Disorders of sex development

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Abstract

Disorders of sex development (DSD) occur in 1–2/10,000 live births, with a specific molecular diagnosis only possible in 20% of cases. Presentation is usually at birth, and gender assignment must be avoided before review by an expert multidisciplinary team. Initial investigations allow a working diagnosis to be made within 48 hours. In 46,XY DSD, surgery may be necessary to correct hypospadias, reposition or remove undescended testes, and remove symptomatic Mullerian remnants. In 46,XX DSD, feminizing surgery is performed less frequently than in the past, but genitoplasty may still be indicated. Psychosocial support is required to promote positive adaptation as gender dissatisfaction can occur in certain conditions. Long-term outcome data are sparse.

Keywords CAH; congenital adrenal hyperplasia; disorders of sex development; DSD; hypospadias; intersex

Nomenclature and definitions

Simple examination of the external genitalia at birth is usually all that is necessary to confirm the sex of a neonate. In a small number of newborns, assignment of sex is not possible simply based on appearance. In the past, these neonates were described using a variety of terms including ambiguous genitalia, intersex, hermaphroditism and pseudo-hermaphroditism. These terms were confusing and potentially stigmatizing for parents and children. Following a consensus statement in 2006, the term 'disorders of sex development (DSD)' was introduced to replace all the above terms and defined as a 'congenital condition in which development of chromosomal, gonadal or anatomical sex is atypical' (Table 1). More recently, the term 'differences in' or simply 'different sex development' has also begun to appear in the literature, and this may prove to be more acceptable.

Psychosexual development is complex and is influenced by many factors, including sex chromosome genes, androgen exposure and social circumstance. Three separate components need to be considered. 'Gender identity' is a person's self-representation as male or female. 'Gender role' refers to sex-typical behaviour, such as toy preference, and is clearly influenced by prenatal androgen exposure (as in congenital adrenal hyperplasia where the most virilized girls play more with boys toys). 'Sexual orientation' can be heterosexual, bisexual or homosexual. It is important to realize that these components are separable, for example, homosexual orientation in an individual with DSD would not indicate incorrect gender assignment and subsequent gender role. 'Gender dysphoria' implies unhappiness with assigned sex, and is more common in individuals with DSD, although the likelihood of this occurring is difficult to predict.

Incidence and aetiology

DSD occurs in 1–2/10,000 live births and with accelerating discovery of the genes involved, a specific molecular diagnosis is now possible in most cases. Nearly 50% of 46,XY individuals will receive a specific genetic diagnosis, and the majority of virilized 46,XX infants will prove to have congenital adrenal hyperplasia (CAH).

Embryology

By 6 weeks of gestation, primordial germ cells migrate from the yolk sac to the genital ridge formed within the intermediate mesoderm. Bipotential gonads develop from these cells under the influence of Wilms' tumour 1 (WT1) and steroidogenic factor 1 (SF1) genes. Further development is dependent upon the presence or absence of the Y chromosome (Figure 1).

In the presence of the Y chromosome, the testis develops under the influence of SRY and SOX9 genes. Sertoli cells within the testis produce anti-Mullerian hormone (AMH), which inhibits development of Mullerian (or paramesonephric) structures (fallopian tubes, uterus, upper two-thirds of the vagina). Leydig cells produce testosterone, which is responsible for the development of Wolffian (or mesonephric) structures (vas deferens, epididymis, seminal vesicles). Testosterone is converted to the more potent dihydrotestosterone (DHT), by the action of 5α-reductase and this facilitates the development of male external genitalia and testicular descent.

In the absence of the Y chromosome, ovaries develop, possibly under the influence of DAX1 and Wnt4 genes. In the absence of AMH and testosterone, Mullerian structures develop, forming the female internal genitalia, whereas the Wolffian ducts regress. Similarly in the absence of DHT, female external genitalia are formed by default.

The presence or absence of Y chromosome fragments of cell-free fetal DNA found in maternal plasma allows non-invasive genetic sex determination from 7 weeks gestation. The angle of the phallus on ultrasonography allows accurate sex determination from 12 weeks gestation in a normal fetus. Mutation in any of the regulatory genes or abnormalities in any of the relevant hormone actions may lead to a DSD.

