Original Article

Variability in Sex Assignment at Birth and Etiological Diagnosis of Differences of Sex Development: A Ten-Year Institutional Experience from Assam

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Abstract

Introduction: Differences of sex development (DSD) also known as disorders of sex development encompass a wide spectrum of conditions with varying clinical presentations across different age groups. This study aims to analyse various aetiologies of DSD in Assam and the variability of sex assignment at birth. **Methods:** This retrospective study included the records of people with DSD presenting to a tertiary centre over 10 years. The age at presentation, sex assignment, gender identity, degree of ambiguity, pertinent hormonal and radiological investigations were noted. Descriptive statistics were used for analysis. **Results:** The age of presentation varied widely, with peaks during infancy and puberty. The most prevalent DSD type was 46, XY DSD (61.2%), followed by 46, XX DSD (19.7%) and sex chromosome DSD (19.1%). Among people with 46, XY DSD, androgen biosynthesis disorders were dominant, particularly 5-a reductase 2 deficiency (46.7%). Among 46, XX DSDs, the most common subtype was androgen excess disorders (51.7%) comprising 21a-hydroxylase deficiency (48,3%) and 11ß-hydroxylase deficiency (3.4%). Turner syndrome was most prevalent among sex chromosome DSD (71.4%) with others being Klinefelter syndrome, 45, XO/46, XY mixed gonadal dysgenesis and 46, XX/46, XY chimerism. The degree of ambiguity was variable depending on the type of DSD and similarly, sex assignment at birth was influenced by the level of ambiguity. **Conclusion:** The study underscores the significance of comprehensive approaches for DSD diagnosis and management, especially in regions with limited resources. The insights gained from this clinical study offer valuable understanding and aid in addressing the complexities associated with these conditions.

Keywords: Ambiguous genitalia, clinical presentation, DSD, sex assignment, sex of rearing

Introduction

Differences of sex development (DSD) encompass a heterogeneous group of conditions, which present across different age groups with a wide spectrum of clinical presentation. It is defined as a condition in which chromosomal, gonadal or anatomical sex is atypical.[1] The classification of DSD includes sex chromosome DSD, 46, XY DSD and 46, XX DSD, with many subclassifications within each category. It is vital to achieve a specific diagnosis to plan appropriate management and long-term care. Diagnosis of the DSD requires hormonal, imaging, and genetic analysis. These diagnostic modalities have changed over time, especially genetic testing which has evolved from traditional karyotyping and sex chromosome fluorescence *in situ* hybridization to quantitative fluorescent polymerase chain reaction, microarray/comparative genomic hybridization, and multiplex ligation-dependent probe amplification for detecting smaller copy number variations in known DSD genes. Additionally, next-generation sequencing is gaining prominence for high-throughput analysis. The recommended approach integrates clinical phenotyping, biochemical data, and genetic results, instead of traditional stepwise stratification, where targeted genetic tests are typically conducted only after biochemical guidance.[2] The management

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of people with DSD poses significant challenges in accurate diagnosis, sex assignment, and intervention, necessitating a specialized comprehensive, team-oriented approach that addresses medical, surgical, social, and psychological aspects. DSD in the neonatal period usually presents with ambiguous genitalia with or without a life-threatening salt-losing crisis whereas during childhood precocious puberty or gender dysphoria may be the presentation. Adolescents may present with delayed puberty or gender dysphoria and adults may have infertility. However, in India, many DSD cases present late due to a lack of awareness, social stigma, and economic constraints. The incidence of different DSD conditions varies, and reliable data on prevalence are limited, especially from the North-East part of India. Hence this study was done to get insight into the patterns of DSD in this part of India.

