Transition of Care of Disorders of Sexual Development: A Twist of Two Cases with Ambiguous Genitalia

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ABSTRACT

Disorders of sexual development (DSD) is a congenital condition that requires an alteration in the development of chromosomal, gonadal, and anatomical sex is atypical. A report showed most of the patients in the 46XX DSD had congenital adrenal hyperplasia (CAH) at 69.23% followed by unknown under-virilization in the 46XY DSD group at 60.09%. Patient 1 diagnosed as DSD 46XX/non-classic congenital adrenal hyperplasia (NCAH) presented with primary amenorrhea, short stature, over-virilization (Prader 2), and 46XX karyotype. Laboratory examination showed elevated 17-hydroxyprogesterone (17OHP): 166.7 ng/ml (2.83 ng/ml), without salt wasting feature. Patient 2 diagnosed with DSD 46XY/type 2 5α-reductase deficiency (SAD) presented with cryptorchidism, under-masculinization (sinecker stage 3b), and 46XY karyotype. Laboratory examination showed elevated testosterone 613 ng/dL (4.6-38.3 ng/dL), decreased dihydrotestosterone (DHT) 11 ng/dL (>20 ng/dL), and elevated testosterone T/DHT ratio 55.73 (8-16). A deep understanding of pathophysiology, and approach to disease in each stage of life is important and warrants special treatment. Comprehensive multidisciplinary team management (MDT) is warranted in DSD management. Disease prognosis varies among each disorder: early detection, treatment compliance, and continuity of care are important to improve patient outcomes.

Keywords: *Disorders of sexual development (dsd), ambiguous genitalia, case series*

INTRODUCTION

Disorder of sexual development is defined as a congenital condition that requires an alteration in the development of chromosomal, gonadal, and if the anatomical sex is atypical (Table 1).[1,2] The diagnosis of DSD may appear within any stage of patient development from early life to adulthood which owing to discordances genital development, fertility, or even hypertension.[3] The incidence of DSD varies from 1:4500 to 1:5000 birth, with consanguinity marriage as the main risk factor.[4] A study by Walia et al. identifies 70.3% of patients among 46XX DSD diagnosed as CAH, and 8.8% of patients among 46XY DSD diagnosed with SAD.[5] Report our hospital showed most of the patients in 46XX DSD are CAH 69.23% followed by unknown under virilization in the 46XY DSD group 60.09%.[6] This case report aims to present two DSD cases with ambiguous genitalia due to NCAH and SAD. (Table 2) Hence showed the importance of MDT and the transition of care from pediatric to adult patients with DSD in our institution.

Table 1. Clinical Classification of DSD

Sex Chromosome DSD	46XY DSD	46XX DSD
5X (Turner syndrome and variants) 47XXY (Klinefelter syndrome and variants) 45X/46XY (mixed gonadal dysgenesis, ovotesticular DSD) 46XX/46XY (chimeric, ovotesticular DSD)	Disorders of gonadal (testicular) development • Complete gonadal dysgenesis (Swyer syndrome) • Partial gonadal dysgenesis Gonadal regression Ovotesticular DSD Disorders in androgen synthesis or action • Androgen biosynthesis defect (17-hydroxysteroid dehydrogenase deficiency, 5α-reductase deficiency) • Defect in androgen action (CAIS, PAIS) • LH receptor defects (Leydig cell hypoplasia) • Disorders of AMH and AMH receptor (persistent Müllerian duct syndrome) Other (severe hypospadias, cloacal exstrophy)	Disorders of gonadal (ovarian) development • Ovotesticular DSD • Testicular DSD (SRY+, dup SOX9) • Gonadal dysgenesis Androgen excess • Fetal (21- or 11-hydroxylase deficiency) • Fetoplacental (aromatase deficiency, POR) • Maternal (luteoma, exogenous) Other (cloacal exstrophy, MURCS)

AMH, anti-Müllerian hormone; CAIS, complete androgen insensitivity syndrome; LH, luteinizing hormone; MURCS, Müllerian duct aplasia, renal aplasia, and cervicothoracic somite dysplasia; PAIS, partial androgen insensitivity syndrome; POR, cytochrome P450 oxidoreductase. Adapted from. Lee PA, Houk CP, Ahmed SF, Hughes IA. Consensus statement on management of intersex disorders. International Consensus Conference on Intersex. Pediatrics. 2006 Aug;118(2):e488-500.

