Cytogenetic Analysis and Clinical Findings in Patients with Disorders of Sex Development

*Asaduzzaman,[1] Khandkar T,[2] Islam SS,[3] Habib S[4]

Abstract

Disorder of sex development (DSD) is not so uncommon in Bangladesh. Frequency, types, clinical presentation and associated karyotypes in patients with sex differentiation errors is mostly unknown in our country. Genetic methods for the diagnosis of DSDs still include determination of the karyotype. It is impossible to manage a case without knowing the exact karyotype. This cross sectional study was conducted at the department of Pathology, Bangabandhu Sheikh Mujib Medical University (BSMMU) from January 2015 to December 2016 to determine the frequency, types, clinical presentation and associated karyotypes of disorders of sex development. A total of 93 cases of disorders of sex development were included in this study. All the cases attended the genetics laboratory, Department of Pathology, BSMMU. Suspected cases of DSD patients of any age group were included in the study and detailed clinical information were obtained. All suspected cases with clinical features, hormonal abnormality or radiological abnormality of disorders of sex development were confirmed by karyotyping analysis by using standard cytogenetic techniques. The commonest age of presentation was in age group between 11 to 20 years. History of parental consanguinity or endogamy was found in 31.18% patients. All the cases were classified according to Chicago nomenclature. Sex chromosome DSD (Turner syndrome and Klinefelter syndrome) was the commonest (69.89%), followed by 46,XY DSD (20.43%) and 46,XX DSD (9.68%). In the 55 studied cases with Turner syndrome phenotype, 39 patients (41.93%) had 45,X and 12 patients (12.90%) had mosaic [45,X/46,XX; 45,X/46,X,i(Xq); 45,X /46,XX /46, X,i(Xq) and 45,X/47,XXX] and 4 patients (4.30%) had long arm isochromosome of X chromosome [46,Xi(Xq)]. In the 8 studied cases with Klinefelter syndrome phenotype, 7 (87.5%) had 47,XXY, and 1 (12.5%) case was mosaic (46XY/47XXY). In our study, out of 93 patients 20.43% had 46, XY karyotype and 9.68% had 46,XX karyotype. In Turner syndrome most common presentation was primary amenorrhoea followed by short stature. In cases of Klinefelter syndrome, common clinical presentations were small atrophic testes, infertility and gynaecomastia. Most common presentations of 46,XY DSD case were primary amenorrhoea, ambigious genitalia and delayed/ absent secondary sex characters. Most of the 46,XX DSD presented with ambigious genitalia, clitoromegaly and with hyperpigmentation of genitalia. This study showed that diagnosis and management of DSD in Bangladesh is possible in many cases despite the limitations of delayed presentation, incomplete investigations and unavailability of gene sequencing and molecular study. This study will guide the future planning and management of the patients with disorder of sex development.

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1. **Dr. Asaduzzaman, Lecturer, Department of Pathology, Sheikh SayeraKhatun Medical College, Gopalganj. dr.asad37@gmail.com*
2. *Dr. Tahmina Khandkar, Resident, Department of Paediatric Nephrology, Bangabandhu Sheikh Mujib Medical University, Dhaka.*
3. *SM Shahedul Islam, Scientific Officer, Department of Pathology, Bangabandhu Sheikh Mujib Medical University, Dhaka.*
4. *Dr. Saequa Habib, Associate Professor, Department of Pathology, Bangabandhu Sheikh Mujib Medical University, Dhaka.*

