DISORDER OF SEXUAL DEVELOPMENT IN NEWBORNS

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INTRODUCTION

In 2006, new nomenclature for conditions previously referred to as intersex was proposed in a consensus statement from the Lawson Wilkins Pediatric Endocrine Society and European Society of Pediatric Endocrinology in response to advanced identification of molecular genetic causes of sex. Disorders of sexual differentiation (DSD) are congenital conditions within which the development of chromosomal, gonadal and phenotypic sex is atypical. These disorders have a broad differential including variations in sex chromosomes, variations in genes involved in gonadal and genital development, disorders in steroidogenesis within the gonads and adrenals, maternal factors, and endocrine disruptors. Classification of these disorders is based on sex chromosomes as such 46XX DSD, 46XY DSD, Ovotesticular DSD, and 46XX testicular DSD.

Approximately 1-2% of live births are affected with atypical genitalia, including isolated hypospadias in males. The incidence of 46XX DSD is 1:15,000. The incidence of 46XY DSD is higher at 1:5000.

CLINICAL RECOGNITION

Given the potential association with glucocorticoid and mineralocorticoid deficiencies in CAH, the birth of a child with atypical genitalia constitutes a medical emergency requiring immediate evaluation. Further, the parents' reaction to the birth of a child with atypical genitalia is one of shock and concern about which gender to assign, whether or not to decide for early genital surgery, and what to expect regarding the long-term outcome in terms of gender, sexual function, fertility, and general quality of life. In order to provide appropriate counseling to the family, there is an urgency to determine the etiology.

PATHOPHYSIOLOGY

The phenotypic sex of a newborn is the result of external genital development that is under the influence of sex-determining genes as well as both endogenous and exogenous hormone exposures.

The commitment of the bipotential primordial gonads to become testes or ovaries begins at 6 weeks and is fully achieved at 13-14 weeks. Gonadal differentiation is controlled by a number of time and dosage-sensitive genes including the SRY gene on

the Y chromosome, SOX9, and WNT4 genes. The expression SRY and SOX9 and suppression of WNT4 expression is crucial to testicular differentiation. The expression of WNT4 in the absence of SRY and SOX9 expression allows for ovarian differentiation. Leydig cells produce insulin like factor 3 (INSL3) which is responsible for transabdominal phase of testicular descent.

Fetal productions of androgens from the Leydig cells within the testes and from the adrenal glands begins at approximately 8-9 weeks. External genitalia develop concurrently around the 9th week of gestation under the influence of androgens, mainly dihydrotestosterone (DHT). Testosterone is the principal hormone produced by the testes and is required for the onset of virilization and promotion of Wolffian ducts. Testosterone is converted to DHT by 5-alpha reductase. DHT leads to the development of the prostate, scrotum and phallus.

Anti-Mullerian Hormone (AMH) produced from Sertoli cells in the testes is required to support the development of Wolffian ducts including vas deferens, epididymis and seminal tubules in males. In females, Mullerian ductal structures including the uterus, fallopian tubes and cervix develop in the absence of AMH.

Disorders of Sexual Differentiation

46XX DSD

Patients with 46XX DSD are genotypic females with virilized characteristics. In 46XX DSD, the degree of genital virilization can be classified into five Prader stages. Stage 1, with the mildest degree of virilization, is characterized by clitoromegaly without labial fusion. Stage 5, with the highest degree of virilization, is characterized by clitoromegaly with the urethral meatus at the tip, labial fusion, and scrotal-like appearance of the labia.

46XX DSD can result from exogenous androgen exposure, endogenous adrenal androgen production or placental aromatase deficiency. Congenital adrenal hyperplasia (CAH) is the most common cause of 46XX DSD. The most common enzyme defects leading to CAH are 21-hydroxylase deficiency and 11-hydroxylase deficiency. In a very rare form of CAH owing to p450 oxidoreductase deficiency, there is a mutation in the P450 oxidoreductase (POR) enzyme which causes partial deficiency of 21-hydroxylase and 17a-hydroxylase/17,20 lyase activities. Affected females can present with virilization of the external genitalia, glucocorticoid deficiency, and skeletal malformations such as craniosynostosis.

