

Study on 46 XY Disorders of Sex Development

Jesmin E¹, Mohsin F², Begum NNF³

DOI: <https://doi.org/10.3329/jafmc.v14i2.45893>

Abstract

Introduction: 46 XY disorders of sexual development (DSD) include a wide sphere of phenotypes which can be ambiguous male genitalia with or without hypospadias, unambiguous female genitalia or dysgenetic gonads or any combination of them. Management of these patients depends on the aetiology, age at presentation, gender orientation and advancement in feminization.

Objectives: To assess the clinical, biochemical, radiological and chromosomal profile of the paediatric patients with suspected DSD attending a tertiary level healthcare centre and plan for appropriate management.

Materials and Methods: This cross-sectional study was carried out among 30 cases of 46XY DSD attending the paediatric endocrine unit of Bangladesh Institute of Research and Rehabilitation in Diabetes Endocrine and Metabolic Disorders (BIRDEM) General Hospital from May 2016 to April 2017. Clinical, biochemical, radiological and chromosomal evaluations were done to identify the cause of DSD.

Results: The mean age of the patients recruited in the study was 3.51 (± 5.03) years ranging from 13 days old to 13 years old. Among these 30 patients, the chief complaint was ambiguous genitalia in 29 (96.7%) cases, 1 (3.3%) case with Micropenis and 1 (3.3%) case with absence of development of secondary sexual characteristics. The gender of rearing was male in 23 (76.7%) cases and rest as female. Among the patients 5 (16.67%) patients were diagnosed with PAIS, 5 (16.67%) patients with CAIS, 3 (10%) patients had a deficiency of 5 α RD and gonadal dysgenesis was found in 5 (16.67%) patients. The corrective surgery was done in 5 (16.67%) patients, 16 (53.3%) patients referred to surgeon for operative treatment and 7 (23.3%) patients were prescribed to administer testosterone.

Conclusions: The early presentation, correct identification of the cause and initiation of cause-based treatment can abate the physical and psychosocial complications and may support better gender orientation related adjustability.

Key-words: 46 XY disorders of sex development.

Introduction

Disorders of sex development (DSD) include a heterogeneous group of heritable disorders of sex determination and

differentiation¹ where there is a discrepancy in the chromosomal, gonadal, and anatomical sex². DSD cases are detected mostly during the time of birth on the ground of atypical genital appearance; in other cases, the condition only becomes evident at the time of puberty³. Though, whether the diagnosis be early or late, there is persistent presence of one or more atypical deviation from normal sex determination (differentiation of the bipotential gonad into either testis or ovary) or differentiation (formation of the internal reproductive anatomy and external genitalia under hormonal influence)⁴ 46, XY DSD have lower virilization of genitals compared to normal 46, XY individuals⁵. The 46 XY DSD is categorized into disorders of gonadal development and disorders of androgen synthesis and action. Disorders of gonadal development refer to gonadal dysgenesis whereas, disorders of androgen synthesis and action refer to 5 alpha-reductase deficiency (5 α RD), androgen insensitivity, 17 β hydroxy-steroid dehydrogenase deficiency etc².

The frequency of patients born with ambiguous genitalia estimated to be approximately 1 in 4,500-5,500⁶. Subjects presented with ovotesticular DSDs have been estimated⁷ to be in 1 in 100,000. Testicular or mixed gonadal dysgenesis is estimated⁸ to be approximately 1:10,000. Considering all genital anomalies including cryptorchidism and hypospadias, the rate⁹ may rise up to 1:200 to 1:300 among these, the incidence of 46, XY DSD has been estimated to be 1 in 20,000 births¹⁰. The risk of gonadal tumours may be as high as 40% in individuals with dysgenetic gonads¹¹. In fact, dysgenetic and undescended testes are listed as major risk factors for testicular cancer, which is the most common malignancy for men between the ages of 15 and 35 years¹².

The 46, XY disorders encompasses a wide spectrum of different conditions such as 46 XY partial gonadal dysgenesis (Denys-Drash syndrome, Frasier syndrome), 46 XY complete gonadal dysgenesis (Swyer syndrome), ovotesticular DSD, testicular regression syndrome (vanishing testes syndrome), Leydig cell aplasia/hypoplasia, testosterone biosynthesis defects, POR gene abnormality, persistent Mullerian duct syndrome, 5 alpha-reductase type 2 deficiency syndrome, complete androgen insensitivity syndromes (CAIS) and partial androgen insensitivity syndromes (PAIS)¹³.

