

The challenge of diagnosing 5alpha-reductase deficiency post gonadectomy

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Background

We present a case of a woman who was referred to Endocrinology as an adult having experienced virilisation in adolescence. The virilisation was managed with a gonadectomy prior to diagnosis of the underlying disorder. Here we discuss how gonadectomy altered the diagnostic approach, and lead to psychosocial challenges for the patient.

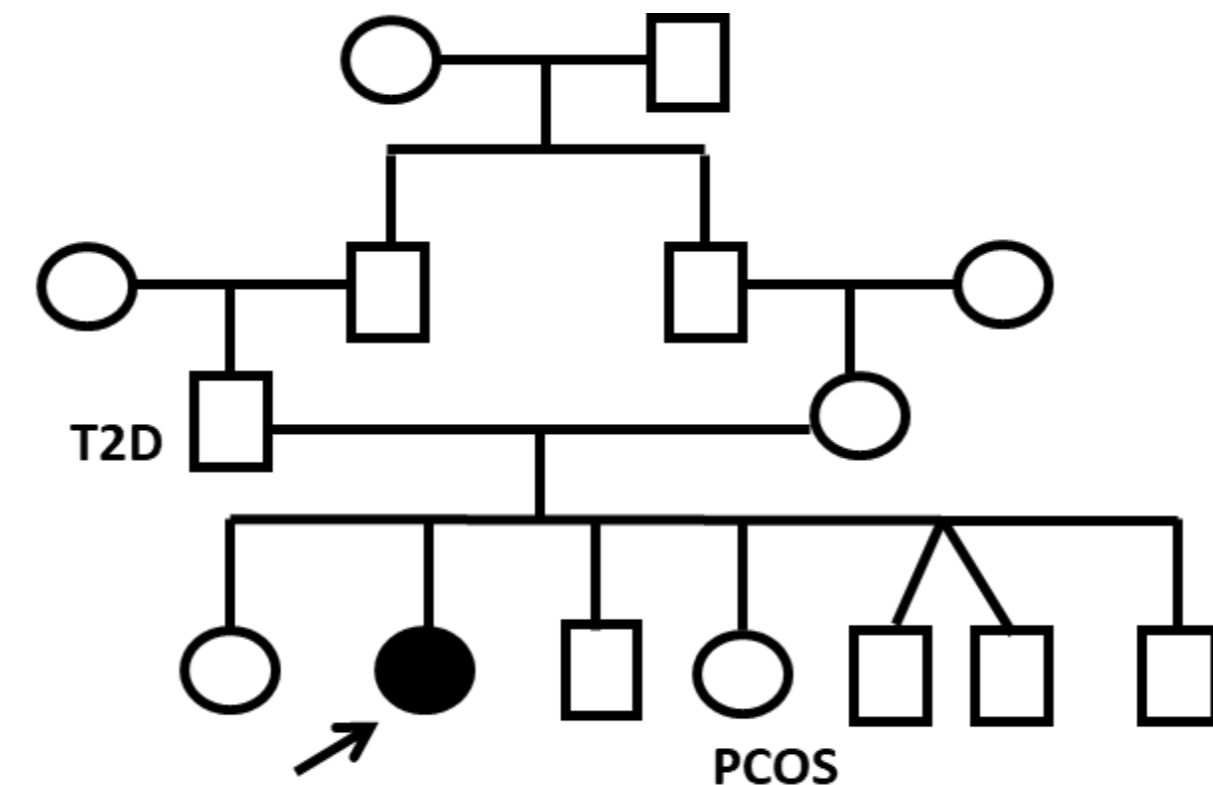
History

A woman of Pakistani origin moved to the United Kingdom aged 28 years. Aged 35 she underwent investigation for pyrexia of unknown origin; imaging demonstrated an absent uterus, and she was referred to Endocrinology.

Medical records from Pakistan had been destroyed. It was reported that she was born phenotypically female with normal female genitalia.

During her late teenage years she experienced virilisation with deepening voice, increased pubic and axillary hair, and clitoromegaly; she had absent breast development.

Her parents were first cousins and her six siblings were unaffected.



The patient reports that original investigations demonstrated a high testosterone and 'small ovaries and uterus'. She underwent the removal of a structure to her right labia majora as well as removal of a 'rudimentary uterus'. There was no surgery to the clitoris. Following surgery she did not receive ongoing medical care.

She had a socially difficult adolescence. At the time of virilisation she started to dress as a male. Following the surgery she identified as female. Due to gender identity issues she dropped out of university and a proposed marriage was broken off due to fertility concerns. She moved to the United Kingdom to resume her studies.

