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

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Introduction
Our 46,XY patient, Alexandra, was born with an ambiguous external genitalia 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 more like a male after induction of female puberty. Grown up she wanted to be addressed as Alexandra to express her feeling to be „between“ this year, at the age of 35 years, the diagnosis of 17β-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 (Sinncke1r 4) with a phallus of 1,5 cm, gonadale 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: testosterone 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.

14 yrs.: 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.

25 yrs.: no female identification, more and more feeling as a male.

34 yrs.: self-medication with testosterone-gel, afraid of inducing prostate-cancer.

35 yrs.: MRI of inner genitalia: no prostate gland, but seminal vesicle present.

Molecular diagnosis (Hiort): homozygote 17β-HSD3 splice site mutation. Alexandra is undecided whether 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 gonadale – testes)

no labia minora

hypospadia (such as sinus urogenitalis)

short vagina 1,0 cm

internal genitalia: no Mullerian structures

no upper vagina

no uterus

no Fallopian tubes

no ovaries

no prostate gland

semenal 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

17β-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 study (Boehmer et al.), more frequent in the Arab population (Roosler and Kohn). 17β-HSD3-deficiency is an inherited 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 testisular steroidogenesis converting androstenedione to testosterone and DHT (see Figure 1). Lack of androgens is the reason for the undervitrification of external genitalia in genetic male patients with 17β-HSD3-deficiency. Isoenzymes or restructitions 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: 17β-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 phalllectomy (30 years ago) she could not go through male puberty with virilization and phallic enlargement.

We know by the recently established diagnosis of 17β-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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