5α-Reductase-2 deficiency: is gender assignment recommended in infancy? Two case-reports and review of the literature

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BRIEF REPORT

5α-Reductase-2 deficiency: is gender assignment recommended in infancy? Two case-reports and review of the literature

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Abstract

Purpose Gender assignment represents one of the most controversial aspects of the clinical management of individuals with Differences of Sex Development, including 5α-Reductase-2 deficiency (SRD5A2). Given the predominant female appearance of external genitalia in individuals with SRD5A2 deficiency, most of them were assigned to the female sex at birth. However, in the last years the high rate of gender role shift from female to male led to recommend a male gender assignment.

Methods We here describe two cases of subjects with SRD5A2 deficiency assigned as females at birth, reporting their clinical histories and psychometric evaluations (Body Uneasiness Test, Utrecht Gender Dysphoria Scale, Bem Sex-Role Inventory, Female Sexual Distress Scale Revised, visual analogue scale for gender identity and sexual orientation) performed at the time of referral at the Florence Gender Clinic.

Results Both patients underwent early surgical interventions without being included in the decision-making process. They had to conform to a binary feminine gender role because of social/familiar pressure, with a significant impact on their psychological well-being. Psychometric evaluations identified clinically significant body uneasiness and gender incongruence in both subjects. No sexually related distress and undifferentiated gender role resulted in the first subject and sexually related distress and androgynous gender role resulted in the second subject.

Conclusions The reported cases suggest the possibility to consider a new approach for gender assignment in these individuals, involving them directly in the decision-making process and allowing them to explore their gender identity, also with the help of GnRH analogues to delay pubertal modifications.

Keywords Differences of sex development · Gender assignment · GnRH analogues · 5alpha reductase-2 deficiency

Introduction

Steroid 5α-Reductase-2 (SRD5A2) deficiency is an autosomal-recessive form of 46,XY Differences of Sex Development (DSD) [1, 2] caused by pathogenetic variants in the SRD5A2 gene located on chromosome 2p23.1 [3, 4]. This gene encodes the enzyme that converts testosterone (T) into the more active metabolite dihydrotestosterone (DHT) [3, 5]. The impaired activity of this enzyme results in variable impairment of DHT synthesis, depending on its residual activity. During foetal development, DHT is required for the male virilization of the external genitalia; then, DHT drives the development of male secondary sexual characteristics at puberty [6]. The phenotype of affected newborns may significantly differ on the basis of the enzyme activity within a wide spectrum of manifestations, ranging from almost female external genitalia to undervirilized male genitalia, including penile hypospadias and isolated micropenis [3, 6]. Due to normal anti-müllerian hormone (AMH) and T levels during prenatal period, individuals with SRD5A2 deficiency are characterized by the absence of müllerian structures and by the presence of male internal reproductive structures, with testes usually located in the inguinal or labioscrotal region [3, 7–10].

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The biochemical pattern is characterized by a normal-to-high male serum concentrations of T, low or low normal concentrations of DHT and increased T/DHT ratio [3]. However, this pattern may be equivocal and its interpretation is not always easy, especially in individuals with partial enzyme deficiency. In these cases, direct genetic testing of the SRD5A2 gene may represent a useful approach to confirm diagnosis [11].

Regarding gender assignment at birth, several individuals are raised as girls at least in Western countries, since ambiguous genitalia and clitoromegaly represent the most frequent genital phenotype in affected newborns [12]. However, virilization occurs at puberty in the form of deepening of the voice, substantial growth of the phallus, rugation, and hyperpigmentation of the scrotum, as well as increased muscle mass, resulting from the residual enzyme activity of SRD5A2 or the action of SRD5 type 1 enzyme stimulated by the increasing concentration of T [7, 10]. Among persons assigned to female sex, in adolescence or young adulthood is reported a high rate (56–63%) of gender role switch from female to male [13].