Examination

As an adult her examination demonstrated:

- BMI 36kg/m²
- Minimal facial, pubic and axillary hair
- Minimal breast tissue
- Blind-ending vagina, clitoromegaly, and minimal breast tissue

Pelvic imaging confirmed absence of internal genitalia. Hormonal evaluation revealed primary hypogonadism.

Assay	Result	Normal range (M)	Normal range (F)
Testosterone (nmol/L)	1.5	8.4-28.7	0.5-2.6
SHBG (nmol/L)	77.4	13-71	18-114
Androstenedione (nmol/L)	2.7	2.6-7	3-9.6
Oestradiol (pmol/L)	<4.5	0-191	17-1470
LH (U/L)	14.9	3-8	3-16
FSH (U/L)	50.4	1.4-18.1	0.5-33
17-hydroxyprogesterone (nmol/L)	<1.0	1-8.7	<18
Prolactin (mU/L)	63	45-375	60-620
TSH (mU/L)	2.51	0.35-5.5	0.35-5.5
IGF-1 (nmol/L)	23	14-47	14-47
Cortisol (nmol/L)	136	180-620	180-620

Investigations

Chromosomal analysis demonstrated a 46 XY karyotype.

Urinary steroid profile indicated 5alpha-reductase deficiency with diagnostically low levels of the 5alpha-reduced metabolites relative to their 5beta-reduced counterparts.

Steroid (ug/L)	Result	Mean	Standard Deviation
Androsterone	194	1526	520
Aetiocholanolone	3124	1308	565
DHA	1442	808	469
11-oxo Aetiocholanolone	482	625	329
11-betahydroxy Androsterone	100	855	244
11-betahydroxy Aetiocholanone	518	545	496
16-alphahydroxy DHA	3172	457	509
Androstenetriol	2868	635	495
Tetrahydrocortisone	4505	3137	1283
Tetrahydro-11-dehydrocorticosterone	65	284	187
Tetrahydrocorticosterone	238	208	100
Allo-tetrahydrocorticosterone	110	323	122
Tetrahydrocortisol	1615	1275	481
Allo-tetrahydrocortisol	3	1205	509

Investigations

The SRD5A2 gene, which encodes 5alpha-reductase, lies on chromosome 2p23. This was sequenced and screened for large scale deletions/duplications. A homozygous point mutation for c.698+1G>T at the exon 4/intron 4 boundary was found.

Outcome

The patient elected to carry on living as a female and received psychological support.

She completed her studies in the United Kingdom and has continued her career in this country.

She was commenced on low dose ethinyloestrodial which has increased her energy levels and led to breast development.

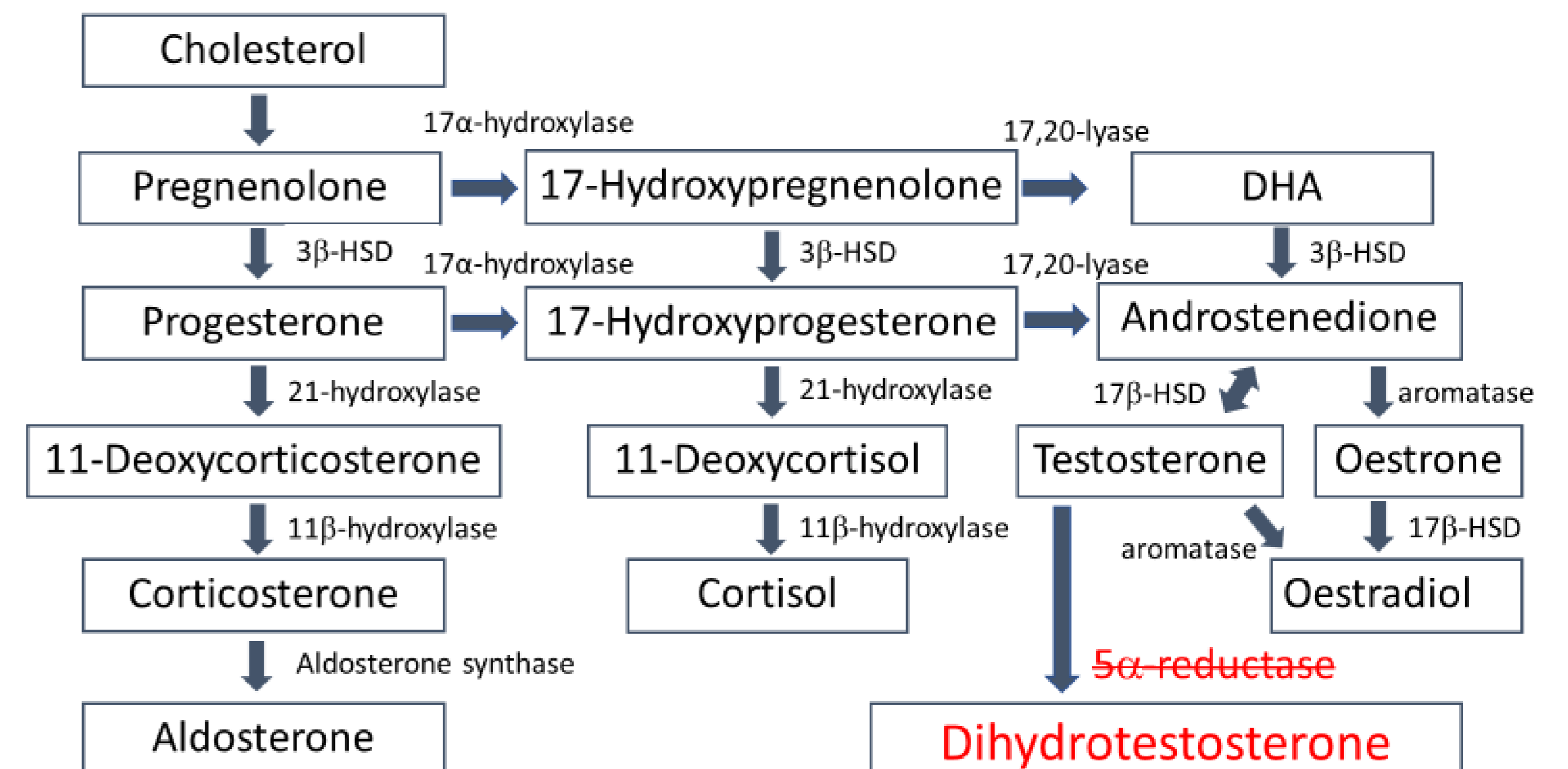
She has been offered a vaginoplasty but has turned this down.

