ORIGINAL ARTICLE

# Clinical Spectrum of Disorders of Sexual Differentiation

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## Abstract

**Objective:** To describe the mode of presentation and causes of the disorders of sexual differentiation in patients presenting in the Endocrine Clinic.

**Study Design:** Observational study.

**Place and Duration of Study:** The Endocrine and Diabetes Unit of Jinnah Postgraduate Medical Centre (JPMC), Karachi, from July 2012 to July 2014.

**Methodology:** Patients with phenotypic, psychosocial gender confusion or absence of gender appropriate secondary sexual maturation were enrolled in the study. Patients having chronic systemic disease, as cause of delayed puberty, were excluded from the study. SPSS 13 was used to evaluate the data.

**Results:** A total of 48 patients registered in the study with mean age of 19.9 ±8 years. Female gender was assigned to 28 (58.3%) of which 8 (28.57%) had genital ambiguity. Male gender was assigned to 20 (41.66%) patients at the time of birth and 7 (35%) of them had ambiguous genitalia. Karyotyping could be done in 36 (75%) patients of which 17 (47.2%) were females and 19 (52.7%) were males. Karyotypic gender of the 19 (48.57%) male patients was 46 XX, 46 XY and 47 XXY; in 4 (21.05%), 5 (26.3%) and 10 (52.6%) patients, respectively with 9 Klinfelter syndrome. Karyotypic gender of 17 (47.42%) female patients were 46 XX, 46 XY and 45 X0; in 5 (29.4%), 3 (17.64%) and 9 (52.9%) patients, respectively.

**Conclusion:** Disorder of sexual development constitutes a small but difficult area of endocrinology with disastrous consequences, especially if assigned wrong sex at birth. Mode of presentation of these cases was diverse ranging from delayed puberty, to gender confusion, to pregnancy in a male. Eventually in an adult patient assignment or reassignment of gender identity was primarily the patient's prerogative.

**Key Words:** *Disorders of sexual differentiation (DSD). Genital ambiguity. Karyotyping.*

## INTRODUCTION

Birth of an infant with ambiguous genitalia is a challenging situation for the family and the physicians. It is described as an endocrine emergency due to the necessity of gender assignment and involvement of multiple specialists to do so.[1] It also requires an ongoing engagement of the same group of professionals, as these patients continue to present many challenges as they progress from childhood to adolescence and adulthood.[2]

Advances in understanding the molecular genetics of abnormal sexual development and heightened awareness of the ethical and patient-advocacy issues mandated a re-examination of pre-existing nomenclature.[3] Terminologies such as intersex, hermaphroditism, and pseudohermaphroditism are controversial and potentially pejorative to patients.[4] In response to these concerns, the Chicago Consensus recommended a new terminology in 2005, based on the umbrella term of 'Disorders of Sex Differentiation (DSDs).[5]

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A clear consensus among clinicians has emerged in paediatric care; however, the same cannot be said of adult care services.[6] Few studies have been conducted in adolescents with DSDs, and a clear and pressing need exists for further research to guide the care of these patients.[7]

No data about DSD in adults is available from Pakistan. Awareness amongst obstetricians, pediatricians and traditional birth assistants is essential so that these complex cases are diagnosed properly, and appropriate management can be started immediately after birth. This will, to some extent, mitigate the psychological trauma faced by the family after the birth of neonates with ambiguous genitalia.

The aim of the study was to determine the mode of presentation and causes of DSD in patients presenting to the Endocrine Unit of Jinnah Postgraduate Medical Centre (JPMC), Karachi.

## METHODOLOGY

This observational study was a retrospective chart analysis of data from the Endocrine and Diabetes Unit of JPMC, prospectively collected from 2012 to 2014. Approval from Hospital's Ethical Committee was taken. All the patients who had presented with ambiguous genitalia (external genitalia not having typical male or female characteristics),[1] failure or delay in development of secondary sexual characteristics, or psychosocial

gender confusion, were included in the study after taking inform consent. All patients who had delayed puberty (absence of secondary sexual maturation by the age of 13 years in girls and 14 years in boys),[8] due to systemic diseases, were excluded from the study.

