

## STUDY OF THE CLINICAL PROFILE AND AETIOLOGY OF VARIOUS DISORDERS OF SEX DEVELOPMENT PRESENTING TO ENDOCRINE OPD OF A TERTIARY CARE HOSPITAL

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### ABSTRACT

#### BACKGROUND

Disorders of Sex Development (DSD), formerly described as intersex conditions, are a conglomerate of rare disorders defined as discrepancy of chromosomal, gonadal or anatomic sex. There are limited data on the incidence of DSD with an overall incidence of 1:5,500, but varies with population. Congenital adrenal hyperplasia and mixed gonadal dysgenesis are the most common causes of ambiguous genitalia constituting approximately 50% of all cases presenting with genital ambiguity at birth.

The aim of the study is to study the clinical profile and aetiology, mean age of presentation of common aetiologies, initial sex of rearing based on genital ambiguity and correctness of sex of rearing since birth as compared to genetic karyotype after diagnosis of patients of various disorders of sex development presenting to endocrine OPD of a tertiary care hospital.

#### MATERIALS AND METHODS

We assessed the records of patients who were evaluated for hypogonadism and genital ambiguity between March 2014 to June 2017 in our endocrine department. The patients were classified on the basis of clinical features, hormonal investigations, imaging studies, karyotype and laparoscopy/biopsy studies as indicated.

Design- Cross-sectional study.

#### RESULTS

Distribution of DSD by category were 46, XY DSD (41.6%); 46, XX DSD (27.3%); SCD DSD (30.9%). Distribution of DSD by subtypes were 46, XY DSD; -5 $\alpha$  reductase (37.1%); IHH (20.1%); Kallmann syndrome (14.28%); bilateral anorchia (11%); PAIS (8.5%); CAIS (2.8%); CAH (2.8%); 46, XX DSD-CAH (34.1%); IHH (21.7%); 46, XX OTD (13%); ACC (8.6%); classic CAH (4.3%); SCD DSD-KFS (53.8%); TS (38.4%) and MGD (7.69%). Mean age of presentation of DSD; 5 $\alpha$  reductase (7.5 yrs.), PAIS (14.33 yrs.), CAH (9.3 yrs.), KFS (25 yrs.) and TS (17 yrs.).

#### CONCLUSION

46 XY DSD comprises 41.6% of cases of which 5 $\alpha$  reductase deficiency is the most common aetiology. CAH was the main subtype of 46, XX DSD. KFS was the main subtype of SCD DSD. DSD pose a serious challenge not only in terms of gender role, identity and sex reassignment, but also in terms of fertility issues, social acceptance and risk of gonadal malignancy in certain subtypes.

#### KEYWORDS

Disorders of Sex Development (DSD); 46, XY DSD; 46, XX DSD; SCD DSD.

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#### BACKGROUND

Disorders of Sex Development (DSD) are a heterogenous group of rare conditions. Few studies estimate a rate of 2.2/10,000 case with ambiguous genitalia at birth.<sup>1</sup> DSD, formerly described as intersex conditions are a conglomerate

of chromosomal, gonadal or anatomic sex. The new classification of DSD in three subgroups, sex chromosome DSD (SCD DSD); 46, XX DSD; and 46, XY DSD was proposed by the international consensus group on management of intersex disorders in Chicago in 2005.<sup>2</sup> The DSD consensus statement<sup>3</sup> recognises that these conditions can exert substantial strain on the family; however, there have been relatively few systematic studies of how early interventions and interactions between healthcare providers and the family effect the quality of life of affected persons or their parents.<sup>4,5</sup> Identifying the correct aetiology of genital ambiguity helps the clinician give the best therapy to the patients. We planned to carry out a systemic study to assess the spectrum of clinical presentation and aetiology of various DSD, mean age of presentation of important aetiologies,

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initial sex assignment by parents basing on genital ambiguity and the correctness of sex of rearing since birth compared to genetic karyotype.

**MATERIALS AND METHODS**

All consecutive patients presenting with various degree of genital ambiguity and hypogonadism to Endocrinology OPD of S.C.B. Medical College, Cuttack, from May 2014 to June 2017, were enrolled in the study. A detailed clinical evaluation including history taking was carried out for all patients. The patients were classified on the basis of clinical features, hormonal investigations, imaging studies, karyotype and laparoscopy/biopsy studies as indicated. Written and informed consent was taken from each subject or their parents. Institutional ethical committee clearance was taken.

