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DESARROLLO SEXUAL DIFERENTE

Gender assignment and identity in DSD

Asignación de género e identidad en DSD

Arianne Dessens, PhD

Erasmus Medical Center Rotterdam. Sophia Children's Hospital. Dept. of Child and Adolescent Psychiatry and Psychology The Netherlands and Ghent University. Faculty of Medicine and Health Sciences. Dept. of Internal Medicine and Pediatrics, Belgium

Summary

Disorders of sex development (DSD) have a large psychosocial impact throughout life and coping with DSD, at any stage of life, remains challenging. For parents the birth of a child with DSD can be an extremely stressful event, particularly when biological sex is in question. The altered sexual development affects genital and sexual functioning and the fertility potential. It may affect physical appearance, and, in some patients, it may affect behavior or identity. Conditions that involve sex, gender, reproductivity and behavior are subject to social stigmatization. Fear for social stigma and preconceived opinions hamper acceptance. Parents and patients may be sad, ashamed, overwhelmed by faced difficulties and fear for being unable to cope.

Parents are the caregivers and parental difficulties in acceptance will affect the relationship with the child in many ways. Psychosocial counseling is helpful to enable parents and patients to accept and to cope.

The vast majority of individuals with a DSD develop a gender identity in agreement with the gender assigned at birth. However, a non-binary gender identity, gender discontentedness, gender discomfort or gender dysphoria is seen in about 8% of individuals with DSD and most frequently seen in patients with 46,XY DSD and genital hypovirilisation at birth. In these patients, development of gender identity should be monitored well, should be evaluated at least once before puberty and should be repeated in case doubts arise.

Introduction

Differences or disorders of sex development (DSD) comprise a heterogeneous group of genetic congenital conditions characterized by an atypical development of the sex organs[1]. The overall incidence of the birth of a child with DSD is estimated to be 1:4,500. The prevalence of most of these conditions is rare, only Klinefelter syndrome is not[1].

Nowadays often the designation 'intersex' is used. Definitions, however, are not fully overlapping. Intersex is often used to refer to a non-binary gender identity. Individuals with DSD, therefore, may identify themselves as intersex, but the majority does not do so.

Although most types of DSD do not involve life-threatening diseases and can be managed well clinically, DSD cannot be cured. It is a condition for life and many patients remain dependent on medical services[2]. The altered sexual development affects genital and sexual functioning and the fertility potential. It may affect physical appearance and in some patients it may affect behavior or identity. DSD has a large psychosocial impact throughout life and coping with DSD, at any stage of life, remains challenging.

Diagnosis and gender assignment

For parents, the birth of a child with DSD can be an extremely stressful event, particularly in case the biological sex is in question and assignment to the male or female social role is postponed[3,4]. Physical, genetic and hormonal evaluation will be necessary in order to establish the cause and necessary medical interventions. Decisions about gender assignment are

usually based on multiple factors, including prenatal hormone exposure, gonadal function, expected future gender identity, the necessity for surgical interventions and expected future fertility potential. By sharing results, professionals and parents can discuss the infant's social identity, medical treatments necessary and eventual surgical options. Parents are involved in decision making but the demand on decision making can be extremely distressing in case parents do not immediately comprehend the child's condition and lack overview of the consequences of decisions[5-7]. In addition to decisions needed for clinical management, parents also need to decide on disclosure of their child's condition to family and friends. Disclosure can be delicate. Disclosure can be beneficial, as parents may receive comfort and support. However, disclosure can be distressing in case parents have difficulties to explain the child's (usually complicated medical) condition to their nearest. Due to a wider social unawareness of DSD and misunderstandings, individuals with DSD and their parents may be confronted with insensitive reactions. Congenital conditions in general, and syndromes and conditions that involve sex, gender, reproductivity and behaviour in particular, are subject to social stigmatization. There is a social vulnerability, the child stand out. Fear for social stigma and preconceived opinions hamper acceptance. Parents may be sad, ashamed, overwhelmed by faced difficulties and fear for being unable to cope. Parents are the caregivers. Parental difficulties in acceptance will affect the relationship with the child in many ways[8-11]. Parental counseling is needed to enable parents to accept and to cope.