A detailed history, especially focused on genital ambiguity,[1] hirsutism (using modified ferrimen-gallwey score), precocious puberty (onset of puberty before 8 years in girls and 9 years in boys),[7] amenorrhea, and sub-fertility, was recorded. General physical examination with special attention to the genital anatomy was done. In particular, a careful examination of the groin, scrotal sac or labial folds was done to determine the presence of palpable gonads. The presence of even a single palpable gonad is highly suggestive of a testis or rarely an ovotestis, because the ovaries and streak gonad do not descend. Criteria of physical findings suggestive of DSD included previously unrecognized genital ambiguity, inguinal hernia in a girl, delayed or incomplete puberty, primary amenorrhea or virilization in a girl and breast development and/or gross or cyclic hematuria in a boy.[1] Diagnostic algorithms do exist, but with the spectrum of findings and diagnoses, no single evaluation protocol can be recommended in all circumstances. Measurements of 17-hydroxyprogesterone (170HP), testosterone (T), gonadotropins, serum electrolytes and Karyotyping were done. Imaging included abdomen-pelvic ultrasound followed by CT scan of pelvis, if needed.

Data was interpreted by using SPSS 13. The results were described as frequencies and percentages.

## RESULTS

A total of 48 patients were included in this study. The mean age at presentation was 19.9 ±8 years. Sex Assigned at Birth (SAB) was female in 28 (58.3%) and male in 20 (41.7%) patients.

The varied presentation of these cases included primary amenorrhea in 14 (29.16%) female sex-assigned patients (Table I). A full term pregnancy was the presentation in one patient who was assigned male SAB. Ambiguous genitalia were the presenting complaint of 9 (18.75%) patients, of which 3 were assigned female and 6 were assigned male SAB. However, clinical examination revealed that there were 6 more patients having ambiguous genitalia; hence, a total of 15 (31.25%) patients had genital ambiguity, of which 8 were assigned male and 7 were assigned female SAB (Tables IIa and b).

Imaging was carried out in 22 (45.75%) patients (Table III). Both male and female internal organs were seen in one male SAB patient. This patient also had laparotomy, and fragments of testicular tissue were seen on biopsy.

**Table I:** Presenting complaints of the patients with disorders of sexual differentiation.

| Presenting complaints (n=48) | Female SAB (n=28, 58.3%) | Male SAB (n=20, 41.7%) |
|---|---|---|
| Primary amenorrhea (n=14 ,29.1%)) | 14 (50%) | 0 |
| Delayed puberty (n=10,20.8% ) | 5 (17.85%) | 5 (25%) |
| Hirsutism (n=4, 8.3%) | 4 (14.28%) | 0 (0%) |
| Gynecomastia (n=4, 8.3%) | 0 (0%) | 4 (20%) |
| Irregular menstruation (n=2, 4.1%) | 2 (7.14%) | 0 (0%) |
| Infertility (n=2, 4.1%) | 0 (0%) | 2 (10%) |
| Incontinent hematuria (n=3, 6.25%) | 0 (0%) | 3 (15%) |
| Loss of libido (n=1, 2.08%) | 0 (0%) | 1 (5%) |
| Full term pregnancy (n=1, 2.08%) | 0 (0%) | 1 (5%) |
| Genital ambiguity (n=9, 18.75%) | 3 (10.17%) | 6 (30%) |

**Table IIa:** Genital ambiguity in male SAB patients on clinical examination (n=8, 53%).

| Genital ambiguity | Number of patients n=number, percentage |
|---|---|
| Small testes | 1, 12.5% |
| Undescended testes | 1, 12.5% |
| Undescended testes with hypospadias | 1, 12.5% |
| Micropenis | 2, 25% |
| Micropenis with absent testes and labia minora resembling anatomy | 1, 12.5% |
| Lack of fusion of scrotum producing labia majora like anatomy with undescended testes | 2, 25% |

