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Clinical Profile and Management of 1-Year-Old Child with 46 XY DSD

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Abstract: ***Background: Gender determination of a child is an important aspect which associated with individual's psychosocial function. The newborn infant with ambiguous external genitalia presents a problem of sex assignment and is frequently described as a clinical emergent situation that is distressing to the parents. Gonad development disorder or defect in androgen synthesis or function may cause ambiguous genitalia in 46 XY disorders of sexual development (DSD). Aim: To cover clinical profile, evaluation, and management of a patient with 46 XY DSD, with an aim to provide better understanding for clinician with similar case findings. Case: A 1-year-old child with male phenotype was presented with imperfect scrotum and impalpable bilateral cryptorchidism. Patient's chromosomal analysis showed 46 XY DSD. Testicular ultrasound (USG) found a suspicion of left testicle in left pelvic region, and right testicle in right inguinal region. Anti-Mullerian hormone test result showed more than 46.000 ng/mL. Testosterone hormone examination after serial human chorionic gonadotropin (hCG) injection showed more than 186-fold increase in level of testosterone hormone compared to baseline. Surgical treatment with diagnostic laparoscopic approach and orchidopexy may be performed to prevent infertility in this patient. Conclusion: Individuals with 46 XY DSD may have testicular development disorder and impaired androgen synthesis or action which may cause ambiguous genitalia. Comprehensive management through multidisciplinary approach is needed in these cases.***

Keywords: genes, gonad development, sex development

1. Introduction

Gender determination of a child is an important aspect which associated with psychosocial function of an individual. The newborn infant with ambiguous external genitalia presents a problem of sex assignment and is frequently described as a clinical emergent situation that is distressing to the parents. Gonad development disorder or defect in androgen synthesis or function may cause ambiguous genitalia in 46 XY disorders of sexual development (DSD). DSD are a very important clinical issue with its different aspects relating to diagnosis, treatment and sex of rearing.

2. Case

A 1-year-old child with male fenotype was presented with imperfect scrotum. In the initial evaluation, physical examination showed impalpable bilateral undescended testes. Additional investigation of chromosomal analysis was performed and found 46 XY DSD. Testicular ultrasound (USG) found a suspicion of left testicle in left pelvic region, and right testicle in right inguinal region. Anti-Müllerian hormone testing result was more than 46.000 ng/mL, which showed that there was a detection of testicular tissue in the body. The test was then followed by testosterone hormone examination. Testosterone hormone was examined after serial human chorionic gonadotropin (hCG) injection. The result showed 186-fold increase in level of testosterone hormone compared to baseline, which may be interpreted as good testicular tissue function. Surgical treatment with diagnostic laparoscopic approach and orchidopexy may be performed to prevent infertility in this patient.

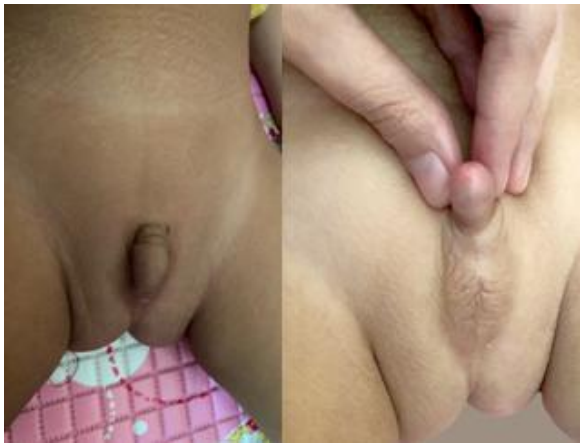

Figure 1: Patient's phenotype profile on physical examination

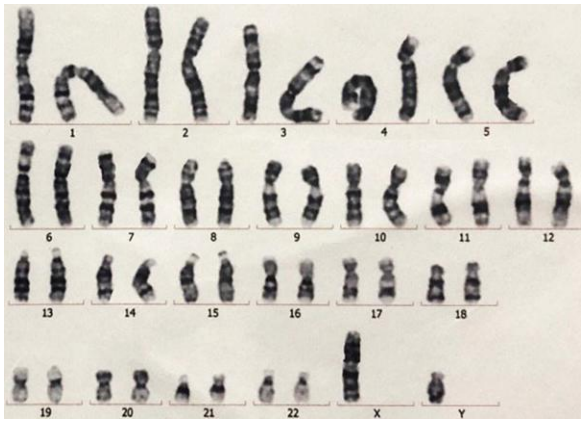

Figure 2: Chromosomal analysis showed 46 XY

The newborn infant with ambiguous external genitalia presents a problem of sex assignment and is frequently described as a clinical emergent situation that is distressing to the parents. Disorders of sex differentiation (DSD) is defined as congenital conditions associated with atypical

development of chromosomal, gonadal, or anatomical sex [1]. In one of every 4.500 births, the genital appearance is abnormal and it is not possible to decide at first glance the sex of the infant [2]. This condition is also known as ambiguous genitalia [3]. Estimated prevalence of 46 XY DSD is 1 in every 100.000 births [4]. Based on the study by Brauner et al (2016), of the 140 patients, familial forms represent 22% (25/114) of the 46 XY DSD. Familial affected individuals presented with DSD and/or premature menopause (4 families) or male infertility (4 families) and/or cryptorchidism [5]. The genetic etiology of most cases of 46 XY DSD is unknown and for the moment it is unclear if the phenotype in these cases is due to rare single-gene defects in a limited or large number of genes involved in male development or if the phenotype is due to cumulative rare and/ or common variants in the human genome [6].

