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Challenges in the Management of 46 XY Disorders of Sex Development (DSD) in Saudi Arabia

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ABSTRACT

Background: *Disorders of sex developmebt (DSD) are defined as congenital conditions in which development of chromosomal, gonadal, or anatomical sex atypical. In 46 XY DSD, the genotype is XY, but the external genitalia is incompletely virilized, ambiguous or completely female.*

Design and Setting: *This is a retrospective, hospital-based study, conducted at the King Saud University Medical City (KSUMC), pediatric endocrine division.*

Objectives: *The management of 46 XY DSD is challenging. We aimed to highlight the interplay of clinical, genetic, and cultural /religious factors, related to this, over three decades of time. Emphasizing the need to individualized approaches to management.*

Materials and Methods: *A retrospective review of medical records of patients, who were diagnosed with 46 XY DSD, over more than three decades were included. The diagnosis was based on recommendation.*

Results: *Sixty-seven patients with 46 XY DSD, aged 0-12 years were included. A wide spectrum of clinical presentation was seen with Androgen Insensivity Syndrome (AIS) was present in 20 (29.9 %), 12 (17.9 %) patients were having 5-alpha-reductase deficiency. Other testosterone biosynthesis defects were diagnosed in nine (13.4%) patients. Hypogonadotropic Hormone deficiency was the diagnosis in four (6%). Unfortunately, four of our patients, who were diagnosed with 5-alpha-reductase deficiency were wrongly assigned female sex which later re-assigned as males.*

Conclusion: *Management of patients with 46 XY DSD is complex, and often facing controversy. Social, cultural, and religious beliefs, often causing challenges. In suspected cases, early sex assignment should be avoided, Emphasizing the need for individualizing our approach in management of 46 XY DSD, by a trained multidisciplinary team. Parents should be involved in the decision that is based on extensive counselling.*

Keyword

Ambiguous genitalia, Disorders of sex development (DSD), Assignment, Reassignment, Karyotype, 46 XY, a, Psychosocial, Cultural Challenges, Controverses, Multidisciplinary Team.

Introduction

Disorders of sex development (DSD) represent a heterogeneous group of congenital disorders, characterized by discordance between chromosomal, gonadal, and phenotypic sex. The biological sex (being male or female) of a baby not match the genital appearance (Figures 1 and 2).

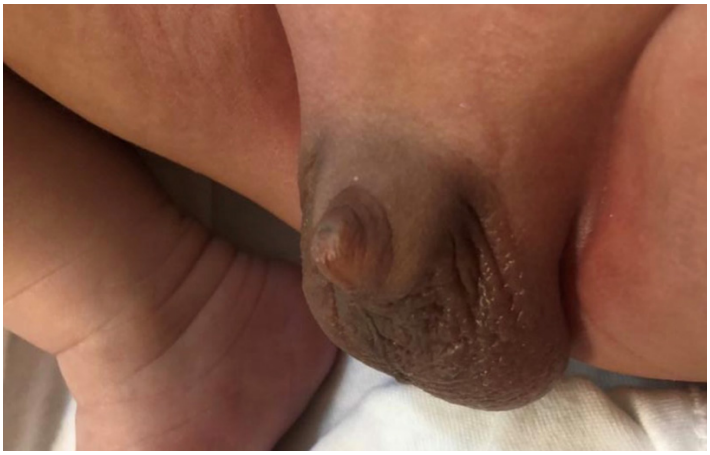

Figure 1: A patient who was assigned a male sex. He was found to have a 46XX karyotype and diagnosed to have 11-b-hydroxydase deficiency. Congenital adrenal hyperplasia.