1. Lt Col Eva Jesmin, MBBS, DCH, FCPS, Classified Child Specialist of Paediatrics, Combined Military Hospital (CMH), Dhaka (E-mail: jesmin882@gmail.com) 2. Professor Fauzia Mohsin, MBBS, FCPS, Professor & Head of Paediatrics Endocrinology Unit, Department of Paediatrics, BIRDEM General Hospital-II, Dhaka 3. Brig Gen Nurun Nahar Fatema Begum, SBP, MBBS, FCPS, FRCP, FACC, FSCAI, Independence Awardee, Professor & Head of the Department of Paediatrics, AFMC, Dhaka.

A careful clinical assessment of the neonate is essential as most DSD patients could be recognized at birth with the presence of ambiguous genitalia and earlier diagnosis allows for initiating a better treatment protocol¹⁴. Nevertheless, they may be diagnosed later in life in individuals with abnormal or delayed puberty or primary amenorrhea, cyclic hematuria in a male, inguinal hernia in a female, unanticipated virilization or gynaecomastia, infertility, or gonadal tumors¹². The first steps for a correct diagnosis are taking family and prenatal history, thorough physical examination and evaluation of genital anatomy. These approaches are followed by a cytogenetic evaluation to assess chromosomal constitution and a combination of those may direct for the requirement for additional testing which may include endocrinological evaluation, imaging (most reliably ultrasonography)¹⁵. Endoscopic and laparoscopic examination and gonadal biopsy are required in very few cases¹⁴.

The basic principles for the management of DSD include a multidisciplinary approach for gender assignment¹³. Initiation of appropriate treatment results in providential outcomes in terms of growth of sexual identity and adaptation¹⁶. As, several biologic factors such as genetic and hormonal influences contribute to gender identity, gender role behaviour, and sexual orientation in patients, also these conditions are modified by psychological, social, and cultural factors and altogether they guide the establishment of the social sex¹³. To establish female social sex in patients with 4XY DSD who have a uterus, hormonal therapy is introduced to stimulate the development of female sexual characteristics in patients with uterus. The treatment should stimulate normal puberty, mense and breast development. Age and response-based hormonal therapy are continued until the expected outcome is accomplished. Among the surgical interventions, feminizing Genitoplasty, Cliteroplasty, Vaginoplasty, Vulvoplasty, dilation of the blind vaginal pouch with acrylic molds¹⁷ or surgical neovagina to promote the development of a vagina adequate for sexual intercourse remained popular treatment choices when these patients wished to start sexual intercourse¹⁸. Contrarily, to establish male social sex for those patients with 4XY DSD who have been raised as males, testosterone replacement therapy is initiated between 10-11 years, simulating normal puberty. Common Surgical treatment in these cases includes Orthophalloplasty, Scrotumplasty with resection of the vaginal pouch, proximal and distal urethroplasty and orchidopexy as per requirement. Additionally, detection of undifferentiated gonadal tissue or testicular tissue suggests a high risk for germ cell tumours and Gonadectomy should be performed in such cases to risk out any malignant transformation¹⁴.

Psychological evaluation of primary caregivers is also crucially important to treat DSD patients. Sex assignment of children with ambiguous genitalia remains a difficult decision for the families involved¹⁹. Every couple that has a child with atypical genitalia must be assessed and receive counselling by an experienced psychologist, specialized in gender identity. A simple, detailed and comprehensive explanation about what to expect regarding integration in social life, sexual activity, need of hormonal and

surgical treatment and the possibility or not of fertility according to the sex of rearing, should also be discussed with the parents, before the attainment of final social sex¹³. Healthy gender identity and the interaction of genetic constitution, physiology, and hormonal assignment and the sex of rearing shape an individual's psychological development²⁰. Most of the well-treated DSD patients present a normal quality of life at adulthood.

