**Case Report**

**46 XX Congenital Adrenal Hyperplasia (CAH) after Clitoroplasty, Labioplasty, and Vaginoplasty**

**46 XX Hiperplasia Adrenal Kongenital (HAK) Setelah Klitoroplasti, Labioplasti, dan Vaginoplasti**

Rahmat Husein, Besut Daryanto, Paksi Satyagraha, Pradana Nurhadi

Department of Urology Faculty of Medicine Universitas Brawijaya Malang

Department of Urology Soiful Anwar General Hospital Malang

**ABSTRACT**

Congenital adrenal hyperplasia (CAH) is the most common cause (60%) of Disorder of Sex Development (DSD), which causes three problems: symptoms and conditions arising due to adrenal endocrine disorders, long-term treatment, and quality of life due to genital ambiguity. An 18-year-old female patient was diagnosed with simple virilizing CAH and had genital ambiguity from birth. The patient was raised as a male. Overall, the examination results indicated a female. Physical examination before surgery showed virilization, such as external genital pigmentation, precocious pubic hair, and bilateral impalpable testis. The karyotype genetic examination confirmed female: 46, XX. Eventually, the patient decided as a female and underwent surgical management consisting of clitoroplasty, labioplasty, and vaginoplasty, followed by long-term corticosteroid therapy. Observations were made for three years after surgery to see the progress of the patient's condition. After undergoing glucocorticoid therapy and surgery, the patient had not experienced menstruation. Her breasts did not enlarge, and mustache and beard were still growing on her face. The patient was concerned about her condition, especially about the risk of infertility and inappropriate physical changes. The management of virilization in CAH with genital ambiguity should be seen from psychological and surgical perspectives. Understanding the disease, the goals of surgery, long-term treatment, and social adaptation help improve quality of life and reduce negative stigma.

**Keywords:** 46 XX, congenital adrenal hyperplasia, DSD

**ABSTRAK**


**Kata Kunci:** 46 XX, DSD, hiperplasia adrenal kongenital

**Correspondence:** Rahmat Husein, Department of Urology Faculty of Medicine Universitas Brawijaya Malang, Jl. Veteran Malang Tel. 081230001521 Email: dr.rahmathusein@gmail.com

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INTRODUCTION

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder caused by a deficiency of the enzymes required for adrenal steroidogenesis. These enzymes include 21-hydroxylase (21OH), 11β-hydroxylase (11βOH), 17α-hydroxylase (17OH), 3β hydroxysteroid dehydrogenase type 2 (3βHSD2), and steroidalgen acute regulatory protein (StAR) (1). CAH is the most common cause (60%) of Disorder of Sex Development (DSD) (2). Approximately 90-95% of cases with CAH are associated with 21-hydroxylase (21OH) deficiency due to mutations in the 21-hydroxylase gene (CYP21A2). The most severe symptoms of classic type CAH are salt-wasting and virilization (3).

The incidence of classical CAH is 1:10000 - 1:20000 live births while non-classical CAH is 1:1000 live births. The non-classical CAH is more common than the classic form, with an incidence of 1:1000. There is a prevalence of non-classical CAH in Hispanic Jews, Yugoslavian, and Ashkenazi (3).

Manifestations of symptoms and severity of the disease vary widely, depending on the patient’s age, gender, and the associated hormonal disorders (4). Surgical procedures for CAH are still controversial in the last decade, regarding indications, timing, and methods used since they are related to the quality of life after surgery (5). The goals of surgery are a.) sex-appropriate genital appearance, b.) normal urination, and c.) satisfactory sexual and reproductive function (1,2).

CASE REPORT

This case report described an 18-year-old female patient diagnosed as simple virilizing CAH and has had genital ambiguity since birth. The patient was raised as a male.

Before surgery, the physical examination showed virilization, such as pigmentation on the external genitalia, premature pubic hair growth, clitoromegaly, and bilateral impalpable testes. The patient grew relatively steadily in height (146 cm) but appeared smaller than her peers.

Figure 2. Karyotype examination, 46 XX

Figure 1. (A). Pubic hair with pigmentation on the external genitalia, (B). Enlargement of the phallus, (C). Orificium Urethra Externa

Figure 3. MRI examination found (A) bilateral adrenal enlargement and (B) uterine structure, (C). Bone age study showed accelerated growth and skeletal maturation (patientis 15-years old female, was suitable for 18-19 years old male)
The results of the karyotype genetic examination confirmed that the patient was female: 46, XX (Figure 2). Laboratory examination revealed a high value of 17-hydroxyprogesterone (17-OHP) (115.9 ng/mL).

