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Review

Approaching a Newborn with Atypical Genitalia: Hints for Pediatricians

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ABSTRACT

Infants born with genitals that do not appear typically male or female, are classified as having a difference/disorder of sex development (DSD). The current terminology and classification of DSD was established as suggested in the Chicago consensus statement in 2006. According to this consensus, patients with a DSD diagnosis are divided into three karyotype-based subgroups: 46,XY DSD; sex chromosome DSD, and 46,XX DSD. A newborn with DSD must be evaluated timely by a multi-disciplinary team including endocrinologist, psychologist, and urologist. The reason for this is two-fold: 1st to assign an appropriate sex of rearing to the infant based on the etiology of the condition and associated medical and psychosexual outcomes, and 2nd to detect any underlying life-threatening disorder if present. Neonates with ambiguous genitalia have various clinical presentations, etiologies, and outcomes. Furthermore, family adjustment and the degree of involvement of health professionals in psychosocial aspects of the condition affect health-related quality of life more than other congenital problems in DSD. For this reason, establishing correct communication with the patient and his/her family and providing appropriate information play a central role in DSD management and correct diagnosis and correct treatment. This review provides some clinical clues about the history, physical examination and laboratory and imaging characteristics of a newborn with DSD, which can allow for timely diagnosis, treatment and family counseling. We also emphasize some important points for an appropriate initial communication with the family of a patient with DSD.

Keywords: Disorders of sexual development, atypical, ambiguous, genitalia

INTRODUCTION

Atypical or ambiguous genitalia basically involves virilization of female genitalia or undervirilization of male genitalia. It is critically important to determine the etiology as quickly as possible when genital ambiguity is noticed. Besides the parental stress due to the unclarity of the condition, ambiguous genitalia may constitute a signal of a medical emergency, including adrenal insufficiency or of an important disorder of the kidneys or the urogenital system. Therefore, the initial evaluation must assess whether there are such disorders accompanying ambiguous genitalia. There are many different diagnoses that can result in atypical genitalia. The local team plays key roles in the initial management and providing support for the parents. Language needs to be used carefully with particular clarity when liaising with parents and local health professionals. Clinical findings should guide the initial investigations. The current article provides an initial approach to the management of a baby born with atypical or ambiguous genitalia.

Sex Development and Typical Genitalia in Males and Females

Gender is not only the structure suggested by the external sex organs but also a whole that includes chromosomes, sex-determining genes, gonadal histology, hormones and anatomy of internal genital organs.

Human sex development occurs in 3 basic steps: 1) It is the "chromosomal sex" that occurs with fertilization. Whether the

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spermatogonia that fertilize the ovum have X or Y chromosomes determine the chromosomal sex. 2) The second step is to determine the "gonadal sex". That is, it is the transformation of the undifferentiated gonad into the testis or ovary. Sex determination is the formation of a testis or an ovary from an undifferentiated bipotential gonad and is driven by the sequential expression of many genes. 3) The differentiation of the internal and external genital organs by the hormones secreted from the testis determines the "phenotypic sex". Anti-Müllerian hormone (AMH) synthesized in Sertoli cells causes regression of Müllerian structures. In the absence of AMH, the fallopian tubules, uterus, and upper 1/3 of the vagina are formed. Testosterone is produced from Leydig cells and stabilizes Wolffian ducts to form epididymis, vas deferens and seminal vesicles. Testosterone is converted to dihydrotestosterone, which provides virilization of the external genitalia. Again, insulin-like factor 3 secreted from Leydig cells is a peptide hormone that ensures the descent of the testis into the scrotum[1]. It is been known for many years that the genital primordium develops toward the female phenotype in case of a lack of testicular hormones[1]. Environmental factors, hormones and socio-cultural variables constitute male or female behavior, that is, "psychological sex"..."

To appreciate the various genital phenotypes associated with ambiguity, it is important to first define typical genitalia for males and females, respectively. A full-term male infant is expected to have bilateral testicles that are descended, complete formation of scrotal folds including midline fusion, and a typical size penis (average penile length is between 2.5-4.5 cm, for a full-term infant), including well-formed corporal bodies and a urethral meatus located at the tip. A full-term female infant is expected to have bilateral separation of the labial folds, no palpable gonads, and separate urethral and vaginal openings. The average clitoral length and width for a full-term infant girl born was between 2-8.5 mm.

