Ambiguous genitalia

What is ambiguous genitalia?

Ambiguous genitalia is a birth defect in which the outer genitals do not have the typical appearance of either a boy or a girl.

Ambiguous genitalia may be a result of a disorder of sexual development (DSD), previously called intersex conditions.[1] The ability to diagnose these conditions has improved greatly in recent years, due to advances in molecular genetics. Prompt, accurate diagnosis and counselling about therapeutic options should be available to parents soon after the baby's birth. It used to be thought that early gender assignment was vital to help social and psychological development.

Recent research has challenged this thinking, so reconstructive surgery may now be deferred until psychological and social implications can be considered. Evidence about long-term outcomes for people with DSD who undergo gender assignment and reconstructive surgery is still lacking.[2] [3] This has particular implications in the situation where parents are demanding early reassignment surgery for a child with DSD.[4] [5]

Terminology

The term DSD is now used for congenital conditions in which chromosomal, gonadal or anatomical sex is atypical.

Current terminology
46,XX DSD
46,XY DSD
Ovotesticular DSD
46,XX testicular DSD
46,XY complete gonadal dysgenesis

Normal sexual determination and differentiation[6]

Management and diagnosis of DSD require understanding of normal sexual determination and differentiation. Chromosomal sex prescribes gonadal sex which, in turn, prescribes the phenotypic sex. The gonad type determines whether the Müllerian or Wolffian ducts develop or regress. Gender identity is affected by prenatal and postnatal brain development and not just by phenotypic appearance.[3]

- Male and female embryos develop in a similar manner until seven weeks of gestation.
- In the presence of a Y chromosome, the undifferentiated gonad develops into a testis and, in the absence, it develops into an ovary. The genetic information for this to happen is held on the short arm of the Y chromosome - the sex-determining region Y (SRY). In the absence of this region, the gonad develops into an ovary. However, other genes are important, as demonstrated by the existence of XX males with testicular tissue without the SRY.

- The primitive gonad develops from primordial germ cells from posterior endoderm of the yolk sac:

    - With Y chromosome, primitive seminiferous tubules develop in the centre of the gonad. Fetal pituitary luteinising hormone (LH) and placental human chorionic gonadotrophin (hCG) encourage fetal Leydig cells to develop and produce testosterone.

    - In the absence of a Y chromosome, the germ cells undergo mitotic and meiotic divisions to form oocytes. These become surrounded by a layer of granulosa cells and are called primordial follicles. These are some seven million in number at the 20th to 25th week of gestation. With the surge of fetal pituitary follicle-stimulating hormone (FSH), the first primary follicles are formed.

- Differentiation of genital ducts:

    - Around the fourth week of gestation, two substances - testosterone and anti-Müllerian hormone (AMH) - are critical for male differentiation of the genital ducts. The testosterone induces primordial Wolffian (mesonephric) duct to become epididymis, vas deferens and seminal vesicle. High local levels of testosterone are needed to achieve this. AMH is produced by Sertoli cells of the testis and this suppresses passive development of Müllerian ducts (into the upper third of the vagina, uterus and Fallopian tubes). Testosterone may enhance the AMH inhibition.

    - In females, the Wolffian ducts disappear and the Müllerian ducts develop into the upper third of the vagina, uterus and Fallopian tubes. Exposure to androgens does not affect this and neither does the presence or absence of ovaries.

- Differentiation of external genitalia. The external genitalia of males and females are identical in the first seven weeks of gestation:

    - In males, from seven weeks, active differentiation towards the male phenotype occurs moderated by testosterone and its conversion to dihydrotestosterone (DHT) by 5-alpha reductase (present in the cells of external genitalia and urogenital sinus). Genital tubercle becomes glans. Fusion of urethral folds and groove forms the shaft of the penis. Labioscrotal swellings fuse and enlarge to become scrotum.

    - In the female, genital tubercle becomes the clitoris, labioscrotal swellings the labia majora and urethral folds the labia minora. The urogenital sinus forms the lower two thirds of the vagina.

- Testosterone-related development begins at six weeks of gestation, co-inciding with a surge in LH but, after about 14 weeks, testosterone levels are dependent on placental hCG. The consequent fetal levels of testosterone help the growth of the phallus and scrotum and testicular descent. Micropenis and cryptorchidism result from congenital gonadotrophin deficiency.

How common is ambiguous genitalia? (Epidemiology)

DSDs are caused by a variety of different conditions which vary greatly in incidence:

- Genital anomalies are estimated to occur in 1 in 4,500 births.[7]
- The most common cause of ambiguous genitalia in the newborn is congenital adrenal hyperplasia (CAH). A study found that the UK incidence is approximately one in 18,000 births.[8] CAH appears to be more common in those of European Jewish, Hispanic, Slavic and Italian descent.
- Mixed gonadal dysgenesis (MGD) is the next most common cause of ambiguous genitalia.