**For correspondence*

Introduction

Phenotypic sex results from the differentiation of internal ducts and external genitalia under the influence of sex-determining genes and hormones.[1-2] In one of every 4500 births, the genital appearance is abnormal and it is not always possible to decide the sex of the infant at first glance. The European Society for Paediatric Endocrinology and the Lawson Wilkins Pediatric Endocrine Society jointly organized a meeting of endocrinologists, surgeons, geneticists, psychologists, and patient advocacy group members, all representing a world community involved with the management of intersex disorders. A consensus document was subsequently published[3] and it has become known as the Chicago Consensus by virtue of its generation in the 'windy city'. There are numerous modes of classification to bewilder the reader with exhaustive lists of all the possible causes of DSD. Instead of using the confusing and/or controversial terms such as "intersex," "hermaphroditism" and "sex reversal", the Chicago consensus statement recommended a new taxonomy based on the umbrella term, "DSD".[4] The term disorders of sex development (DSD) embraces all the medical conditions characterized by an atypical chromosomal, gonadal, or phenotypical sex.[4]

The diagnostic terms that came out of the 2006 Chicago consensus meeting were designed to eliminate the more confusing and stigmatizing elements of the previous classification lexicon. They were confusing because a number of different terms and definitions could be used to describe a particular diagnosis. The terms such as 'pseudo-hermaphrodite' and 'intersex' were considered pejorative. The new classification system has made a significant improvement, in that it creates structure and definitions that are suitable for universal use, and also eliminates odious terminology.

Frequency of different types of DSD is mostly unknown in Bangladesh and many other countries of the world. Only limited data is available regarding these disorders. In our country DSD diagnosis is based on hormonal evaluation, imaging studies and most importantly, cytogenetic analysis which is done at cellular level. Cytogenetic analysis is a reliable procedure, can be done from peripheral blood and relatively inexpensive. It is done only in few centers in Dhaka.

Methods

This cross sectional study was conducted at the department of Pathology, Bangabandhu Sheikh Mujib Medical University (BSMMU) from January 2015 to December 2016. A total of 93 cases of disorders of sex development were included in this study. Most of the patients were included from outpatient department of Paediatrics, BSMMU and Department of Endocrinology and metabolic disorder, Dhaka Shishu (Children) Hospital. Other cases were included from various outpatient departments of BSMMU. All the cases attended the genetics laboratory, Department of Pathology, BSMMU.

Suspected cases of DSD patients based on clinical, biochemical and imaging studies of any age group were included in the study. Patient with autosomal disorder, severe psychiatric comorbidity and mental disabilities and patients not willing to take part in this study were excluded from the study.

A detailed history was taken including presence of similar conditions in the family. A thorough clinical examination was done including body hair distribution (hirsutism) and external genitalia examination with giving importance on body stature, genital ambiguity, apparent female genitalia with clitoromegaly, posterior labial fusion or

inguinal/labial mass, and apparent male genitalia with non-palpable testis, micropenis, isolated perineal hypospadias or mild hypospadias with undescended testes. In ambiguous genitalia cases virilization was assessed by Prader score. Assessment of primary and secondary sex characteristics (pubic hair and breasts in females and testis, penis and pubic hair in males) were done according to Tanner sexual maturity ratings. Abdomino-pelvic ultrasound was done to evaluate ambiguous genitalia, anomalies of the pelvic organs and to see internal genital organ.

All suspected cases with clinical features, hormonal abnormality or radiological abnormality of disorders of sex development were confirmed by chromosomal analysis. Standard cytogenetic technique was used. With all aseptic precaution 2 – 3 ml of venous blood was taken in a heparinized syringe for cytogenetic analysis. After completion of all procedures two slides were made for each case. Each of the slides was scanned under low magnification (10X) first to locate good quality spread. Then in oil immersion (100 X) 15-20 well spread metaphase were counted and analyzed for aneuploidy and other structural abnormalities.

Classification of cases according to Chicago nomenclature

DSD cases were categorized on the basis of karyotype, hormonal level and results of imaging studies and sub classified according to Chicago nomenclature (Table I).