Conditions where the chromosome structure, gonads, or external genitalia are incompatible or atypical are defined as disorders/ differences of sex development (DSD). The classification of DSD was proposed at the first international consensus in 2005 and based mainly in the chromosomal constitution[2,3] (Table 1).

46,XY infant with bilateral cryptorchidism, bifid scrotum and hypospadias, or isolated penoscrotal hypospadias, should be investigated for DSD. Isolated undescended testes were more frequent in preterm males. Isolated micropenis (<2.5 cm), if both testes are descended and normal in size, is not considered a presentation of ambiguous genitalia. The penis may falsely appear smaller simply because of a suprapubic fat pad, thus palpation of size, corporal volume and consistency is important. Penis size varies among various populations and changes according to gestational age and can be assessed using reference charts[4,5]. Similarly, distal hypospadias with no other atypical genital features in males are not usually indicative of DSD[6]. For a 46,XX infant, clitoromegaly (>1 cm) labial fusion or palpable gonads in what appears to otherwise be typical female external genitalia should be investigated further. Perceived clitoromegaly is not usually associated with an underlying DSD if the newborn is born prematurely. The labia minora can be prominent in the female preterm infants with little subcutaneous fat, but without no labioscrotal in the absence of excess androgen. The clitoral skin may also be misinterpreted as clitoromegaly[2].

Management

History

Important questions guiding the diagnosis and management are listed below:

* Drugs used in pregnancy
* Maternal virilization during pregnancy, for example, voice change and hirsutism (important for the diagnoses of maternal virilizing tumours, P450 oxidoreductase deficiency or placental aromatase deficiency)
* Consanguinity (as many of the causes of ambiguous genitalia have a genetically inherited)
* History of previous unexplained neonatal deaths, ambiguous genitalia, infertility, or genital surgery in the family.

Physical Examination

There are numerous important points to consider while examining a newborn with ambiguous genitalia that may help in differential diagnosis:

* As in all newborns vital signs including blood pressure, capillary refill and heart rate should be checked. Excessive pigmentation (areolar, genital or diffuse pigmentation) should be noted. These are particularly important for DSD etiologies related to adrenal insufficiency.
* Midline defects (cleft lip/palate), and dysmorphic features, and other associated renal, cardiac, and skeletal features may help guide etiologic diagnosis.
* Palpation of the gonads, in the labioscrotal folds or along the inguinal region. A palpable gonad usually implies the presence of a Y chromosome and a testicular tissue on that gonad, rarely the gonad could still be an ovary or ovotestis where a testicular tissue is present in the same gonad. A baby with asymmetric genitalia may also suggest chromosomal mosaicism such as 45,X/46,XY karyotype (mixed gonadal dysgenesis). These babies present with substantial phallic enlargement and hypospadias and a palpable testis in the labioscrotal fold on one side but no palpable gonad on the other side. At laparoscopy, a streak gonad and hemi-uterus are typically identified on the side contralateral to the descended or palpable gonad.
* Length and size (diameter) of phallus should be measured.
* Degree of labial fusion and measurement of anogenital distance are noted to assess prenatal androgen exposure.
* Position and number of urethra/urogenital sinus openings are recorded. Severe hypospadias can develop because of

Table 1. Classification of DSD	
Sex chromosomal DSD	
45,X0	Turner syndrome and variants)#
47,XXY	(Klinefelter syndrome and variants)
45,X/46,XY and 46,XX/46,XY	(Mixed gonadal dysgenesis, gonadal chimerism)
46,XX DSD	
Disorders of gonadal development	• (Ovo) testicular DSD
	• Monogenic forms of primary ovarian insufficiency (mutations in genes involved in gonadal (ovarian) development; ie *NR5A1* and *WT1*)
	• Syndromic forms
Disorders of androgen excess	• Aromatase (CYP19A1) deficiency
	• Congenital adrenal hyperplasia (mutations and/or deficiencies in CYP21A2, HSD3B2, CYP11B1 and POR)
	• Luteoma
	• Iatrogenic
Unclassified disorders	• MRKH type I and II syndrome
	• Complex syndromic disorders
46,XY DSD	
Disorders of gonadal development	• Complete or partial gonadal dysgenesis, monogenic forms (for example, SRY, NR5A1 and WT1)
	• Testicular regression
	• Ovotesticular DSD
	• Syndromic forms
Disorders of androgen synthesis	• Associated solely with androgen biosynthesis defects (mutations or deficiencies in HSD17B3 and SRD5A2, for example)
	• Associated with congenital adrenal hyperplasia and early androgen biosynthesis defects (mutations and/or deficiencies in STAR, CYP11A1, HSD3B2, POR and CYP17A1)
	• Associated with placental insufficiency or endocrine disruption
	• Syndromic forms (for example, Smith-Lemli-Opitz)
Disorders of androgen action	Complete and partial androgen insensitivity
Persistent Müllerian duct syndrome	Due to mutations or deficiencies in *AMH* and *AMHR2*
Unclassified disorders	• Hypospadias of unknown origin
	• Epispadias
	• Complex syndromic disorders

