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Article Review: The Disorders of Sex Development (DSD) According to the Type of Gonad Found in the Patient

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ABSTRACT

Sexual development disorders (DSD) are categorized based on the patient's gonad type (ovary, testicle, or ovary). abnormalities of gonadal development and abnormalities of androgen synthesis or action are currently recognized etiologies and are classified as Mendelian. Sex determination and sex differentiation are the two successive stages of human sexual development. The expression of gene networks that guide the development of undifferentiated dipotent gonads into testes or ovaries is referred to as "sex determination." Throughout fetal development and adulthood, the testicles and ovaries release hormones that encourage additional gender differentiation in the body. DSD is caused by mutations found in the genes that regulate both steps. A comprehensive history, physical examination, and appropriate diagnostic testing are needed to determine the underlying etiology.

Congenital abnormalities known as disorders of sex development occur when chromosomal, gonadal, or anatomic sex development is abnormal. A substantial public health burden is associated with DSD, a group of chronic medical diseases that collectively afflict approximately 1% of the population and often necessitate lifetime care from numerous experts. Certain life-threatening conditions, like adrenal crises in congenital adrenal hyperplasia, are linked to DSD. Infertility, cancer, gender dysphoria, psychosocial suffering, and widespread obstacles to health-related quality of life for patients and their families are all linked to DSD.

A condition known as ambiguous genitalia occurs when it is difficult to determine a person's sex by their outward appearance. Males with ambiguous features and hypovirilization (micropenis, II absence of scrotal fusion, incomplete testicular descent, hypospadia) or females with ambiguous features and virilization (clitoromegaly, labio-scrotal fusion) are among the possible genital presentations.

The family history, clinical assessment and evaluation, karyotype inquiry, imaging, and molecular testing are crucial in the workup of a newborn with ambiguous genitalia. Serum gonadotropins (LH, FSH), androgens and androgen precursors (17-hydroxypregnenolone, 17hydroxyprogesterone, androstenedione, testosterone, and dihydrotestosterone), adrenal steroids (cortisol, aldosterone, and their precursors), and Müllerian inhibiting substance (MIS) are among the detailed hormone studies that are recommended.

Keywords- Sexual development disorders (DSD), Gonad type, Abnormalities, Gonadal development, Androgen synthesis, Sex determination, Sex differentiation, Undifferentiated dipotent gonads, Congenital abnormalities, Anatomic sex.

I. INTRODUCTION

An anomaly of the chromosomal, gonadal, or phenotypic characteristics that normally determine sex development is the hallmark of a set of uncommon illnesses known as disorders of sex development (DSD). According to Kyriakou et al. (2015), these diseases typically manifest as delayed puberty in adolescents or as typical genitalia in newborns. The phrase "ambiguous genitalia" refers to the way a baby's genitalia differ from those of the majority of other boys and girls (Achermann et al., 2011).

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According to estimates, genitalia that are sufficiently ambiguous to delay sex assignment occur in approximately 1 in 4500 live births (Michala et al., 2014). However, some genital anomalies may occur in as many as 1 in 300 births.

Families with ambiguous children worry about their child's sex, and there is a lot of social pressure to identify as one's gender. Unresolved gender identity issues can have a big impact on the connection between parents and children. To identify the sex of raising and to start the required medical interventions, evaluation and diagnosis must be completed quickly. Consultation with a doctor, pediatric endocrinologist, geneticist, and surgeon should begin as soon as a kid with ambiguous genitalia is born (Henry et al, 1996).

It might be difficult to evaluate a newborn with ambiguous genitalia, and the underlying cause needs to be quickly investigated. When assessing newborns with ambiguous genitalia, a multidisciplinary team approach involving neonatology, endocrinology, gynecology, urology, genetics, ethics, social work, and psychology is advised. Kate (2016). As previously stated, it is critical that a multidisciplinary team, ideally one with experience in DSD screening and treatment, promptly assess a newborn with ambiguous genitalia. This is done for two reasons: (1) to determine the infant's proper sex of raising based on the condition's etiology and related medical and psychosexual outcomes, and (2) to identify any underlying, potentially fatal disorders that may be present (Hughes, 2006).

