Review Article

Radiological imaging of disorders of sex development (DSD)

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ABSTRACT

The birth of a child with ambiguous genitalia is a matter of a medical and social emergency to decide the appropriate sex rearing and eventually to prevent the associated metabolic disturbances. It must be taken with immediacy and great sensitivity. The pediatric endocrinologist should share the care with a team consists of a pediatric urologist, or surgeon, a pediatric radiologist, geneticist and a child psychiatrist or psychologist who should work closely with the family. Ultrasonography is the primary modality for demonstrating internal organs while genitography is used to assess the uterus, vagina, and any fistulas or complex tracts. Magnetic resonance imaging (MRI) is used as an adjunct modality to assess the internal gonads and genitalia. Early and appropriate gender assignment is necessary for healthy physical and psychological development of children with ambiguous genitalia.

Keywords:
Ambiguous genitalia; Disorders of sex development; Radiological imaging; Ultrasound; Genitogram; Magnetic resonance.

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INTRODUCTION
Disorder of sexual development (DSD) formerly termed intersex conditions, are among the most fascinating conditions encountered by the clinicians. The ability to diagnose these conditions has advanced rapidly in recent years. It is a matter of a medical and social emergency to decide the appropriate sex of rearing and eventually to prevent the associated metabolic disturbances [1-11].

EMBRYOLOGY OF SEXUAL DIFFERENTIATION (Figure 1)

Gonadal Differentiation
During the second month of fetal life, the undifferentiated gonads are guided by the genetic information present on the short arm of the y chromosome into a testes. This is determined by the so-called Testis-determining factor (TDF), which is a 35 kilobase pair sequence on the 11.3 subband of the Y chromosome and the named sex-determining region of Y chromosome (SRY). When the region is absent, the undifferentiated gonad develops into an ovary. Other genes important to testicular development include DAXI on the x-chromosome, SFI on band 9q33 WTI on band 11 p 13, so x 9 on bands 17 q 24-25, and Anti Mullerian hormone (AMH) on band 19q13.3 i.e., fetal ovaries develop when TDF gene (genes) is absent.

Differentiation of Internal ducts
Development of the internal ducts results from a paracrine effect from the ipsilateral gonads. When testicular tissue is absent, the fetus morphologically develops into the internal female organs and external phenotypic female. When testicular tissue is present, that produces testosterone and Mullerian-inhibiting substance (MIS) or AMH, which appears to be critical for development of sex ducts and external male phenotype. Testosterone is produced by testicular Leydig cells and subsequently the primordial Wolffian (mesonephric) duct develops into epididymis, vas deferens, and seminal vesicle.

Differentiation of external genital
The external genitalia of both sexes are identified during the first 8 weeks of gestation, without the hormonal action of testosterone and dihydrotestosterone (DHT), external genitalia appear phenotypically female. In the gonadal male, differentiation to a male phenotype actively occurs. The testosterone rise, at the time, in response to luteinizing hormone (LH) from the placenta [1,3,11].

Classification of Disorders of Sexual Development and Nomenclature:
Recently, the Lawson Wilkins Pediatric Endocrine Society (LWPES) and the European Society for Pediatric Endocrinology (ESPE) have published proposed changes to the nomenclature and definition of disorders of sex development (DSD) to reflect the recent advances in our understanding (Table 1) [12-14].
### Table 1 - Change in Nomenclature of disorders of sex development

<table>
<thead>
<tr>
<th>Previous</th>
<th>Revised</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female pseudohermaphrodite</td>
<td>46 XX DSD</td>
</tr>
<tr>
<td>Male pseudohermaphrodite</td>
<td>46 XY DSD</td>
</tr>
<tr>
<td>True Hermaphrodite</td>
<td>Ovotesticular DSD</td>
</tr>
<tr>
<td>XX – male</td>
<td>46, XX testicular DSD</td>
</tr>
<tr>
<td>XY – sex Reversal</td>
<td>46, XY Complete gonadal dysgenesis</td>
</tr>
</tbody>
</table>

DSD have been defined as congenital conditions in which development of chromosome, gonad, or anatomic sex is atypical. DSD vary in frequency depending on their etiology (Table 2). Congenital adrenal hyperplasia (CAH) is the most common of ambiguous genitalia in the newborn worldwide, while, mixed gonadal dysgenesis (MGP) is the second most common cause of DSD. Hypospadias occur at a rate of 1 case per 300 live male.[1-11,15,16].

