucial for appropriate sex of rearing.
- For patients raised female who undergo early orchiectomy, more data regarding outcomes of gender identity, quality of life, and sexual function is needed.
- For patients raised male with retention of testes, more data regarding outcomes of masculinizing genitoplasty, sexual function, fertility, and malignancy risk is needed.

RESULTS

One year old girl was referred with the complaint of swelling in the right inguinal area. There was consanguinity in the family in which the parents were first cousins. In physical examination bilateral gonads were palpable in inguinal regions. She had a fallus of 1.5 cm in size and vaginal and urethral orifices were seperate.The karyotype was 46 XY. On ultrasonography no Mullerian structures could be seen and gonads were in the inguinal canal. Human chorionic gonadotropin (hCG) stimulation test was performed and following injection of 3000 U/m^2 hCG for 3 days serum androgen concentrations were measured (Table 1). The test results showed that there was impairment in testosterone biosynthesis. Testosterone/dihydrotestosterone ratio was 3.6 which was normal. Testosterone/androstenedione ratio was found to be 0.107 (N>0.8) suggesting HSD17B3 deficiency.

Table 1. Serum androgen concentrations before and after hCG stimulation

	Pre-hCG	Post-hCG
Testosterone (T) (ng/dl)	<20	29.9
Dihydrotestosterone (DHT) (pg/ml)	14.35	82.48
Androstenedione (A) (ng/ml)	<0.3	2.78
T/DHT		3.6
T/A		0.107

Molecular analyis of the HSD17B3 gene showed a homozygous mutation c.761_762delAG corresponding to p.E254VfsX10 in the patient and both parents were heterozygous. A deletion of two nucleotides in exon 10 was found, which lead to a frameshift and subsequently to premature termination within the protein. This deleterious mutation caused HSD17B3 deficiency in this patient.

The parents did not accept sex reassignment into male and bilateral gonadectomy was performed. The histopathology of gonads were consistent with testis and spermatic cord.

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