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Case Report

Challenges in the Diagnosis and Management of Congenital Adrenal Hyperplasia: A Case Report

Ganesha Pratama Biyang*, Ashon Sa'adi*

ABSTRACT

Background: Congenital adrenal hyperplasia (CAH) is an autosomal recessive endocrine disorder resulting in 21-hydroxylase enzyme deficiency. Nonclassical congenital adrenal hyperplasia is commonly found in adult patients with menstrual disorders, growth delays, secondary sexual characteristic abnormalities, or infertility. Diagnosing and managing CAH presents several challenges that can hinder patients from achieving therapeutic targets. **Case Presentation:** A 19-year-old female was referred from the Internal Medicine Polyclinic to the Reproductive Endocrinology and Infertility Polyclinic at Dr. Soetomo General Academic Hospital (RSUD Dr. Soetomo), presenting with primary amenorrhea and no breast development. Examination revealed signs of virilization, such as hirsutism, acne, and clitoromegaly. Ultrasound examination showed a hypoplastic uterus with normal ovaries. Elevated serum 17-OHP and testosterone from laboratory examination confirmed the diagnosis. Treatment with glucocorticoid replacement therapy using hydrocortisone, along with antiandrogenic contraceptive pills, showed therapeutic progress within six months. **Discussion:** Diagnosing CAH is challenging and often results in delays in patients receiving appropriate care. The primary therapeutic goal of CAH is to prevent hyperandrogenism and provide glucocorticoid replacement therapy to suppress ACTH activity. Long-term administration of hydrocortisone and contraceptive pills for puberty induction is a viable and accessible option. However, long-term therapy can lead to side effects that impact the patient. **Conclusion:** There are several challenges in diagnosing and managing congenital CAH. Long-term management should be personalized, prioritizing the patient's goals and maximizing the benefits of multidisciplinary therapy.
KeyWords: Congenital adrenal hyperplasia, 21-hydroxylase, Disorder of sexual development.

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BACKGROUND

Congenital adrenal hyperplasia (CAH) is an autosomal recessive monogenic genetic disorder that results in a failure of cortisol synthesis.[1] CAH is divided into classic and nonclassic types. The global incidence of classic CAH is 1 in 13,000 to 1 in 15,000 live births.[1,2] Classic congenital adrenal hyperplasia is characterized by salt wasting due to mineralocorticoid deficiency and simple virilizing resulting from disrupted steroid sex hormone formation. The nonclassical type presents with milder symptoms and is generally more prevalent because it is not associated with salt wasting. Approximately three-quarters of classic CAH cases are salt-wasting compared to simple virilizing.[3]

Nonclassical congenital adrenal hyperplasia is the most frequently diagnosed type of CAH in adult patients. This type presents with hyperandrogenic symptoms such as external genital ambiguity, acne, hirsutism, and alopecia. Some patients seek clinical attention in adulthood due to menstrual disorders like amenorrhea or infertility.[3,4]

Several conditions that manifest with hyperandrogenic features, such as polycystic ovarian syndrome, Cushing's disease, and androgen-secreting tumors, can complicate the clinical diagnosis of CAH, necessitating additional examinations to exclude other diagnoses.[3,5] This can contribute to delays in diagnosing and managing patients with CAH.

Long-term management of CAH presents a challenge for patients. Although glucocorticoid replacement therapy is the mainstay of treatment, various therapeutic approaches can be tailored to individual patient goals.[6,7] Therefore, comprehensive counseling between doctors and patients with CAH is essential.

CASE PRESENTATION

A 19-year-old female was referred from the Internal Medicine Polyclinic to the Reproductive Endocrinology and Infertility Polyclinic at Dr. Soetomo General Academic Hospital, presenting with primary amenorrhea and no breast development. The patient also reported having genital pemphigus but had never sought medical attention for it. She complained of a lack of breast development compared to her peers, faster body hair growth, and acne. This hair growth was present on her upper lip, chin, and extremities. There was no history of exposure to androgenic drugs or pesticides during her mother's pregnancy. The patient is the second of five siblings with no family history of similar complaints among her sisters or close relatives.

On physical examination, the patient was found to be short-statured with a height of 140 cm, which is in the 5th percentile according to the WHO height-for-age chart. Her breast growth corresponded to Tanner Stage 1. Signs of virilization were noted, including acne, hirsutism with a Ferriman-Gallwey score of 12, and clitoromegaly with a phallus length of 2 cm and width of 1 cm. A rectal examination revealed a palpable cervix and uterus, suggestive of hypoplasia. The anogenital Prader ratio was 0.32, with a ratio > 0.5 indicating virilization and a degree of labioscrotal fusion.