In advices for gender assignment, future fertility potential and expected future gender identity play a major role. In most countries, registration of birth is necessary to obtain citizenship and requires a gender specification of male or female. Intersex registration only recently became available in a few countries. Most parents prefer to register and raise their child in the male or female social role. Follow-up data on children that have been raised as intersex is anecdotal. Gender assignment is under debate; it is argued that in infants with DSD a social role can be given that can make the child unhappy later in life. Gender assignment ignores the child's intersexuality and unicity. On the other hand, it can be argued that gender assignment will facilitate to develop a gender identity. Gender is a basic personality characteristic. In the development of one's identity, being a member of a social group based on gender, age, ethnicity, culture, religion, socioeconomic status, profession etcetera, can be an important aspect of identification. Three years old preschoolers already identify themselves and others according to gender. Being intersex will make the child unique in the social network. Birth file registration will not explain the full identity and will not prescribe behavior. Parents can inform their child when he or she is old enough to comprehend and nearest about the child's intersexuality and use the legal status in public situations.

Gender role behavior and gender identity

Steroid hormones are active in brain development. Prenatally, masculine levels of androgens establish masculine behavior and interests. This was first observed by Phoenix and colleagues in 1959 who conducted a series of experiments in rodents and demonstrated that delivering androgens after development of the genitals but before ultimate neonatal brain maturation will masculinize sex-specific behavior in adult female rats. These researchers also demonstrated that prevention of androgen action during this sensitive period of brain development will lead to female sex-specific behavior in adult male rats.

Experimental studies in different types of species including primates demonstrated that this action of early androgens can be generalized to all types of species, including human beings. Today this is known as the organizational-activational hypothesis. Berenbaum and Beltz, Front Neuroendocrinol 2012[12].

In human beings, naturally occurring abnormalities in prenatal gonadal hormone secretion are seen in individuals with a disorder/difference in sex development. DSD gives us the opportunity to study the contribution of genetic, hormonal and social factors in different aspects of gender. Most studies have been carried out in 46,XX females with congenital adrenal hyperplasia (CAH) and in females with 46,XY and complete androgen insensitivity (CAIS). CAH and CAIS are the most common types of DSD, with a prevalence of 1: 15,000 in western countries (CAH)[13] and quoted prevalences of 5:100,000 up to 1:99,000 up to (CAIS) based on estimates derived from otherwise healthy phenotypic females found to have histologically normal inguinal or abdominal testes[14,15]. The first publication on the influence of androgens on behavior carried out in girls with CAH date from 1968. Studies on the influence of androgens have been conducted in girls and women with CAH of different ages, of different ethnicities and living in different cultures, with refinements in study methods and measures. All data collected by now strongly indicate that it is likely that several of the hormonal mechanisms that establish different types of sex dimorphic behaviors in animals, are also applicable to human beings. However, the neural systems that regulate these altered behaviors remain largely unknown.

Table I. Gender development in DSD.

Type of DSD	Prenatal androgens	Psychosexual variable	Research findings
Chromosomal Turner, Klinefelter	No – normal	Behavior Identity Sexual orientation	Conform population More psychiatric diagnosis
46,XX MRKH	No	Behavior Identity Sexual orientation	Female conform population
46,XX CAH	Hyperproduction adrenal androgens	Behavior Identity Sexual orientation	Masculinization of behavior, interests 5% non-binary, gender dyscomfort-dysphoria Raised percentage non-androphilic
46,XY CAIS 46,XY CGD	No androgen effect No production	Behavior Identity Sexual orientation	Female conform population
Remaining 46,XY PAIS 46,XY PGD 46,XY DBT	Variable (levels and time window)	Behavior Identity Sexual orientation	8% non-binary, gender dyscomfort-dysphoria

In CAH a gene mutation in the enzymes 21-hydroxylase or 11 beta hydroxylase enables the adrenal to produce excessive amounts of androgens, starting in fetal life from the sixth week of gestational age, when the adrenal fetal cortex starts to secrete steroids[16]. The excessive amount of adrenal production will masculinize the external female genital. Ovaries, fallopian tubes and the uterus remain female; the internal genital already developed before adrenal maturation reaches capacity to produce excessive amounts of androgens[17]. Despite (severe) masculinization of the external genital, newborns with 46,XX CAH are usually raised as girls because their internal genitalia are female and they are fertile as women.

