Spectrum of Disorders of Sex Development: Our Experience

N. Anil Kumar[1], S. R. Sree Gouri[2], S. Venkata Chaitanya[3], Satish Bezawada[3], Prasad Pulla[3]

ABSTRACT

Introduction: Disorders of Sex Development (DSD) are defined as congenital conditions associated with atypical development of chromosomal, gonadal or anatomical sex. In this study we evaluate our experience with DSD with focus on profile, management and its challenges, and outcome of treatment.

Material and methods: The case notes which include prenatal and maternal history, sex of rearing, genital phenotypic appearance, general physical examination, karyotype, imaging studies of gonads and internal genitalia, laboratory investigations and management (surgery and gender assignment) were reviewed retrospectively for patients diagnosed as DSD between 2010 - 2015 at Sri Venkateswara Institute of Medical Sciences.

Results: Among the 14 patients, 2 patients had 46,XX DSD - congenital adrenal hyperplasia, 10 patients had 46,XY DSD which included a case of bilateral vanishing testis, 2 cases of mixed gonadal dysgenesis, 2 cases of testosterone biosynthesis defects, 3 cases of 5 alpha reductase deficiency and 2 cases of complete androgen insensitivity syndrome and the remaining 2 had sex chromosome DSD which were 46 XX males. Median age of presentation was 9 years ranging from 2 to 23 yrs. Gender reassignment was done in a case of 5 alpha reductase deficiency and in a case of testicular biosynthesis defect(from female to male). Surgical management was required in all cases.

Conclusion: DSD is a rare disorder requiring prompt investigation and early gender assignment logically based on a sound knowledge of normal sex determination and differentiation. Focused education of healthcare personnel, public awareness programs and improvement of diagnostic facilities and personnel through enhanced funding and international collaboration may improve outcome and minimize psychological morbidity.

Keywords: 5 alpha reductase deficiency, Disorders of Sex Development, Gonadal dysgenesis,

INTRODUCTION

The Jost paradigm states that four steps must occur during sexual differentiation: establishment of chromosomal sex at fertilization, formation of undifferentiated gonads, gonadal differentiation into testes or ovaries and development of the internal and external genitalia.[1] Disorders of sex development (DSD) refer to a spectrum of congenital conditions in which there is biological discrepancy between chromosomal, gonadal, and phenotypical sex.[2] Currently the disorders are broadly classified as 46, XX DSD, 46, XY DSD and sex chromosome DSD.[2,3] DSD commonly manifest as ambiguity of the genitalia and has been shown to vary in frequency depending on their aetiology.[2-4]

Individuals with DSD have variable phenotypes ranging from completely female external genitalia to male appearing genitalia with hypospadias, bifid scrotum and descended gonads. The cornerstone of management of DSD is thorough investigations to adequately elucidate the nature of the genetic sex, the gonad and the phenotype and based on this, proper gender is assigned and appropriate genital reconstruction undertaken.[5] This is best achieved with early diagnosis, multidisciplinary team management and communication between the surgeon and the patients and families. Recent studies show that though significant improvement of outcome has been observed with advances in diagnostic testing and genital repair, controversies still exist in the timing for gender assignment and definitive genital reconstruction.[2,5,6] Despite these, the management of DSD is challenging and remains a traumatic experience in some cases.[2,3,7] This study was conducted to review our experience with DSD with focus on clinical evaluation, diagnosis, medical, surgical, and psychological management and challenges encountered in management of these disorders.

MATERIAL AND METHODS

This is a retrospective study conducted at Department of urology, Sri Venkateswara Institute of Medical Sciences and all patients who were diagnosed as DSD between January 2010 to January 2015 were included in study.