The data was analysed using standard statistical methods. The graphs and tables were generated using Microsoft Excel 2007 software.

**RESULTS**

A total of 84 patients were evaluated in the study period. Various data were analysed using appropriate statistical methods using Microsoft excel version 2007. Distribution of DSD by category included- 46, XY DSD - 41.6% (N=35); 46, XX DSD - 27.3% (N=23); SCD DSD - 30.9% (N=26) (Figure 1). Distribution of DSD by subtypes; 46, XY DSD; 5 $\alpha$  reductase - 31.1% (N=13); IHH - 20% (N=7); Kallmann syndrome 14.28% (N=5); bilateral anorchia - 11% (N=4); PAIS - 8.5% (N=3); CAIS - 2.8% (N=1); cryptorchidism - 2.8% (N=1); CAH - 2.8% (N=1) (Figure 2a); 46, XX DSD; SV-CAH - 34.1% (N=8); IHH - 21.7% (N=5); 46, XX OTD - 13% (N=3); ACC - 8.6% (N=2); CL-CAH - 4.3% (N=1) (Figure 2b); SCD-DSD; KFS - 53.8% (N=14), TS 38.4% (N=10); MGD - 7.69% (N=2) (Figure 2c). The mean age of presentation of major aetiologies of DSD were 5 $\alpha$  reductase (7.5 yrs.); PAIS (14.33 yrs.); SV-CAH (9.3 yrs.); KFS (25 yrs.); and Turner syndrome (17 yrs.), respectively (Figure 3). Classification of cases by presence or absence of ambiguous genitalia was 46, XY DSD - yes (n=17), no (n=18); SCD DSD - yes (n=2), no (n=24); 46, XX DSD - yes (n=11), no (n=12) (Figure 4). Correctness of sex of rearing since birth as compared to genetic karyotype; 46, XY DSD - yes (n=34), no (n=1); SCD DSD - yes (n=24), no (n=2); 46 XX DSD - yes (n=12), no (n=11) (Figure 5).

