

**RESEARCH ARTICLE****Genital Ambiguity in a 46, XY individual : a Rare Case**Zata Yuda Amaniko¹, Haviz Yuad^{2,*}¹ *Department of Obstetrics and Gynecology, Faculty of Medicine, Andalas University - Dr. M. Djamil Central General Hospital, Padang, Indonesia*² *Reproductive Endocrinology division, Department of Obstetrics and Gynecology, Faculty of Medicine, Andalas University – Dr. M. Djamil Central General Hospital, Padang, Indonesia***Corresponding Author:** Haviz Yuad; yuadhaviz@gmail.com; +62 813-6313-5810**Received :** November 2, 2024; **Accepted:** January 2, 2025; **Published:** January 22, 2025**Doi :** <https://doi.org/10.25077/aoj.9.1.153-160.2025>**Abstract****Introduction:** Ambiguous genitalia/disorders of sexual development (DSD) is a disorder of sexual development that is atypical chromosomally, gonadally and anatomically, which is generally characterized by the presence of unclear external genitalia, which can cause biological, social and psychological problems in the patient. as well as family.**Objective:** To report a rare case of 46 XY disorders of sexual development.**Case Report:** A 20 years old patient was reported with complaints of primary amenorrhea, breasts that had not yet grown and genitals resembling male genitals. Through physical examination, fine hair appeared above the lips, acne, prominent thyroid cartilage, mammary tanner stage M1, and a structure resembling a penis on the genitalia. The patient was examined according to the algorithm for patients with DSD, namely an ultrasound examination with the result that no gonads were found, then the patient underwent a karyotyping examination with results of 46 XY. In the investigation, it revealed LH: 58.45 mIU/ml, FSH: 57.74 mIU/ml, testosterone: 228 ng/dl. Next, the patient is planned for further imaging examinations.**Conclusions:** DSD is genetically heterogeneous and careful assessment by a multidisciplinary team is essential to accurately diagnose DSD. Many forms of DSD go undiagnosed. It is important for physicians to have a clear decision-making pathway in evaluating patients with DSD**Keywords:** Disorders of Sexual Development, Ambiguous Genitalia, 46 XY

INTRODUCTION

Ambiguos genitalia is a disorder of sexual development that is atypical chromosomally, gonadically and anatomically, which is generally characterized by the presence of external genital organs that are not clearly male or female, or have the appearance of both sexes. Abnormalities may include hypospadias, undescended testicles, enlarged micropenis or clitoris, labial fusion, and labial masses.¹

The birth of a baby with multiple genitalia poses difficult medical, surgical, ethical, psychosocial, and physical problems for patients and their parents. Phenotypic sex results from the differentiation of the internal ducts and external genitalia under the influence of hormones and other additional factors. When mismatches occur between three processes (chromosomes, gonads, phenotypic sex determination), DSD is the result. The incidence of a child with a disorder of sexual development (DSD) is approximately 1 in 1000 to 4500 live births.² The most common etiology is congenital adrenal hyperplasia, followed by androgen insensitivity and mixed gonadal dysgenesis.²

Terminologies, such as hermaphrodite, pseudo-hermaphrodite, and intersex, are considered pejorative. These terms have been replaced by the term disorders of sexual development (DSD).^{2,3} Disorders of sexual development are defined as congenital conditions characterized by atypical development of chromosomes, gonads, or sexual anatomy. The development of the 2006 consensus guidelines was a turning point in DSD classification, with three broad categories: sex chromosome DSD, 46XX DSD and 46XY DSD.⁴

The objective of this report is to describe the process of diagnosing and planning subsequent medical actions for cases of Disorders of Sexual Development (DSD). The scope of this case report includes identifying the etiology of DSD through clinical and supportive examinations and outlining management steps, which encompass medical, psychosocial, and ethical approaches. Thus, this report aims not only to present the diagnostic processes but also to provide guidance for managing and following up on these cases.

