Disorders of Sex Development – Ambiguous Genitalia

Kate Davies, RN (Child), Dip. H. E., BSc (Hons), MSc, NMP

Corresponding Author: Kate Davies

Senior Lecturer in Children’s Nursing, London South Bank University

&

Research Nurse in Paediatric Endocrinology, Barts and The London School of Medicine

Address: 103, Borough Road, London. SE1 0AA

Email: kate.davies@lsbu.ac.uk

Phone: +44 (0)20 7815 7981
 Fax: +44 (0) 20 7815 8490

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Disorders of sex development (DSD) encompass a wide range of congenital conditions with diverse features and pathophysiology, which usually present in the newborn period or during adolescence (Ahmed et al., 2015), where the development of chromosomal, gonadal or anatomic sex is atypical (Rothkopf & John, 2014). Ambiguous genitalia is a term to describe how a baby’s genitals look different than the genitals of most other boys and girls (Achermann, Eugster, & Shulman, 2011). It may mean that parents and healthcare professionals may not be able to correctly identify the sex of the baby. In some cases, it may be that a girl’s clitoris is so enlarged that it may look like a small penis, or the labia may be so fused together that it looks like a boy’s scrotum. It has been estimated that in around 1 in every 4500 live births, babies have genitalia that is ambiguous enough to not be able to assign a sex immediately (Michala, Liao, Wood, Conway, & Creighton, 2014), but some types of genital abnormalities may occur in as many as 1 in every 300 births (Rothkopf & John, 2014). True cases of absolute ambiguous genitalia are rare, but it is likely that the paediatric nurse will come across a case in their career.

**Causes of Ambiguous Genitalia**

It is difficult to give a specific description, as there are so many causes for different types of ambiguous genitalia. A consensus statement released in 2005 (Hughes, Houk, Ahmed, Lee, & Lawson Wilkins Pediatric Endocrine Society/European Society for Paediatric Endocrinology Consensus Group, 2006) grouped the disorders into the chromosomes present in the baby: 46,XX DSD; 46,XY DSD; and sex chromosome DSD, where there is an atypical number of combination of sex chromosomes. If the baby is diagnosed as 46,XX DSD, then this is due to the female foetus being exposed to too many male hormones (Achermann et al., 2011) when the genitals are forming. Sex chromosomes determine either male or female anatomy, and hormones need to act on these structures at specific times of embryological development (Wisniewski, Chernausek, & Kropp, 2012). Gonads will develop into testes or ovaries at around 7- 8 weeks gestation (Hutson, 2012a). XY chromosomes (male) will activate the SRY gene, which is only found on the Y chromosome, which starts testis development. Primary sex cords develop into Sertoli cells, which produce anti-Müllerian hormone (AMH). Leydig cells outside the testicular tubules form and make testosterone, which stimulates the Wolffian ducts to form internal male genitalia: the epididymis, vas deferens and seminal vesicles. Testosterone converts to dihydrotestosterone (DHT), which causes the development of the penis (Hutson, 2012b). In females, ovaries do not produce AMH, so the Müllerian ducts develop into female reproductive structures (Wisniewski et al., 2012).

If there are any abnormalities in this pathway of development, such as inappropriate hormone levels (Ogilvy-Stuart & Brain, 2004) or a mutation or deletion of the SRY gene, then the gonads may fail to develop into either an ovary or a testis (Hutson, 2012b). This may therefore result in ambiguous genitalia with ‘undervirilisation’ of an XY baby or ‘virilisation’ of an XX baby (Ogilvy-Stuart & Brain, 2004).

One of the most common reasons why a baby may present with ambiguous genitalia is 46,XX female infants with congenital adrenal hyperplasia (CAH) (Hughes, 2005). An affected female foetus will make excess adrenal androgens from around 8 weeks gestation when the gonads will develop into ovaries or testes. An excess of masculinizing adrenal androgens will result in an enlarged clitoris and potentially fused labioscrotal folds. Classical CAH due to 21-hydroxylase deficiency also leads to glucocorticoid and mineralocorticoid deficiency, so these will need to be replaced with lifelong oral hydrocortisone and fludrocortisone (Hindmarsh, 2009). Girls are diagnosed usually shortly after birth because of the virilisation; boys usually present within the first few weeks of life with a salt-wasting adrenal crisis (Hindmarsh, 2009). A case study can be seen in Box 1.

**Evaluation of a Child with Ambiguous Genitalia**

A full history will need to be taken, including any family history of consanguinity, DSD, or adrenal disorders. Full details of maternal and paternal health will also be needed, as well as the pregnancy history (Rothkopf & John, 2014). The baby will need to be fully examined (Devlin & Wilkinson, 2008), including a close examination of the external genitalia. This is to ascertain if there are palpable gonads, and how virilised they are, according to a Prader staging score (Ogilvy-Stuart & Brain, 2004). Box 2 demonstrates how Prader stages I-V show increasing virilisation in a girl with mild clitoromegaly to a male with hypospadias.

Close attention will be given to any signs of dehydration and low blood pressure, which may be altered in severe salt-wasting CAH (Rothkopf & John, 2014). Other diagnostic tests will also be carried out, including:

- Karyotype

This can be a standard karyotype or rapid karyotype analysis, such as FISH (fluorescence *in situ* hybridization) (Brain et al., 2010), which is where a certain gene or DNA sequence can be located in a genome.

- Hormone levels

These may include 17-hydroxyprogesterone, testosterone, adrenal androgens, gonadotrophins and AMH.

