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46, XY DSD Due To 5-Alpha-Reductase Type 2 Deficiency in 1 Years Old Children: A Case Report

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Abstract:
Background*: Disorders of sex development (DSD) are congenital abnormalities in the development of chromosome, gonads and anatomical atypical reproductive systems. Many kind of DSD is autosomal recessive inherited defect causes the impaired conversion of testosterone to Dihidrotestosterone (DHT). DHT deficiency will lead to externally imperfect genetic virilization. In type 2 alpha-reductase deficiency usually at birth and pre-puberty clinically will be predominantly female. This change will generally cause patients to change their gender identity to men.*
Case*: A one years old presented with ambiguous genitalia since birth. The clinical manifestation of external genetalia is ambiguous genetalia (prader III) with length of phallus is 1.3 cm. Laboratory finding 17-OH progesterone found normal. Ultrasonography examination found no testicular appearance and not yet visible uterus formation. From the results of chromosome analysis, found she has chromosome 46, XY DSD. Testosterone level before beta Hcg stimulation < 2.5 ng / dL and Dihydrotestosterone (DHT) level before beta Hcg stimulation is 0.4 nmol / L. Testestosterone level after 3 times 24 hours stimulation is 187.9 ng / dL and Dihydrostestosteron level after 3 times 24 hours stimulation is 0.47 ng / dL.*
Conclusion: *5-alpha-reductase type 2 deficiency can be a long-term problem such as a child's psychological problem as an adult and fertility.*
Key Word*: ambiguous genitalia* ; *46, XY DSD* ; *5-alpha-reductase type 2 deficiency*

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I. Introduction

Disorders of sex development (DSD) are congenital abnormalities in the development of chromosome, gonads and anatomical atypical reproductive systems (1). In Indonesia, a case of type 5 alpha reductase deficiency is found in clinical practice and until 2018, 37 cases have been reported (2). This autosomal recessive inherited defect causes the impaired conversion of testosterone to Dihidrotestosterone (DHT) (3). DHT deficiency will lead to externally imperfect genetic virilization. In type 2 alpha-reductase deficiency usually at birth and pre-puberty clinically will be predominantly female, although the genetalian. This change will generally cause patients to change their gender identity to men. Infants or children belonging to this category have a small phallus, with a cord, posterior hypospadias, bifidum scrotum formed imperfectly with or without cryptorchidism.

The conversion of testosterone into DHT by steroid 5α-RD *isoenzymes* is a key reaction in the androgen action and is essential for the male phenotype development during embryogenesis and for postnatal androgen-mediated growth of tissues (4). Isolated micropenis was rarely described in patients with 5α-RD2 deficiency. Normal internal male genetalia with prostate hypoplasia were observed in these patients. The testes were usually located in the inguinal region, suggesting that DHT influences testis migration to the scrotum. Development of muscle mass, deepening of the voice, and virilization of external genitalia occur at puberty (5).

For patients with 5α-RD2, assessment of T/DHT levels in serum after hCG injection has been widely used as a diagnostic tool. During early infancy and puberty, T levels increase, and the diagnosis of 5α-RD2 can be made based on an elevated ratio of T to DHT (normal <30:1), either with or without beta-hCG stimulation. Follicle stimulating hormone (FSH) and LH levels are normal. In the newborn period, the T/DHT ratio is high. During infancy and childhood, hCG stimulation also results in normal serum levels of T but subnormal serum levels of DHT. In the first of few months of life, when plasma levels of T and DHT are detectable, the normal T/DHT ratio is less than 12. Although diagnosis is best made on the basis of an elevated T/DHT ratio after administration of hCG, this disorder cannot be ruled out by absence of an elevated T/DHT ratio, making the diagnosis somewhat difficult (3).

II. Case

A children, 1 years old, Balinese, were reffered to the Pediatric Endocrinology Clinic at Sanglah Hospital in Denpasar with chief complaints of ambiguous genitalia since birth. The patient was raised as a girl at birth until 1 years old. The patients complained has two genitals that are realized from birth. Initially genitals that resemble a penis are still small, but gradually genitals grew bigger and longer. Beside that, the parents said that pee out through a hole at the bottom.