Initial evaluation should include karyotyping, which is usually performed on peripheral leukocytes. Depending on the karyotype, patients are categorized into three main types 46XX DSD, 46 XY DSD, and mixed chromosome DSD. Another important test is Fluorescent in Situ Hybridization (FISH) for the SRY gene. This gene is the main regulator of male sexual development. The absence of the SRY gene in the 46XY karyotype indicates a deletion and can cause DSD ranging from ambiguous genitalia to sex reversal.²

CASE REPORT

20 years old patient who complained of never menstruating, but she denied cyclic pain in the lower abdomen every month. The patient admitted that the breasts were not growing. Pubic hair begins to grow from the age of 12 years. The part of his body that resembles the male genitalia never has an erection. The patient was raised as a woman, feels like a woman, and has a sexual attraction to men. The patient urinates from a hole at the bottom of his genitals. In the birth history,

at birth the patient's gender was found to be ambiguous, but the parents never took the patient to be examined by a doctor. There is no family history of similar complaints.¹

On physical examination, fine hair appears above the lip, acne is present, no weblike neck is visible, and the thyroid cartilage is prominent. In puberty status, Mamma Tanner stage M1, the genitalia look like a structure resembling a penis measuring ± 3 cm, the testes are not palpable. Labial fusion (-). The external urethral orifice is 0.5 cm below the penis. No separate vaginal introitus was seen (Prader 3). On palpation of the abdomen and inguinal ligament, there was no palpable mass indicating an undescended gonad.



Figure 1. Clinical Manifestation of Patient

Ultrasound examination results showed no gonad in patient. The patient underwent Karyotyping examination with 46 XY results. The hormonal examination showed an increase in LH and FSH respectively with results of 58.45 and 57.74 mIU/ml, and Testosterone 228 ng/dl. So the patient was diagnosed with DSD 46 XY.

Ultrasound examination results showed no gonad in patient. The patient underwent Karyotyping examination with 46 XY results. The hormonal examination showed an increase in LH and FSH respectively with results of 58.45 and 57.74 mIU/ml, and Testosterone 228 ng/dl. So the patient was diagnosed with DSD 46 XY.

