

Case Report

Male pseudohermaphroditism due to 5-alpha reductase type-2 deficiency in a 20-month old boy

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Intersex conditions are the most fascinating conditions encountered by clinicians. The ability to diagnose infants born with this disorder has advanced rapidly in recent years. In most cases, clinicians can promptly make an accurate diagnosis and give the advice to the parents on therapeutic options. Intersex conditions traditionally have been divided into the following 5 simplified classifications based on the differentiation of the gonad, i.e. 1) female pseudohermaphrodite characterized by two ovaries, 2) male pseudohermaphrodite characterized by two testes, 3) true hermaphrodite characterized by ovary and or testis and or ovotestis, 4) mixed gonadal dysgenesis characterized by testis plus streak gonad, and 5) pure gonadal dysgenesis characterized by bilateral streak gonads.¹⁻³

5-alpha-reductase (5-ARD) type 2 deficiency is an autosomal sex-linked disorder, resulting in the inability to convert testosterone to the more physiological active dihydrotestosterone (DHT). DHT is the most potent androgen, bound selectively to the androgen receptors in genital skin and fibroblasts, making its action necessary for the development of normal male genital anatomy. Since DHT is required for normal masculinization of the external genitalia in utero, genetic males with 5-ARD are usually born with ambiguous genitalia (male pseudohermaphroditism).²⁻⁴ The hallmark of 5-ARD is elevated ratio of serum testosterone to DHT. In healthy prepubertal children, the baseline testosterone-to-DHT ratio is 1:2.^{2,4-6} This

paper reports a 20-month old patient with male pseudohermaphroditism due to 5-alpha reductase type-2 deficiency.

Report of the case

A 20-month old "girl", came to the outpatient clinic of the Department of Child Health, Sanglah Hospital, Denpasar, with the chief complaint of a bump on the urinary duct noted since three months before admission. The urination and defecation were normal. History of pregnancy and delivery were normal. There was no history of the same condition among the family. No history of oral contraceptive, alcohol intake, hormonal, or traditional medication during pregnancy. His growth and development were normal.

Physical examination revealed an alert baby with regular pulse rate of 120x/minute, respiratory rate of 30x/minute, axillary temperature of 36.5°C. Bodyweight

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was 12 kilograms, body height 85 centimeters, and he was well nourished. There were no abnormalities of head and neck; conjunctiva and sclerae of both eyes were normal, the pupils were isocoric, and reflexes were positive. The chest was symmetrical, the mammae appropriate to Tanner stage 1, the heart and lungs were normal. Abdomen was normal and no mass on palpation. Both extremities were normal.

Genitalia examination revealed the length of phallus was 1.3 cm, there were normal preputium, ventral frenulum, and external urethral orificium. No mass was palpable in labioscrotal area, but a mass with a diameter of 1 centimeter was palpable in right inguinal (**Figure 1**).

Laboratory results showed WBC of 15,030/ μ l, haemoglobin of 12.7 g/dl, hematocrit of 40.2%, and platelets count of 250,000/ μ l. Urinary examination revealed normal result, renal function test revealed normal with BUN of 10.8 mg/dl, and serum creatinine of 0.3 mg/dl. Chromosomal analysis revealed 46, XY; and the 17-alpha OHP concentration level was

22.0 ng/dl, still within normal values. Before performing hCG test, FSH, LH, testosterone, and DHT levels were 11.5 mIU/ml, 0.6 mIU/ml, <2 ng/dl, and <2 ng/dl, respectively. After hCG test, testosterone level increased to 146 ng/dl while DHT level to 24 ng/dl.

Pelvic USG showed an absence of uterus and testes were suspected to be localized in right and left inguinal (**Figure 2**).

The diagnosis was male pseudohermaphrodite due to 5-alpha reductase type-2 deficiency. The parents were informed about this disorder, and they expected that their child adopts a male gender identity.

Discussion

A deficiency of the type-2 isozyme 5-ARD, which transforms testosterone to DHT is the main cause of ambiguous genitalia.^{5,6} Most individuals with 5-ARD are identified in neonatal periods because



FIGURE 1. EXTERNAL GENITAL EXAMINATION SHOWED BILATERAL LABIOSACRAL FOLDS AND SMALL-SIZED PHALLUS.

