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Spectrum of Genital and Extragenital Anomalies in Malformation Syndromes Associated With 46, XY Disorders of Sex Development: A Single Center Experience

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ABSTRACT

Objectives: This study aimed at integrating the clinical and phenotypic characteristics, hormonal profile and genetic diagnosis of children with malformation syndromes associated with XY disorders of sex development (DSD) in a single-center in Egypt.

Methods: This retrospective study included patients with syndromic XY DSD recruited from the Pediatric Endocrinology and Surgery units at Alexandria University Children's hospital (AUCH), Alexandria, Egypt, during the period between 2018 and 2023. All patients included in the study underwent a detailed clinical and laboratory evaluation, ultrasonography (and laparoscopy if needed); and decision making was done accordingly.

Results: The study included 30 children with syndromic XY DSD; most of these children were diagnosed at birth. The most common extragenital malformations included skeletal anomalies (70%), facial dysmorphism (46.7%), cerebral malformations and congenital heart disease (23.3%). Ventricular septal defect was the most common congenital heart disease.

Conclusion: Integration between clinical, laboratory and genetic data is the cornerstone in the management of XY DSD patients for appropriate decision making of surgical intervention and sex assignment, in addition to screening for other associated features of each mutation.

***Keywords*:** 46 XY DSD, Ambiguous genitalia, Gonadal dysgenesis, Sexual differentiation, Syndrome

INTRODUCTION

Disorders of sex development (DSD) are rare congenital conditions associated with atypical gonadal, chromosomal or anatomical sex. Due to the heterogeneous clinical presentation and genetic architecture, achieving a definitive diagnosis is challenging, especially in XY DSD [1,2]. In majority of the cases, neither the clinical presentation nor the phenotype-genotype correlation is indicative enough to make a precise diagnosis [1]. Similar to the diverse pathophysiology, the genetic background varies with more than 40 genes being implicated in its pathogenicity [1]. Some DSD conditions may result from copy number variations (CNVs), especially in cases with gonadal dysgenesis or in the presence of associated malformations [3]. Recent findings indicate oligogenicity as a possible mode of inheritance in DSD [4]. Introduction of next-generation sequencing (NGS) has significantly improved the diagnostic yield in children with DSD [5] while whole-exome and/or genome sequencing (WES/WGS) are evolving as useful clinical diagnostic tools [6].

Neonates with DSDs associated with malformation syndromes may be classified into 'hormonal DSD' with defective hormone function, and 'nonhormonal DSD' with no primary abnormality of gonadal differentiation or hormones [6-9]. Distinguishing hormonal from nonhormonal DSDs by examination of the external genitalia is simple. Defects of androgen synthesis or action are associated with a morphology of the external genitalia which will be somewhere between normal male and normal female phenotype. In contrast, in a nonhormonal DSD, external genitalia are abnormal [10].

Additionally, many of these patients may have other, extragenital malformations, which makes their management even more challenging. Due to the scarcity of studies that collectively analyze malformation syndromes associated with XY DSD, this study aimed at integrating the clinical characteristics of syndromic 46, XY DSD patients, including genital and extragenital features, with their hormonal profile and genetic diagnosis, wherever available.

METHODS

This retrospective study included patients with syndromic 46, XY DSD recruited from the Pediatric Endocrinology and Surgery units at Alexandria University Children's Hospital (AUCH), Alexandria, Egypt, between 2018 and 2023. The study was approved by the institutional ethics committee. Informed consent was obtained from parents for utilizing the data of their children in this study while ensuring privacy and confidentiality of all participants. Syndromic DSD was suspected where the children had associated extragenital manifestations. Patients with congenital adrenal hyperplasia and sex chromosomal DSD were excluded from the study. All patients had karyotyping done to confirm their categorization as XY DSD, besides detecting any chromosomal abnormalities. Age at the time of study, and at diagnosis, and the initial and final sex assignment were recorded.

