PARTIAL ANDROGEN INSENSITIVITY SYNDROME IN A PATIENT REARED AS FEMALE WITH AMBIGUOUS GENITALIA: A CASE REPORT AND MINI-REVIEW

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ABSTRACT
Partial androgen insensitivity syndrome (PAIS) is a rare disorder. This disorder has a clinical picture that varies depending on the level of mutation of the androgen receptor gene. An understanding of psychosexual development, genital appearance, and fertility expectations of patients is a consideration for further treatment. PAIS generally present with the chief complaint of ambiguous genitalia, small penis, hypospadias, undescended testicles, or cryptorchidism. A twenty-seven-year-old patient presented in the outpatient department of Andrology with the complaint of wanting to confirm his genitalia. The patient's father and mother are not related. When the patient was pregnant, the patient's mother was 18 years old, and the father's age was 27 years. His parents saw the external genitals as female and were raised as female. Meanwhile, entering the age of 17 years, the patient realized that the penis began to appear like the shaft of the penis in the genital area. From a psychological perspective, it is necessary to consider counseling and assistance for one year so that patients can make decisions. This case report concludes that PAIS management requires multidisciplinary cooperation by considering the patient's physical, psychosexual and fertility development.

Keywords: Partial Androgen Insensitivity Syndrome, Ambiguous Genitalia, Reifenstein's Syndrome, Testicular Feminization

1. INTRODUCTION

Androgen insensitivity syndrome (AIS) is a rare genetic disorder. The incidence of AIS is estimated to be 1:20,000 male births. [1] Androgen Insensitivity Syndrome is classified into three types: complete androgen insensitivity syndrome (CAIS) with typical female genitalia; partial androgen insensitivity (PAIS) with predominantly female, predominantly male, or ambiguous genitalia; and mild androgen insensitivity syndrome (MAIS) with typical male genitalia. [2, 3]

In CAIS, the patient has a female phenotype, so she is raised and raised as a woman. Patients usually come for treatment because they have primary amenorrhea despite having perfect breast development and female external genitalia. Furthermore, in CAIS, it is usually found that the testes is located in the abdomen, and there is an absence of a uterus and ovaries with female external genitalia. [4, 5]

The patient's phenotype can vary in PAIS depending on the androgen receptor (AR) gene mutation level. [3, 6] The critical period of virilization occurs between the 8th and 14th weeks of intrauterine life. If there is a partial mutation in the AR gene, the development of the external genitalia will be less than perfect and ambiguous genitalia will occur. [6] The patients generally present with the chief complaint of ambiguous genitalia, small penis, hypospadias, undescended testicles, or cryptorchidism. In this report, we will discuss the case of a 27-year-old woman with a male phenotype and ambiguous genitalia diagnosed as PAIS.

2. CASE PRESENTATION

The twenty-seven-year-old patient presented in the outpatient department of Andrology with the complaint of wanting to confirm his genitalia. The patient's father and mother are not related. When the patient was pregnant, the patient's mother was 18 years old, and the father's age was 27 years. The patient's mother had no history of abortion. During pregnancy, the patient's mother only took vitamins given by the village midwife. He is the eldest of two children. Bleeding or history of hospitalization during pregnancy was denied. His mother stated that the patient was born at term with a vaginal delivery assisted by a traditional birth attendant, and during the antenatal period, the patient's mother said it was expected that there were no significant problems with a birth weight of 3200 grams. His parents saw the external genitals as female and were raised as female. Growth and development of both gross motor, fine motor, verbal, and social interactions are well developed. Patients can also follow lessons at school well and never miss class.

Entering the age of 17 years, the patient realized that the penis began to appear like the shaft of the penis in the genital area. Patients say that when stimulated, the part can enlarge and harden. When experiencing orgasm, the patient claimed to be able to come out with white fluid from the hole in the folds of his genitals. As a result of this condition, the patient began to doubt his gender identity, breast development was minimal, but menarche did not occur. There is no family history similar to that experienced by the patient. At that time, the patient had not sought medical help because he was embarrassed. When he checked himself, the patient said that he already had a female partner and planned to get married the following year. The patient's family supports the patient's decision.

