Differences of Sexual Development including ambiguous genitalia Full Clinical Guideline – Derby only

Reference no.: NIC MIS 13/May 2023/v005

Important Note: This guidance should be read in conjunction with Ref CLIN G 102 'Guideline on the Management of Children with Congenital Adrenal Hyperplasia'

1. Introduction

The newborn infant with disordered genital development presents a social emergency as well as a diagnostic and treatment challenge. While it is important that a definitive diagnosis be made quickly to minimise medical, psychological and social complications, it is essential that gender assignment is based on a confident pathological and functional basis. Professionals should be aware of the rights of family and individual to be involved in decisions regarding gender assignment. Parents should not be left with an uncertain attitude as to their child's sex of rearing. They should be encouraged to avoid ambiguous names and, if necessary, apply for a deferment of birth registration.

The diagnosis and longer term management requires a multidisciplinary approach based on the regional network of experts. It is important to involve professionals experienced in managing patients at the earliest possible stage. In the first instance the on-call consultant neonatologist in Derby should be contacted to discuss the case further. Contact can then be made with regional services as soon as possible. At discharge a copy of the confidential discharge letter must be sent to all the professionals involved.

2. Aim and Purpose

To ensure a standardised approach to the investigation and initial management of children with suspected differences of sexual development/ambiguous genitalia.

This guideline outlines the initial approach to management of these children and highlights key contacts for their ongoing care.

3. Definitions, Keywords

The current term 'difference of sexual development' (DSD) is defined as 'congenital conditions inwhich development of chromosomal, gonadal or anatomical sex is atypical'.

4. Main body of Guideline

i) Useful contacts:

Contact the on-call neonatal consultant for advice on immediate management if on the postnatal ward or NICU; or the general paediatric consultant on call if presenting via the emergency department.

ii) Regional expertise:

- Paediatric Endocrinology: Dr. Denvir, Dr Randell and Dr Sachdev
- Paediatric Urology: Mr. Williams and Mr Shenoy
- Genetics: Dr Dixit

iii) Newborns needing investigation:

- Indeterminate genitalia

- Apparent male:
  - Bilateral impalpable testes in a full term infant
  - Hypospadias associated with bifid scrotal folds
  - Undescended testes with hypospadias
- Apparent female:
  - Clitoral hypertrophy
  - Vulva with single opening
  - Inguinal hernia containing a gonad

iv) Clinical assessment:

- **Obstetric history:**
  - Endocrine disturbance in pregnancy?
  - Abnormalities of antenatal ultrasound scans?
  - Maternal drug ingestion (e.g. Danazol, progestogens)?

- **Family history:**
  - Consanguinity
  - Unexplained neonatal deaths (can suggest undiagnosed adrenal crisis)
  - Genital anomalies (e.g. X linked recessive conditions like androgen insensitivity)
  - Abnormal pubertal development (including virilisation of females and delayed/ absent menarche)
  - Infertility in close relatives.

- **General physical examination:**
  - Hydration status
  - Dysmorphic features
  - Document weight, length and head circumference.
  - Look for other malformations, e.g. imperforate anus, midline defects (may be associated with pituitary hypoplasia), skull abnormalities
  - Jaundice is more common in a child with pituitary dysfunction.

- **Genital examination**:
  - Length and girth of phallus: Stretched penile length (pubic ramus to distal glans): Term infant normal mean= 3.5cm. Micropenis = <-2.5SD = < 2 cm
  - Position of urethral, vaginal/urogenital orifices.
  - Palpable gonads. Palpate for gonads by flat finger palpation from the internal inguinal ring down to labial folds/ scrotal sac.
  - Note the fullness, symmetry and rugosity of labio-scrotal folds
  - Skin pigmentation may be suggestive of CAH
  - It may be helpful to describe the appearance of the external genitalia according to the Prader classification (below).