Maternal hyperandrogenism during gestation can cause virilization of the external genitalia in females when the placental aromatase is overwhelmed. The hyperandrogenism can be due to luteomas, androgen producing tumors and exogenous exposure.

Maternal aromatase deficiency leads to decreased production of estrogen from androgen precursors. This leads to conversion of fetal DHEAS to androstenedione and testosterone by placental 3-beta hydroxysteroid dehydrogenase and virilization of female fetus.

The majority of 46XX testicular DSD cases are caused by translocation between the X and Y chromosome, involving the SRY gene.

46XY DSD

Patients with 46XY DSD are genotypic males with under-virilization. Micropenis is defined as a penile length less than 2.5 standard deviations below the mean penile length (<2.5 cm in a full-term newborn). The severity of hypospadias is based on the distance of the urethral opening from its normal position at the

tip of the phallus. Lack of testicular palpation in the scrotum may signify cryptorchidism, vanishing testes, or gonadal dysgenesis.

46XY DSD can be caused by atypical testicular formation, low testosterone or dihydrotesterone production, or defects in the androgen receptor. In complete gonadal dysgenesis, there is no testicular development and patients present as phenotypic female with delayed puberty or amenorrhea. Up to 20% of these cases occur due to deletion or mutation of the SRY gene.

Defects in androgen biosynthesis can lead to under-virilization in a 46XY patient. These defects can occur at various points along the production pathway of testosterone from cholesterol. Adrenal dysfunction is associated with defects in steroidogenic enzymes such as steroidogenic acute regulatory protein (StAR), p450 side chain cleavage enzyme, 3 beta HSD type 2, 17 alpha hydroxylase/17,20 lyase. Other defects of testosterone production can occur in the following enzymes: 7-dehydrocholesterol reductase causing Smith Lemli Opitz syndrome and 17 beta hydroxysteroid dehydrogenase. Affected males with 5-alpha-reductase deficiency have atypical genitalia (small phallus and perineal hypospadias). With rises in testosterone at puberty, progressive virilization with phallic enlargement and testicular descent is seen.

Androgen insensitivity syndrome has been reported to be the main cause of 46XY DSD and is due to mutation in the androgen receptor. In complete androgen insensitivity, the androgenic effects of testosterone and dihydrotestosterone are abolished and patients have unambiguously female appearing external genitalia. In partial androgen insensitivity, the androgenic effects are attenuated and patients can present on a spectrum of under-virilization.

Mutations in genes responsible for sex determination such as SRY, SOX9, and SF1 lead to 46XY complete gonadal dysgenesis. Duplication of the DAX1 gene is associated with male to female sex reversal.

Endocrine disruptors with anti-androgenic effects such as diethylstilbestrol or phthalates can also lead to atypical genitalia in males.

Table 1. Laboratory Values to Differentiate Between Etiologies of Ambiguous Genitalia in Newborns with a 46, XY Chromosomal Complement.

Diagnosis	T	DHT	MIS
Androgen Insensitivity Syndrome (AIS)	Normal/up	Normal/up	Normal
5α-Reductase Deficiency	Normal/up	Low	Normal
Testosterone Biosynthetic Defect orLeydig Cell Hypoplasia	Low	Low	Normal
Gonadal Dysgenesis	Low	Low	Low

T=testosterone, DHT=dihydrotestosterone and MIS=müllerian inhibiting substance.

