# CLINICAL SPECTRUM OF 46, XY DISORDER OF SEX DIFFERENTIATION IN CHILDREN PRESENTING AT NICH

Dr. Muhammad Nasir Javed, Dr. Mohsina Noor Ibrahim, Dr. Ikramullah Shaikh, Dr. Zubair Khoso, Dr. Versha Rani Rai, Dr. Heera Nand

National Institute of Child Health, Pakistan

**ABSTRACT:**

**Objective:**

To determine different Clinical spectrum, biochemical and radiological profile, External masculinization score (EMS) of 46, XY disorder of sex differentiation (DSD) and its etiological diagnosis.

**Methodology:**

This is a cross-sectional, observational study conducted at National Institute of Child Health, Pakistan. Patients with clinical presentation of DSD who were labeled XY on karyotyping were enrolled in the study after explanation of study protocol in the language of understanding to parents/guardians. A thorough clinical examination consisting of height, weight, blood pressure, presence of hyperpigmentation, assessment of pubertal stage, penile length, The External Masculinization Score (EMS) scoring, associated anomalies or dysmorphic features were made and recorded for each patient. Statistical Package for Social Sciences (SPSS) version 23 was used to enter, sort and analyze the data. Shapiro – Wilk test was used to determine the normality of data.

**Results:**

Mean age of study participants was reported as 5.0 ± 4.1 years at the time of presentation, the most frequently reported presenting complain was Atypical genitalia in 54 (43.2%) followed by Bilateral Inguinal Hernia in 21 (16.8%) of patients. Mean EMS scoring associated with presenting complain, Atypical Genitalia reported mean EMS scoring of 4.43 ± 2.4, bilateral inguinal hernia as 8.4 ± 3.2, Hypospadias as 6.6 ± 1.0, Micro penis as 8.2 ± 1.2, Precocious puberty as 11.6 ± 0.4, Right inguinal hernia as 5.1 ± 4.0, Small phallus as 8.3 ± 0.7 and small testis as 10.5 ± 1.6 respectively. HCG stimulation test was presented as positive in 106 (84.8%) and negative in 16 (12.8%).

**Conclusion:**

This study concludes that 46 XY DSD has higher incident rate in Pakistan, however, by understanding the diversity of presenting complaints, examination findings, radiological anatomy and hormonal profile these cases can be predicted and manage accordingly, these cases are presented in a variety of ways.

**Keywords:** DSD, 46XY, Sex differentiation, External masculinization score (EMS)

## INTRODUCTION:

Disorders of sex development (DSD) are congenital diseases characterized by abnormalities in the development of gonadal, chromosomal, or anatomical sex[1]. The terms used to characterize abnormal sexual differentiation have been updated by the European Society for Pediatric Endocrinology and the Lawson Wilkins Pediatric Endocrine Society consensus. Three major categories were used to classify the disorders:

1. Chromosome X/46, XY mixed gonadal dysgenesis [MGD] and chromosomal XO Turner and variants (45, 47, XXY Klinefelter and variants, 45, X/46, XY) and chromosomal XX/46, XY chimeric type or mosaic type
2. 46, XY DSD (abnormalities in androgen synthesis/action or disorders of testicular development)
3. 46, XX DSD (fetal androgen excess or abnormalities of ovarian development)[2]

