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CLINICAL AND LABORATORY PROFILE OF PATIENTS WITH DISORDERS OF SEX DEVELOPMENT: EXPERIENCE FROM TWO TERTIARY CARE HOSPITALS IN BANGLADESH

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ABSTRACT

ORIGINAL RESEARCH ARTICLE

Disorders of sex development (DSD) are relatively rare conditions where, gender assignment remains uncertain, presented with ambiguous genitalia in newborns and atypical sex development in adolescents. Management remains challenge for all professionals involved and largely depends on the participatory factors responsible for the causation of the disorders. **Patients and Methods:** All patients with the complaint of atypical features of sex development, attending the paediatric endocrine unit of two tertiary level hospitals in Dhaka city, in a period of 24 months from May 2017 to May 2019 were incorporated in this study and their clinical, hormonal and cytogenetic findings have been documented. **Results**: Among 77 DSD patients under this study, there were 43 (55.84%) 46, XX DSD cases, 30 (38.96%) 46, XY DSD cases and 4 (5.19%) sex chromosome DSD cases. The age of presentation ranged from 0 days to 19 years with the mean of 2.29±4.2 years. Only 16.9% of the cases presented in their neonatal period. Almost all (98.7%) patients featured with genital ambiguity. Congenital Adrenal Hyperplasia (CAH) had been found in all of the 46, XX DSD cases and in 1 sex chromosome DSD case. Among the patients with 46, XY DSD, 5 patients had PAIS (Partial Androgen Insensitivity Syndrome), 5 patients had CAIS (Complete Androgen Insensitivity Syndrome), 3 patients had 5αRD (5α Reductase Deficiency) and 5 patients had GD (Gonadal Dysgenesis). The gender of rearing was male in 25 (32.5%) cases and female in 52 (67.5%) cases. During the study period, 12 (15.58%) patients had undergone surgical intervention, 35 (45.54%) patients had been referred for surgery, 36(46.8%) patients was

under hormonal therapy, and for 2 (2.6%) patient's operation had been planned. **Conclusions**: As according to the finding of this study, AIS was the most common etiological findings among 46, XY DSD cases and CAH was exclusively present among all 46, XX DSD cases.

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I INTRODUCTION

Disorders of sexual development (DSD) are a wide range of conditions with diverse features and pathophysiology that most often present in the newborns with atypical genitalia or in the adolescent with delayed or atypical pubertal outcomes.[1,2] Disorders of Sex Development (DSD) are defined as the genetic conditions in which development of chromosomal, gonadal, or anatomical sex is atypical.[3-5] Sexual differentiation of human being is a very complex process, controlled by gene and hormones.[6-8] Atypical sexual differentiation observed to occur in roughly 1 per 4500 live births.[2,9] Every so often, in these cases of atypical sexual development, the management of the patients depends on the decision regarding sex assignment, which is extremely distressing and difficult for the families and also for the healthcare professionals, particularly in cases with uncertain sex of rearing.[10] Developing a logical and rational plan for which investigations to be carried out to establish the diagnosis and building up an understanding relationship with the affected child and the parents, to support them therapeutically and psychologically, is the most primary and significant approach of the management.[2]

DSDs have been historically classified according to corresponding categories[11]:

- Disorder of sex chromosome component - 46,XX, 46,XY, other, mosaic
- Disorder of gonadal structure - testicular DSD, ovo-testicular DSD, gonadal dysgenesis
- Disorder of the functional status of the Gonads - gonadal dysgenesis, disorders of androgen biosynthesis