Materials and Methods

This was a retrospective study that was conducted at a tertiary care centre in the North-East part of India. The study design involved the analysis of the records of 147 patients with DSD of any age group who presented to the Department of Endocrinology over ten years, from January 2013 to February 2023. The clinical presentation, age at presentation, sex assigned at birth, gender identity, gender role, and any gender dysphoria were recorded. The clinical examination records of the degree of ambiguity (External Masculinization Score – EMS [Table 1]/Prader score) were noted. The relevant hormonal investigations including baseline serum Cortisol, Follicular stimulating hormone (FSH), Luteinizing hormone (LH), total testosterone (T), Anti Mullerian Hormone (AMH), 17-hydroxyprogesterone (17OHP) and inhibin B (where needed) were recorded. Post-human Chorionic Gonadotropin (hCG) stimulated (500 IU in infants, 1000 IU for children aged 1–10 years, and 1500 IU for > 10 years for 3 days subcutaneously) testosterone, dihydrotestosterone (DHT), and androstenedione (A) were noted. However, for infants who were in mini puberty, hCG stimulation was not done. FSH, LH, AMH, and T were measured by chemiluminescence assay (IMMULITE 1000 analysers till the year 2017) and electrochemiluminescence (ECLIA) assay (Cobas e 411 analysers, Roche Diagnostics from 2017 onwards). DHT, A, and inhibin B were measured with enzyme-linked immunosorbent assay (ELISA). The inter and intra-assay coefficient of variation was < 10%. Imaging including ultrasonography (USG) and/or magnetic resonance imaging (MRI) was done to look for Mullerian and Wolffian structures as well as the gonads. Laparoscopy was done only in selected cases and records were noted. Karyotyping was done in all patients of DSD.

46, XY DSD: Among the 46, XY DSDs, 5-α reductase 2 deficiency was diagnosed when hCG stimulated T/DHT ratio was more than 10, and 17-β hydroxysteroid dehydrogenase (HSD) 3 deficiency was diagnosed when hCG stimulated T/A was less than 0.8. Complete androgen insensitivity syndrome (CAIS) was diagnosed when a 46, XY subject with female phenotype presented with primary amenorrhoea and breast development with elevated T and LH with no Mullerian structures on imaging. If genital ambiguity or hypospadias was associated with elevated T and LH without Mullerian structures, a diagnosis of partial androgen insensitivity syndrome (PAIS) was made. Vanishing testes syndrome was diagnosed when a 46, XY subject with male phenotype presented with empty scrotal sacs, low T, elevated FSH and LH, low AMH and inhibin B, and absent gonads on imaging. A diagnosis of isolated hypospadias was made with normal T, normal gonadotropins, T/DHT < 10 and T/A > 0.8. Swyers syndrome was diagnosed in a 46, XY phenotype female with absent secondary sexual characters, elevated gonadotropins, low T, and presence of Mullerian structures whereas partial gonadal dysgenesis was diagnosed when the patient had ambiguous genitalia, Mullerian structures, and elevated gonadotropins.

46, XX DSD: Among subjects with 46, XX DSD, 21α-hydroxylase deficiency congenital adrenal hyperplasia (CAH) was diagnosed when basal or cosyntropin stimulated 17OHP was elevated more than 1000 ng/dL whereas 11β-hydroxylase deficiency CAH was diagnosed with cosyntropin stimulated plasma 11-deoxycortisol more than 1800 ng/dL and low cortisol. Subjects with absent secondary sexual characters with primary amenorrhoea without genital ambiguity with elevated gonadotropins were labelled as gonadal dysgenesis. When both testicular and ovarian components were detected in the gonads and the subject presented with genital ambiguity with the presence of both Mullerian and Wolffian structures then the diagnosis of ovotesticular DSD was made. XX testicular DSD was diagnosed if Mullerian structures were absent and AMH and T were in the male range. Mayer–Rokitansky–Küster–Hauser (MRKH) syndrome was diagnosed with normal

Table 1: External masculinization score (EMS)

3	Yes	No	Normal		
2			Distal		
1.5				Labio-scrotal	Labio-scrotal
1			Mid	Inguinal canal	Inguinal canal
0.5				Abdomen	Abdomen
0	No	Yes	Proximal	Absent	Absent
Score	Scrotal fusion	Micro penis	Urethral meatus	Right	Left
				Gonad	Gonad

adult female phenotype, primary amenorrhoea with absent Mullerian structures.

Sex chromosome DSDs were diagnosed based on typical clinical features and karyotype.

Statistical analysis was performed using SPSS version 21. The distribution of data was analysed using the Shapiro–Wilk test. Quantitative data were expressed using frequency, percentage, means, median, range and standard deviation. Categorical variables were described using numbers and percentages. Correlation between variables was assessed using Spearman correlation.

Ethical aspects

The study was approved by Gauhati Medical College and Hospital Ethics Committee vide letter MC. No. 190/2007/Pt-II/April2023/16 on 23/06/2023. Consent was waived due to the retrospective nature of the study. Patient confidentiality was maintained. All study procedures were according to the guidelines laid down in the Declaration of Helsinki 1964 and as revised later.