Today, many countries have neonatal screening programs for early detection of CAH in order to save children from a hyponatremic crisis. In the past, however, neonatal screening was not available and health care workers sometimes missed the diagnosis in infants with severely masculinized genitalia. These children were identified and raised as boys. In case CAH was identified early in life, usually the infant or toddler was reassigned the female gender but in older children who were already aware about their gender, gender changes were less common.

Human sexuality is considered multidimensional, and includes at least three components: (a) gender role behavior refers to behaviors which, on average, are more typical of one gender or the other and includes preferences for specific toys, playmates and play styles; an observable pattern of behaviors that is culturally associated with gender or that show sex differences and characteristics specifically prescribed for or expected of a gender, (b) sexual orientation, the romantic or sexual attraction, in fantasy or behavior, to men, women or both, or lack thereof, (c) gender identity is a category of social identity and refers to the sense of self as male, female or non-binary[18].

As a group, girls with CAH more often like boys as playmates, like to play with boy's toys and boy's games and display masculine play styles, such as games that involve a lot of rough and tumble play and require a high activity level. These changes in childhood play behavior are well-established in many studies carried out in different western and non-western countries, all reporting more masculine play behavior in girls with CAH compared to their unaffected female relatives (sisters, cousins) or matched controls[19-23]. The degree of masculinization of behavior is related to the type of CAH and the amounts of androgens prenatally produced in a dose-response manner. The salt wasting type of CAH is related to CYP21A2 allele null and I2splice mutations, the simple virilizing type of CAH is related to I172N mutation and the non-classical type of CAH is related to the V281L mutation. In case of CYP21A2 mutations, the adrenals produce highest amounts of androgens; girls with this type of CAH are born with the most severely masculinized genitalia whereas in girls with a V281L mutation the androgen production is low and progressive masculinization of the external genital is often detected later in life. Females with the salt wasting type of CAH are more masculine in their behavior than the females with the simple virilizing type[19,24,25], the females with the CYP21A2 allele nul genotype being more masculine than females with the I2splice mutation, females with the I2splice mutation more masculine than females with I172N mutation[26,27] whereas females with the non-classical type of CAH (V281L mutation) do not differ from healthy females in their gender role behavior[27,28]. No influences of parental permissiveness

or encouragement of masculine behavior in the girls' behaviour and preferences has been observed[25,29-32]. Studies that compared gender role behavior in girls with CAH with the gender role behavior in their non-affected sisters and non-affected control girls, demonstrated that non-affected sisters and non-affected controls girls had equal feminine scores on the rating scales whereas the scores of the CAH girls were significantly more masculine[29,31]. Pasterski observed that most parents encouraged feminine behavior but encouragement could not override their daughter's interest in boy's toys[31]. Behavioral masculinization has also been reported in Javanese girls and women with CAH, living in the most muslim-orthodox area in Indonesia, with greatest pressure to behave according to gender norms[22]. Adolescent girls and adult women show elevated interest in male-typical activities and careers and reduced interest in female-typical activities and careers[27,28,31,33-35].