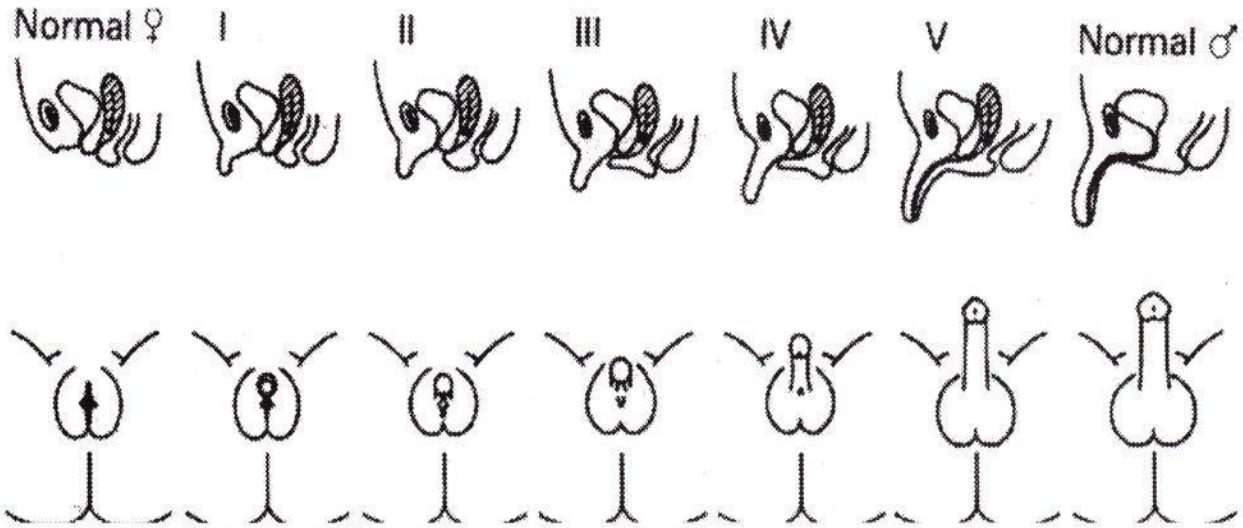

Fig. 2 Prader classification of ambiguous genitalia. Adapted from Prader A, Helv Paediatr Acta 1954; 9: 231.

- Assess the appearance of the mother:
  - Virilisation may be due to placental aromatase deficiency or maternal endocrine tumour.

v) Communication with parents:

The initial contact with parents of a child with DSD is important; first impressions will persist. While privacy needs to be respected, DSD is not shameful. A positive atmosphere is essential for parents to develop their relationship with their child. If possible, offer the family a side room as this allows easier, open discussions. Encourage both parents to be present at any conversations wherever feasible.

No attempt should be made to guess or suggest a diagnosis leading to gender assignment. The infant should be referred to as “your baby” or “your child” and not “he”, “she” or “it”. If well, the infant should stay with the parents while evaluation and investigations are performed.

Discussions regarding gender assignment should be dealt with by the specialist DSD team. In the meantime parents should avoid ambiguous names and, if necessary, apply for a deferment of birth registration. The office of the registrar of births must be contacted to explain that sex will be assigned and that the parents must not be pressurised to register the birth.

The following websites offer helpful information for families:
www.nhs.uk/conditions/disorders-sex-development

Home :: DSD Families

vi) Investigations:

Guidance should be sought from the paediatric endocrinology team (discuss urgently, usually in daytime hours). Contact the paediatric endocrinologist on call via QMC switchboard. Some investigations for DSD need to be deferred for a couple of days in order to obtain accurate and reliable results.

<table>
<tr><th colspan="2">Day One/Immediately</th></tr>
<tr><td colspan="2">

Karyotype (1ml Lithium Heparin –request urgently)*.
FISH – X centromere & SRY probes (EDTA – Result next working day).
Save DNA
LH, FSH, testosterone, oestradiol
Blood glucose monitoring – 3 – 4 hourly before feeds

*Note that samples must arrive in the laboratory by 12:00 (midday) Mon to Fri to be sent to Nottingham on the same day.
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<tr><th colspan="2">Day 3</th></tr>
<tr><td>Essential (2 plain clotted (red top) tubes + Urine)</td><td>Consider (3 x 1.5ml EDTA tubes)</td></tr>
<tr><td>

Urea and Electrolytes
Random cortisol (+/- synacthen test if < 150nmol/l)
Anti-Mullerian hormone (AMH)
17-α-hydroxyprogesterone (17-OH-P)
Request TSH, FT4 and FT3 (?pituitary dysfunction)
Urine steroid profile

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ACTH (purple top ON ICE sent to lab immediately
Aldosterone (purple top)
Plasma Renin activity (purple top MUST NOT BE ON ICE but arrive at lab within 15 min)

</td></tr>
</table>

* It is important to ring the genetics service to get it processed urgently.

Note: some of these investigation results may take several weeks.

Note: If analysis is urgent, please phone the Duty Biochemist (ext

89383) to discuss e.g. urine steroid profile.

Imaging is not usually needed.

5. References (including any links to NICE Guidance etc.)

I A Hughes, C Houk, S F Ahmed, P A Lee and LWPES/ ESPE Consensus group
Consensus statement of management of intersex disorders
Arch. Dis. Child. 2006;91;554-563

P A Lee, A Nordenstrom, C Houk, SF Ahmed et al. Global disorders od Sex development update since 2006: Perceptions, approach and care. Horm Res Paediatr 2016; 85: 158-180

6. Documentation Controls

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Development of Guideline: Tracy Tinklin				
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