Results

The records of 147 people with DSD were included in the present study. The age range of presentation was 3 days to 35 years with median age of 8 years. A good proportion of cases (40.1%) presented in the first 5 years of life with approximately 17.6% of them presented in infancy. A second peak of presentation was seen at the age of puberty [Figure 1]. The clinical presentation of DSDs is depicted in Figure 2.

Among all types of DSDs, 46, XY DSD was the most common DSD (61.2%) followed by 46, XX DSD (19.7%) and sex chromosome DSD (19.1%). The etiological diagnosis, sex assigned at birth, and age of presentation are depicted in Tables 2–4.

46, XY DSD: Among 46, XY DSD, disorders of androgen biosynthesis were the most common (57.8%). Disorders of androgen action constituted 18.9%, disorders gonadal of development 3.3% and others were 20%. The majority of the 46, XY DSDs were due to 5-α reductase 2 deficiency (46.7%) with a median age of presentation of 2.88 years with an EMS score ranging from 1 to 11. Most of the 5-α reductase 2 deficiency DSDs (88%) were assigned male sex at birth (median EMS 6) whereas only 11.9% of these subjects were assigned as female sex at birth (median EMS 2). The EMS correlated negatively with the T/DHT ratio (Spearman's rho: -0.433 P – 0.004). The other androgen biosynthetic defects that were seen in our study were 17β-HSD 3 deficiency (10%, n = 9) and 3β-HSD 2 deficiency (n = 1). Out of the 9 cases of 17β-HSD 3 deficiency, 8 were assigned as female at birth with a median EMS of 3.

All subjects of CAIS were assigned as female at birth and the mean age of presentation was 26 years due to primary amenorrhoea. The subjects with PAIS presented with a wide spectrum of ambiguity with an EMS ranging from 1.5 to 10. Among the PAIS cases, 28.6% (n = 4) of the subjects were assigned as female at birth with a median EMS of 3 with gonads located from the inguinal canal to labioscrotal swellings.

The median age of presentation of complete gonadal dysgenesis and partial gonadal dysgenesis was 28.5 and 13 years, respectively. All of these subjects were assigned as female at birth and presented with absent secondary sexual characters and primary amenorrhoea. All subjects of vanishing testes syndrome and isolated hypospadias were assigned as male at birth with a median EMS of 6 and 9, respectively.

46, XX DSD: In 46, XX DSD, disorders of gonadal development, androgen excess and others were 24.1%, 51.7% and 24.2%, respectively. A total of 21 hydroxylase deficiency CAH was the most common 46, XX DSD which included both salt wasting and simple virilizing variants. Subjects with salt-wasting CAH presented from 2 to 3 weeks of life with

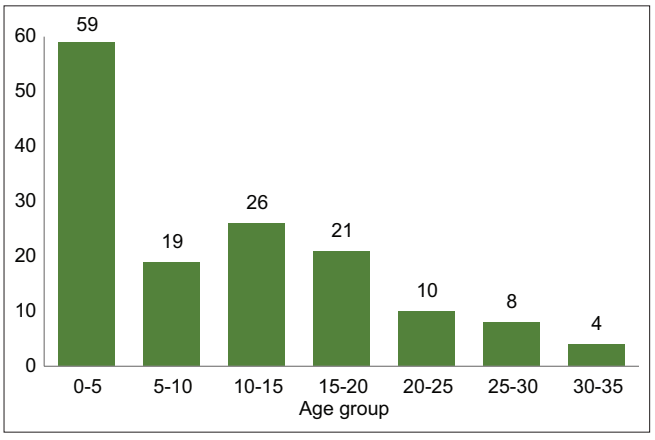

Figure 1: Age distribution of DSD at presentation (n=147)