CASE ILLUSTRATION

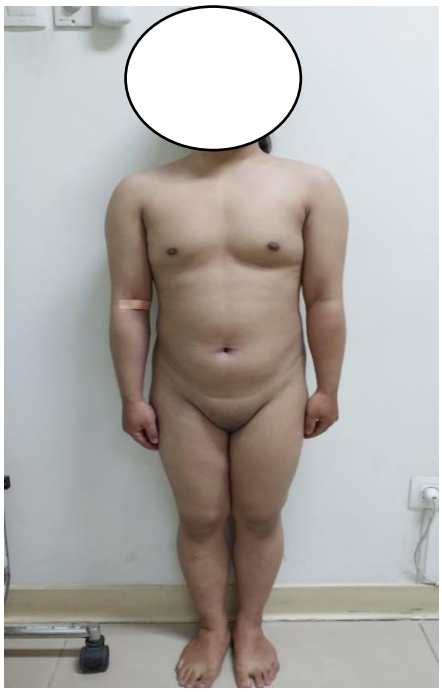
Case 1

An 18-year-old female was referred from the pediatric endocrinology clinic with a diagnosis of 46XX DSD/NCAH. The patient was well until the age of 2 when they noticed enlargement of the phallus. Her pregnancy status was a full-term pregnancy, with a birth weight of 3100 grams, and she showed normal genital appearance upon delivery. She was the third daughter among three siblings in the family with a history of consanguineous marriage. She developed as a female with normal intelligence for her age. Two years prior, she sought a consultation with a pediatric endocrinologist due to genital ambiguity and delayed puberty. Physical examination showed normal vital signs, body height (BH): 143 cm, body weight (BW): 48 kg, father's height (FH): 155 cm, mother's height (MH): 155 cm, mid parenteral height (MPH): 156.5 cm, and arm span (AS): 117 cm. Her secondary sexual evaluation showed breast development tanner stage I (M1), pubic hair tanner stage III (P3), and a Ferriman-Galloway score of 3. Genital examination pre-reconstruction showed a phallus, external urethral orifice, vagina, and

posterior labial fusion (Prader scale 3) (Figure 1). Karyotype examination was compatible with 46XX, and 17-OH progesterone (17-OHP) was elevated at 166.7 ng/ml (2.83 ng/ml). Pelvic ultrasonography (UTZ) revealed a visualized uterus. Magnetic Resonance Imaging (MRI) of the abdomen revealed the presence of an ovary, hypoplastic uterus, and normal adrenal gland. The bone age was consistent with 17 years old (*Greulich-Pyle*). Hydrocortisone 15mg/day was immediately started, and she underwent psychiatric and obstetric evaluation. However, she was non-compliant with treatment, and genital reconstruction was delayed 1.5 years due to the COVID-19 pandemic.

After 1 year of consultation in an adult endocrinology clinic, despite good compliance, the 17OHP evaluation still showed a high elevation (180.38 ng/mL). As a result, the hydrocortisone dose was increased to 30mg/day. Additionally, a combination of estradiol valerate 2mg and 0.5mg norgestrel preparation was given for 3 cycles to promote the development of her secondary sexual appearance. The psychiatric evaluation confirmed a diagnosis of gender dysphoria in adults, with the patient identifying as female.

A.