Table 1. Laboratories examination results

Examination	Results
LH	58.45
	mIU/ml
FSH	57.74
	mIU/ml
Testosterone	228 ng/dl

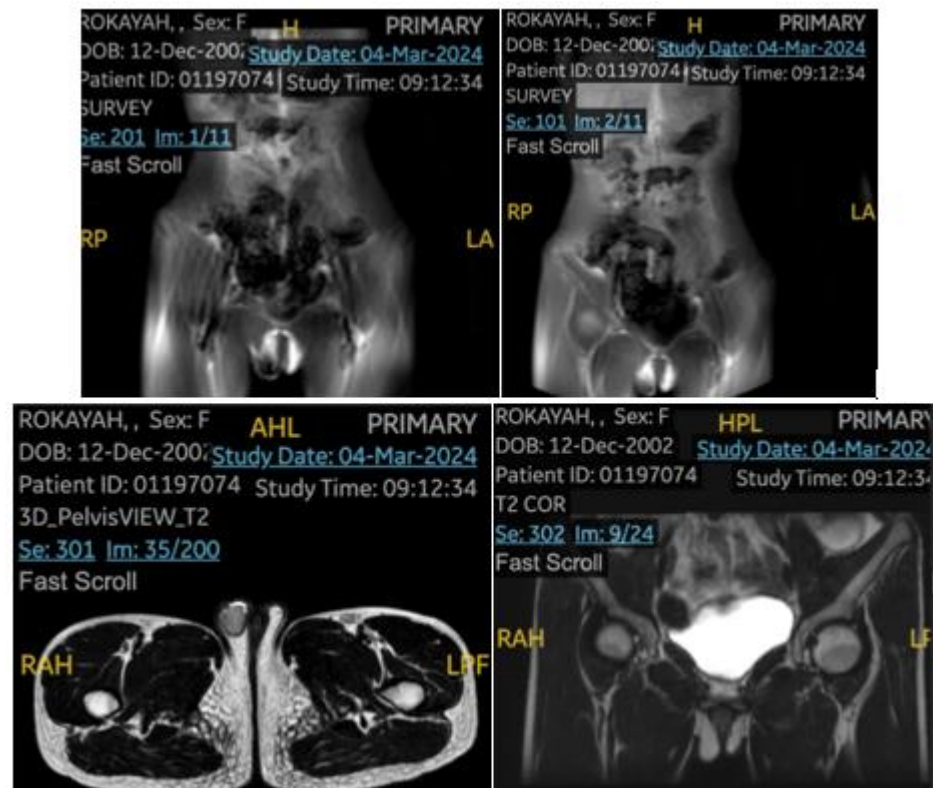


Figure 2. MRI Examination of the Patient

DISCUSSION

This case report details a 20-year-old individual presenting with primary amenorrhea, underdeveloped secondary sexual characteristics, and ambiguous genitalia. Socially assigned female at birth, the patient has experienced ongoing identity alignment with the female gender, including sexual attraction to men. Physical and laboratory examinations, combined with imaging and karyotyping, suggest a provisional diagnosis of 46,XY Disorder of Sex Development (DSD), likely linked to disruptions in androgen synthesis or action.⁵ This comprehensive discussion reviews the case alongside literature on 46,XY DSD, diagnostic protocols, and therapeutic considerations, integrating perspectives from endocrinology, urology, genetics, and psychology.

Disorders of Sex Development (DSD) are rare conditions characterized by atypical chromosomal, gonadal, or anatomical sex development.⁶ A diagnosis of 46,XY DSD specifically refers to individuals with a typical male karyotype but with variations in gonadal or phenotypic sex development due to disruptions in testosterone production or action.⁷ The complexity of DSD cases like this one requires a multidisciplinary approach that considers diagnostic nuances and management options, with a particular emphasis on optimizing psychological and physiological outcomes.⁸ This case of a 20-year-old with ambiguous genitalia and primary amenorrhea provides an opportunity to delve into the diagnostic challenges and therapeutic implications of 46,XY DSD.

The patient presented with a history of primary amenorrhea, absence of cyclical abdominal pain, and significantly delayed secondary sexual characteristics. Breast development had not

occurred (Tanner stage M1), though pubic hair was present from age 12, and the patient denied erectile function of the phallic structure. Socially female, the patient identified with the female gender and showed sexual attraction towards men. On physical examination, the presence of upper lip hair, acne, and prominent thyroid cartilage was noted, alongside genital ambiguity consistent with Prader stage 3. Ultrasound revealed no gonadal structures, and karyotyping confirmed a 46,XY genotype. Despite extensive examination, the lack of definitive gonadal structures warranted further imaging, and MRI findings were inconclusive for Müllerian structures. A tentative diagnosis of 46,XY DSD was made, with subsequent hormonal and genetic evaluations planned to guide treatment and management.

Figure 1 illustrates the clinical manifestations observed in this patient. Fine hair was present above the lip, accompanied by acne, but no weblike neck was visible. The thyroid cartilage was prominent. The genitalia appeared as a structure resembling a penis measuring approximately 3 cm, with no palpable testes and no labial fusion. The external urethral orifice was situated 0.5 cm below the penile structure, and no separate vaginal introitus was identified, consistent with Prader stage 3.

Laboratory findings further elucidate the case, as shown in Table 1. Elevated levels of luteinizing hormone (LH) at 58.45 mIU/ml and follicle-stimulating hormone (FSH) at 57.74 mIU/ml suggest gonadal dysfunction. These hormonal profiles indicate a disruption in normal gonadal development or function, a common feature in 46,XY DSD cases.

The MRI examination, presented in Figure 2, revealed inconclusive findings regarding Müllerian structures. This lack of clarity highlights the challenges in imaging for DSD, where advanced techniques may still fail to provide definitive insights into internal anatomy, particularly in cases with atypical or ambiguous development.