Management

General principles

Management of an infant with DSD should include the following:

- Gender assignment must be avoided prior to expert review. Use of specific male or female pronouns and terms such as ambiguous genitalia should be avoided as this adds to parental anxiety. The parents should be advised to delay registration of the birth, which is permissible for up to 42 days

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Classification of DSD

46,XY DSD (under-virilized genetic male)
Disorders of testicular development
Complete gonadal dysgenesis (Swyer syndrome; 46,XY sex reversal)
Partial gonadal dysgenesis
Gonadal regression
Ovotesticular DSD
Disorders of androgen synthesis/action
Synthesis: 17-hydroxysteroid dehydrogenase or 5α-reductase deficiency
Action: complete or partial androgen insensitivity syndromes
Receptor defects: Leydig cell hypoplasia
Disorders of AMH and receptor: persistent mullerian duct syndrome
Others
Severe hypospadias
Cloacal exstrophy

46,XX DSD (over-virilized genetic female)
Disorders of ovarian development
Ovotesticular DSD
Testicular DSD (e.g. duplication SOX9)
Gonadal dysgenesis
Androgen excess
Fetal: congenital adrenal hyperplasia (21- or 11- hydroxylase deficiency)
Fetoplacental: aromatase deficiency
Maternal: luteoma, exogenous

Sex chromosome DSD (variable)
45,X (Turner's syndrome)
47,XYY (Klinefelter syndrome and variants)
45,X/46,XY (mixed gonadal dysgenesis, ovotesticular DSD)
46,XX/46,XY (chimeric, ovotesticular DSD)

AMH: anti-Mullerian hormone.

Table 1

- Evaluation and management should be performed in a centre with a multidisciplinary team, comprising paediatric specialists in surgery, usually urology, endocrinology, neonatology, nursing, psychology, genetics and medical ethics.
- Gender assignment should be performed as promptly as possible. This is usually, but not always, in accordance with karyotype.
- Communication with parents, and the patient if possible, must be open and they should be encouraged to contribute to decision-making. Locally derived and additional web-based information may be useful for parents.

Clinical examination

Initial clinical examination should include the Prader classification (Figure 2), a description of the phallus (length, width, presence of bend/chordee), the scrotum or labio-scrotal folds, and the presence or absence of a palpable gonad on either side. The skin colour and rugosity should be recorded, and the location and number of orifices present on the perineum.

Criteria that suggest DSD include:

- overt genital ambiguity
- apparent male genitalia with bilateral undescended testes (Figure 3), isolated perineal hypospadias (Figure 4), or hypospadias of any degree with an undescended testis
- apparent female genitalia with an enlarged clitoris, posterior labial fusion or an inguinal/labial mass (possible herniated testis)
- discordance between genital appearance and a prenatal karyotype.

In general, a symmetrical appearance of the genitalia suggests a biochemical aetiology (e.g. CAH), whereas asymmetrical appearances may mean an underlying chromosomal abnormality (e.g. 45,X/46,XY mixed gonadal dysgenesis).

Most babies with DSD are well at birth, but CAH can be associated with salt loss, which may be life threatening if undiagnosed.

The majority of cases of DSD present in the neonatal period. Prenatal diagnosis of a DSD is unusual unless there is a positive family history. Later presentations include:

- inguinal hernia in a female
- virilization in a female
- primary amenorrhoea (e.g. complete androgen insensitivity syndrome)
- breast development in a male
- delayed or incomplete puberty.

Investigations

Initial investigations should include:

- karyotype with X and Y-specific probe detection
- blood and urine biochemistry (including plasma glucose 17-hydroxyprogesterone, electrolytes)
- Imaging (ultrasound).