At our institute patients with DSD are managed by the department of Urology. The patients were managed in conjunction with the Endocrinologist, Gynaecologists, Radiologists and Clinical Psychologists. The initial evaluation of these patients was geared towards defining the anatomy of the internal genitalia and the gonad, and the likely genetic sex. For the former we used abdominopelvic ultrasonography, MRI pelvis (where required) and when this is inconclusive we resorted to diagnostic laparoscopy. The genetic sex was determined with karyotyping. Serum studies for ketosteroids were obtained as appropriate. Decision on gender assignment and gender reconstruction was based on the findings of the investigations and the appearance of the external genitalia and with aid of pshyciatric counseling. Patients with congenital adrenal hyperplasia after evaluation were given long-term oral prednisolone 2 mg/m2 /day to suppress excess adrenocorticotropin hormone production (ACTH). Hormonal therapy was given as appropriate based on final gender assignment. Surgical management was required in all cases either in form of hypospadias repair/ gonadectomy/ clitoroplasty/scrotoplasty/hysterectomy depending upon gender assignment.

[1]Associate Professor, [3]Post Graduate, Department of Urology, [2]Assistant Professor, Department of Obstetrics and Gynaecology, Sri Venkateswara Institute of Medical Sciences, Tirupati, Andhra Pradesh, India

Corresponding author: Dr. Nallabothula Anil Kumar, Associate professor, Dept of Urology, SVIMS, D.No.5/5/346, 1st floor 2nd house, Near Sneha Hospital, Sarojini Devi Layout, Tirupati, Andhra Pradesh State, India, PIN: 517501.

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The case notes which includes prenatal and maternal history, sex of rearing, genital phenotypic appearance, karyotype, imaging studies of gonads and Mullerian/Wolfian structures, laboratory investigations for hormonal activity of steroidogenesis and associated disorders and imaging studies and management with surgery and gender assignment were reviewed retrospectively after obtaining ethical clearance from institutional ethics committee for patients diagnosed as DSD between 2010 - 2015 at Sri Venkateswara Institute of Medical Sciences.

Inclusion criteria

All patients who were diagnosed as DSD between January 2010 – January 2015 at Sri Venkateswara Institute of Medical Sciences were included in study.

STATASTIC ANALYSIS

These patients data was coded into a Microsoft Excel (Redmond, WA) spreadsheet and results were expressed as percentages, median or mean.

RESULTS

Overall, 8 (57.14 %) of the 14 cases were reared as female and 6 (42.8 %) reared as male at presentation. Median age of presentation in our series was 9 years ranging from 2 to 23 years. Table-1 summarizes the age and gender distribution of the cases at presentation.

External Genitalia at Presentation

A total of 8 (57.14 %) of the patients presented with enlarged phallus with unfused labia with perineal urethral meatus and vagina (TYPE A); 2 (14.2%)cases presented with proximal penile hypospadiasis with small testis (TYPE B) ; 4 cases (28.4%) presented with small phallus with empty labioscrotum and urethral meatus on perineum (Type C). Overall, cases with type A clinical finding were reared as female while the type B and Type C patients were reared as male prior to presentation (Table-2).

Investigations

Abdominopelvic ultrasonography did not demonstrate adrenal enlargement in any of the 14 patients. However, ultrasound demonstrated inguinal gonads in 4 (28.4%); but was inconclusive in 2 (14.2%) patients. MRI pelvis demonstrated utricle in 1 case (7.1%) and showed gonads in abdomen in 2 cases (14.2%). Two patients had diagnostic laparoscopy because of inconclusive results, confirming bilateral vanishing testis in one patient and demonstrating uterus with bilateral abdominal gonads in another case.

Age at Presentation	Gender at Presentation		Total
	Female	Male	
< 4 years	-	3	3
5 – 8 years	3	1	4
9 – 12 years	1	-	1
13 – 16 years	3	1	4
> 17 years	1	1	2
Total	8	6	14

Table-1: Age and gender distribution

Types of DSD And Gender Assignment

Among the 14 patients that were diagnosed DSD between 2010 - 2015, two patients had 46,XX DSD, ten patients had 46,XY DSD, the remaining 2 had sex chromosome DSD. Both 46 XX DSD patients had congenital adrenal hyperplasia.

The ten 46 XY DSD patients included a case of bilateral vanishing testis, 3 cases of mixed gonadal dysgenesis, 2 cases of testosterone biosynthesis defects, 2 cases of 5 alpha reductase deficiency and 2 cases of complete androgen insensitivity syndrome. The two cases of sex chromosomal DSD in our study were 46 XX males.