At the Chicago Consensus Meeting in 2005, the term "congenital conditions within which the development of chromosomal, gonadal, and anatomic sex is atypical" was used to describe disorders of sex development (DSDs)[3]. This definition was then published as a Consensus Statement in 2006. However, there have been and continue to be a number of controversies surrounding DSDs. These controversies stem from the negative connotations that organizations and professionals associate with terms like "disorders," as well as the fact that some health professionals view terms like "intersex," "pseudo-hermaphroditism," "hermaphroditism," and "sex reversal" as inaccurate, non-descript, and confusing. While other authors believe that the classification and nomenclature suggested in the Chicago agreement is not the most appropriate, others prefer the term "differences" and use the same acronym—DSD—to refer to differences of sex development[4]. A person's phenotypic sex is determined by the type of gonad that develops in the embryo, a process that is in turn determined by their individual constitution or genetic inheritance. However, the development of gonads differs from the development of any other organ because they have the capacity to differentiate into either the ovaries or the testes, two functionally distinct organs[5]. But there are a lot more factors that go into determining a person's sex; for example, a person's sexual identity encompasses any actions that have a sexual connotation, like speaking patterns, gestures and habits, leisure choices, and dream themes. Hormonal impacts have been found to impact not only the development and differentiation of the internal and external genitalia, but also the differentiation of the embryo's brain into a sexual organ, possibly via regulatory systems akin to those established in the external genitalia. However, it's also likely that adult sexual behavior is influenced by patterns of hormonal secretion as a result of the induction of the central nervous system (CNS) by hormones[4-5].

Data about the prevalence of DSD is limited, indicating a reported range of 1 in 3,000 to 1 in 5,500 incident worldwide[6]. It is frequently impossible to tell the sex at first glance. According to data that has been published, genital ambiguity occurs between 1:2000 and 1:4500 times every year. The reported incidence of DSD among 46 XY persons is 1 in 20,000 births[6]. Testicular or mixed gonadal dysgenesis occurs in 1 in 10,000 live births, while ovotesticular DSDs occur in 1:100,000. However, the incidence rises to 1:200 to 1:300 when all congenital defects such as hypospadias and cryptorchidism are taken into account. Gonadal dysgenesis, an early fetal-onset primary hypogonadism characterized by insufficient production of androgen and anti-Müllerian hormone (AMH), can occur in individuals with XY chromatin material. This disrupts the process of fetal sex differentiation at the gonadal differentiation stage and results in the development of atypical or female-like genitalia. Isolated abnormalities in either or both of the AMH or androgen secretion pathways can also cause disruptions in the genital development stage of the sex differentiation process[7-9]. Patients with 46, XY DSD present with a wide range of external genitalia patterns at birth, ranging from a phallus that looks virtually entirely feminine to genitalia that nearly entirely resemble female genitalia with modest phallus hypertrophy. The testes can lie in the inguinal or abdominal regions. The ability of the testicles to synthesize testosterone, the 5-alpha-reductase enzyme's ability to convert testosterone into dihydrotestosterone (DHT), or the existence of testosterone-sensitive receptors are all necessary for the development of the genital system[6,9]. Comparing subjects with 46, XY DSD to typical 46, XY people, the former exhibit less virilization of the genitalia. The genesis could be linked to Leydig cell hypoplasia, disruptions in the manufacture of testosterone, insufficiency of the 5-alpha-reductase enzyme (DEF5α), androgen insensitivity syndrome (AIS), gonadal dysgenesis (GD), testicular regression syndrome, or ovotesticular DSD [10].
In 30–40% of cases, XY's precise etiology cannot be determined despite having numerous genetic factors (46). 46, Children with decreased prenatal development are often shown to have XY DSD, even in the absence of any other related deformity or steroidogenic abnormality.

According to other research, low birth weight is linked to approximately 30% of cases of unexplained 46 XY DSD, suggesting that early pregnancy adverse events are a common cause of congenital non-genetic 46 XY DSD[11-12].

The rationale behind this study is to gain better understanding of the condition and its associated characteristics. By studying the clinical profile of 46, XY DSD we anticipate classifying individuals according to the new DSD consensus. As cases of DSD invite enormous challenges for accurate diagnosis, sex assignment and intervention.

This study aims to determine different Clinical spectrum, biochemical and radiological profile, External masculinization score (EMS) of 46, XY disorder of sex differentiation (DSD) and its etiological diagnosis in children and adolescents presenting to the Pediatrics endocrine department of National Institute of child health (NICH), Karachi.