Table I: DSD Classification according to Chicago consensus nomenclature[3]

Sex Chromosome DSD	46,XY DSD	46,XX DSD
45,X (Turner syndrome and variants)	Disorders of gonadal (testicular) development: (a) complete gonadal dysgenesis (Swyer syndrome); (b) partial gonadal dysgenesis; (c) gonadal regression; and (d) ovotesticular DSD	Disorders of gonadal (ovarian) development: (a) ovotesticular DSD; (b) testicular DSD (eg, SRY^{+}, duplicate SOX9); and (c) gonadal dysgenesis
47,XXY (Klinefelter syndrome and variants)	Disorders in androgen synthesis or action: (a) androgen biosynthesis defect (eg, 17-hydroxysteroid dehydrogenase deficiency, 5αRD2 deficiency, StAR mutations); (b) defect in androgen action (eg, CAIS, PAIS); (c) luteinizing hormone receptor defects (eg, Leydig cell hypoplasia, aplasia); and (d) disorders of anti-Müllerian hormone and anti-Müllerian hormone receptor (persistent Müllerian duct syndrome)	Androgen excess: (a) fetal (eg, 21-hydroxylase deficiency, 11-hydroxylase deficiency); (b) fetoplacental (aromatase deficiency, POR [P450 oxidoreductase]); and (c) maternal (luteoma, exogenous, etc)
45,X/46,XY (MGD, ovotesticular DSD)		Other (eg, cloacalexstrophy, vaginal atresia, MURCS [Müllerian, renal, cervicothoracic somite abnormalities], other syndromes)
46,XX/46,XY (chimeric, ovotesticular DSD)		

Statistical analysis and result

Statistical analyses have been carried out by using the Microsoft office 2013 packages software. The mean values were calculated for continuous variables. The quantitative observations were indicated by frequencies and percentages.

Ethical implication

Every ethical issue was discussed with the patients regarding the study and informed written consent was obtained. The research protocol was approved by the Institutional review board (I.R.B.) of BSMMU, Dhaka.

Results

A total of 160 suspected DSD cases were evaluated clinically and according to their hormonal and imaging status. Out of these 93 cases were cytogenetically and clinically proved as DSD. Remaining cases were diagnosed as normal or other disorders and excluded from the study.

Age of the patient at diagnosis

The commonest age of presentation was in between 11 to 20 years. Majority of DSD patients (60.22%) present at this age group. Only 20.43 % patients presented below 10 years. Above 20 years this rate was 18.28%. In this study no case of 46,XX DSD was presented after 20 years of age (Figure 1).