Gonadal dysgenesis (ovarian agenesis, gonadal dysplasia) is a clinical syndrome which there is an absence of secondary sexual characteristics in puberty [4]. 46 XY DSD is characterized by reduced androgenization and causes include complete gonadal dysgenesis (CGD) or partial gonadal dysgenesis (PGD) or a defect in androgen synthesis or action [6]. Twenty-eight percent of patient with gonadal dysgenesis had bilateral undescended testes (UDT), or CDG, and 22% had unilateral UDT, or PDG [4].

The Lawson Wilkins Pediatric Endocrine Society (LWPES) and the European Society for Paediatric Endocrinology (ESPE) consensus group proposed the classification of DSD into: 1) Sex chromosome DSDs (45 X Turner and variants, 47 XXY Klinefelter and variants, 45 X / 46 XY mixed gonadal dysgenesis (MGD) and chromosomal ovotesticular DSD (46 XX/46 XY chimeric type or mosaic type); 2) 46,XY DSD (disorders of testicular development or disorders in androgen synthesis/action); and 3) 46 XX DSD (disorders of ovarian development or fetal androgen excess).

The differentiation of the male genital tract and external genitalia is dependent on anti-Müllerian hormone (AMH) and testosterone [5]. The production of anti-Müllerian hormone (AMH) by Sertoli cells and androgens by Leydig cells in a critical concentration-dependent and time-dependent manner induces male sexual differentiation by means of a hormone–dependent process. Testosterone and AMH cause regression of Müllerian structures and differentiation of the Wolffian duct into the epididymis, vas deferens, and seminal vesicles. The Leydig cells also produce insulin-like factor 3 (INSL3, relaxin-like factor), which causes the testes to descend to the scrotum [2]. In 46 XY males, testosterone is converted to 5-dihydrotestosterone (DHT) by the enzyme 5-AR, resulting in the development of male external genitalia [3].
Diagnosing and constructing a management plan for DSD is challenging. The evaluation and management of DSD is complex, and a multidisciplinary team approach including a pediatric urologist, a psychiatrist, and a pediatric endocrinologist is required for optimal management [1]. Initial investigations should include a thorough history and clinical examination of the infant. Clinical examination should not simply focus on the external genitalia, but also seek to determine if there are any dysmorphic features or evidence of further developmental anomalies [3]. Common findings suggesting DSD are male appearance with associated abnormalities of genitalia including severe hypospadias with bifid scrotum, UDT or testes with hypospadias, bilateral non-palpable testes, and micropenis with chordee. Gonadal dysgenesis of 46 XY DSD cannot be diagnosed only by physical examination of the external genitalia, hence additional hormonal profile examination is required [4]. After initial examination, first line investigations should include a karyotype, abdominopelvic ultrasound examination for Müllerian structures, and serum levels of AMH. Additional investigations should include serum testosterone, cortisol, androstenedione, gonadotropins, and urinalysis. Genetic testing may be performed according to clinical suspicions [3]. Patients physical findings of bilateral UDT lead to suspicion of DSD, hence the examination for karyotype was obtained, which showed a 46 XY DSD. Ultrasound examination was then performed, which showed the presence of both testes. Hence, in order to find out whether the testes were functional, serum AMH testing was ordered.

Serum AMH determination is a powerful means to assess Sertoli cell function. In XY patients, AMH is low in presence of abnormal testicular determination (including complete and partial gonadal dysgenesis) but normal or elevated in patients with impaired testosterone secretion. A serum AMH level higher than 75 pmol/L is indicative of the presence of testicular tissue and correlates with the mass of functional testicular parenchyma [2]. In certain circumstances, additional hormonal stimulation testing such as human chorionic gonadotropin (hCG) to assess testicular function are needed [1]. Testosterone level should be measured at baseline and 72 hours after hCG stimulation. The testosterone increment should be at least threefold [2]. In this patient, high AMH level was interpreted as presence of testicular tissue in the body. Testosterone hormone stimulation test showed significant increase compared to baseline, which may be interpreted as good testicular tissue function. Hence, the cause of DSD in this particular case was suspected to be disorder in Leydig cell, particularly in production of INSL3 which facilitates the testes to descend to scrotum.

The aim of surgery is in DSD to make ambiguous external genitalia compatible with assigned gender, preventing urinary obstruction or infections, preserving sexual and reproductive potentials, and maximizing anatomy to enhance sexual function. There are still controversies regarding the optimal timing of the surgery. Masculine reconstruction may include 1) orchiopexy, 2) hypospadias repair, and 3) removal of retained müllerian duct structures [1].

Genetic testing as basis of molecular diagnosis is useful in the management of DSD, potentially providing information about long-term fertility, adrenal health, and germ-line tumor risk as well as an understanding of the etiology and recurrence risks for affected individuals and their parents [3]. Thus, knowing the cause not only helps with explaining the condition to the parents and the growing child but also allows the clinician and the patient and their family to plan for the future [6].

3. Summary

DSD with ambiguous genitalia is a rare disorder requiring prompt investigation and early gender assignment that is logically based on a sound knowledge of normal sex determination and differentiation. Individuals with 46 XY DSD may have testicular development disorder and impaired androgen synthesis or action which may cause ambiguous genitalia. In this particular case, cryptorchidism was considered to be caused by a deficiency of INSL-3 hormone, thus surgical treatment is needed so that the testes may function optimally. Comprehensive management through multidisciplinary approach is needed in these cases.

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