The cause of genital ambiguity in neonates affects a number of management issues, such as the requirement to replace hormones like cortisol, aldosterone, and/or steroid hormones, recommendations for sex of raising, and risk assessment for gonadal cancer. Therefore, it's critical to start a suitable work-up as soon as possible (Krishnan and Wisniewski, 2015). Gonadoplasty, vaginoplasty, and gonadectomy are surgical procedures that should only be carried out by skilled surgeons and should be postponed until a definitive diagnosis has been made. Any medical or surgical procedure must have well-established advantages over disadvantages, and any needless operations should be postponed until the kid is mature enough to make an educated choice (Migeon et al., 2002). Following a choice regarding sex-assignment, the kid and family will require ongoing monitoring with healthcare professionals who have DSD experience. Since many of these individuals may need surgery and hormone therapy, ongoing education is crucial. It's critical to evaluate the parents' and patients' contentment with the choice of sex assignment. Regular psychological evaluation is advised to support families and screen for mental health conditions including gender dysphoria (Bonnie, 2017).

II. EPIDEMIOLOGY OF DSD

The prevalence rate of patients with ambiguous genitalia at birth is unknown, and only a small percentage of them provide a significant problem in terms of male or female assignment. Nonetheless, Sax (2002) estimates that it is roughly 1 in 4,500 to 5,500. There is insufficient data to pinpoint the precise prevalence of particular DSDs, and only a tiny percentage of people with DSDs need a thorough multidisciplinary evaluation before being recommended for gender assignment. One in 20,000 births is thought to be the incidence rate for individuals with 46, XY to have a DSD. One out of every 100,000 live babies is thought to have ovatesticular DSDs (Nistal et al, 2015).

According to Skakkebaek et al. (2001), the prevalence of testicular or mixed gonadal dysgenesis is estimated to be 1 in 10,000. According to estimates, the global incidence of 46,XX DSD, which is mainly caused by CAH, mainly 21-hydroxylase deficiency, is 1 in 14,000–15,000 live births (Pang et al., 1988). However, this varies by location due to ethnic variances in the frequency of gene mutations. About half of all DSD patients who report with genital ambiguity have CAH and mixed gonadal dysgenesis (Thyen et al, 2006). The rate could reach 1: 200 to 1: 300 when all congenital genital abnormalities, such as hypospadias and cryptorchidism, are taken into account (Nordenvall et al, 2014). At the moment, only patients with proximal hypospadias and cryptorchidism are often diagnosed with distinct DSD disorders. Klinefelter syndrome (estimated at 1 in 500 to 1 in 1000 live births) and Turner syndrome (about 1 in 2,500 live births) are also included in the overall incidence estimates. Hopefully, these established estimations offer a helpful viewpoint (Lee et al, 2016).

III. DIAGNOSIS OF DSD

A thorough history, physical examination, and laboratory analysis are all part of a newborn's overall evaluation if DSD is suspected. (Kamal and others, 2016).

IV. HISTORY

1. Drug use by the mother, particularly during the first trimester (virilization of a female fetus).
2. A mother's history of virilization may indicate an androgen-producing tumor (arrgonoblastoma).
3. A sibling's early death in infancy could indicate an androgenital deficit that was overlooked in the past.
4. Affected sibling or family member's family history of testicular feminization or CAH (Hughes et al., 2006).

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V. HANDLING DSD

Families experience stress and distress when they are unsure about their infant's gender. When assessing these individuals, it is critical that a multidisciplinary team with expertise in DSD be brought in as soon as possible (fig 1) (Bonnie, 2017). Endocrinology, urology, gynecology, genetics, psychology, social work, and ethics should all be on this team. First and foremost, life-threatening situations like CAH should be ruled out. All conversations on sex assignment should involve the parents, and they should be informed as soon as test results are available. Parents are excited to share their newborn's sex with friends and family, but it's crucial to give it great thought and conduct a comprehensive assessment before deciding on a sex assignment. Prior to creating the final sex assignment, it's crucial to refer to the newborn using gender-neutral language, such as "baby," rather than "she" or "he." It is advised that parents consult a psychologist who can offer them coping mechanisms and advice on how to discuss their infant with friends and family.

