NOVEL MUTATION IN A NEWBORN WITH A RARE CAUSE OF 46,XY SEX REVERSAL: 17β-HYDROXYSTEROID DEHYDROGENASE TYPE 3 DEFICIENCY

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Testicular 17β-hydroxysteroid dehydrogenase type 3 deficiency

*Defect in conversion of androstenedione to testosterone.

*Rare, phenotype varies between completely external female genitalia - micropenis and hypospadias.

*Mostly unnoticed and raised as females and virilization during puberty.

*Gender reassignment from female to male: 39-64%

*Diagnosis: Low serum testosterone/androstenedione (T/A) ratio after hCG stimulation (normal, >0.8) and genetic analysis.[1]

8-day-old newborn

Complaint: Bilateral inguinal swelling.

Past history: Birth weight of 3300 g, family history unremarkable except first-degree consanguinity between parents.

Physical examination: Normal auxology, vital signs, and systemic examination (Figure 1)

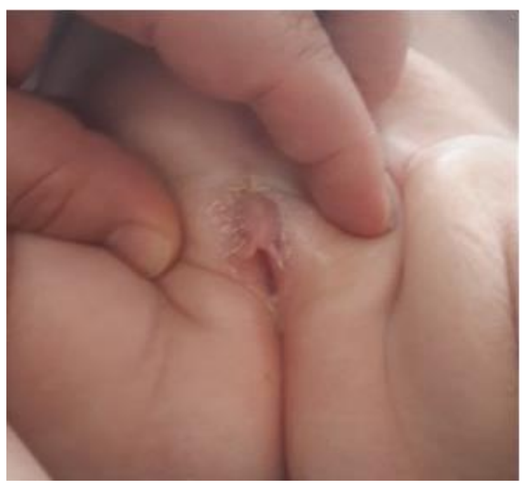

Figure 1. Genital examination disclosed normal female external genitalia with no cliteromegaly, separate vaginal and urethral openings, and gonad-like structures in the inguinal region.

Table 1. Hormonal values throughout the follow-up

	8th d	33rd d	39th d*	42nd d#	81st d	81st d$
FSH, mIU/mL	0.43	0.81	-	-	0.75	2.18
LH, mIU/mL	<0.1	<0.1	-	-	<0.1	4.87
Total testosterone, ng/dL	25	<2.5	<2.5	26.7	<10	-
Androstenedione, ng/dL	300	-	38	120	-	-
AMH, ng/mL	-	-	160	-	-	-
ACTH, pg/mL	13.7	-	-	-	-	-
Cortisol, µg/dL	10.7	-	-	-	-	-

*Basal levels before hCG test, #levels obtained 24 hours of the last dose of hCG, $ peak levels during LHRH test.

Ultrasonogprahy: No uterus or ovary but testis and epididymis tissue in the inguinal regions bilaterally.

Karyotype: 46,XY by both QF-PCR and conventional method.

Genetic analyses: No androgen receptor or 5α-reductase mutation

hCG test: Suggested 17β-HSD3 deficiency

*inadequate total testosterone response despite an >10-fold increase

*a normal testosterone/dihydrotestosterone ratio of 2

*a low testosterone/androstenedione ratio of 0.22 (normal, >0.8)

Mutation analysis of *HSD17B3*

*Homozygous for a novel missense mutation in exon 6: p.H155P (c.464A>C). Bioinformatic analyses with PolyPhen2 and Mutation Taster were in aggreement: probably damaging (score, 0.997) and disease causing (probability, 0.919), respectively.

*Genetic counseling including information regarding preimplantation genetic testing was provided.

Decision on gender

Thorough discussion with the parents yielded female gender preference but gonadectomy was deferred to be performed during childhood after gender identity can be evaluated.

Discussion

HCG stimulated T/A ratio of less than 0.8 is very suggestive of the diagnosis, however, low T/A ratios may also be encountered in cases with gonadal dysgenesis and high T/A ratios have also been reported.[2, 3]

In CAIS but not PAIS, normal surge of plasma LH and testosterone during the first few months of life is absent. Hormonal data regarding mini-puberty in 17β-HSD3 deficiency are scarce. In addition to our case, we observed a similar situation in a report by Bilbao JR.[4] This unique condition can be attributed to lack of prior androgen action on gonadotropic axis.[5]

Despite rearing such infants as males was reported to be successful, majority have been reared as females.[3, 6, 7] An intermediate risk of germ cell tumors, unknown fertility issues, and requirement for several surgical procedures

In 46,XY cases with normal testicles and female external genitalia

*Lack of mini-puberty should not directly lead to CAIS.

*17β-HSD3 deficiency should be sought via testosterone/androstenedione ratio and mutation analysis.

*In order to prevent virilization, orchiectomy should be performed before puberty starts if reared as females.

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