## METHODOLOGY:

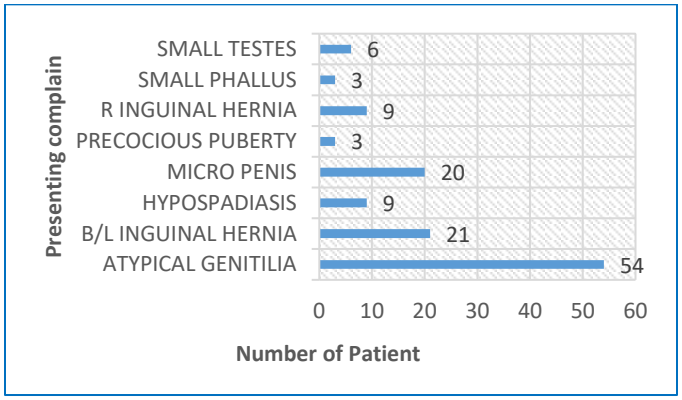
This is a cross-sectional, observational study conducted at National Institute of Child Health, Pakistan. The data was collected after obtaining approval from institutional review board of ethics (IERB approval # 56-2023) for the duration of four months starting from 31.12.2023 till 30.04.2024.
Sampling method was non-Probability consecutive, Patients with clinical presentation of DSD who were labeled XY on karyotyping were enrolled in the study after explanation of study protocol in the language of understanding to parents/guardians. Patients without karyotyping results, isolated hypospadias and, Patients with mixed sex chromosome or XX on Karyotypes were excluded from study.
Sample size was calculated by considering a similar article from Dar SA[13] conducted at Jammu and Kashmir for the duration of 02 years, the obtained sample size for referenced study was 41, upon considering the frequency of cases in past 1 year we have used WHO sample size calculator and required minimum sample size was n=125.
A pre-structured questionnaire was used to gather data, with required details of demographics such as age, family history of short stature, antenatal details, infertility, sibling death and precocious puberty along with the details of clinical features including age at presentation, presenting complaints, and assigned gender were also recorded.
Criteria suggesting DSD included atypical genitalia (i.e. apparent female genitalia with clitoromegaly, posterior labial fusion or inguinal/labial mass and apparent male genitalia with non-palpable testes, or inguinal/labial mass and apparent male genitalia with non-palpable testes), micropenis, undescended testis (testes presenting as inguinal hernia or abdominal testes found on imaging studies), incomplete or delayed puberty and primary amenorrhea were noted. A thorough clinical examination consisting of height, weight, blood pressure, presence of hyperpigmentation, assessment of pubertal stage, penile length, The External Masculinization Score (EMS) scoring, associated anomalies or dysmorphic features were made and recorded for each patient. Measurements of penile length was taken with a rigid ruler, graded millimeters.

As a part of evaluation of XY, DSD, we have performed abdominopelvic ultrasound, karyotype, and hormone measurement (testosterone, FSH, LH, 17-hydroxy progesterone, and HCG stimulation test). We proceeded for Genito-gram (to display the type of urethra, presence of vagina, cervix, and urogenital sinus) before laparoscopy and gonadal biopsy in patients with cryptorchidism, atypical genitalia and in patients who have Mullerian duct structure on ultrasonography. Confidentiality of data was made sure by primary investigator, and data was kept secured only accessible to PI. Patient's identification and information was kept safe and digital record of data was encrypted, and password protected.
Statistical Package for Social Sciences (SPSS) version 23 was used to enter, sort and analyze the data. Shapiro – Wilk test was used to determine the normality of data. Mean ± SD was calculated for continuous variables such as age, serum LH, FSH and testosterone levels. Frequencies and percentages were determined for age distribution, gender, presenting complaints, etiological diagnosis, and HCG stimulation test. Effect modifier like age, height, and weight were controlled through stratification. Post stratification Chi-square test was applied and p-value of $<0.05$ was considered as significant.

