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A rare case of sex reversal during puberty

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Background:

Disorders of sexual development (DSD) are rare and, in particular in developed countries, they are predominantly diagnosed during early childhood. DSD show a wide variety of phenotypes and can be difficult to classify.

Clinical Case:

A 34-year-old refugee from Somalia was referred because of a suspected DSD. Due to ambiguous, but predominantly female external genitalia at birth he was classified and raised as a girl in Somalia, whereas his subjective gender identity has always been male. Puberty led to a significant virilization of the body but only to a very limited virilization of the external genitalia. The patient presented himself with an undoubtedly male-type body composition, a deep voice, an adequate androgenic hair distribution, ongoing androgenetic alopecia and no gynecomastia. External genitalia were ambiguous, but now predominantly male with micropenis and hypospadia glandis [fig1]. Small testes could be palpated in both labia, between which a small perineal orifice appeared.

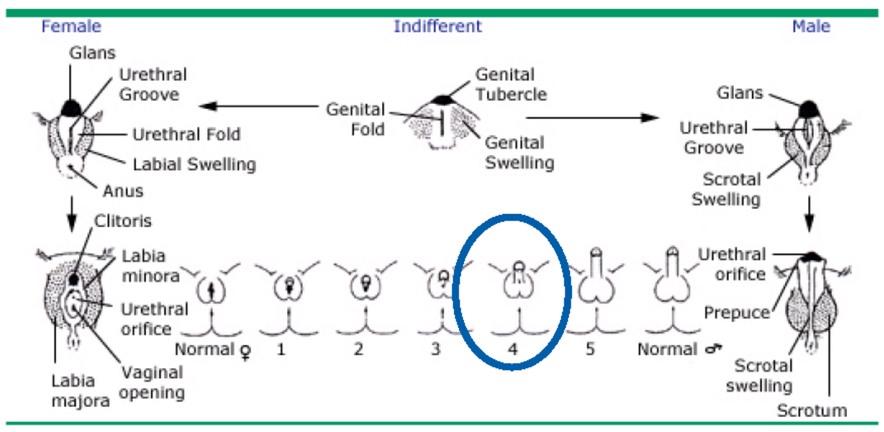

Fig 1: Prader`s classification of grades of genital ambiguity (4); patient`s finding marked by circle

Diagnostic laparoscopy did not show any female internal genitalia. Sex hormones lay within normal male ranges: LH 8.4 mE/ml (n 1.7-8.6), FSH 7.1 mE/ml (n 1.5-12.4), testosterone (T) 704 ng/dl (n 249-836), dihydrotestosterone (DHT) 13.3 ng/dl (n 10-60), DHEAS 214.8 µg/dl (n 160-449), androstenedione 3 ng/ml (n 1.23-3.75). Estradiol level was borderline elevated (54 pg/ml, n 27.1-52.2), whereas Müllerian inhibiting hormone was remarkably increased (35.48 ng/ml, n 1.5-4.3) [table 1]. Chromosome analysis showed a regular male karyotype 46,XY.ishYp11.3(SRY+) [fig2]. Highly increased T/DHT-ratio of 54 (n 8-16) [fig 3] in combination with the masculinization defect strictly limited to external genitalia without gynecomastia led to the clinical diagnosis of steroid 5 alpha-reductase 2 deficiency (SRD).

	Results	normal range
LH	8.4 mE/ml	1.7 - 8.6
FSH	7.1 mE/ml	1.5 – 12.4
Testosterone (T)	704 ng/dl	249- 836
Dihydrotestosterone (DHT)	13.3 ng/dl	10 – 60
DHEAS	214.8 µg/dl	160 - 449
T/DHT ratio	**54**	**8 - 16**
Androstenedione	3 ng/ml	1.23 – 3.75
Estradiol	**54 pg/ml**	**27.1 – 52.2**
Müllerian inhibiting hormone	**35.48 ng/ml**	**1.5 – 4.3**

