BANGLADESH J CHILD HEALTH 2023; VOL 47 (2) : 103-108

A Study of 67 Cases with Disorders of Sex Development: An Experience of A Tertiary Care Hospital

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Abstract:

Introduction: *Disorder of sex development (DSD) is defined as a condition where the development of gonadal, chromosomal or anatomic sex is atypical.*

Objective: *To study the clinical and laboratory profile of patients with disorders of sex development (DSD) and classify them.*

Methods: *A retrospective study was conducted in BSMMU from 1st May 2016 to 31st December 2021 including all patients diagnosed with DSD. Data were obtained by reviewing the medical records of the patients.*

Results: *A total 67 patients were diagnosed as DSD. Among them 30 patients (44.8%) had 46,XX DSD, 22 patients (32.8%) had 46,XY DSD, 13 patients (19.4%) had sex chromosome DSD and 2 patients (2.9%) had ovotesticular DSD. Majority (60%) of the patients with 46,XX DSD were diagnosed as congenital adrenal hyperplasia (CAH) followed by adrenal tumor (16.7%) and patients with partial trisomy of chromosome 9q (16.7%). Among 22 patients with 46,XY DSD, eight patients (36.3%) had androgen biosynthetic defect, 6 cases (27.2%) were under virilized CAH and 2 patients (9%) had androgen insensitivity syndrome. Majority of sex chromosome DSD were turner syndrome (69.2%). Only 2 patient had mixed gonadal dysgenesis. Thirteen percent of the children with 46, XX DSD were reared as male and 27% of the 46, XY DSD cases were reared as female.*

Conclusion: *Congenital adrenal hyperplasia is the most common cause of DSD. Majority of 46 XY, DSD is due to androgen bio synthetic defect while CAH is the most common cause of 46XX, DSD. Rare chromosomal disorders are also found among DSD cases.*

DOI: https://doi.org/10.3329/bjch.v47i2.77681

Introduction:

Disorder of sex development (DSD) is a condition where the development of gonadal, chromosomal or anatomical sex is atypical.[1] The incidence is 1:4500 to 1:5000 live births.[2,3] Diagnosis and subsequent management of these cases must involve endocrinologists, paediatricians, geneticists, radiologists, surgeons and urologists with a good laboratory set up. With all these efforts, in only 30-50% of 46, XY DSD patients novel approach is possible.[4,5] Management of 46, XX DSD cases who present with virilization of external genitalia and diagnosed as CAH are comparatively easier than the 46,XY DSD cases.[4] The incidence of CAH in Asian population is 1:44,000.[6,7] While worldwide it is 1:14,199 live births based on neonatal screening. Sex assignment in DSD cases is challenging and it should be done considering the genetic sex, restoration of normal appearance of external genitalia, degree of virilization, chance of fertility and preference of the parent or patient.[8] Parental insistence to rear as a male significantly influences the issue of sex of rearing in a male-dominated society of Bangladesh. In South

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East Asia there is limited data on the clinical profile of children with DSD and most of them are available in the form of case reports or case series.[9-15] Here we present the clinical profile and diagnosis of 67 patients with DSD.

Materials and methods:

