Clinical Brief

Pediatric Disorders of Sex Development

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ABSTRACT

The management of disorders of sexual differentiation (DSD) involves a multidisciplinary approach. The main aim of analysis was to study the phenotype-karyotype correlation in North Indian children with DSD. The records of pediatric DSD were retrieved and characteristics noted. Of total of 58 children, 43 (74.1%) and 10 (17.2%) were raised as males and females respectively. The mean age at presentation was 31.3±9 months. The karyotype was 46XY in 45 (77.6%) and 46XX in 12 (20.7%). CAH was commonest cause of DSD (36.2%), followed by gonadal dysgenesis. Of the 15 patients of 46 XY CAH, there were 5 with 17-α hydroxylase deficiency, 2 with 3-β HSD deficiency and one case of lipoid adrenal hyperplasia. There was an excess of genetic males, possibly due to prevalent socio-cultural factors and gender bias favoring males. There is a need to improve the diagnostic facilities and incorporate a team approach in management of DSD. **[Indian J Pediatr 2009; 76 (9) : 956-958]** *E-mail: inupan@yahoo. com.*

Key words : *Ambiguous genitalia; Children; Hypospadias; Karyotype; Phenotype*

Disorders of sex development (DSD) include conditions wherein chromosomal, gonadal, or anatomical sex is atypical. Management includes a team oriented approach and is directed towards medical surgical and psychological aspects.[1-3] However, in India many patients avoid interactions with healthcare providers. There is paucity of data pertaining to diagnosis and management of DSD from developing nations.

MATERIALS AND METHODS

Data of children with DSD registered in the period between January 2003 to December 2007 was analyzed. Essential data related to diagnosis and management was recorded in a predesigned proforma. The karyotypes were obtained from the cytogenetic laboratory. Based on their karyotype, gonadal histology and external anatomy, the patients were classified into 3 groups-46XX DSD, 46XY DSD and ovotesticular DSD-in accordance with criteria enlisted by Lee *et al.*[4]

Percentage, mean and range were used to describe continuous and categorical variables, respectively. Statistical analysis was performed using descriptive statistics and Chi-square test for the categorical variables (SPSS version 13). The conduct of the study was approved by the Ethics Committee of the institute.

Abbreviations

ABS	:	Antley-Bixler syndrome
CAH	:	Congenital adrenal hyperplasia
DSD	:	Disorders of sexual differentiation
GD	:	gonadal dysgenesis
HSD	:	hydroxysteroid dehydrogenase
MHKR S	:	Mayer Hauser Kuster and Rokitansky syndrome
PAIS	:	partial androgen insensitivity syndrome
POR	:	cytochrome P450 oxidoreductase
5α RD	:	5 α reductase deficiency

RESULTS

The mean age at presentation of 58 children with DSD was 31.3±9 months (range: 1 day to 144 months). There were 21 (36.2%) patients who presented in infancy of whom 7(12%) presented in the neonatal age group. The majority of the patients (87.9%) presented before 5 years of age. The distribution and characteristics of the patients is depicted in table 1.

Caretakers had reared 43 (74.1%) patients as males and 10 (17.2%) as females. The inability to determine gender in 5 (8.6%) neonates (age: 2-30 days) prompted a referral to our institute.

Genitalia were recorded as ambiguous in 28 (46XY karyotype was seen in 18) patients. The phallic length

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(mean 15.0mm) was recorded in 25 patients and the number of orifices was documented in 22. Thirteen had a single orifice and 9 had 2. Penoscrotal hypospadias and bifid scrotum were observed in 17 (29.3%) and 2 (3.4%) patients respectively. Cryptorchidism and perineal hypospadias were observed in 1 patient each. 1 or 2 gonads were palpable in 7 (12.1%) and 32 (55.2%) patients respectively.

The karyotype was 46XY in 45 (77.6%) and 46XX in 12 (20.7%) patients whilst a solitary case had isochromosome Xp. Out of the 43 patients reared as males, 39 (90.7%) were genetic males and 4 (10.3%) were genetic females. No case of mosaicism was detected. Of the 10 patients reared as females 70% were genetic females. In 3 of the 5 neonates referred for gender assignment, the karyotype was 46XY. In genetic males, 1 or both gonads were palpable in 7 (15.6%) and 24 (53.3%) patients respectively. A solitary patient with 46XX karyotype had 2 palpable gonads. 46XY karyotype was significantly associated with gonadal palpability (p=0.001, r=0.441). A 46XY karyotype was found in 88% of the patients with penoscrotal hypospadias. The patient with perineal hypospadias had 46XY karyotype. All 3 patients with isolated clitoral hypertrophy without labial fusion were genetic females.

Ultrasonographic evidence of Mullerian structures was observed in 2 and 9 patients with a 46XY and 46XX karyotype respectively (p<0.001, r=0.49). The uterus was normal in 7 and reported as small or hypoplastic in 4 patients. The Fallopian tubes were recorded to be normal in 5 and hypoplastic/ nonvisualised in 2 of these patients.

