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BACKGROUND

Disorders of androgen synthesis are rare causes of 46,XY disorder of sex development (DSD) that present with undervirilization or sex reversal.

OBJECTIVE

A history of a female adolescent with 46,XY DSD, initially suspected to have complete androgen insensitivity is presented.

CASE REPORT

The patient with prenatal karyotype 46,XY, born with female genital appearance, was first evaluated 3 days postnatally. She was found not to have Mullerian structures; the gonads were located in inguinal regions, with the ultrasound appearance of testes, and were left in situ. Testosterone (T) and dihydrotestosterone (DHT) were detected by immunoassay (T 0,6 nmol/L, DHT 1,1 nmol/L), and complete androgen insensitivity was suspected. No mutations or deletions in *AR* and *SRD5A2* genes were identified.

At the time of presentation her age was 12 years. She had no clinical signs of puberty or virilisation, but gonadotropins were in pubertal range (Table 1).

Adrenal androgen levels were very low basally and with adrenocorticotropin stimulation.

There were no signs of gonadal failure, salt losing, salt retention or hypocorticism. The level of 17-OH progesterone was borderline elevated (Table 2).

time	0'	20'	30'	60'
LH(U/L)	5,0	38,9	43,4	37,3
FSH (U/L)	2,3	3,6	3,7	4,5
Estradiol (nmol/L)	0,16			
Inhibin B (ng/L)	361			
AHM (µg/L)	19,6			

Table 1. Results of GnRH stimulation and gonadal function at 12 years of age

time	0'	60'	Normal range
Testosterone (nmol/L)	<0.1	0.1	0.1-0.2
AD2 (nmol/L)	0.2	0.3	0.7-10.8
DHEA-S (µmol/l)	0.5	0.6	3.6-12.9
17-OHP (nmol/L)	9.06	8.65	
ACTH (pmol/L)	3.49		<10.20
Aldosterone (nmol/L)	0.28		
PRA (µg/L/h)	0.30		
Potassium (mmol/L)	4.4		3.8-5.5
Sodium (mmol/L)	139		3.6-6.1

Table 2. results of ACTH stimulation test and adrenal function at 12 years of age

time	0'	60'
ACTH (pmol/L)	4.00	
Cortisol (nmol/L)	149	243

Table 3. results of ACTH stimulation at 13 years of age

No suspicious changes in the gonads were detected by ultrasound during regular follow-up.

Urinary steroidmetabolome analysis by gas chromatography-mass spectrometry (GC-MS) showed increased 17-deoxygenated steroids, normal glucocorticoids and subnormal sex hormones pointing to a general weakness of the 17-hydroxylase/17,20- lyase system with strongly impaired lyase function. This constellation was highly suspicious of "isolated" 17,20-lyase deficiency. Targeted genetic analysis showed that the patient is compound heterozygote for *CYP17A1* gene (NM_000102: c.1040G>A (p.R347H; rs61754278) in exon 6 and NM_000102: c.1247G>A (p.R416Hrs104894155) in exon 8). Both variants are classified as pathogenic in ClinVar database.

At the age of 13, ACTH stimulation test was repeated and adrenal insufficiency was detected. She was started on hydrocortisone replacement therapy. At the same time puberty was stimulated with estrogen patches.

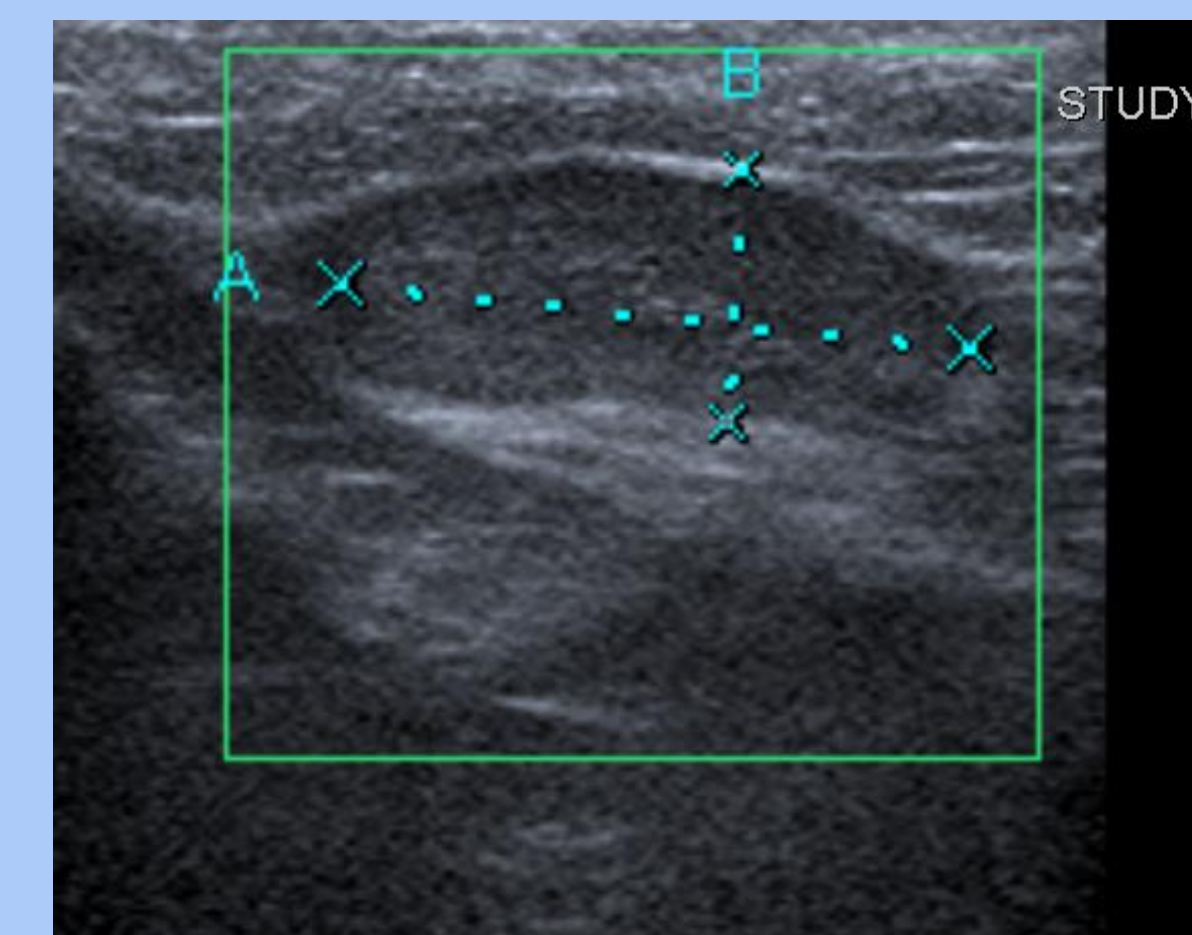


Figure 1. US image of the gonad at the age of 12

METHODS

Patient history was obtained from the medical records. Urinary steroid profile was performed using gas chromatography/mass spectrometry. The genetic analysis was performed by TruSight One sequencing panel using MiSeq desktop sequencer. Genetic variants with coverage >10× were analyzed with Variant Studio 3.0 software.

CONCLUSIONS

A disorder of androgen synthesis due to isolated 17,20-lyase deficiency was identified in a patient with complete sex reversal. Unlike immunoassays, GC-MS urinary steroid metabolome analysis is independent of cross reactivity and also due to its high differential diagnostic potential is extremely helpful in the delineation of DSD.