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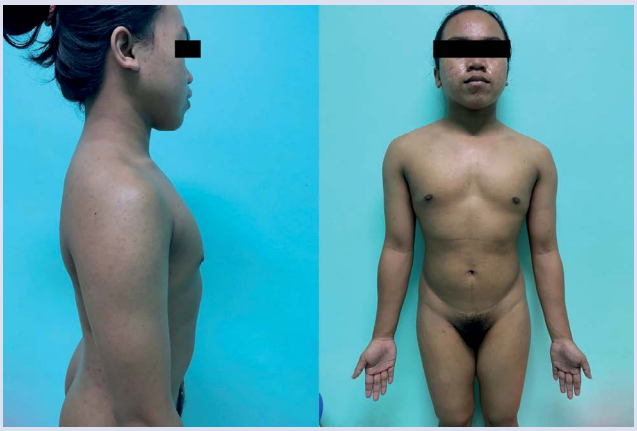

Figure 1. Patient before receiving therapy.

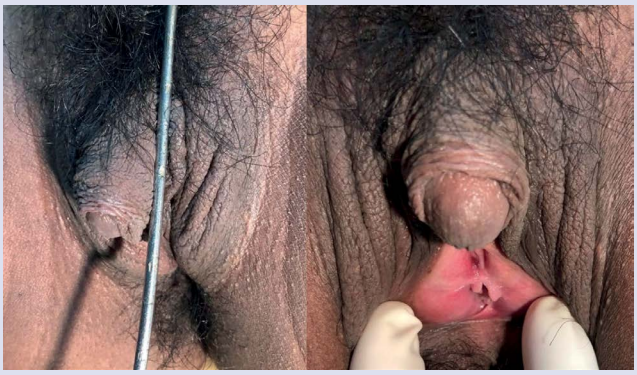

Figure 2. Clitoromegaly before receiving therapy.

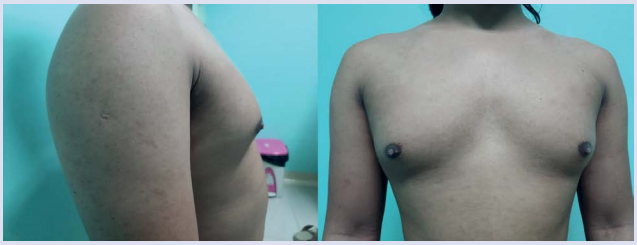

Figure 3. Patient after receiving six months of therapy.

Abdominal sonography revealed an anteflexed uterus measuring 36.8 x 18 x 15 mm, indicating hypoplasia, with both ovaries containing follicles. An abdominal MRI showed bilateral adrenal hyperplasia measuring 23 mm and 27 mm. Bone age examination indicated no growth lines/plates in the examined joints.

Karyotype analysis revealed a 46, XX result, with testosterone at 16.87 nmol/mL, 17-OH progesterone at 101.60 ng/mL, DHEAS at 338.5 µg/mL, ACTH at 113 pg/mL, AMH at 0.26 ng/mL, and serum cortisol at 6.80 µg/mL.

The patient was prescribed hydrocortisone at 15 mg/day in divided doses and combined birth control pills with an antiandrogenic progestin component.

At the six-month evaluation, the patient showed improvement with reduced acne, a Ferriman-Gallwey score of 10 for hirsutism, and Tanner stage 2 breast development, although she had not yet started menstruating. Testosterone levels decreased to 3.92 nmol/mL, and serum cortisol increased to 13.0 µg/mL. Therapy was continued with clinical and laboratory follow-ups every three months.

DISCUSSION

Congenital adrenal hyperplasia (CAH) is an endocrine disorder that can cause primary amenorrhea, with a prevalence of 1%.[1,8] One of the challenges in managing CAH is the delay in diagnosis and subsequent treatment. Patients with the classic type are usually diagnosed early in life through immediate screening, often due to the presence of genital abnormalities commonly seen in these patients.[9] However, patients with the nonclassical type may be diagnosed later in life, typically due to symptoms such as precocious puberty, inappropriate height gain, or menstrual cycle disorders.[3,4,10]

Our patient presented at the age of 19 with a complaint of primary amenorrhea and lack of secondary sexual characteristics. She also reported genital abnormalities, specifically clitoromegaly, and had previously visited the urogynecology clinic for this issue.

To diagnose CAH, a combination of clinical signs, symptoms, and supportive examinations are necessary. In the nonclassical type, in addition to signs of growth retardation and primary amenorrhea or other menstrual disorders, several clinical and laboratory examinations are required. Enzymes, particularly 21-hydroxylase, are essential for cortisol synthesis. Due to the low cortisol levels, the hypothalamic-pituitary axis responds by increasing the secretion of adrenocorticotropic hormone (ACTH), leading to hyperplasia of the adrenal cortex. Consequently, cortisol precursors are produced in excess, causing characteristic clinical symptoms. Therefore, the diagnosis of CAH is based on elevated levels of 17-hydroxyprogesterone (17-OHP) and other cortisol precursors, as well as DHEAS. According to the literature, 17-OHP levels below 200 ng/dL can rule out CAH, while levels above 800 ng/dL help confirm the diagnosis. An ACTH stimulation test is required for intermediate values.[6,9,11]

