Approach to Disorders of Sex Development (DSD)

Old name:
“The Approach to Intersex Disorders

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Outline

• “DSD”: a new nomenclature
• Normal sexual development
• An approach to child with genital anomalies
• Focus on some DSD conditions
“Is it a boy or a girl?”
Disorders of Sex Development (DSD)

• Social emergency
• Medical Dilemma
Is it a boy or a girl?
Is it a boy or a girl?
Human sexual differentiation

- Incidence 1:4500 live births
- Human sexual differentiation is a highly complex process under the control of multiple genes and hormones
The Y chromosome

A Functional Map of the Y Chromosome
(from Lahn & Page 1997, Science 278:675)
<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosome location</th>
<th>Human disorder</th>
<th>Associated malformations</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT-1</td>
<td>11p13</td>
<td>yes</td>
<td>Wilm’s Tu., nephropathy</td>
</tr>
<tr>
<td>LIM-1</td>
<td>11p12-13</td>
<td>no</td>
<td>----</td>
</tr>
<tr>
<td>SF-1</td>
<td>9q33</td>
<td>yes</td>
<td>Adrenal insufficiency</td>
</tr>
<tr>
<td>SRY</td>
<td>Yp11.3</td>
<td>yes</td>
<td>none</td>
</tr>
<tr>
<td>DAX-1</td>
<td>Xp21</td>
<td>yes</td>
<td>Duplication – sex reversal, Mutation – adrenal insufficiency</td>
</tr>
<tr>
<td>SOX-9</td>
<td>17q24.3-25.1</td>
<td>yes</td>
<td>Campomelic dysplasia</td>
</tr>
<tr>
<td>DMRT1/DMRT2</td>
<td>9p24.3</td>
<td>yes</td>
<td>Renal malformation, Mental retardation</td>
</tr>
</tbody>
</table>
46, XY

WT-1
LIM-1
SF-1

Bipotential gonad

SRY
DAX-1
SOX-9
DMRT1&2

Testis

Sertoli cells

Inhibin B

MIS

Regression of Mullerian structures

Leydig cells

Testosterone

Star
P450scce
P450c17
3β-HSD
17β-HSD

5α reductase

DHT

Virilization

AR
Human sexual differentiation

• Differentiation of the bipotential gonad into testis or ovary due to presence or absence of Y-chromosome genes especially SRY gene

• Differentiation of the Wolffian ducts into epididymis, vasa deferentia and seminal vesicles due to effect of testosterone

• Differentiation of the müllerian ducts into uterus, fallopian tubes & upper vagina due to absence of AMH (anti-mullerian hormone)

• Development of the external genitalia into penis, scrotum ( due to DHT) or clitoris and labia majora & minora (due to estradiol)
Differentiation of external genitalia

- The external genitalia of both sexes are identical during the first 7 weeks of gestation
- Without the hormonal action of the androgens testosterone and dihydrotestosterone (DHT), external genitalia appear phenotypically female
- In the gonadal male, differentiation toward the male phenotype actively occurs over the next 8 weeks
- This differentiation is moderated by testosterone, which is converted to 5-DHT by the action of an enzyme, 5-alpha reductase, present within the cytoplasm of cells of the external genitalia and the urogenital sinus
- DHT is bound to cytosol androgen receptors within the cytoplasm and subsequently is transported to the nucleus, where it leads to translation and transcription of genetic material
• In turn, these actions lead to normal male external genital development from primordial parts
  – forming the scrotum from the genital swellings
  – forming the shaft of the penis from the folds
  – forming the glans penis from the tubercle
  – The prostate develops from the uro-genital sinus
• Incomplete musculanization occurs when testosterone fails to convert to DHT or when DHT fails to act within the cytoplasm or nucleus of the cells of the external genitalia and urogenital sinus
The Brain is a sexual organ: the most poorly understood

- **Gender identity** = sense of self as a boy or girl
- **Gender role** = preferential adoption of behaviors more frequently observed in males vs. females
- **Sexual orientation** = preferred sex of partner e.g. heterosexual, homosexual, bisexual

*These are not all the same!*
Approach to Disorders of Sex Development (DSD)

