Original Article

Clinical, Etiological and Laboratory Profile of Children with Disorders of Sexual Development (DSD)-Experience from a Tertiary Pediatric Endocrine Unit in Western India

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ABSTRACT

Objectives: To present the clinical profile, diagnostic work-up, and management of children with Disorders of Sexual Development (DSD). **Materials and Methods:** A retrospective study from a tertiary pediatric endocrine unit of western India. We included 39 patients who presented over a period of 9 years from June 2009 to June 2018. **Results:** Nineteen patients (48.7%) were diagnosed with 46 XY DSD, 16 (41%) with 46 XX DSD, and 4 (10.3%) with sex chromosomal DSD. Out of 46 XY DSD, androgen insensitivity was observed in 8 (42.1%) patients, 5 alpha-reductase deficiency in 5 (26.3%), gonadal dysgenesis in 3 (15.8%), ovotesticular DSD in 2 (10.5%) and 17 beta-hydroxylase (17β-HSD3) deficiency in 1 (5.3%). Congenital adrenal hyperplasia was the most common cause in 46 XX DSD observed in 11 (68.75%) out of 16 patients, ovotesticular DSD was seen in 4 (25%) patients and testicular DSD in 1 (6.25%) patient. In sex chromosomal DSD 3 (75%) patients had mixed gonadal dysgenesis and 1 (25%) had ovotesticular DSD out of a total of 4 patients. At presentation gender of rearing was assigned as male in 16 (41%) patients, female in 20 (51.3%) patients, and no gender was assigned in 3 (7.7%). The gender of rearing was changed after diagnosis in 6 (16.7%) children. **Conclusion:** CAH was the most common etiology of 46 XX DSD whereas androgen insensitivity among 46 XY DSD. Assigning the sex of rearing should not be hurried and should be done only after diagnosis and parental counseling. A multidisciplinary and systematic approach is required for children with DSD.

Keywords: Androgen insensitivity syndrome, congenital adrenal hyperplasia, disorders of sex development

Introduction

Disorders of sex development (DSD) are defined as conditions in which the development of chromosomal, gonadal, or anatomic sex is atypical.[1] This happens either due to a defect in gonad formation or function.[2] DSD can present at any time in life. However, they usually present in the newborn period or adolescence.[3] The diagnosis is often delayed in India due to the social stigma and lack of neonatal care in many parts of the country.[4] The incidence of DSD is about 1:4500 to 1:5000 live births.[5] DSD is not only a social emergency with regards to gender assignment of the child; it can also be a medical emergency when there is associated adrenal insufficiency. It is challenging in terms of making a diagnosis and proper gender assignment. Hence the management of children with DSD is a team approach consisting of a pediatrician, pediatric endocrinologist, neonatologist, pediatric surgeon, radiologist, pathologist, psychologist, and social worker.

In this paper, we present a tertiary level unit experience from western India with regards to the clinical profile, diagnostic work-up, and management of children with DSD.

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Methodology

A retrospective study was conducted at a tertiary pediatric endocrine unit from western India. The study population was children with DSD diagnosed and managed over a period of 9 years (June 2009 to June 2018). Detailed clinical data including age, sex assigned before the presentation, birth weight, and clinical history including antenatal, family, and past history were noted from the records. The examination included detailed genital anatomy, anthropometry, blood pressure, syndromic features, and systemic examination. The genital examination included the presence, number, position and size of the palpable gonads, number of openings and location, size of the genital tubercle, labio-scrotal folds, and hyperpigmentation if any. We included patients with overt genital ambiguity, apparent male genitalia with bilateral impalpable testes, isolated perineal hypospadias, apparent female genitalia with clitoromegaly, posterior labial fusion, and inguinal/labial mass and family history of DSD.[1]