Numerous elements, such as hormonal sex (hormonal profile: testosterone), genotypic sex (karyotype), and phenotypic sex (appearance of the external and internal genitalia), Sex assignment is influenced by reproductive sex (the possibility of having biological children), parental perception, DHT, and the adrenal steroid profile. (Ahmed and others, 2011). As families engage in the sex assignment process, talking about each of these aspects of sexual development can demystify the procedure and ease their worry. Gonadoplasty, vaginoplasty, and gonadectomy are surgical procedures that should only be carried out by skilled surgeons and should be postponed until a definitive diagnosis has been made (Hughes et al., 2006).

Before a child is mature enough to make an educated decision, any needless medical or surgical operations should be postponed until the advantages of the procedure are evidently greater than the risks. Following a sex-assignment decision, the kid and family will require ongoing care from medical professionals who have knowledge of DSD. Since many of these individuals may need surgery and hormone therapy, ongoing education is crucial. Evaluating how satisfied the patient and parents are with the choice of sex assignment is crucial. Regular psychological evaluation is advised to support families and screen for mental health conditions including gender dysphoria. Bonnie (2017).

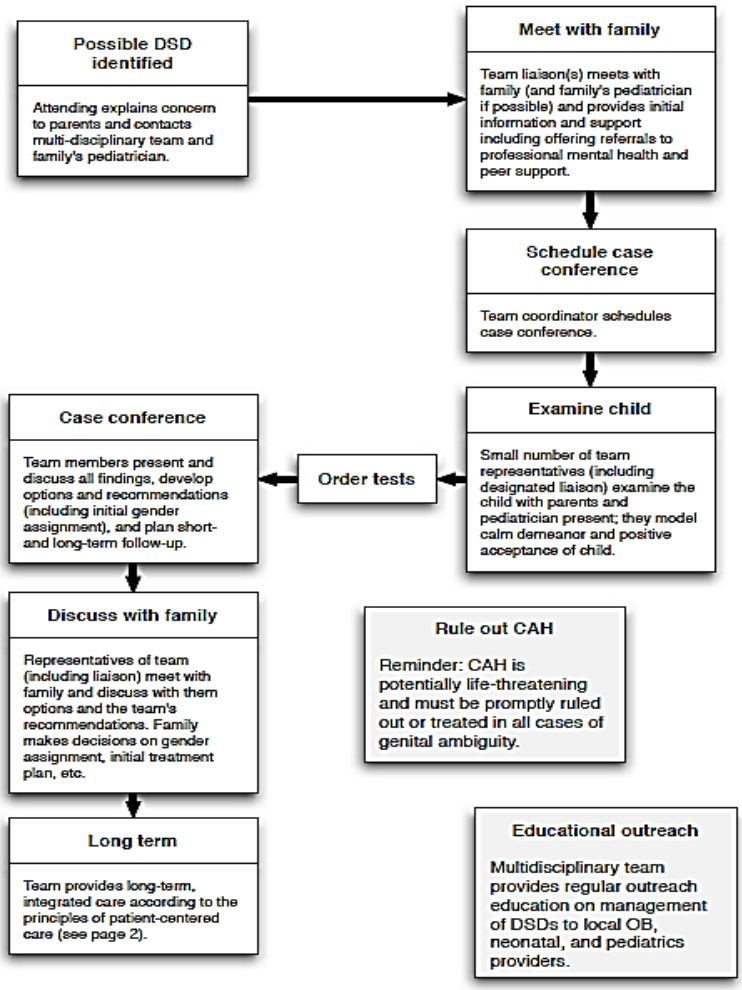

Figure (1): Steps of management for DSD (Bonnie *et al*., 2017).