All patients in this study underwent clinical evaluation including anthropometric measurements, and careful genital examination, including stretched penile length (SPL). A diagnosis of micropenis was considered when the SPL was < 2.5 cm in a full-term newborn, or more than -2.5 standard deviation (SD) below the mean for the corresponding age [11]. Any extragenital anomalies, including skeletal, dental, cardiac, renal anomalies, and dysmorphic features were documented. Laboratory investigations included hormonal evaluation included 10 AM basal serum luteinizing hormone (LH) and follicular stimulating hormone (FSH) levels to assess hypothalamic-pituitary-gonadal axis function. Basal total testosterone (T) and dihydrotestosterone (DHT) levels were tested during minipuberty. In those above 4 months of age, Leydig cell function was assessed with human chorionic gonadotropin (HCG) stimulation test; 1500 units of HCG was given intramuscularly on three successive days with blood sampling done before the first injection and 24 hours after the third injection. Anti-mullerian hormone (AMH) and inhibin B levels were assayed in some patients to determine Sertoli cell function [12]. Good testicular function was considered when both Leydig cell and Sertoli cell function were within normal reference ranges for age. Poor Leydig cell function was defined as T increment less than twice the baseline value after HCG stimulation, or absolute T below the normal prepubertal range [13]. Serum AMH and inhibin B levels below the lower limit of normal range for age indicated poor Sertoli cell function [14]. Ultrasonography of the abdomen and pelvis was performed to screen for congenital anomalies and detect the presence of female internal genitalia with inguinoscrotal area assessment for testes. Laparoscopy was done in children with undetectable testes on ultrasonography. Molecular genetic tests including NGS and WES were performed where feasible.

Rational management decisions were taken and recorded including hormonal treatment with intramuscular T injections before surgical correction, if required. Surgical management such as masculinizing genitoplasty, orchiopexy, or gonadectomy for risk of gonadoblastoma.

Statistical analysis: Descriptive statistics were performed using IBM SPSS software package version 20.0. **(**Armonk, NY: IBM Corp**)**. Quantitative data were presented as mean (SD) and median (minimum, maximum), while qualitative data were presented using number and percentages. $P < 0.05$ was considered to be statistically significant.

RESULTS

The study included 30 patients with syndromic 46, XY DSD. The mean (SD) age at the time of enrollment was 38.73 (32.7) months; age range 4 to 168 months; median age 27 months. Most of these patients were diagnosed at birth (86.7%); 28 were assigned as males at birth. Two infants were assigned as females at birth but later reassigned as males; the age at reassignment was neonatal period for one and 4 months for the other. All except one presented with genital ambiguity during early infancy; one presented with delayed puberty.

The clinical characteristics of the studied patients were diverse as shown in **Table I**. Six of them (20%) had poor Sertoli and Leydig cell function (gonadal dysgenesis). Twenty-one patients (70%) had normal Leydig cell function with normal T/DHT ratio and a high ratio in 3 patients (10%) was suggestive of 5 alpha-reductase deficiency. About two-thirds of the cases had average testicular size for age by inguinoscrotal ultrasonography. Seventeen children had cryptorchidism, either bilateral (n = 11) or unilateral (n = 6). Four patients underwent laparoscopy due to non-palpable testes, and were either found to have abdominal testes or atrophied testes. **Table II** shows the spectrum of associated extragenital manifestations. The most common associated malformation was skeletal anomalies (70%). Associated congenital heart disease (CHD) was detected in 7 boys (23.3%), with ventricular septal defect being the most common; other anomalies included atrial septal defect and pulmonary stenosis. Five children had intellectual disability and one child with hydrocephalus also had cognitive dysfunction.