- Hypospadias is quite common (1 in 300 live births) but this is combined with undescended testes in less than 1% of such cases.[9] It is estimated that 13% of infants with hypospadias and cryptorchidism will have a chromosomal anomaly.[5]

The pathophysiology and classification of disorders of sex development

To make a diagnosis, it is essential not only to understand normal development but also to understand the different pathophysiological mechanisms responsible for DSDs.

Current terminology

The old classification and terminology have been deemed unhelpful to management by many and abandoned in favour of a classification which not only highlights the underlying pathophysiology but which avoids pejorative terminology.[5]

Virilised females

- Virilisation by androgens of fetal origin. This may be from CAH or persistent fetal adrenocortical steroids.
- Virilisation by androgens of maternal origin. These may be from drugs (anabolic steroids, testosterone, danazol, progestogens, etc), tumours (ovarian or adrenal) or maternal CAH.
- Dysmorphic syndromes (eg, Beckwith-Wiedemann syndrome, Seckel's syndrome, Zellweger's syndrome).[10]
- Local abnormalities (eg, lipomas, neurofibromatosis).
- Idiopathic.

Inadequately virilised males[5]

- Leydig cell agenesis or hypoplasia.
- LH deficiency.

- Inborn errors of testosterone biosynthesis. These may affect testes and adrenal glands (eg, cholesterol side chain cleavage deficiency, 3 beta-hydroxysteroid dehydrogenase deficiency, 17 alpha-hydroxylase deficiency) or just testes (eg, 17,20-lyase deficiency).
- Target tissue defects. This includes defects in testosterone metabolism (eg, 5-alpha reductase deficiency) or androgen receptor defects.
- Persistent Müllerian duct syndrome. AMH deficiency will cause this.
- Dysmorphic syndromes such as Dubowitz's syndrome, Smith-Lemli-Opitz syndrome, etc.

Disorders of gonadal differentiation [5]
The role of the testis in development of internal and external genitalia means that dysgenetic gonads produce combinations of abnormalities of internal and external genitalia. Examples include:

- Gonadal dysgenesis. Patients often have XO (often with mosaicism - eg, Turner syndrome) or XY karyotypes and present as females with amenorrhoea.
- Mixed gonadal dysgenesis. Patients may typically have testes palpable (inguinal or scrotal) with perineal hypospadias. On the side of testes (ipsilateral) Wolffian structures, absent Müllerian but Müllerian and absent Wolffian same side as streak gonad.
- 'Vanishing testes syndrome' or anorchia. Boys presenting with normal male genitalia and bilateral cryptorchidism, who must have had testicular function in the fetal period.
- True hermaphrodites. Well-developed ovarian and testicular tissues are found in either the same or opposite gonads. Genital duct development is according to the ipsilateral gonad. Can present with ambiguous genitalia or at puberty.

Presentation [5]

Most cases of DSD will be diagnosed at birth because of ambiguous genitalia. However, disorders associated with phenotypic males and females may only be diagnosed much later - eg, at puberty. For instance, phenotypic females may only be diagnosed as 46,XY when they are investigated for primary amenorrhoea.

Infants who are born with ambiguous genitalia represent a neonatal medical emergency for physical, social and psychological reasons. Immediate referral to an experienced multidisciplinary team (MDT) is essential. Urgent medical assessment is needed; for example, 75% of infants with CAH have associated salt-wasting nephropathy which can cause hypotension, collapse and death.

Gender assignment of infants with DSD will involve discussion with a team including geneticists, neonatologists, endocrinologists, surgeons, ethicists and counsellors. The timing of both gender assignment and surgery is still under debate and further trials are needed to clarify these difficult decisions.[4]

Common findings in the newborn, suggesting a DSD[11]

- Male appearance but with associated abnormalities of genitalia:
  - Severe hypospadias *with* bifid scrotum.
  - **Undescended testis/testes** *with* hypospadias.
  - *Bilateral* non-palpable testes in a full-term apparently male infant.
- Female appearance but with associated abnormalities of genitalia:
  - Clitoral hypertrophy of any degree, non-palpable gonads.
  - Vulva with single opening.
- A baby with indeterminate sex where it is impossible to identify whether they are male or female immediately:
  - Ambiguous genitalia.

Team effort is required in diagnosis and this begins with taking time to take a detailed history. Diagnosis should follow an orderly process and jumping to conclusions should be avoided. The most commonly seen condition will be the virilised 46,XX female with CAH and often the challenge is to identify less common causes. There is a strong possibility of misdiagnosis and gender misassignment, particularly with CAH, where virilisation can be extreme.

History

The history should incorporate maternal, family and neonatal history:

- Maternal:
    - Medication history including any exposure to androgens.
    - Any history or signs of virilisation in the mother.
    - A history of unexplained early or neonatal deaths may indicate missed adrenogenital deficiency.
    - Any history of a DSD in other children.
    - A history of parental consanguinity.
- Family history suggesting a genetically transmitted trait - for example, of:
    - Ambiguous genitalia.
    - Infertility.
    - Primary amenorrhoea.
    - Late puberty.

    Recessive traits will tend to occur in siblings and X-linked abnormalities will be seen in males scattered across the family tree.
- Neonatal history of failure to thrive, vomiting or diarrhoea.