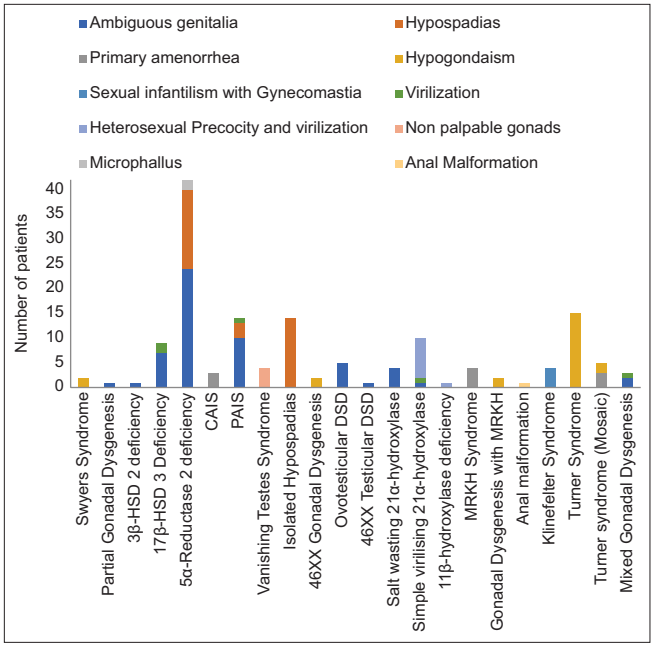

Figure 2: Spectrum of clinical presentation in the different categories of DSD

Table 2: Clinical characteristics of 46, XY DSD

46, XY DSD N=90 (61.2%)	Age of presentation (Median years)	Sex assigned at birth		
		Female	Male	Not assigned
Disorder of Gonadal Development				
Swyers syndrome – 2 (2.2%)	28.5	2	0	0
Partial gonadal dysgenesis – 1 (1.1%)	13	1	0	0
Disorder of androgen synthesis				
3β-HSD 2 deficiency – 1 (1.1%)	0.16	0	1	0
17β-HSD 3 deficiency – 9 (10%)	0.16	8	0	1
5α-reductase 2 deficiency – 42 (46.7%)	2.88	5	36	1
Disorder of androgen action				
CAIS – 3 (3.3%)	26	3	0	0
PAIS – 14 (15.6%)	4.5	4	10	0
Others				
Vanishing testes syndrome – 4 (4.4%)	15	0	4	0
Isolated hypospadias – 14 (15.6%)	9.5	0	14	0

Table 3: Clinical characteristics of 46, XX DSD

46, XX DSD N=29 (19.7%)	Age of presentation (Median years)	Sex assigned at birth		
		Female	Male	Not assigned
Disorder of Gonadal Development				
Gonadal dysgenesis – 2 (6.9%)	22	2	0	0
Ovotesticular DSD – 4 (13.8%)	2.5	0	4	0
Testicular DSD – 1 (3.4%)	0.16	0	1	0
Disorder of androgen excess				
Salt wasting 21α-hydroxylase – 4 (13.8%)	0.05	3	0	1
Simple virilising 21α-hydroxylase – 10 (34.5%)	4.5	8	2	0
11β-hydroxylase deficiency – 1 (3.4%)	2.5	1	0	0
Others				
MRKH syndrome – 4 (13.8%)	23.5	4	0	0
Gonadal dysgenesis with MRKH syndrome – 2 (6.9%)	19	2	0	0
Anal malformation – 1 (3.4%)	0.16	1	0	0

Table 4: Clinical characteristics of Sex chromosome DSD

Sex Chromosome DSD	Age of presentation (Median years)	Sex assigned at birth		
N=28 (19.1%)		Female	Male	Not assigned
47, XXY and variants – 4 (14.3%)	25.5	0	4	0
45, XO and variants – 20 (71.4%)	15	20	0	0
45, XO/46, XY and variants – 3 (10.7%)	0.33	2	1	0
46, XX/46, XY – 1 (3.6%)	11	0	1	0

a median Prader stage of 3. Subjects with simple virilising CAH presented at a median age of 4.5 years of whom 2 out of 10 were assigned as male at birth. The most common presentation was heterosexual precocious puberty. One subject with 11β-hydroxylase deficiency presented with heterosexual precocious puberty at the age of 2.5 years. Among 46, XX ovotesticular DSDs (n = 5) all of them were assigned as male sex at birth but presented as ambiguous genitalia at a median age of 2.5 years with a median EMS of 3.