Patau syndrome and chromosome 13q deletion were identified in two patients on karyotyping. Genetic mutations were detected in 5 out of 8 patients; 4 of them using targeted NGS, and one by WES (**Table III**). The other syndromes diagnosed based on clinical characteristics included Robinow (n = 3), Noonan (n = 3), and Silver-Russell syndromes (n = 3). Three children were diagnosed with Robinow syndrome; of these, one child had proximal hypospadias and micropenis, another had micropenis and bifid transposed scrotum and the third had micropenis, transposed scrotum and bilateral cryptorchidism. Three patients were diagnosed with Silver-Russell Syndrome (SRS) using the Netchine-Harbison Clinical Scoring System criteria [15]. One of them had bilateral cryptorchidism and a small penis, another had micropenis with bilateral cryptorchidism, and the third had proximal hypospadias with micropenis. Two of them had normal testicular function with normal T/DHT; one had high T/DHT ratio suggestive of 5 alpha-reductase deficiency. One patient presented with delayed puberty; examination revealed micropenis and small testes and based on his typical facies and short stature was diagnosed as Noonan syndrome. Another child had typical phenotype of Cornelia de Lange syndrome.

DISCUSSION

Genetic disorders are often associated with a spectrum of anomalies which are the result of defective gene leading to impaired embryogenesis. Consequently, syndromic DSD are often associated with several extragenital malformations which can give a clue to diagnosis [16]. Evaluation of child with DSD involves a multidisciplinary

approach including endocrinological, surgical and genetic testing to enable prompt sex assignment. This also further enables predicting the risk for future malignancy and fertility potential [17].

We evaluated the phenotypic variability in 30 patients with syndromic XY DSD. Of them, 86.7% were diagnosed at birth, similar to the finding by Amolo et al [18] wherein 95.7% of the 71 patients with DSD presented with ambiguous genitalia at birth. All except one presented with genital ambiguity during early infancy; one presented with delayed puberty and was diagnosed with Noonan syndrome. External genitalia presentations were variable including hypospadias (53.3%), micropenis (60%), or cryptorchidism (56.7%), bilateral or unilateral. Extragenital malformations were diverse including skeletal anomalies (limb and dental anomalies, short stature, and pectus excavatum), congenital heart disease, neurological, renal, ear, and eye malformations.

Hutson et al [16] suggested classifying XY DSD into hormonal and nonhormonal groups. In our patients, the hormonal group of 9 patients had gonadal dysgenesis (poor Sertoli and Leydig cell function) in 6, and normal Leydig cell function with high T/DHT ratio in 3.

Based on clinical characteristics three children were diagnosed with Robinow syndrome. Previously, Gerber et al have reported micropenis and cryptorchidism in association with Robinow syndrome [18]. Three of our patients were diagnosed with SRS; ambiguous genitalia have been reported in association with SRS previously [20, 21]. Like our study, Cornelia de Lange syndrome has been shown to be associated with micropenis and cryptorchidism [22,23].

Eight patients underwent molecular genetic testing. The first one had poor testicular function, steroid-resistant nephrotic syndrome, and *WT1* and *CBX2.2* gene mutations, confirming the diagnosis of Denys Drash syndrome. *CBX2.2* is critical for sex determination and differentiation; its variant mutation has been described in patients with complete gonadal dysgenesis [24]. Kohler et al [25] studied 210 XY DSD patients in a German DSD network and found that 7 out of 8 patients who had *WT1* mutation developed Wilms' tumor and/or nephropathy in childhood or adolescence. Another patient with genital ambiguity, poor Sertoli cell function, short stature, subclinical hypothyroidism, and unilateral renal aplasia, without features of Robinow syndrome, had *WWOX* and *ROR2* mutations. Another boy had genital ambiguity, learning disabilities, unilateral ear skin tags, and urodynamic dysfunction with mutations in both *NR5A1* and *FRAS1* genes suggestive of Fraser syndrome, a rare genetic condition characterized by genitourinary, and laryngeal malformations [26]. One of the patients had atypical genitalia and hypothyroidism and was diagnosed as having cytochrome P450 oxidoreductase gene mutation without adrenal insufficiency. Nuclear receptor subfamily 5, group A, member 1 (*NR5A1*) mutations are involved in the pathogenesis of DSD with varieties of phenotypic features of external genitalia, with or without adrenal insufficiency [27].