## RESULTS:

Mean age of study participants was reported as 5.0 ± 4.1 years at the time of presentation, mean weight was 14.6 ± 12.8 kgs, the most frequently reported presenting complain was Atypical genitalia in 54 (43.2%) followed by Bilateral Inguinal Hernia in 21 (16.8%) of patients. (Fig I)

Fig I: Commonly reported presenting complaints.

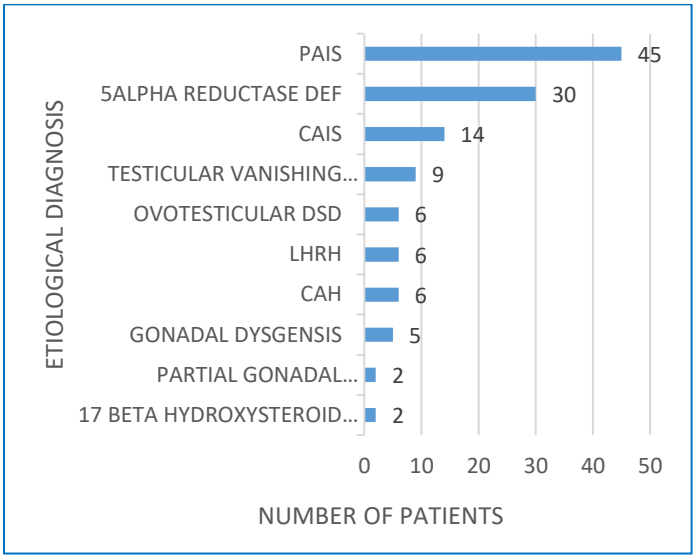



Genito-gram findings were reported as type of urethra indicating as male urethra in 74 (59.1%) and female urethra as 51 (40.8%), Any fistulous communication indicated in Genito-gram were reported in 23 (18.4%) patients, Mullerian duct remnant was reported in 24 (19.2%) patients and two perineal openings were reported in 9 (7.2%).

Mean EMS scoring associated with presenting complain, Atypical Genitalia reported mean EMS scoring of 4.43 ± 2.4, bilateral inguinal hernia as 8.4 ± 3.2, Hypospadias as 6.6 ± 1.0, Micro penis as 8.2 ± 1.2, Precocious puberty as 11.6 ± 0.4, Right inguinal hernia as 5.1 ± 4.0, Small phallus as 8.3 ± 0.7 and small testis as 10.5 ± 1.6 respectively. HCG stimulation test was presented as positive in 106 (84.8%) and negative in 16 (12.8%).

15 (12%) had female gender as assigned, while 107 (85.6%) had male gender assigned however, 3 (2.4%) patients didn't had any assigned gender at the time of presentation. In total 125 included patients, Etiological characterization was reported in Fig I, with the most commonly reported etiology of Partial androgen insensitivity syndrome (PAIS) in 45 (36%) patients followed by 5-alpha reductase DEF reported in 30 (24%) patients. Complete androgen insensitivity syndrome (CAIS) was reported in 14 (11.2%), Testicular vanishing syndrome in 9 (7.1%), Congenital adrenal hyperplasia CAH in 6 (4.8%), Luteinizing hormone releasing hormone receptor defect (LHRH) in 6 (4.8%), Ovotesticular DSD in 6 (4.8%), Gonadal dysgenesis in 5 (4%), Partial gonadal dysgenesis in 2 (1.6%) and 17-Beta Hydroxysteroid dehydrogenase DEF in 2 (1.6%) patients respectively.

Fig II: Etiological presentations of study participants.




Physical examination at presentation was reported in table I, indicating highest frequency of small size penis 88 (70.4%), Proximal urethral meatus 23 (18.4%), Gonads were mostly located in Scrotum 41 (32.8%) and in bilateral inguinal region 36 (28.8%), Labioscrotal folds were fused in 70 (56%) respectively.