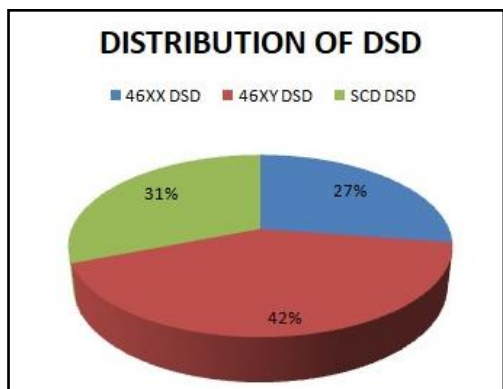


Figure 1. Pie Chart Showing Distribution of DSD

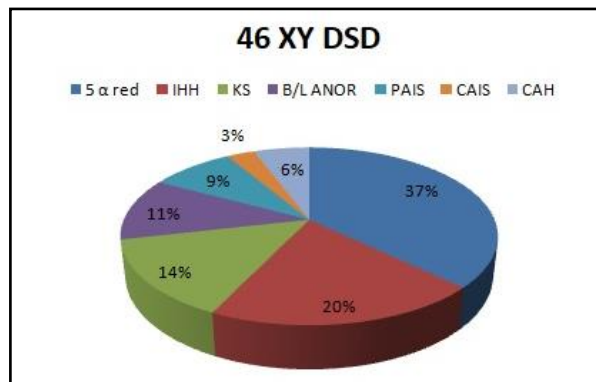


Figure 2a. Pie Chart Showing Various Aetiologies of 46 XY DSD

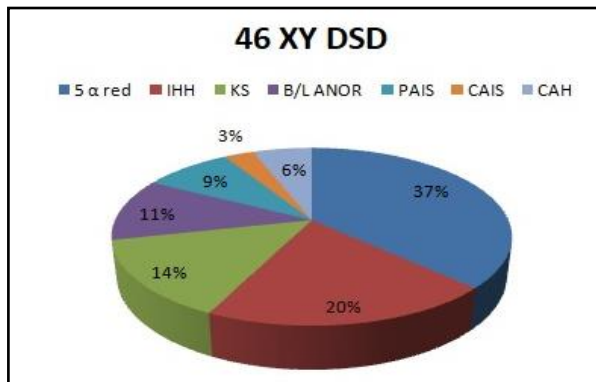


Figure 2b. Pie Chart Showing Various Aetiologies of 46 XX DSD

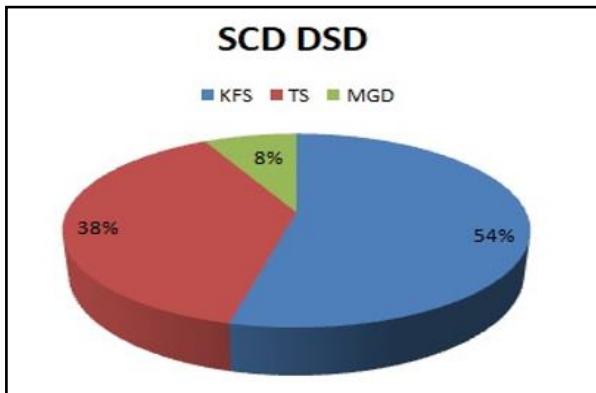


Figure 2c. Pie Chart Showing Various Aetiologies of SCD DSD

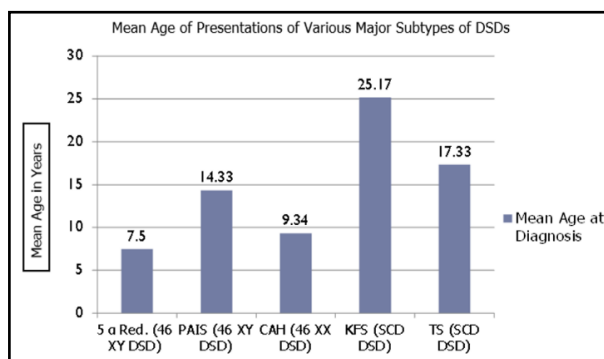
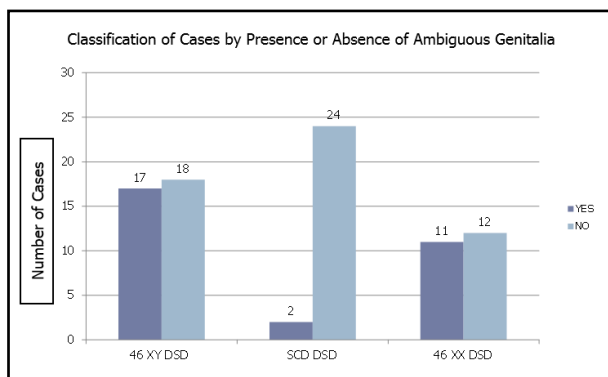
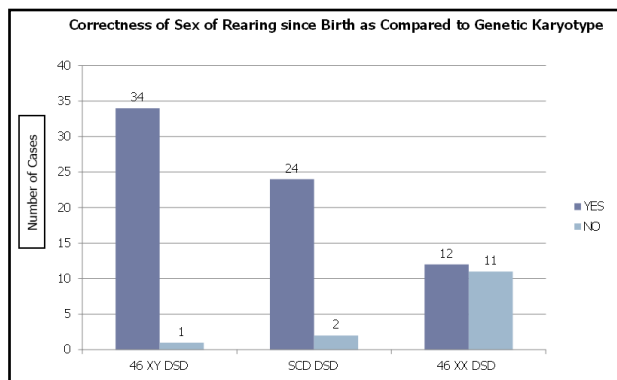


Figure 3. Graph Showing Mean Age of Presentations of Various Major Subtypes of DSD



**Figure 4. Graph Showing Classification of Cases by Presence or Absence of Genital Ambiguity**



**Figure 5. Graph Showing Correctness of Sex of Rearing Since Birth as Compared to Genetic Karyotype**

**DISCUSSION**

The birth of a child with ambiguous genitalia is highly distressing to families. The birth of a newborn with ambiguous genitalia comes as a surprise for both the parents and doctors. Although, some research report that 60% of affected children are diagnosed prenatally, many parents are faced with the situation at birth.<sup>6</sup> There are limited data on the incidence of DSD. It is estimated that the overall incidence of DSD is 1:5500.<sup>7,8</sup> Congenital Adrenal Hyperplasia (CAH) and Mixed Gonadal Dysgenesis (MGD) are the most common causes of ambiguous genitalia constituting approximately over 50% of all cases of genital ambiguity in the newborn period.<sup>9</sup> The incidence of CAH and MGD worldwide is 1:15,000 and 1:10,000, respectively, but varies considerably in different population.<sup>10,11</sup> In our study, simple virilising CAH in 46 XX patients was most common cause of genital ambiguity, whereas 5 $\alpha$  reductase was the most common aetiology in 46 XY patients. The correctness of sex of rearing after identification of aetiology was 97%, 92% and 52% for 46 XY DSD, SCD DSD and 46 XX DSD respectively in our study.