This retrospective study was done with the objective to study the clinical and laboratory profile of patients with disorders of sex development (DSD) and classify them. It was done in Paediatric Endocrinology division of department of Paediatrics, Bangabandhu Sheikh Mujib Medical University (BSMMU), a tertiary care centre in Dhaka, Bangladesh. Patients diagnosed as DSD during the period of 1st May 2016 to 31st December 2021 were included in the study. Their medical records were reviewed thoroughly. Apparent male genitalia with non palpable gonad, small phallus, perineal hypospadias, apparent female genitalia with clitoromegaly, fusion of labium, inguinal mass, apparent female genitalia with bilateral palpable gonads in labial folds and karyotype/ genital discordance were the features suggesting DSD. Detailed history, findings of clinical examination and investigation were reviewed thoroughly. The diagnosis of CAH was based on clinical evidence of glucocorticoid and/or mineralocorticoid deficiency, androgen excess with elevated basal and/or ACTH-stimulated 17-hydroxyprogesterone (17-OHP) levels. Patients with serum sodium level<135mmol/L and/or serum potassium levels >5.5mmol/L were classified as salt wasting (SW) type CAH. Those with early features of androgen excess only were classified as simple virilizing (SV) form. Patients with late presentation of mild androgen excess were classified as non classic form.[16] Initial laboratory tests included serum electrolyte, LH, FSH, testosterone,17-OHP, basal cortisol, basal ACTH, DHEA-S and ultrasonogram of abdomen and pelvis. Genetic sex was confirmed by karyotyping. Short Synacthen test (rapid ACTH stimulation test) was done to confirm CAH. In selected cases, Human chorionic gonadotropin (hCG) stimulation test was done by administering 2000 IU of hCG intramuscularly for 3 days and sample for stimulated testosterone was collected 24 hour after the last dose. The response was considered adequate if the stimulated testosterone level was at least 9 nmol/L.[17] Androgen biosynthetic defect is usually diagnosed when there is abnormally high ratio of serum androstenedione to testosterone following hCG stimulation test. In this study children having 46XY karyotype who had hypergonadotropic hypogonadism (low testosterone and high LH, FSH level) and even after hCG stimulation testosterone level was low were categorized as having androgen biosynthetic defect. The diagnosis of androgen insensitivity syndrome was based on a discordance between a female phenotype and a karyotype of 46,XY having high basal LH and testosterone level and normal response of rise of testosterone following hCG stimulation[18]. LH, FSH and Testosterone hormones were measured with radioimmunoassay. Ultrasonography and/or magnetic resonance imaging was done to look for Mullerian structures, ovaries and undescended testis. Ovotesticular DSD was identified when gonadal biopsy revealed both ovarian and testicular tissues either in the same or opposite gonads with either of the karyotyping-XX, XY or XX/XY. Sex chromosomal DSD included any condition in which there is atypical arrangement of the sex chromosomes. All data were statistically analyzed by SPSS software (version 17.0). The results were described as mean±SD, median with range. Comparison of mean data was done using independent-sample t-test and P value<0.05 was considered as statistically significant. Ethical issue was considered and the identity of the patients were kept confidential.

Results:

Out of 67 patients, 30 (44.8%) had 46,XX DSD, 22 (32.8%) patients had 46,XY DSD, 7 (19.4%) had sex chromosome DSD and ovotesticular DSD was identified in 2 patients (2.9%). Median age with range at first consultation in Paediatric endocrine out patient department (OPD) was 36 (0.2-192) months. Among 30 patients with 46,XX DSD, only 4 patients were reared as male while 6 out of 22 children with 46, XY DSD were reared as female. As we could not confirm 5 alpha reductase deficiency due to unavailability of dihydrotestosterone level, in 5 patients with 46, XY DSD the etiological diagnosis could not be made. The various aetiology of DSD are shown in Table I. Congenital adrenal hyperplasia was the commonest disorder which was diagnosed in 24 patients (35.8%). Twelve patients with 46, XX DSD had salt wasting CAH with earlier presentation just after birth and 6 patients had simple virilizing form with comperatively late presentation. Among the 46,XY DSD cases, 6 children were diagnosed as undervirilized CAH and all of them had salt wasting form. Table II shows the clinical and laboratory profile of patients with CAH. The most common cause of 46,XY DSD was androgen

Table I

Distribution of the DSD patients according to aetiology (N=67)

Type(N)	Aetiology	n(%)
46,XX DSD (30)	CAH (Salt wasting)	12 (40)
	CAH (Simple virilizing)	6(20)
	Adrenal tumor	5(16.7)
	Partial trisomy of chromosome 9q	5(16.7)
	Mayer-Rokitansky- Kuster Hauser syndrome	2(6.6)
46, XY DSD (22)	Androgen biosynthetic defect	8 (36.4)
	Undervirilized CAH	6(27.3)
	Androgen insensitivity syndrome	2 (9.1)
	Unclassified	6(27.4)
Sex chromosome DSD (13)	Turner syndrome (45,X0)	9 (69.2)
	Mixed Gonadal dysgenesis	2 (15.4)
	46,X inv (Y)	1 (7.7)
	46,iso (Xq)Y	1 (7.7)
Ovotesticular DSD (2)		