46 XX DSD

Ages of presentation of 46 XX DSD were at 5 and 7 years and both were diagnosed as 17 apha hydroxylase deficiency. Both presented with type A genitalia with female internal genitalia with presenting complaint being cliteromegaly. Both were reared as females at presentation and were assigned same gender after reduction cliteroplasty.

46 XY DSD x

Median age of presentation among 46 XY DSD was 13.5 years ranging from 2 – 19 years. Overall of 10 patients, 4 patients presented with type C, while 6 patients presented with type A phenotypic appearance (Table-3).

All patients who presented with type C were reared as males. Three cases presented at 2 years, 3 years, 16 years and all were diagnosed as mixed gonadal dysgenesis and presented with perineoscrotal hypospadiasis with bilateral nonpalpable gonads. Ultrasound could not demonstrate gonads in all cases while MRI showed gonads in two cases and uterus in one patient. All underwent diagnostic laprascopy which showed streak gonads in and a rudimentary uterus in one of them. Bilateral gonadectomy +/- hysterctomy with staged hypospadias repair was done and male gender assignment was done in all.

Another case with type C external genitalia was bilateral vanishing testis which was diagnosed with diagnostic laprascopy showing bilateral absent gonads with utricle cyst and perineal hypospadias and was continued to rear as male with utricular cyst excision and staged hypospadias repair.

The 6 patients who presented with type C were reared as females and presented at median age of 13.5 years ranging from 8 to 19 years of age. This group included two cases of 5 alpha reductase deficiency, 2 cases of testosterone biosynthesis defects, 2 cases of complete androgen insensitivity.

Among 2 cases of 5 alpha reductase defiicency one presented

Mode of Presentation	Gender at presentation		Total
	Female	Male	
Enlarged phallus with unfused labia with perineal urethral meatus and inguinal/nonpalpable gonads with vagina/vagina dimple(TYPE A)	8	-	8
Proximal penile hypospadias with small testis (TYPE B)	-	2	2
Small phallus with fused labia and urethral meatus on perineum inguinal/nonpalpable gonads (Type C)	-	4	4
Total	8	6	14

Table-2: External genitalia at presentation

at age of 9 years with bilateral undescended testis, perineal hypospadias and underwent Bilateral orchidopexy with scrotoplasty with hernia repair and staged hypospadias repair and sex was reassigned to male while another case presented at age of 16 years with cliteromegaly and bilateral inguinal testis and was continued to be reared as female by reduction cliteroplasty, orchidectomy and vaginoplasty.

Among the two cases of testosterone biosynthesis defects the case that presented at 13 years of age with bilateral undescended testis with perineal hypospadias and underwent Bilateral orchidopexy with scrotoplasty with hernia repair and staged hypospadias repair and sex was reassigned to male while another case that presented at 8 years of age continued to rear as female with reduction cliteroplasty, orchidectomy and vaginoplasty.

Both cases of complete androgen insensitivity underwent bilateral orchidectomy and reduction cliteroplasty and were continued to rear as female.

Both cases of Sex Chromosomal DSD were 46 XX Males who were reared as males presenting with penile hypospadias and underwent staged hypospadias repair and final gender reassignment was male.

After treatment male gender was assigned in 8 cases while female gender was assigned in 6 cases (Table-4). Overall Gender reassignment was done in 2 cases (14.2%) from female to male.

Treatment

Of the 8 cases that were assigned male gender, 6 cases (75%) required preoperative penile size augmentation with parenteral testosterone. Bilateral Gonadectomy was done in 3 cases

