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Aetiological classification and clinical spectrum of Egyptian paediatric patients with disorders of sex development — single-centre experience

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Abstract

Introduction: The aim of the current work was to review the clinical profile, aetiological classification, as well as the management of Egyptian paediatric patients with disorders of sex development (DSD) presenting at a tertiary centre in Cairo.

Material and methods: The study was a cross-sectional observational study that included Egyptian patients who attended the Endocrinology clinic during a period of one year from January to December 2019. All patients with overt genital ambiguity aged from 0 to 18 years were recruited in the study. Diagnosis of DSD was based on clinical features and hormonal profile.

Results: Out of 100 patients, 71% had 46XY DSD, 24% had 46XX DSD, while sex chromosome DSD was identified in 5%. The median age of presentation was 12 months with 19% presented during infancy. The most common cause of 46XY DSD was due to either defect in androgen synthesis or action (40%) with the majority due to androgen insensitivity syndrome (28%). Most of the 46XX DSD (21/24) patients were diagnosed as classic congenital adrenal hyperplasia secondary to deficiency of 21 hydroxylase enzyme, with 90% being salt wasters.

Conclusion: Our series revealed that 46XY DSD was the most frequent DSD aetiological diagnosis, with androgen insensitivity syndrome representing the commonest cause. CAH with classic salt wasting type was the second most common disorder. Management of children with DSD is challenging especially with lack of adequate resources. The crucial issues that stand against proper diagnosis and management are late presentation combined with economic constrains, and social and cultural issues. **(Endokrynol Pol 2021; 72 (5): 558–565)**

Key words: *disorders of sex development; aetiology; clinical profile; paediatric; Egypt*

Introduction

Disorders of sex development (DSD) are rare congenital conditions that often create challenging circumstances for patients and their families in addition to health care providers [1].

The Lawson Wilkins Paediatric Endocrine Society (LWPES) and the European Society for Paediatric Endocrinology (ESPE) in 2006 categorized causes of DSD according to karyotype analysis into three diagnostic categories: sex chromosome DSD, 46XY DSD, and 46XX DSD [2]. There are scarce data on the incidence of DSD, with an estimated overall incidence of 1:4500 to 1:5000 newborn [3]. In Egypt, the incidence of DSD was previously estimated at 1:3000 livebirths [4].

Although DSD are chiefly genetic congenital disorders, they could present later on in life and not only at birth [5]. DSDs are not only organic disorders but also represent a social emergency due to the possibility of failure of immediate sex assignment of the newborn. For that reason, management of patients with DSD must be accomplished by a skilled multidisciplinary team at a specialized centre [2]. Diagnosis of patients with DSD requires substantial diagnostic procedures. The first-line tests for accurate aetiological diagnosis are the genomic technologies [6]. However, application of these technologies is faced with many obstacles including high costs, lack of insurance approval or national healthcare system coverage, and difficulties in the interpretation of the results; thus, diagnosis in limited resources countries depends mainly on hormonal tests and diagnostic imaging, which are less accurate [5].

There is a paucity of published data on this condition from Egypt. The aim of the current work is to review the clinical profile, aetiological classification, diagnosis, and management of Egyptian patients presenting with DSD at a tertiary centre in Cairo.

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Material and methods

This was a cross-sectional observational study including 100 Egyptian patients who attended the Paediatric Endocrinology Clinic at the Children's Hospital of Cairo University during a period of one year from January 2019 to December 2019. All patients with overt genital ambiguity and suspected to have DSD aged from 0 to 18 years were recruited in the study. DSD was suspected in case of phenotypic male genitalia with non-palpable gonads, micropenis (defined as stretched penile length less than 2.5 standard deviations below the mean for age [7]), isolated penoscrotal or perineal hypospadias, apparent female genitalia with clitoromegaly, posterior labial fusion, inguinal/labial mass, or genital/karyotype discrepancy. Informed consent was obtained from patient's guardians before inclusion in the study, and all of them agreed to participate. Thorough history was taken including the following: age at presentation, chief complaint, initial sex of rearing, family history of similar conditions, consanguinity, history of any medical problem, and history of any previous surgical intervention. Detailed clinical examination was done with rigorous genital examination including the size of phallus or clitoris, palpation of gonads, number and site of orifices, and labial/scrotal status, and then scoring them using the Prader Scale in virilized females [8] or the External Masculinization Score (EMS) in under-virilized males [9]. Additionally, assessment of any features of dysmorphism, or anomalies, and skin hyperpigmentation were recorded.