We here describe two persons with SRD5A2 deficiency assigned to female sex at birth, reporting their clinical histories and psychometric evaluations assessed at the time of the referral to our clinic. They both underwent early surgical interventions to "normalize" external genitalia under parental and health professional's recommendation. They discovered their true condition only in late adolescence-adulthood and were not included in the decision-making process, resulting in significant impact on their psychological well-being. We asked these patients to complete different psychometric questionnaires, including the Body Uneasiness Test (BUT) [14], the Utrecht Gender Dysphoria Scale (Utrecht GD) [15] and the Bem Sex-Role Inventory (BSRI) [16] to assess body uneasiness, gender dysphoria and gender role, respectively. In addition, sexually related distress was measured by the Female Sexual Distress Scale Revised (FSDS-R) [17]. Finally, a visual analogue scale (VAS) for gender identity and sexual orientation was used, to dimensionally assess these dimensions [18]. The VAS gender identification with the opposite genotypic sex ranges from 0 when the subject has an absolute identification with the opposite genotypic sex to 10 when the identification was with their own genotypic sex. The VAS for sexual attraction towards men or women rates 0, 10 and >0 and <10 when the subject has a homosexual, heterosexual or bisexual sexual orientation, respectively.

The study protocol was approved by the Institution's Ethics Committee and patients have provided their informed consent.

Patients and methods

Case 1- (S.)

S. was born in 1977 from non-consanguineous parents without family history of ambiguous genitalia or atypical sexual development. She was assigned female at birth based on apparently female external genitalia. At the age of 2 months, physical examination showed clitoral and labia majora hypertrophy and ectopic external urethral meatus. Bilateral palpable testes were located in the inguinal region, descending at the level of labioscrotal folds. The karyotype analysis confirmed a normal 46,XY chromosomal pattern and uretrovaginography revealed a 2 cm deep blind-ending vaginal duct. At that time, a diagnosis of androgen insensitivity syndrome was formulated. Informed of possible risks derived from potential gonadal malignancy, parents decided to confirm female gender assignment. At the age of five, S. underwent bilateral gonadectomy, clitoroplasty and vulvoplasty with removal of cavernous bodies. During her childhood years, the mother pressed S. to conform to a rigidly "feminine" gender role: this implied, for example, not allowing the daughter to show interest in sports or hobbies that were considered "too masculine". The patient started oestrogen replacement treatment when she was 12 years old.

She underwent the last surgery (colonvaginoplasty) in 1996, when she was 19 years old; during her first sexual intercourse, she had experienced pain, and, only then, she was informed on her condition and the opportunity to create a deep-enough vagina.

The truth about her being intersex brought about a lot of resentfulness towards her parents, and also towards the surgeon who operated on her.

S. found out that, over the years, the father had collected a lot of information about her condition, but he never talked to her openly.

Deep feelings of shame, a vague sense of "uneasiness" she had experienced all her life, and the family's secrecy over her condition led her to try cocaine until she got addicted. Cocaine was also used to make sexual intercourses with male partners less painful at to feel more at ease in her sexual role.

She showed severe impulsivity (which, besides drug use, led her to binge eating and shoplifting), till she finally decided to enter a therapeutic community where she was treated with psychotherapy and psychiatric care.

When S. was 30 years old, a SRD5A2 sequencing revealed a compound heterozygosis for two variants (p.A207D in exon 4 and p.Y235F in exon 5). No mutations were found in the androgen receptor gene. At the time of the referral to our clinic, the patient was 40 and

was no longer taking oestrogen replacement treatment and physical examination revealed a Ferriman Gallwey score 0 [19], normoconformated labia and a hypo-represented clitoris due to early surgery.

Psychometric evaluations completed at the time of the referral showed high levels of body uneasiness (BUT-Global Severity Index 1.91) and the absence of sexually related distress (FSDS score 0). The patient scored 42/60 at the Utrecht Gender Dysphoria Scale. Visual analogue scale for gender identity and sexual orientation resulted in gender variant identity and bisexual orientation (5.1 and 5.4 cm respectively). Concerning gender role (BSRI), the patient scored 2.90 on masculinity and 3.80 on femininity scores, resulting in undifferentiated gender role.