There was only one subject of 46, XX testicular DSD, who presented at the age of 2 months with an EMS of 3. The genetic analysis of this baby did not show the SRY (sex-determining region Y) gene on FISH (Fluorescence *in situ* hybridization) but the diagnosis was made based on absent Mullerian structures and inguinal gonads. Two subjects of pure gonadal dysgenesis (46, XX gonadal dysgenesis) presented with absent secondary sexual character and primary amenorrhoea. MRKH syndrome was diagnosed in six subjects and 2 of them co-existence of gonadal dysgenesis was found. In these 2 subjects, primary amenorrhoea was associated with sexual infantilism whereas the other 4 subjects presented with only primary amenorrhoea. There was only one neonate who

presented with an anal malformation in the form of anal atresia, rectovaginal fistula, and poorly developed labioscrotal folds with phallus-like structure and this was categorized under other forms of DSD.

Sex chromosome DSD: A total of 28 subjects out of 147 had sex chromosome DSD and Turner syndrome was the most common. Turner syndrome subjects presented at a median age of 15 years with the most common presentation being absent secondary sexual characters and primary amenorrhoea. Five of them had mosaic karyotypes and these subjects presented even later at a median age of 18 years. Three of them had Tanner stage 3 breast development but presented for primary amenorrhoea. Among the Klinefelter syndrome subjects, one had a karyotype of 48, XXXY, and others had 47, XXY. 3 subjects with mixed gonadal dysgenesis 2 were assigned as female at birth and one of them had a karyotype of 45, XO/47, XYY. These 2 subjects had mullerian structures and gonads in the pelvis. The male sex-assigned subject with mixed gonadal dysgenesis presented with ambiguous genitalia without Mullerian structure on imaging, with one gonad in the inguinal canal and the other gonad in the scrotal sac. One subject with ovotesticular DSD had a chimeric karyotype of 46, XX/46, XY and this child was assigned as male at birth but later presented at the age of 11 years with ambiguous genitalia, bilateral pelvic gonads, and Mullerian structure on imaging.

Gender dysphoria was present with one subject of 46, XY DSD with 17β-HSD 3 deficiency who presented at the age of 22 years, and was assigned as female at birth. This subject had a gender identity of male and an EMS of 3 with a phallus length of 6 cm.

Discussion

The present retrospective study investigated a diverse cohort of people with DSD who presented to a tertiary hospital in North-East India. A total of 147 people with DSD were included. The current study demonstrates consistency with previous studies reported in India with the distribution of DSD subtypes which also reported 46, XY DSD as the most prevalent subtype, ranging from 52.3% to 77.6%.[3–5] Similar to our study, the prevalence of 46, XX DSD has been reported to vary from 19.7% to 27.5% in these studies. It is worth noting that one study excluded Turner syndrome and Klinefelter syndrome from their analysis.[5] However, some studies have reported 46, XX DSD more than 46, XY DSD[6] and some have reported equal incidence of both 46, XY and 46, XX DSD.[7]

Several studies conducted outside India also show similar results as our study showing a higher prevalence of 46, XY DSD ranging from 48.7% to 71% than 46, XX DSD varying from 21.5% to 46.2%.[8–15] However, Finlayson *et al*.[16] reported a higher prevalence of 46, XX DSD than 46, XY DSD (57% vs 34%). Kohva *et al*.[17] reported a higher proportion of sex chromosome DSDs (37.1%) in their study. The variations in reported DSD prevalence globally may be due to the influence of diverse factors such as social, cultural, and genetic within the study populations. Disparities in awareness of DSDs, access to healthcare, and the availability of diagnostic tools between regions can affect the identification and reporting of different DSD subtypes.

The age of presentation in our study ranged from the neonatal period to 35 years, with 17.6% of the subjects presenting in the first year of life and 59.9% presenting after the age of 5 years. Also, there was a notable increase in presentations during puberty in the form of delayed puberty and heterosexual puberty seeking medical care. Various other studies have also reported a wide age range of presentation starting from birth to 65 years.[5,7–9,16] In a recently published study by Man *et al*.,[11] where DSD cases were referred to a multidisciplinary team, almost 80.1% of cases presented in the neonatal period with 3.8% presenting in the antenatal period. This variation in age of presentation may be attributed to the difference in knowledge and attitude towards DSDs and delay in referral to higher centres.

