preference for behavior appropriate to other sex." They also found that there was widespread ignorance of their condition among patients who had AIS [74]. They reported that these mental and counseling problems need attention.

- Preves [75] reported on extensive interviews with 37 randomly gathered intersexed adults who had various diagnoses. "At the time of interview 24% of the sample presented as a gender different from their sex of assignment and rearing; six were transitioning or had transitioned from male to female, and three from female to male."

- Wisniewski et al [45] found that 5 of 18 patients who had congenital micropenis had been reared as girls; 4 of 5 were dissatisfied with their genital appearance. Of those who were reared as boys, 50% reported satisfaction with their genitalia. All claimed to be satisfied with their sex of rearing. It is not clear, however, if these respondents were informed that there was an option as to sex of rearing and offered their response without this information.

- Schober [76] reported that of 10 intersexed individuals she interviewed, 8 identify as "intersexual" rather than as male or female; 9 have a homosexual orientation. Two of the 10 originally who were assigned as girls are undergoing transformation to male [77].

- Migeon et al [78] studied a select population of men and women who have a 46,XY karyotype but different intersex diagnoses. Five men (24%) and four women (22%) were dissatisfied with their sex of rearing.

- Migeon et al [79] found, in an examination of a population of 46,XY individuals, that 66% of those living as women and 38% of those living as men were satisfied with their knowledge of their medical and surgical history.

- Colapinto [34] reviewed Money's original thesis [80] and found that most of the intersex patients studied seemed, at that time, to be making an adequately normal adjustment within the sex of rearing without any cosmetic surgery. Money had written: "Far from manifesting psychological traumas and mental illnesses, the study showed, the majority of patients rose above their genital handicap and not only made an 'adequate adjustment' to life, but lived in a way virtually indistinguishable from people without genital difference." Thus, genital ambiguity, without surgery or medical treatment, did not pose a hindrance to a satisfactory life. Had this been publicized, a great deal of surgery could have been averted.

- Reiner [59] found from following a considerable number of children and adolescents who had cloacal exstrophy, that a significant number of males rebelled against their sex reassignment as female, and, without knowing their histories, declared themselves to be boys.

Where are we now?

Many physicians who used to sex reassign males who had traumatic early loss of their penis or were born with a micropenis, are now more likely to believe that if there were no accompanying intersex condition, such procedures would be a thing of the past [81]. The evidence indicates that past infant cosmetic surgery may not succeed; procedures exist that can provide a phallus for the affected boy should he desire one [82,83]. Surgeons also are less likely to reduce an enlarged clitoris in a girl who has CAH; many others are examining critically how the new and old research regarding intersex treatment should be evaluated [84]. Increasingly, attention from medical ethicists is being called upon for their considerations [85]. This is a marked step forward.

Two other gender-related matters pertain to psychologic management and deserve discussion. One involves dealing with homosexuality. In individuals who are diagnosed as intersexuals, considerations of sexual orientation exist at a different level. This factor deserves discussion with the adolescent. A parallel issue in management is how intersexed individuals are treated when, and if, they present for gender reassignment. Patients often complain that they are not given credit for their own feelings. The treatment that they receive is similar to that of transsexuals when they seek reassignment; they feel as if they are made to prove themselves.

Clinical advice: summary and final words

A review of some of the historic findings and controversy regarding gender-related conditions was presented with a major focus on intersex syndromes. This area is one of intense activity and transformation. Change is rapid among the intersex populations themselves. Many have come out of their closets in a way that was unheard of only a few years ago and they operate with a new degree of activism. Instead of seeing themselves as males or females, some are identifying openly as intersexed [76,86] or are willing to mix and match gender and sex. Be open to what your young patients tell you and help them probe their questions and doubts about identities and preferred behaviors.

The medical communities also are changing markedly. Physicians should be aware of the shifting attitudes and needs of their patients and be aware that one's sexual profile is complex and are not made up only of what gender typical or atypical behaviors are manifest or what type of sexual orientation is professed. One's sexual profile is a constellation of a host of factors that should be explored to get a fill appreciation of the patient's feelings and understandings [87,88]. This is not intrusive and usually will be welcomed by those patients who want their psychiatrist to be able to truly understand them.