The results of these should be available within 48 hours, and will usually be sufficient to provide a working diagnosis. Further investigations might include:

- hormonal assays (testosterone, AMH and hCG and ACTH stimulation tests)
- imaging studies (MRI, cystogram/genitogram)
- diagnostic surgical procedures — cystovaginoscopy, laparoscopy (Figure 5), skin/gonadal biopsy.

Gender assignment

Gender assignment can be difficult and is influenced by a number of factors in addition to the DSD diagnosis, including genital appearance, surgical options, fertility potential and the views of the family. For certain conditions, there is data suggesting good outcomes, for example, all 46,XY complete androgen insensitivity individuals assigned the female gender in infancy identify as female. Similarly, >90% of 46,XX CAH individuals identify as female. For other conditions, outcomes appear mixed, for example, in patients with partial androgen insensitivity, androgen biosynthetic defects, and incomplete gonadal dysgenesis, there is dissatisfaction with the sex of rearing in about 25%, irrespective of whether the individual was raised male or female. Research has shown an increase in male gender assignment over time.

Timing of surgery

The timing of genital surgery for patients with a DSD is controversial, namely early versus late (Table 2). Surgical practice is evolving, taking into consideration the opinions of experts within

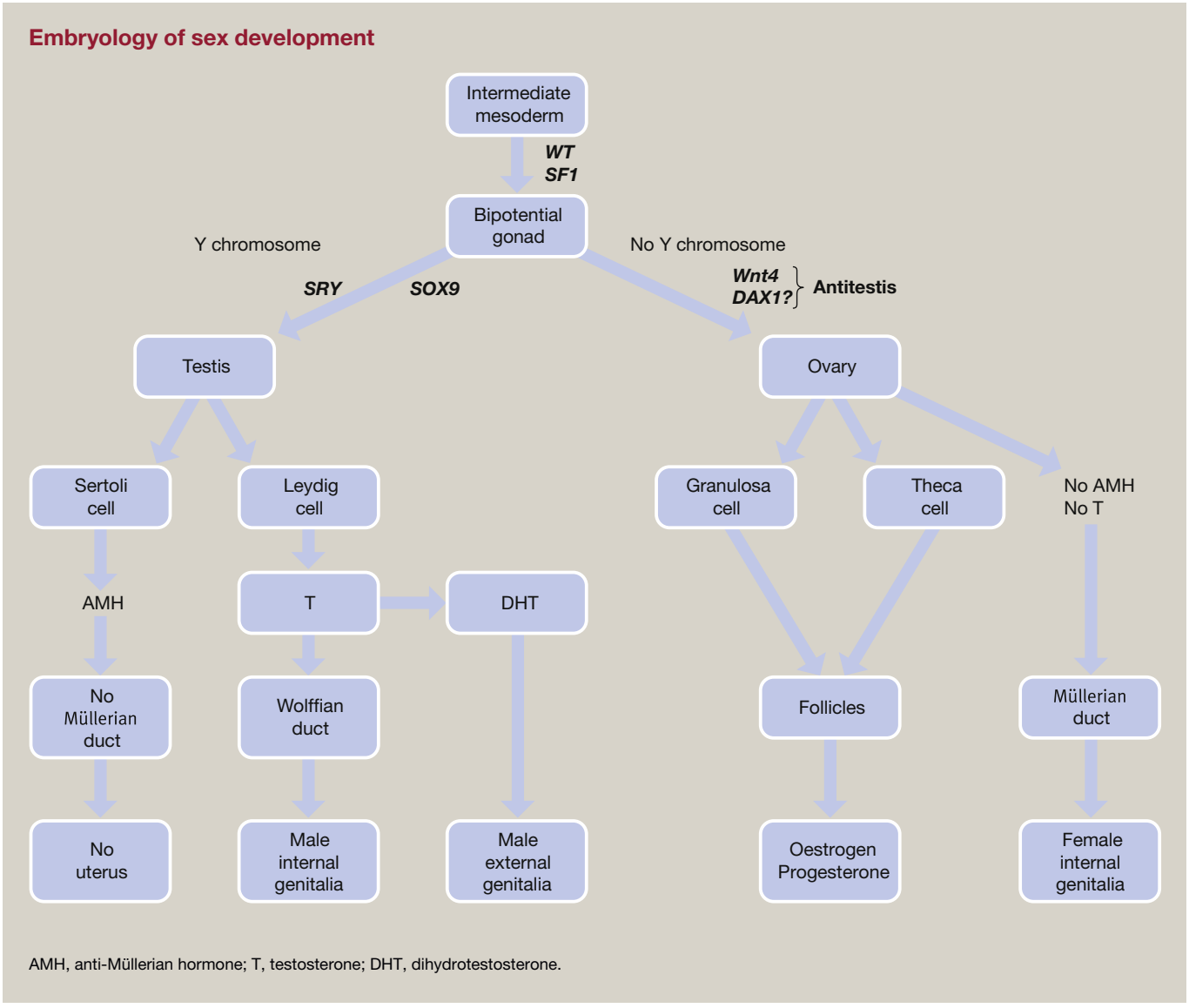


Figure 1

the medical community alongside patient advocacy groups, governmental agencies, ethicists and legal entities. This is happening in parallel with a wider conversation in society about the binary description of gender and the promotion of human rights for people with a DSD.

Proponents of early surgery argue that the psychological impact on a child living with atypical genitals is unknown and acknowledge parents' wishes to align the genital appearance with the gender of rearing. There is also concern that the technical expertise for performing late surgery is lacking, as is data regarding its morbidity and outcomes for the child as a whole.

The arguments against early surgery focus on the autonomy of the child, the need for informed consent (impossible in infancy) and the right to an open future given the irreversibility of surgery. Poor outcomes have been reported from patients having undergone early surgery (need for revision surgery, altered clitoral sensation) and many feel surgery is medically unnecessary and therefore shouldn't be performed. This view point is championed by the Human Rights Watch Interact report 'I want to be like nature made me'.

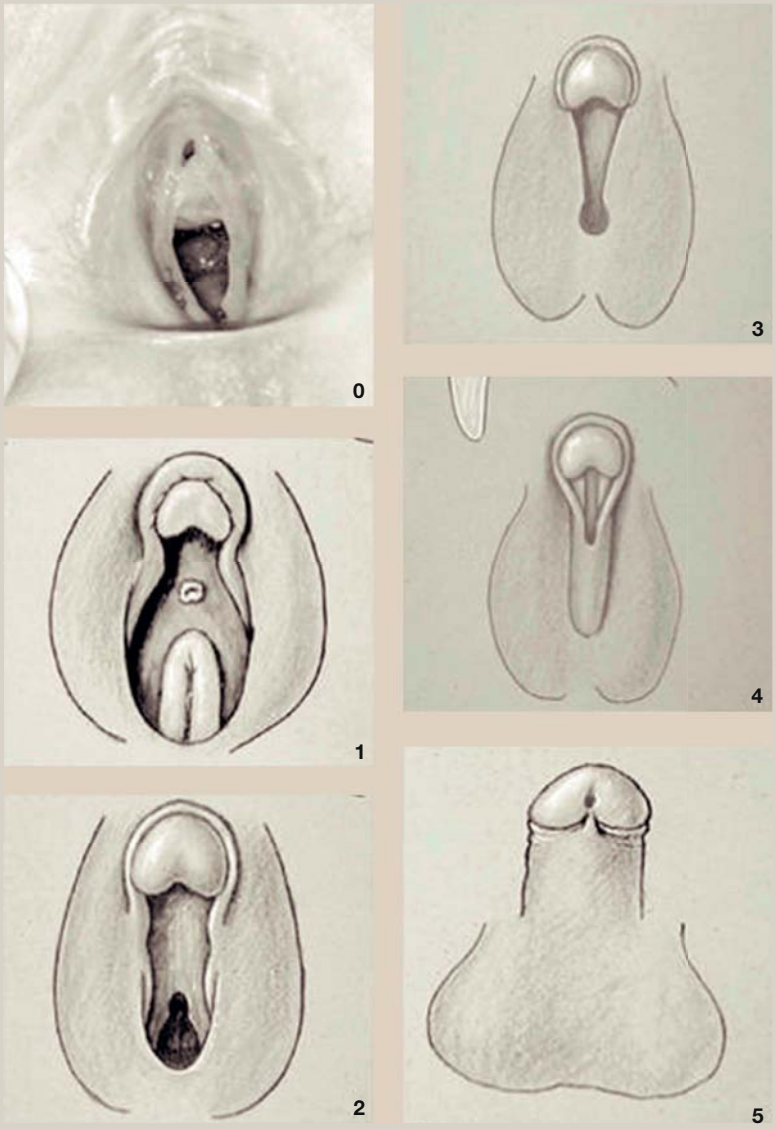
For those patients at high risk of gonadal malignancy the decision making is clearer, as surgical intervention is accepted as medically indicated.