The results of karyotype analysis for all patients were recorded. In addition, the hormonal and biochemical profiles for patients were recorded including the following: 17- hydroxy progesterone (17-OHP), testosterone (T), androstenedione, dehydroepiandrosterone sulphate (DHEA-S), plasma renin activity, cortisol, and adrenocorticotrophic hormone (ACTH). In patients in whom assessment of functioning testicular tissue was required, short human chorionic gonadotropin (hCG) stimulation test and measurement of anti-Müllerian hormone levels (AMH) were performed. The test is done by administrating 1500 units of hCG intramuscularly for three consecutive days, then a blood sample is collected 24 hours after the last dose for measurement of stimulated testosterone (T) and dihydrotestosterone (DHT). The response was considered adequate if the stimulated testosterone level climbed above the maximum cut-off for the normal pre-pubertal range or a rise of more than double the pre-stimulatory value [10, 11]. Ratios of stimulated androgen values were used to presumably diagnose androgen biosynthetic defects. 5-alpha reductase deficiency was the supposed diagnosis if the ratio between stimulated testosterone/ DHT was greater than 30 [12]. However, a ratio between testosterone and androstenedione smaller than 0.8 was suggestive of 17 -hydroxysteroid dehydrogenase (17 -HSD) deficiency [13]. Androgen insensitivity syndrome was diagnosed in any patient with 46XY karyotype with normal stimulated testosterone and DHT response with absent Müllerian remnants. It is divided into two types: partial or complete. Complete androgen insensitivity disorder was considered in patients who had completely normal female phenotype associated with the previously mentioned hormonal profile.

In patients who had 46XX DSD, congenital adrenal hyperplasia was the first suspected diagnosis. Evaluation of the serum levels of 17(OH) progesterone, testosterone (T), androstenedione, dehydroepiandrosterone sulphate (DHEAS), 11 deoxycortisol, plasma renin activity, cortisol, and ACTH was done. Accordingly, the diagnosis of CAH with 21 hydroxylase deficiency was confirmed if 17-OHP levels > 100 ng/mL (300 nmol/L). Genetic analysis to confirm the diagnosis is not available at our centre.

The results of radiological investigations (ultrasound or MRI) were retrieved from the patient's records. Surgical history including procedures and histological examination was reported. The aetiological classification of our cohort was based upon the suggested classification by the Lawson Wilkins Paediatric Endocrine Society (LWPES) and the European Society for Paediatric Endocrinology (ESPE) of 2006 [2]. The study protocol was approved by the Research Ethics Committee of the Faculty of Medicine, Cairo University.

Statistical analysis

SPSS (Statistical Package for the Social Sciences, version 16; SPSS) software was used for data analysis. Descriptive analyses for numerical values were presented as mean ± standard deviation (SD) for parametric variables, and median and interquartile range (IQR) for non-parametric variables. Numbers and percentages were used for categorical variables.

Results

The studied cohort comprised 100 patients who presented with any degree of genital ambiguity. Those patients represented 2% from a total number of 4870 patients who were attending the paediatric endocrinology clinic during the same year. The age of presentation ranged widely from 0.25 months to 204 months, with median age at presentation of 12 months. Nineteen (19%) patients presented during infancy and 60% of patients presented at age ≥ 12 months. Consanguinity was reported in nine (9%) patients. Five (5%) patients were found to have positive family history of affected siblings with similar condition.

Karyotyping data was available for all recruited patients; accordingly, they were classified into 71 (71%) patients with 46XY DSD, 24 (24%) with 46XX DSD, and sex chromosome DSD in 5 (5%) patients. The aetiological classification of our patients is shown in Table 1. The most frequent aetiological diagnosis reported among the whole cohort was androgen insensitivity syndrome. However, congenital adrenal hyperplasia was the second most common aetiology.