The differential diagnosis in this case included a range of potential etiologies. Karyotyping confirmed the 46,XY chromosomal composition, consistent with male sex chromosomes but contrasting with the patient's physical presentation. The primary classification of 46,XY DSD encompasses a spectrum of causes, from partial or complete gonadal dysgenesis to androgen biosynthesis defects.⁹ Advanced genetic sequencing could provide further clarity by identifying specific mutations affecting gonadal differentiation pathways, such as SOX9, WT1, and NR5A1 (SF-1), which are known contributors to dysgenetic or ambiguous genitalia. Hormonal assessments, particularly measuring testosterone, anti-Müllerian hormone (AMH), and luteinizing hormone (LH), were instrumental in evaluating gonadal function. Potential factors such as LH resistance, 5 α -reductase deficiency, and biosynthetic enzyme defects required careful consideration. Imaging techniques, including ultrasonography and MRI, also played a crucial role in identifying anatomical features, though challenges remained in accurately visualizing intra-abdominal structures.⁹⁻¹²

In terms of classification and pathophysiology, the case illustrated the diverse subtypes of 46,XY DSD, which are defined based on the degree of gonadal development and androgen biosynthesis. Partial or complete gonadal dysgenesis, often linked to mutations in genes such as SRY or SOX9, could lead to incomplete masculinization or ambiguous genitalia.¹⁰ Similarly, androgen

biosynthesis deficiencies, such as 5 α -reductase type 2 deficiency, impaired DHT formation and contributed to undervirilized genitalia. In some cases, complex genetic syndromes involving mutations in SOX9 or WT1 were associated with syndromic presentations that affected multiple systems.¹³⁻¹⁶

The management of this case required a multifaceted approach. Hormonal therapy was a key component, with testosterone or DHT supplementation considered for patients who opted for male gender identity, while estrogen therapy could assist feminization for those aligning with a female identity.¹⁷ Psychological support was equally essential, addressing the unique challenges faced by individuals whose gender identity and body image may not align with their physical characteristics.¹⁸ Collaboration among endocrinologists, psychiatrists, and counselors ensured that care was comprehensive and patient-centered. Surgical interventions were approached with caution, with delayed or staged procedures preferred to allow for informed consent and reduce the likelihood of future regret. The risks associated with early surgical interventions, including complications and potential gender dysphoria, highlighted the importance of a careful, individualized approach. Long-term follow-up was necessary to address ongoing hormonal needs, fertility considerations, and the potential risk of gonadal tumors in cases with retained dysgenetic gonads.¹⁹

Future management plans for this case include a continuation of the diagnostic workup to refine the understanding of the underlying etiology, incorporating advanced genetic testing and specialized hormonal assays. Therapeutically, the focus will remain on aligning medical and psychosocial interventions with the patient's preferences and long-term well-being. Lifelong follow-up care will be essential to monitor hormonal balance, address any emerging health concerns, and provide continuous psychological support. The challenges in this case highlight the broader issues in managing 46,XY DSD, including ensuring access to advanced diagnostic tools and multidisciplinary care, addressing societal stigmas, and advocating for patient autonomy.²⁰

The management of 46,XY DSD also underscores the need for continued research and innovation. Advances in molecular genetics could offer more precise diagnostic insights, while improved therapeutic strategies may enhance outcomes for individuals with atypical sex development. Building robust care networks that integrate medical, psychological, and social support will be critical in overcoming the multifaceted challenges associated with these conditions. Ultimately, fostering an environment of understanding and support can significantly contribute to the well-being and quality of life for individuals navigating the complexities of 46,XY DSD.

CONCLUSION

DSD is genetically heterogeneous and careful assessment by a multidisciplinary team is essential to accurately diagnose DSD. Molecular technologies can help clarify the etiology and facilitate the diagnosis of DSD. However, many forms of DSD go undiagnosed. It is important for physicians to have a clear decision-making pathway in evaluating patients with DSD. The wide clinical variability of this disorder requires that each patient receive individualized management and support for his or her medical and psychological needs.