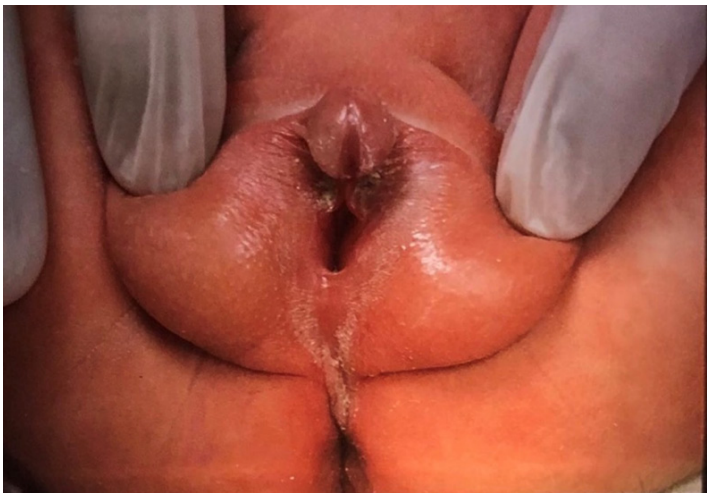

Figure 2: Ambiguous genitalia in a 46 XY DSD with the diagnosis of androgen insensitivity (testicular feminization) syndrome. Note the two palpable gonads (testes) within the labioscrotal folds and urogenital slit.

Among these, 46,XY DSD refers to individuals with a male karyotype who demonstrate varying degrees of undervirilization or ambiguous genitalia due to abnormalities in testicular development, androgen synthesis, or action. There is very limited data available on the incidence rate and prevalence of DSD; however, it is not that rare. The spectrum of 46,XY DSD is so wide [1-12].

The management is so complex, with life-long challenges [13,14], that primarily centered on gender assignment and genital surgery which require an appropriately trained multidisciplinary team of experts [15,16], consisting of a pediatric endocrinologist, geneticist, pediatric surgeon, urologist, plastic surgeon, and psychologist, to determine the best path for the individual. Early diagnosis allows for a better outcome. The availability of recent and powerful techniques helps us understand some of its pathology, gender assignment, surgical intervention, and the integration of cultural/religious beliefs.

This article focuses on the challenges related to the management of 46,XY DSD, which is not that rare. In Saudi Arabia with high incidence of consanguinity, the disorder is often more common. The management is so complex and challenging. This involve early gender assignment, and favoring male roles due to cultural views and beliefs. Efforts to improve public awareness and health-care professionals could help in the long-term outcomes.

Materials and Methods

During the period under review, all patients who were diagnosed to have disorders of sex development (DSD) at King Saud University Medical City (KSUMC), Riyadh, Saudi Arabia, were retrospectively reviewed.

An aetiological diagnosis, detailed clinical history, physical examination, laboratory, and radiological investigations were obtained. The data were collected in a special form. The surgical and/or the medical management provided were also obtained. Laparotomy or laparoscopy with gonadal biopsies were performed when appropriate.

The diagnosis of DSD was based on standard recommendations, set by experts [10-12].

Results

Patients with 46 XY disorders of sex development (DSD), seen and evaluated at the King Saud University Medical City (KSUMC), Pediatric Department, Endocrine Service, Riyadh, Saudi Arabia, were retrospectively reviewed for their clinical characteristics and outcomes over a long period of time.

A total of 67 patients had 46 XY DSD. Their clinical characteristics varied and indicated poor androgenization. Most patients presented with normal female external genitalia or variable degrees of virilization. Table 1 shows the clinical diagnosis and frequency in this series. The androgen insensitivity syndrome (AIS) was the most frequent. It was present in 20 (29.9%) patients, with complete androgen insensitivity syndrome (CAIS) in 13, and partial androgen insensitivity syndrome (PAIS) in 7. Steroid 5-alpha reductase enzyme 2 deficiency (5ARD) was diagnosed in 12 (17.9%) patients. Various types of testosterone biosynthesis defects were encountered, accounting for a total of nine (13.4%) patients. Congenital adrenal hyperplasia (CAH) due to deficiency of the enzyme 3-beta-hydroxysteroid dehydrogenase (3-b-HSD) in 4, 17-beta-hydroxysteroid dehydrogenase deficiency in 2, and dysgenic gonads, as in gonadal dysgenesis and vanishing testis syndrome, in 3. Further to this, four (6%) patients were diagnosed to have hypogonadotropic hormone deficiency, either isolated or as a part of hypopituitarism.

