„Female“, „Male“, or „Between“ in a 46, XY-Patient with a 17ß-HSD3-Mutation

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Disclosure statement: nothing to declare

Introduction

Our 46,XY patient, Alexandra , was born with an ambiguous external genetalia in 1980. The child was assumed to suffer from androgen insensitivity syndrome or from gonadal dysgenesis. It was raised as a female following gender adjusting operations.
But she started to feel as a male after induction of female puberty. Grown up she wanted to be addressed as Alexandrao to express her feeling to be „between“.
This year, at the age of 35 years, the diagnosis of *17ß-HSD3*-mutation could be established in Luebeck (O. Hiort et al.).
name was changed for subject protection

Case Presentation

birth: Alexandra was born to a healthy mother (19 yrs.), length 51 cm, weight 3 kg
Mother and father (both of German origin) were addicted to alcohol.
Ambiguous external genitalia (Sinnecker 4) with a phallus of 1,5 cm , gonades palpable in the upper labia majora and in the inguinal canal, respectively.
1 yr: genitographic studies: short vagina (1 cm), no uterus, no Fallopian tubes.
Chromosomes: 46,XY.
2 yrs: HCG-stimulation: testostone increased from 0,55 up to 1,24 nmol, no DHT.
5 yrs: Gonadectomy was performed to rule out gonadal dysgenesis: normal testes.
6 yrs: Incomplete androgen insensitivity syndrome was assumed; phallus reduction-operation (glans saving, but insensitive) to raise the child as a girl.
14yrs: Estrogene/gestagene-therapy was started to induce female puberty with breast development (T4), pubic hair (T3). - But no phallic enlargement could occur after phallectomy and gonadectomy. The glans turned out to be insensitive with the exception of a small area.
25yrs: no female identification, more and more feeling as a male.
34yrs: self-medication with testosterone-gel, afraid of inducing prostate-cancer.
35yrs: MRI of inner genitalia: no prostate gland, but seminal vesicle present.
Molecular diagnosis (Hiort): homozygote *17ß-HSD3*-splice site mutation.
Alexandrao is undecided wether to live as a woman or as a man or to remain inbetween.