In our study 5α-reductase 2 deficiency was most common among 46, XY DSD, and ambiguous genitalia was the most common presentation with a median EMS of 6 (1–11). This is in concordance with the study by Misgar *et al*.[7] who reported it as 58.6%. However, it is noteworthy that many other studies have reported androgen insensitivity as the most common DSD.[4,5,9,10] In our study majority of the 5α-reductase 2 deficiency subjects were assigned male sex at birth due to higher EMS scores and only 5 (11.9%) of these subjects were assigned female sex at birth. One subject who was assigned as female at birth presented at 13 years of age with inguinal pain caused by testicular torsion. This person had a female gender identity while the other 4 subjects were less than 4 years of age and hence needed regular assessment for gender dysphoria. Previous studies show that in 5α-reductase 2 deficiency, both male and female sex assignment at birth is possible but male sex assignment is more common and those with female sex assignment may develop gender dysphoria in the future.[18] Previous studies have also reported that 56% to 63% of these patients had gender roles changed from female to male.[19] However, in a study, the majority (72.7%) were assigned female gender at birth with 49.1% presenting as clitoromegaly.[20] Also in our study, EMS negatively correlated with T/DHT ratio which is however not concordant with a previous study where T/DHT ratio was not consistently associated with phenotypic severity.[21] A T/DHT ratio of 8.5 cutoff in the neonatal period has been proposed in a case report for possible 5α-reductase 2 deficiency.[22]

In the present cohort, 9 subjects had 17β-HSD 3 deficiency of which 8 were assigned as female at birth and one gender was not assigned at the time of presentation. The median EMS was 3 with a median T/A ratio of 0.34 (0.2 – 0.63). One subject who presented in adulthood had gender dysphoria and was assigned as female at birth. In a systematic review, 78.5% were assigned as female, and 15.2% of these subjects had a change in gender role from female to male.[23] Other studies have shown gender role change in 39%–64% from female to male.[19] Also, these patients have phenotype variability with the same genotype.[24] As the majority of subjects in the present

study were prepubertal, it is difficult to predict how many of our cohort will have a change in gender roles.

All subjects with PAIS in our study had some degree of testicular descent. A total of 28.6% of these patients were assigned as female at birth. In the literature, it has been reported that PAIS patients present with varying degrees of undervirilization, pubertal gynecomastia, impaired phallic growth and a poor genotype-phenotype correlation.[25,26] Previous studies have shown that sex assignment in PAIS had both concordance and discordance with gender identity and those with discordance had been reassigned the sex from both male to female and vice-versa during their lifetime.[27]

In the present study out of 14 subjects with 21α-hydroxylase deficiency CAH, 2 patients were assigned as male, and in 1 patient sex was not assigned at birth. In a study, it has been shown that females assigned CAH had higher gender identity scores compared to control girls indicating towards risk of gender dysphoria.[28] In the same study, gender identity did not correlate with the degree of virilization, suggesting that moderate androgen exposure prenatally poses a risk of atypical gender identity.[28] In a review, it was found that 5.2% of subjects with CAH who were assigned as female experienced gender dysphoria, whereas in those who were assigned as male, it was 12.1%.[29]

In the present cohort, 2 out of 6 subjects of MRKH syndrome presenting with absent secondary sexual characters with primary amenorrhoea were found to have hypergonadotropic hypogonadism. Similar cohorts have been reported in the literature previously.[30,31] No genetic cause has been reported till now, however, endocrine disruptors cannot be ruled out.[30]

The current cohort had 5 subjects with ovotesticular DSD out of which 4 had 46, XX and 1 had 46, XX/46, XY karyotype. All these subjects were assigned as male at birth with a median EMS of 3. On imaging Mullerian structures were present with varying degrees of gonadal descent. One subject presented at the age of 35 years with regular menstrual cycles but his gender identity and role were male. Another subject who presented at 17 years of age with cyclical abdominal pain also had a male gender identity and role. Our findings are discordant with a long-term study where 50% were assigned as female with gender reassignment done in 1 subject from male to female.[32]

Limitations

The limitations of the present study include the retrospective study design which depends on records. Additionally, the lack of genetic testing hinders the exploration of genomic data within the study population. A specific genetic aetiological diagnosis is important to predict the risk of gonadal tumours. Furthermore, a single-centre study analysis limits the generalizability to the wider population.

Conclusion

The present study identified 46, XY DSD as the most prevalent subtype predominantly attributed to 5-α reductase 2 deficiency whereas in 46, XX DSD, congenital adrenal hyperplasia was the most common. A definitive etiological diagnosis requires a detailed examination and thorough investigative procedure which is often challenging in resource-limited settings. The sex assignment at birth may vary based on the degree of ambiguity but the aetiology of DSD and gender identity may guide towards sex re-assignment. A long-term follow-up of these subjects is essential for normal growth and development, psychological well-being, sexual health and fertility potential.