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VI. GENITAL AMBIGUITY AND HORMONAL IMBALANCE

Patients with non-palpable gonads and ambiguous genitalia should be highly suspected of having CAH. Measurements of serum electrolytes to check for salt wasting, low serum glucose in cases of cortisol deficiency, 17-hydroxyprogesterone to check for 21-hydroxylase deficiency, and a corticotropin (ACTH)-stimulation test to assess the cortisol response and enzymatic deficiencies that can cause CAH should all be part of the initial evaluation. Cortisol, 17-hydroxyprogesterone, 17-hydroxypregnenolone, progesterone, androstenedione, dehydroepiandrosterone, deoxycorticosterone, 11-deoxycortisol, and testosterone levels at baseline and when provoked by ACTH can be obtained. Treatment for suspected CAH should not be postponed because of the ACTH-stimulation test. Renin and aldosterone levels should also be measured in any suspected CAH patient. Tables 2–5 provide a summary of the normal value (Moshiri et al, 2012). Baseline gonadotropin levels (LH) and follicle-stimulating hormone (FSH) are also tested for hypogonadotropic hypogonadism, as they may be low in these conditions and suggest a potential pituitary insufficiency. 46, XY people may have micropenis due to hypogonadotropic hypogonadism. The presence and function of testicular tissue can be reliably indicated by the AMH level, which is also useful for assessing undervirilized XY males. If you have chronic Müllerian duct syndrome, XY gonadal dysgenesis, or disappearing testes, your AMH levels will be low. When hypogonadotropic hypogonadism and androgen insensitivity occur, AMH levels may rise. Testosterone production from testicular tissue is assessed using the HCG-stimulation test. In order to perform the hCG-stimulation test, baseline and stimulated testosterone and DHT levels must be measured. A 5a-reductase deficit will result in an increased testosterone to DHT ratio. An XY person's poor reaction to HCG stimulation may be a sign of hypogonadotropic hypogonadism, ovotesticular DSD, gonadal dysgenesis, or an LH receptor abnormality. Moshiri and colleagues (2012).A 46, XY patient who is undervirilized and has high testosterone levels should be suspected of having androgen insensitivity, and genetic testing should be taken into consideration. It is necessary to interpret hormone levels in light of the particular assay parameters as well as the typical values for gestational and chronological age. In certain situations, it can be necessary to perform stimulation tests or serial measurements.

When the external genitalia are sufficiently unclear to interfere with sex assignment or do not match the findings of prenatal examinations, a thorough investigation is necessary. Serum 17-OHP is typically unreliable in the salt-losing variant of CAH and before the age of 36 hours.Before the day of life, serum electrolyte levels often do not become abnormal. To allay worries about analytical specificity, steroid hormone determination ought to be carried out following an extraction or chromatography (Tomlinson et al., 2004, Bergadá et al., 2006).

Results should be viewed in the context of the normal male newborn's low serum testosterone levels during the first 7–14 days of life, which gradually rise until the age of 2–3 months. In 2006, Bergadá et al. Results should be viewed in the context of the normal male newborn's low serum testosterone levels during the first 7–14 days of life, which gradually rise until the age of 2–3 months. In 2006, Bergadá et al. Despite the fact that both ovarian granulosa cells and testicular Sertoli cells express AMH, boys are born with much higher levels of AMH in their blood than girls (Bergadá et al, 2006). Elevated 17-OHP and testosterone levels are characteristic of CAH in 46, XX infants, with salt-wasting variations exhibiting hyperkalemia and hyponatremia. A salt-losing crisis is no longer necessary for the diagnosis of this variation due to the availability of genotyping.

Ovotesticular DSD is expected when both androgen and AMH levels are higher than those of women; aromatase insufficiency should be suspected when both levels are higher but AMH is within the normal range for women. Maternal virilizing tumors may be the cause if testosterone levels gradually decline along with the level of virilization (Rey and Grinspon, 2011). Low levels of AMH and androgen indicate dysgenetic gonads in babies with Y chromosomes, while normal/high levels of both AMH and androgen indicate steroid production abnormalities or androgen insensitivity or nonendocrine malformative DSDs.(Grinspon and Rey, 2014; Rey and Grinspon, 2011).

Since gonadotropin levels are typically normal or only slightly higher in steroid synthesis abnormalities and partial androgen insensitivity, while they are typically quite high in dysgenetic DSDs, they may also be beneficial. According to Bouvattier et al. (2002), they may even be low in patients with full AIS.