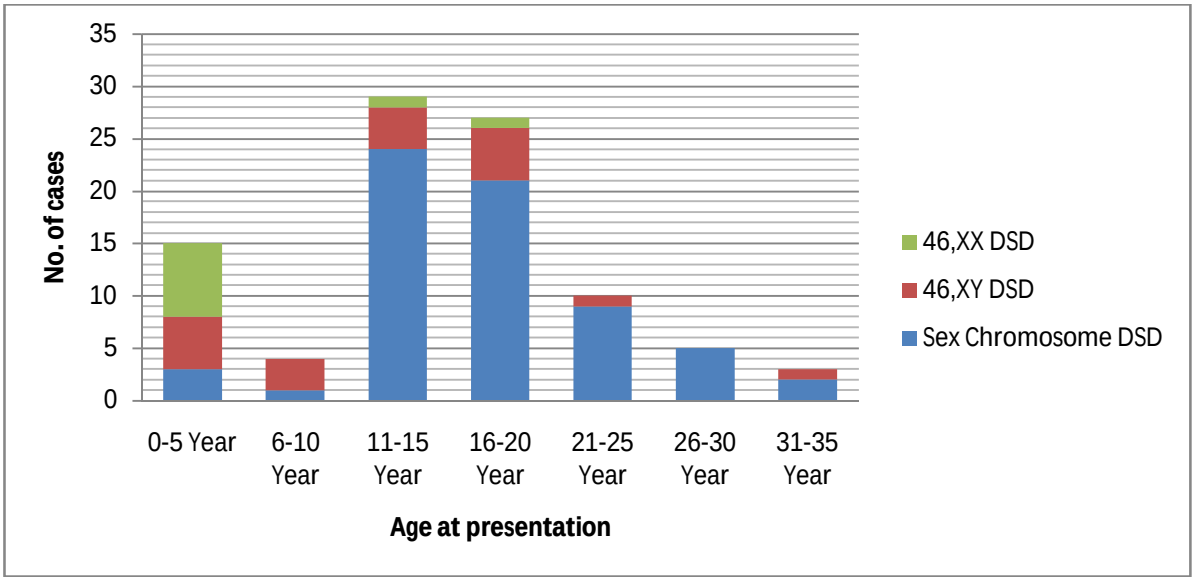

Figure 1**.** Age distribution of 93 DSD cases

Epidemiological Profile

Most of the DSD patients (82.80%) were found to be raised as female in this study. Among these 19.35% patients who raised as female proved to be male according to karyotyping. History of parental consanguinity or endogamy was seen in 31.18% patients. Small number of cases had family history of such disorders (5.38%).

Categorization of DSD cases according to Chicago nomenclature

Disorders of sex chromosomes (Turner syndrome and Klinefelter syndrome) were the commonest (69.89%), followed by 46,XY DSD (20.43%) and 46,XX DSD (9.68%). In many cases exact sub-classification was not

possible as gene analysis was not included in this study. Classic Turner syndrome (41.93%) (Figure 2) and mosaic Turner syndrome (17.20%) (Figure 2) were subdivided according to cytogenetic analysis pattern. Klinefelter syndrome (7.53%) and mosaic Klinefelter syndrome (1.08%) were also classified accordingly. 46,XY DSD cases were found to be 20.43% and 46, XX DSD cases were 9.68%. Sub-classification and exact frequency found in this study are shown in Table II.

Table II**:** Frequency & types of disorders of sex development (DSDs)

Type of Disorder	No.	%
Sex chromosome DSD	65	69.89
Turner syndrome and variants		
Classic Turner syndrome	39	41.93
Mosaic Turner syndrome	16	17.20
Klinefelter syndrome		
Classic Klinefelter syndrome	7	7.53
Mosaic Klinfelter syndrome	1	1.08
Mixed (Gonadal dysgenesis/ Chimeric)	2	2.15
46, XY DSD	19	20.43
Androgen insensitivity syndrome	5	5.38
Defect in androgen synthesis/ action	4	4.30
Gonadal dysgenesis	5	5.38
Persistent mullerian duct syndrome	1	1.08
Others	4	4.30
46,XX DSD	9	9.68
Congenital adrenal hyperplasia	2	2.15
Others	7	7.52
Total	93	100