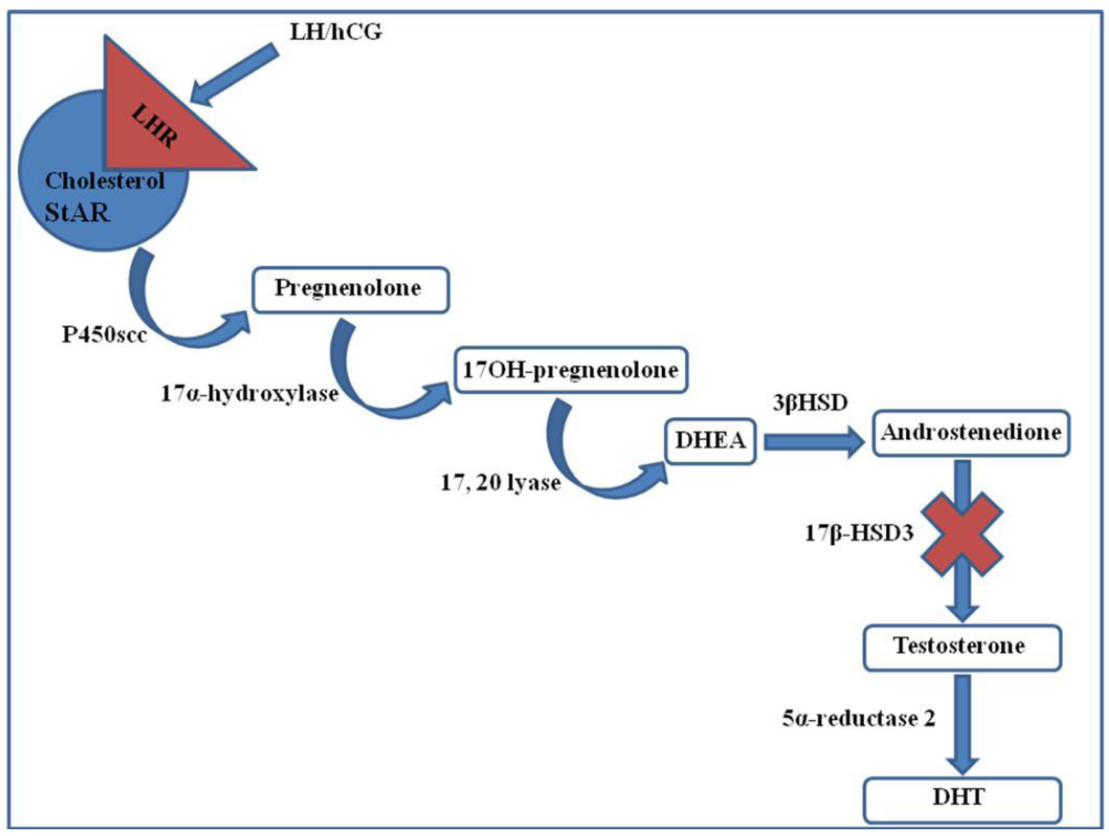
Clinical Findings

external genitalia: Sinnecker 4
phallus 1,5 cm
labia majora (palpable gonades = testes)
no labia minora
hypospadia (such as sinus urogenitalis)
short vagina 1,0 cm
internal genitalia: no Muellerian structures
no upper vagina
no uterus
no Fallopian tubes
no ovaries
no prostate gland
seminal vesicle in situ
chromosomes: 46, XY
HCG-Test: testosterone increase from 0,55 to 1,24 nmol
DHT under detection limit
gonadectomy (normal testes, no Leydig-cells)
phallus reduction, glans saving (mostly insensitive)
breast development
molecular genetics: *17HSD3*- splice site mutation, homozygote

Background

17beta-Hydroxysteroid-Dehydrogenase-3- (= 17-Ketosteroid-Reductase) – deficiency is a rare cause of 46,XY – DSD. The frequency of the disease was estimated to be 1:147.000 in a Dutch nation wide stydy (Boehmer et al), more frequent in the Arab population (Roesler and Kohn). 17ß-HSD3-deficiency is an inheritated autosomal recessive disorder.
It is generated by mutations at q22.32 on chromosome 9. At least 27 iso-enzymes are known (Galdiero et al). Type 3 has its main activity in testiular steroidogenesis converting androstenedion to testosterone and DHT (see Figure 1). Lack of androgens is the reason for the undervirilization of external genitalia in genetic male patients with 17ß-HSD3-deficiency. Isoenzymes or restfunctions of dehydrogenase 3 stimulate testicular testosterone production or peripheral conversion of testosterone during puberty (George et al). XY-patients raised as females notice enlargement of their („clitoris“) penis. Up to 64 % (Cohen-Kettenis) change their social gender from female to male according to their chromosomal and their gonadal status.

Figure 1: 17ß-HSD3-deficiency blocks the conversion from androstendion to testosterone (fig. taken from M F Faienza and L Cavallo, 2012)



Conclusion

The 46,XY-patient was raised as a female. Due to prior gonadectomy and phallectomy (30 years ago) she could not go through male puberty with virilization and phallic enlargement.
We know by the recently established diagnosis of *17ß-HSD3*-mutation that a male shift occurs in untouched subjects with this diagnosis. More than 50 % of female raised patients prefer to live as males after puberty. Our patient is not content with her or his gender assignment and tries to live inbetween.

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ESPE 2015 791--P3
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Rolf Peter Willig
DOI: 10.3252/pso.eu.54espe.2015
Poster presented at: 54th Annual Meeting 1-3 October ESPE 2015 BARCELONA European Society for Paediatric Endocrinology
PosterSessionOnline.com