Chromosomal aberrations and defects of developmental genes may lead to disorders of gonadal development and associated malformations.[12-15] Disturbances of steroid biosynthesis or action may prevent the realization of the phenotypic sex by either deficiency or excess of certain metabolites or by constructing a resistance to them. These cause virilization in genetically female patients and lack of virilization in genetically male patients.[14,16] The worldwide incidence of DSD has been estimated at a rate of 1 person in 5,500 (18: 100,000).[17] Among the causes of ambiguous genitalia in the neonate CAH is the most common cause, which may represent approximately half of all such cases. Worldwide this incidence is estimated to be 1 in 15,000 live births.[18,19] Neonatal screening program in Germany recorded 1 case of ambiguous genitalia per 10,558 live births, where ambiguous genitalia in a newborn with female genotype was mainly due to hypervirilization.[20] Survey in Europe observed that, defect of 21-hydroxylase enzyme is estimated to affect 3 to 11 neonates per 100,000 births per year.[21]Mixed gonadal dysgenesis thought to be the second etiological diagnosis of DSD with an incidence of 1: 10,000.[22]Complete androgen insensitivity syndrome (AIS) is estimated at a incidence rate between 1:60000 and 1:99000 whereas, partial androgen insensitivity syndrome found to be much more common.[23,24] Though the incidence of 17-hydroxysteroid dehydrogenase deficiency is found to be quite lower, may be 1: 150,000, 5αRD (5 -RD) deficiency may be even less common.[25] There is only limited national data on the incidence and prevalence of DSD with a causal explanation, which can portray the real scenario of the status of the

patients with DSD in our country. Therefore, this study aims to observe the paediatric patients suspected with DSD and to plan an appropriate management by assessing their clinical, biochemical, radiological and chromosomal profile.

II METHODOLOGY

Subjects and Methods: This study was a cross-sectional observational study carried out in the paediatric endocrine OPD of Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM), and Combined Military Hospital (C.M.H.) in a period of 24 months from May 2017 to May 2019. Ethical approval was taken before conducting the study from the respective hospitals. Evaluation was done on 77 suspected DSD cases, in the age group of 0–19 years who came to the hospital primarily with the complaint of ambiguous genitalia or atypical sexual development.

Case diagnosis and data collection: After taking written informed consent form the caregiver and verbal consent from the subject as applicable, the detailed history taking and examination was done. Cases were diagnosed by clinical, hormonal and cytogenetic analysis. Data including age at presentation, karyotyping, hormonal, biochemical and radiological investigation and treatment approaches have been recorded.

Statistical analysis: With the use of SPSS version 22, percentage, mean and range were calculated and used to describe continuous and categorical variables. Frequency distribution table and cross tables were formulated to describe various features under the etiological diagnosis of the disorders.

III RESULTS

Among the 77 patients, the mean age of presentation was 2.29 years with SD ±4.2 years, almost 17% and 43% patients were presented at their neonatal and infantile period respectively. Around 4% of the cases presented at their adolescent period (Table I). Among the patients, 30 (38.96%) patients were identified with 46, XY DSD, 43(55.84%) patients had 46, XX DSD and sex chromosome DSD was found in 4 (5.19%) patients. The most common etiological diagnosis among 46, XY DSD was androgen insensitivity syndrome (AIS); there were 5 (6.5%) five alpha reductase deficient patients and 3 (3.9%) patients with gonadal dysgenesis and in 12 (15.6%) cases, a definite diagnosis couldn't be made. All the cases of 46, XX DSD diagnosed with congenital adrenal hyperplasia (CAH), among whom 19 (24.7%) cases were simple virilizing type and 24 (31.2%) cases were salt-wasting type. Aromatase deficiency had been identified in one patient with simple virilizing CAH. Among the patients with sex chromosome disorder gonadal dysgenesis had been found in 3 (3.9%) cases and 1 case was diagnosed with CAH who had precocious puberty (Table II). All the patients came to the hospital with the primary complaint of genital ambiguity. Delayed puberty was reported in one patient with 46, XY DSD, small penis was the primary complaint in 2 cases, each from the group of 46, XX DSD and sex chromosome DSD. Short stature was the recorded complaint in one patient with sex chromosome DSD. All 24 patients with salt losing CAH presented with the complains of vomiting, diarrhea, sunken eyes and in one case there was previous history of shock and one sib death was recorded. Among the 46, XY DSD group of patient's bifid scrotum was recorded in 10 cases, micro-penis in 12 cases, hypospadiasis in 17 cases, absence of one of the gonads in 9 cases, enlarged clitoris in 6 cases, presence of vaginal orifice in 7 cases and presence of Mullerian structures in one case have been recorded. The 46, XX DSD patients mostly presented with enlarged clitoris (38 cases) and absence of vaginal orifice (14 cases). Similar to that, sex chromosome DSD patients also presented with 3 cases of enlarged clitoris, in