The management of CAH is multidisciplinary and involves several scientific fields. CAH is an endocrine disorder that affects multiple organ systems, leading to issues such as impaired height growth, secondary sexual characteristic abnormalities, menstrual disorders, and even disorders of sex development (DSD). Consequently, patients with CAH require comprehensive, multidisciplinary care from specialists in gynecological endocrinology, pediatric or adult endocrinology, urogynecology, radiology, and psychiatry. Pediatric and adult endocrinologists provide glucocorticoid replacement therapy and aim to maximize height growth after evaluating epiphyseal plates and growth potential through radiological assessments. Gynecological endocrinologists evaluate the development of secondary sexual characteristics, address menstrual disorders and infertility, manage any DSDs, and work closely with psychiatrists for gender determination and psychological support. Urogynecologists are essential for cases requiring genital reconstruction due to impaired sexual development.[3,7,10]

For adults with 21-hydroxylase deficiency, the main priorities are preventing gonadal neoplasia and adrenal hyperplasia, managing the chronic effects of long-term glucocorticoid therapy, and restoring fertility for those who seek it. Thus, to optimize the risk-to-benefit ratio and address individual patient needs, the treatment regimen's intensity and complexity are adjusted and personalized as time progresses.[8,12,13]

Glucocorticoid replacement therapy is the cornerstone of managing adult patients with 21-hydroxylase enzyme deficiency. Given the long-term nature of this therapy, counseling is crucial to ensure patients understand their treatment and do not alter it independently. Hydrocortisone, administered at a dose of 5-15 mg/m² body surface area in 2-3 divided doses, is considered a safe long-term replacement therapy. However, a significant issue with long-term glucocorticoid replacement is the side effects, which can almost invariably lead to iatrogenic Cushing's syndrome.[7,13]

For women with CAH, other main concerns include: (1) managing symptoms of androgen excess and (2) addressing fertility concerns if the patient is trying to conceive.[14] Hydrocortisone and fludrocortisone acetate replacement therapy should be administered to all women with 21-hydroxylase enzyme deficiency, in line with treatments for other adrenal insufficiency conditions. The assessment of these issues determines whether higher doses and stronger steroids should be administered. Indications of effective glucocorticoid treatment include normal serum testosterone levels and the absence of signs of androgen excess. When these conditions are not met, the assessment of control involves measuring 17-OHP and androstenedione levels.[6,15]

Women with CAH frequently experience androgen excess, although the extent and clinical presentations can vary significantly. Unless a definitive benefit is anticipated, there is no reason to prescribe higher doses of corticosteroids. A childhood diagnosis of CAH, coupled with poor control, may render the patient more vulnerable to androgen excess, possibly resulting from increased adrenal hyperplasia. Additionally, secondary polycystic ovary syndrome (PCOS) is commonly seen in women of reproductive age with CAH. As a result, ovarian production of androgens and 17-OHP may continue even after adrenal suppression with steroids, possibly causing persistent irregular menstruation despite effective control of the adrenal axis.[5,16]

For women with CAH who do not yet desire pregnancy, combined oral contraceptive pills offer several benefits, including reducing ovarian androgen production, regulating menstruation, and increasing sex hormone-binding globulin (SHBG), which decreases free testosterone. This can alleviate some signs of hyperandrogenism with low-dose glucocorticoid therapy.[17]

Antiandrogen therapy is a logical approach for treating hyperandrogenism due to 21-hydroxylase deficiency.[17] Spironolactone is an inexpensive and effective agent for treating hirsutism, but its use in 21-hydroxylase deficiency is challenging because it is an androgen and mineralocorticoid receptor antagonist, which can cause salt loss in the salt-wasting type of CAH. Other androgen antagonists and 5α-reductase inhibitors, such as finasteride and dutasteride, have not been thoroughly studied in women with 21-hydroxylase deficiency, although some studies on flutamide provide insights into managing hyperandrogenism. Topical agents like eflornithine cream and mechanical methods (laser, electrolysis, shaving, and depilation) have not yielded conclusive results.[13,17]

Our patient was prescribed combined contraceptive pill therapy with ethinyl estradiol and cyproterone acetate. The estrogen component is expected to induce secondary sexual characteristics, although this process may take time, given the low dose. Cyproterone acetate is a progestin with antiandrogenic properties intended to suppress the hyperandrogenic activity experienced by the patient.

CONCLUSION

Managing adult patients with CAH is a long-term process requiring multidisciplinary expertise. One of the primary challenges is the delayed diagnosis, making it essential to tailor therapy to meet the specific needs of each patient. Adequate counseling is crucial for achieving optimal long-term management with minimal side effects.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

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ETHICAL CONSIDERATION

This case series does not require ethical approval from the Ethics Committee of Dr. Soetomo General Academic Hospital due to its nature as a case presentation. The patient and their family have understood and agreed to the publication of this article.

AUTHOR'S CONTRIBUTION

All authors contributed to this study, including literature research, data collection, data analysis, and manuscript preparation.

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