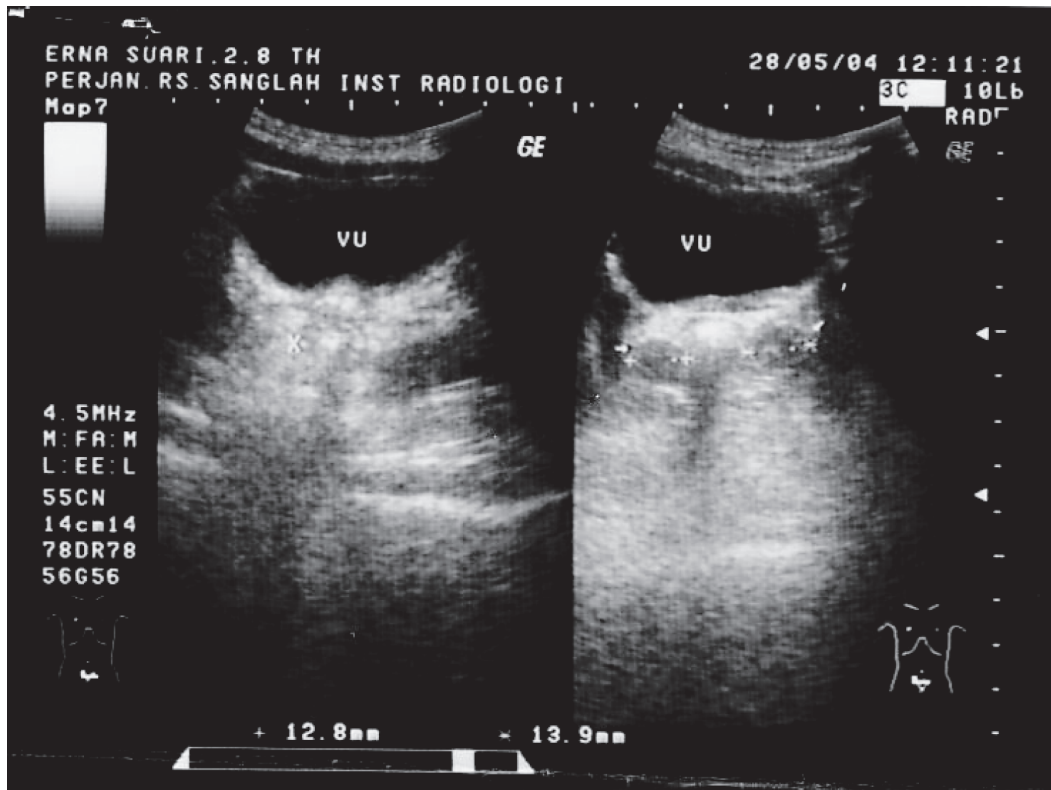


FIGURE 2. PELVIC USG SHOWED THE ABSENCE OF UTERUS AND THE LOCATIONS OF BOTH TESTICLES.

of ambiguous genitalia. However, some of these children are misdiagnosed as having partial or complete androgen insensitivity syndrome (AIS), which can produce almost identical phenotypes. The clinical abnormalities range from infertility with normal male genital anatomy to underdeveloped male with hypospadias to predominantly female external genitalia, most often with mild clitoromegaly. The phallus was indeterminate in size with the length falls between 1.0 cm (usual maximum for clitoris) and 2.0 cm (lower limit of normal for a penis).^{5,7-9}

The diagnosis of 5-ARD can be confirmed in a patient with 46, XY karyotype. Currently mutation analysis of 5-ARD type-2 gene located at band 2p23 is available only for research purposes and not commercially. An elevated ratio of serum testosterone to DHT (T/DHT) occurs, demonstrated by the presence of high ratio of testosterone serum to DHT. Usually, testosterone level was normal to moderately elevated, while DHT level is low to undetectable. This level can be measured at birth during testosterone surge

that occurs when an infant aged 1-3 months or after hCG stimulation.^{5,6}

In this case, chromosomal karyotype was 46, XY and following hCG stimulation serum testosterone level increased to 146 ng/dl while DHT was 24 ng/dl. This result showed an elevated ratio of serum testosterone to DHT. USG can verify the location of the testes and the absence of the uterus, which may be present in other conditions.^{6,7} Vaginogram is a useful tool to assess vaginal length by introducing small catheter or feeding tube into the vagina. This study can verify that no fistula connections present between urinary tract and vagina.⁶ In our case, pelvic USG showed the absence of uterus while the testes were suspected to be located in right inguinal. Based on clinical manifestations, chromosomal karyotype report, hormonal serum examination, and pelvic USG, the final diagnosis was male pseudohermaphrodite due to 5-alpha reductase type 2 deficiency. The differential diagnosis such as congenital adrenal hyperplasia, androgen insensitivity syndrome and 17-ke-

tosteroid reductase deficiency could be excluded.¹⁰⁻¹⁵

The major issues for individuals with 5-ARD are gender assignment. Almost all children with 5-ARD are assigned as female at birth. In many cultures which early surgery was not performed, some individuals with 5-ARD adopt male gender identity and male gender role at puberty.⁶

No medical treatment required in infancy and childhood; some evidence suggested that DHT therapy administered prior to puberty may increase penile size.^{16,17} Providing accurate and complete information to the child and family with 5-ARD is of paramount importance. Problems about gender and sexuality can extremely provoke anxiety and emotional upset. Multidisciplinary team approach including geneticist, pediatric endocrinologist, pediatric psychiatrist or pediatric psychologist, pediatric surgeon or pediatric urologist is mandatory.

The geneticist is responsible for verifying the karyotype and discussing with the family about this abnormality, include the recurrence risk of 1:8 for each subsequent pregnancy. Pediatric endocrinologist is responsible for verifying the biochemical nature of the defect. Pubertal hormone replacement is usually instituted under supervision of a pediatric endocrinologist when the child attains the appropriate age. Pediatric psychiatrist or pediatric psychologist can help the family work with psychological issues (e.g. any feelings of guilt or blame) that accompany the birth of a child with 5-ARD, also help to facilitate communication between the family and medical consultants. Pediatric urologist surgeon assesses the potential for surgical reconstruction as either male or female. This assessment may affect the initial assignment of the gender rearing. Long term follow-up was necessary to evaluate the virilization process until the time of puberty.^{6, 7}

Hormonal replacement therapy such as hCG injection 500 IU twice a week for 5 weeks should be administered for the undescended testes, DHT cream 2% was not given because at that time this medicine is not available in Indonesia. Surgical reconstruction would be performed if hormonal replacement therapy was failed. Psychosocial support for the child and family was given.

We are of the opinion that the prognosis of fertility of pseudohermaphroditism due to 5-alpha reductase type-2 deficiency is good. Males with 5 alpha reductase deficiency have chance to be a father, although infertility could happen due to a low sperms count. Females with 5-alpha reductase deficiency will not be able to be pregnant but they still can have a family by either surrogacy or adoption.

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