History of pregnancy and delivery were normal. The patient was the second child of two siblings. There was no consanguinity in the family. The patient had a sister. No history of the disorder was found in the rest of the family. Physical examination showed that the patient was alert. Vital signs were in normal limits. Body weight was 9 kg (Weight/Age is Z score 0 SD), and height was 77 cm (Length/age is Z score 0 – 2 SD). No dysmorphism was noted. External genetalia is ambiguous genetalia with length of phallus is 1.3 cm. the prader stage was 3. **(Figure 1)**

Chromosomal analysis revealed 46, XY DSD (*Disorders of Sex Development*). Before performing hCG test, testosterone level was < 2.5 ng / dL and dihydrotestosterone level was 0.4 nmol / L. After hCG test, testosterone level increased to 187.9 ng/dL and dihydrotestosterone level decreased to 0.47 ng/dL. Testosterone to dihydrotestosterone ratio was 400:1. Laboratory 17-OH progesterone found 1.17 (normal < = 1.15 ng / mL). Abdominal ultrasound revealed no testicular appearance and not yet visible uterus formation.

The diagnosis of this patient was 5-alpha-reductase deficiency. The parents were informed about that disorder. The patient and family were consulted to urology surgery department. External genitalia reconstruction was planned to perform.

Figure 1: picture of the patient external genitalia

III. Discussion

DSD can be subdivided into three main groups: disorders associated with gonadal dysgenesis; disorders associated with undervirilization of 46,XY individuals; and conditions associated with prenatal, and possibly also postnatal, virilization of 46,XX subjects. DSD are always challenging to manage. Choosing the optimal gender is difficult when the genitalia are ambiguous.

5-alpha-reductase deficiency is an autosomal recessive sex-linked condition resulting in the inability to convert testosterone to the more physiologically active DHT. Since DHT is required for the normal masculinization of the external genitalia in utero, genetic males with 5-alpha-reductase deficiency are born with ambiguous genitalia. They are usually identified as female at birth as in this case (6). The described 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 (7). Phenotypic findings in a newborn are limited to the genitalia. Most commonly, the external genitalia exhibit labial appearance to the labioscrotal folds with some mild rugation or pigmentation, clitoris-like phallus, perineoscrotal hypospadia, and pseudovagina blind ending introitus. The testes are usually in the inguinal canals bilaterally; howver in some individuals with 5-alpha-reductase deficiency, the testes can be found in the labioscrotal folds or retained in the abdomen. Clear signs of virilization predominate at puberty. The phallus exhibits definite enlargment. Generally no breast development (8). In this case, the patient came with external genetalia is ambiguous genetalia (prader III) with length of phallus is 1.3 cm and ultrasonography examination found no testicular appearance and not yet visible uterus formation. Chromosomal analysis was performed to determine the genotype of the patient. Chromosomal analysis in this case revealed 46 XY.

Classic biochemical hallmarks of 5α-reductase type 2 deficiency (5ARD) include a normal to high male concentration of serum testosterone, low concentration of DHT, and increased T/DHT ratio at baseline or after human chorionic gonadotropin (hCG) stimulation (9). In this case, low level of DHT and hCG stimulated T/DHT ratio of > 17 supported the diagnosis of 5-alfa-reductase deficiency type 2.

Management of 5-alfa-reductase deficiency type 2 is started with gender assignment. Almost all children with 5-alfa-reductase deficiency are assignes as female at birth. More than 70% of individuals with 5-alfa-reductase deficiency adopt male gender identity and male gender role at puberty(10). If the patient adopts male gender identity and micropenis is found, hormonal therapy with 2% of DHT cream shoukd be immediately started, but DHT 2% cream is still not available in Indonesia. A multidisciplinary team approach, including pediatric endocrinologist, child psychiatrist, plastics surgeon or pediatric surgeon or pediatric urologist, and geneticist, is needed in diagnosis and management of 5-alfa-reductase deficiency (11). In this case, patient are proposed for urology reconstruction for penis reconstruction.

IV. Conclusion

5-alfa-reductase type 2 deficiency is a rare disease. It can be a long-term problem such as a child's psychological problem as an adult and fertility. In addition to requiring appropriate medical treatment, must fulfill the rights of children as human beings who are guaranteed protection through law. So, it is expected that children who have identity problems because DSD can grow and develop according to their potential without any difference from other children.

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