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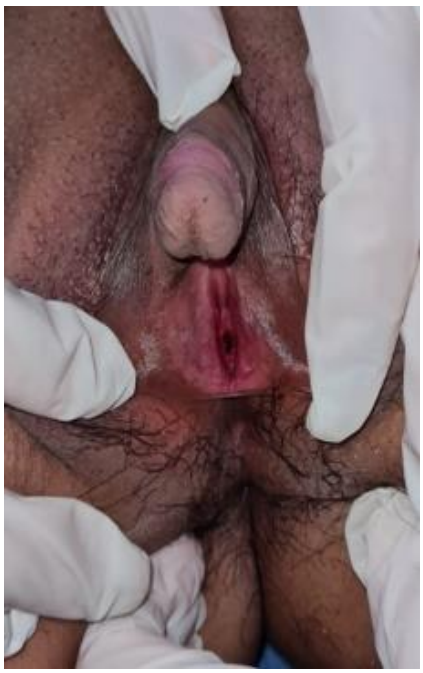
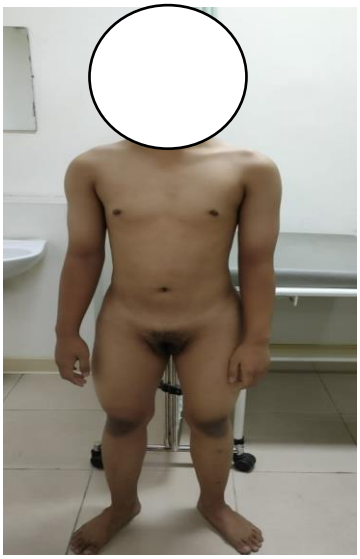


C. 

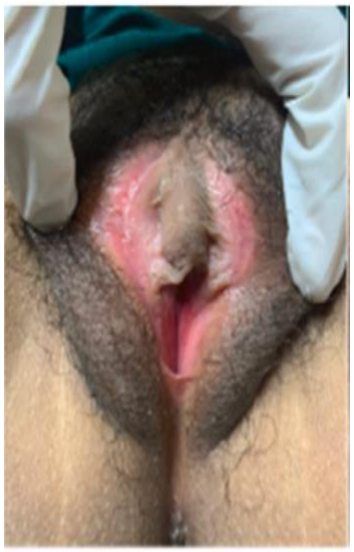
D. 

Figure 1. A. Physical appearance of patient 1, and B. Ambiguous genitalia (Prader 2). C. Physical appearance patient 2, and D. Ambiguous genitalia (Sinecker 3b)

Case 2

An 18 year old male was referred from pediatric endocrinology with a diagnosis of 46XYY SRD. Two years prior, he sought consultation to obstetric endocrinology due to primary amenorrhoea. He denied any disorders in micturition and vaginal discharge. He developed as female and showed good physical development and intelligence appropriate for his age. He experienced pubarche and wet dreams at the age of 13. His family history revealed a consanguineous marriage. Among his eight siblings, three of them (his 2nd and 4th younger siblings) also have the same diagnosis.

Physical examination showed normal vital signs, body weight (BW): 51 kg, body height (BH): 158 cm, arm span (AS): 120 cm, mother's height (MH): 148 cm, father's height (FH): 160 cm, and mid-parental height (MPH): 160.5 cm. No Adam's apple was found during the neck examination. His secondary sexual evaluation revealed breast development tanner stage I (M1), pubic hair tanner stage III (P3),presence of phallus with stretched penile length (SPL) 2.5 cm, perineoscrotal hypospadias, along with vulva, major and minor labia, and palpable gonad (5 ml) in the right labia major (Sinecker score 3b).

Laboratory examination showed elevated FSH at 19.75 IU/mL (2.5-10.2 IU/ml), testosterone at 613ng/dL (4.6-38.3 ng/dl), DHT at 11 ng/dL (>20 ng/dL), and T/DHT ratio of 55.73 (8-16). The testicular biopsy showed testicular tissue with some atrophic fibrosis, and the sperm analysis showed azoospermia. The karyotype test showed 46XY. Pelvic MRI showed bilateral testis, corpus cavernosa, and bulbospongiosus muscle.

The bone age was consistent with 17 years old (*Greulich-Pyle*). The psychiatric evaluation revealed gender dysphoria in an adolescent-adult with a male gender identity. The patient underwent left sided orchidopexy, and DHT 2.5% cream at 5 mg/day was applied over the phallus. After 6 months, the stretched penile length (SPL) extended to 6 cm, and a deeper voice was noticed. The patient will be planned to undergo sinus urogenital reconstruction in conjunction with psycho-supportive care prior to surgery. The ethics committee and the MDT team collaborated patient to fulfil several qualifications for gender disposition.