Furthermore, non-hormonal causes for 46 XY DSD were encountered, accounting for 32.8% presenting as congenital anomalies.

Regarding sex assignment, four patients with 5-alpha-reductase deficiency had severe undervirilization, and were therefore

Table 1: Pattern and Clinical Presentation of 67 patients with 46XY DSD.

Diagnosis (No. of patients %)	Sex at presentation	Clinical presentation	Final sex assigned	Remark
Hormonal				
45 patients (67.2 %)				
Androgen insensitivity 20 (29.9%) Complete (CAIS) (13) Partial (PAIS) (7)	(M – 3) (F – 11) (U – 6)	- Normal appearing external female genitalia to severe hypospadias with cordee and undescended testicles	M 8 F 12	
5-a-reductase deficiency 12 (17.9%)	(M – 8) (F – 4)	- Normal appearing female genitalia to severe penile hypospadias	M 12	4 patients needed reassignment
Androgen biosynthesis defects 9 (13.4%) 3 B HSD deficiency (4) 17 B HSD deficiency (2) Testicular dysgenesis (2) Vanishing testis syndrome (1)	(M – 7) (F – 0) (U – 1) (M – 1)	- Undescended testis - Micropenis	M 9	
Hypogonadotropic hypogonadism 4 (6%)	(M – 4)	- Micropenis, undescended testicles and hypoplastic scrotum	M4	
Non-Hormonal				
22 patients (32.8 %)				
Congenital anomalies associated with DSD	(M – 22)		M22	

Abbreviations

M: Male, F: Female, U: Undetermined, 3-b HSD: 3-b hydroxy steroid dehydrogenase deficiency, 17-b HSD: 17-b hydroxy steroid dehydrogenase deficiency, DSD: Disorders of sex development.

wrongly assigned to the female sex; two of whom were siblings. All were re-assigned to the male sex at a later age. Patients with complete androgen insensitivity syndrome (CAIS) were assigned to female, except one, who was assigned to male sex. Parents insisted on the male sex assignment.

Table 2: Associated anomalies in 22 patients with 46,XY DSD.

Anomaly Classification	Specific Condition	
Isolated Anomalies (8)		
	Hypospadias (8)	
Multiple Anomalies (14)		
Syndromic (6)		
	Reminiscent hydrolethalus and pseudo trisomy (13)	2
	Klinefelter syndrome	2
	Prader-Willi syndrome	1
	Swyer syndrome	1
Non-Syndromic (8)		

Furthermore, our results showed that patients with 46 XY DSD had variable other associated congenital anomalies. Table 2, These could be either isolated or multiple. Multiple congenital anomalies were the association in 14, while variable hypospadias were encountered in eight patients. Various genetic syndromes were present. Reminiscent hydrolethalus and pseudo trisomy 13 and Klinefelter syndromes were present in two each. while Prader-Willi and Swyer syndromes, in one each.

Discussion

Sexual differentiation during prenatal development involves a series of processes whose initiation and regulation involve numerous genes, proteins and hormones. The first stage in gonadal and genital development is shared by both sexes and spans the first six weeks following conception, an interval during which the embryo is pluripotent.

Gonadal differentiation starts in the seventh week and is regulated by a multitude of genes, with the SRY gene in the Y chromosome playing a key role in the development of the testes. Genital differentiation (internal and external) is regulated by the effects of hormones synthesised by the testes in male embryos, or by their absence in female embryos. Hormonal levels may also result in inadequate development of the gonads (gonadal dysgenesis). [1-3,17-20]. These abnormalities may be apparent at birth manifesting as genital ambiguity or discordance between genotype and phenotypic sex. DSDs are relatively rare worldwide, with congenital adrenal hyperplasia (CAH) being the commonest. Androgen Insensitivity Syndrome (AIS) is common among 46,XY DSD.