Case 2-(M.)

M. was born from a Caucasian non-consanguineous couple and was assigned to female sex at birth despite physical examination revealed ambiguous genitalia with separate vaginal and urethral openings, as well as clitoromegaly. At the age of 12, M. experienced pubertal changes characterized by deepening of voice, body hair growth and increase of the clitoris size with the absence of breast development. Ultrasound imaging identified the presence of testes in the inguinal region. At that time, an hCG stimulation test was performed according to standard protocols (2000 IU/i.m. daily for 3 consecutive days with sampling at days 0, 3 and 5). The peak testosterone/DHT ratio suggested SRD5A2 deficiency (22), considering a cut-off value of 10 [10, 20]. However, the patient received a diagnosis of androgen insensitivity syndrome. Given the external genital phenotype, physicians recommended a female sex assignment and bilateral removal of gonads, according to the parents' preference. At the age of 13, gonadectomy and vaginoplasty were performed. Increasing doses of oestrogens were started to induce female puberty and then progestogens were added. Probably the patient also underwent clitoroplasty, but no medical records of the latter surgical correction are available. Histological analysis on the removed testes excluded evidences of malignancy.

Like S., during her adolescence, M. was constantly pressed to conform to a rigidly "feminine" gender role. In addition, she was asked to "control" her voice while in public, to avoid embarrassing situations for the family.

At the age of 20, M. discovered her intersex condition, after finding her medical records hidden by parents. She feels anger towards her family and healthcare providers, who kept this condition secret until adulthood, excluding her from the decision-making process.

Shame for her body (i.e. her height, clitoris size and deep voice) was an issue for her all her life, and had a significant impact on her relational and sexual well-being.

At the time of the referral to our clinic, the patient was 42 and she was taking oestrogen/progestin replacement hormone therapy. Physical examination revealed Ferriman Gallwey score 3 [19], normoconformated labia and clitoris length of 5.4 cm with a diameter of 1.6 cm [21]. SRD5A2 deficiency was considered during the diagnostic process and SRD5A2 was sequenced revealing the presence of heterozygous pathogenic variants in SRD5A2 gene (p.Gly183Ser and p.Leu111Hisfs*24), already reported in the literature [22, 23]. No duplications/deletions of genes DMRT1 (doublesex and mab-3 related transcription factor 1), CYP17A1 (cytochrome P450 family 17 subfamily A member 1), SRD5A2 and HSD17B3 (hydroxysteroid 17-beta dehydrogenase 3) were identified.

Psychometric evaluations identified the presence of a clinically significant body uneasiness (BUT GSI 1.65), sexually related distress (FSDS total score 25) and an androgynous gender role (BSRI scores 4.80 on masculinity and 5.30 on femininity). The patient scored 34/60 at the Utrecht Gender Dysphoria Scale. Visual analogue scale for gender identity and sexual orientation rated 2.4 and 3.2 cm, respectively.

Discussion

Gender assignment represents one of the most critical aspects in the clinical management of newborns with DSD diagnosis. As DSD are a rare condition, in the literature very few studies explored outcomes regarding gender identity, gender role identification and sexual orientation in this population [24–32]. Common beliefs concerning gender assignment in DSD individuals have deeply changed in the last years [33]. In the past, Money [34] postulated the "optimal gender policy", based on the idea that gender identity was completely neutral at birth and developed only in the postnatal period with the influence of social, familiar and cultural factors. According to this theory, if a child with an intersex condition was raised without gender ambiguity supported by hormonal treatment at puberty and early surgical interventions, gender identity was expected to develop in line with the assigned sex. This approach did not contemplate the patient's participation in the decision-making process and parents were advised not to discuss the intersex state with their child, keeping the condition in secret [35], as here reported. This approach led to early gender assignments and surgical corrections of atypical genitalia according to assigned sex. In fact, gender assignment was mainly based on expected surgical outcomes and aimed "to normalize" the ambiguous genitalia, allowing an adequate sexual functioning in late adolescence/adulthood. Since most newborns with SRD5A2 deficiency present with female appearance of external genitalia, they were usually assigned to female sex at birth and raised as girls to ensure a proper sexual

functioning. However, as in Case 2, female gender assignment at birth does not necessarily lead to a satisfying sexuality, since sexual well-being results from interactions among organic, intrapsychic and relational factors.