OVOTESICULAR DSD

Ovotesticular DSD, one of the rarest forms of DSD, describes patients that were previously categorized as true hermaphrodites. The gonads of patients with ovotesticular DSD contain both ovarian and testicular tissue. Thus, the presentation of genital ambiguity can be variable. In ovotesticular DSD in which the gonads contain both ovarian and testicular tissue, the majority have an XX chromosomal constitution. Complex mosaicism (XX/XY) are seen in approximately 10% of cases. Patients can present with a wide variety of genital ambiguity as well as a mixture of Wolffian and Mullerian structures.

DIAGNOSIS

Determination of chromosomal sex by karyotype with FISH analysis for SRY and pelvic ultrasound to evaluate for the presence of a uterus should be performed immediately. Currently, the only newborn screening test for steroid disorders is the measurement of 17-hydroxyprogesterone for 21-hydroxylase deficiency. Further laboratory evaluation to accurately diagnose the specific underlying defect should be directed by a pediatric endocrinologist. If CAH is suspected, measurement of adrenal hormones, ACTH stimulation testing, and molecular genetic testing can elucidate the form of CAH. Each form of CAH has its own unique hormonal profile, consisting of elevated levels of precursors and elevated or diminished levels of adrenal steroid products. HCG stimulation testing to assess testosterone and dihydrotestosterone response may be particularly helpful in 46XY DSD to assess testicular androgen production. Molecular genetic evaluations should be guided by chromosomal and hormonal evaluations.

Chromosomal sex can be determined prenatally invasively by chorionic villus sampling and amniocentesis and noninvasively via free fetal DNA in the maternal blood. Thus, DSD may be suspected in utero if the phenotype on prenatal ultrasonogram is discordant with the chromosomal sex.

THERAPY

When considering the gender of rearing, the prognosis for masculinization of brain and behavior, the anatomic and physiologic character of the reproductive tract with its potential for development and function in regard to both sexuality and fertility, and the social environment of the infant should be taken into account along with the genetic sex. Both male and female gender assignment should be thoroughly considered.

Sex hormone replacement is needed to induce pubertal development. Testosterone is used in the treatment of patients with testosterone deficiency (46XY DSD). Different forms of testosterone (topical and intramuscular) are available and treatment will vary depending on what is best for the patient. A short course of testosterone can be given during infancy to induce penile growth prior to surgical correction. For 46XY DSD patients with functioning Sertoli cells, HCG can be used to stimulate testicular production. Estrogen is used in the treatment of those reared female. Estrogen is available as an oral tablet or transdermal patch. Estrogen doses should be initiated at the lowest dose possible and slowly increased to a maximum of 0.625 mg/day of conjugated estrogen to allow for gradual breast development. Progesterone supplementation with estrogen is recommended in patients with a uterus.

Glucocorticoids are needed to treat congenital adrenal hyperplasia. They suppress the pituitary glands oversecretion of adrenocorticotropic hormone and thus decrease the production of precursor hormones. This also leads to a decrease in adrenal androgen production in forms of CAH associated with 46XX DSD.

The aim of surgical repair in patients with atypical genitalia reared in the female gender is generally to remove the redundant erectile tissue, preserve the sexually sensitive glans clitoris, and provide a normal vaginal orifice. A medical indication for early surgery other than for sex assignment is recurrent urinary tract infections as a result of pooling of urine in the vagina or urogenital sinus. In the past, it was routine to recommend early corrective surgery for neonates born with ambiguous genitalia. However, in recent years, the implementation of early corrective surgery has become increasingly controversial due to lack of data on long-term functional outcome. It is advised that all surgical decisions remain the prerogative of families in conjunction with experienced surgical consultants.

The process of assigning and accepting a gender of rearing for a child with ambiguous genitalia and of deciding the necessity of genital surgery is challenging. A team approach that combines the insights of the DSD-experienced pediatrician, endocrinologist, psychologist/psychiatrist, surgeon, and the child's parents or guardian is essential. Although there is no consensus as to the appropriate age to disclose a condition, it is recommended to proceed gradually in line with the child's cognitive and psychological development.

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