two patients vaginal orifice was absent and also micro-penis was seen in one patient and urethral meatus was absent in one patient (Table III). The sex assignment since birth was recorded as, 25 (32.5%) male and 52 (67.5%) female. Among the 46, XY DSD cases, 8 of them were reared as female, from them 2 were with CAIS, 3 with GD and in 3 female cases, etiology was not being defined by then. Among the 46, XX DSD cases, 1 patient had been assigned to male sex having CAH-SL. Among the patients with sex chromosome disorder, 2 was reared as female having gonadal dysgenesis and 2 were reared as male, one of them had gonadal dysgenesis and one had CAH (Table IV).

Table I: Age distribution of the patients (n=77)

Age	**Frequency**	**Percent**
Neonate	13	16.9
Infant	33	42.9
1-5 years	13	16.9
Above 5 years- below 13 years	15	19.5
13 years and above	3	3.9
Total	77	100.0

Table II: Etiological diagnosis among the patients.

		Frequency	**Percent**
46,XY DSD		30	38.96
PAIS		5	6.5
CAIS		5	6.5
5αRD		3	3.9
GD		5	6.5
Undefined		12	15.6
46,XX DSD		43	55.84
CAH-SV		19	24.7
CAH-SL		24	31.2
Sex chromosome DSD		4	5.19
46XY/47XYY	GD	1	1.3
45,XO/46,XY	GD	1	1.3
46,XY/46XXq^{-}	GD	1	1.3
46,XX/46,XY	CAH	1	1.3

Table III: Distribution of presenting complaints and clinical features.

Features		**46, XY DSD n (%)**	**46, XX DSD n (%)**	**Sex chromosome DSD n (%)**
Presenting complaints	AG	29 (37.7%)	43(55.8%)	4 (5.2%)
	Delayed puberty	1(1.3%)	-	-
	Micro penis	-	1(1.3%)	1(1.3%)
	Vomiting, diarrhea, sunken eyes, refusal to eat, not gaining weight	-	24(31.2%)	-

	Short stature	-	-	1(1.3%)
Clinical features	Bifid scrotum	10(12.9%)	-	-
	Micro-penis	12(15.6%)	1(1.3%)	1(1.3%)
	Urethral meatus absent	-	-	1(1.3%)
	Hypospadiasis	17(22.1%)		
	Left gonad absent	6(7.8%)	-	-
	Right gonad absent	3(3.9%)	-	-
	Enlarged clitoris	6(7.8%)	38(88.37%)	3(3.9%)
	Vaginal orifice absent	23(29.9%)	14	2(2.6%)
	Mullerian structures present	1(1.3%)	-	-

Table IV: Distribution of sex of rearing at birth among the spectrum of disorders of sexual development.

Diagnosis		**Male n (%)**	**Female n (%)**
46, XY DS (n=30)	PAIS	5 (6.5%)	-
	CAIS	3 (3.9%)	2 (2.6%)
	5αRD	3 (3.9%)	-
	GD	2 (2.6%)	3 (3.9%)
	Not classified	9 (11.7%)	3 (3.9%)
46, XX DSD (n=43)	CAH-SV	-	19 (24.7%)
	CAH-SL	1 (1.3%)	23 (29.9%)
SSD (n=4)	GD	1 (1.3%)	2 (2.6%)
	CAH	1 (1.3%)	-
Total		25 (32.5%)	52 (67.5%)

Table V: Frequency distribution of the hormonal and biochemical findings among the patients.