REFERENCES

1. Cunningham F, Leveno K, Bloom S, Spong CY, Dashe J. William obstetrics. 2018. 25 th ed. Philadelphia McGraw-Hill.
2. Mehmood KT, Rentea RM. Ambiguous Genitalia And Disorders of Sexual Differentiation. [Updated 2022 Aug 29]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-.
3. Mampilly, et al. Disorders of Sexual Differentiation: A Clinicopathological and Histological Study. Journal of Clinical & Diagnostic Research. 2022; 16 (2): 10-13.
4. Witchel SF. Disorders of sex development. Best Pract Res Clin Obstet Gynaecol. 2018; 48: 90-102.
5. Alkhzouz C, Bucerzan S, Miclaus M, Mirea AM, Miclea D. 46, XX DSD: developmental, clinical and genetic aspects. Diagnostics. 2021 Jul 30;11(8):1379
6. Cools M, Köhler B. Disorders of sex development. Brook's Clinical Pediatric Endocrinology. 2019 Oct 2:105-31
7. Domenice S, Batista RL, Arnhold IJP, et al. 46,XY Differences of Sexual Development. [Updated 2022 Aug 21]. In: Feingold KR, Anawalt B, Blackman MR, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK279170/>
8. Lucas-Herald AK, Scougall K, Ahmed SF. Delivery of multidisciplinary care in the field of differences and disorders of sex development (DSD). Expert Review of Endocrinology & Metabolism. 2022 May 4;17(3):225-34
9. Wisniewski AB, Batista RL, Costa EM, Finlayson C, Sircili MH, Dénes FT, Domenice S, Mendonca BB. Management of 46, XY differences/disorders of sex development (DSD) throughout life. Endocrine reviews. 2019 Dec;40(6):1547-72
10. Gomes NL, Chetty T, Jorgensen A, Mitchell RT. Disorders of sex development—novel regulators, impacts on fertility, and options for fertility preservation. International Journal of Molecular Sciences. 2020 Mar 26;21(7):2282.
11. Granada ML, Audí L. The laboratory in the multidisciplinary diagnosis of differences or disorders of sex development (DSD) III) Biochemical and genetic markers in the 46, XYIV) Proposals for the differential diagnosis of DSD. Advances in Laboratory Medicine/Avances en Medicina de Laboratorio. 2021 Nov 29;2(4):494-504
12. Ahmed SF, Achermann J, Alderson J, Crouch NS, Elford S, Hughes IA, Krone N, McGowan R, Mushtaq T, O'Toole S, Perry L. Society for Endocrinology UK Guidance on the initial evaluation of a suspected difference or disorder of sex development (Revised 2021). Clinical endocrinology. 2021 Dec;95(6):818-40
13. Eapen A, Chandramohan A, Simon B, Putta T, John R, Kekre A. Imaging evaluation of disorders of sex development. Journal of Gastrointestinal and Abdominal Radiology. 2020 Jul;3(02):181-92
14. Délot EC, Vilain E. Disorders of sex development. InYen and Jaffe's Reproductive Endocrinology 2019 Jan 1 (pp. 365-393). Elsevier

15. Susilo AF, Tjandraprawira KD, Bayu P, Bayuaji H. Disorders of sex development (DSD) 46. XY due to type 2 5- α reductase deficiency in three siblings: Case report from a low-resource setting. *Annals of Medicine and Surgery*. 2022 Oct 1;82
16. Nagaraja MR, Gubbala SP, Delphine Silvia CW, Amanchy R. Molecular diagnostics of disorders of sexual development: an Indian survey and systems biology perspective. *Systems Biology in Reproductive Medicine*. 2019 Mar 4;65(2):105-20.
17. O'Connell MA, Hutson JM, Grover SR. Medical management of DSD. *Disorders| Differences of Sex Development: An Integrated Approach to Management*. 2020:193-219.
18. Ernst MM, Kogan BA, Lee PA. Gender identity: a psychosocial primer for providing care to patients with a disorder/difference of sex development and their families [individualized care for patients with intersex (Disorders/differences of sex development): Part 2]. *Journal of pediatric urology*. 2020 Oct 1;16(5):606-11.
19. Hutson JM, Grover SR, Bouty A. Surgical management in DSD. *Disorders| Differences of Sex Development: An Integrated Approach to Management*. 2020:221-36.
20. Delforge X, Brachet C, Damry N, Segers V, Luyckx S, Heinrichs C, Khelif K. A novel approach in the intraoperative management of ovotesticular DSD. *Journal of pediatric urology*. 2020 Dec 1;16(6):768-70.
21. Kencana I, Ariani T, Anum Q, Rizal Y. Clinical Appearance Of Tinea Corporis Resembles With Tinea Imbricata And Condyloma Acuminata Genital In A Reproductive Woman With HIV : A Case Report. *Andalas Obstet Gynecol J*. 2021;5(2):287-302. doi:10.25077/aoj.5.2.287-302.2021