Surgery

Gonadal surgery: Testes with an increased risk of tumour formation should be removed to prevent malignancy in adult life. In complete or partial androgen insensitivity, orchidectomy can be deferred until adolescence, whereas streak gonads should be removed in early childhood. In individuals with gonadal dysgenesis and a scrotal testis, testicular biopsy at puberty may be recommended, followed by sperm banking and radiotherapy or orchidectomy if carcinoma-in-situ is demonstrated.

Genital surgery: In 46,XY DSD, single- (e.g. Snodgrass) or two-stage (e.g. Bracka) hypospadias repairs may be necessary,

Prader classification



0, normal female external genitalia; 1, female external genitalia with clitoromegaly; 2, clitoromegaly with partial labial fusion forming a funnel-shaped urogenital sinus; 3, increased phallic size with complete labioscrotal fusion forming a urogenital sinus with a single opening; 4, complete scrotal fusion with the opening of the urogenital sinus at the base of the phallus; 5, normal male external genitalia.

Figure 2

depending on the size of the phallus, the quality of the urethral plate and the degree of chordee. The complexity and likely outcome of the repair must be discussed in detail with the parents, particularly if successful gender assignment is dependent on the procedure. Persistent Mullerian remnants are generally only removed if symptomatic, usually by a laparoscopic route.

Feminizing surgery for 46,XX DSD (over-virilized female) is controversial. There is now a body of literature demonstrating significant psychosexual problems in adult women who underwent feminizing clitoral surgery in their infancy. Surgical practice has evolved and functional outcomes are now considered much more relevant than simple cosmetic appearances. Parents are also less likely to choose surgery for less severe clitoromegaly.

If surgery is performed after parental counselling, the clitoral component is anatomically based, aimed at preserving innervation and erectile function, and in many units simply involves concealment or recession. A vaginoplasty is generally performed at the same time, with the aim of producing separation of the urethra and vagina at perineal level. This usually involves partial or 'total urogenital mobilization' (TUM), in which the common urogenital sinus is mobilized en bloc. Introitoplasty ± monsplasty is usually performed to produce a more feminized appearance of the labia and introitus.

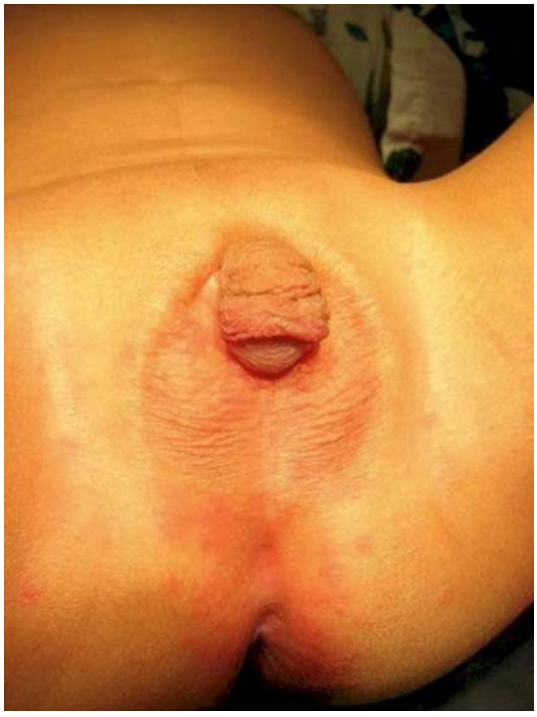


Figure 3 46,XX DSD – marked virilization secondary to congenital adrenal hyperplasia with a large phallus but bilateral impalpable undescended gonads.