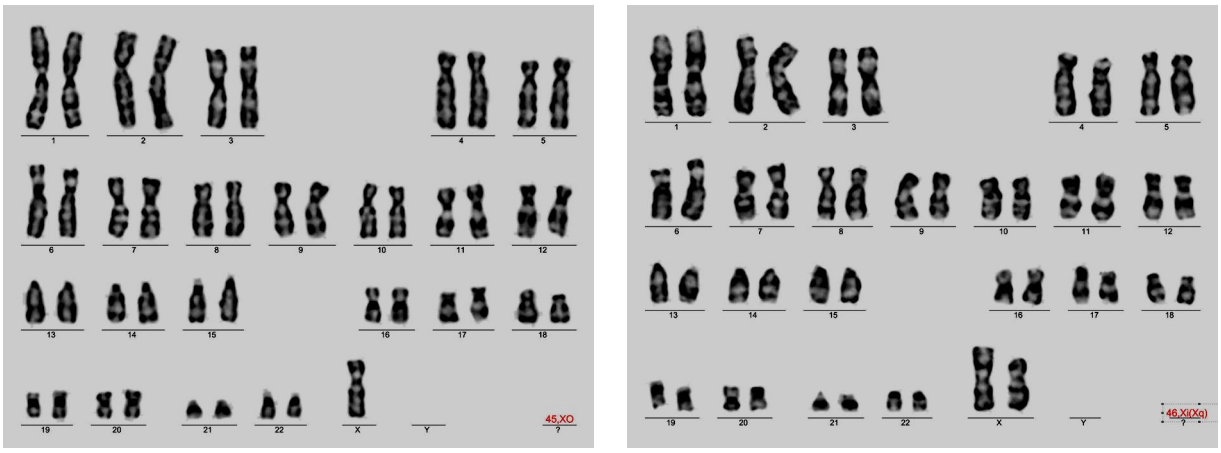

Figure 2. Karyotypes of Sex Chromosome DSD; 45, X classic Turner Syndrome (Case no. 58) and 45,X/46,Xi(Xq) mosaic Turner syndrome (Case no. 7).

Chromosomal variations defined among the most common DSD

In the 55 studied cases with Turner syndrome phenotype, 39 (41.93%) patients had 45,X and 12 (12.90%) patients had mosaic [45,X/46,XX; 45,X/46,X,i(Xq); 45,X /46,XX /46, X,i(Xq) and 45,X/47,XXX] and 4 (4.30%) patients had long arm isochromosome of X chromosome [46,Xi(Xq)]. In the 8 studied cases with Klinefelter syndrome phenotype, 7 (87.5%) had 47,XXY (Figure 3) and one case (12.5%) was mosaic (46XY/47XXY). Among the rest, 19 (20.43%) had 46,XY DSD and 9(9.68%) had 46,XX DSD (Table II, Figure 3).

Table III: Cytogenetic findings of various DSD

Cytogenetic findings	No of cases.	%
Sex Chromosome DSD		
Turner syndrome		
45,X	39	41.93
45,X/46,X,i(Xq)	6	6.45
45,X/46,XX	3	3.23
45,X /46,XX /46, X,i(Xq)	1	1.08
45,X/47,XXX	2	2.15
46,X,i(Xq)	4	4.30
Klinefelter syndrome		
47,XXY	7	87.5
47,XXY/46,XY	1	12.5
Others (Gonadal dysgenesis/ Chimeric)		
45,X/46XY	1	1.53
47,XXX	1	1.53
46, XY DSD and 46, XX DSD		
46,XY	19	20.43
46,XX	9	9.68

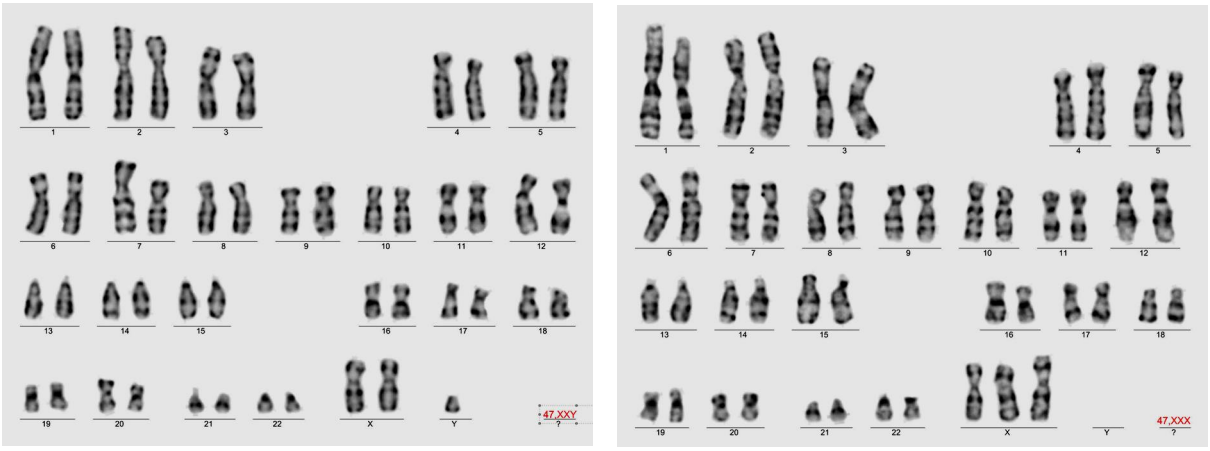

Figure 3**.** Karyotypes of Sex Chromosome DSD; 47,XXY, Klinefelter syndrome (Case no. 19) and 47,XXX syndrome (Case no.43).