The limitations of our study included small sample size due to rarity of XY DSD. Genetic studies were not possible in all patients due to the cost constraints. We conclude that integration between clinical features, hormonal profile, and molecular genetics gives us a better understanding of syndromic DSD and may help in early detection based on clinical characteristics, and prompt management of anomalies.

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Table I: Demographic, Clinical, Laboratory Profile and Management of Study Participants

Demographic data	*n (%)*
Age at time of study (months)	
0 – 24	11 (36.7)
24 – 36	9 (30)
> 36	10 (33.3)
Age at diagnosis	
At birth	26 (86.7)
4 months	1 (3.3)
1 year	2 (6.7)
Delayed puberty	1 (3.3)
Clinical characteristics	*n* (%)
Scrotum	
Transposed scrotum	3 (10%)
Bifid scrotum	9 (30%)
Developed scrotum	20 (66.7%)
Underdeveloped	10 (33.3%)
Stretched penile length (SPL)	
Micropenis	18 (60%)
Small	9 (30%)
Average	3 (10%)
Penis	
Perineal hypospadias	2 (6.7%)
Scrotal hypospadias	4 (13.3%)
Penoscrotal hypospadias	7 (23.3%)
Proximal hypospadias	2 (6.7%)
Distal hypospadias	1 (3.3%)
No hypospadias	14 (46.7%)
Laboratory and Radiological Investigations	*n (%)*
Hypothalamic pituitary gonadal axis	
Normal for age	29 (96.7)
High FSH (Primary gonadal failure)	1 (3.3)
Sertoli cell function	
Normal	11 (36.7)
Low	6 (20)
Not done	13 (43.3)
HCG test	
Good response	21 (70)
Poor response	6 (20)
Mini-puberty (normal Testosterone)	3 (10)
T/DHT ratio	
High	3 (10)
Normal	21 (70)
Not assessed	6 (20)
Testicular size by ultrasonography	
Average	20 (66.7)
Unilateral atrophied	4 (13.3)
Bilateral atrophied	3 (10)
Bilateral small	3 (10)
Testicular site by ultrasonography	
Scrotal	13 (43.3)
Bilateral inguinal	8 (26.7)
Unilateral inguinal	2 (6.7)

Bilateral atrophied	3 (10)
Inguinal	2 (6.7)
Abdominal	1 (3.3)
Unilateral atrophied	4 (13.3)
Inguinal	1 (3.3)
Abdominal	3 (10)
Laparoscopy	
No	26 (86.7)
Unilateral abdominal testis	1 (3.3)
Unilateral atrophied testis	2 (6.7)
Bilateral atrophied testes	1 (3.3)

DHT Dihydrotestosterone, FSH Follicle-stimulating hormone, HCG Human chorionic gonadotropin, T Testosterone

Table II: Spectrum of extragenital manifestations in study participants (*n* = 30)

Extra-genital manifestations	*n (%)*
Renal anomalies	6 (20)
Steroid resistant nephrotic syndrome	1 (3.3)
Unilateral absent kidney	1 (3.3)
Bilateral nephropathy	1 (3.3)
Wilms tumor	1 (3.3)
Nephrocalcinosis	1 (3.3)
Urinary bladder dysfunction	1 (3.3)
Cardiac	
Congenital heart defects	7 (23.3)
Dysmorphic features	14 (46.7)
Skeletal anomalies	21 (70)
Overriding toes	1 (3.3)
Short limbs	2 (6.7)
Multiple	4 (13.3)
Short stature	6 (20)
Dental anomalies	2 (6.7)
Polydactyly in hands and feet	1 (33.3)
Pectus excavatum	1 (33.3)
Fingers anomalies, syndactyly	1 (33.3)
Cleft lip and palate	1 (33.3)
Talipes equinovarus	1 (33.3)
Cleft lip and palate- rocker bottom feet - finger anomalies	1 (33.3)
Hypothyroidism	3 (10)
Cerebral anomalies	9 (30)
Brain atrophy	3 (10)
Hydrocephalus	1 (3.3)
Eye anomalies	3 (10)
Squint	1 (3.3)
Myope	1 (3.3)
Microphthalmia - persistent pupillary membranes – bilateral large optic disc cup	1 (3.3)
Simian crease	3 (10)
Unilateral	1 (3.3)
Bilateral	2 (6.7)
Ear anomalies	2 (6.7)
Unilateral ear skin tag	1 (3.3)
Small abnormal ears	1 (3.3)