If the vagina is absent or inadequate in isolation, vaginoplasty should not be performed until adolescence, when the patient will be psychologically prepared and motivated. Intermittent vaginal self-dilatation is likely to be required in the post-operative period, irrespective of the surgical technique used.

Figure 4 46,XY DSD – severe hypospadias in partial androgen insensitivity.

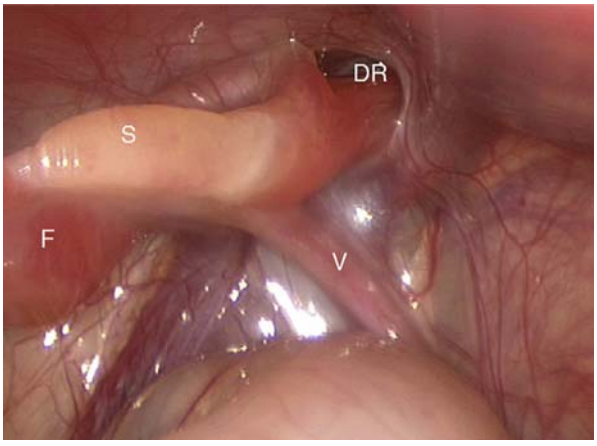


Figure 5 Complete gonadal dysgenesis (46,XY sex reversal) – laparoscopy reveals streak gonad (S) with both an associated fallopian tube (F) and vas (V) emerging from an open deep ring (DR).

Sex steroids

Hormonal induction of puberty may be necessary as hypogonadism is common in individuals with dysgenetic gonads. Intramuscular depot injections of testosterone are usually used in males. Oestrogen supplementation ± progestins are used in females. Cyclic progesterone is not required in a female without a uterus.

Timing of genital surgery

Arguments for early surgery	Reduction in stigma associated with growing up with atypical genitalia Parent's wishes and desire to align the genitals with the gender of rearing The unknowns of later surgery: • limited surgical expertise in performing genital surgery on adolescents • lack of outcome data Psychological impact of surgery which may be reduced in an infant compared to an adolescent Positive feedback from previous patients who have undergone early surgery
Arguments against early surgery	Infants cannot give informed consent The irreversibility of genital surgery, thus taking away an open future and right for a patient to choose for themselves Rejection of binary gender and the need to conform to societies description of 'normality' Previously reported poor surgical outcomes; reduced clitoral sensitivity and the need revision surgery Early surgery is medically unnecessary as the vagina is functionally unused in a child Negative feedback from previous patients who have undergone early surgery

Table 2

Psychosocial

Psychosocial support will be required to facilitate positive adaptation. Particular issues may include initial gender (re-) assignment; gender dissatisfaction; ability to develop relationships; sexual functioning; and fertility.

Specific conditions

Complete gonadal dysgenesis (46,XY sex reversal)

The phenotype is more often female and, as in complete androgen insensitivity syndrome, presentation may be at puberty with primary amenorrhea. There is high risk of malignancy in the associated streak gonads, and gonadectomy is recommended in infancy or at diagnosis.

Ovo-testicular DSD

Previously known as 'true hermaphroditism', patients with this condition have both ovarian and testicular tissue in varying combinations. The phenotype is thus variable and asymmetrical. Gender assignment is based on functional potential. For a female assignment, orchidectomy is necessary while the male patient may require orchidopexy.

5α-Reductase deficiency

In the absence of DHT, virilization is poor. Secondary virilization can occur at puberty, although the phallus remains small and infertility is common.

