46,XY Siblings With 5α-Reductase Deficiency with Different Gender of Rearing: Adult Follow-up

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Topic: Gonads and Disorders of Sex Development

Introduction

- Stability of gender identity (GI) depends on an interaction among multiple biological and psychological factors.
  - 1950's: theory of psychosexual neutrality at birth (J. Money).
  - 1990's: theory challenged – biological (hormonal) factors exert effects on psychosexual differentiation.
- Individuals with DSD resulting from errors in androgen biosynthesis (eg, 5α-reductase deficiency (5-ARD), 17β-hydroxysteroid dehydrogenase-3 deficiency), reared as girls, exhibit high rates of GI instability (56–63%[1]).
- 2006 and 2016: DSD Consensus Statement[2] and Update[3], male gender assignment recommended for 5-ARD.
- 2011: Out of 55 patients with documented 5-ARD, 40 were initially reared female, of whom only 5 transitioned[4].
- Change in GI in patients having undergone prepubertal gonadectomy has not been documented.
- This report examines GI in siblings with 5-ARD: one reared as a girl, the other as a boy, because of differing degrees of genital masculinization.

Hypothesis

- Prepubertal orchidectomy reduces the likelihood of gender self-reassignment in patients reared female.

Methods

- Review of medical records.
- With ethics committee approval, letter sent *separately* to the two patients, the mother and the father, requesting their participation in a follow-up study of gender-related behavior, psychosexual adaptation, and general psychosocial adaptation.
- So far, only the mother has agreed to be interviewed, father has refused and patients have not replied.

Results

Patients (chronology)

- Sib 1: Typical female external genitalia, but bilaterally palpable gonads. No uterus on ultrasound. 46,XY karyotype. During hernia repair, both gonads were biopsied, and histology showed normal testicular tissue, leading to presumptive diagnosis of Complete Androgen Insensitivity syndrome and a female gender of rearing.
- Sib 2: Microphallus with ventral curvature, proximal hypospadias, bilaterally palpable gonads. No uterus on ultrasound. 46,XY karyotype. Testosterone enanthate im (50 mg, then 100 mg), resulted in phallic size of 3.0 x 1.4 cm. Male gender of rearing.
- Due to Sib 2's phenotype, Sib 1's diagnosis was revised (partial AIS), followed by orchidectomy (age 5) and estrogen replacement (age 11). Clitoral length estimated 2.5 cm, vaginal depth 3 cm (15 y 10 mos); urogenital sinus was mobilized, but clitoral surgery deferred.
- Sib 2 underwent two surgeries for hypospadias repair (5 and 18 mos) Spontaneous puberty beginning age 11.
- Ages 16 and 13: genetic testing revealed compound heterozygosity for mutations in SRD5A2 for both sibs (patients #50-51 in ref [4]).
- Age 22: Sib 1 reported satisfactory peno-vaginal intercourse.
- Age 18: Sib 2 was G5P5 (penis 8 x 2 cm).
- Age 18: both sibs were fully informed of their genetic diagnosis.
- Ages 28 and 25: both sibs living in a heterosexual relationship, without apparent gender dysphoria.

Interview with Mother

Sib 1 (girl/woman)

- Age 3: imitated her mother by pretending to breastfeed a stuffed animal.
- Pre-school through primary school: described as tomboy and disliked typical feminine activities. Interests revolved around animals and nature, dinosaurs, playmobiles, role playing in the middle ages as a warrior. Friends predominantly male. Never stated she was a boy, nor expressed desire to be a boy, to want a penis, or to pee standing-up.
- Teenage years: became interested in boys and had a few boyfriends. Expressed dissatisfaction with insufficent breast development despite estrogen replacement; experienced depressed mood, feelings of hopelessness and passive suicidal ideation; became more socially isolated and had limited friends. Saw a therapist, but refused follow-up. Completed junior college.
- Age ~19-20: experienced homosexual relationship (lasting a few months) followed by heterosexual relationship lasting years.
- Currently: described as being strong, but has few friends. Mother stated "(she) would not be surprised if (her daughter) ever decided to change her gender to male, although she has never expressed this to (her)." Discontinued hormone replacement therapy because of negative effects on her mood.

Sib 2 (boy/man)

- Early childhood: similar interests for games (such as the outdoors, playmobiles,…) as sibling 1 and siblings played together.
- High school: Experienced bullying and difficulty making friends (causes unknown), but did experience neither depressed mood nor suicidal ideation like sibling 1.
- Currently: described as gentle and kind, introverted, a dreamer who had his head in the clouds; has a stable job, is in a long-term heterosexual relationship and is talking about starting a family.

Both siblings have recently agreed to complete standardized questionnaires focusing on gender development and general psychosocial adaptation.

Conclusions

- Comprehensive assessment (including genetic diagnosis) should ideally precede gender assignment.
- Variability in 5-ARD genotype-phenotype associations (even within a sibship) suggests gender assignment should not solely be based on genetics.
- As genetic diagnosis will become more rapidly available in the near future, a genetic diagnosis should not overrule the examination of the external genitalia.
- Prepubertal orchidectomy in those reared female is a viable option.
- Full disclosure and sustained engagement with the family during the pediatric years, and with patients when adults, are believed to be key elements to positive psychological outcomes. However, the prognosis for mood, social relations and eventual gender dysphoria seems to be more guarded for sibling 1.

References

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