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CASE REPORT

Clinical, Hormonal and Cytogenetic Analysis of Familial DSD: A Case Report

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Abstract

Disorder of Sex Development (DSD) comprises a heterogeneous group of conditions associated with atypical development of internal and external genitalias. Affected patients may be recognized due to the ambiguity of external genitalias. History taking, clinical examination, hormonal profile, and genetic analysis will help reach definitive diagnosis among patients with ambiguous genitalia. We report an Indonesian case of 27-year-old patient reared as a male with atypical genitalia. The patient presented with severe hypospadias, poor virilization, and development of gynecomastia at puberty. Laboratory examination showed 46,XY karyotype, normal of luteinizing hormone (LH), normal follicle-stimulating hormone (FSH), and high serum testosterone levels. His youngest brother of 3 siblings has the same condition. Both cases were suspected to be partial androgen insensitivity syndrome (PAIS). Diagnosis of a DSD can be devastating to patient and family. Patient management need to be individualized by a multidisciplinary team especially for decisions related to sex assignment or rearing. Although molecular analysis has not been done yet, the possible diagnosis of this patient is PAIS based on the karyotype, hormonal assays, familial cases, undermasculinisation of external genitalia, and predominantly abnormal male phenotype such as hypospadias, micropenis, and gynecomastia at puberty. AR gene analysis should be done to confirm the diagnosis.

Keywords: Disorder of sex development; Indonesia; Partial Androgen Insensitivity syndrome

Introduction

Ambiguous genitalia is a rare condition that happens under the diagnosis of Disorders of Sex Development (DSD) with the incidence of 1:4500 to 1:5000 live births (Acimi, 2019). It has been suggested to use the term DSD when addressing ambiguous genitalia because of a potentially sensitive issue (Lee et al., 2021). DSD are conditions which leads to differences in development of urogenital tract and different clinical phenotypes.

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Diagnosis of specific DSD followed the classifications adopted by Consensus Conference are 46,XY DSD, 46,XX DSD, or Sex Chromosome DSD (Hughes et al., 2006). Assessment of prenatal history, family history, physical examination with attention to the genital anatomy or any dysmorphic features are the first step of care in patients with DSD (Abo Howla et al., 2016).

The most common cause of male undermasculinisation is androgen insensitivity syndrome (AIS), a recessive X-linked inherited diseases with the prevalence of 2-5 in 100,000 (Batista and Mendonca, 2018). The pathophysiology of this syndrome is based on the mechanism of androgen actions. The result of

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dysfunctional androgen is due to the inability of cell to respond to androgen caused by mutation in androgen receptor (AR) (Petroli et al., 2011, Farhud et al., 2016, Fulare et al., 2020). AR gene is located on the X-chromosome at Xq11-12 and is formed by eight exons and seven introns that span 90 kb of DNA. Mutation in the AR gene is found differently distributed throughout the gene sequence (Petroli et al., 2011). Mutation of AR gene during fetal development results in the cells failing to respond to androgen hormone, preventing masculinisation of male genitalia and later on the development of male secondary sexual characteristic. AIS is classified as complete, partial and mild AIS according to the degree of genital masculinization (Fulare et al., 2020).

Partial androgen insensitivity syndrome (PAIS) has variable degrees of external ambiguity and would be diagnosed if mutation in the androgen receptor (AR) gene is detected (Lee et al., 2021, Belengeanu, 2008, Hughes et al., 2012, Lucas-Herald et al., 2016). External genitalia ambiguity varies from 1) predominantly female with inguinal/labial testes, clitoromegaly and labial fusion, and distinct urogenital sinus; 2) microphallus (<1 cm) or clitoris-like underdeveloped glans, labia majora-like bifid scrotum, descended or undescended testes, perineoscrotal hypospadias, and gynecomastia in puberty, and 3) predominantly male, that is; simple or severe "isolated" hypospadias with normal-sized penis and descended testes, severe hypospadias with micropenis, bifid scrotum, and descended or undescended testes (Gottlieb and Trifiro, 1993). Hypospadias is a common male congenital malformation in PAIS and typical type is severe hypospadias with bifid scrotum that might contain gonads (Hughes et al., 2012). We present an adult male case referred to multidisciplinary DSD team of Dr Kariadi Hospital-Faculty of Medicine Diponegoro University with ambiguous genitalia and severe hypospadias.

Case report

A 27 year old male [III.1] was referred to our multidisciplinary team for an evaluation of ambiguous genitalia. The patient identified himself as a male and had a preference for male activity in his society. He was about to marry and looking for a doctor to perform surgery on his condition. He had not taken folk remedies nor exogenous sex steroids. According to this patient, his youngest brother [III.4] had the same particular condition to this patient. Unfortunately his youngest brother [III.4] refused to come to our clinic for physical examination and blood collection. Furthermore, there was no family history of infertility or unexplained neonatal deaths. A history of parental consanguinity was unclear because they were from the same clan and village (figure 1).