All children with DSD had karyotype with a minimum of 20 metaphases analyzed. Laboratory workup included complete blood count, serum electrolytes, renal function test, and blood gas analysis in all the children. The hormonal analysis was guided by the clinical features. In 46 XX DSD, serum cortisol (8 AM), 17-hydroxy-progesterone, LH, FSH, estradiol, and testosterone (T) were done as baseline parameters. Congenital adrenal hyperplasia (CAH) due to 21-Hydroxylase Deficiency was diagnosed when 17-OHP was >1000 ng/dL with no hypertension at the time of presentation.[6] However, when 17-OHP was >1000 ng/dL along with hypertension it was diagnosed as 11 beta hydroxylase (11βHSD) deficiency.[6]

Children with 46XY DSD underwent hCG stimulation test with 500-1500 units of human chorionic gonadotropin on 3 consecutive days. Blood samples were taken before the 1st injection (baseline) and 24 hours after the last injection (stimulated) for serum T, androstenedione, and dihydrotestosterone (DHT). Increment in T levels by three folds or more was inferred as an adequate response. Testosterone to DHT ratio of >20 post-stimulation was suggestive of 5α-reductase type-2 deficiency.[7] The presence of low T with high LH & FSH with testosterone to androstenedione ratio <0.8 in response to hCG stimulation test was considered suggestive of 17β-hydroxysteroid dehydrogenase type-3 (17β-HSD3) deficiency which was later confirmed by genetic analysis. The presence of atypical genitals with high basal LH and T from the 1st few weeks to 10 months of age was suggestive of Partial Androgen Insensitivity Syndrome (PAIS).

High LH, FSH with low/normal testosterone was indicative of gonadal dysgenesis. LH, FSH, and T were assessed using chemiluminescent micro particle immunoassay (CMIA) (Abbott ARCHITECT; Abbott Diagnostics). The detection limit for LH, FSH, T and estradiol (E2) were 0.07 mIU/ml, 0.05 mIU/ml, 0.07 ng/ml and 10 pg/ml respectively. 17-OHP was measured by Chemiluminescence Immuno Assay (CLIA) with a lower limit of 3 ng/dL.

Ultrasound abdomen and pelvis and/or MRI pelvis for Mullerian structure and gonads were performed as clinically indicated. Surgical laparoscopy or exploratory laparotomy was performed on a case-to-case basis. Diagnosis of ovotesticular DSD or gonadal dysgenesis was made after histopathological examination of the gonads. Sex assignment was done after discussion with the parents regarding the child's gender identity, sex of rearing, and fertility prospects. The study was approved by the institutional ethical committee.

Results

Among 39 children, 16 (41%) children had XX DSD and 19 (48.7%) had XY DSD. Chromosomal DSD was identified in 4 (10.3%) children. The various etiologies are as shown in Figure 1.

The age at presentation ranged from neonatal age to 16 yrs. The age at presentation was infancy in 34 (87.2%) whereas 3 (7.7%) presented in childhood and 2 (5.1%) in adolescence. Atypical genitalia were noticed in 30 babies (76.9%) at the time of birth.

At the time of presentation, gender was not assigned by parents or doctors in only 3 (7.7%) children, 16 (41%) were being reared as males and 21 (51.3%) as females. Consanguinity was observed in 15 (38.5%) patients. History of the previous sibling with DSD was found in 3 (7.7%) and previous sibling death was recorded in 2 (5.1%) respectively.

The detailed clinical, radiological and treatment profile is shown in Table 1 and Figure 1

46 XX DSD: A total of 16 children were diagnosed with 46 XX DSD. Among them, CAH was diagnosed in 11 (68.75%). Ovotesticular DSD was seen in 4 (25%), and testicular DSD in 1 (6.25%). Of the 11 children with CAH- 10 were having 21 alpha-hydroxylase (21-αHSD) deficiency (9-salt-wasting CAH and 2-simple virilizing CAH) and 1 child had 11 beta-hydroxylase (11βHSD) deficiency. All children with 21-αHSD deficiency CAH were noticed to have atypical genitalia at birth and diagnosed in the neonatal period. Among them, 1 child was assigned male gender before the assessment and after diagnosis, gender of rearing was changed to female. One with 11βHS deficiency being reared as a female was diagnosed at 15 months of age. The child had clitoromegaly and was admitted with an episode of lower respiratory tract infection. She also had ketotic hypoglycemia with