Table 1: hormone levels

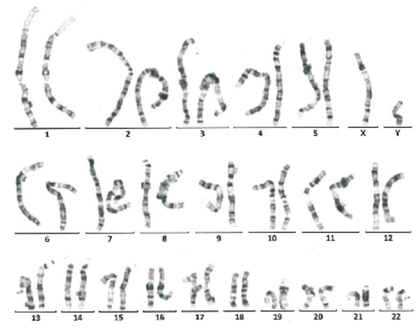

Fig 2: karyogram

SRD is an autosomal recessive, 46, XY disorder of sexual development leading to an impaired virilization during embryogenesis due to defective conversion of T to DHT, which as the most potent androgen is essential for full masculinization of the external genitalia. In affected subjects, 5-alpha-reductase activity is reduced in genital skin fibroblasts. Clinical presentation is highly variable from almost entirely female to almost entirely male external genitalia. (1, 2) Pubertal increase in T can be sufficient for virilization of the remainder body at the time of expected puberty as seen in our patient. Consanguinity of patient`s parents suggests a homozygous mutation in the SRD5A2 gene and a molecular genetic analysis is ongoing in order to identify the mutation. Over 50 different mutations have been described in the past (3).

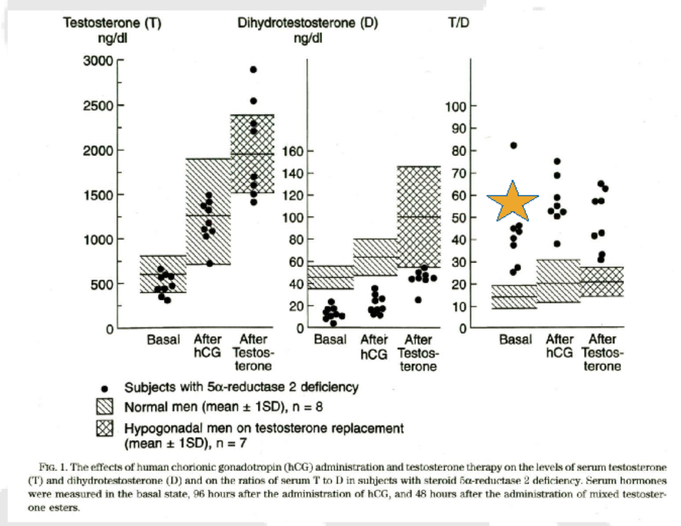

FIG. 1. The effects of human chorionic gonadotropin (hCG) administration and testosterone therapy on the levels of serum testosterone (T) and dihydrotestosterone (D) and on the ratios of serum T to D in subjects with steroid 5α-reductase 2 deficiency. Serum hormones were measured in the basal state, 96 hours after the administration of hCG, and 48 hours after the administration of mixed testosterone esters.

Fig 3: remarkably elevated T/DHT-ratio in patients with 5a-reductase 2 deficiency (5); patient`s findings added as ★

Conclusions:

This case of a rare DSD elucidates impressively how an enzyme deficiency affects the mechanisms of androgen action in the process of sexual differentiation.

References:

(1) Sinnecker GH et al. Phenotypic classification of male pseudohermaphroditism due to steroid 5 alpha-reductase 2 deficiency. Am J Genet. 1996; 63;223-230.
(2) Wilson JD et al. Steroid 5 Alpha-Reductase 2 Deficiency. Endocr. Rev. 1993;14;577-93.
(3) The Human Gene Mutation Database at the Institute of Medical Genetics in Cardiff.
4) White PC, Speiser PW. Congenital adrenal hyperpasia due to 21-hydroxylase deficiency. Endocr Rev. 2000; 21:245-291.www.hgmd.cf.ac.uk/ac/index.php
(5) Mendonca BB et al. Male Pseudohermaphroditism Due to Steroid 5a-Reductase 2 Deficiency. Medicine (Baltimore). 1996 Mar;75):64-76.