The DSD team consisted of a paediatric endocrinologist, a paediatric surgeon, a psychiatrist, and a geneticist. The team is responsible for clinical evaluation of the patients and setting up the management plan, which is shared with the parents. Concerning sex assignment, all patients were already assigned at the time of presentation to our centre. They were reared as 67 (67%) males and 33 (33%) females. However, after psychiatric evaluation and clinical diagnosis, 10 patients were reassigned. Seven patients among 46 of the XYDSD group and one patient among the sex chromosomal DSD group were finally reassigned as males. Two patients from the 46XX group were reassigned as females. Finally, we had 73 males and 27 females.

46XY DSD

46XY DSD was the most frequently reported aetiology in our series, constituting 71% of the reported cohort. The most common cause of 46XY DSD was either a defect in androgen synthesis or action (40%) with the majority due to androgen insensitivity syndrome (28%). The chief complaint at presentation among the

Table 1. *Overview of aetiological classification and diagnosis of our cohort (n = 100)*

Aetiological classification	Aetiological diagnosis	N (%)
46XY DSD (n= 71)	**Disorder of androgen synthesis or action**	
	Androgen insensitivity syndromes	28 (28%)
	5 alpha reductase deficiency	10 (10%)
	20,22 desmolase deficiency	1 (1%)
	Smith-Lemli-Opitz syndrome	1 (1%)
	Disorder of testicular development	
	Ovotesticular DSD	4 (4%)
	Partial gonadal dysgenesis	4 (4%)
	Vanishing testis syndrome	2 (2%)
	Persistent Müllerian duct syndrome	4 (4%)
	Others	
	Isolated hypospadias	7 (7%)
	Bilateral cryptorchidism	7 (7%)
	Pan hypopituitarism	1 (1%)
	Syndromic	2 (2%)
46XX DSD (n = 24)	Congenital adrenal hyperplasia	20 (20%)
	46XX testicular DSD (male sex reversal)	2 (2%)
	Others	
	Vaginal atresia	2 (2%)
Sex chromosome DSD (n = 5)	Mixed gonadal dysgenesis (45XO/46XY DSD)	4 (4%)
	Klinefelter syndrome (47XXY)	1 (1%)

46XY DSD group was genital ambiguity of variable degrees. This included: micropenis (45.1%), hypospadias (57.7%), underdeveloped bifid scrotum (35.2%), and impalpable gonads, whether unilateral (22.5%) or bilateral (36.6%).

Three patients were diagnosed with complete androgen insensitivity (CAIS). Those patients presented in different age groups (6, 36, and 44 months) with completely normal female external genitalia and palpable swellings in the labial folds. They were reared as females.

Partial androgen insensitivity (PAIS) was the presumed diagnosis in 25 patients. The age of presentation ranged from 1 month to 60 months, with a median age of 12 months. They presented with variable forms of undervirilization, mostly with penoscrotal hypospadias and bifid scrotum. The median EMS was 6 (range: 1 to 11). Four patients were reassigned as males after diagnosis; however, the rest of this group were reared as males since birth.

Ten (10%) patients were diagnosed to have 5-alpha reductase deficiency. All of them were reared and continued as males.

Disorder of testicular development was found in 10 (10%) patients. Vanishing testis syndrome was the diagnosis in two patients, partial gonadal dysgenesis in four patients, and four patients were diagnosed as ovotesticular DSD.

The diagnosis of patients with ovotesticular DSD was based upon the results of laparoscopy and histopathologic examination of the gonadal biopsy. All of them had 46XY karyotype. The detailed clinical profile is shown in Table 2.

The two patients with vanishing testis syndrome were reared as males and presented with bilateral cryptorchidism, normal penile length, and normal urethral opening. The hormonal profile showed flat testosterone response after hCG stimulation, and low level of anti-Müllerian hormone (AMH). Diagnostic laparoscopy revealed non-visualization of any gonad or any Müllerian structures. Both patients had other associated anomalies, with one of them having both cleft lip and palate and the other one having a congenital cataract.