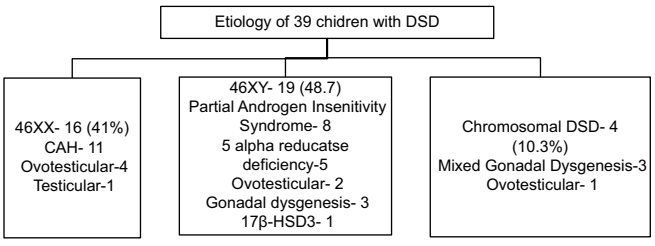

Figure 1: Overview of different etiology of DSD observed

Table 1: Profile of Children With DSD

Parameter	46XX DSD (*n*=16)	46XY DSD (*n*=19)	Sex chromosomal DSD (*n*=4)	Total (*n*=39)
Infancy	13	17	3	33
Childhood	2	1	1	4
Puberty	1	1	--	2
Sex assigned at presentation				
Male	3	11	2	16
Female	12	6	2	20
Not assigned	1	2	--	3
Noticed at birth	11	16	3	30
Consanguinity	3 (18.8%)	9 (47.4%)	2 (50%)	14
H/O sibling with DSD	1	2	--	3
Unexplained death- elder sibling	1	1	--	2
Birth Weight (kg)	2.75±0.4	2.6±0.5	2.9±0.65	2.68±0.5
Phallus	8	19	3	30
Number of opening(s)	One- 3 Two- 13	One- 15 Two- 4	One-3 Two-1	--
Urethral Opening	Base of phallus- 9 Normal- 7	Tip-4 Penile-2 Base Of Phallus-2 Penioscrotal-10 Scrotal-1	Penile-1 Perineal-1 Normal-2	--
Chordee	2	6	1	9
Palpable gonads				
U/L	2	5	1	8
B/L	1	14	1	16
Hyperpigmentation	3	1	--	4
Scrotum	Poorly formed in 2 children	Poorly developed- 6 Bifid- 7 Well formed- 6	Bifid-1 Poor-1 Absent- 1	--
Mullerian Structures Visualized	14	2	3	19
Surgical Intervention	Clitoroplasty-6 Hypospadias repair- 1	Mullerian structure removed-2 Gonadectomy-3 Hypospadias repair-4	Gonadectomy Bilateral- 2 Unilateral- 1	--
Medical Intervention	Female-11for CAH Male-4 testosterone	Male-14 testosterone given	Male-1 testosterone given	--
Gender Changed after Diagnosis	1	4	1	6

hypertension. Based on the biochemical profile (hyponatremia, hyperkalemia, elevated testosterone, and 17-OHP) was diagnosed as 11βHSD deficiency. The child was continued to be reared as a female and started on hydrocortisone and fludrocortisone replacement.

Ovotesticular DSD was diagnosed among 4 children. Before the assessment, one child was being reared as male, two as females, and the gender was not assigned in 1. All children presented with atypical genitals. One child presented, whose gender of rearing was not decided, at the age of 1 month with 1.5 cm phallus, penoscrotal hypospadias, right gonad palpable in the inguinal canal, and labio-scrotal folds. USG showed Mullerian structures, right gonad solid with the epididymis, and left gonad was intra-abdominal. The biopsy was suggestive of ovotesticular tissue in the right gonad and testicular tissue in the left gonad.

Another 2-month-old child being reared as a female was having a phallus of 1.6 cm, 2 distinct openings, no palpable gonads, and bifid scrotum. USG was inconclusive hence MRI was performed which showed the presence of a uterus, right undescended testis, and the left gonad was not visualized. Biopsy of both gonads showed ovarian and testicular tissue. The child continued to be reared as a female. A 11-month infant being reared as a female was presented with clitoromegaly, 2 distinct openings, no palpable gonads, and fused labia with rugosity. USG showed the presence of Mullerian structure, right gonads intra-abdominal at the location of the ovary, and left gonad was not visible. Biopsy revealed the presence of ovarian tissue in the right gonad and both ovarian and testicular tissue in the left gonad.