Table II

Clinical and laboratory profile of patients with CAH (n=24)

Type of CAH	Salt wasting	Simple virilizing	P-value
Number of patients	18	6	
Median age at with range (months)	1.5 (0.5-90)	90 (36-114)	0.063
Clinical presentation	Vomiting, dehydration, genital ambiguity, FTT	Genital ambiguity	
Median 17OHP (ng/ml)with range	12 (0.09-46)	4.08(2.56-15.57)	0.077
Karytyping 46, XX	12	6	
Karyotyping 46, XY (Undervirilized)	5		

biosynthetic defect followed by undervirilized CAH and androgen insensitivity syndrome. In this study 2 patients were diagnosed as androgen insensitivity syndrome. Both of them presented at early age with phenotypically female genitalia with presence of palpable gonads in both labioscrotal folds (Table III).We found 5 cases of partial trisomy of chromosome 9q and 2 cases of Mayer-Rokitansky- Kuster Hauser syndrome among the 46XX DSD patients. The presentation was different in those having partial trisomy of chromosome 9q and all of them were reared as female. Radiological examination in two patients with DSD revealed agenesis of Mullerian structures and were diagnosed as Mayer-Rokitansky- Kuster Hauser syndrome. Both of them were reared as female. Among the sex chromosome DSD, we found 9 cases of Turner syndrome and 2 cases of mixed gonadal dysgenesis. 45, X/ 46, XY gonadal dysgenesis is known as mixed gonadal dysgenesis. Few rare sex chromosomal DSD are also diagnosed. Two patients were diagnosed as ovotesticular DSD. Both having karyotype 46 XY. One was reared as male and another one was reared as female. Table IV shows the clinical and laboratory profile of 2 patients with ovotesticular DSD.

Table III

Clinical profile of 2 patients with androgen insensitivity syndrome

Age at 1st Endocrine OPD visit	Positive family history	Reared as (at1st Endocrine OPD visit)	Clinical presentation
18 days	Nil	Male	Micropenis, bifid scrotum, bilateral palpable gonad present, no vaginal orifice
4 months	Family history of consanguinity present	Female	Features of Down syndrome with micropenis, bifid scrotum, bilateral palpable gonad, vaginal orifice present

Table IV

Clinical and laboratory profile of 2 patients with ovotesticular DSD

Age at 1st Endocrine OPD visit (month)	Clinical presentation	Sex of rearing at 1st visit to endocrine OPD	Right Gonad	Left Gonad	Karyotype
4	Small phallus, both gonads palpable, labioscrotal fusion	Male	Both ovary and testis	Both ovary and testis	46XY
3.5	Enlarged phallus, no palpable gonad, separate urethral and vaginal orifice	Female	Ovary	Ovotestis	46XY

Discussion:

In this study 46, XX DSD was more common than 46, XY DSD, which is consistent to the previous studies.[19,20] but differs from several case series.[21-23] Median age at first consultation in Paediatric endocrine out patient department (OPD) was 36 months with the range of 0.2-192 months. In previous studies children with DSD presented even earlier.[20-23] This is expected because majority of those presented early had salt wasting variety of CAH. In our study majority of the DSD cases had congenital adrenal hyperplasia and this result was consistent with the previous case series.[24-27] Worldwide the most common cause of DSD is CAH. Routine new-born screening is done abroad to diagnose this disorder at birth by estimating the level of 17-hydroxy progesterone.[28] New-born screening is not done routinely in India and Bangladesh. As a result CAH cases are diagnosed late when they present with salt wasting crisis and/or virilization.[1] Twenty four patients in this study had salt wasting CAH, which is a life-threatening condition. We should always consider the possibility of CAH in a child who presents with vomiting and failure to thrive especially in our setting where newborn screening is not done routinely. Simple virilizing variety of CAH was diagnosed in 6 patients with 46XX, DSD having comperatively late presentation than the salt wasting variety. The 17OHP level was comparatively high in salt wasting variety. These results were consistent with the previous study done in Bangladesh.[21]