Past medical history revealed mother did not suffer any particular illness before and during pregnancy. There was no history of maternal virilisation or exposure to androgen substances during pregnancy. He was born at full-term by vaginal delivery at home by midwife without any perinatal complications and genital ambiguity was recognized at birth. He did not have any history of salt-losing crisis nor failure to thrive. The patient and his young brother had not seek medical care earlier because of financial problem.

His weight was 51 kg and 168 cm in height indicating a BMI score 18.1 kg/m2. Physical examination showed bilateral symmetrical gynecomastia (Tanner stage 5), pubic hair growth was in normal development and axilla hair growth was lack in development (Tanner stage 2). Clinical findings exhibited undermasculinised genitalia including penoscrotal hypospadias with a 3 cm stretched penile length and diameter of 2 cm and chordae. There was bifid scrotum, bilaterally descended testes with volume of 10 ml on right side and retractile testis with volume 5 ml on left side, scrotal sac rugae, and normal pigmentation. (Figure 2).

Hormonal analysis results showed normal LH level 11.81 mIU/mL (normal ref. 0.57-12.07), normal FSH level 5.23 mIU/mL (normal ref. 0.95-11.95), increased level of testosterone 1,847.1 ng/dL (normal ref. 142.39-923.14).

Cytogenetic examination was conducted using G-banding analysis showed 46,XY. Written informed consent was obtained for the treatment of the patient, blood collection and genital photography. Ethical board approval was deemed unnecessary for the case report.

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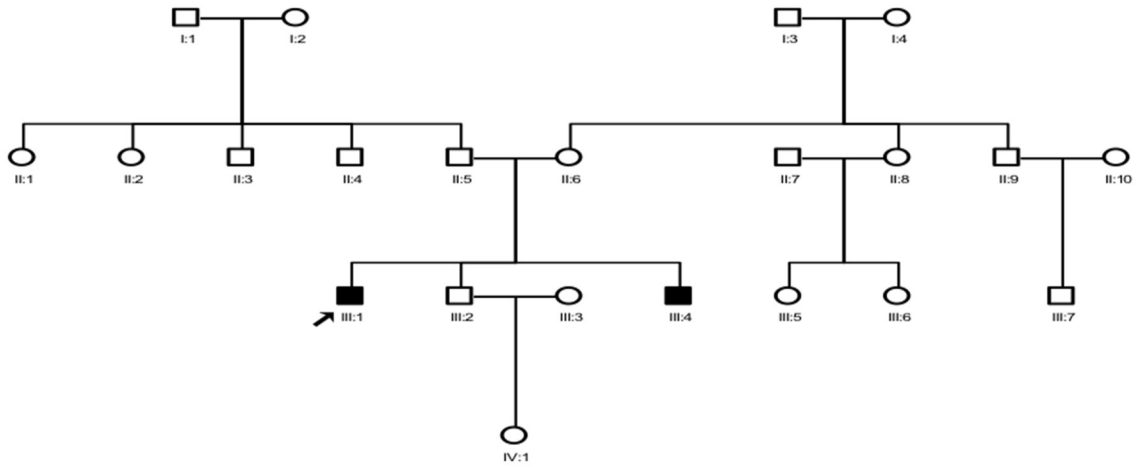

Figure 1. The filled square denoted by arrow represents affected patient. [III.1] Pedigree of the family showed the youngest brother had the same particular condition. [III.4] Circles represent female and squares represent male. Open symbols are unaffected.

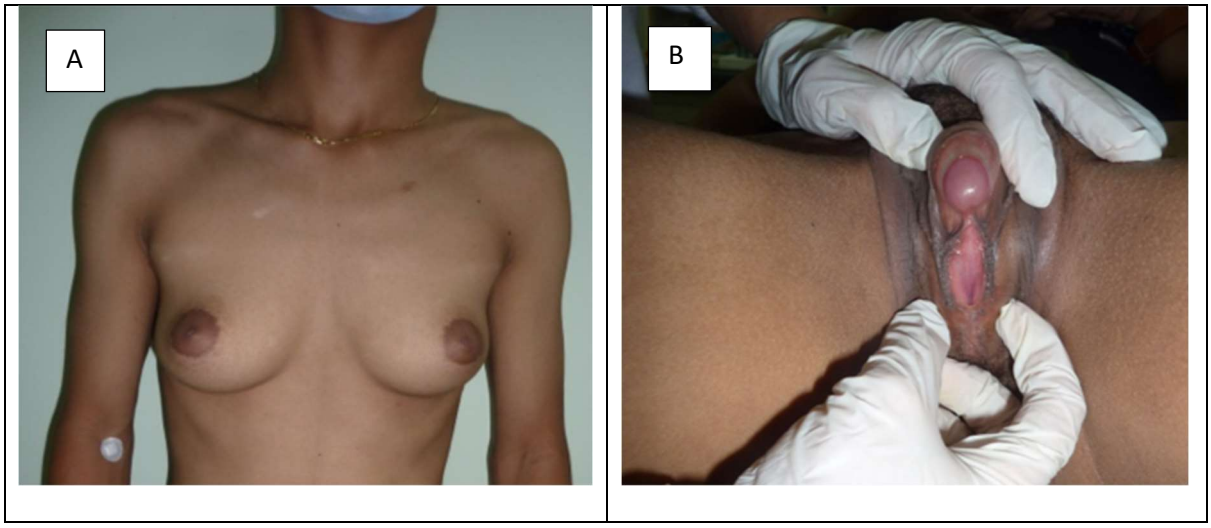

Figure 2. Physical Examination.
A. The patient had gynecomastia (Tanner breast stage 5) B. Evaluation of external genitalia showed micropenis and severe hypospadias.