DISCUSSION

DSDs present at a variable age. In our study, the majority (87.9%) presented before the age of 5 years with a mean age of 31.3±9 months. Similar results have been reported by investigators from Mumbai and Trivandrum.[5,6] In contrast, Ammini *et al* documented that 70% children presented after 5 years of age.[7] The varied age at presentation, in different geographic areas, could be due to socioeconomic, cultural and educational factors.

In our study cohort, a higher number of patients (74.1%) were being reared as males, which is in concordance with the results reported by other Indian investigators.[5] A general preference for male gender in the Indian society at large which could explain the desire to rear majority of the patients as males.

The majority (77.6%) of the patients in our series were genetic males. Joshi *et al* and Gollu *et al* showed that 46XY DSD constituted 52.3% and 31.7% of the cases respectively.[5,8] Rajendran *et al* reported 46XY DSD in 40% of the cases.[6] Similar results were reported from Thailand and other parts of India.[9,10] Arcari *et al* documented 46XY (dysgenetic and non-dysgenetic) DSD in 34.7% of the patients.[11]

No case of mosaicism was detected. The policy of screening only 20 metaphases may not be sufficient to detect of low grade (<5%) mosaicism. Palpability of gonads and evidence of Mullerian structures were

Table 1. Distribution of Pediatric Patients with DSD in Present Study (n=58)

Class	Diagnosis	Number of patients	Mean age at presentation (months)	Palpable gonads	Evidence of Mullerian structures
46XX DSD	CAH	8	19.9	-	8
	GD	2	48.1	1	1
	MKHR S	1	18.0	-	-
	Iso Xp	1	30.0	-	-
46XY DSD					
	CAH	15	45.7	9	-
	GD	11	22.9	8	1
	Yp deletion	4	38.0	3	-
	Long Y	3	36.0	1	-
	WT1	2	36.0	1	-
	Swyers S	1	48.0	-	1
	5 α-RD	2	9.0	2	-
	PAIS	1	11.0	1	-
	Unclassified	6	34.2	6	-
Ovotesticular DSD	46XX Ovotesticular DSD	1	0.4	-	-

Note: (CAH: Congenital adrenal hyperplasia, GD: gonadal dysgenesis, 5α-RD: 5α-reductase deficiency, PAIS: partial androgen insensitivity syndrome, MHKR S: Mayer Hauser Kuster and Rokitansky syndrome, WT1: WT1 mutation).
(46XY DSD with CAH: 17-α hydroxylase deficiency-5, 3-β hydroxysteroid dehydrogenase-2, Lipoid adrenal hyperplasia-1, suspected cytochrome P450 oxidoreductase (POR) deficiency-2, unclassified-5)

significantly associated with 46XY and 46XX karyotype, respectively. Arcari *et al* showed that palpable gonads predicted dysgenetic testis in 46XY patients with high efficiency.[11]

In the present series, there were 2 patients with 5α-reductase deficiency and 1 patient with androgen insensitivity. In contrast, Joshi *et al* documented 11.9% patients with 5α-reductase deficiency and 28% patients with androgen insensitivity syndrome in their series.[5] The differences could be attributed to the evaluation of the cases and diagnostic facilities available. The long Y chromosome in 3 patients is possibly due to Y chromosome heteromorphism. Ovotesticular DSD was reported in 5.7%, 4.8% and 14.3% of the cases by Arcari *et al*, Nimkarn *et al* and Rajendran *et al* respectively which was in contrast to a solitary patient in our cases.[6,10,11]

CAH and gonadal dysgenesis were the commonest etiology for DSD. Most authors across the world have documented similar results.[5,6,9,10,12] We had a higher number (n=15) of 46XY patients diagnosed to have CAH compared to 46XX patients (n=8). In North India caretakers, in view of the prevalent socioeconomic and cultural factors, are more willing for medical care, investigations and follow up of male patients despite financial constraints and guarded outcome. It is likely that babies perceived as females are neglected or even allowed to die without appropriate medical care leading to an abnormally large tilt of the gender ratio towards males. This social evil of biased parenting could explain the difference in the gender distribution of CAH patients in our series. Also, it is likely that some 46XX patients with CAH died before reaching or being referred our institute due to adrenal crisis and/or sepsis or did not reach the hospital.

In India, there is a general neglect, social taboo and lack of awareness regarding DSD. Reaching an etiological diagnosis is often difficult in limited resource settings because of variability of individual cases. Indian parents rear their children as male or female based on the gross appearance of external genitalia. The usual reasons for medical consultation are enlargement of clitoris, absence of testis on one or both sides, hypospadias and gynaecomastia or virilization.

It is essential to have a sound knowledge about DSD to analyze the attitude of parents and to provide adequate counseling. Uniform classification, good cytogenetic facilities and individualized approach with emphasis on integrated team management form mainstay of management of DSD. There is a crying need for prospective long term follow up of these patients to determine their psychosocial, sexuality and identity outcomes.

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