Optimal care of patients which requires a multidisciplinary team and begins in the newborn period itself. A family history, prenatal history, general physical examination with attention to any associated dysmorphic features and an assessment of the genital anatomy are the first steps towards a correct diagnosis. The diagnostic evaluation of DSD includes hormone measurements, imaging, cytogenetic and molecular studies and in some

cases endoscopic, laparoscopic and gonadal biopsy.<sup>12,13,14,15,16,17,18,19,20,21,22</sup> The genetic evaluation includes karyotype, FISH and more recently specific molecular studies to screen the presence of mutations or gene dosage imbalance. However, current molecular diagnosis is limited by cost, accessibility and quality control. Imaging studies shows the presence or absence of Mullerian/Wolffian structures and can help locate the gonads and identify the presence of associated malformations such as renal abnormalities if any.<sup>23,24</sup> An assessment based on the location of the gonads and presence or absence of Mullerian/Wolffian structures will provide a provisional clinical diagnosis.<sup>15</sup> This information combined with karyotype will provide the basis for more further focused investigation. A gonadal biopsy is required to classify the type of gonadal dysgenesis and ovotesticular DSD to assess gonadal chromosomal mosaicism and to detect the presence of gonadal tumour if any. Hormone measurements should be interpreted in relation to specific assay characteristics and also considering normal values for gestational and chronological age. In some case, serial measurements may be needed. The results of decision making algorithms are available to guide further investigation. Supported by good families for investigation, clinicians can follow an algorithm that in many cases will lead to an aetiological diagnosis, but with the spectrum of findings and diagnosis, no single evaluation protocol can be recommended in all circumstances.<sup>25,26</sup> Chromosomal characteristics, gonadal histology and presence or absence of uterus are taken into consideration in the classification of DSD. The psychological and social implications of gender assignment and those relating to treatment are very important and require a multidisciplinary approach. The current debate on the management of patients in intersexuality and related conditions focuses on four major issues, namely aetiological diagnosis, assignment of gender, indications for and timing of genital surgery, and discussion of medical information to the patient.<sup>27,28,29,30,31,32,34,34,35,36,37,38</sup> Recommendations for sex of rearing especially in infants with genital ambiguity, testicular differentiation disorders and Y chromosome continue to be challenging. Genital masculinisation is a poor indicator of the masculinisation of the brain.<sup>29</sup> Surgical technique of feminisation and masculinisation and their outcomes have also evolved overtime.<sup>37,38</sup> However, functional outcome should be taken into consideration rather than a strictly cosmetic appearance.

**CONCLUSION**

DSD with ambiguous genitalia is a rare disorder requiring prompt investigation and early gender assignment that is logically based on a sound knowledge of normal sex determination and differentiation. Despite the significant advances that have been achieved, much remains to be clarified in terms of the accurate evaluation and optimal management of patients with DSD. The complexity of the problem requires a multidisciplinary team working together for proper management of patients with DSD. Affected patients and their parents should be provided with full

information to make an appropriate choice for gender assignment. The aims of management in a newborn with DSD should be provision of a stable gender identity, psychological support to the family, potential sexual function and fertility, and affirmative body image. The surgical correction technique and the timing of the operation need to be individualised according to medical conditions, experience of the surgeon and complexity of each case. The general trend is towards early reconstruction with subsequent early and long-term management of the patient. The discussion of evaluation and management of patients with DSD continues. Future studies with further data is essential to suggest enhanced clinical guidelines and recommendations fitting the case of each individual patient.

### Abbreviations

Congenital Adrenal Hyperplasia (CAH), SV - simple virilising, CL - Classical, Mixed Gonadal Dysgenesis (MGD), Isolated Hypogonadotropic Hypogonadism (IHH).

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