An abdominal ultrasound examination revealed an uterine. This finding was confirmed by an MRI examination that also found bilateral adrenal gland enlargement consistent with congenital adrenal hyperplasia (CAH). The study of the patient’s bone age showed a picture consistent with the bones of an 18-year-old man. This suggests accelerated growth and bone maturation in congenital adrenal hyperplasia (CAH).

The genitogram examination revealed the structure of female genital organs. The results of the endourology examination confirmed the findings of the genitogram that showed two openings, the external urethral orifice and the vagina. The bladder was obtained within normal limits.

Overall, the examination results indicated that the patient has female gender. Psychiatric examination showed that the patient had an internal conflict because all the examination results indicated that the sex was female, while the patient was raised as a male. The patient routinely underwent psychotherapy before surgery. However, the patient finally could accept and choose to be a female.

The surgical management of this patient consisted of clitoroplasty, labioplasty, and vaginoplasty. The surgery was successful, and the patient routinely performed check-ups for postoperative wound care. The patient was

Figure 4. (A). Genitogram obtained female genitalia. Endourology examination: there are two openings, (B) external urethra orifices (blue arrow) and (C) vagina (red arrow)

Figure 5. (A). Traction suture was placed into the glans of the clitoris, (B). A circular incision was made just proximal to the glans. The dorsal skin was completely degloved to the base of the clitoris, (C). Neurovascular bundle was dissected free to the glans, (D). Clitoral reduction, excision of the corpora and leaving the glans with its intact blood supply through the neurovascular bundle, (E). The clitoral skin flaps are used to construct labia minora, (F). The urethral opening is accessible (catheter is inserted)
satisfied after undergoing surgery and was able to urinate normally. Before and after the surgery, the patient received long-term corticosteroid therapy as a substitute for glucocorticoids that the adrenal glands cannot produce. After receiving glucocorticoid therapy for a year, the patient’s bone mineral density (BMD) was examined, and the examination results revealed osteopenia. The patient’s progress was observed for three years after the surgery.

Figure 6. (A). External genitalia after three years of surgery, (B). Female genitalia: clitoris, external urethral orifice, and vagina

The patient was concerned about her condition, especially the risk of infertility and inappropriate physical changes. After undergoing glucocorticoid therapy and surgery, the patient has not started her monthly periods. breasts did not grow as in friends of her age, but mustache and beard still grew on her face. The patient claimed to have an interest in the opposite sex but has not wanted to have a relationship.

Her parents mentioned that the patient felt embarrassed, anxious, and depressed. The patient was tired of taking long-term medications. She had difficulty adapting from masculine behaviors and interests in masculine activities, such as playing football, thus limiting socializing with others. Negative stigma from the surrounding environment becomes a psychological burden for the patient’s parents. Parents felt under pressure to face rumors from neighbors about their child’s disorder. Parents also felt guilty and worried about their children’s future, so they tended to be overprotective and limit their child’s interactions with others.

Currently, the patient is at year 18, studying in a vocational high school. The patient routinely underwent psychotherapy from stigma effect that contribute to the increased rates of psychiatric problems such as depression. Although sometimes getting negative stigma from the people around her, the patient admitted that she could accept her condition and continued to hang out with friends of her age. Full support from the family made the patient happy with her condition.

**DISCUSSION**

This article reports an 18-year-old female patient diagnosed with CAH, has karyotype test result in 46, XX with simple virilizing, and had genital ambiguity since birth due to being raised as a male. The patient does not have chromosome disorder but has problems with virilization due to gonadal or hormonal abnormalities. About 60% of Disorders of Sex Development (DSD) are caused by Congenital Adrenal Hyperplasia (CAH) (2). As many as 95% of total CAH cases are caused by enzyme 21-hydroxylase (21-OH) deficiency, and 5% of cases are caused by 11-hydroxylase (11-OH) deficiency (6). Deficiency of the enzyme 21-hydroxylase (21-OH) plays a role in the biosynthesis of the cortisol and aldosterone enzymes in steroidogenesis. In CAH, the gene of the 21-hydroxylase (CYP21A2) enzyme is defective, causing a decrease in the production of glucocorticoids (cortisol) and mineralocorticoids (aldosterone) (7,8). The deficiency of the 21-OH enzyme will cause the accumulation of 17-hydroxyprogesterone (17-OHP) because it cannot be converted into a steroidogenesis product, so that it will be converted by the 17-hydroxylase (OH) and 17,20-lyase enzymes to produce another steroidogenesis product, testosterone. High testosterone level in plasma causes external genitalia virilization in female (8).