Examination

Broadly, this should include:

- A search for other congenital abnormalities.
- Identification of dysmorphic features.
- Looking for increased pigmentation of the genital and areolar area (adrenogenital syndrome).

- Careful examination of the external genitalia (size of phallus, degree of differentiation - eg, Prader stages, clitoromegaly, hypospadias, position of meatus). Labioscrotal folds may be fused to give the appearance of a scrotum and be rugose or pigmented in adrenogenital syndrome.
- Examination of gonads. Careful examination of the labioscrotal folds, which usually identifies testicular material, although ovotestes may descend as well. The inguinal regions should also be carefully examined for gonads.
- Rectal examination which may identify cervix and uterus.
- Measurement of blood pressure.

Investigations[5] [12]

Work-up may include a variety of tests. In practice one of the most important is pelvic ultrasound. If a uterus is present, the baby is almost certainly a virilised female and most likely to have CAH. If the uterus is absent, the diagnosis is likely to be more difficult.

- Laboratory studies:
    - Chromosomal analysis for karyotype. Rapid karyotyping from buccal smears takes less than 24 hours as compared to five days for chromosome analysis.
    - Endocrine screening:
        - Testosterone androstenedione, DHT, dihydroepiandrosterone (DHEA), 17 alpha-hydroxyprogesterone.
        - LH and FSH.
        - Adrenocorticotrophic hormone (ACTH), renin, aldosterone, etc.
        - Synthetic ACTH stimulation test.
        - Serum AMH is much higher in boys than in girls and can help in neonatal diagnosis. The hCG stimulation test can identify functioning testicular tissue but should be reserved as a second-line investigation due to its invasive nature.
    - Electrolytes, urea and creatinine.
    - Androgen receptor levels.
    - 5-alpha reductase levels.
- Imaging:
    - Pelvic/renal/bladder ultrasound. Adrenal glands may be seen to be enlarged. Virilisation with a uterus makes CAH likely.
    - Genitography. This helps to define ductal anatomy.
    - CT and MRI scanning are not usually necessary but can further help identify anatomy.
- Other procedures include laparotomy or laparoscopy with or without gonadal biopsy. This can differentiate ovaries, testes, ovotestes and streak gonads.

- Urine tests for steroid excretion, stimulation tests and other invasive tests are rarely needed.

Diagnosis

- This should be made with great care and after proper diagnostic work-up which should include external appearance, internal anatomy, genetic make-up and hormone profile.[5] The authors of one study commented that despite thorough investigation, in as many as 50% of cases of 46, XY DSD a definitive diagnosis could not be made.[13]
- Referral and consultation between specialties (for example, geneticists, neonatologists, paediatric and adult endocrinologists, gynaecologists, psychologists, ethicists and social workers).[5] [11]

Differential diagnosis

The range of possibilities is considerable and can be appreciated from the classification of the causes of DSDs.

Management of ambiguous genitalia

Prompt referral is essential. The four key issues in management are:

- Accurate diagnosis.
- Gender assignment.
- Indications and timing of major surgery.
- Sharing of medical information with patient and parents.

Gender assignment

- Parents should be advised to delay registering the birth (it can be legally difficult to alter later) and naming the baby, until the sex of rearing is decided.
- This should be done after completion of the diagnostic process, including full clinical, genetic and biochemical investigation.
- It should be done involving the parents in full discussion and explanation.

- The assignment should aim to offer the best opportunity for normal puberty and sex life with unambiguous, functionally normal external genitalia and occasionally reproductive capability.

When considering the male gender, the size of the penis is important but so is the potential to grow. It is important to establish the potential for growth with a trial of testosterone.[14] Finding out later (at puberty) that androgen insensitivity prohibits masculinisation is to be avoided. It is important to identify virilised females, particularly where virilisation is extreme, as it can be, for example, in CAH.

Full discussion and explanation of the diagnosis often avoids medicolegal difficulties.

Gender identity disorders and gender dysphoria require highly specialised and sensitive management, howsoever they become manifest.[5]

Emergency treatment[12]

CAH can present with adrenocortical crisis, hyponatraemia or hypoglycaemia and emergency treatment of these complications is required.

Monitoring for this (eg, weight, potassium, glucose) is important.

Long-term management

As well as achieving early diagnosis and emergency treatment of complications, there are longer-term aspects to management which will vary according to the condition. CAH requires long-term care, for example.

- Medical care. Supplemental hormone therapy may be required if gonadal function is inadequate.

- Surgical treatment may be required. The timing of surgery can be controversial. Examples of the requirement for surgery include:[11] [12]

    - Hypospadias in males.
    - Vaginoplasty and clitoroplasty, which may be required In virilised females.
    - Gender reassignment, which may require surgery (multiple procedures).
    - Gonadectomy, which may be advisable for patients with dysgenetic or nonfunctional gonads because of the risk of malignant change.
    - Bilateral adrenalectomy, especially in carefully selected adult females who have not responded to medical therapy.

- Psychological support. Families will need intensive support, full explanations and information. This helps bonding with their child and probably the development of the child.

Further reading

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