History

- Family history of genital ambiguity, infertility, or unexpected changes at puberty may suggest a genetically transmitted trait.
- History of early death of infants in a family may suggest a previously missed adrenogenital deficiency (CAH).
- Maternal drug ingestion is important, particularly during the first trimester, when ambiguity may be produced exogenously in a gonadal female.
- Although extremely rare, a history of maternal virilisation may suggest an androgen-producing Adrenal / Ovarian tumor.
Examination

- Dysmorphic features
- Palpable gonad (s)
- Blood pressure measurements
- Asymmetry of the external genitalia (mixed gonadal dygenesis)
- Phallus length
- Assessment of urogenital sinus openings
- Position of the urethral meatus
- Labioscrotal fold assessment for degree of fusion, ruge and hyperpigmentation
Laboratory evaluation

- Chromosomal analysis (essential)
- $17\alpha$- hydroxyprogesterone level
- Blood glucose level
- Serum electrolytes & renal function
- Plasma ACTH & Cortisol
- Plasma renin activity & Aldosterone
- HCG stimulation tests
- Testosterone / DHT ratio (pre & post HCG stimulation test)
- Urinary steroid profiles
Imaging studies & Laparoscopic

• Pelvic U/S (presence / Absence internal male or female internal organs)
• Adrenal U/s (size of Adrenal gland / hyperplasia or tumor)
• Genitogram (presence / absence of vaginal tract and urogenital fistula)
• MRI of the pelvis (if U/S not conclusive)
• Laparoscopy / Laparotomy
• Gonadal biopsy & histology (pure ovarian /testicular / ovotestis/ mature or dysgenetic structures)
Parental counseling

- Parents should see the genitalia
- Clear statement that it will be possible to decide whether the child is either male or female
- Investigations are needed to determine the sex identity
- Postpone naming of the baby & birth certificate till tests results are ready
• When results back, the diagnosis, prognosis and treatment options are fully discussed

• Parent’s should be involved in taking the decision of “gender assignment” and how the child will develop sexually as an adult?
Gender Assessment Team

Diagnostic Approach

- Multiple malformations
  - Syndrome identification:
    - Multiple congenital anomaly syndrome
    - Autosomal chromosomal abnormality
    - Exstrophy of the cloaca

- Isolated genital abnormality
  - Determination of:
    - Chromosomal sex
    - Gonadal sex
    - Phenotypic sex
GOAL

- Chromosomal sex
- Gonadal sex
- Phenotypic sex

Sex of Rearing

**Timing:** As soon as possible based on best information
Disorders of sexual Differentiation

• Female pseudohermaphrodite (46 XX DSD)
  – Two ovaries

• Male pseudohermaphrodite (46 XY DSD)
  – Two testes

• True hermaphrodite
  – Ovary and/or testis and /or ovotestis

• Mixed gonadal dysgenesis
  – Testis plus streak gonad

• Pure gonadal dysgenesis
  – Bilateral streak gonads
## Proposed changes

<table>
<thead>
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<th>Previous</th>
<th>Proposed</th>
</tr>
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<tbody>
<tr>
<td>Intersex</td>
<td>DSD</td>
</tr>
<tr>
<td>Male pseudohermaphrodite, undervirilization of an XY male, and undermasculinization of an XY male</td>
<td>46,XY DSD</td>
</tr>
<tr>
<td>Female pseudohermaphrodite, overvirilization of an XX female, and masculinization of an XX female</td>
<td>46,XX DSD</td>
</tr>
<tr>
<td>True hermaphrodite</td>
<td>Ovotesticular DSD</td>
</tr>
<tr>
<td>XX male or XX sex reversal</td>
<td>46,XX testicular DSD</td>
</tr>
<tr>
<td>XY sex reversal</td>
<td>16,XY complete gonadal dysgenesis</td>
</tr>
</tbody>
</table>

46 XX DSD

- 30-50% of all cases with sexual ambiguity
- CAH (21- OHP deficiency) is major cause
- 46 XX karyotype
- Normal internal Müllerian structures
- No wolffian structures
- Virilization of external genitalia
46 XX DSD

Causes

- Fetal androgens
  - CAH (21-OHP deficiency)
- Maternal Androgens
  - Drugs, virilizing ovarian or adrenal tumors
- Placental Aromatase enzyme deficiency
46 XY DSD