MRKH: Mayer-Rokitansky-Küster-Hauser syndrome, DSD: Disorders/differences in sex development, AMH: anti-Müllerian homone

3β-hydroxysteroid dehydrogenase deficiency, partial androgen insensitivity, 5-alpha reductase deficiency in up to 40% the cases[7].

A five-stage Prader grading system is used to describe the degree of genital atypia and degrees of virilization[8] (Figure 1):

Stage 1: Clitoromegaly without labial fusion.

Stage 2: Clitoromegaly with posterior labial fusion.

Stage 3: Significant clitoromegaly, single perineal urogenital orifice, almost complete labial fusion.

Stage 4: Phallic clitoris, urethra like urogenital sinus at the base of clitoris, complete labial fusion.

Stage 5: Penile clitoris, urethral meatus at the tip of the phallus, scrotum-like labia (appearance of bilaterally cryptorchid male).

A Quigley grading system from grades 1 through 6 is used to describe the degree of genital atypia in androgen insensitivity[9] where grade 1 indicates a fully masculinized external genitalia, grade 6 indicates fully feminized genitalia and grades 2 through 5 qualify as increasingly feminized genitalia. Recently, some other scoring systems were developed to assess external genital masculinization in detail including external masculinization score

Table 2. External musculinisation score					
Scoring	**Scrotal fusion**	**Micropenis**	**Urethral meatus**	**Right gonad**	**Left gonad**
3	Y	N	Normal		
2			Distal		
1.5				Labioscrotal	Labioscrotal
1			Mid	Inguinal	Inguinal
0.5				Abdominal	Abdominal
0	N	Y	Proximal	Absent	Absent
A score <11 out of 12 needs further investigation					

Table 3. Initial investigations in a newborn with atypical/ambiguous genitalia	
Investigation	**Comment**
Karyotype/FISH or PCR for *SRY*	Karyotype should be studied for each case with a suspicion of DSD. The result of a formal karyotype can be obtained in 2-3 weeks. A fluorescent *in situ* hybridisation (FISH) or PCR for *SRY* gene is more rapid to have an information for the existence of Y chromosome in the karyotype.
ACTH, electrolytes, blood sugar, 17-OH progesterone, renin, blood pressure monitoring	To assess adrenal insufficiency, especially CAH. Salt-wasting generally starts after first week of life in the majority of cases with CAH adrenal insufficiency. Adrenal steroid measurements are suggested to perform after 2nd postnatal day. High dose synacthen testing to assess glucocorticoid synthesis may be needed.
Pelvic USG for Müllerian structures, adrenals (presence? enlarged?) and gonads (including examination of the inguinal canal and labial folds for the gonads)	Inguinal or labial gonads suggest the presence of functional testis and Y chromosome, presence of unilateral or bilateral Mullerian structures suggests absence of functional testicular tissue on the same side.
Urinanalysis, urine protein creatinine ratio	Important for identifying additional renal abnormalities or some etiologies associated with severe renal involvement (eg associated oliguria, proteinuria or hematuria may suggest *WT1* mutations). A renal USG can be needed in selected cases.
FSH, LH, testosterone, anti-Müllerian hormone	To investigate the function of gonads. These tests provide useful information particularly after 1-2 weeks of life, during the minipuberty period. Low AMH, high FSH and low testosterone in a 46,XY patient suggests a gonadal dysgenesis. Normal AMH concentration excludes gonadal dysgenesis.
ACTH: Adrenocorticotropic hormone, AMH: anti-Müllerian hormone, CAH: Congenital adrenal hyperplasia, USG: Ultrasound, DSD: Disorders/differences in sex development	

(EMS) (Table 2)[10]. The EMS was modified as external genital scores to be used for external genitalia in premature and term babies up to 24 months[11].