Persistent Müllerian duct syndrome was diagnosed in four (4%) patients. All of them had 46XY karyotype and were reared as males (Tab. 3). Ultrasound failed to visualize the Müllerian duct remnants (MDR) in three patients, but laparoscopy was the standard for diagnosis in all patients. Testosterone response was normal after

Table 2. *Clinical profile of patients with ovotesticular DSD (n = 4)*

Age [months]	Genital examination	Initial sex	Gender reassignment	Gonads	
				Right	Left
12	Bilateral impalpable gonads, underdeveloped scrotum, penoscrotal hypospadias, normal penile length.	Female	Male	Ovary	Testis
7	Left impalpable gonad, asymmetrical labioscrotal folds, penoscrotal hypospadias, microphallus (1.5 cm).	Female		Testis	Ovary
19	Left impalpable gonad, asymmetrical labioscrotal folds, penoscrotal hypospadias, microphallus (1 cm).	Female		Testis	Ovary
16	Left impalpable gonad, underdeveloped scrotum, scrotal hypospadias, microphallus (1 cm)	Male		Testis	Ovary

Table 3. *Clinical characteristics of patients with persistent Müllerian duct syndrome (n = 4)*

Age [months]	Genital examination	Ultrasound findings	Intervention
10	Normal penile length with normal urethral opening Bilateral non palpable gonads with underdeveloped scrotum	Visualized one testis, but the other non-visualized Non visualized Müllerian remnants.	**Laparoscopy:** Visualization of the gonads with biopsy proved testicular tissue Visualization of MDR Division of MDRS and staged orchidopexy
108	Normal penile length with normal urethral opening, Bilateral non palpable gonads with underdeveloped scrotum	Bilateral small sized testis. Non-visualized Müllerian remnants.	
16	Micropenis with normal urethral opening Bilateral non palpable gonads with underdeveloped scrotum	Visualized one testis, the other one non-visualized Non visualized Müllerian structures	
12	Micropenis with mid-shaft hypospadias Unilateral non-palpable gonad with well-developed scrotum	Visualized one testis Uterine shadow	**Laparoscopy:** Visualized gonad with biopsy proven testicular tissue Excision of MDRS and orchidopexy

MDR — Müllerian duct remnants

hCG stimulation in all patients. The AMH level was normal in two patients but was not performed for the other two patients. Genetic testing for confirmation of the diagnosis is not available at our centre. Division of MDR was done in three patients because excision was not technically feasible and carries the risk of gonadal injury. Those patients were scheduled for regular follow up every six months to exclude any malignant transformation from the existing parts of Müllerian remnants. Excision of MDR was done in one patient.

Isolated bilateral cryptorchidism was the presentation in 12 (12%) patients. Isolated anatomical defect was the diagnosis in seven patients after assessment of the hormonal profile (good hCG stimulated response and normal AMH). However, the other five patients had different diagnoses. One patient was diagnosed as pan hypopituitarism and presented at the age of three months with hypoglycaemic convulsions. The other patients were diagnosed as the following: Klinefelter syndrome, Robinow syndrome, Smith-Lemli-Opitz syndrome, and Kallmann syndrome.

46XX DSD

The majority of patients in the 46XX DSD (21/24) group were diagnosed as classic congenital adrenal hyperplasia (Tab. 1). Deficiency of 21 hydroxylase enzyme was the reported enzymatic defect in all patients based upon the biochemical analysis. Nineteen patients had salt wasting type, and only two patients were simple virilizing. The median age at diagnosis of salt wasters was 0.25 months. All of them presented with salt losing crisis (severe dehydration, electrolyte disturbance, occasional hypoglycaemia). Five patients were found to have history of affected siblings with the same condition. One of the patients had a history of unexplained male sibling death at the age of seven months. The degree of external genital virilisation according to Prader score was diverse: three patients