Materials and Methods

This cross-sectional study was carried out among 30 cases of 46XY DSD attending the paediatric endocrine unit of Bangladesh Institute of Research and Rehabilitation in Diabetes Endocrine and Metabolic Disorders (BIRDEM) General Hospital from May 2016 to April 2017. Data including age at presentation, biochemical and radiological investigation, clinical diagnosis, treatment given were collected. Cases were diagnosed by clinical, hormonal and cytogenetic analysis. The clinical features examined for the diagnosis of DSD included genital ambiguity, apparent male genitalia with non-palpable testis, micropenis, hypospadias, apparent female genitalia with clitoromegaly, inguinal or labial mass. The hormonal assay was done to evaluate included luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone (T) and un-stimulated and/or stimulated 17-hydroxy progesterone 17(OH)P levels (where indicated). Abdominopelvic ultrasound was done for the localization of gonads (magnetic resonance imaging (MRI) also when required to determine the nature and structure of the internal sex organs and to detect any disagreement with external genital structures. Percentage, mean and range were used to describe continuous and categorical variables respectively.

Results

With the mean age of 3.51 years and SD±5.03, almost 18 (60%) of the cases presented at their infantile period while the earliest coming over to this hospital during the study was on the 13th day followed by 6 (20%) patients who were 1-5 years old, 3 (10%) patients of more than 5 to 10 years old and 3 (10%) patients who were aged above 10 years, with the eldest patient as recorded for this study was 13 years old. Among the patients, majority 23 (76.7%) of them have been brought up as male and rest 7 (23.3%) of them were reared as female (Table-I). Ambiguous genitalia was the main complaint from the patients' side which was seen in 29 (96.7%) patients. Absence of development of secondary sexual characteristics was complained by 1 (3.3%) patient who was 12 years old and one patient (3.3%) presented with micropenis (Table-II).

Principally, three hormonal assessments were carried out among the patients- luteinizing hormone (LH), Follicle Stimulating Hormone (FSH), testosterone (T) and 17(OH)P (17 Hydroxy Progesterone). The hormonal assessment showed that LH was increased by 50% of the patients, decreased in 16.7% of the patients and was normal in 33.3% patients. FSH was increased in 56.6% of the patients, decreased in 6.7% of the patients and was normal in 36.7% patients. The level of testosterone was

increased in 53.3% of the patients, decreased in 3.3% of the patients and was normal in 43.3% patients. The level of 17(OH) P was increased by 50% of the patients, decreased in 3.3% of the patients and was normal in 23.3% patients (Table-III). Patients of the study have been found to be diagnosed with four kinds of disorders among the spectrum of 46 XY DSD. They were partial androgen insensitivity syndrome (PAIS), complete androgen insensitivity syndrome (CAIS), Deficiency of five alpha-reductase (5αRD) and gonadal dysgenesis (GD). It has been recorded that 5 patients had PAIS, 5 patients had CAIS, 3 patients had a deficiency of 5αRD and 5 patients had GD. Cases remained unclassified under any spectrum at the time of the study were 12 in number.

Among the clinical features of the 46 XY DSD, hypospadias was the most common phenotype, found in 17 (56.64%) cases where 5 (16.67%) cases found in patients with PAIS, 3 (10%) cases in patients with CAIS, 2 (6.67%) cases in patients with deficiency of 5αRD, 1 (3.3%) case in patients with GD and 6 (20%) cases with hypospadias remained unclassified. Micropenis was found in 12 (40%) cases; among them, 1 (3.3%) case was found in PAIS patients, 3 (10%) cases in CAIS patients, 2 (6.67%) cases in 5αRD deficit patients, 1 (3.3%) case in patients with GD and 5 (16.67%) remained unclassified. The bifid scrotum was identified in 10 (33.3%) cases where 3(10%) cases were found in PAIS patients, 1 (3.3%) case in CAIS patients, 2 (6.67%) cases in 5αRD deficit patients and 4 (13.3%) cases of bifid scrotum remained unclassified. Urethral meatus was absent in 1 (3.3%) unclassified case. Absence of left gonad and right gonad were seen in 6 (20%) and 3 (10%) patients respectively wherein both cases 2 (6.67%) cases were in patients with GD and rests remained unclassified. Patients with gonads palpable in the inguinal region were 2 (6.67%), among them one (3.3%) had PAIS and rest had CAIS. Enlarged clitoris was present in 6 (20%) patients, 3 (10%) cases with GD and 3 (10%) cases remained unclassified. Vaginal orifice was present in 7 (23.3%) cases where 3 (10%) cases were with CAIS, 1 (3.3%) case was with 5αRD deficiency, 1 (3.3%) with GD and 2 (6.67%) remained unclassified. Lastly, 1 (3.3%) patient was identified with the presence of Mullerian structure that was diagnosed with GD (Table-IV). By the time of the study, there were 5 (16.6%) already operated patients, among whom 1 patient had undergone phallus reconstruction, 16 (53.3%) patients were referred to surgeon for subsequent operative treatment, 7 (23.3%) patients were recommended administration of testosterone and 2 (6.7%) patients were planned to be undergone the required operative procedure.