- Serum electrolytes

These are imperative in order to potentially avoid a salt-wasting crisis.

- Urinalysis

- Pelvic ultrasound

- Laparoscopy

(Rothkopf & John, 2014)

A diagnosis can usually be made within a few days or sometimes longer (Achermann et al., 2011).

**Factors to Consider when Deciding on Sex Assignment**

One of the first questions parents will ask when their baby is born, or at an antenatal scan, is what is the sex of the baby? This is especially pertinent in cases of babies with a DSD, and parents may be faced with whether to bring their baby up as a boy or a girl. Factors to consider will include: the child’s condition, and the likely cause; the appearance of external and internal genitalia; possible surgical options; how well the ovaries or testes will function later in life, and if the child will be fertile; and the parental preferences or cultural beliefs will also be considered (Achermann et al., 2011). When faced with such a complex array of factors, it is important to include a full multidisciplinary team (MDT) to help the parents make the best decision for their child.

**The Multidisciplinary Team**

To ensure a child with ambiguous genitalia receives the best care, it is important to utilize all members of the MDT (Ahmed et al., 2011), which can be reached through regional, larger centres. The team should include paediatric specialists in endocrinology, surgery and/or urology, clinical psychology, radiology, neonatology, and nurse specialists (Ahmed et al., 2015). Other team members can include biochemists, geneticists, gynaecologists, ethicists, and even cultural leaders (Brain et al., 2010).

**The Role of the Nurse**

Nurse specialists are in an ideal position to coordinate the MDT and provide a link for the families (Brain et al., 2010). Clinical nurse specialists are key healthcare professionals in providing education to parents and families (Leary et al., 2008), and this education is a pivotal role in CNS functionality (Hamric & Spross, 1989). Parents of children with a DSD want information and guidance on the condition (Crissman et al., 2011). Paediatric nurses can liaise with the CNS to disseminate information at key moments when the MDT is unavailable. Community paediatric nurses may also offer support and become actively involved in regular serum sampling for sodium levels if the infant has CAH. Liaison is imperative with fellow adult nursing colleagues at transition (Hullmann, Chalmers, & Wisniewski, 2012; Schober et al., 2012).

**Conclusion**

It is important to investigate ambiguous genitalia as early as possible in order to ascertain the cause and assign the sex of rearing (Ahmed et al., 2011). A holistic, multidisciplinary approach is essential (Brain et al., 2010), and the paediatric nurse is in prime position to be the main point of liaison, and educate and support the family.

*Resources*

DSD Families: [www.dsdfamilies.org](http://www.dsdfamilies.org) (UK)

Living with Congenital Adrenal Hyperplasia: [www.livingwithcah.com](http://www.livingwithcah.com) (UK)

Intersex Society of North America: [www.isna.org](http://www.isna.org) (USA)

Cares Foundation: [www.caresfoundation.org](http://www.caresfoundation.org) (UK & USA)

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Box 1: A case study of an infant with ambiguous genitalia

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|  Baby A was referred to the paediatric tertiary hospital at three weeks of age for a second opinion and potential future management. Baby A was born at term, weighing 4.53 kg, to non-consanguinous parents, with no family history of DSD. Antenatal ultrasound scans showed that the parents were expecting a boy. The family decorated the baby’s nursery in blue colours and had bought boy’s clothes. When Baby A was born, the midwife announced that the baby was indeed a boy. At the paediatric neonatal examination prior to discharge, however, the paediatrician felt no palpable testes in the scrotum and an urgent pelvic ultrasound was performed. No testes or ovaries were seen, but normal bladder and kidneys were observed. Blood was taken for chromosome analysis, which showed a normal female karyotype of 46,XX. A baseline blood sample for 17-hydroxyprogesterone was elevated at 101.9 nmol/L (normal range 0-5 nmol/L) (Butler & Kirk 2011). A urine steroid profile showed characteristic markers of 21-hydroxylase deficiency. This led the paediatrician at the local hospital to make a diagnosis of Baby A being a female infant with classical 21-hydroxylase deficiency CAH, and the baby was commenced on oral hydrocortisone and fludrocortisone. Baby A and her parents met with the specialist DSD team for further input, increased support, and to discuss potential genital reconstructive surgery in the future (Crouch, Liao, Woodhouse, Conway, & Creighton, 2008). The team reassured the parents, and an intensive support programme commenced. A repeat pelvic ultrasound showed ovaries, and an examination of Baby A’s genitalia was classified as Prader V. Full education was given in managing Baby A’s medication. She was already started on hydrocortisone suspension, and this needed to be changed to hydrocortisone tablets, in accordance with recent guidelines (Speiser et al., 2010), as suspension has been proven to provide inadequate control of adrenal androgens (Merke, Cho, Calis, Keil, & Chrousos, 2001; Davies, 2015). Further guidance was given by the CNS in administering tablets, sodium solution, and sick day and emergency management. Baby A’s parents had met with the CNS, endocrinologist, geneticist, psychologist, and urologist. They then felt confident with the multidisciplinary team approach, and care was transferred to the team. Baby A is now thriving and is followed up regularly in the paediatric endocrinology clinic. |

Box 2: The Prader staging system

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| http://image.slidesharecdn.com/approachtodysmorphicchild-150225152007-conversion-gate01/95/approach-to-dysmorphic-child-42-638.jpg?cb=1424877649 |

Note. Reprinted with permission from “Early assessment of ambiguous genitalia,” by A. L. Ogilvy-Stuart & C. E. Brain, 2004, *Archives of Disease in Children, 89,* p. 404.