### Table 2 - Major causes of Disorders of Sex Development (DSD) according to karyotype

#### 46, XX Karyotype

<table>
<thead>
<tr>
<th>46 XX DSD</th>
<th>Congenital Adrenal Hyperplasia (CAH)</th>
<th>Enzyme Deficiency:</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>21α-Hydroxylase</td>
<td></td>
</tr>
<tr>
<td></td>
<td>11β-Hydroxylase</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 β- Hydroxysteroid dehydrogenase</td>
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</tbody>
</table>

- Ovarian/Adrenal Tumors (mother-child)
- Exposure to exogenous medication (synthetic progestin preparation)

#### Ovotesticular DSD

- Lack of synthesis of testosterone
- Testicular differentiation
  - Pure gonadal dysgenesis
  - Absence of Leydig cells or luteinizing hormone receptor
  - Testicular regression
  - Gonadotrophine Hormone Deficiency
- Enzyme deficiency in testosterone pathway
  - 20, 22-demolase
  - 17, 20-lyase
  - 3β-hydroxysteroid dehydrogenase
  - 17-ketoreductase

- Lack of synthesis of dihydrotestosterone
- 5α-reductase deficiency

- End-organ-unresponsiveness (resistance)
  - Partial
  - Complete

#### Mixed Karyotype

- Ovotesticular DSD 46,XX/46 XY
- Mixed gonadal dysgenesis 45 X/46 XY
RADIOLOGICAL IMAGING

Management starts with the initial contact with the family by a member of DSD team and taking a detailed medical history. An assessment of the genital appearance and whether gonadal tissue is present are crucial. Chromosomal and other genetic studies if needed and specific hormonal studies should be undertaken.

The disorders of sex development (DSD) team is consisted of a pediatrician, a pediatric endocrinologist, a pediatric urologist, or surgeon, geneticist, a pediatric psychiatrist or psychologist, and a pediatric radiologist [17]. Imaging plays an important role in evaluating the internal organs and urogenital anatomy in children with ambiguous genitalia. Ultrasonography remains the primary modality for evaluation of the internal reproductive organs, whereas genitography and voiding cystourethrography are used for evaluation of urethral and vaginal tracts and fistulas and hence used as an important marker for surgical strategy. MR imaging may serve as a problem solving modality for clarifying the internal anatomy and searching for internal gonads [18-32].

Ultrasonography

Ultrasonography remains the primary modality for establishing the presence or absence of a uterus, figure 2. It is safe and quickly performed without sedation and it does not expose the patient to radiation. An ultrasound examination should include the inguinal, perineal, renal, and adrenal. In US, identification of a uterus was found in 90%, while ovary has been seen in 40%. Adrenal glands, with a limb over 20 mm long and 4 mm wide, with normal cortico-medullary differentiation are suggestive of congenital adrenal hyperplasia (CAH) (Figure 2).

Figure 2 - A Sagittal view of a pelvic ultrasound of a newborn female baby with ambiguous genitalia caused by congenital adrenal hyperplasia, due to 21 hydroxylase deficiency showing a uterus (Ut) with echogenic endometrium.
However, the presence of normal-sized adrenal glands will not exclude the diagnosis. It is believed that it is not just the size of the gland, but a combination of a limb with greater than 4 mm, a lobulated surface (cerebriform appearance) (Figure 3), and increased echogenicity are suggestive the diagnosis of CAH [18-23]. Alwan et al, found a combination of a limb greater than 4 mm, a lobulated surface and stippled echogenicity with a sensitivity of 92% and a specificity of 100% [21].

Fluoroscopy-Genitography

This helps determining ductal anatomy. A catheter can be inserted into the distal urogenital sinus. It is more invasive and exposes the patient to much radiation. Genitography demonstrates a male or female type urethral configuration and any fistulous communication with the vagina or rectum [Figure 4]. An adequate genitogram should help identifying the exact location where the urethra and the vagina are joined. These anatomic characteristic are very important for mapping surgical strategy [24].

Magnetic Resonance (MR)

T1 and T2 weighted MR imaging sequences with their multiplanar capability superior tissue characteristics can provide detailed anatomic information. MR imaging was found useful in evaluating ambiguous genitalia with detecting the uterus in 93% of cases, the vagina in 95%, the penis in 100%, the testis in 88%, and the ovary in 74% (Figure 5α, b). MR imaging is more sensitive than US in the evaluation of the gonads [25-32].
MR imaging and US are considered equally sensitive in the evaluation of intrapelvic structures. However, MR imaging is more sensitive than US in detecting the gonads [29].

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**REFERENCES**


http://www.sudanjp.org