Another 4-year child being reared as a male presented with a phallic structure of 1.9 cm, 2 distinct opening, penoscrotal hypospadias, right palpable gonad in the inguinal canal, and poorly formed scrotum. USG pelvis showed the presence of both Mullerian and Wolffian structures, the right gonad was seen with epididymis in the inguinal canal and the left streak

Table 2: Profile of Children with Ovotesticular DSD

Age	Presentation	Karyotype	Gender assigned at birth	Gender assigned after diagnosis	Right Gonad	Left Gonad
11 months	Atypical genitalia	46 XX	Female	Female	Ovaries	Ovotestis
4 yrs 4 months	Atypical genitalia	46 XX	Male	Male	Testis	Ovotestis
1.5 months	Atypical genitalia	46 XX	Not assigned	Female	Ovotestis	Testis
2 months	Atypical genitalia	46 XX	Male	Female	Ovotestis	Ovotestis
1yr 1 month	Atypical genitalia	46 XY	Male	Male	Ovaries	Testis
9 yrs	Atypical genitalia	46 XY	Female	Female	Ovotestis	Ovaries
9 months	Atypical genitalia	46 XO	Male	Male	Ovaries	Immature testis

gonad was intra-abdominal. The biopsy report was indicative of testis on the right side and ovotestis on the left side. The child was continued to be reared as male after family counseling. Mullerian structures and the left gonad were removed. The details of these children are shown in Table 2.

One child being reared as male presented with breast development at the age of 16 years. He had bilateral palpable gonad measuring 3 ml each in scrotal folds. There was penoscrotal hypospadias with chordee. USG showed no Mullerian structure. The karyotype was 46XX and histopathological examination of the gonadal biopsy showed bilateral atrophic testis. Hence the diagnosis of testicular DSD was made and the child was treated with testosterone replacement therapy and hypospadias repair was done. The child continued to be reared as a male.

46 XY DSD: Out of 19 children, 8 children (42.1%) were diagnosed with androgen insensitivity syndrome (AIS), 5 (26.3%) with 5 alpha-reductase deficiency, 3 (15.8%) with gonadal dysgenesis, 2 (10.5%) with ovotesticular DSD and 1 (5.3%) with 17β-HSD3 deficiency.

Of 8 children with AIS, seven children had hypospadias, bilateral gonads were palpable in the scrotum, except in one child who had unilateral palpable gonad. The scrotum was well-formed in 2, bifid in 4 and labio-scrotal folds were seen in 2. Immediately after birth 5 children were assigned male gender whereas 3 were assigned female gender. After diagnosis, counseling, and discussion with parents, the remaining three children were also reared as males. Hypospadias repair was done in 3 children and was planned in the rest. The diagnosis was AIS was based on clinical features, 46 XY karyotype, and HCG stimulation test ruling out 5 alpha-reductase deficiency and high LH and testosterone levels (during infancy). We could not check androgen receptor sensitivity as this was not available in India. Also, a genetic diagnosis could not be made due to financial constraints.

Five children were diagnosed with 5-alpha reductase deficiency. Four were assigned the male gender at birth. Elder sibling history of DSD was positive in 2 children. Bilateral gonads were palpable in 4 children and unilateral in 1. Hypospadias was noticed in 4 patients. The scrotum was underdeveloped in 3 and well-formed in 2. After diagnosis, parental counseling, and discussion the gender of rearing was assigned as male in all 4 children. The surgical repair was performed in all children with hypospadias.

Among 3 children with gonadal dysgenesis, 1 child was being reared as female and no gender was assigned to the other 2 children at presentation. One of the patients had a family history of infertility. After diagnosis and counseling 1 was reared as female and 2 as males.