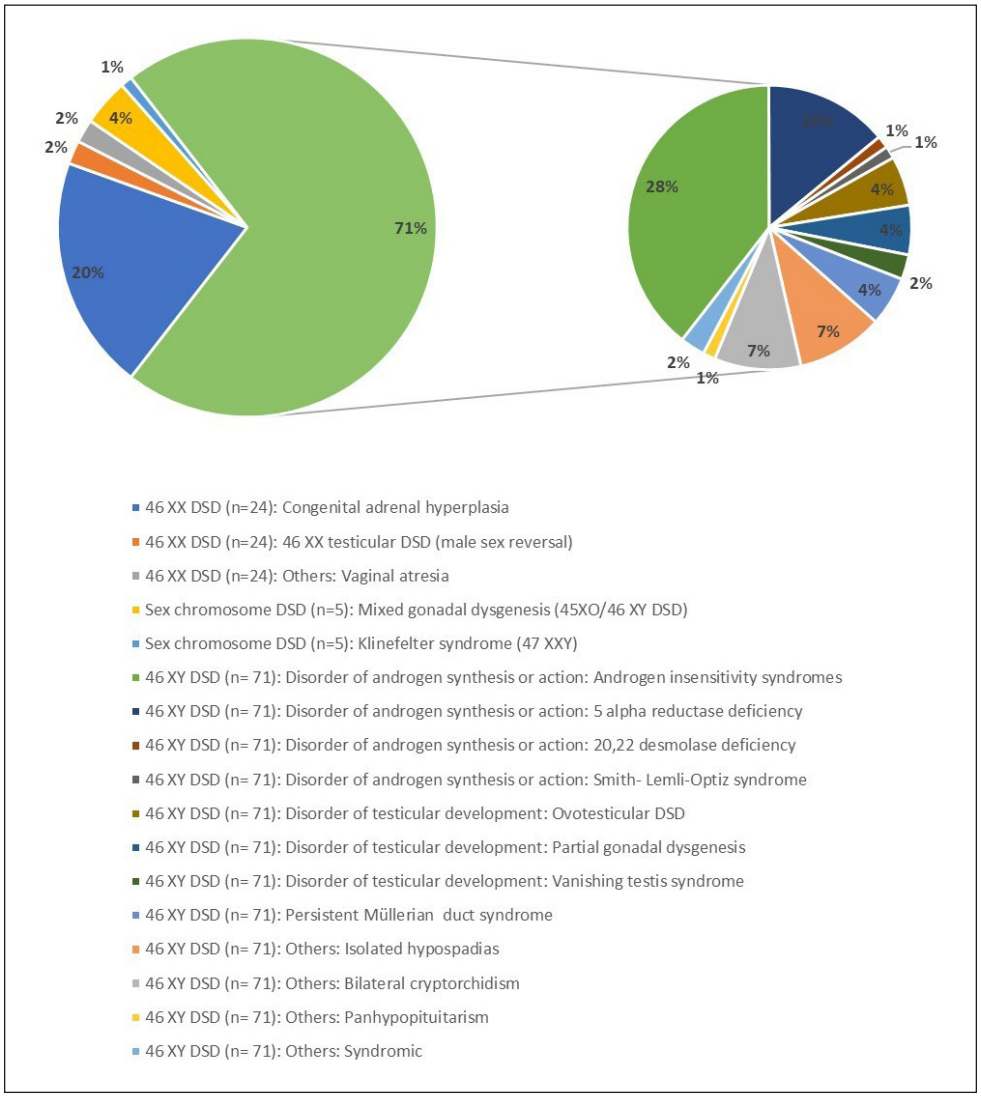

Figure 1. *Aetiological classification of disorders of sex development (DSD)*

had stage 2, 12 patients had stage 3, and the remaining six patients had stage 4. All patients were reared as females except two patients who were reassigned as females after diagnosis. All patients underwent feminizing genitoplasty.

Regarding patients with simple virilizing type, one of them presented at the age of 42 months with clitoromegaly and hyperpigmentation. The other one presented at the age of 60 months with heterosexual pseudo precocious puberty.

