Disorders of Sex Development

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Overview

Disorders of sex development (DSDs) are a heterogeneous group of conditions where genetic, gonadal, and phenotypic sex are discordant. DSDs are often diagnosed soon after birth due to variation in genital appearance on newborn exam. With the invention of noninvasive prenatal testing (NIPT), DSDs are increasingly diagnosed prenatally when sex chromosome complement is altered or found to be discordant from phenotypic sex. Fetal imaging alone may identify genital ambiguity, sometimes prompting further workup prenatally. DSDs that are not diagnosed prenatally or in infancy may be diagnosed later in life due to pubertal abnormalities (e.g., primary amenorrhea, progressive virilization in a phenotypic female, etc.) or infertility.

DSDs can be divided into three categories: 46,XX, 46,XY [1], and sex chromosome DSDs [2, 3]. Sex chromosome DSDs involve changes in the number of sex chromosomes, such as in Turner syndrome (45,X), Klinefelter syndrome (47,XXY), and mixed gonadal dysgenesis (MGD) (45,X/46,XY). Individuals with 46,XX DSDs demonstrate virilization on exam, and individuals with 46,XY DSDs are under-virilized. Alteration in virilization can be due to aberrant gonadal development, abnormal androgen synthesis or action, or in utero exposure to exogenous compounds. The ability to make a molecular diagnosis varies widely based on type of DSD [1] and also specific underlying etiology (80–90% in complete androgen insensitivity syndrome (CAIS) compared with ~20% in gonadal dysgenesis) [4]. Currently, there are gene panels that are used to diagnose DSDs clinically, and there is ongoing research using whole exome and genome sequencing [5]. The incidence of DSDs varies widely based on the underlying etiology, but it has been estimated that the incidence of ambiguous genitalia in infants is 1 in 5500 [6].

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In 2006, the American Academy of Pediatrics, the Pediatric Endocrine Society, and the European Society for Paediatric Endocrinology released a joint consensus statement on the management of DSDs. While the title of the article used the term "intersex," the groups noted the controversial nature of such terminology (e.g., intersex, hermaphroditism, etc.) and recommended using "disorders of sex development" [2, 7]. However, even this term remains somewhat controversial, and some prefer the term "differences in sex development" [8].

The consensus statement highlighted the importance of a supportive initial interaction between medical personnel, the patient (depending on the age), and the family [2]. Oftentimes, it is the primary care physician who makes the diagnosis of a DSD, and that first interaction is crucial to setting the stage for future interactions. In the case of newborns, it is recommended that gender assignment occur after evaluation at a center with a multidisciplinary team comprised of pediatric subspecialists (endocrinology, urology/surgery, and psychology/psychiatry). Additionally, there must be good communication between the multidisciplinary team and the primary care provider. All members of the medical team must respect the family's desire for privacy and work together to support the family's needs and provide information to assist the family in medical decision-making [2]. Additionally, many families find support and advocacy groups to be a helpful resource. An update to the 2006 consensus statement published in 2016 included an extensive, international list of DSD support and advocacy groups [9].

Clinical Key

Making a gender assignment should not be considered an "emergency," nor should performing genital surgery (unless there is an urgent indication). Consensus recommendations suggest a multidisciplinary approach with multiple discussions between the family and providers to discuss gender assignment and timing of genital surgery.

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Urgent/Emergent Considerations and Initial Management

Critical first steps in communication and management for an infant with a DSD are shown in Table 46.1, and recommended initial laboratory evaluation is shown in Table 46.2. From a medical perspective, the one emergent issue is salt-wasting congenital adrenal hyperplasia (CAH). Salt-wasting CAH can be caused by deficiency of steroid acute regulatory (StAR) protein, 3ß-hydroxysteroid dehydrogenase (3ß-HSD), or 21-hydroxylase (21-OHD) (see Chap. 49) [10]. Salt-wasting, due to mineralocorticoid deficiency, results in hyperkalemia and hyponatremia between a few days to a few weeks after birth [10]. Once CAH is suspected, a pediatric endocrinologist should be contacted immediately to discuss workup, monitoring, and management. Electrolytes should be monitored daily, and medical management with hydrocortisone, fludrocortisone, and, if needed, sodium supplementation should be initiated.

