Human 3beta-hydroxysteroid dehydrogenase deficiency associated with a normal spermatic numeration, despite a severe enzyme deficit and after an accomplished transition period

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INTRODUCTION

Human 3 beta-hydroxysteroid dehydrogenase (3βHSD) deficiency is a rare form of congenital adrenal hyperplasia resulting from *HSD3B2* gene mutations, leading to steroido-genesis impairment in both adrenals and gonads, but detailed fertility evaluation is lacking in this rare disease.

We evaluated testicular function in a patient carrying *HSD3B2* mutation.

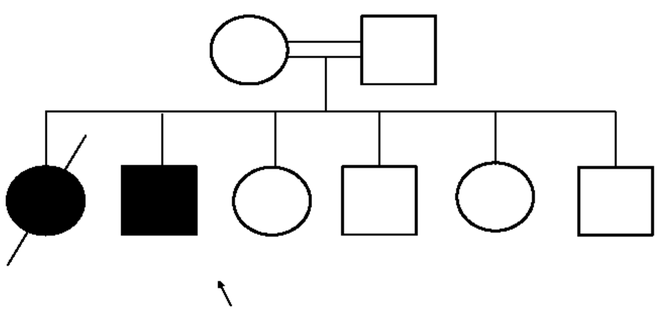

Figure 1

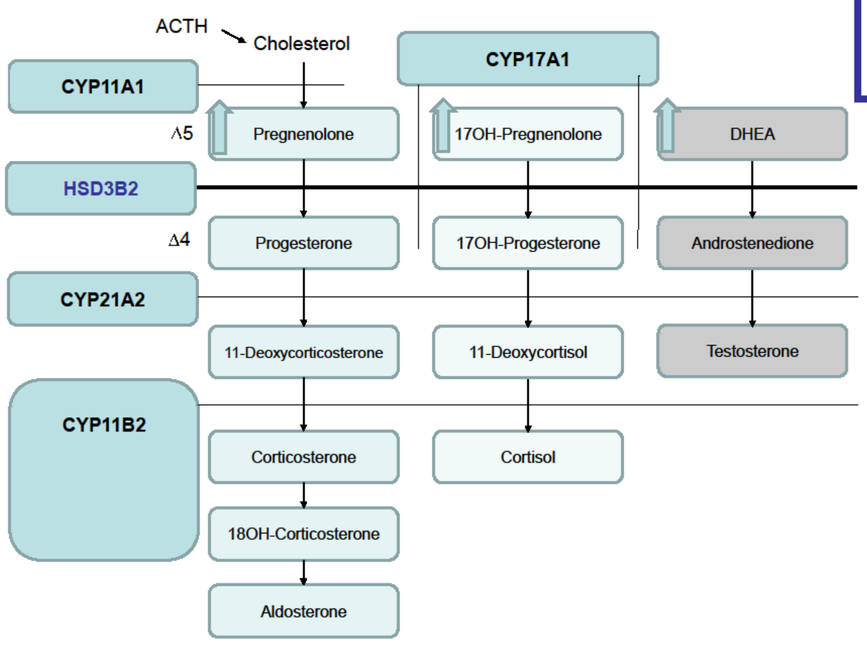

Figure 2

CASE REPORT

- The patient, issued from a consanguineous family, presented with salt wasting at birth, in Trousseau pediatric Hospital. His parents were first cousins (Fig 1) and their first child had died at birth, probably from salt wasting. The patient presented with a micropenis and two intrascrotal testes. A perineal hypospadias was surgically corrected at the age of 2. His karyotype was 46,XY. Highly elevated 17OH-Pregnenolone levels, contrasting with low 17OH-Progesterone, were in favor of 3βHSD deficiency (Fig 2). His hormonal status at birth is reported in Table 1.
- DHEA-s levels mostly remained controlled and normal puberty was achieved at age 15. His final height is 170cm (target height: 164cm). The patient was transferred to the adult unit at the age of 19 and his hormonal levels were: 17OH-Pregnenolone 2.2 nM (N: 1.5-10.8) ; DHEA-s 2.6 µM (N: 3-14); Total testosterone 28 nM (N: 11-40); ACTH 21 pg/ml (N:9-52); Renin 18.1 pg/ml (N: 5-30). Those hormonal levels remained stable ever since under his current treatment: hydrocortisone 20 mg/d and fludrocortisone 100 µg/d.
- Sequencing *HSD3B2* gene revealed a 687del27 homozygous mutation, defined as a 27-bp deletion in exon IV, deleting the terminal base pair of codon 229 and all of codons 230-237, in addition to the first two base pairs of codon 238 (1,2). This deletion did not alter the reading frame, but deleted the amino acid residues Ala-His-Leu-Ala-Leu-Arg-Ala. Both parents were found to be heterozygous for this mutation.
- *In vitro* activity of this mutant, evaluated by DHEA/D4-Dione conversion was very low (2).

  - Testicular ultrasound found two scrotal testes of 21 ml each,without any evidence of testicular adrenal rest tumors. No suspect testicular mass was detected (3).
  - At the age of 19, plasma inhibin B was 139 pg/ml (N: 135-350), in favor of normal Sertoli cell function. His sperm count (Table 2) was normal according to WHO 2010 criteria (4) and sperm cryopreservation was performed.

Hormonal status at birth	Values	(ng/ml)
Pregnenolone	0.7	N: < 5
Pregnenolone/synacthen (60')	15.5	-
17OH-Pregnenolone	16	N: < 5
17OH-Preg/synacthen (60')	68	-
17OH-Progesterone	<0.1	N: 1-3
17OH-Prog/synacthen (60')	1.9	-
D4-Androstenedione	<0.1	N: 0.5-2.5
Testosterone (total)	1	N: 3,5-12
DHEA	0.6	N: 3-10
DHEA/synacthen (60')	1.8	-
11-Deoxycortisol	<0.05	N: 0.5-2
11-Deoxycortisol/synacthen(60')	<0.05	-
Cortisol	12	N: 70-230
Cortisol/synacthen (60')	13	N>21

Table 1

Spermogram at age 22	Units	Norm (5)
Volume	3 ml	N>1.5
pH	7.9	N>7.2
Concentration	57.6 M/ml	N>15
Numeration	172.8 M	N>39
Vitality	41 %	N>58
Mobility	(H1+H2) -	
a (rapid progressive)	0% -	N a+b>32%
b (slow progressive)	20% -	N a+b+c>40%
c (mobile)	20% -	
d (immobile)	60% -	
Cytogram	-	
Typical form	21% -	N>23%
Abnormal acrosome	48/36 -	
Abnormal flagelle	10/06 -	

Table 2

CONCLUSIONS

This patient illustrates the role of an accomplished transition from pediatric to adult units, since an hormonal control under treatment is not only vital in the short term, but a long term control is also required for a future fertility. Interestingly, cryopreservation was performed. This case reports normal sperm count and therefore potential male fertility, in a patient with severe *HSD3B2* deficiency.

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