Age	Gender At Presentation	External Genitalia	Gonads	Internal Genitalia	Final Diagnosis	Surgery	Gender Assigned
2 years	Male	Type C	B/L Non-palpable Streak Gonads	Rudimentary Wolfian Duct Structures	Mixed Gonadal Dysgenesis	B/L Gonadectomy + Hypospadias Repair	Male
16 years	Male	Type C	B/L Non-palpable Streak Gonads	Rudimentary Wolfian Duct Structures And Uterus	Mixed Gonadal Dysgenesis	B/L Gonadectomy+ Hysterctomy+ Hypospadias Repair	Male
18 years	Male	Type C	B/L Vanishing Testis	B/L Blind Ending Cord Structures With Utricle Cyst	Bilateral Vanishing Testis	Utricular Cyst Excision + Hypospadias Repair	Male
16 years	Female	Type A	Rt Inguinal Testis And Left Iliac Fossa Testis	B/L Vas Deferens With Vagina	5 Alpha Reductase Deficiency	Cliteroplasty + B/L Orchidectomy + Vaginoplasty	Female
9 years	Female	Type A	B/L Inguinal Testes	B/L Vas Deferens With Seminal Vesicle S Rudimentary Prostrate, Vaginal Dimple	5 Alpha Reductase Deficiency	B/L Hernia Repair + B/L Orchidopexy + Scrotoplasty + Hypospadias Repair	Male
13 years	Female	Type A	B/L Inguinal Testes	B/L Vas Deferens With Seminal Vesicles	Testosterone Biosynthesis Defect	B/L Hernia Repair + B/L Orchidopexy + Scrotoplasty + Hypospadias Repair	Male
8 years	Female	Type A	B/L Illiac Testis	B/L Vas Deferens With Vaginal Pouch	Testosterone Biosynthesis Defect	Cliteroplasty + B/L Orchidectomy + Vaginoplasty	Female
14 years	Female	Type A	B/L Inguinal Testis	B/L Vas Deferens With Vaginal Pouch	Complete Androgen Insensitivity Syndrome	Cliteroplasty + B/L Orchidectomy + Vaginoplasty	Female
3 years	Male	Type C	B/L Non-palpable Streak Gonads	Rudimentary Wolfian Duct And Mullerian Duct Structures	Mixed Gonadal Dysgenesis	B/L Gonadectomy+ Hypospadias Repair	Male
19 years	Female	Type A	Rt Inguinal Testis And Lt Illiac Testis	B/L Vas Deferens With Rudimentary Vagina	Complete Androgen Insensitivity Syndrome	Cliteroplasty + B/L Orchidectomy + Vaginoplasty	Female

Table-3: Spectrum of 46 XY DSD

Gender at presentation	Total	Definitve gender	
		Female	Male
Female	8	6	2
Male	6	-	6
Total	14	6	8

Table-4: Gender assignment

(37.5%) while bilateral orchidopexy with scrotoplasty was done in 2 cases (25%). Staged Hypospadias repair was done in all cases.

Among the 6 patients that were assigned female gender, 2 cases (33.33%) had reduction clitoroplasty, 3 cases (50%) had reduction clitoroplasty, vaginoplasty with bilateral orchidectomy while one case (16.6%) had bilateral orchidectomy only. Histology of the removed gonads did not show neoplastic changes.

Outcome

Duration of follow-up ranged from 1 month to 4 years. A total of 3 (21.42%) developed procedure-related complications which include meatal stenosis (n=2) and urethrocutaneous fistula (n = 1). The cases with meatal stenosis responded to dilatation. Urethrocutaneous fistula was managed by operative closure. There were no gender assignment issues. However fertility remained a concern in 10 of 14 patients.

DISCUSSION

DSD are congenital conditions in which the development of chromosomal, gonadal or anatomical sex is atypical or ambiguous.[3] In the newborn period, virilisation or over-virilisation of the external genitalia in girls and under-virilisation in boys, presenting as micropenis, hypospadias and undescended testes are the most common presentations. However, there are more complex situations in which the determination of rearing might not be possible. In such cases, gonadal structure and the anatomy of the internal genitalia should also be considered and an appropriate laboratory delineation is required. These disorders are now classified into three major categories: sex chromosome DSD, 46,XX DSD and 46,XY DSD.

Disorders of sexual development (DSDs) are estimated to be prevalent in 0.1 to 2 % of the global population.[8] In the past decades, important advances have refined the diagnosis and management of these disorders.[2,3] This notwithstanding, the affected patients, their parents and the medical staff are still confronted with challenges in areas of gender assignment, genital surgery and lifelong care, functional outcome and psychosexual adjustments.[2,3,8] This study has shown that the types of DSD, definitive treatment and short-term outcomes in our setting may be comparable to what has been previously reported.

