Differences in Sexual Development: Physical, Psychosocial, and Ethical Issues

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Conflict of Interest Disclosure
I am a member of the Novo Nordisk Speakers’ Bureau

How many of you remember these terms?
- Hermaphrodite
- Ambiguous genitalia
- Male/female pseudohermaphroditism
- Intersex
- Disorders of sexual development
• These terms emphasize gonadal anatomy which is neither clinically or socially useful
  • Dreger, et.al, JPEM;18:729-733 (2005)

DSD- Definition
• “congenital conditions in which development of chromosomal, gonadal, or anatomical sex is atypical...may have biological characteristics of both the male and female sexes”

DSD- prevalence
• 1% of live births
• 0.1%-0.2% come to medical attention
Specific genes are needed to produce a girl as well

Timing is everything

<table>
<thead>
<tr>
<th>Pregnancy week</th>
<th>Event</th>
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<tbody>
<tr>
<td>6</td>
<td>Somatic cells begin to differentiate into male or female cells</td>
</tr>
<tr>
<td>7-8</td>
<td>SRY gene activates and leads to male development</td>
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<tr>
<td>−15</td>
<td>Female development begins</td>
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Female development:
- Somatic cells → Genital ridge
- Genital ridge
- Bipotential gonad
- Female development

External genitalia:
- Wolffian ducts regress
- Median ducts

Ovary

DAFT

SRY

FSH

LH
Most Common Disorders of Sexual Development

- XX DSD
- CAH- 21-hydroxylase deficiency
- XY DSD
- Defect in androgen sensitivity (PAIS, CAIS)
- CAH- 5 alpha reductase deficiency
- Chromosomal DSD
- Turner Syndrome
- Klinefelter Syndrome

An algorithmic approach to DSD

From Kolod, Penn Handbook of Urology, 2007

Evaluation of DSD

- History
- Physical Examination
- Imaging
- Laboratory Studies
Only a couple of important items in the history

- Infertility in aunts & uncles
- Hirsutism in females
- Ambiguity in family members
- Maternal exposure to androgens, anabolic steroids, progestins during pregnancy

Describe physical findings in sex-neutral terms

- Palpable gonads
- Phallus
- Size
- Position of urethral opening
- Bend, tethering, chordee
- Labioscrotal folds
- Thinning or rugation
- Perineal orifice
- Symmetry
- Dysmorphic features

Diagnostic imaging

- Pelvic ultrasound for uterus, sometimes gonads
- Contrast study of urogenital opening
Diagnostic tests

In nearly all:
• Karyotype
• 17-hydroxyprogesterone
• Testosterone, LH, FSH

More selectively:
• Anti mullerian hormone
• Dihydrotestosterone
• CAH profile
• Androgen receptor gene
• Specific FISH tests

Nonstandard genital anatomy

• Small penis or large clitoris?
• Underdeveloped scrotum or overdeveloped labia?
• Anorchia or undescended testes?

DSD includes infants with

• Nonstandard genital anatomy- Aphallia
• Abnormalities of internal reproductive structures- Turner Syndrome
• Hormonal abnormalities related to genital development- CAH
• Chromosomal sex not analogous to phenotypic sex- CAIS
Ethical issues

• Gender assignment
• Reconstructive surgery
• Clinical decision making

Modern reconstructive surgery claims that it is possible to create functionally and cosmetically normal-appearing genitalia; however, there is still no consensus regarding indication, timing or procedures of choice.

Such assessments must include documentation of complication rate, functional outcome (micturition (urination) and sexuality), cosmetic outcome, quality of life, psychosexual functioning and, finally, re-evaluation of the indication. Although genital surgery can involve a radical approach to the urinary tract, the effects on urinary function and the pelvic floor (including safe urine storage and drainage, urinary continence and risk of infection) are often insufficiently addressed.

Current debate

• Is non-urgent genital surgery in infancy ever justified?
• Should parents be allowed to give permission for genital surgery?
• What gender assignment is appropriate for a completely virilized female?
Caring for individuals with a Difference of Sex Development (DSD): a Consensus Statement.

22. That our American Medical Association support optimal management of DSD through individualized, multidisciplinary care that: (1) seeks to foster the well-being of the child and the adult he or she will become; (2) respects the rights of the patient to participate in decisions and, except when life-threatening circumstances require emergency intervention, defers medical or surgical intervention until the child is able to participate in decision making; and (3) provides psychosocial support to promote patient and family well-being. (New HOD Policy)

DSD: Ethical principles
- Autonomy
- Beneficence/Nonmaleficence
- Truth telling
- Freedom from discrimination
- Medical knowledge