Table I: Physical examination of study participants.

| Physical examination at presentation | | | |
|---|---|---|---|
| Variables | | Frequency | Percent |
| Penis | SMALL | 88 | 70.4 |
| | CLITORIS | 9 | 7.2 |
| | SMALL WITH CHORDAE | 6 | 4.8 |
| Urethral Meatus | PROXIMAL | 23 | 18.4 |
| | FEMALE LIKE | 9 | 7.2 |
| | MID | 3 | 2.4 |
| | DISTAL | 3 | 2.4 |
| | PERINEAL | 11 | 8.8 |
| Gonads | B/L INGUINAL REGION | 36 | 28.8 |
| | B/L SCROTAL FOLDS | 3 | 2.4 |
| | LEFT IN INGUINAL REGION | 6 | 4.8 |
| | LEFT IN SUPRASCROTAL | 2 | 1.6 |
| | NOT PALPABLE | 15 | 12.0 |
| | RIGHT IN ABDOMEN LEFT NOT PALPABLE | 2 | 1.6 |
| | RIGHT IN INGUINAL LEFT NOT PALPABLE | 6 | 4.8 |
| | RIGHT IN SCROTUM LEFT NOT PALPABLE | 2 | 1.6 |
| | SCROTUM | 41 | 32.8 |

| | | | |
|---|---|---|---|
| | SINGLE TESTIS IN SCR | 3 | 2.4 |
| | SUPRASCROTAL REGION | 9 | 7.2 |
| Labiosactoral folds | UNDER DEVELOPED SCROTUM | 3 | 2.4 |
| | FUSED | 70 | 56.0 |
| | UNDER DEVELOPED | 12 | 9.6 |
| | UNFUSED | 40 | 32.0 |
| Right Gonadal Location | Abdomen | 8 | 6.4 |
| | Labioscrotal folds | 11 | 8.8 |
| | Inguinal Region | 43 | 34.4 |
| | Supra Scrotal region | 20 | 16.0 |
| | Pelvis | 3 | 2.4 |
| Left Gonadal Location | Abdomen | 9 | 7.2 |
| | Inguinal region | 46 | 36.8 |
| | Labioscrotal folds | 9 | 7.2 |
| | Scrotum | 41 | 32.8 |
| | Supra Scrotal region | 15 | 12.0 |
| Mullerian Duct Remnants | Absent | 102 | 81.6 |
| | Present | 23 | 18.4 |

Ultrasound findings determined gonadal location and Mullerian duct remnants, indicating highest frequency of right and left gonad located in inguinal region with 43 (34.4%) and 46 (36.8%) frequency respectively. Mullerian duct remnant was reported as present in 23 (18.4%) of patients.

Table II: Ultrasonography findings in study participants.

| **Ultrasound findings** | | | |
|---|---|---|---|
| **Variables** | | **Frequency** | **Percent** |
| | Scrotum | 37 | 29.6 |

Association of laboratory parameters and etiological diagnosis were reported in table II, indicating elevated FSH, LH in 5Alpha reductase DEF, Ovotesticular DSD and CAIS. However, OHP was reported as elevated in CAIS followed by Testicular vanishing syndrome. The significance of mean values was reported as significant in all variables.

Table III: Association of etiological diagnosis with laboratory parameters.