Ovotesticular DSD was observed in 2 children. One child was being reared as male and one as female at the time of presentation. Hypospadias and unilateral palpable gonad were noticed in both the children. The uterus was seen in both the children on USG examination. The gender of rearing was maintained as was at the presentation.

One child was diagnosed to have partial 17 beta HSD based on hCG stimulation test which showed testosterone of 0.04 ng/ml (Ref- 0.75-4 ng/ml), dihydrotestosterone 42.8 pg/ml (<98 pg/ml) and androstenedione <0.3 ng/ml (0.1-0.3 ng/dl) at baseline and on stimulation testosterone was 4.2 ng/ml, dihydrotestosterone was 92.99 pg/ml and androstenedione was 6.9 ng/ml. Testosterone: androstenedione ratio was 0.6. This shows that the rise in testosterone is disproportionate to androstenedione. However, definitive diagnosis requires a genetic study as this could be partial 17B HSD deficiency. The child was being reared as a male. The gonads were located in the bilateral inguinal canal with a small phallus and no hypospadias. The child was continued to be reared as male after diagnosis and counseling.

Sex Chromosomal DSD: Among the 4 children diagnosed with sex chromosomal DSD, 3 had mixed gonadal dysgenesis and 1 had ovotesticular DSD. Out of 3 children with MGD, 2 had parental consanguinity. A 9-month-old infant, being reared as a male, had a 2 cm phallic structure with perennial hypospadias, under-developed scrotum, and a single left gonad palpable. USG examination showed no gonad on the right side whereas the left gonad was in the scrotal sac and Mullerian structures were present. Karyotype was 45 X with SRY gene-positive, high testosterone (116 ng/dL), and undetectable estradiol. A diagnosis of ovotesticular DSD was established after biopsy; Mullerian structures were removed and the child was decided to be raised as a male.

Another 5-month-old child had a 1.7 cm phallic structure with no gonads palpable and urethral opening at the tip of the phallus. The child was being reared as a female. USG pelvis revealed intraabdominal gonads with the presence of Mullerian

structure. Biochemistry showed elevated androgens. The karyotype was 45X/46XY with biopsy suggestive of gonadal dysgenesis side. Hence with the diagnosis of mixed gonadal dysgenesis, the girl was decided to be reared as a female. Due to the risk of malignancy bilateral gonadectomy was performed.

A 6-month-old infant being reared as male presented with 2 cm phallus, penoscrotal hypospadias, single opening, and bilateral palpable gonads in the bifid scrotum. USG suggested left gonad as the testis and the right gonad was not well developed. The karyotype was 45XO[14]/47XXY[3]/46XY[3]. Biopsy showed one side immature testicular tissue and another side testicular tissue. On discussion with the parents, it was decided to raise the child as a male.

Another 3-month-old child being reared as a female had 2 cm phallus, 2 distinct urethral, and vaginal opening. Ultrasound examination showed bilateral intra-abdominal gonads suggestive of ovaries with Mullerian structures present. The karyotype was 45X/46 XY with the left gonad being streak testis and right gonad as normal testicular tissue. Parents decide to raise the child as a female and hence bilateral gonadectomy was performed due to the high risk of malignancy of abdominal gonads in the future.

The details of children with ovotesticular DSD and gonadal dysgenesis are shown in Tables 2 and 3 respectively.

Discussion

In the present study, most children with DSD presented in infancy (33/39, 84.6%) and the majority of atypical genitalia was noticed at birth (30/39, 76.9%). Our observations are similar to other studies from India.[8-11]

The most common etiology of DSD was CAH in our study comprising of nearly 1/4th of the study population. These observations are consistent with those from other reports from our country[8-12] making it the most common cause of DSD. In some developed countries, there exists a neonatal screening program for CAH. However, there is no national program for newborn screening for CAH in India, and males can be very easily missed as the genitals look normal at birth. Hence careful genital examination at birth and suspicion of CAH in a neonate presenting with the salt-wasting crisis is paramount in making an early diagnosis. Among CAH patients 90% had CYP21A defect and were noticed to have virilization in the newborn period. Only 1 child with CAH had 11 Beta HSD. These children must be diagnosed early so that treatment can be started early to prevent severe virilization, hirsutism, short stature, and premature pubarche.[12] The gender of rearing in our series was not changed in any of these patients. One child was being reared as male and parents continued the same. Such situations can be avoided by early diagnosis and counseling. No hurry should be done to assign gender.