Decision-making algorithms incorporate imaging investigations, a gonadal tissue sample, and repeated assessments of basal AMH and androgen levels. They also use HCG and ACTH stimulation tests to evaluate testicular and adrenal steroid production and urinary steroid analysis by LC-MS/MS. The mass of functioning Sertoli and Leydig cells is indicated by basal levels of androgen and AMH. They can have normal male values in mildly dysgenetic DSDs or ovotesticular DSDs with considerable testicular tissue, or they can be very low in XY patients with substantially dysgenetic gonads or XX patients with ovotesticular DSDs with predominate ovarian tissue. Repeated assessments may be required because the levels of androgens and AMH in male newborns are typically low and gradually rise after the third week of life. When a steroidogenic abnormality affecting both the gonads and the adrenal glands is suspected, an ACTH test may be helpful (Lindhardt et al, 2013). The laboratory tests and diagnostic findings in infants with DSD were compiled in table 1 (Moshiri et al., 2012).

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Table (1): Laboratory Tests and Diagnostic Findings in Infants with DSD (Moshiri et *al*,2012)

Test	Diagnostic Findings
17-hydroxyprogesterone level	Elevation is suggestive of CAH
11-deoxycortisol and 11-deoxycorticosterone levels	Both are elevated in 11-b-hydroxylase deficiency and depressed in 21-hydroxylase deficiency associated with CAH
Testosterone-to dihydrotestosterone ratio*	A ratio of more than 20:1 is indicative of a 5a-reductase deficiency
Human chorionic gonadotropin stimulation	Nonresponse (i.e, absence of increase in the testosterone level) is indicative of nonfunctioning Leydig cells, anorchia, or luteinizing hormone receptor defect
Antimullerian hormone and inhibin B levels	Normal values in the postnatal period are suggestive of normal Sertoli cell function and the presence of at least one testis

***The ratio is determined when testosterone levels are normal.**

Almost all people with Turner syndrome (TS) experience growth loss; those who do not receive treatment end up 20 cm shorter than their classmates on average as adults. The current standard of care for girls with TS is GH therapy. In addition to identifying the proper timing and dosage of hormone replacement therapy, gonadotropin levels may be helpful in forecasting future gonadal function (Stephure, 2005).42.2% of the 478 girls with TS, whose mean age was 15.5 years, had positive thyroid autoantibodies, of whom 27% (29/106) were hypothyroid and 3% were thyrotoxic, according to Radetti et al.'s 1995 study. There are no research examining the release of sex steroids in Klinefelter syndrome throughout infancy, and there is a dearth of information on serum testosterone and estradiol levels in healthy prepubertal children.

When hypogonadal signs and symptoms begin and/or worsen, serum T concentrations in young adults with KS typically fall into the mid-low range. The age at which hypogonadism first appears varies greatly, though. Serum T can occasionally be within the normal range, although in the literature, varying percentages (65–85%) of individuals with KS had lower than normal serum T concentrations (<12 nmol/L). Even in patients whose serum testosterone levels are still within the normal range, hypogonadism is invariably accompanied by elevated gonadotropins (hypergonadotropic hypogonadism), which are typically greater than normal (Bonnie et al., 2017).

VII. CONCLUSIONS

1. A multidisciplinary team must be included in a step-by-step diagnosing process.
2. A thorough history, a thorough physical examination, and the right laboratory and radiographic tests help with early diagnosis and prevent major consequences.
3. A fundamental comprehension of the DSD differential diagnosis can aid in directing the assessment of these infants.
4. All choices about sex assignment and surgical management must involve the families, and there should be open communication between the families and the medical staff.
5. A crucial first step in the diagnosis and therapy of DSD is hormonal evaluation.

RECOMMENDATION

1. One recommendation is the creation of a pediatric hospital specialty unit with a multidisciplinary team for the early detection and treatment of DSD.
2. The creation of a laboratory section with cutting-edge technologies for DSD detection in pediatric hospitals.
3. All newborns should have their external genitalia evaluated clinically.
4. Prenatal screening is advised for all expectant mothers with a history of giving birth to an unclear child.

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