Table III: Integrated Clinical, Hormonal and Molecular Genetic Findings in Patients who Underwent Molecular Studies

Age (m) at diagnosis	Clinical characteristics	Hormonal profile	Mutation	Zygosity	Variant	cDNA	Position	Diagnosis	Outcome
At birth	Steroid-resistant nephrotic syndrome and genital ambiguity	• Poor Leydig and Sertoli cell function	*WT1* *CBX2.2*	Het Het	splice p.Ala101Thr	c.1432+1G>A c.301G>A	Chr11:32,413,517 Chr17:77,755,613	Gonadal dysgenesis Denys Drash syndrome	Masculinizing genitoplasty Screening for tumors
At birth	Genital ambiguity, bilateral simian creases, depressed nasal bridge, short stature, and unilateral renal aplasia	• Poor Sertoli cell function • Normal Leydig cell function • Subclinical hypothyroidism	*WWOX* *ROR2*	Het Het	p.Trp268Ter p.Ser762Leu	c.803_807delGGGCT c.2285C>T	Chr 16:79,245,892 Chr 9:94,486,491	Syndromic (hormonal DSD)	Masculinizing genitoplasty
At birth	Genital ambiguity, arrested hydrocephalus, learning disabilities, mental sub-normality, unilateral ear skin tag, urodynamic dysfunction	• Good testicular function	*FRAS1* *NR5A1*	Het Het	p.Lys1022Thr p.Pro131Leu	c.3065A>C c.392C>T	Chr 4:79,295,319 Chr 9:127,262,847	Fraser syndrome	Masculinizing genitoplasty
At birth	Genital ambiguity	• Good testicular function • Subclinical hypothyroidism	*POR*	Het	p.Gly151Ser	c.451G>A	Chr 7:75,614,265	Syndromic Hormonal DSD	Masculinizing genitoplasty

		• Normal adrenal function							
At birth	Microphthalmia, bilateral congenital persistent pupillary membrane, bilateral large optic disc cup, VSD, bilateral increased renal echogenicity, bilateral overriding toes, unilateral choanal atresia	• Good testicular function • Normal adrenal function	Not identified	-	-	-	-	Syndromic non-hormonal DSD	Died due to cardiac and renal anomalies
78	Genital ambiguity, mental subnormality	• Good Leydig cell function	*SRD5A2*	Hom	p.Gly195Ser	c.583G>A	2-31754489C-T	Syndromic hormonal DSD	Masculinizing genitoplasty
36	Thalassemia trait, VSD and ASD, short stature	• Good testicular function	Not identified	-	-	-	-	Syndromic non-hormonal DSD	Masculinizing genitoplasty
55	Tall stature, protruded tongue, dental anomalies malocclusion, speech delay	• Good testicular function	Not identified	-	-	-	-	Syndromic non-hormonal DSD	Masculinizing genitoplasty

VSD: ventricular septal defect; ASD: atrial septal defect; Het: Heterozygous; Hom: Homozygous; *WT1:* Wilms tumor 1*; CBX2.2:* chromobox homolog 2.2; *WWOX*: WW domain containing oxidoreductase; *ROR2:* receptor tyrosine kinase-like orphan receptor 2*; FRAS1:* Fraser extracellular matrix complex subunit 1; *NR5A1:* nuclear receptor subfamily 5, group A, member 1; *POR:* P450 (cytochrome) oxidoreductase; *SRD5A2:* steroid-5-alpha-reductase, alpha polypeptide 2