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Authors' contribution

PN was involved in the concepts and design of the study, literature search, data acquisition, analysis, and writing the first draft of the manuscript. AKB was involved in the design, data acquisition, analysis, and manuscript editing and reviewing. AB contributed to the design, literature search, data analysis, and manuscript editing and reviewing. UKS was involved in the concepts and design of the study, literature search, data acquisition, analysis, supervision, manuscript editing and reviewing, and served as guarantor.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Data availability

The data supporting the findings of this study can be obtained from the corresponding author upon request, maintaining the confidentiality of the study subjects and with due approval from institutional authority.

References

1. Hughes IA. Consensus statement on management of intersex disorders. Arch Dis Child 2005;91:554–63.
2. Audí L, Ahmed SF, Krone N, Cools M, McElreavey K, Holterhus PM, *et al*. Genetics in endocrinology: Approaches to molecular genetic diagnosis in the management of differences/disorders of sex development (DSD): Position paper of EU COST Action BM 1303 'DSDnet'. Eur J Endocrinol 2018;179:R197-206.
3. Kulkarni KP, Panigrahi I, Das R, Kaur S, Marwaha RK. Pediatric disorders of sex development. Indian J Pediatr 2009;76:956–8.
4. Joshi R, Rao S, Desai M. Etiology and clinical profile of ambiguous genitalia -An overview of 10 years experience. Indian Pediatr 2006;43:974-9.
5. Walia R, Singla M, Vaiphei K, Kumar S, Bhansali A. Disorders of sex development: A study of 194 cases. Endocr Connect 2018;7:364–71.
6. Dar SA, Nazir M, Lone R, Sameen D, Ahmad I, Wani WA, *et al*. Clinical spectrum of disorders of sex development: A cross-sectional observational study. Indian J Endocrinol Metab 2018;22:774–9.
7. Misgar RA, Bhat M, Masoodi S, Bashir M, Wani A, Baba A, *et al*. Disorders of sex development: A 10 years experience with 73 cases from the Kashmir Valley. Indian J Endocrinol Metab 2019;23:575–9.
8. Heeley JM, Hollander AS, Austin PF, Merritt DF, Wesevich VG, Amarillo IE. Risk association of congenital anomalies in patients with