| Variables | ETIOLOGICAL DIAGNOSISN | | | | | | | | | P-Value |
|---|---|---|---|---|---|---|---|---|---|---|
| | PAIS | 5ALPHA REDUCTASE DEF | CAIS | TESTICULAR VANISHING SYNDROME | OVOTESTICULAR DSD | LHRH | CAH | GONADAL DYSGENSIS | 17 BETA HYDROXYSTEROID DEHYDROGENASE DEF | |
| FSH | 1.61 ± 0.12 | 47.1 ± 2.5 | 18.52 ± 2.78 | 11.82 ± 2.14 | 32.4 ± 12.8 | 2.48 ± 1.27 | 1.89 ± 2.54 | 11.9 ± 2.45 | 1.29 ± 0.48 | <0.0001 |
| LH | 0.30 ± 0.04 | 8.18 ± 0.84 | 2.54 ± 1.78 | 9.12 ± 2.48 | 3.81 ± 2.54 | 9.14 ± 1.5 | 2.81 ± 1.99 | 14.9 ± 8.2 | 11.9 ± 2.7 | 0.003 |
| OHP | 1.24 ± 0.08 | 0.48 ± 0.04 | 14.0 ± 0.41 | 4.59 ± 4.98 | 0.26 ± 0.20 | 2.19 ± 0.04 | 0.19 ± 0.03 | 1.84 ± 2.46 | 0.94 ± 0.14 | 0.024 |
| HCG Pre Testo | 31.6 ± 42.4 | 1.26 ± 1.35 | 26.2 ± 26.1 | 15.69 ± 19.0 | 6.25 ± 4.1 | 16.1 ± 2.7 | 0.91 ± 1.19 | 6.3 ± 1.71 | 5.4 ± 1.24 | 0.019 |
| HCG Post testo | 93.5 ± 60.7 | 1.2 ± 1.45 | 115.0 ± 27.3 | 140.4 ± 92.1 | 105.9 ± 59.2 | 30.4 ± 0.08 | 65.86 ± 69.2 | 42.3 ± 1.28 | 32.4 ± 13.9 | 0.031 |

## DISCUSSION:

Studies conducted in affluent nations revealed that the majority of patients arrived during the neonatal stage and that the majority of treatments, including surgery, were started usually before six months of age, though this is sometimes delayed in our setting[14]. The fact that so many patients present at a later age speaks to the stigma and misinformation surrounding DSD in our society and emphasizes the need to educate parents and medical

professionals on the value of early detection of these conditions. The chromosomal abnormalities included in the new categorization include Turner syndrome, in which external genitalia are normal but chromosomal and gonadal sex are deviant. These illnesses may, as demonstrated in our study, present later due to small stature or delayed puberty, raising the average age of presentation. A consensus statement on the treatment of "intersex" illnesses was released in 2006 by the LWPES and the ESPE, along with a revised DSD classification proposal[15]-[16]. In our study the hormonal distribution has indicated significant alliance with available literature and reported elevated FSH and LH and low testosterone levels. The age at which XY DSD manifests varies. From the first day of birth until late adolescence, it may manifest. Different geographic areas' presentations of varying ages may be the result of socioeconomic, cultural, and educational variables. In a different research, the majority (55.6%) lists one to ten years[16]. Our study results indicated similar results and the eldest patients enrolled in the study was 14 years. The current findings also suggest that the clinical manifestations of XY DSD range widely, encompassing unclear genitalia as well as isolated hypospadias, micropenis, cryptorchidism, delayed puberty, and female-like genitalia with gonads and inguinal mass akin to that of the Migeon et al[17]. study. Even though 21.5% of the patients experienced genital ambiguity, a greater proportion of patients (86.6%) were raised as males. The urge to rear the majority of patients as men may be due to the general preference for male gender in Pakistani society. According to the statistics, AIS (33.1%), CAIS (4.8%) and PAIS/5 alpha reductase deficiency (28.3%), was the most common cause of XY DSD[18]. This study's PAIS patient percentage is higher than the findings of earlier research and is comparable to that of Erdogan et al.'s[19] study from 2010. Molecular genetic tests are required to validate the diagnosis of PAIS and 5 α-reductase deficiency in the 46 XY DSD patients. Furthermore, isolated hypospadias (10.2%) and micropenis (11.8%) without overt genital ambiguity were present in our 46 XY DSD patients. The likelihood of additional causes of XY DSD in these patients was eliminated[20]. These individuals might have been cases of a single, unexplained anatomical defect. In 46 XY DSD individuals, the frequency of disappearing testes syndrome was 1.6%; however, the study by Erdogan et al.[21] revealed a high prevalence of 13.3%.