In most of the reported large series, 46, XX DSD was indicated as the commonest type of DSD.[9-11] However, in some reports,[4,12,13] cases of 46, XY DSD outnumbered the other types of DSD as in our study. These variations may reflect deficiencies of representative patient sampling or more likely it may be the result of the new DSD classification system leading to expanded clinical spectrum of the disease with a change in the distribution of etiological diagnoses of DSDs.[4]

Historically, the management of DSD has focused on gender assignation and surgical/medical treatment to ensure congruent bodily appearance. Though this emphasis has not changed over the years, the current protocol of treatment highlights the need to dispel the traditional binary concept of sexes, ethical considerations, informed consent and appropriately timed genital repair with the ultimate goal of achieving results that are in the best interest of the patients.[2,3,14] In the light of this, it is evident that the management of DSD in our setting may be imbued with challenges. Similar observations have been reported in studies from some other developing countries.[15-17] The challenges are mostly in the areas of delayed diagnosis, inadequate facilities and trained personnel, and high proportion of cases that need gender reassignment. Training and retraining of these personnel to recognize features of these disorders and the need for early referral to appropriate health facility may improve time to diagnosis.

In this study a total of 2 cases were wrongly reared as female prior to presentation. In these select cases, positive parental support, social support, medical support, and counseling may be needed for adjustment.[18] Studies have shown that thorough investigation is critical in the management of DSD.[2-4,19] The operative procedures undertaken on our cases did not differ from the procedures reported elsewhere.[3,6,20]

In patients assigned female gender the procedure involves removal of all testicular tissues, and depending on the degree of virilization staged genital repair is undertaken. For cases with isolated clitoromegaly, clitoroplasy will suffice.[21] If there is associated labial fusion, vulvoplasty is usually undertaken in the same procedure to improve cosmesis. However, cases with single urogenital orifice will require vaginoplasty the extent of which depends on the length of the urogenital sinus. Cutback vaginoplasty may be sufficient for vagina entering at the level of anterior urethra, but for patients with vagina entering at the level of posterior urethra, substitution or pull-through vaginoplasty may be undertaken. In cases with ‘‘penile’’ clitoris, phalloplasty may be required for optimal cosmetic result. In this procedure, the glans is mobilized with its neurovascular bundle, the corpora cavernosa is reduced symmetrically in length and diameter, and the volume of the glans reduced as appropriate.[22]

DSD assigned male gender undergoes masculinizing genitoplasty. The present report and some previous studies have shown that a significant number of these cases will require penile size augmentation with either parenteral or topical testosterone prior to genital repair.[23,24] For patients with mullerian duct remnant and or ovarian tissue, salping-oophorectomy is undertaken. Orchidopexy is also carried out for cases with undescended testes. Definitive genital repair involves single or staged hypospadias repair and scrotoplasty as required.[23-25]

The outcome of treatment of DSD can be defined in shortterm and long-term. The short-term outcomes relate mostly to the physical appearance and functionality of the genitalia to the patient, the parents, and the surgeon.[3,9,13,14] In this aspect the outcome in the present report compares with the results of treatment previously reported.[9,13,25] Some complications of treatment like vaginal stenosis and meatal stenosis if mild may respond to dilatation, but severe stenosis may require revision of the vaginoplasty, and meatotomy respectively.[24] On the other hand persistent urethrocutaneous fistula following hypospadias repairwill require operative closure.[24,25] Long-term follow-upof DSD patients is invariable to monitor for long-term outcomessuch as personal satisfaction, gender

satisfaction,social adaptation, quality of life, sexual function, and other psychosexual parameters.[2,3,9,24] These underscore the importance of psychological, social, and family support in the treatment of children with DSD.

CONCLUSION

DSD 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. Affected patients and the parents should be provided with full information to make an appropriate choice for gender assignment**.** Focused education of healthcare personnel, public awareness programmes, and improvement of diagnostic facilities and personnel through enhanced funding and international collaboration may improve outcome and minimize psychological morbidity.

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