Among 30 patients with 46,XX DSD, only 4 patients were reared as male. In a male-dominated society parental choice for rearing as a male significantly influence the sex of rearing. Moreover gender identity and the role of these patients as male role also strengthened the hypothesis that as a result of prenatal exposure to androgens there is masculinization of their brain.[29] Six patients out of 22 children with 46, XY DSD were reared as female. Among them 2 had androgen insensitivity syndrome with phenotypically female genitalia having testis bilaterally palpable in labioscrotal folds. Other four children were unclassified and were reared as female as per parental wish.

In this study 5 patients had 46, XX DSD due to adrenal tumors (4 patients with adrenal adenoma and 1 with adrenocortical carcinoma). Adrenocortical tumors are very rare (<0.2% of pediatric malignancies) and produce excess androgen and glucocorticoid having

manifestations of hypercortisolism (Cushing syndrome).[30] In this study, all of the children with adrenal tumor had presentations like Cushing syndrome. Similar number of children with 46,XX DSD had a rare finding on karyotyping-partial trisomy of chromosome 9q giving idea of an emerging cause of 46, XX DSD. It was proven that recurrent distal 9p microdeletion syndrome may present with atypical genitalia and affected male child with mosaic Trisomy 9 can present with micropenis, hypospadias and undescended testis.[31,32] But we did not get any case report of partial trisomy of chromosome 9q presenting with atypical genitalia.

Among the 46,XY DSD cases majority hadandrogen biosynthetic defect (36.3%). The percentage of androgen biosynthetic defect was similar in the previous study of India.[8] We diagnosed only 2 cases with androgen insensitivity syndrome. Both of them presented at early age with phenotypically female genitalia with presence of palpable gonads in both labioscrotal folds. One was reared as female and another one was reared as male at the time of hospital visit. This result differs from the previous two studies of Bangladesh where the percentage of androgen insensitivity syndrome was higher and it was considered the prevalent cause of 46, XY DSD.[8,20]

Undervirilized CAH was another important cause of 46, XY DSD. All of them presented with salt wasting crisis, a life-threatening condition. We should always consider the possibility of CAH if a child presents with vomiting and failure to thrive especially in countries where routine newborn screening is not done.[8]

Due to unavailability of dihydrotestosterone level, the etiological diagnosis could not be made in 5 patients with 46, XY DSD. It is known that even with appropriate approach, in 30-50% of patients with 46, XY DSD a specific molecular diagnosis is possible.[33]

Among the sex chromosome DSD, we found 9 (13.4%) cases of Turner syndrome and 2 cases of mixed gonadal dysgenesis. Few rare sex chromosomal DSD are also diagnosed. Turner syndrome (TS) is a sex chromosomal abnormality affecting approximately 1 in 2,500 to 1 in 3,000 live female births which corresponds to 1.5 million women per year.[34] In a previous study of Bangladesh the Tuner Syndrome was 4.83% of all suspected cases.[35]

Two patients of mixed gonadal dysgenesis (MGD) presented with primary amenorrhoea and none of them had manifestations of TS. This is in contrast to the study from Mexico in which 10 out of 16 patients with MGD had clinical features of Turner syndrome.[36] Both of them were reared as female having 45,X/46,XY karyotype which is consistent with the published literature.[8]

In this study, we could diagnose 2 patients with ovotesticular DSD both having karyotype 46, XY. In most cases 46,XX was the most common karyotype while only 7% had 46,XY karyotype in a previous study.[37]

Conclusion:

Congenital adrenal hyperplasia is the most common cause of DSD. Majority of 46 XY, DSD is due to androgen bio synthetic defect while CAH is the most common cause of 46XX, DSD. Rare chromosomal disorders are also found among DSD cases. Multicenter prospective study with opportunity of genetic diagnosis is required to confirm the aetiology of DSD cases.

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