Table 2. Clinical, Radiologic, and Laboratory Examination of 2 Cases

	Patient 1	Patient 2
Age at diagnosis	15 years old	16 years old
Sex upon diagnosis	Female	Female
Secondary Sex Appearance	Breast: Tanner I (M1) Pubic hair: Tanner III (P3) Ferriman-Gallwey Score 3	Breast: Tanner 1 (M1) Pubic hair: Tanner III (P3)
Karyotyping	46XX	46XY
Body dysmorphic, and genital ambiguity	Short stature Prader scale 3	Cryptorchidism Sinecker scale 3b
Sex Hormone		
LH	4.2 IU/ml (1.9-12.5 IU/ml)	12.65 IU/mL (1.8-12.5 IU/mL)
FSH	8.3 IU/ml (2.5-10.2 IU/ml)	19.75 IU/mL (2.5-10.2 IU/ml)
Estradiol	73.17 pg/mL (60- 190 pg/mL)	23.29 pg/mL (Male 10-50 pg/mL)
Testosterone		613 ng/dL (4.6-38.3 ng/dl)
Dihydrotestosterone		11 ng/dL (>20 ng/dL)
T/DHT		55.73 (8-16)
17OHP		
Baseline	166.7 ng/ml (<2.83 ng/ml)	
After 1 year of evaluation	180.38 ng/mL	
Thyroid Function Test		
TSH	1.4 mIU/mL (N: 0.3 - 0.5 mIU/mL	4.6 mIU/mL (N: 0.3 - 0.5 mIU/mL)
FT4	1.0 ng/dL (N: 0.7 - 1.8 ng/dL)	1.3 ng/dL (N: 0.7 - 1.8 ng/dL)
Blood Chemistry		
Na/ K/ Glucose	140 mEq/L / 3.9 mEq/L / 104 mg/dL	140 mEq/L / 3.9mEq/L / 85 mg/dL
MRI	Abdominal: Adrenal gland not enlarged. The uterus, vagina, ovaries, corpus cavernosa, and bulbospongiosus are visible.	Pelvis: Bilateral testis (right testes volume 8.3 cc within the inguinal canal, and left testis volume 8.1 cc within labia major), corpus cavernosa, and bulbospongiosus muscle are visible.
Diagnosis	46XX DSD/NCAH	46XX DSD/SAD
Gender Disposition	Female	Male
Medical Treatment	Hydrocortisone 30 mg/day	DHT cream 2.5% 5 mg/day for 6 months
Surgical Management	Feminization clitoroplasty	Orchidopexy left

DISCUSION

Ambiguous genitalia among older children is highly suspected in patients with the following conditions: (1) Previously unrecognized ambiguous genitalia; (2) Inguinal hernia in a girl; (3) Delayed or incomplete puberty; (4) Primary amenorrhea or virilization in a girl; (5) Breast development in a boy; and (6) Gross or cyclic haematuria in a boy.[2] Patient 1 presented with signs of virilization (Prader scale 2), and primary amenorrhoea, while patient 2 showed the presence of under-masculinization, hypospadias, and the presence of vulva (Sinecker scale 3b).[7]

Understanding the disease patho-genesis and clinical course at each stage of life for these two distinct disorders is crucial. In our cases, the androgenic steroid pathway and gene mutations resulting in enzyme (21-hydroxylase, and type 2 5α-reductase) deficiencies were responsible.[8-10] The diagnoses of our patients followed diagnostic pathways based on paediatric experience for disorder of sex development (DSD).[11] The biological diagnosis is established through biochemical or genetic tests. In patient 1, the diagnosis was determined by an elevated 17OHP level at 08.00 am: 165.7 ng/ml (>10 ng/ml). In borderline cases (2-10 ng/ml), a dynamic test with cortico-tropin stimulation is recommended.[10] In patient 2, the diagnosis was determined by increased T/DHT ratio after human chorionic gonadotropin (HCG)

stimulation (first-line test in infants and pre-pubertal children). The cutoff point for the T/DHT ratio was suggested to be 20, but a ratio of 8.5 after HCG stimulation was found to be more reliable.[8]

Patient 2 had a basal T/DHT ratio of 55.73 (>9.5).[12] In cases with inconclusive results, a corticosteroid panel, urine corticosteroid profile, or genetic testing is recommended, although these options are limited in our setting.[10,11] Pelvic UTZ and abdominal MRI were performed in both patients to distinguish between Wolffian or Mullerian structure maturation and adrenal gland enlargement.[6]

The patients were referred for genetic counselling and further genetic testing (karyotyping test) to help classify the DSD into three distinct groups. Subsequently, fluorescence in situ hybridization (FISH), and genetic testing with next-generation sequencing (NGS) were recommended to determine various cases of monogenic DSD (CYP21A2 gene (6p21)[9], SRD5A2 gene (2p23).[3,8] However, the use of these test is still limited in our institution.