Discussion

Disorders of sexual development can present in a wide spectrum of presentations attributable to a number of disorders; commonly patients present with atypical genitalia at birth or during sexual development in adolescence(1). Presentation in adulthood and following gonadectomy is unusual(2).

Once the 46 XY karyotype was established, differentiating between the key differential diagnoses of 17beta-hydroxysteroid deficiency, 5alpha-reductase deficiency and partial androgen insensitivity was challenging due to the primary hypogonadism. A urinary steroid profile was required to distinguish between the differential diagnoses and guide genetic sequencing.

5alpha-reductase deficiency is a rare disorder of sexual development(3). The condition is usually autosomal recessive, as in this case, but can be compound heterozygous(4). 5alpha-reductase is responsible for the conversion of testosterone to the potent metabolite dihydrotestosterone, and deficiency leads to reduced virilisation of the male foetus. The phenotype of the external genitalia ranges widely, but female external genitalia, as in this case, is rare(2).



In patients with 5alpha-reductase deficiency, who are raised as female, it is reported that 56-63% change gender role to male (3); this was considered by the patient in this case. This patient experienced social and psychological challenges due her condition; this is replicated in studies which demonstrate high levels of stress and anxiety but these suggest an early diagnosis may improve psychosocial outcomes and this is reflected in management guidelines (1,5).

References

- Ahmed SF, Achermann JC, Arlt W, Balen A, Conway G, Edwards Z, et al. Society for Endocrinology UK guidance on the initial evaluation of an infant or an adolescent with a suspected disorder of sex development (Revised 2015). Clin Endocrinol (Oxf). 2015 Aug 13;84(5):771-88.
- Maimoun L, Philibert P, Cammas B, Audran F, Bouchard P, Fenichel P, et al. Phenotypical, Biological, and Molecular Heterogeneity of 5α-Reductase Deficiency: An Extensive International Experience of 55 Patients. J Clin Endocrinol Metab. 2011 Feb 1;96(2):296-307.
- Cohen-Kettenis PT. Gender Change in 46,XY Persons with 5α-Reductase-2 Deficiency and 17β-Hydroxysteroid Dehydrogenase-3 Deficiency. Arch Sex Behav. 2005;34(4):399-410.
- Thigpen AE, Davis DL, Milatovich A, Mendonca BB, Imperato-McGinley J, Griffin JE, et al. Molecular genetics of steroid 5 alpha-reductase 2 deficiency. J Clin Invest. 1992 Sep 1;90(3):799-809.
- D'Alborton F, Assante MT, Foresti M, Balsamo A, Bertelloni S, Dati E, et al. Quality of Life and Psychological Adjustment of Women Living with 46,XY Differences of Sex Development. J Sex Med. 2015 Jun;12(6):1440-9.