Clinical presentations of DSD

The variability in the manifestation of DSD covers a spectrum ranging from normal external female and male phenotypes to ambiguous genitalia. In this study, major clinical manifestations of DSD cases were evaluated separately.

In Turner syndrome most common presentation was primary amenorrhoea (69.23% in classic and 56.25% in mosaic Turner syndrome) followed by short stature (51.28% in classic Turner syndrome). Twenty one (53.84%) patients of classic Turner syndrome presented with delayed/absent secondary sex characters, whereas 5 (31.25%) patient in mosaic Turner group. Webbing of neck was present in 9 (23.07%) patients and most of them were under 10 years of age. Two (5.13%) patient in classic TS group and 1 (6.25%) patient in mosaic TS group presented with infertility (Table IV).

Table IV: Clinical features in Turner syndrome

Clinical features	Classic Turner syndrome (N=39)	Frequency (%)	Mosaic Turner syndrome (N=16)	Frequency (%)
Primary amenorrhoea	27	69.23	9	56.25
Secondary amenorrhoea	2	5.13	1	6.25
Menstrual irregularity	2	5.13	0	0
Short stature	29	74.36	7	43.75
Delayed/Absent secondary sex character	21	53.84	5	31.25
Sparse axillary, pubic hair	9	23.01	2	12.25
Shield chest	6	15.38	1	6.25
Webbing of neck	9	23.07	0	0
Infertility	2	5.13	1	6.25

In cases of Klinefelter syndrome, common clinical presentations were small atrophic testes (62.5%), infertility (50%) and gynaecomastia (25%). One patient also presented with ambiguous genitalia and one with lack of secondary sex characters (Table

V). Two other sex chromosome DSD (1.53% of each) includes XXX syndrome and mixed gonadal dysgenesis. The Triple X syndrome presented with normal female phenotype, with infertility and menstrual irregularity. The 45,X/46XY patient presented with female phenotype with virilization of external genitalia, absent secondary sex characters and primary amenorrhoea (Table V).

Table V: Clinical features in Klinfelter syndrome

Clinical features	Klinefelter syndrome (N=8)	Frequency (%)
Small atrophic testes	5	62.5
Infertility	4	50
Sparse axillary and pubic hair	1	12.5
Gynaecomastia	2	25
Ambiguous genitalia	1	12.5

Common presentations of 46, XY DSD cases were primary amenorrhoea (42.11%), ambigious genitalia (31.58%) and delayed/ absent sex characters (27.78%). Eleven (57.89%) patient was adolescence or adult in this category. Cases of 46,XX DSD presented with ambigious genitalia (55.56%), clitoromegaly (44.45%) and hyperpigmentation of genitalia (22.2%). Two (22.22%) patients of this category were in adolescent age. These results are shown in Table VI.

Table VI: Clinical features of 46,XX and 46,XY DSD

Clinical features	46, XY DSD		46,XX DSD	
	(N=19)	Frequency (%)	(N=9)	Frequency (%)
Primary amenorrhoea	8	42.11	0	0.00
Delayed/absent secondary sex character	5	27.78	0	0.00
Ambiguous genitalia	6	31.58	5	55.56
Clitoromegaly	0	0.00	4	44.45
Small penis	5	26.32	0	0.00
Hypospadias	1	5.26	0	0.00
Hyperpigmentation of genitalia	0	0.00	2	22.22