At the time of examination, the patient was cooperative without any pressure. The patient's vital signs were found to be within normal limits. Based on the Asia-Pacific BMI calculation, the patient is classified as obese. A bodyweight of 72 kg and a patient's height of 160 cm corresponds to the average woman in Indonesia. Breasts are not fully developed, namely Tanner 2, axillary hair growth is sparse, and pubic hair is by Tanner 3 development (Figure 1a). From the External Masculine Score (EMS) calculation, the score was < 7, which means ambiguous genitalia. On genital examination, the phallus structure was 4 cm long and 3 cm in

circumference (Figure 1a). Penoscrotal hypospadias was found (Fig. 1b). On scrotal examination, a bifid scrotum was found with a palpable spongy mass in the right scrotum with a size of 4±x3 cm, while the left scrotum was palpable empty.

Figure 1. (a) Examination of the length of the phallus, (b) the location of the urethral opening showed penoscrotal hypospadias, (c) a mass in the right scrotum and an empty left scrotum, (d) a hole resembling the vaginal introitus

From laboratory examination, FSH was 9.86 mIU/ml (Normal: 1.5-11.8 mIU/ml) and testosterone 5.32 ng/ml (Normal 2.2-10.5 ng/ml). Ultrasound results from the lower abdomen to the scrotum showed that the right scrotum showed a testicle with a size of 1.34 x 3.3 x 2.79 cm, intratesticular vascularization was good on Doppler, while the testes did not appear in the left scrotum (Figure 2). Prostate measuring ± 1.18 x 2.56 x 2.74 cm (volume ± 4.3 cc), parenchymal echo intensity appeared normal. From the CT Scan of the abdomen results, it was found that there was a mass in the right scrotum area of 1.4 x 3.1 x 2.7 cm, and while in the inguinal canal, it was found to have an oval shape measuring 2.1 x 2.2 x 3.5 cm.

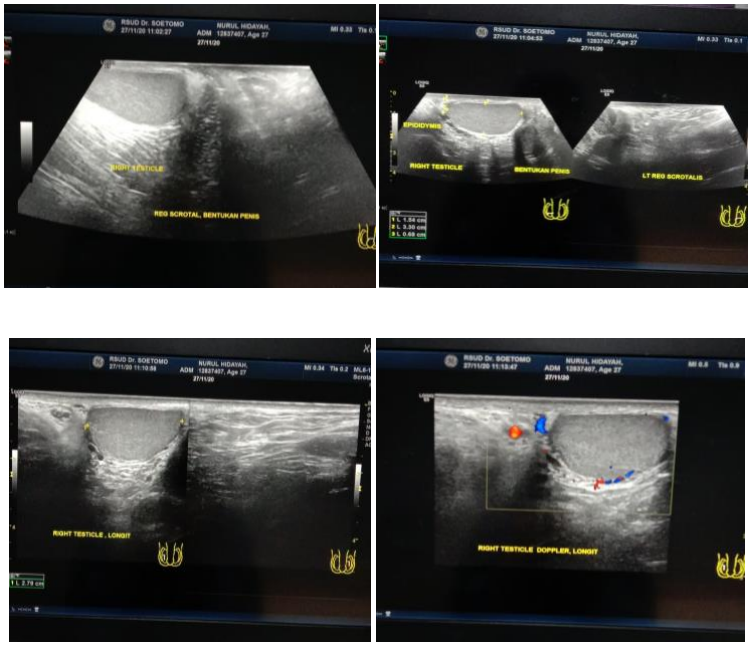

Figure 2. The results of the ultrasound examination showed the presence of a testicle in the right scrotum, while the left scrotum was empty

Subsequently, a supporting examination in the form of karyotyping was carried out with the result 46, XY (Figure 3). Now, she represented a case of 46 XY DSD, and the differentials included partial androgen insensitivity syndrome (PAIS) or any defect in the testosterone biosynthesis pathway. Our patient consulted the Urology and Psychiatry for further management.