These patients had no genital ambiguity and their testes were not descending. The incidence of vanishing testes syndrome within DSD is unknown because it was not included in the previous etiological classifications of intersex disorders[22]. 1.6% to 9% of live newborns are affected by cryptorchidism and hypospadias, two of the most prevalent genitourinary abnormalities in male children.18 (20.8%) of the individuals in this study had cryptorchidism, 3.7% had it unilaterally, and 17.1% had it bilaterally. In another study, the percentage of newborn patients with cryptorchidism was 5.9%, and almost one-fourth of the patients had non-palpable testes. 46, XY DSD can result from errors in testis determination or impairments in sex differentiation caused by mutations in genes found in the X, Y, or autosomal chromosomes. Sex before determining the gender of XY patients with under-manifestation—which is typically challenging—careful and accurate morphological, chromosomal, hormonal, and molecular genetics examinations must be performed in both clinical and laboratory settings[23-25].

Social stigmas, a widespread lack of awareness, and general disregard of DSD exist in Pakistan. Because each case is different, it might be challenging to determine the cause in settings with limited resources. 46, XY DSD can result from mutations in genes found in the X, Y, or autosomal chromosomes that cause anomalies in testis determination or disorders in sex differentiation. Prior to gender assignment in XY patients with under-virilization—which can be challenging in most cases—clinical and laboratory research must comprise meticulous and exact morphological, chromosomal, hormonal tests (both baseline and after stimulation), and molecular genetics analysis[26-29].

In Pakistan, DSD is mostly ignored, societal taboos exist, and many are not aware of its existence[32]. The patient that came in was about 20 years old on average. There have been reports of a comparable age at presentation from China[33]. There have been reports of this disorder's delayed appearance from various parts of the world, particularly the developing world, which highlights the unmet need for an early diagnosis and appropriate treatment of such disorders. The reason for even longer delays in presentation in these circumstances might be the taboo nature of discussing gender and sexuality in our society, which discourages parents from bringing up these topics, even with medical specialists[34]. In addition, the medical staff lacks the necessary training and resources to assist these patients and their families. [21,28,30]

Genital ambiguity in patients with 46 XY DSD may be caused by a partial or total impairment in androgen production (5α−reductase deficiency) or action (receptor insensitivity).[25] Given the significant diversity in masculinization, these patients can be raised as either boys

or girls.[21] Despite being raised as females, three of these patients sought clarity on their gender due to a gradual increase in masculinization[28]. DSD is one of the most challenging endocrine illnesses to treat in any civilization, but it is more challenging in communities that are very traditional, like our own. The difficulties of handling these patients is further compounded by social ideals, stigmatization, and cultural taboos. Recently, significant strides have been achieved in the acceptance of various gender identities through the adaption of laws to recognize the rights of individuals who identify as third gender. However, tremendous societal prejudice still makes their lives very difficult. The endocrinologist's job is to raise awareness of these disorders among the general public and medical professionals so that they can be treated early and effectively, allowing the affected individuals to lead normal, productive lives and be accepted by society rather than being mocked and despised.

The limitation of this study is cross-sectional study design and absence of follow up for further investigations,

## CONCLUSION:

This study concludes that 46 XY DSD has higher incident rate in Pakistan, however, by understanding the diversity of presenting complaints, examination findings, radiological anatomy and hormonal profile these cases can be predicted and manage accordingly, these cases are presented in a variety of ways. Age at presentation is crucial, as specific etiology alter the presenting complaints and consequently delay presentation.

## DECLARATIONS:

Authors declared no conflict of interest.

No funding (agency or individual) are included.

Ethical approval was taken prior to data collection.

**Corresponding Author:**

**Dr Muhammad Nasir Javed**

**Post-graduate (FCPS) trainee**

**National Institute of Child Health**
nasir.javed2012@gmail.com

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