* Clitoral enlargement with or without hypospadias but with impalpable gonads in hyperpigmented genitalia should suggest congenital adrenal hyperplasia (CAH) until proven otherwise. CAH secondary to 21-hydroxylase deficiency is the most common cause of such a presentation, followed by 11β-hydroxylase deficiency.

* A typical female genital should be further investigated for DSD in 2 important clinical scenarios:

1. A female presenting with severe adrenal insufficiency (This suggests etiologies that cause severe impairment of adrenal and gonadal steroidogenesis such as *StAR* and *CYP11A1* gene mutations in a 46,XY patient).
2. Inguinal herniae in an clear female baby who was found to have a gonad found in the hernial sac at surgery. This presentation may indicate 46,XY gonadal dysgenesis, 17β-hydroxysteroid dehydrogenase deficiency, and 5-alpha reductase deficiency and CAIS.

Laboratory Assessment and Imaging

A list of the initial laboratory and imaging assessments is provided in Table 3. A simplified diagnostic approach is shown in Figure 2.

Communication with the Family/Parents

When a baby is born with ambiguous genitalia, it is common for parents to describe the initial meeting with a health professional as an indelible and sometimes traumatic memory. Poor communication or incorrect use of language at this time can have long-lasting consequences. It is, therefore, wise to think about terminology and content in advance[12-16].

