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 Müllerian 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' (Box 1).

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 hetero-, bi- 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.

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 Müllerian 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,XO (Turner's syndrome)
- 47,XYY (Klinefelter syndrome and variants)
- 45,XO/46,XY (mixed gonadal dysgenesis, ovotesticular DSD)
- 46,XX/46,XY (chimeric, ovotesticular DSD)

AMH: anti-Müllerian hormone

Box 1

Incidence and aetiology

DSD occurs in 1–2/10,000 live births and with accelerating discovery of 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

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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-Müllerian hormone (AMH), which inhibits development of Müllerian (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, Müllerian 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

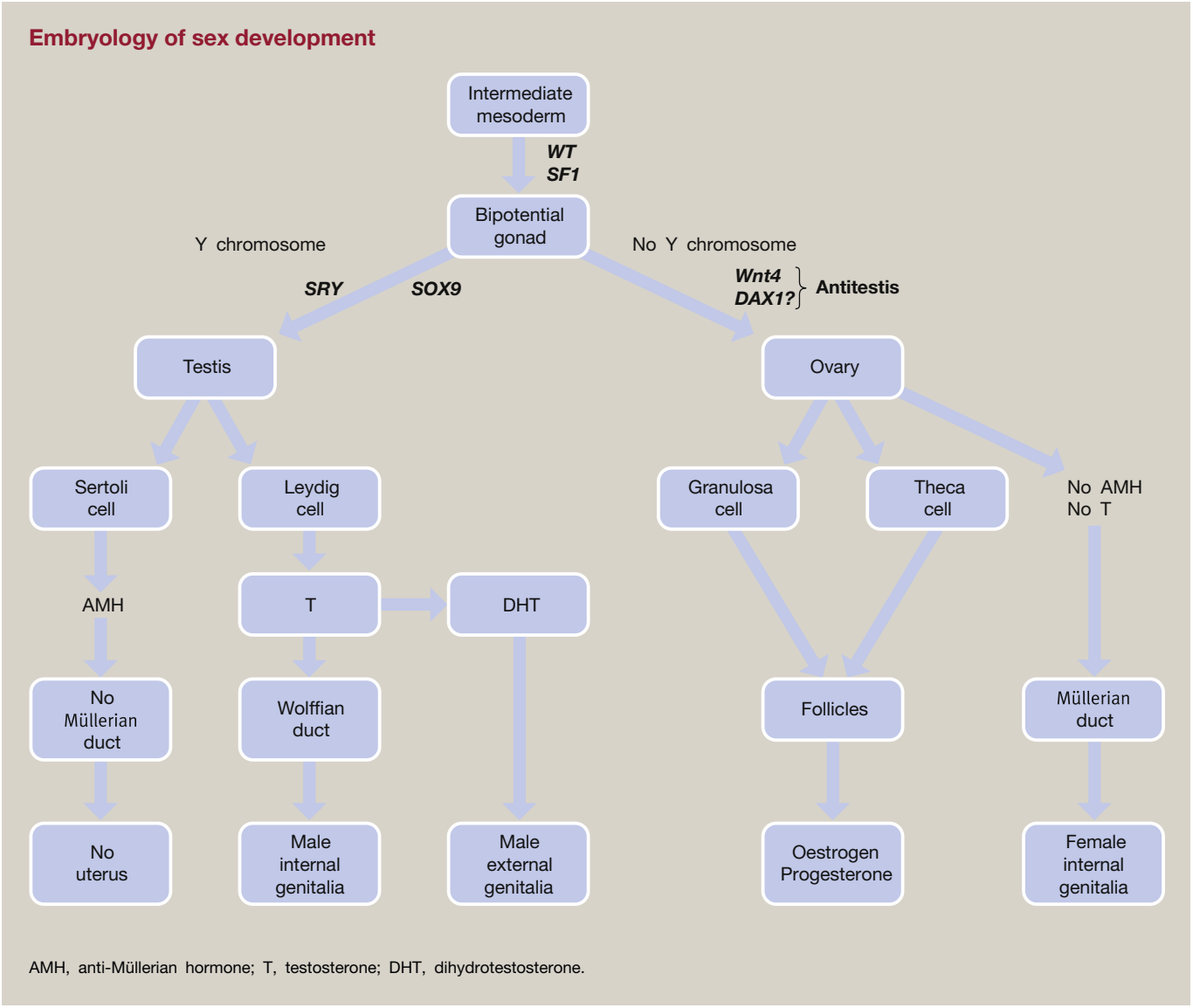

Figure 1