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END NOTES

[1] Much depends upon how intersex is defined. The narrow definition holds that intersex is a condition that is marked by genital ambiguity. Obvious cases are those with congenital adrenal hyperplasia (CAH) or partial androgen insensitivity syndrome (PAIS). A broad definition includes any individual whose biology

includes an identifiable mixture of male and female characteristics, regardless of the appearance of the genitalia at birth. Examples here are persons who have the complete androgen insensitivity syndrome or Klinefelter's syndrome.

[2] The case justified such coverage because the reported success of John's reassignment to Joan had become one of the most cited clinical cases, not only in medicine but also in psychology, women's studies, political science, and other disciplines.

[3] At the AAP presentation, I introduced Cheryl Chase to physicians who were involved with intersex management. Until then, she and ISNA, using the name "Hermaphrodites with Attitude," had met with professional rejection. The previous year, ISNA had applied for an opportunity to address or meet with attendees at the AAP conference in Boston and was refused. ISNA's response was to picket in front of the meeting hall [51]. Henceforth, Ms. Chase was accepted as a representative of the intersex community.

[4] It has been conjectured that part of the difficulty in obtaining data from past treatments is that physicians would have to tell their patients aspects of their treatment that they do not want to reveal or that the patients were not told originally. For instance, researchers cannot easily question former patients on the effects of surgery done in infancy when the patients had never been informed of the surgery or that there had been other options or especially, the true reasons for it.

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Gender dysphoria associated with disorders of sex development

Paulo Sampaio Furtado, Felipe Moraes, Renata Lago, Luciana Oliveira Barros, Maria Betânia Toralles and Ubirajara Barroso Jr

Abstract | Disorders of sex development (DSDs) are estimated to be prevalent in 0.1–2% of the global population, although these figures are unlikely to adequately represent non-white patients as they are largely based on studies performed in Europe and the USA. Possible causes of DSDs include disruptions to gene expression and regulation—processes that are considered essential for the development of testes and ovaries in the embryo. Gender dysphoria generally affects between 8.5–20% of individuals with DSDs, depending on the type of DSD. Patients with simple virilizing congenital adrenal hyperplasia (CAH), as well as those with CAH and severe virilization, are less likely to have psychosexual disorders than patients with other types of DSD. Early surgery seems to be a safe option for most of these patients. Male sex assignment is an appropriate alternative in patients with Prader IV or V DSDs. Patients with 5α-reductase 2 (5α-RD2) and 17β-hydroxysteroid dehydrogenase 3 (17β-HSD3) deficiencies exhibit the highest rates of gender dysphoria (incidence of up to 63%). Disorders such as ovotesticular DSD and mixed gonadal dysgenesis are relatively rare and it can be difficult to conclusively evaluate patients with these conditions. For all DSDs, it is important that investigators and authors conform to the same nomenclature and definitions to ensure that data can be reliably analysed.

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Introduction

Over the past two decades, many studies have contributed to a better understanding of the mechanisms underlying normal and abnormal sexual differentiation. One of the most important discoveries was the identification of the sex-determining region Y (*SRY*) gene by Sinclair and collaborators in 1990.[1] Another important development in the field was the identification of oogenesis genes on chromosome 1, including wingless-type MMTV integration site family, member 4 (*WNT4*), which is involved in female foetal genital development, and R-spondin 1 (*RSPO1*), which modifies expression of *WNT4*.[2] *SRY*—which is located on the Y chromosome—modifies expression of both *WNT4* and *RSPO1*. Thus, it has been suggested by some investigators that the term 'sex chromosomes' should be replaced by the terms 'X chromosome' and 'male sex chromosome' (Y chromosome). However, presence of the SRY gene does not unequivocally determine gender. Autosomal genes—such as SRY (sex determining region Y)-box 9 (*SOX9*), fibroblast growth factor 9 (glia-activating factor; *FGF9*), Wilms tumor 1 (*WT1*), and nuclear receptor subfamily 5, group A, member 1 (*NR5A1*; also known as *SF-1*)—are also involved in this process.[3] For example, *SOX9* regulates transcription of the anti-Müllerian hormone gene and protects against autosomal sex reversal, and disruption of the *FGF9* gene has been shown to result in male-to-female sex reversal in mice, suggesting a role in testicular differentiation. To avoid confusion regarding the complex association between the sex chromosomes and the process of sexual differentiation, some authors prefer to use the term 'molecular sex' instead of 'chromosomal sex'.[4–7]