ambiguous genitalia: A 22-year single-center experience. J Pediatr Urol 2018;14:153.e1-7.
9. Juniarto AZ, van der Zwan YG, Santosa A, Ariani MD, Eggers S, Hersmus R, *et al*. Hormonal evaluation in relation to phenotype and genotype in 286 patients with a disorder of sex development from Indonesia. Clin Endocrinol (Oxf) 2016;85:247–57.
10. Shamma RA, Atef S, Arafa N. Etiological classification and clinical spectrum of Egyptian pediatric patients with disorder of sex development, single center experience. Endokrynol Pol 2021;72:558–65.
11. Man E, Mushtaq I, Barnicoat A, Carmichael P, Hughes CR, Davies K, *et al*. A Single-center, observational study of 607 children and young people presenting with differences of sex development (DSD). J Endocr Soc 2022;7:1–12.
12. Ganie Y, Aldous C, Balakrishna Y, Wiersma R. Disorders of sex development in children in KwaZulu-Natal Durban South Africa: 20-year experience in a tertiary centre. J Pediatr Endocrinol Metab 2017;30:11–8.
13. De Paula GB, Barros BA, Carpini S, Tincani BJ, Mazzola TN, Sanches Guaragna M, *et al*. 408 cases of genital ambiguity followed by single multidisciplinary team during 23 years: Etiologic diagnosis and sex of rearing. Int J Endocrinol 2016;2016:1–9.
14. Ata A, Özen S, Onay H, Uzun S, Gökşen D, Özkınay F, *et al*. A large cohort of disorders of sex development and their genetic characteristics: 6 novel mutations in known genes. Eur J Med Genet 2021;64:104154.
15. Amolo P, Laigong P, Omar A, Drop S. Etiology and clinical presentation of disorders of sex development in Kenyan children and adolescents. Int J Endocrinol 2019;2019:1–9.
16. Finlayson C, Rosoklija I, Aston CE, Austin P, Bakula D, Baskin L, *et al*. Baseline characteristics of infants with atypical genital development: Phenotypes, diagnoses, and sex of rearing. J Endocr Soc 2018;3:264–72.
17. Kohva E, Miettinen PJ, Taskinen S, Hero M, Tarkkanen A, Raivio T. Disorders of sex development: Timing of diagnosis and management in a single large tertiary center. Endocr Connect 2018;7:595–603.
18. Shabir I, Khurana ML, Joseph AA, Eunice M, Mehta M, Ammini AC. Phenotype, genotype and gender identity in a large cohort of patients from India with 5α-reductase 2 deficiency. Andrology 2015;3:1132–9.
19. Cohen-Kettenis PT. Gender change in 46, xy persons with 5α-reductase-2 deficiency and 17β-hydroxysteroid dehydrogenase-3 deficiency. Arch Sex Behav 2005;34:399–410.
20. Maimoun L, Philibert P, Cammas B, Audran F, Bouchard P, Fenichel P, *et al*. Phenotypical, biological, and molecular heterogeneity of 5α-reductase deficiency: An extensive international experience of 55 patients. J Clin Endocrinol Metab 2011;96:296–307.
21. Fan L, Song Y, Polak M, Li L, Ren X, Zhang B, *et al*. Clinical characteristics and genotype-phenotype correlations of 130 Chinese children in a high-homogeneity single-center cohort with 5α-reductase 2 deficiency. Mol Genet Genomic Med 2020;8:e1431.
22. Walter KN, Kienzle FB, Frankenschmidt A, Hiort O, Wudy SA, Van Der Werf-Grohmann N, *et al*. Difficulties in diagnosis and treatment of 5α-reductase type 2 deficiency in a newborn with 46, XY DSD. Horm Res Paediatr 2010;74:67-71.
23. Yang Z, Ye L, Wang W, Zhao Y, Wang W, Jia H, *et al*. 17β-Hydroxysteroid dehydrogenase 3 deficiency: Three case reports and a systematic review. J Steroid Biochem Mol Biol 2017;174:141–5.
24. Boehmer A, Brinkmann AO, Sandkuijl LA, Halley DJ, Niermeijer MF, Andersson S, *et al*. 17β-hydroxysteroid dehydrogenase-3 deficiency: Diagnosis, phenotypic variability, population genetics, and worldwide distribution of ancient and de novo mutations*. J Clin Endocrinol Metab 1999;84:4713–21.
25. Hellmann P, Christiansen P, Johannsen TH, Main KM, Duno M, Juul A. Male patients with partial androgen insensitivity syndrome: A longitudinal follow-up of growth, reproductive hormones and the development of gynaecomastia. Arch Dis Child 2012;97:403–9.
26. Deeb A, Mason C, Lee YS, Hughes IA. Correlation between genotype, phenotype and sex of rearing in 111 patients with partial androgen insensitivity syndrome. Clin Endocrinol (Oxf) 2005;63:56–62.
27. Mazur T. Gender dysphoria and gender change in androgen insensitivity or micropenis. Arch Sex Behav 2005;34:411–21.
28. Berenbaum SA, Bailey JM. Effects on gender identity of prenatal androgens and genital appearance: Evidence from girls with congenital adrenal hyperplasia. J Clin Endocrinol Metab 2003;88:1102–6.
29. Dessens AB, Slijper FME, Drop SLS. Gender dysphoria and gender change in chromosomal females with congenital adrenal hyperplasia. Arch Sex Behav 2005;34:389–97.
30. Shah V, Ganatra P, Parikh R, Kamdar P, Baxi S, Shah N. Coexistence of gonadal dysgenesis and Mayer-Rokitansky-Kuster-Hauser syndrome in 46, XX female: A case report and review of literature. Indian J Endocrinol Metab 2013;17(Suppl 1):S274-7. doi: 10.4103/2230-8210.119605.
31. Kebaili S, Chaabane K, Mnif M, Kamoun M, Kacem F, Guesmi N, *et al*. Gonadal dysgenesis and the Mayer-Rokitansky-Kuster-Hauser Syndrome in a girl with a 46, XX karyotype: A case report and review of literature. Indian J Endocrinol Metab 2013;17:505-8.
32. Matsui F, Shimada K, Matsumoto F, Itesako T, Nara K, Ida S, *et al*. Long-term outcome of ovotesticular disorder of sex development: A single center experience. Int J Urol 2011;18:231–6.