The Chicago Consensus (2006) advocates for a multidisciplinary team (MDT) approach in DSD cases. Medical, surgical, and psychological care are the three main aspects to optimize medical care for DSD patients (Figure 2).[6,13] In our cases, the patents were initially seen by a paediatric endocrinologist and obstetric-endocrinology section. The MDT team consisted of a surgeon, clinical geneticist, psychiatrist, radiologist, pathologist, ethics committee, and pharmacist. Once the patients reach 18 years old, they will be referred to an adult endocrinologist.

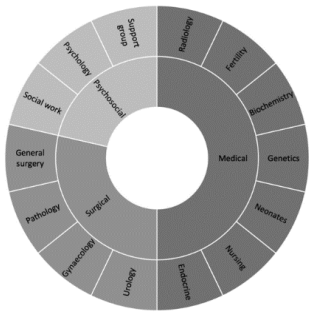


Figure 2. The multidisciplinary team model in the management of DSD[16]

Medical management is the cornerstone for various DSD cases. In patient 1, hydrocortisone at a dose of 15mg/day was started to alter androgen synthesis. Glucocorticoids are indicated in patients with early pubarche, increased bone age, and signs of over-virilization. The benefits of glucocorticoid are seen in children below 9 years old (to optimize patient height) and even in adults (to ameliorate hyperandrogenism, infertility, and other related symptoms).[14,15] In cases of severe enzyme deficiency and critical illness, higher doses of glucocorticoids may be required, with consideration of the side effects.[16]

In patient 1, hormonal replacement aimed to develop secondary sexual appearance and treat severe hirsutism. Estrogen replacement (estradiol valerate at a dose of 0.5mg/day, titrated up to 2 mg/day) was initiated after the patient reached puberty. Two years later, consecutive progesterone (medroxy-progesterone 100-200 mg/day, or norethidone 2.5-5 mg/day) can be given in patients with an intact uterus.[17] Alternatively, ovarian or peripheral androgen blockade (using drospirenone or cyproterone asetate) is preferred.[18,19] In patient 2, testosterone replacement for SAD cases is not generally required, as testicular function is preserved. However, high doses of testosterone (testosterone cypionate 200-500 mg twice a week intramuscular (IM) or DHT cream (5-10 mg/day) are given to improve male secondary sexual characteristics.[8] Patient 2 was given DHT cream for 6 months to achieve the maximum effect.

For patient 1, feminization surgery is the treatment of choice, while patient 2 will require sinus urogenital reconstruction and masculinization surgery. Before surgery, both patients receive psycho-supportive treatment. The timing of surgery is debatable, but previous reports suggest that CAH and SAD patients should undergo surgery before 5 years old and 2 years old, respectively. Ethical considerations regarding gender disposition should be considered. After a psychiatric evaluation, patient 1 was suggested for female gender after

feminizing surgery was contemplated, while patient 2 was suggested for male gender disposition.[1] Psychological evaluation is ideally performed before 27 months old, before hormonal or surgical intervention is decided.[8]

The transition from pediatric to adult care is important for DSD patients.[6] Various aspects, including the patient's sexual function, risk of malignant transformation, physiological problems, and information about the patient's illness should be considered.[1] Patient prognosis varies, and early detection, treatment compliance, and long-term management are crucial.

DISCUSSION

Various cases of disorder of sex development (DSD) with genital ambiguity were encountered from early life to adulthood. It is important to have a deep understanding of the pathophysiology, disease burden, and the approach to managing DSD at each stage of life. Therefore, the management of DSD cases with a MDT approach should be considered to ensure a favourable prognosis.

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