This patient had genital ambiguity since birth but was examined by health services at the age of 12. Physical examination before surgery revealed virilization, such as pigmentation on the external genitalia, precocious pubic hair, clitoromegaly, and bilateral impalpable testes. Patients who are not treated early or receive treatment but are not adequately treated will have long-term exposure to large amounts of androgen hormones (9). Prolonged exposure to androgens will trigger the hypothalamic-pituitary-gonadal axis, causing precocious puberty (5). Manifestations of symptoms and degree of CAH disease vary widely, depending on the patient’s age, gender, and the associated hormonal disturbances (8). Lack of patient adherence to hormonal treatment can lead to severe virilization, premature pubic hair development, and increased bone maturation due to long-term high exposure to systemic androgens. Enlargement of the clitoris can occur and keep continuing in women, thus resembling a penis (5,9).

The patient’s growth was relatively constant (146 cm) but seemed smaller than her peers. Increasing androgen production by adrenal glands leads to premature closure of the epiphyseal plate so that as adults, CAH patients appear short compared to the average height for their age (10). A meta-analysis shows that the adult height in patients with classical type is about 1.4 SD below the population’s average height (8). Overexposure to androgen hormones causes rapid bone maturation, and overexposure to glucocorticoids causes growth retardation (8). However, high androgen stimulation in childhood causes both boys and girls to look taller than other children of their age (10). The patient’s bone mineral density (BMD) test revealed osteopenia after receiving glucocorticoid therapy. Long-term steroid therapy is known to cause a decrease in BMD because it can suppress osteoblast activity and increase osteoclast activity in the bone (10).

This patient had not started to have her period before and after the surgery. The mustache and beard were still growing on her face, and her breasts did not grow. Patients with CAH will experience reproductive problems, including hormonal disorders, anatomical abnormalities, and psychological effects from the condition (8). Accumulation of 17-hydroxyprogesterone (17-OHP) during the follicular phase can thin the endometrial lining and change cervical
mucus, causing oligomenorrhea or amenorrhea. Breast growth in this patient was blocked because of increased testosterone due to competition with estrogen for receptors in the breast (11).

Female with genital ambiguity requires surgery (4). Clitorectomy was used in the past. The advantage of this procedure is that the cavernous corpus cannot regrow in the future if the patient has poor adherence to hormonal treatment, but it will cause anorgasmia (12). The clitoris is recognized as an important sensory organ involved in sexual response (11). Clitoroplasty is performed to maintain intact clitoral sensation, sexual function, and satisfaction (12,13).

This patient is currently studying at a vocational high school and has difficulty adapting from masculine behaviors and interests, thus limiting socializing with others. The patient claims to be interested in the opposite sex but has not wanted to have a relationship. Reportedly, most women with CAH behave like males during childhood in terms of toy selection, games, and aggressiveness (14,15). Some women with classic CAH experience internalization of intersex stigma and tend to avoid intimate relationships (14). The interest in the opposite sex with the desire to have sexual relations is part of adolescence, but it can be challenging for adults with CAH (16). Masculine behavior and interest in masculine activity can limit socialization and make her unhappy with her life as a female (16).

The patient was concerned about her condition, especially about the risk of infertility and inappropriate physical changes. The quality of life for patients with CAH is reported to have many variations, depending on how early they get health services, the symptoms, and gender (8). The quality of life for patients with CAH varies according to gender, but all patients experience emotional stress due to living with a chronic disease (8,16). Females with CAH often feel dissatisfied with characteristics of their body related to primary and secondary sex characteristics, feel depressed about the possibility of infertility, and are afraid to face the consequences of infertility (16,17).

The management of virilization in CAH with genital ambiguity must be measured from psychological and surgical perspectives. Understanding the disease, the goals of surgery, long-term treatment, and social adaptations help the patient improve the quality of life. Adaptation in a new society can reduce negative stigma in this patient.

**DATA AVAILABILITY**

All data underlying the results are available as part of the article, and no additional source data are required.

**COMPETING INTERESTS**

No competing interests were disclosed.

**CONSENT**

Written informed consent for publication of the details and clinical images was obtained from the patient.

**ETHICS**

Ethical approval for this case report was obtained from The Ethics Committee of Saiful Anwar General Hospital, Malang, through the approval letter number 400/003/CR/302/2021.

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