Disorders of Sexual Development

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KEYWORDS

• Disorders of sexual development (DSDs) • Ambiguous genitalia • Sex assignment • Neonates

KEY POINTS

- Disorders of sexual development (DSDs) are classified into 3 categories: 46,XX DSD, 46,XY DSD, and sex chromosome DSD. There are many genes that are involved in normal sexual development, and mutations in most of these genes have been identified in individuals with DSD.
- Initial evaluation of a neonate with ambiguous genitalia must include a thorough history, physical examination, and laboratory evaluation including routine chromosomal analysis to identify the underlying cause. This process is of the utmost urgency to arrive at a diagnosis for treatment and gender assignment. It is critical to evaluate for life-threatening conditions such as congenital adrenal hyperplasia (CAH) in any infant presenting with ambiguous genitalia.
- A multidisciplinary team, including a neonatologist, pediatric urologist, endocrinologist, gynecologist, geneticist, medical ethicist, and psychologist, must be involved in the diagnosis and management of any neonate with a suspected DSD.

INTRODUCTION

Disorders of Sexual Development (DSDs) encompass a large group of congenital conditions in which there is abnormal development of chromosomal, gonadal, or anatomic sex.[1] In these disorders, anatomic sex and hormonal sex are discordant with sex chromosomes. DSDs commonly present in the newborn period because of the presence of ambiguous genitalia. The differential diagnosis is often broad, and management of DSDs can be challenging. These challenges are both medical/scientific and psychological and require the collaborative efforts of an experienced multidisciplinary team, including a neonatologist, pediatric urologist, endocrinologist, gynecologist, geneticist, medical ethicist, and psychologist. DSDs are classified broadly into 3 categories based on the

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underlying cause: 46,XX DSD, 46,XY DSD, and sex chromosome DSD. Specific diagnoses can often be made within each of the major categories based on further investigation, although occasionally a specific diagnosis or cause remains elusive. Ambiguous genitalia in a neonate should be treated as an emergency, and a thorough evaluation should take place to establish the diagnosis and gender assignment of the infant. This article focuses on the clinical presentation, diagnostic evaluation, and differential diagnoses of DSDs.

NORMAL SEXUAL DEVELOPMENT

Normal sexual development is a complex process that relies on proper expression of specific genes as well as normal hormone production/function. In early development, the gonads and internal genital structures are bipotential, meaning that they can further differentiate into male or female depending on the gene expression that occurs.[2,3] In early embryology, the bipotential gonad develops from the urogenital ridge. Germ cells migrate from the yolk sac to the bipotential gonad around the fourth or fifth week of gestation and intermingle with pre-Sertoli and pregranulosa cells.

NORMAL MALE DEVELOPMENT

Expression of the sex determining region on the Y chromosome (SRY) around the sixth week of gestation leads to the organization of pre-Sertoli cells and germ cells into primitive sex cords. Further sex-determining genes and transcription factors such as *SOX9*, *SF1,* and *WT1* lead to further maturation and development of the testes.[4] The primitive testes begin to produce hormones beginning at approximately 8 weeks of gestation. The Sertoli cells produce anti-Müllerian hormone (AMH) and inhibin B, whereas the Leydig cells produce insulinlike factor 3 (INSL3) and testosterone. AMH leads to regression of the Müllerian (female) ducts. INSL3 is important in the transabdominal phase of testicular descent.[5] Production of testosterone leads to development of the wolffian (male) ducts into the epididymis, vas deferens, and seminiferous tubules. Further differentiation of the urogenital sinus into external male genitalia occurs from the activity of dihydrotestosterone (DHT), which is converted from testosterone locally in the sexual skin by the enzyme 5-α reductase. In the presence of DHT, the genital tubercle differentiates into the penis, the urogenital slit fuses to form the urethra, and the labioscrotal folds fuse to form the scrotum.

NORMAL FEMALE DEVELOPMENT

In the absence of proper SRY expression, the bipotential gonad develops into an ovary. If AMH is insufficient or absent, the Wolffian ducts regress and the Müllerian structures develop into the upper part of the vagina, uterus, and fallopian tubes. In the absence of circulating testosterone, DHT, or normal androgen receptors, the genital tubercle becomes a clitoris, the urogenital folds become the labia minora, and the labia majora form from the labioscrotal swelling, leading to a female external phenotype. Thus, the presence or absence of SRY leads to determination of gonadal sex (testes or ovary), followed by sex differentiation, which under normal circumstances, leads to either a male or female phenotype.

CLINICAL PRESENTATION OF DISORDERS OF SEXUAL DEVELOPMENT

Infants who have the following clinical features should be evaluated for a DSD:

- Micropenis with bilateral nonpalpable testes
  - Micropenis is defined as stretched penile length less than 2.5 cm in full-term infants

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