		46, XY DSD					46, XX DSD		Sex chromosome DSD		
		PAIS	CAIS	5αRD	GD	Not classified	CAH-SV	CAH-SL	GD	CAH	Total
Hormonal findings											
LH	↓	1	1	-	-	3	-	-	3	1	39
	↑	2	3	3	3	2	1	1	-	-	
	N	-	1	-	2	6	4	2	-	-	
FSH	↓	-	-	-	-	2	3	1	3	1	42
	↑	4	2	2	4	4	3	1	-	-	
	N	1	3	1	1	5	-	1	-	-	
T	↓	1	-	-	-	-	1	3	-	-	70
	↑	3	3	2	1	7	9	6	1	1	
	N	1	2	1	4	5	7	10	2	-	

17-OHP	↓	-	1	-	-	-	-	1	-	-	54
	↑	4	-	2	2	7	10	10	1	1	
	N	-	2	1	-	4	4	3	1	-	
DHEAS	↓	-	-	-	-	-	3	1	-	-	21
	↑	-	-	-	-	1	2	1	-	-	
	N	-	2	1	-	-	3	6	-	1	
Cortisol	↓	-	-	-	-	-	2	7	1	-	40
	↑	-	-	-	-	-	-	-	-	-	
	N	4	2	1	2	5	10	5	-	1	
ACTH	↓	-	-	-	-	1	1	1	1	-	27
	↑	-	-	-	-	-	3	4	-	-	
	N	3	1	-	-	-	5	7	-	-	
Biochemical findings											
Na	↓	1	2	-	1	3	1	15	-	-	66
	↑	-	-	-	-	-	-	-	-	-	
	N	4	1	3	1	8	17	9	-	1	
K	↓	-	-	-	-	-	-	1	-	-	57
	↑	-	-	-	-	-	-	-	-	-	
	N	5	3	3	2	1	18	23	-	1	
Cl	↓	1	-	-	-	-	1	10	-	-	52
	↑	1	1	2	-	1	1	4	-	-	
	N	3	1	1	1	6	10	8	-	-	
TCO_2	↓	1	-	-	-	1	1	6	-	-	38
	↑	1	1	1	1	2	1	4	-	-	
	N	-	1	1	-	3	8	5	-	-	
LH-luteinizing hormone, FSH-follicle stimulating hormone, T-testosterone, 17-OHP-17 hydroxi progesterone, DHEAS-Dehydroepiandrosterone sulfate, ACTH- adrenocorticotropic hormone, Na- sodium, K-potassium, Cl- chlorine, TCO_2- total carbondioxide											

Table VI: Management of the patients.

Diagnosis		Operated	Referred to surgeon	Hormonal therapy	Hormonal therapy and referred to surgeon	Surgery planned
46, XY DS (n=30)	PAIS	2	1	-	2	-
	CAIS	-	4	-	1	-
	5αRD	-	3	-	-	-
	GD	1	1	-	-	2
	Not classified	2	6	-	3	-
46, XX DSD (n=43)	CAH-SV	2	8	6	3	-
	CAH-SL	3	-	19	2	-
SSD (n=4)	GD	1	1	-	-	-
	CAH	1	-	-	-	-