Table-I: Distribution of patients according to age and sex (n=30)

Traits	Frequency	Percentage	
Age	1 year or below	18	60
	1.1 – 5 years	6	20
	5.1- 10 years	3	10
	More than 10 years	3	10
Sex	Male	23	76.7
	Female	7	23.3

Table-II: Distribution of patients according to presenting complaints (n=30)

Features	Frequency	Percentage
Ambiguous Genitalia	29	96.7
Micropenis	1	3.3
Absence of development of secondary sexual characteristics	1	3.3

Table-III: Hormonal assay of the patients (n=30)

	Decreased	Normal	Increased
LH (Luteinizing Hormone)	5 (16.7%)	10 (33.3%)	15 (50%)
FSH (Follicle Stimulating Hormone)	2 (6.7%)	11 (36.7%)	17 (56.6%)
T (Testosterone)	1 (3.3%)	13 (43.3%)	16 (53.3%)
17-OHP (17 Hydroxy Progesterone)	1 (3.3%)	7 (23.3%)	15 (50%)

Table-IV: Phenotypical expressions* among the etiological diagnosis (n=30)

	Diagnosis						Total
	PAIS	CAIS	Deficiency of 5αRD	GD	Not classified		
Phenotype	Bifid scrotum	3 (10%)	1 (3.3%)	2 (6.67%)	0	4 (13.3%)	10 (33.3%)
	Micro penis	1 (3.3%)	3 (10%)	2 (6.67%)	1 (3.3%)	5 (16.67%)	12 (40%)
	Urethral meatus absent	0	0	0	0	1 (3.3%)	1 (3.3%)
	Hypospadias	5 (16.67%)	3 (10%)	2 (6.67%)	1 (3.3%)	6 (20%)	17 (56.64%)
	Left gonad absent	0	0	0	2 (6.67%)	4 (13.3%)	6 (20%)
	Right gonad absent	0	0	0	2 (6.67%)	1 (3.3%)	3 (10%)
	One/both gonads in inguinal region	1 (3.3%)	1 (3.3%)	0	0	0	2 (6.67%)
	Enlarged clitoris	0	0	0	3(10%)	3(10%)	6 (20%)
	Vaginal orifice	0	3 (10%)	1 (3.3%)	1 (3.3%)	2 (6.67%)	7 (23.3%)
	Mullerian structure	0	0	0	1 (3.3%)	0	1 (3.3%)
	Total	5 (16.67%)	5 (16.67%)	3 (10%)	5 (16.67%)	12 (40%)	

*Multiple presentations

Discussion

An individual with a chromosomal pattern of one X chromosome and one Y chromosome in each cell, which is the usual chromosomal pattern found in male has ambiguous external genitalia that is not clearly male or female is regarded as 46 XY DSD patient. In some instances, these patients have fully to underdeveloped female reproductive organs while others may present normal external genitalia with discordance in internal structures. They may be raised as male or female according to the gender assigned at birth which often depends on the corresponding resemblance of the genitalia to male or female and later according to the gender identity. Treatment involves corrective surgery and hormone replacement therapy. Patients with 46, XY DSD have discordance between the karyotype and the phenotypical expression regarding external genitalia and gonadal sex. These patients mostly are seen to have an autosomal recessive pattern of inheritance, which

is correspondent to their X chromosome^{21,22}. In comparison to normal 46, XY individuals, patients with 46, XY DSD have lower virilization pattern. Aetiology may be associated with hypoplasia of Leydig cells, enzyme disturbances of testosterone synthesis, a deficit of 5- α -reductase enzyme (DEF5 α), testicular regression syndrome, gonadal dysgenesis (GD), anorquia, partial or complete androgen insensitivity syndrome (PAIS/CAIS) or ovotesticular DSD²³. At birth, patients with 46 XY DSD show atypical external genitalia patterns ranging from a male looking phallus to almost normal female genitalia with a slight increase of clitoris. Testes may be located in the abdominal or in inguinal region instead of scrotal folds⁵.