When evaluating an infant for a DSD, it is important to obtain a thorough prenatal history, including maternal medical conditions, medication use during pregnancy, exposures, maternal virilization during pregnancy, and results of prenatal testing [10]. A family history should also be obtained, including consanguinity, genetic conditions, infertility, lack of menstruation, ambiguous genitalia, and unexplained deaths [10]. A physical exam should be completed, including vital signs (particularly blood pressure), anthropomorphic measurements, evaluation for dysmorphology, and assessment of the genitals. In cases where the karyotype is unknown and the genital anatomy is ambiguous, it may be appropriate to use non-gendered terms such as "labioscrotal" instead of "labial" or "scrotal." A complete genital examination includes assessing the length and width of the clitorophallus, palpation for phallic tissue, assessing labioscrotal fusion, labioscrotal hyperpigmentation, presence of inguinal/labioscrotal masses, location of the urethral meatus, and Prader or Quigley staging [11]. Anogenital length was previously used as a metric of androgen action, but insufficient normative data have made this measurement less useful [12]. Quantitative scoring systems, such as the external masculinization score, have also been developed to standardize the assessment of ambiguous genitalia in infants [13].

Table 46.1 Initial steps in communication and management for newborns with DSD

Diagnostic priorities
The medical priority is to ensure the absence of salt-wasting CAH, which causes electrolyte abnormalities and virilization in 46,XX infants. This is done with assessment of 17-hydroxyprogesterone and serial electrolyte measurements.
If hypopituitarism is suspected, additional pituitary hormones should be assessed, and testing performed for hypoglycemia.
Beyond these two issues, the diagnostic evaluation should be expedited to provide parents with additional information as soon as possible, but this is not emergent.
Communication priorities
Acknowledge the difficulty of the situation while providing reassurance to families regarding the infant's overall health when appropriate.
Discourage premature decisions about gender assignment and naming until all necessary diagnostic information is available.
Provide the family with vetted information regarding online support groups for DSD.
Enlist specialist consultation from a pediatric endocrinologist, mental health professional (psychiatrist, psychologist, and/or social worker), pediatric urologist and/or pediatric surgeon, and, when possible, a geneticist, gynecologist, and neonatologist.

Table 46.2 Initial laboratory management of an infant with ambiguous genitalia

Laboratory testing	
Test	*Comments*
Karyotype	Call lab to request expedited testing
17-hydroxyprogesterone	Elevated in the most common forms of CAH (21-hydroxylase deficiency, 11-hydroxylase deficiency, and 3β-HSD deficiency). For newborn screening values, interpret and manage based on gestational age and algorithms provided by screening programs. Note that the reference units used by the newborn screen may be different than those used by the hospital laboratory.
Gonadotropins (luteinizing hormone (LH) and follicle stimulating hormone (FSH))	Helpful in differentiating primary (high LH and FSH) vs. secondary/tertiary (inappropriately low LH and FSH) gonadal dysfunction.
Total testosterone	Testosterone peaks around day 1 of life, and then there is a physiologic nadir during the first week of life. Testosterone should ideally be measured after 1 week of life. Low values during the first week of life should be verified with subsequent measurement.
Anti-Mullerian hormone (AMH)	Produced by Sertoli cells in response to FSH; values in the male range indicate functioning testicular tissue.
Electrolytes (sodium and potassium)	In infants with salt-wasting forms of CAH, electrolytes may be normal during the first 1–3 weeks of life and should be followed every 1–3 days as long as CAH remains on the differential.

If the patient is peri- or postpubertal, a history of pubertal development, menstrual history, and surgeries (e.g., repair of an inguinal hernia) should be obtained. The exam may include anthropomorphic measurements, vital signs (particularly blood pressure), evaluation for dysmorphic features, Tanner staging [14, 15], measurement of gonadal volume using an orchidometer, virilization status (e.g., Ferriman-Gallway scale [16]), evaluation for inguinal hernias, and evaluation for breast tissue in designated males.