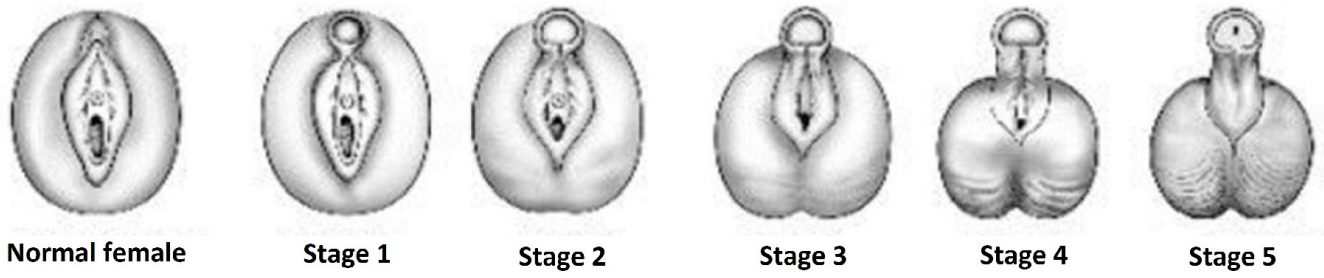

Figure 1. Prader scale of genital virilization

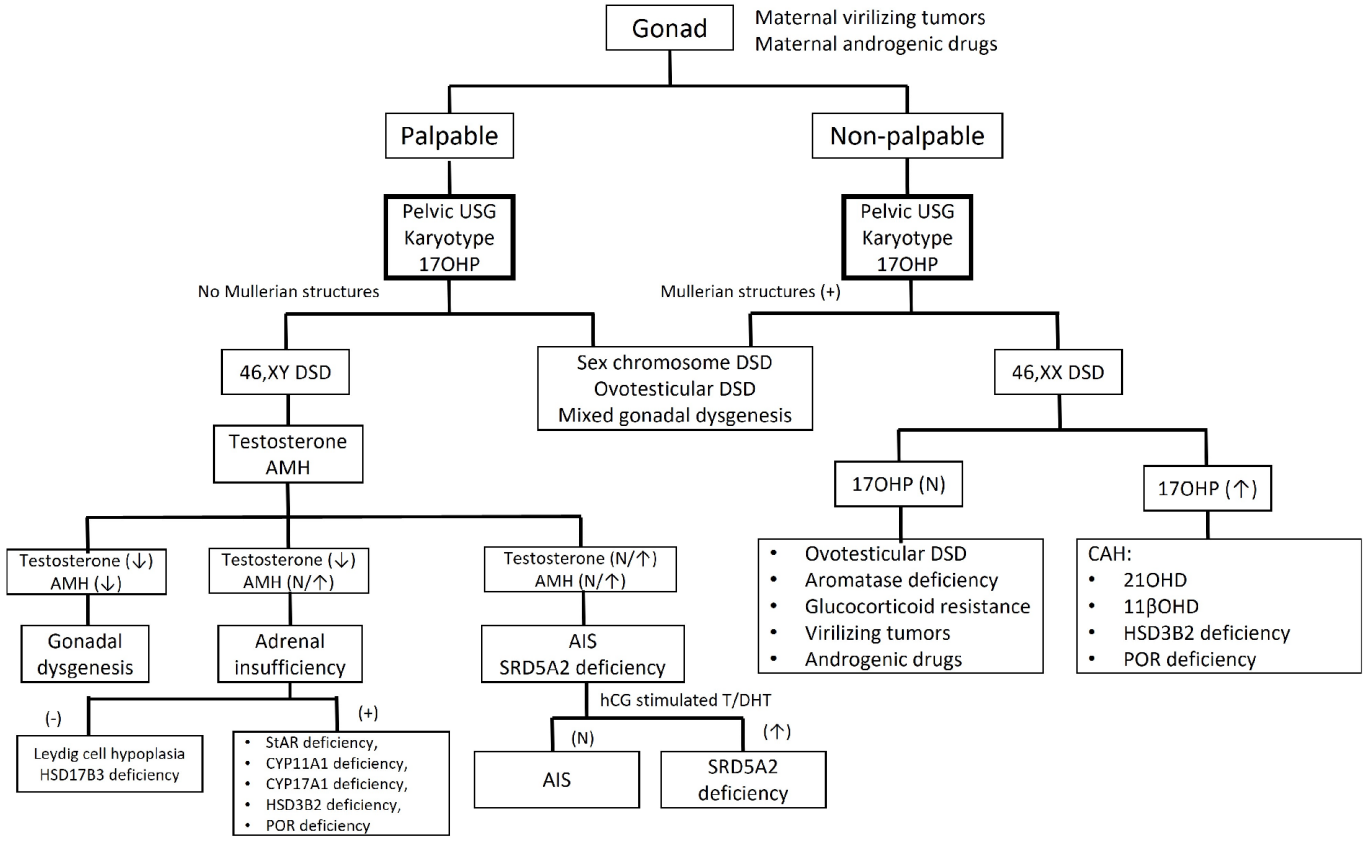

Figure 2. Flowchart for the differential diagnosis of DSD

DSD: Disorders/differences in sex development, 17OHP: 17OH-Progesterone, AMH: Anti-Müllerian hormone, USG: Ultrasound, AIS: Androgen insensitivity syndrome, SRD5A2: 5-alpha reductase, 21OHD: 21-alpha-hydroxylase, 11βOHD: 11β-hydroxylase, POR: P450 oxidoreductase

* It is appropriate for the most experienced "multidisciplinary team representative" to give the first speech with the family.
* The positive findings should be emphasized by the parents first, for example, congratulating the parents on the arrival of their baby and reporting all the normal findings from the examination.
* It is important to avoid terms such as "your daughter/son" that would suggest gender.
* Estimated or probable diagnoses and approaches should never be mentioned, particularly in the first conversation.
* First information can be given as "There is a problem/delay related to the development of your baby's reproductive system, so we cannot answer this question by just examining it. You will be given much a more comprehensive and reliable information at every stage with detailed blood and imaging tests". "Examinations and evaluations will be carried out in detail and carefully by a team of specialist doctors".

* In the examination process, it is suggested to provide information about not naming the baby.
* It is important to convey the message that as a multidisciplinary DSD management team, we understand the family`s situation very well, to make the family feel that we are willing to listen and, if necessary, to talk again about matters that are not understood.
* It should be emphasized that the most important issue is that the baby needs parents like all other healthy babies and that baby's care should be done without interruption.
* If the baby is to be examined, it should be accompanied by the parents.
* It should be respectful to the socio-cultural dynamics within the family, expectations and concerns should be listened to.
* Confidentiality should be respected during the genital examination.
* Disturbances in genital development can be explained by simple drawings in the following conversations.
* Confusing terminology, including bisexual, etc. should definitely be avoided.

Developing a plan early during treatment so that all information is provided to children gradually but ultimately fully is an important aspect of optimal DSD care.

The physician's desire to inform the child sometimes encounters resistance from the parents. This resistance results from parents who mistakenly believe that hiding details will protect their children from harmful information. The process of informing can be made more difficult, as conceptualizations and values about gender and sexuality vary greatly across cultures. The child's age and mental development status are decisive in the process of sharing information. Compared with children who are ignorant or misinformed about their situation, children who receive timely education will have better opportunities to develop adaptive coping skills, including expectations for a positive self-image and a fulfilling adult life despite bodily limitations.

Ethics

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