- Undervirilization of the external genitalia
- Wide spectrum from completely feminized to male with hypospadias
- Have 46 XY karyotype
- No müllerian duct structures
- Inadequate androgen exposure in the first trimester → absent or deficient Wolffian duct structures
46 XY DSD

Causes

- Testicular Aplasia / Hypoplasia
- Testicular Dysgenesis (incomplete gonadal dysgenesis)
- Testosterone biosynthesis defects
- $5\alpha$ - reductase deficiency
- AIS (complete & partial forms)
Androgen Insensitivity

- X-linked recessive
- Wide range of presentations
- Complete form (testicular feminization)
- Incomplete form (partial)
- AR gene is localized to Xq11-Xq12
Complete Androgen Insensitivity (CAIS)

- Must be suspected in normal female with a palpable gonad (s) at inguinal region
- 1-2% of phenotypic females with inguinal hernias have AIS
- Testes are normal prepubertal
- After puberty, the somniferous tubules become atrophic, with no spermatogenesis
- Risk of malignancy is low < 25 years of age
Partial Androgen Insensitivity (PAIS)

• The external genitalia are predominantly male or ambiguous
• Wide range of presentations

Pubertal changes
• Pubic & axillary hair develops
• Gynaecomastia
• Poorly developed male sex characters
5α reductase enzyme deficiency

• Converts T → DHT
• Under musculanization of the external genitalia
• Autosomal Recessive
  – Isoenzyme 1 in liver cells function
  – Isoenzyme 2 in genital tissues
• Mapped to 2p23 chromosome
• Finastreride (isoenzyme 2 inhibitor) used for alopecia & prostatic hyperplasia disorders can cause this disorder as iatrogenic cause if mother took it in pregnancy
XY Gonadal dysgenesis

- XY karyotype & gonadal dysgenesis
- Bilateral dysgenetic gonad development
- Ranging from gonadal streaks, dysgenetic testis to normal testis
- 30% risk of malignancy > age of 30
- Normal amount of SRY gene
- The degree of musculanization depends on the extent of testicular differentiation
XY Gonadal dysgenesis

- Testosterone level low – normal
- hCG test is blunted (dysgenetic gonad)
- Presence of both müllerian & wolffian structures
- The diagnosis is made by gonadal histology
- Preferred sex of rearing is female (presence of uterus)
- Dysgenetic testes have to be removed
Mixed Gonadal Dysgenesis

• Mosaicism of 2 or more different karyotypes
• 45 X / 46 XY, 45 X/ 47XXY,…..etc
• The mosaicism is caused by loss of Y chromosome by nondisjunction
• 45 X / 46 XY is the most common karyotype
• Have at least one dysgenetic testis, streak ovary in one side and ovotestis in other side
Mixed Gonadal Dysgenesis

• Subnormal production of testosterone
• Insufficient production of MIS
• Presence of both structures internally
• Gonadal tumors occur in 30%
• Early removal of dygenetic gonads to prevent risk of gonadoblastoma or germinoma
• 90% of 45X / 46XY have normal male genitalia, remaining 10% have ambiguity
Ovotosicular DSD (formerly True Hermaphrodites)

- Presence of both mature ovarian & testicular mature tissues
- The most common combination is ovary in one side & testis in other side
- Presence of both structures internally
- 60% have 46XX karyotype, 15% are mosaic
- The genitalia may be male, female or ambiguous, depending on the amount of functioning testicular tissue
- The definite diagnosis by gonadal histology
DSD associated Syndromes

- Trisomy 13  Smith-Lemli-Opitz
- Trisomy 18  Meckle-Gruber
- Aniridia-Wilms  Ellis-Van Creveld
- Aarskog  Triploidy
- Camptomelic dwarfism  4P -
- Carpenter  13q-
- CHARGE
- VACTERL
Management consideration

Gender assignment depends on:
• Potential for future sexual and reproductive functions
• Anatomical abnormalities
• Capabilities of reconstructive surgery
• In micropenis, if penile size doesn’t reach 2.5 cm (after 3 injections of 25 mg testosterone), male assignment is not advisable
• Religious consideration is important
نذابني قفوم
"للا