In healthy boys, testosterone peaks are between week 12 and 18 and from week 34 of gestational age into the first three months after birth. As males with CAH do not differ from non-CAH boys with respect to masculinity of their gender role behavior[19], these findings suggest that in human beings hormonal brain masculinization for gender role behavior does not start before week 12 but probably takes place in these two peak periods. The fair correlation between the severity of masculinization of the external genitalia and masculinization of gender role behavior in CAH females suggests that the establishment of gender role behavior will start during the first testosterone peak. During this peak testes of males and the adrenals of females with CAH probably produce sufficient androgens to establish masculine / masculinized gender role behavior. The observation that males with CAH do not differ from healthy males in their behavior suggest that a specific amount of androgens is enough to influence brain development to establish this behavior; higher levels will not lead to supermasculinity. Studies in females with the non-classical type of CAH indicate that the hormonal masculinization of gender behavior takes place prenatally[24,28]. Studies on gender identity revealed that the vast majority (about 95%) of adolescent girls and adult women have a female gender identity[23,36-43]. A somewhat reduced female gender contentedness, female gender discomfort, gender dysphoria or non-binary gender identity has been reported in about 5% of females[36,44]. The proportion of individuals who had chosen to change their gender is estimated to be between 1.5% - 3%. Studies in girls aged 4-11 years old revealed reported more cross gender identification is more often reported in these prepubertal girls in comparison to their sisters or first cousins or to population norms[18,45]. Compared to the proportion of adolescent and young adults with CAH who changed gender, it seems that many of these young girls will become more satisfied with their female gender in adolescence.

We can conclude that dissatisfaction with gender is more frequently seen among females with CAH compared to non-affected women[36,44]. Contrary to their gender role behavior, no relationship has been found between genital masculinization at birth and social gender change[46,47]. Patients who changed gender[22,46-49] are characterized by delay of diagnosis, and progressive masculinization with inconsistent or absent glucocorticoid replacement therapy.

Follow-up data in individuals with 46 XX CAH who have been raised as males are scarce but revealed that they were satisfied being a man[23,50-53].

Findings in individuals with 46,XX CAH who have undergone progressive masculinization due to absence or insufficient compliance to glucocorticoid therapy[22,23, 46-53] suggest that a combination of pre- and postnatal androgen action in the brain can lead to the satisfaction with the male gender later in life (46,XX CAH and male assignment at birth) or progressive confusion and dissatisfaction with the female gender (46,XX CAH and female assignment at birth). However, we do not know to what extend progressive body masculinization play a role in confusion and dissatisfaction of gender[22,46].

Complete androgen insensitivity syndrome (CAIS) is a condition that results in the complete inability of the body to respond to produced androgens, due to a mutation in the androgen receptor. The unresponsiveness of the body to the presence of androgenic hormones prevents the masculinization of male internal and external genitalia in the developing fetus, as well as the development of male secondary sexual characteristics at puberty. The physical appearance is female. Women with CAIS produce and are sensitive to anti-muelllerian hormone, which causes regression of Muellerian structures prenatally. This condition is usually identified in childhood or in adolescence. In their behavior and identity, girls with CAIS do not differ from non-affected girls[54-57]. These studies suggest that the ovaries or the X or Y chromosomes are not involved in the development of the female gender identity.

The combination of a 46,XY karyotype and hypovirilization is also seen in other diagnoses. These diagnoses are rare or extremely rare and all types of diagnoses have large varieties in phenotype. Depending on genital virilization at birth, a child is assigned the male or female gender.

In the past a female gender assignment was often chosen in children born with a moderately virilized genital. Follow-up studies and case reports revealed that masculinized behavior, gender discontentedness, gender discomfort, gender dysphoria and gender change were most frequently seen among individuals with 46, XY DSD and a moderately virilized genital

raised as girls[22,56-61]. The gender problems in these individuals may be related to the prenatally produced and active androgens. However, many of these individuals had not received medical treatment in childhood and in adolescence, due to lack of knowledge and resources[22,48-53,59,62,63]. In puberty, they started to masculinize. The pubertal testosterone may have reinforced the male gender identity and subsequently induced gender discomfort or gender dysphoria. This is similar as in individuals with 46, XX CAH who underwent progressive masculinization due to the absence or insufficient compliance to glucocorticoid therapy[22-23, 46-53].

Studies in females with 46,XX CAH and 46, XY CAIS show us the dominance of prenatal androgens on gender role behavior and interests. Cultural influences, encouragement of female activities of interests or discouragement of male behavior hardly seemed effective. The findings correspond well with findings in non-primate and primate research. It therefore can be concluded that also in humans masculine gender role behavior and the brain structures that are involved are probably programmed by prenatal androgens.