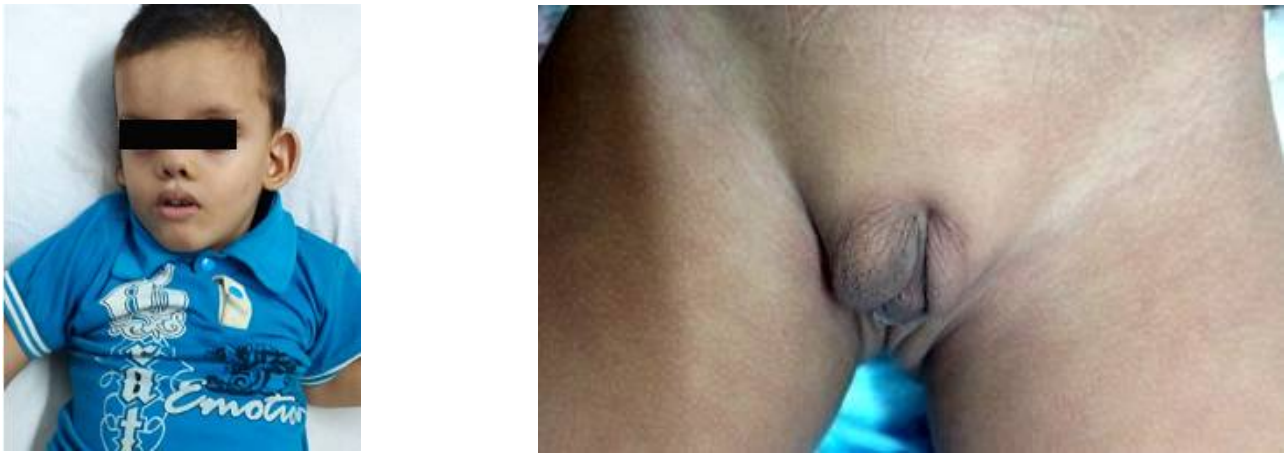

Figure 4. A child with 46, XX DSD presented with ambiguous genitalia

Discussion

The present study data demonstrated that sex chromosome DSD (Turner syndrome and Klinefelter syndrome) were the commonest disorders as it represented 69.89% of our patients. Turner syndrome constituted a significant proportion of DSD cases (59.14%) and Klinefelter syndrome represented 8.61%. In present study 46,XY DSD was found 20.43% , followed by 46, XX DSD (9.68%). This finding is consistent with other studies by Erdogan et al. (2011) and Shawky et al.(2012).[5,6] A cross-sectional study was done at the department of Pediatric Surgery, Chittagong Medical College & Hospital (CMCH), Chittagong, Bangladesh, from January 2006 to December 2012 and they found that among 50 DSD patients, 22% had 46, XX DSD with congenital adrenal hyperplasia (CAH), 64% with 46, XY DSD, 8% with mixed gonadal dysgenesis (MGD), and 6% with ovotesticular DSD.[7] Other studies like Mazen et al., have also reported a relatively higher incidence of 46,XY DSD excluding sex chromosome DSD.[8] In present series 46, XY DSD was found to be 67.85% and 46,XX DSD 32.14%.

According to studies done by White and Speiser (2000) and Kovács et al. (2001), most (>80-90%) of the DSD patients of developed world presented in the neonatal period, with <10% presenting in adolescence.[9,10] In contrast, in our study the commonest age of presentation was in between 11 to 20 years. Majority of DSD patients (60.22%) presented at this age group. Only 20.43 % patients were below 10 years. In developing countries like Bangladesh, this delayed presentation may be due to lack of awareness associated with other social factors.

Data on the actual prevalence of DSD in developing countries associated with high rates of consanguinity or endogamy is largely unavailable.[11] In present study 31.18% patients have history of parental consanguinity or endogamy. A study done by Shawky et al.(2012) in Egyptian population comprised of 908 patients with sex differentiation errors showed that, consanguineous marriage was reported among parents of 504 patients (55.50%).[6] This study result is consistent with the present study. Therefore, in case of disorders of sex development, consanguinity may have a role. Although most of the published data from western countries have showed low rates of consanguinity which may not be a true reflection of the worldwide prevalence.