The 30 cases in the present study have been diagnosed with 5 PAIS cases, 5 CAIS cases, 3 5 α RD deficit cases 5 GD cases. Cases remained unclassified under any spectrum at the time of the study were 12 in number. The most common phenotype of 46 XY DSD was hypospadias which was found among 17 cases mostly in PAIS (16.67%) and CAIS (10%) cases, 2 (6.67%) cases in patients with deficiency of 5 α RD, 1 (3.3%) case in patients with GD and 6 (20%) cases with hypospadias remained unclassified. Micropenis was found in 12 (40%) cases; among them 1 was with PAIS, 3 were with CAIS, 2 were 5 α RD, 1 with GD and 5 remained unclassified. Bifid scrotum was identified in 10 cases where 3 with PAIS patients, 1 with CAIS patients, 2 with 5 α RD deficit were diagnosed and 4 cases remained unclassified. Urethral meatus was absent in 1 unclassified case. Absence of left or right gonads seen some in GD and rests remained unclassified. Patients with gonads palpable in inguinal region were 2, among them one had PAIS and another had CAIS. Enlarged clitoris was present in 6 patients, 3 cases with GD and 3 cases remained unclassified, Vaginal orifice was present in 7 cases where 3 with CAIS, 1 case was with 5 α RD deficiency, 1 with GD and 2 remained unclassified. Lastly, 1 patient was identified with the presence of Mullerian structure, who was diagnosed with GD. The gender of rearing was male for 23 patient and female for 7 patients.

Other studies on disorders of sexual development that focused primarily on 46 XY DSD, observed nearly similar results which are substantial with our study findings, described as followed. A prospective study with an assessment of eleven 46 XY DSD patients recorded that 3 cases were diagnosed with 5 α -reductase deficiency (5 α RD), 2 with partial gonadal dysgenesis, 3 with PAIS, 1 each with ovotesticular, complete gonadal dysgenesis, and CAIS. Gender assigned at birth was female in eight and male in three patients²⁴. A retrospective study of medical records of survey data of 93 patients with 46, XY DSD observed that among the patients, 50.5% had no defined aetiology and 20.4% had androgen insensitivity syndrome (AIS), They also found that all patients with CAIS had pure gonadal dysgenesis had female genitalia. Others have been diagnosed with genital ambiguity or severe hypospadias and cryptorchidism. The gonads were palpable

at the first consultation in 75.3% of patients⁵. Another study showed, among 102 patients with 46 XY DSD, 32 (31.4%) had androgen insensitivity syndrome which substantiates with our findings where we found 33.3% of patients with androgen insensitivity syndrome²⁵. A study with 19 patients with 46 XY DSD found one case with CAIS, 3 (15.8%) cases with PAIS and 4 (21.05%) cases with 5 α RD²⁶.

Conclusion

The most frequent aetiology in the present study was androgen insensitivity syndrome followed by gonadal dysgenesis and the most common phenotype was hypospadias, micropenis and bifid scrotum. A careful clinical evaluation at the neonatal or infantile period can identify most of the DSD cases and precocious diagnosis allows a better and earlier therapeutic approach which can avail them to live healthy adulthood.