**Table IIb:** Genital ambiguity in female SAB patients on clinical examination (n=7, 46.6%).

| Genital ambiguity | Frequency (n=number, percentage) |
|---|---|
| Clitoromegaly | 2, 28.57% |
| Clitoromegaly with fused labia | 1, 14.28% |
| Underdeveloped external genitalia | 1, 14.28% |
| Labia minora abnormality | 1, 14.28% |
| Labia minora abnormality with absent vaginal opening | 1, 14.28% |
| Labia majora with palpable testis | 1, 14.28% |

Due to high cost, 30 patients had complete hormone work up (Table III). Karyotyping could be done in 36 (75%) patients again due to cost constraints (Table III). On the basis of Karyotyping, a total of 8 patients were found to assign wrong gender at the time of birth. One male SAB patient had ectopia vesicae, which was repaired soon after birth; his Karyotyping showed 46 XX pattern.

Klinefelter's Syndrome (KS) was the main diagnosis in 10 patients, all were male SAB. Nine patients were diagnosed with Turner's Syndrome (TS) and all were rightly assigned female SAB. Congenital Adrenal Hyperplasia (CAH) was diagnosed in 9 female patients, 3 of whom had been assigned male SAB. Partial Androgen Insensitivity (PAIS, 5$\alpha$–reductase deficiency/ receptor defect) was diagnosed in 3 patients and all of them were assigned female SAB. Hypogonadotrophic Hypogonadism (HH) was diagnosed in two patients, of

**Table III:** Investigations performed.

| Investigations | | | | | | |
|---|---|---|---|---|---|---|
| Radiological findings (n=22) | Female SAB (n=17, 77.27%) | | | Male SAB ( n=5, 22.73%) | | |
| Female gonads (n=11) (50%) | 9 (52.9%) | | | 2 (40%) | | |
| Male gonads (n=3) (13.64%) | 2 (11.76%) | | | 1 (20%) | | |
| Rudimentary female gonads (n=5) (22.73%) | 5 (29.41%) | | | 0 (0%) | | |
| Absent gonads (n=1) (4.55%) | 1 (5.88%) | | | 0 (0%) | | |
| Testes in inguinal canal (n=1) (4.55%) | 0 (0%) | | | 1 (20%) | | |
| Both male and female gonads (n=1) (4.55%) | 0 (0%) | | | 1 (20%) | | |
| Hormonal analysis n=38 | Female SAB (F. SAB) | | | Male SAB (M. SAB) | | |
| | Normal | Increased | Decreased | Normal | Increased | Decreased |
| FSH (F.SAB=20, M.SAB=18) | 9 (45%) | 8 (40%) | 3 (15%) | 4 (22.22%) | 13 (72.22%) | 1 (05.56%) |
| LH (F.SAB=19, M.SAB=18) | 10 (52.63%) | 6 (31.58%) | 3 (15.79%) | 6 (33%) | 11 (61%) | 1 (06%) |
| Testosterone (F.SAB=10, M.SAB=18) | 4 (40%) | 6 (60%) | 0 (0%) | 2 (11%) | 3 (17%) | 13 (72%) |
| Estradiol (F.SAB=5, M.SAB=5) | 1 (20%) | 1 (20%) | 3 (60%) | 3 (60%) | 2 (40%) | 0 (0%) |
| Progesterone (F.SAB=1, M.SAB=2) | 1 (100%) | 0 (0%) | 0 (0%) | 1 (50%) | 1 (50%) | 0 (0%) |
| ACTH (F.SAB=2, M.SAB=2) | 1 (50%) | 1 (50%) | 0 (0%) | 0 (0%) | 2 (100%) | 0 (0%) |
| CORTISOL (F.SAB=4, M.SAB=2) | 4 (100%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (50%) | 1 (50%) |
| PROLACTIN (F.SAB=8, M.SAB=4) | 6 (75%) | 2 (25%) | 0 (0%) | 3 (75%) | 1 (25%) | 0 (0%) |
| 17OH PROG (F.SAB=8, M.SAB=2) | 0 (0%) | 8 (100%) | 0 (0%) | 1 (50%) | 1 (50%) | 0 (0%) |
| DHEA -S (F.SAB=6, M.SAB=2) | 3 (50%) | 2 (33%) | 1 (17%) | 1 (50%) | 0 (0%) | 1 (50%) |
| Karyotyping n=36 | Female SAB (n=17, 47.2%) | | | Male SAB (19, 52.7%) | | |
| 46XX (n=9) | 5 (29.4%) | | | 4 (21.05%) | | |
| 46XY (n=8) | 3 (17.6%) | | | 5 (26.3%) | | |
| 45X0 (n=9) | 9 (52%) | | | 0 (0%) | | |
| 47XXY (n=10) | 0 (0%) | | | 10 (52.6%) | | |