Although many important aspects of phenotypic sexual differentiation have been clarified, the phenomenon of psychosexual differentiation requires further investigation. Psychosexual development determines gender identity (whether the individual sees themselves as male or female), gender role (interest in gender-typical possessions and display of gender-typical temperaments or behaviours), and sexual orientation (desires, fantasies, and erotic attractions).[8] The criteria described in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition for gender dysphoria are desire to be the opposite gender, frequently being mistaken for the opposite gender, desire to live or be treated as the opposite gender, presence of feelings and reactions that are typical of the opposite gender, and persistent discomfort or sense of inappropriateness with current gender.[9]

The concept of prenatal psychosexual differentiation—whereby foetal exposure to androgens influences an individual's sexual behaviour and gender role—has been proposed by several research groups.[10–12] Environmental influences on sexual behaviour are well established and there is increasing evidence to suggest the importance of testosterone in foetal brain development, gender identity,

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and sexual orientation.[12,13] For example, prenatal androgenization has been shown to affect the gender-related behaviour of girls with congenital adrenal hyperplasia (CAH)—an adrenal gland disorder that results in increased androgen production. These girls are often more interested in games and clothing that are typically associated with boys.[14]

It is extremely difficult to predict the psychosexual characteristics that each individual will develop in adult life—even for children with normal genitalia at birth. The concept of normality, from the psychosexual perspective, is a matter of great complexity on which there is no clear consensus in the literature. Thus, to optimally treat psychosexual disorders such as gender dysphoria, the limited available data must be analysed with scrutiny. In this Review, we evaluate the different treatment approaches available to patients with gender dysphoria secondary to CAH and other types of DSDs.

Key points

- Although many important aspects of phenotypic sexual differentiation have been clarified, the phenomenon of psychosexual differentiation requires further investigation
- Rates of gender dysphoria generally vary from 8.5–20% in patients with disorders of sex development (DSDs)
- Patients with either simple virilizing congenital adrenal hyperplasia (CAH) or CAH and severe virilization are associated with lower incidences of psychosexual disorders than patients with other types of DSDs
- Early surgery seems to be a safe option for most individuals with DSDs
- With respect to patients with CAH, low rates of reported gender dysphoria demonstrate that assigning female gender and performing premature surgery is safe for the majority of patients
- Increased global use of the Chicago Consensus definitions and diagnostic criteria could increase the reliability of future studies

DSD-associated gender dysphoria

The role of foetal androgens on female gender identity was first investigated in 1968.[15] In the wake of this report, 18 studies have been published relating to DSDs and associated gender dysphoria.[14,16–31] From a total of 550 patients included in these studies, 458 were raised as girls and 92 were raised as boys. Just over a quarter of all patients ($n = 144$) had gender dysphoria; three of these patients were raised as boys and 141 were raised as girls. However, these results were skewed by one particular study, which included a large proportion of patients with severe DSDs and reported a particularly high rate of gender dysphoria (38%).[16] With respect to age of presentation, seven studies evaluated individuals under the age of 18 years,[14,15,17,22–24,29] two did not report on patient age,[16,30] and nine studied patients over the age of 21 years.[18–21,25–28,31] Analysis of the available data revealed a slightly lower rate of dysphoria in younger patients (under age 18 years) than in older individuals. However, as psychosexual alterations often manifest in adulthood,[23] it is possible that the true incidence of dysphoria in the younger demographic is higher than these studies suggest.