46 XY (48.7%) was the commonest type of DSD in our cohort, which is in line with other reports.[9,10,13] Various researchers have observed androgen insensitivity syndrome as the most common entity in this group which is similar to ours.[9,13] The most common cause in the 46 XY group is reported to be of 5 alpha-reductase deficiency by Misgar *et al*. from North India. The higher incidence was ascertained by authors to high rates of consanguinity and DHT assessment.

We however found this in only about 1/4th of our patient with 46XY DSD despite having high consanguinity in our cohort. On discussion with parents, it was decided to change the gender of rearing among 3 patients with PAIS who were assigned the female gender before the presentation. A similar change in male gender from the female was observed in 1 patient with 5 alpha-reductase deficiency with almost no phallic development. This reinforces the finding of bias towards the male gender of rearing in our setting too.[9,12,13] Gonadectomy was performed in 3 children who had intra-abdominal gonads with Y chromosomes, due to a high risk of malignancy.[14] It is therefore important to check for the presence of Y material which may not be picked up on routine karyotype.

In patients with ovotesticular DSD atypical genitalia had a varied presentation. There was an equal distribution of 46XX & 46XY karyotype which is different when compared with previous reports where 72% and 96% of patients had a karyotype of 46XX.[13,15] The gender of rearing was changed in one child out of 9 in our cohort. No preponderance of testis or ovaries was observed on either side as reported in another report from North India.[13]

In the gonadal dysgenesis group, the most common karyotype was 46XY which is in concurrence with published literature.[16] We had 14 patients with turner syndrome during this period we have not included them in our study as they do not present with atypical genitalia. The gender of rearing was

Table 3: Profile of Children with Gonadal Dysgenesis

Age	Presentation	Karyotype	Gender at Presentation	Gender after diagnosis	Right Gonad	Left Gonad
1yr 4 months	Atypical Genitalia	46XY	Female	Female	Dysgenic Testis	Dysgenic Testis
3 days	Atypical Genitalia	46XY	Not Assigned	Male	Dysgenic Testis	Dysgenic Testis
3 days	Atypical Genitalia	46XY	Not assigned	Male	Dysgenic Testis	Dysgenic Testis
5 months	Clitoromegaly	MOSAIC 45X/46 XY	Female	Female	Streak- Testis	Testis
9 months	Atypical Genitalia	45XO[14]/47XXY[3]/46XY[3]	Male	Male	Immature Testis	Testis
1y 1 month	Atypical Genitalia	45, X/46XY	Female	Female	Immature Testis	Atrophic Gonad

reversed in 6 children. Such difficult decisions may only be taken after discussion with the family, androgen exposure to the developing brain, internal anatomy, and functionality of genitalia. Literature reports a high rate of subjective gender dissatisfaction among patients with DSD.[17,18]

The strength of our study is that we had a complete clinical, biochemical, radiological, and histopathological workup of these children. The limitations are the retrospective nature of our study. We do not have a genetic diagnosis in all cases and Anti Mullerian Hormone (AMH) was not assessed due to cost issue. Also, the sample size is modest as it is from a single center.

Conclusion

The most common cause of DSD is CAH in our series. 46XY DSD was more common than 46 XX DSD. The largest group was PAIS among 46XY DSD. Sex of rearing should not be done in a hurry. A multidisciplinary and systematic approach is required for the management of children with DSD.

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Conflicts of interest

There are no conflicts of interest.

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