In newborns, initial laboratory evaluation includes a karyotype and levels of 17-hydroxyprogesterone, gonadotropins, testosterone, anti-Mullerian hormone, and electrolytes (Table 46.1) [10]. Measurement of 17-hydroxyprogesterone should occur at least 36 hours after birth as there is a surge immediately after birth, which may result in a false positive [9]. Abdominal and pelvic ultrasound is useful to evaluate internal structures and gonads. Depending on the results, further evaluation in the subspecialty clinic can occur. Before obtaining laboratory and imaging studies, it is beneficial to contact a pediatric endocrinologist to discuss testing recommendations and to determine if testing should be sent by the primary care physician or the subspecialist as different laboratories use different assays, and some laboratories may process specimens more emergently.

While not medically urgent, the issue of sex designation in an infant with ambiguous genitalia can instill a sense of psychosocial urgency [4]. It can be very stressful when families are confronted with the diagnosis of a DSD, calling into question the sex of the baby. Additionally, recommending that families wait to designate the infant's sex until after the medical workup has been completed can be very difficult for families. Multidisciplinary teams in dedicated DSD clinics can provide assistance navigating such interactions, but the initial interaction between a family and their primary care provider is critical. Refraining from the use of gendered-pronouns (he/his or she/her) and instead using gender-neutral terms such as "your child" or "your baby" may be helpful. It may also be appropriate to ask parents what pronouns they prefer.

Historically, several factors contributed to the designation of sex, including the type of DSD, degree of virilization, surgical options, future fertility, and familial beliefs/culture [2]. Over time, the relative contributions of some of these factors have shifted, but it is still important to discuss each factor with the family. While many physicians wish they could provide a definitive answer regarding sex of rearing based on the underlying etiology of the DSD, there remain insufficient data on the affirmed genders of individuals with DSDs. As each type of DSD is distinct, gender outcomes cannot be studied in aggregate, and some DSD subtypes are rare. The two DSD diagnoses with the most data on gender outcomes are 46,XY CAIS and 46,XX CAH. In these conditions, the vast majority of individuals affirm a female gender, but there remain individuals who affirm a male gender or lie somewhere along the gender spectrum. Part of the job of the multidisciplinary DSD team is to discuss what is known about gender outcomes based on the underlying diagnosis but also to explain that there is always a degree of uncertainty.

Surgery and Considerations for Referral

The question of surgery is often one of the most ethically complex issues in the care of individuals with DSDs [17]. There are different types of surgeries depending on the underlying diagnosis and genital appearance, including genitoplasty (i.e., clitoroplasty, vaginoplasty, and phalloplasty), urogenital sinus mobilization, hypospadias repair, and gonadectomy. Some surgeries are indicated to prevent malignancy, such as gonadectomy in the case of gonadal dysgenesis with Y-chromosome material. Other surgeries, such as hypospadias repair, are generally agreed upon to maintain function. However, many surgeries are elective and may not have sufficient data on long-term outcomes such as rates of additional surgeries or complications [18]. There has been a shift away from performing surgery solely for cosmesis and toward preserving function and innervation. There has also been a shift toward delaying surgery until the individual with a DSD has affirmed their gender identity or attained decisional capacity to engage in discussions regarding surgery.

Regardless of age, all individuals with a DSD should be referred to a multidisciplinary DSD clinic. The needs of an individual with a DSD and the family will change over time [3], and having access to a team of knowledgeable subspecialty providers to help navigate the medical and psychosocial decisions is key. Issues such as whether or when to undergo surgery, what type of surgery should be undertaken, assistance with progression through puberty, and questions about future fertility may arise over time. Discussions surrounding these issues need to be tailored to the specific diagnosis and circumstances, again requiring the input from multiple subspecialists working together with the primary care provider.

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