CAH

The majority of research regarding DSDs and gender dysphoria (11 out of 18 studies) relates specifically to patients with CAH ($n = 267$). Overall, about 10% of the patients with CAH from these studies were shown to have gender dysphoria. Four studies described degree of masculinity using Prader's scale, which has been used as a clinical tool for decades.[14,15,19,20] A lower incidence of dysphoria was observed in children with a high degree of virilization. In three of these studies, none of the individuals classified as Prader IV or V (the maximum levels of masculinity according to the scale) had gender dysphoria ($n = 40$).[14,15,19] The fourth study reported three cases of dysphoria (18% incidence) in patients with high virilization scores who were initially raised as boys.[20] Interestingly, only six individuals—from a total of 16 patients in the study—were diagnosed with CAH within the first month of life. As cryptorchid testes are normally only investigated after the first year of life, this is likely to contribute to the delayed diagnosis of CAH.

Up until about 30 years ago, incidence of the simple virilization form of CAH was greater than that of the salt-wasting form, possibly because the salt-wasting form was associated with an increased risk of mortality in early infancy. However, it would seem that this trend has since reversed. In many more-recent studies, prevalence of the salt-wasting form of CAH has exceeded that of the simple virilization form.[14,17,18,21,22,24,26,28] Of the 126 patients included in these studies, 96 had the salt-wasting form and 30 had the simple virilization form (ratio of approximately 3:1). The simple virilization form is associated with reduced cortisol production and increased androgen production, as well as genital changes ranging from mild clitoromegaly to highly virilized genitalia. Patients also sometimes present with premature epiphyseal fusion and decreased adult height. However, the ovaries and uterus are generally normal. The salt-wasting form, on the other hand, can result in aldosterone production deficiency, leading to low sodium levels and high serum potassium levels. This form of CAH can cause severe clinical dehydration.

It is worth noting that salt-wasting CAH has also been associated with a higher degree of virilization. There is evidence to suggest that patients with salt-wasting CAH are less frequently assigned to the female gender at birth than those with simple virilization CAH and are more likely to display behavioural differences during childhood. For example, in one study, girls with the salt-wasting form showed a greater interest in masculine clothing or toys than those with the simple virilization form. However, there is insufficient evidence to draw definite distinctions between the two patient subgroups in terms of diagnosable gender dysphoria.

Non-CAH DSDs

The first study to report on the incidence of gender dysphoria in patients with DSDs other than CAH was published in 1998.[17] In this work and subsequent studies,[13,16,19–22,25,27,28,30,31] patients with 5α-RD2 deficiency ($n = 99$), 17β-HSD3 deficiency ($n = 28$), partial androgen insensitivity syndrome (PAIS; $n = 29$), complete androgen insensitivity syndrome (CAIS; $n = 30$),

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cloacal exstrophy ($n = 49$), penile agenesis ($n = 1$), mixed gonadal dysgenesis ($n = 24$), ovotesticular DSD ($n = 8$), and other diagnoses such as Leydig cell hypoplasia, rudimentary gonad syndrome, and 17-keto-reductase deficiency ($n = 15$) were investigated. The incidence of gender dysphoria varies significantly between patients with these different conditions (Table 1). Mean incidence rates associated with each DSD are 63% for 5α-RD2 deficiency, 57% for 17β-HSD3 deficiency, 20% for PAIS, 5% for CAIS, 39% for cloacal exstrophy, 100% for penile agenesis, 29% for mixed gonadal dysgenesis, 12.5% for ovotesticular DSD, and 44% for other diagnoses.