Hormonal and biochemical tests were selectively done in patients as per requirement. Patients with 46, XY DSD mostly showed increased LH (in 13 cases), FSH (in 16 cases), testosterone (in 16 cases) and 17-OHP (in 15 cases) levels. Whereas, among patients with 46, XX DSD, who took LH level test, mostly found within normal level (in 6 cases), FSH level was increased and decreased in same number of patients (in 4 cases); testosterone level was increased in 15 patients and was within normal range in 17 patients. 17-OHP found to be increased in 20 patients and normal in 7 patients with CAH. Among the patients with CAH the DHEAS level was decreased in 4 cases, increased in 3 cases and normal in 9 cases. Patient with 46, XY DSD who took cortisol level test (in 14 cases), found to have normal cortisol level. Cortisol level was normal in 15 cases and decreased in 9 cases with CAH. ACTH level was investigated mostly among patients with CAH. It was found that, among them, the level of ACTH was increased in 2 cases, decreased in 7 cases and within normal range was in 12 cases. Among the patients with sex chromosome DSD, LH and FSH level found to be decreased, testosterone level was increased in 2 patients and normal in 2 patients. Among the patients with 46, XY DSD the biochemical findings were mostly normal, though the level of total CO_2 was increased in 6 patients. Among the patients with CAH, the Na, K and Cl level was decreased in 16, 1 and 11 patients respectively (Table V). Among the 46, XY DSD patients, 5 patients were already undergone genital surgical procedure, 21 cases were referred to surgeon for operation among them in 6 patients, hormonal therapy had been initiated. In 2 cases surgery was planned which were pending. Among the 46, XX DSD patients, operation was already done in 5 patients, 13 patients were referred to surgeon, 5 of them had been given hormonal therapy, 25 patients were being treated with hormonal therapy only. Patients with sexual spectrum disorder, 2 of them were already operated and 1 patient had been referred to surgeon. Treatment had not been started in one patient by then (Table VI).

IV DISCUSSION

Age presentation:

This study was presented with the age range of 7 days to 13 year 8 months, where the mean age was 2.29 years with the SD of ± 4.2 years. Neonatal presentation was 16.9% and majority of the cases were infants (42%). Three patients (3.9%) had been presented at their adolescence. Study among the pediatric group of patients with disorder of sexual development by K. P. Kulkarni et al. and Dar et al., found near about similar age range and mean age, which were 1 day to 12 years with the mean age of 2.63 years and 1 day to 16 years with the mean age of 7.15 years respectively.[10,26]

Karyotype:

Among the 77 patients in this study 30 (38.96%) patients had 46, XY DSD, 43 (55.84%) patients had 46, XX DSD and 4 (5.19%) patients had sex chromosome DSD. Kulkarni et al., 2009 also found majority of 46,XY DSD (77.6%) cases in their study.[27] The incidence of 46,XY DSD found to be more common than 46,XX DSD found in some other studies also.[28-30]Study among 194 cases with DSD by Walia et al., found 102 (52.5%) patients had 46,XY DSD and 74 (38.1%) patients had 46,XX DSD and sex chromosome DSD was identified in 7 (3.6%) patients.[31] Though a study from Saudi Arabia found 46,XX DSD (65.4%) more common than 46,XY DSD (34.6%) which was substantial with our findings.[32]Dar et al., also found 46,XX DSD to be the most common DSD.[10]

Sex of rearing:

In this study, the sex of rearing was male in 25 (32.5%) cases and female in 52 (67.5%) cases. Among the 46, XY DSD cases,

8 of them were reared as female and among the 46, XX DSD cases, 1 patient had been assigned to male sex. Among the patients with sex chromosome disorder, 2 was reared as female and 2 as male. Kulkarni et al. found in their study, the sex of rearing was male among 43(74.1%) patients, and as female in 10 (17.2%).[26]

Etiological Diagnosis:

This study recorded AIS to be the most common cause for 46, XY DSD whereas CAH was the only etiological diagnosis among the patients with 46, XX DSD. AIS to be the most common cause for 46, XY DSD and CAH for 46, XX DSD, was also found in some other studies.[27,31] Among the 30 patients with 46, XY DSD in this study, 10 (12.9%) patients were diagnosed with AIS, among them 5 were PAIS cases and 5 were CAIS cases; 5αRD was found in 3 patients and GD in 5 patients, no etiology was defined in 12 cases. A prospective study with 11 cases of 46,XY DSD, 3 cases were diagnosed with 5αRD, 3 with GD, 3 with PAIS, 1 with CAIS.[33] A retrospective study of 93 patients with 46,XY DSD observed that, among the patients 50.5% had no defined etiology and 20.4% had AIS.[34] Another study showed, among 102 patients with 46,XY DSD, 32 (31.4%) had androgen insensitivity syndrome.[31] A study with 19 patients with 46,XY DSD found 1 case with CAIS, 3 (15.8%) cases with PAIS and 4 (21.05%) cases with 5αRD.[35] Walia R. et al., found 9 (4.6%) cases of 5αRD, in their study, GD was recorded in 17 cases, 2 (1.5%) with 46,XY DSD and 14 (7.2%) with 46,XX DSD. In this study, all 43 patients with 46, XX DSD had been diagnosed with CAH, among whom 19 (44.18%) patients were simple virilizing type and 24 (55.81%) patients were salt wasting type. Walia R. et al., found 52 (26.8%) cases of CAH, among them 42 (21.6%) cases were simple virilizing type and 10 (5.2%) cases were salt wasting type.[31]

Clinical and laboratory findings: The syndromic appearance of disorder of sexual development was, genital ambiguity in almost all cases in our study, which was also in line with various other studies where ambiguous genitalia found in more than half of the patients.[10,36] Patients with salt wasting CAH primarily came with wasting, diarrhea and vomiting refusal to eat. Sib death was recorded in one patient with salt wasting CAH. Unexplained sib death was recorded in 33% cases in the study of Dar et al.[10] The most common clinical presentation of atypical genital anatomy in case of 46, XY DSD was hypospadiasis, micropenis and bifid scrotum whereas, enlarged clitoris and absence of vaginal orifice was the most common features found in 46, XX DSD cases. Clitoromegaly and micropenis with hypospadias found to be the most common phenotypes in studies done by Maimoun et al., and Walia et al..[31,37] Among the 44 cases with CAH in this study 21 (47.7%) of them showed increased level of serum 17-OHP thus indicated underlying deficiency of 21-hydroxylase enzyme. Similar observation was found in other studies, Dar et al., 2018 found, 51% of patients with CAH had deficiency of 21-hydroxylase enzyme and Gupatientsa et al. reported that over 90% of CAH have the 21-hydroxylase deficiency.[10,38]

Interventions:

Corrective genital surgery was already performed by the study, in five 46, XY DSD patients and five 46, XX DSD patients. 21 46, XY DSD cases and 13 46, XX DSD cases were referred to surgeon for operation. Hormonal therapy had been initiated in 6 46, XY DSD patients, and 30 46, XX DSD patients. Operation had been planned in 2 cases of 46, XY DSD. Patients with sexual spectrum disorder, 2 of them were already operated and 1 patient had been referred to surgeon. Treatment had not been started in one patient yet, by then. In the study of Walia et al., gonadectomy was performed where gonads were palpable in inguinal regions of patients with CAIS and hormonal therapy was initiated; corrective surgeries for hypospadias

and testosterone supplementation to enhance virilization in patients with male sex of rearing was done and with simple virilizing CAH who had strong male gender identity and severe virilization behavior underwent removal of the female internal genital organs implantation of testicular prosthesis.[31]

V CONCLUSION

There is only limited data on the incidence and prevalence of DSD in our country to provide an understanding of the current status of these disorders. Seeking care for the diagnosis and management of newborn with ambiguous genitalia still is very low in proportion, which is explainable in the socio-cultural setting of the country, where disorder of the sexual development is regarded as a social taboo and the families face stigmatization on such finding. Genetic composition of female seen to have more exposed to this disorder where in some cases the associated manifestations can be life threatening such as in salt wasting CAH. Early evaluation and management may can simplify to live a normal and healthy adulthood with the definite gender assignment according to the gender identity and anatomic sex.

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ETHICAL CLEARANCE: Ethical clearances have been taken from the corresponding hospitals where the study has been conducted.

CONFLICT OF INTEREST: There was no conflict of interest.

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