In human studies, however, it is difficult to separated nature and nurture; an experimental study cannot be conducted. Sibling controlled design seems to be second best, but this design still allows variables that cannot be controlled and variables that are not known. Only after 50 years of studies in human populations from different countries and cultures demonstrated us the large similarities in gender role behavior in women with CAH.

What is needed in clinical management? psychological counseling?

Studies on caregiver distress revealed that the birth of a child with DSD can be extremely stressful and may have long-lasting consequences[3,4]. Parental post-traumatic stress, caused by the medical condition of the child, will interfere with parenting and will affect the relationship with the child in many ways[63]. Parental counseling is needed to help parents to comprehend the diagnosis, to answer questions, to clarify misunderstandings to cope with their sadness and fears and to empower, parents in their coping abilities[8-11].

Disclosure is helpful; it enables parents to receive support from their nearest. Parents, however, need to be comfortable to discuss their child's condition in their family, and in a wider social network and in informing their child[64]. Parents who are comfortable to talk about their child's condition, will be able to support their child well. They can empower their child and help their child to cope. Discussing disclosure helps parents to reflect on information they want to share and information they prefer to keep private, with whom they want to share information and how to share information.

DSD is a condition for life, has a large psychosocial impact throughout life and coping with DSD, at any stage of life, remains challenging. Psychosocial counseling therefore should be offered as soon as DSD is suspected (in antenatal care) or identified (after birth or later in life) and in any stage of life needed.

The child needs to be informed about the medical condition in a continuous - and age- appropriate process. By discussing how to inform the child already at an early stage, parents will be able to prepare themselves. Parents need to understand and be prepared for the physical, psychological and social changes during adolescence in order to become aware of the challenges their child will come across. Advisory booklets or informative websites on how to prepare and support their child will empower parents and make it easier for them to communicate with their child about the medical condition and faced challenges[66]. For adolescents with DSD, timely information and sex education is important. Psychological counselling, dedicated educational websites and contacts with other patients may be helpful. All DSD-conditions per se may intensify parental focus on their child's behavior, particularly in case of past gender (re) assignment. Some parents seek reinforcement of the decisions made and may start worrying when they experience insufficient reassurance. In psychological counselling, information on psychological aspects of child development including play behavior, development of gender preferences and development of knowledge on sex and gender will be helpful to take away the turmoil.

For some parents, it is difficult to accept their child's cross gender role behavior. Importantly, gender role behavior, interests and preferences are mostly not possible nor desirable to change[21,32,33] and cannot be used to predict gender identity[61]. Acceptance of behavior is needed to enable the child to develop a positive self-esteem necessary to cope with the challenges that children with DSD will meet in puberty and adulthood. Children need support from their parents. Parents who feel shame, shyness or inability to cope or to protect will need support and reinforcement of their parental competency[67].

The vast majority of individuals with a DSD developed a gender identity in line with the gender assigned at birth. A non-binary gender identity, gender discontentedness, gender discomfort or gender dysphoria is seen in about 8% of individuals with DSD. Most of the data are based on case reports and small studies with methodological imperfections, making it difficult to draw firm conclusions, particularly in patients with 46,XY DSD and genital hypovirilization at birth. Development of gender identity should be monitored

well, and evaluation of gender identity should be conducted before gonadectomy and/or hormonal induction of puberty, and preferably from the age of 8 years and conducted by an experienced psychologist. Assessment can be repeated in case gender doubts or uncertainties arise. Careful counselling by a multidisciplinary team is therefore required before any decision about hormonal treatment is taken[67].

In case there are uncertainties about the gender identity, puberty can be delayed by using GnRH agonists. Delay of puberty can be helpful to get an opportunity to find out which gender will suit best without the disadvantages of a quickly developing physical appearance. Psychological follow-up is needed to evaluate gender development over time and keep an eye on the adolescent's mental health (emotional problems such as social phobia or depression need to be identified and treated). Recognizing that gender identity is a non-binary phenomenon can facilitate satisfaction with one's gender. However, pubertal treatment is essential for long term wellbeing in all patients, and a decision regarding hormonal treatment eventually has to be made[67].

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