which one was brought up as male and one as female which was in accordance with their Karyotypes gender. Primary testicular failure, ovotesticular DSD, 46 XXDSD was seen in one patient each and all of these patients were assigned male SAB.

Gender reassignment was based on patient's express wishes ultimately after detailed psychological evaluation and family counselling, presence of dominant gonad, and development of external genitalia. After all of the preliminary evaluations, 5 out of 8 wrongly assigned patients had gender reassignment. These patients included 3 male SAB who were actually female CAH patients out of whom one patient had gender reassignment; the other two patients underwent surgical treatment for removal of internal sex organs and appropriate hormone replacement therapy. All the three female SAB with partial androgen insensitivity were re-assigned to male sex in accordance with their wishes. One male patient who had presented with pregnancy was reassigned female gender and a healthy full term baby was delivered through c-section.

## DISCUSSION

A DSD child is born in approx 1 in 2000 births globally (2% of live births).[9] Certain areas of the world have a high incidence of certain genetic forms of DSD; 5α-reductase deficiency is prevalent in southern Lebanon but is relatively rare in Caucasians and 17 β-hydroxysteroid dehydrogenase deficiency is very common in the Gaza Strip.[10] It is difficult to ascertain the incidence and the types of DSD in Pakistan for multifarious reasons.

The average age of the patient who presented was around 20 years. A similar age at presentation has been reported from China.[11] Delayed presentation of this disorder has been recorded from other regions of the world, especially the developing world, reflecting the unmet need for earlier diagnosis and proper management of such disorders.[11] The reason for even more delayed presentation in these cases may be because discussion of all things pertaining to gender and sexuality are taboo in our society which make parents reluctant to discuss these issues even with medical professionals. Moreover, the medical professionals are also ill-trained and ill-equipped to help these patients and their families. In addition, certain conditions like 5α-reductase deficiency and 17 β-Hydroxysteroid dehydrogenase deficiency can lead to a gradual transition in gender identity from female to male.[12] This adds to the complexity of gender reassignment process. Moreover, in many cases presenting early, it may be better to delay the process till adolescence is achieved, when it should be undertaken with the consent of the patient primarily, also including the family in the discussion as far as possible.[13]

KS is the most common sex chromosome disorder in males, affecting 1 in 660 men, which makes around 20% of male patients with XY DSD.[14] In this study, 20.8% of

DSD patients were diagnosed with KS and all were assigned male SAB. As KS patients have normal male external genitalia at birth, they are not assigned wrong sex. Diagnosis is delayed until delay in puberty, gynecomastia or even sub/infertility raises concern. This trend has been observed worldwide as only 10% of KS were diagnosed before puberty, indicating a severe delay in diagnosis.[15] The KS phenotype is a consequence of the supernumerary X-chromosome with increased number of CAG trinucleotide repeats in the Androgen Receptor (AR) in KS males thus reducing their sensitivity to testosterone.[16] Similarly, in newborns affected by TS (45, XO, 46 XX/45 XO mosaic), the external genitalia are appropriate for female sex assignment, regardless of whether the remaining X chromosome is maternal or paternal in origin.[17] Hence, wrong sex assignment at the time of birth is not seen in these patients, as seen in this case series also. In this study, 52% of the female SAB presented with delayed puberty or infertility were diagnosed with TS, which is comparable to 47% reported earlier.[18]