Two (2%) male patients presented with genital ambiguity in the form of unilateral undescended testis and proximal penile hypospadias. Their karyotyping was 46XX with negative SRY gene. Laparoscopic exploration and biopsy taken from the intra-abdominal gonad showed testicular tissue, and laparoscopic orchidopexy was performed with subsequent diagnosis as testicular DSD (XX Sex reversal).

Chromosomal DSD

Sex chromosomal DSD was the aetiological diagnosis in five patients. Mixed gonadal dysgenesis was found in four patients with 45XO/46XY karyotype. The most common presentations of patients with mixed gonadal dysgenesis were unilateral or bilateral impalpable gonads with underdeveloped scrotal sac. The ages of presentation of patients who were reared as males were 6, 11, and 12 months. However, there was one patient who presented at the age of 54 months with complete normal female phenotype with two palpable inguinal swellings, and was reared as female.

Discussion

Giving birth to a newborn with abnormal genital development with unidentified sex is considered a social problem, and in some situations a medical emergency.

In Egypt, the prevalence of DSD is unidentified, due to the absence of a nationwide registry. However, it was reported by Mazen et al. in 2010 **[14]** that the incidence of DSD is 1 per 5000 after screening 20,000 newborns and infants in two large governorates.

In the current series we included 100 patients who fulfilled the criteria of DSD. Those patients represented 2% from the total number of patients who were attending the endocrine clinic during the same period. The frequency of patients presenting with DSD in our cohort confirmed what was previously reported, i.e. that DSD is not an uncommon disorder among Egyptian children [14]. This large number of patients in a relatively short period (1 year) when compared to lower numbers in other previously published reports from other countries [15–17] highlights the extent of the problem of genital ambiguity in our community. This necessitates the establishment of a nationwide registry or larger multicentre studies to evaluate the actual prevalence and incidence of this problem. The prevalence of DSD among other African countries is not reported. However, a single-centre study in South Africa including 416 patients reported that the prevalence of DSD was 15.1% [18].

According to the new classification of DSD by the Lawson Wilkins Paediatric Endocrine Society (LWPES) and the European Society for Paediatric Endocrinology (ESPE) [2], [19], our data revealed that the most common cause of DSD was 46XY DSD (71%), with 46XX DSD in second place (24%), and lastly chromosomal DSD (5%). According to previously published data from Egypt, 46XY DSD was also the most prevalent cause of DSD, representing 65.9% of all cases. It was concordant with results from other African countries; Ganie et al. in 2016 retrospectively reviewed 416 children from South Africa presented with ambiguous genitalia with 57.5% of patients with 46 XY DSD [20]. Our finding is in contrast to other series of patients with DSD from Sudan, where 46XX DSD was the most common cause (57%) [21].

In the 46XY DSD group, the most common cause was androgen insensitivity syndrome (28%). Out of them, 25 patients had partial androgen insensitivity syndrome, and three patients had complete androgen insensitivity syndrome. Furthermore, 10 patients (10%) were diagnosed as 5α reductase deficient. The proportion of patients with PAIS among our cohort is relatively high compared to what was reported by Mazen et al. in 2008, who found that 5α reductase deficiency is the most prevalent cause of defects of androgen synthesis and action [22]. We assume that this difference is caused by the diagnostic method used to differentiate between PAIS and 5α reductase deficiency among our cohort, which was based on hormonal assay (ratio between T/DHT > 30). We emphasize that one of the major limitations in reaching a definitive diagnosis among patients with 46XY DSD in our series is the unavailability of molecular genetic analysis at our centre.

It is well known worldwide that CAH is the most commonly reported cause of DSD [23]. In our series, CAH was the second most common cause of DSD (21%) among the whole group but the most prevalent aetiological diagnosis among the 46XX DSD group (90.5%). The classic form of CAH due to 21 hydroxylase deficiency was the only presenting form, with most patients being salt wasters (19/21). Most of those (15/19) patients were diagnosed during infancy. We suppose that the earlier age of diagnosis among this group, in spite of a lack of neonatal screening for CAH in Egypt, is due to the salt wasting manifestations associated with abnormal genitalia, which raise clinical suspicion, leading to earlier referral.