Cytogenetic variants of our studied patients with Turner syndrome are consistent with

other studies.Huang et al., (2002) reported the karotypes of Turner syndrome as, 45,X (53%); mosaicism 45X/46XX (15%); X isochromosome, 46,Xi(Xq) (10%); mosaicism 46,Xi(Xq)/46XX (8%); deletions 46,Xdel(Xp) or 46,X del (Xq) (6%); other mosaicism (8%).[12] Another study on Turner syndrome patients in northeastern Malaysia (2008) showed that, the incidence of the most frequent karyotypes of the Turner syndrome were found to be 45,X (57.1%), followed by 46, Xi(Xq) (21.4%), 45,X/45,X,+mar (7.1%), 45, X/46,Xi(Xq) (7.1%) and 45, X/46,XY (7.1%)[13]. These results are similar with this present study.

In present study, The common causes of 46, XY DSD cases were androgen insensitivity syndrome(26.31%), gonadal dysgenesis (26.31%) anddefect in androgen synthesis/ action (21.05%). The causes of 46,XY DSD were numerous and heterogeneous, as described in other studies byLadjouze et al., (2016).[14] In present study further sub categorization was not possible as gene analysis was not done and all the hormonal evaluation was not possible due to lack of resources.

In other studies, the 46,XX DSD group, the most common condition was CAH due to 21-hydroxylase deficiency, a finding compatible with its worldwide incidence of 1:14 000 live births.[15] Present study results are not in agreement with these study results. In present study 22.22% cases were diagnosed as congenital adrenal hyperplasia. However a study done in Bangladesh by Chowdhury et al., in 2014 supports the present study findings.According to that study, the percentage of CAH patients, which usually accounts for more than half of the patients with DSD in a developed country, made up only 22%. This suggested many babies may have died of a salt-losing crisis in the second or third week of life, and hence are no longer represented. This was probably also true for boys with CAH, who have no genital anomaly but probably succumb to an adrenal crisis shortly after birth. This was more likely to be the case in lower socioeconomic classes, which is supported by the fact that they were under-represented the study.[7] This explains the causes of reduced number of CAH in present study. Further sub categorization was not possible in 46, XX DSD cases, as it requires genetic analysis.

In present study, most common presentation in Turner syndrome was primary amenorrhoea, short stature, delayed/absent secondary sex characters and webbing of neck. A small number of patients presented with infertility. In cases of Klinefelter syndrome, common clinical presentations were small atrophic testes, infertility andgynaecomastia. One patient also presents with ambiguous genitalia and one with lack of secondary sex characters. Most common presentation of 46, XY DSD case were primary amenorrhoea, ambigious genitalia and delayed/ absent sex characters. Most of the 46,XX DSD presented with ambigious genitalia, clitoromegalyand with hyperpigmentation of genitalia. These study results are consistent with study done by Shawky et al., in 2012[6]. In that study presentation of DSD cases were primary infertility, primary amenorrhea, male infertility, ambiguous genitalia at birth, short stature and delayed secondary sexual characters, males with microtestes, and hirsutism. However frequency of different presentations slightly varies.

Conclusion

Although a number of diagnostic algorithms exist for DSD classification, no single evaluation protocol is suitable for all circumstances and some basic tests, such as hormone assay, ultrasonography and cytogenetic analysis are very important for classification and management of DSD. Further

studies using molecular genetic analyses are needed to give a more precise diagnosis. This study will strengthen the proper management of DSDs andwill facilitate the sharing of experiences, thereby reducing the stress and isolation felt by patients and their families. Despite all the odds a number of individuals with DSD are highly resilient, true to the words of Helen Keller 'Although the world is full of suffering, it is also full of overcoming it'.

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