The genes of Y chromosome, in particular the sex-determining region of Y gene (SRY), plays a major role in encoding a Testis Determining Factor (TDF).[19] However, because of abnormal X/Y terminal exchange during paternal meiosis, some patients may develop testes in the absence of Y chromosome and then present at adolescence with gynecomastia, short stature, and rarely as ambiguous genitalia.[20] According to Vorona *et al*., 100 cases of XX reversal have been reported between 1996 and 2006 worldwide.[20] One male patient aged 35 years presented with gynecomastia and normal sized male genitalis. His Karyotyping was 46 XX. As it was not possible to do a PCR or FISH technique at that time, he could not be evaluated for the presence of SRY gene.

CAH is the most common cause of ambiguous genitalia in female patients, constituting approximately 50% of all cases of genital ambiguity in the newborn period.[21] CAH constituted 60% of the cases presenting with genital ambiguity in this case series. The most frequent defect (95% of the cases) being 21-hydroxylase deficiency. The increased androgen concentration triggers a variable degree of virilisation in female newborns, leading to wrong sex assignment at birth.

A defect in androgen synthesis (5$\alpha$–reductase deficiency) or action (receptor insensitivity), either complete or partial, may be responsible for genital ambiguity in patients of 46 XY DSD.[22] These patients can be reared as girls or boys, as there can be a marked variation in masculinization.[22] Three such patients were reared as girls, but due to progressive increase in masculinization, they had presented for clarification of sex/gender.

Reassignment of sex is a very difficult task. In comparison to the previous 'Optimal Gender Policy', introduced by John Hopkins which stated early reconstruction, newer recommendations, 'Full Consent Policy' requires feminizing and masculinizing procedures to be delayed till full consent from the patient can be obtained.[13] While performing surgery, emphasis is now on functional outcome rather than a strictly cosmetic appearance, as sexual dissatisfaction is very common in DSD patients who have undergone genitoplasty procedures. This may go on to affect the physical and mental health and social adjustment in these patients.[1] In future, the biological and tissue engineering materials (penile/testicular prosthesis) may be beneficial for surgical intervention in patients with assignment of male sex.[24]

All these patients were evaluated not only physically but psychological evaluation was also done in the presence of parents as well as individually. Final decision regarding gender identity was made by the patient. Hence, two female patients, who were assigned male SAB, refused reassignment of sex/gender. Patients of PAIS/ 5$\alpha$–reductase deficiency assigned female SAB, went through a long process of counselling, after which sex/gender reassignment and appropriate hormonal and surgical interventions were instituted.

In any society, particularly in overly conservative societies such as ours, DSD is one of the most difficult endocrine disorders to handle. Social values, stigmatization and societal taboos further compound the complexity of managing these patients. Recently, tremendous progress for acceptance of different gender identities has been made by adaptation of legislation for acceptance of the rights of people who choose the third gender. However, tremendous societal prejudice still makes their lives very difficult.

The goal of the endocrinologist is to make people and general practitioners aware of these disorders, so that they can be managed early and appropriately, such that they can become well adjusted and productive members of the society, with society looking upon them with compassion rather than disdain and ridicule.

There were issues of cost constrains; hence, few patients were not able to complete investigations. However, they were not excluded from the study so that the magnitude of the disorder and the financial and psychological implications on the families could be highlighted.

## CONCLUSION

Disorder of sexual development constitutes a small but difficult area of endocrinology with disastrous consequences, especially if assigned wrong sex at birth. Mode of presentation of these cases was diverse

ranging from delayed puberty, to gender confusion, to pregnancy in a male. Eventually in an adult patient assignment or reassignment of gender identity was primarily the patient's prerogative.

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