Sex chromosomal DSD was found to be the least frequent aetiological diagnosis among our cohort. Mixed gonadal dysgenesis with karyotype 45X, 46XY was the commonest cause in this category.

Establishment of early diagnosis of DSD is crucial in sex assignment and decision-making regarding the management plan. It is preferably accomplished immediately after delivery. Unfortunately, this was not the scenario in our series. The median age at presentation was 12 months, ranging from 0.25 months to 204 months. Only 19 patients (19%) presented during infancy, most of them (15%) being 46XX DSD. However, 60% of our patients presented at age ≥ 12 months. We assume that this late age of presentation was due to an improper genital examination by the general health professional attending the delivery. Additionally, the basic cytogenetic analysis and the hormonal profile, which are mandatory for the initial classification and diagnosis for patients with genital ambiguity, are not available except in a few tertiary hospitals in Egypt. Moreover, the early diagnosis is hindered not only by the lack of laboratory facility availability but also by the high expenses of those assays, which are not affordable to most patients. In addition to what was previously mentioned, the taboo associated with that condition in our society leads to a delay in seeking medical advice. Our reported age at presentation is relatively young compared to other reports from developing countries like India (87 months) [24] and Nigeria (20 months) [25]. However, other series from developed countries like Australia report earlier age of presentation, mostly during the neonatal period [26].

As regards sex of rearing, all patients with 46XX DSD were assigned as females from the start except for two patients who were reassigned after diagnosis. However, the sex of assignment among the 46XY

DSD group is much more complicated. The preference of male sex assignment among our cohort was obvious even if the degree of undervirlization and the whole profile wwas not in favour of that. This is attributed to the strong impact of sociocultural beliefs among Egyptian society concerning marriage and future fertility, which could be prohibited by female sex. Long-term follow-up studies regarding the quality of life and fertility of such patients in our community are highly recommended, which could have an impact on clinical practice in the future.

Interestingly, parental consanguinity was reported in only nine patients (9%). This is much less than was reported previously regarding the consanguinity rate among Egyptian children with DSD (62.8%) [22]. Also, this is less than the general consanguinity rate among Egyptian families, which ranged from 13.2% to 43.6% according to the region [27]. We assume that the different rate of consanguinity may be attributed to population selection bias reflecting the regional differences.

Limitations

The cross-sectional descriptive nature of this study conducted at a single centre during a short period (one year) are the main limitations. Additionally, the lack of molecular genetic analysis limited the decision regarding final diagnosis in many patients, especially those with 46XY DSD. The availability of the molecular analysis may change the aetiological classification of our cohort. Larger multicentre coordinated studies with long-term follow-up are needed to establish the actual prevalence and outcome of children with DSD in our society.

Conclusions

Our series revealed that 46XY DSD was the most frequent aetiological diagnosis, with androgen insensitivity syndrome representing the commonest presumed cause. CAH with classic salt wasting type was the second most common disorder, which highlights the importance of establishing its routine screening in the Egyptian neonatal screening program. Management of children with DSD is a real challenge, especially with the lack of adequate resources. The crucial issues that stand against proper diagnosis and management are late presentation combined with economic constrains, and social and cultural issues. Finally, improvement of health care services provided for children with DSD necessitates a proper, continuous training program provided to paediatricians, and improving public health awareness regarding this problem, which facilitate early management and prevention of future critical crisis.

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Authorship contribution

R.A.S. shared in the study design, data collection and sorting for statistical analysis, drafting of the article, and final revision for publication. S.A. shared in data collection, data entry, data analysis, and interpretation. N.A. shared in the study design, critical revision of the article, and interpretation of data, statistical analysis, drafting and writing the manuscript, and final revision of the version to be published.

Ethical approval

The study was approved by the Local Research Ethics Committee of the Paediatric department, Cairo University and was conducted in accordance with the Helsinki Declaration.

Conflict of interest

The authors declare absence of conflict of interest and that they had complete access to data and information relevant to the study.
Authors declare the integrity of the work.

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