References

1. van Mil EG, Hiort O. Three out of four: a case discussion on ambiguous genitalia. *European Journal of Endocrinology* 2008; 159(suppl_1):S91-3.
2. Hughes IA, Houk C, Ahmed SF et al. Consensus statement on management of intersex disorders. *Journal of Pediatric Urology* 2006; 2(3):148-62.
3. Sandberg DE, Pasterski V, Callens N. Introduction to the Special Section: Disorders of Sex Development. *J Pediatr Psychol* 2017; 42(5):487-95.
4. Achermann JC, Domenice S, Bachega TASS et al. Disorders of sex development: effect of molecular diagnostics. *Nat Rev Endocrinol* 2015; 11(8):478-88.
5. Mota BC, Oliveira LMB, Lago Ret et al. Clinical profile of 93 cases of 46, XY disorders of sexual development in a referral center. *Int Braz J Urol Off J Braz Soc Urol* 2015; 41(5):975-81.
6. Sax L: How common is intersex? A response to Anne Fausto-Sterling. *J Sex Res* 2002; 39:174-8.
7. Nistal M, Paniagua R, Gonzalez-Peramato P et al. Ovotesticular DSD (true hermaphroditism). *Pediatr Dev Pathol* 2015; 18:345-52.
8. Skakkebaek NE, Rajpert-De Meyts E, Main KM. Testicular dysgenesis syndrome: An increasingly common developmental disorder with environmental aspects. *Hum Reprod* 2001; 16:972-8.
9. Nordenvall AS, Frisen L, Nordenstrom A et al. Population based nationwide study of hypospadias in Sweden, 1973 to 2009: Incidence and risk factors. *J Urol* 2014; 191:783-9.
10. Nistal M, Paniagua R, Gonzalez-Peramato P et al. Ovotesticular DSD (true hermaphroditism). *Pediatr Dev Pathol* 2015; 18:345-52.
11. Ostrer H. 46,XY Disorder of sex development and 46,XY complete gonadal dysgenesis. In: Pagon RA, Adam MP, Bird TD, eds. *GeneReviews*. Seattle, WA: University of Washington, Seattle. [http:// www.ncbi.nlm.nih.gov/books/NBK1547/](http://www.ncbi.nlm.nih.gov/books/NBK1547/). Published May 21, 2008. Updated September 15, 2009.

12. Ostrer H. Disorders of sex development (DSDs): An update. *J Clin Endocrinol Metab* 2014; 99(5):1503–9.
13. Ahmad A, Ayub F, Saleem I et al. Initial assessment of a child with suspected disorder of sex development. *JPMA J Pak Med Assoc* 2019; 69(5):711–7.
14. Domenice S, Arnhold IJP, Costa EMF et al. 46,XY Disorders of Sexual Development. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, Dungan K, Grossman A, et al., editors. *Endotext*. South Dartmouth (MA): MDText.com, Inc.; 2000
15. Walia R, Singla M, Vaiphei K et al. Disorders of sex development: a study of 194 cases. *Endocr Connect* 2018; 7(2):364–71.
16. Praburam Pm. Medical Audit Of Children With Ambiguous Genitalia- Review Of Children Treated Over 18 Years. In 2015.
17. Tan MH, Li J, Xu HE et al. Androgen receptor: structure, role in prostate cancer and drug discovery. *Acta Pharmacol Sin* 2015; 36:3-23
18. Lee DK, Chang C. Expression and degradation of androgen receptor: mechanism and clinical implication. *The Journal of Clinical Endocrinology & Metabolism* 2003; 88(9):4043-54.
19. Atta I, Ibrahim M, Parkash A et al. Etiological diagnosis of under virilized male/ XY disorder of sex development. *J coll Physicians Surg Pak* 2014; 24:714-8.
20. Cohen-Kettenis PT. Psychosocial and psychosexual aspects of disorders of sex development. *Best Practice & Research Clinical Endocrinology & Metabolism* 2010; 24(2):325-34.
21. Nussbaum RL, McInnes RR. *Thompson & Thompson-Genética Médica*. Elsevier 2008; 7:111-4.
22. How common is intersex? Intersex Society of North America. Available at <https://isna.org/faq/frequency/>.
23. Paris F, Gaspari L, Philibert P et al. Disorders of sex development: Neonatal diagnosis and management. *Endocr Dev* 2012; 22:56-71.
24. Gangaher A, Chauhan V, Jyotsna VP et al. Gender identity and gender of rearing in 46 XY disorders of sexual development. *Indian J Endocrinol Metab* 2016; 20(4):536–41.
25. Walia R, Singla M, Vaiphei K et al. Disorders of sex development: A study of 194 cases. *Endocr Connect* 2018; 7(2):364–71.
26. Vasundhera C, Jyotsna VP, Kandasamy D et al. Clinical, hormonal and radiological profile of 46XY disorders of sexual development. *Indian J Endocrinol Metab* 2016; 20(3):300–7.