In this study, a diversity of aetiological causes were identified among patients with 46,XY DSD. Androgen Insensitivity Syndrome (AIS) was the most common, found in 20 (29.9%) patients. It is inherited in an X-linked manner and results from alterations in the androgen receptor gene, leading to hormonal resistance, which may present clinically in three forms: complete (CAIS), partial (PAIS), or mild (MAIS), and is characterized by under-masculinization of the individual, bilateral testes, and absent Mullerian structures, with a 46,XY karyotype.

Typically, laboratory diagnosis is made through elevated levels of luteinizing hormone and testosterone [21-27]. Steroid-5-alpha-reductase type two enzyme deficiency (5aR2D) or (SRD5A2) was the second most common disorder in our series, present in 12 (17.9%) patients. The SRD5A2 is a rare autosomal recessive condition, characterized by the inability to convert testosterone (T) into the physiologically active dihydrotestosterone (DHT), which is essential for the formation of male external genitalia. Individuals with this condition may present with ambiguous or completely typical female genitalia at birth. Human chorionic gonadotrophin

(hCG) stimulation is valuable [28-32]. Also, as a consequence, testosterone biosynthesis defects may lead to differences in sexual development. It is not that uncommon and varied between gonadal (gonadal dysgenesis or even testicular absence), and even testicular enzyme deficiency, as in 3-beta-hydroxysteroid dehydrogenase deficiency congenital adrenal hyperplasia and 17-beta-hydroxysteroid dehydrogenase deficiency [33-37]. Furthermore, four (6%) patients were found to have hypogonadotropic hypogonadism, an extremely rare disorder caused by deficient production, secretion, or action of gonadotrophin-releasing hormone (GnRH), which is either isolated or associated with other pituitary or hypothalamic hormone deficiencies [38,39].

Managing 46,XY DSD in Saudi Arabia, with a high prevalence of consanguineous marriages [40-43], involves complex and interdisciplinary care addressing genital ambiguity and gender identity. Gender assignment and rearing should be the basis of genital appearance. There is no consensus regarding the choice, timing, and method of sex assignment in neonates with DSD [44-46]. Whether to perform early surgery remains controversial.

Biomedical, cultural, religious, and psychosocial factors, among others [47-54], are influential. Kuhnle and Krahl [55] demonstrated earlier the impact of these factors on DSD patients. In males-focused 46 X Y DSD, culture heavily influences decisions toward raising children as males to fit societal norms Therefore, males with DSD may experience reduced quality of life, including challenges in social contacts and potential for increased depressive moods. Psychological and social support is a necessity. Parents should be involved in the decision.

Comprehensive mental health support is crucial for patients and families [56-58]. Life-long hormonal replacement therapy is often required to ensure a proper outcome [59-61]. Four of our patients with steroid 5-alpha-reductase deficiency needed sex reassignment, as they presented with typical female external genitalia. Sex reassignment involves medical, surgical, and psychological interventions. This should be typically managed by a multidisciplinary team of experts [62-66].

Finally, our results showed that patients with 46,XY DSD were associated with various other congenital anomalies [67-70]. Twenty-two (32.8%) patients were involved. As associated conditions, isolated hypospadias were present in 8 patients, and 14 others had different multiple congenital anomalies. Of these, six patients with known syndromes were encountered; reminiscent hydrolethalus and pseudo trisomy 13 syndrome, Klinefelter, Swyer, and Prader-Willi syndromes [71-76]. These findings provide direction for further studies on genetics and environmental causes of DSD [67,68,77-80].

Conclusion

The diagnosis of 46,XY DSD carries many challenges for patients, families, and medical care providers. Making the correct diagnosis earlier is a necessity for a proper sex of rearing. Unfortunately, early diagnosis is not always possible. Regardless, a multidisciplinary team approach may improve the outcomes, with the emphasis on the need for individualized approaches.

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