Discussion

Ambiguous genitalia documented to range from 1:1000-5000 live births. Over 80% of cases with ambiguous genitalia are raised as males and have a presumed or actual XY karyotype (Ahmed et al., 2013).

The diagnosis of 46,XY DSD is based on family history taking, physical examination, laboratory testing, imaging and cytogenetic analysis (Khanna et al., 2019). In this case, this patient was diagnosed with 46,XY DSD based on his clinical presentation and available laboratory investigations.

Patients with DSD have a higher incidence among areas with greater consanguinity (Nelwan et al., 2021, Bashamboo and McElreavey, 2014). Some evidence for a higher rate of DSD in societies with a higher rate of consanguinity of 62.8% (Bashamboo and McElreavey, 2014). The extent of AIS in 46, XY DSD is not rare in communities with high prevalence of consanguineous marriages (AlFaifi et al., 2018, Ramamurthy and Karuppusamy, 2018). A history of parental consanguinity was suspected in this patient because they were from the same clan and village. The AR gene is located on the X chromosome,

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however, the pattern of inheritance of PAIS in most cases is X-linked and may not be responsible directly unless 46,XY DSD is due to novel recessive mutations responsible for the phenotype (Bashamboo and McElreavey, 2014). High mutation rate of within the AR gene relatively frequent occurrence in 40% cases of PAIS (AlFaifi et al., 2018). In our case, the youngest brother also had the same condition with this patient Affecting two individuals of a single family in this case with no history of ambiguous genitalia from previous generation can be due to consanguineous marriage or polygenic inheritance.

Normal male genital development depends on the differentiations of the testes, the ability to produce testosterone and the effects of this hormone to the body (Lee et al., 2021). Ambiguous genitalia in a 46,XY DSD can be due to abnormal formation of the early fetal testes (testicular dysgenesis), decreased production of testosterone or the inability to respond to androgens (AIS). AIS is one of the most common causes of 46,XY DSD (Listyasari et al., 2021, Bashamboo and McElreavey, 2014). The phenotype of men external genitalia in AIS is varied widely, appearing of external genitalia with small phallus, hypospadias, bifid scrotum with or without palpable testes and gynecomastia (Lucas-Herald et al., 2016). The gynecomastia may be presenting symptom during puberty and is more common in males with PAIS (Nordenström, 2020). Additionally in our patient, his external genitalia were male-like with micropenis, bifid scrotum with bilateral gonad and severe hypospadias, therefore the diagnosis PAIS was suspected.

Hormonal profile investigations in this patient showed normal LH levels, normal FSH levels, increased levels of testosterone. In PAIS, at puberty, elevated LH, and testosterone levels are observed (AlFaifi et al., 2018, GULÍA et al., 2018). However in this patient only testosterone level was markedly increased. Previous study has reported the absolute values of these markers in AIS were not remarkable (Lucas-Herald et al., 2016). Cytogenetic analysis of this patient revealed a male 46,XY karyotype.

It is very rare to have a complete molecular diagnostic in Indonesia for identification of the AR gene responsible for PAIS (Listyasari et al., 2017). We were not able to perform mutation analysis of the androgen receptor (AR) gene for this patient because of no facilities in our laboratory.

Following consultation with the patient, the decision was made to maintain the male gender identity. Such decisions are based on sexual attraction towards females, genetics evaluation and anatomic sex. This conditions requiring medical or surgical attention may be difficult and suffered more emotional problems.

Early surgery for patient with DSD is highly preferable to late surgery because during adulthood hyper vascularization of the penis which hypersecretion of androgen makes the surgical repair will be more difficult. However, the surgical repair of these urogenital malformations lately has been improved (Acimi, 2019). Breast cancer occurs rarely in males with PAIS (Hughes et al., 2012). In this case late surgery should be done as soon as possible for hypospadias repair and reduction mammoplasty.

Psychological distress is more common in adults with PAIS than those with CAIS. It is, therefore, important that the patient receive timely psychological counselling to improve acceptance of the diagnosis (Chikkanayakanahally, 2014). Genetic counselling indication is needed to avoid gender dysphoria, sex assignment, pattern of inheritance and reproductive effect. Fertility issues are common in DSD, and therefore, these issues should be discussed with the patients in adult life (Nordenström, 2020, Wisniewski et al., 2019). In addition cultural background is also considered to make gender assignment decision.

Conclusion

An appropriate clinical examination, hormonal profile and cytogenetic analysis should be performed to propose the best rearing sex. A multidisciplinary medical team and molecular study is needed in order to provide the best diagnosis and approach to management in the cases of DSD. Despite the limitations, our findings could contribute in the investigations of patients with ambiguous genitalia and severe hypospadias for the possibility of DSD diagnosis.

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