In recent years, the clinical management of this condition has been revolutionized by the new conception of psychosexual development, as the result of genetic, hormonal and psychosocial influences [36, 37]. This was confirmed by increasing evidences regarding high rates of gender dysphoria (56–63%) in individuals with SRD5A2 deficiency assigned as females at birth [13]. The high rate of gender role switch from female to male during puberty may be partly explained by the prenatal exposition of the brain to androgens. Other factors involved could be represented by cultural and environmental pressures, body image and body changes occurring during puberty. For this reason, nowadays male gender assignment -in line with genetic and gonadal sex—is normally recommended in individuals with SRD5A2 deficiency, despite the possibly female appearance of external genitalia at birth [1]. Other factors may explain the recommendation for male gender assignment. First of all, fertility potential became an important issue to evaluate before performing early gonadal removal [38, 39], as specific techniques of assisted reproduction could be performed in these subjects. Furthermore, new evidences showed that the gonadal cancer risk is low in those who did not undergo orchiectomy and does not seem sufficient to recommend early gonadectomy, since regular testicular evaluation could be an adequate approach [40, 41]. Finally, the past recommendation for female assignment on the basis of surgical outcomes seems to be overcome by the improvement of male reconstructive surgical techniques.

However, in line with the two cases reported here, other examples of individuals with SRD5A2 deficiency raised as females who did not experience gender dysphoria and did not decide to undergo a gender-affirming path later in life are reported in the literature [10, 13, 30, 31, 42]. This underlines the fact that male gender identity does not necessarily represent the rule in these subjects. Since the advancement of molecular technologies and the increase of knowledge about DSD among healthcare professionals have led and will lead more and more to an early diagnosis, the clinical management of these individuals should be reconsidered.

Bearing in mind that every subject with DSD is unique and should be treated with individualized care by a multidisciplinary team (including an endocrinologist, a mental health professional, surgeons, an ethicist and a geneticist), it could be appropriate to delay gender assignment at the time the person is able to explore and express his gender identity and to actively participate in the decision-making process. This applies above all to the timing of genital surgery, to avoid early irreversible surgical corrections, which represent an abuse of human rights of these persons [43]. In this perspective, families should be largely counselled regarding possible concerns about early and late gender assignment. We would like to stress the opportunity to evaluate the use of gonadotropin-releasing hormone analogues (GnRHa) in adolescents with a diagnosis of DSD. As in gender dysphoric adolescents [44], GnRHa may represent a useful approach to temporary suspend puberty, allowing to arrest pubertal body changes and preventing irreversible changes due to virilization. In fact, puberty in these adolescents may be traumatic, inducing important changes in external appearance up to the switch in the phenotypic sex. GnRHa could allow the adolescent to gain time to explore his gender identity and actively participate in the decision on gender assignment.

In conclusion, the cases presented underline the complexity of clinical management of newborns with a diagnosis of DSD particularly SRD5A2 deficiency- and the criticalities of early gender assignment in these individuals. We would like to stress the idea that current recommendations based on small evidences may not be generalizable to all patients. In our opinion, it may be time to consider a new approach for gender assignment in these patients, involving them directly in the decision-making process and allowing them to explore their gender identity, even with the help of GnRHa during adolescence.

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Compliance with ethical standards

Conflict of interest The authors have no potential conflict of interest.

Ethical approval The study protocol was approved by the Institution's Ethics Committee.

Informed consent All patients included in this study provided their informed consent.

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