The majority of these patients were investigated in a single study, which established a strong association between cloacal exstrophy and gender dysphoria.[16] Other groups of patients who are at risk of developing gender dysphoria include those with 5α-RD2 and 17β-HSD3 deficiencies.[31] Patients with 17β-HSD3 deficiency demonstrate reduced levels of testosterone (17β-HSD3 is necessary for testosterone production), whereas patients with 5α-RD2 deficiency experience high levels of testosterone exposure to the brain (5α-RD2 is necessary for the conversion of testosterone to dihydrotestosterone). In theory, if prenatal exposure to testosterone were the predominant factor in determining gender identity, one might expect all patients with 5α-RD2 deficiency to develop a masculine identity, which does not seem to be the case. Furthermore, although patients with 17β-HSD3 deficiency exhibit reduced levels of testosterone, production of this hormone still occurs via the action of 17β-HSD isoenzymes, suggesting that prenatal androgens have only a minor influence in these patients.[31] However, reported rates of gender dysphoria range from 56–63% for patients with 5α-RD2 deficiency and from 39–64% for patients with 17β-HSD3 deficiency. Thus, other factors—such as the impact of the individual mutation on enzyme production (resulting in more or less brain exposure to hormones), cultural factors, and psychological factors (for example, the views of the patient and those close to them regarding the appearance of their genitalia)—are likely to have an effect.[31]

Cultural and social factors

Varying rates of gender dysphoria have been reported in patients with 5α-RD2 deficiency from different societies, suggesting that cultural and social factors could influence the development of gender roles. Cultural considerations include parental expectations (for example, preference for male children in certain societies) and fertility issues. In some societies, the inability to procreate makes it almost impossible for women to marry.[8] In a study by Maimoun and colleagues,[32] up to 30% of patients with 5α-RD2 deficiency reported consanguinity between their parents, which is not uncommon in some societies. The investigators also identified different types of genetic mutations in individuals from different ethnic groups, which could influence subsequent psychosexual development.[32]

In the Gaza Strip, Muslim children with 17β-HSD3 deficiency who are initially raised as girls have been shown to develop male sexual characteristics, even in the presence of low levels of DHT.[33] A study of 46,XY patients with 5α-RD2 deficiency living in the Dominican Republic showed that brain exposure to normal levels of testosterone *in utero*, during the postnatal period, and during puberty contributed significantly to the development of male gender identity.[34] In this study, 16 of 38 patients who were initially raised as girls opted for the male gender during puberty.[32] The study authors suggested that the effect of testosterone will always predominate in the absence of sociocultural factors and eventually overcome a female upbringing.[34]

Sexual orientation

There is no evidence to suggest that homosexuality or bisexuality implies dissatisfaction with one's gender.[8] On the whole, rates of homosexuality and bisexuality for patients with DSD-associated gender dysphoria do not seem to differ greatly from those of the general population. However, it is worth noting that only seven studies (out of the 18 studies evaluated) considered the sexual orientation of patients,[18,21,25,27–30] and only four of these studies assessed sexual orientation for the entire study population.[18,25,27,29] In these four studies, estimated rates of heterosexuality, homosexuality, and bisexuality ranged from 77–93%, 4–8%, and 2–16%, respectively.[28] Only one study reported on the sexual orientation of patients with androgen insensitivity syndrome. In this study, 33% of patients with CAIS ($n = 3$) were bisexual and 50% of patients with PAIS were homosexual ($n = 4$).[21] One limitation that applies to all of these studies is the use of questionnaires or interviews to determine sexual orientation, as some patients might be reluctant to disclose details regarding their sexuality.[19]

Treatment approaches

With respect to patients with CAH, the low rate of gender dysphoria reported in this Review demonstrates that assigning female gender and performing premature surgery is safe in the majority of cases. Similarly, for patients who display a high degree of virilization, the male gender can be chosen without substantially increasing the risk of gender identity. However, further studies are needed to evaluate gender dysphoria in highly virilized patients with CAH who are raised as girls. For patients with CAIS, there are few controversies with respect to raising patients as girls; virtually all of these patients are assigned a female gender and the incidence of dysphoria is extremely low in this patient group. However, for patients with PAIS, there is a need for further studies—preferably with patients classified according to the Prader scale. To date, two small studies have suggested a more problematic gender assignment in patients with PAIS than in patients with CAIS.[35,36]

In the groups with cloacal exstrophy or penile agenesis, a high rate of dysphoria in patients raised as girls suggests that raising patients as boys might be a better option. In the past, it has been very common for these patients to be routinely feminized. De Castro *et al.*[37] described a group of four patients with penile agenesis who underwent reconstructive surgery, using the abdominal flap for

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