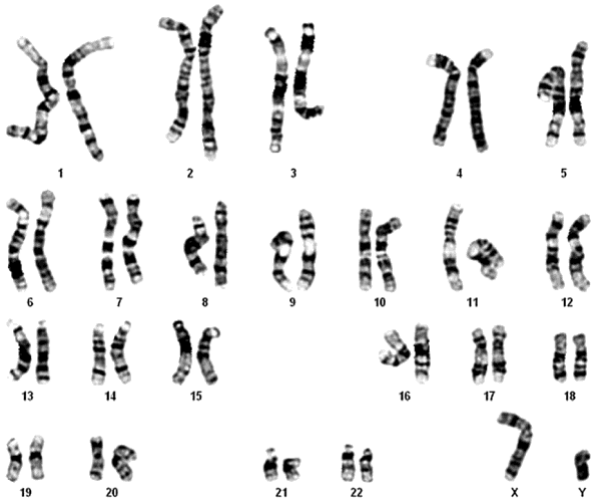

Figure 3. The karyotyping results show 46,XY

3. DISCUSSION

Partial androgen insensitivity syndrome (PAIS) is a rare disorder. When entering puberty, such patients may present with microphallus, hypospadias, and labia majora like a bifid scrotum, cryptorchidism, or gynecomastia. [3, 7] AIS, including CAIS, PAIS, and MAIS, is related to the mutations in Androgen Receptor (AR) gene, located in Xq 11-12, resulting in decreased peripheral responsiveness to circulating androgens. AIS is inherited as an X-linked trait. [8]

In PAIS, testosterone (T) and its metabolite dihydrotestosterone (DHT) and anti-mullerian hormone (AMH) are typically produced. Nonetheless, since androgen-dependent target tissues are partially responsive to testosterone and DHT, Wolffian duct structures do not fully develop and cause ambiguous genitalia. [3, 9]

In our case, the patient presented with a phallus, bifid scrotum, and palpable mass in the right scrotum. He had an adverse past medical and family history. Although it is inherited, less than 50% of patients with PAIS have a family history. [3] On systemic examination, no abnormalities were detected. External genitalia examination revealed that the patient presented with a phallus, bifid scrotum, and palpable mass in the right scrotum, which needed confirmation. After an ultrasound examination, a suspicious testicular mass was found in the right scrotum and left the inguinal canal, suggestive of undescended testis.

To establish the diagnosis of PAIS, karyotyping result 46, XY is needed, as well as evidence of normal or increased T level and average DHT level. [10] Measurement of DHT is essential to exclude a 5α-reductase type II deficiency diagnosis.10 Another differential diagnosis that also needs to be ruled out is 17-β hydroxysteroid dehydrogenase type III deficiency, in which the androstenedione: testosterone ratio is elevated when the hCG challenge test is performed (Table 1). [11] The gold standard for diagnosing PAIS is detecting AR gene mutation.9 In our case, karyotyping results showed 46, XY. Unfortunately, the measurement of DHT, androstenedione, and AR mutation testing was not performed due to limited patient costs.

Table 1. Differential Diagnosis of PAIS based on Characteristic Differences

Disorder	External Genitalia	Gonads	Mullerian (M)/Wolffian (W) Ducts	Hormonal Profile	Inheritance
Partial Androgen Insensitivity Syndrome	Ambiguous; blind vaginal pouch	Testes	M – absent W – present	Normal FSH Normal/High T High LH	X-linked recessive
5α-reductase Type II Deficiency	Ambiguous	Testes	M – absent W – present	Increased serum T:DHT ratio	Autosomal recessive
17-β Hydroxysteroid Dehydrogenase Type III Deficiency	Female or severely ambiguous	Testes	M – absent W – present	hCG stimulation results in increase androstenedione:T ratio	Autosomal recessive

The management of PAIS requires multidisciplinary cooperation by considering the patient's physical, psychosexual, and fertility development. Genetic and psychological counseling is also needed to assess the patient's readiness and expectations in the future.[12] From a psychological perspective, it is necessary to consider counseling and assistance for one year so that patients can make decisions after undergoing a 'real-life experience.' [12] If the patients have previously determined gender and gender roles, then the subsequent management can be considered. In patients with PAIS who were raised as a male, measures such as orchidopexy and hypospadias repair may be considered. If raised as a woman, gonadectomy procedures to prevent malignancy and the administration of estrogen therapy from developing secondary sex characteristics may be considered. Vaginal dilatation may also be performed to avoid dyspareunia and, in some cases, mammoplasty to increase self-confidence. [13–15]

If the patient wishes to be male, external genital reconstruction procedures and trials of testosterone and DHT may be considered with the aim of prolonging penis size and stimulating virilization.

4. CONCLUSION

Partial Androgen Insensitivity Syndrome (PAIS) is one of the rare disorders that manifest as ambiguous genitalia as causes of undervirilization. This condition is usually suspected at birth. Management of PAIS requires multidisciplinary collaboration by considering various aspects of physical development, psychosexuality, and fertility.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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