Androgen insensitivity syndrome (AIS) 46,XY

A point mutation in the androgen receptor gene (AR) results in either partial (PAIS) or complete (CAIS) failure of receptor function. Affected individuals have a normal female phenotype, and usually present at puberty with primary amenorrhea. Earlier presentation is possible, usually at the time of inguinal hernia repair, when a testis may be noted in the hernial sac. The vagina will be short, and the testes intra-abdominal. Bilateral orchidectomy may be deferred until after puberty as the risk of malignancy is low.

Leydig cell hypoplasia

Testosterone production is lacking, and the presentation and management is similar to CAIS.

Disorders of AMH production/receptor function

There is persistence of Mullerian structures despite a male phenotype. The testes may be undescended, and orchidopexy can be difficult due to adherence of the vas deferens to the Mullerian structures. Fertility is usually very low in these patients.

Congenital adrenal hyperplasia (CAH)

This is the most common DSD. In 46,XX CAH, the degree of virilization can range from mild clitoromegaly to an apparently normal male phallus, but with impalpable gonads. The Mullerian system is fully developed with uterus, fallopian tubes and upper vagina present, joining a common urogenital sinus.

CAH arises as a result of a deficiency of a key enzyme, most commonly 21-hydroxylase (21-OHD), required for the production of cortisol. Precursors accumulate and these are diverted into sex steroid pathways, resulting in androgen excess and virilization. In type 1 'non-salt wasting' 21-OHD deficiency, the defect only affects the zona fasciculata of the adrenal gland, and normal mineralocorticoid production occurs from the zona glomerulosa. In type 2 'salt-wasting' 21-OHD deficiency, mineralocorticoid production is also affected, which can be potentially life-threatening if untreated.

Maternal dexamethasone may be used to ameliorate the genital virilization of female fetuses with congenital adrenal hyperplasia. However, treatment must start early in pregnancy and concerns have been raised regarding both effects on gene expression early in fetal development and long-term effects on cognitive function.

Initial investigations include measurement of serum electrolytes, and also 17-hydroxyprogesterone and androstenedione levels, which will be increased. Treatment includes replacement therapy with hydrocortisone and also fludrocortisones in the salt-wasting variety. Gender assignment is female. Surgical reconstruction is dependent upon the severity of virilization. Other conditions resulting in over-virilized female can be treated in a similar way.

Turner's syndrome and variants (45,X)

Individuals have a female phenotype with other stigmata such as web neck and shield chest.

Klinefelter's syndrome (47,XXY)

Individuals have a male phenotype pre-pubertally. Following puberty, they develop abnormal secondary characteristics such as tall stature, sparse facial hair, female pattern fat distribution and small hard testes. Infertility is expected and patients can also develop gynaecomastia and breast cancer.

Mixed gonadal dysgenesis (MGD)

The karyotype is usually a 45,X/46,XY mosaic. Individuals may have hypospadias, with a testis present on one side, and a streak gonad on the other. There is an increased risk of gonadal tumour development either in the streak gonad, and possibly also in the apparently normal testis.

Long-term outcomes

Long-term outcomes are difficult to quantify. DSD is not a diagnosis; it comprises a spectrum of abnormalities so it is dangerous to extrapolate findings from one diagnosis to another. Health outcomes include cancer risk in abnormal gonads, lower urinary tract symptoms after reconstructive surgery, poor fertility outcomes and the effects of long-term steroid use on bone density, blood pressure and growth.

Psychological and sexual quality of life outcomes are particularly challenging to quantify scientifically. The effect of parental psychology on eventual patient outcome adds an important variable. Recent literature reviews suggest that there is much dissatisfaction with sexual quality of life, function and genital appearance.

Patient advocacy groups have added an invaluable perspective which can both inform and support patients, families and healthcare workers. Their views, however, may reflect a treatment approach to DSD which has changed vastly over the last decade. It must be remembered that each patient can only speak from their own experience and by that token, all advocacy group opinions should be considered with equal weight.

The International DSD Registry is a database for the systematic, prospective recording of data from birth to adulthood to increase understanding of DSD conditions and facilitate research. It is hoped that with such data, it should be possible to better evaluate outcomes in the future. ◆

FURTHER READING

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