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Dyschronism Between the Anatomical Growth of the Sex Organ and Gender Caused by Hormonal Imbalance: A Very Rare Case

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ABSTRACT

Introduction: Congenital Adrenal Hyperplasia (CAH) is a rare autosomal recessive disorder, most commonly caused by 21-hydroxylase deficiency, leading to impaired cortisol and aldosterone synthesis and excess androgen production. It manifests with varying degrees of virilization, salt-wasting crises, or ambiguous genitalia. Early diagnosis and multidisciplinary management are crucial to improving patient outcomes and quality of life.

Case Presentation: A 17-year-old female presented with primary amenorrhea and mild virilization, including facial hair growth and underdeveloped breast tissue. Physical examination and Tanner staging confirmed the ambiguous genitalia and incomplete secondary sexual development. Elevated testosterone levels (3.01 ng/mL; normal: 0.1–0.9), normal imaging of internal genitalia and observed during laparoscopy within normal limit were consistent with non-classical CAH, likely due to 21-hydroxylase deficiency.

Discussion: Non-classical CAH, caused by a mild 21-hydroxylase deficiency due to CYP21A2 mutations, is characterized by late-onset hyperandrogenic symptoms such as hirsutism, amenorrhea, and mild virilization. Diagnosis requires a combination of clinical evaluation, laboratory testing, and imaging, with 17-hydroxyprogesterone measurement as the diagnostic standard. Management includes glucocorticoid therapy to suppress androgen excess, along with genetic counseling, fertility support, and psychosocial care.

Conclusion: This case emphasizes the diagnostic challenges of non-classical CAH, particularly in resource-limited settings. A multidisciplinary approach, including medication, hormonal therapy and psychosocial support, is essential for enhancing the physical and psychosocial well-being of affected individuals.

INTRODUCTION

Congenital adrenal hyperplasia (CAH) refers to congenital enlargement or hyperplasia of the adrenal glands, paired glands situated above the kidneys. As part of the endocrine system, the adrenal glands are essential for hormone production, particularly cortisol, aldosterone, and androgens. Cortisol regulates energy levels, blood pressure, glucose metabolism, and the immune system, whereas aldosterone manages salt excretion through urinary, sweat, and intestinal excretion. Androgens contribute to male reproductive organ development and pubic hair growth in both sexes during normal puberty (Bajpai & Menon, 2014).

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CAH represents a group of autosomal recessive disorders typically caused by mutations in the CYP21A2 gene, resulting in enzymatic deficiencies essential for cortisol and aldosterone synthesis. The resulting steroidogenesis imbalance leads to excessive production of sex steroids, particularly testosterone, which alters the development of female sexual characteristics in individuals with a 46, XX karyotype, resulting in features resembling male characteristics (Cheng & Speiser, 2012).

Over 90% of CAH cases are attributed to 21-hydroxylase deficiency. This deficiency results in increased accumulation of progesterone and 17-hydroxyprogesterone and reduced 11-deoxycorticosterone and 11-deoxycortisol levels. Consequently, aldosterone and cortisol production diminish, leading to disrupted metabolic pathways and heightened peripheral testosterone synthesis (Falhammar & Thorén, 2012). The adrenal glands synthesize three principal hormone classes: mineralocorticoids, glucocorticoids, and androgens. Mineralocorticoids are produced in the zona glomerulosa, glucocorticoids in the zona fasciculata and reticularis, and androgens primarily include testosterone (Speiser et al., 2010).

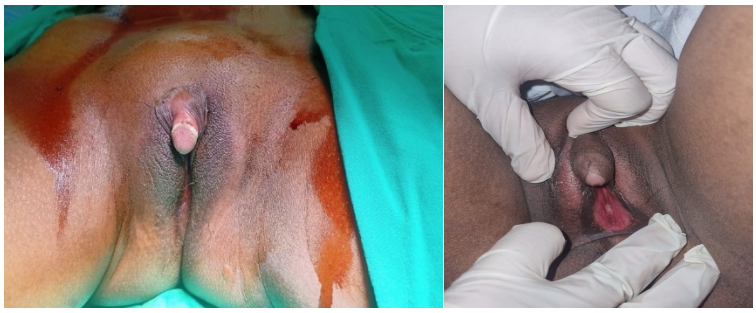
These hormones serve vital physiological roles. Cortisol aids in stress response, aldosterone ensures adequate salt retention, and testosterone facilitates male secondary sexual characteristic development, including hair distribution and genital organ development. Testosterone levels are naturally higher in males than in females (Merke et al., 2002).

CASE PRESENTATION

A 17-year-old patient presented with primary amenorrhea. The patient reported the absence of menstruation since puberty and expressed concern about the lack of breast development compared to peers, although sparse pubic hair was noted. The patient also reported the presence of fine hair growth on the face and limbs. There was no history of abdominal pain, vaginal discharge, weight loss, or changes in appetite, and there was no palpable abdominal mass. Urinary and bowel functions were reported as usual. The patient's medical history was unremarkable, with no known history of asthma, hypertension, diabetes mellitus, allergies, or cardiac disease. Similarly, the family history was nonsignificant, and there was no history of medication use.

On physical examination, the patient appeared in good general condition and was alert (compos mentis). Vital signs were within normal limits: blood pressure was 120/90 mmHg, pulse rate 87 beats per minute, respiratory rate 20 breaths per minute, and body temperature 36.6°C. Anthropometric measurements showed a height of 155 cm, a weight of 43 kg, and a body mass index (BMI) of 17.8 kg/m^2.

Systemic examination revealed no pale palpebral conjunctivae, no scleral icterus, normal heart sounds without murmurs or gallop, and vesicular breath sounds bilaterally with no abnormalities. Abdominal examination was unremarkable, with a soepel abdomen, active bowel sounds, and no palpable mass or tenderness. Examination of the extremities revealed warm skin with no edema.



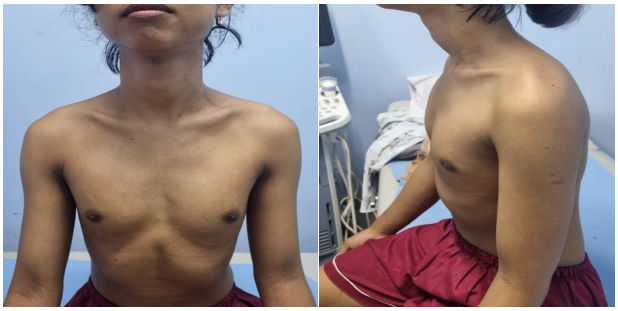


Figure 1. Tanner stage examination

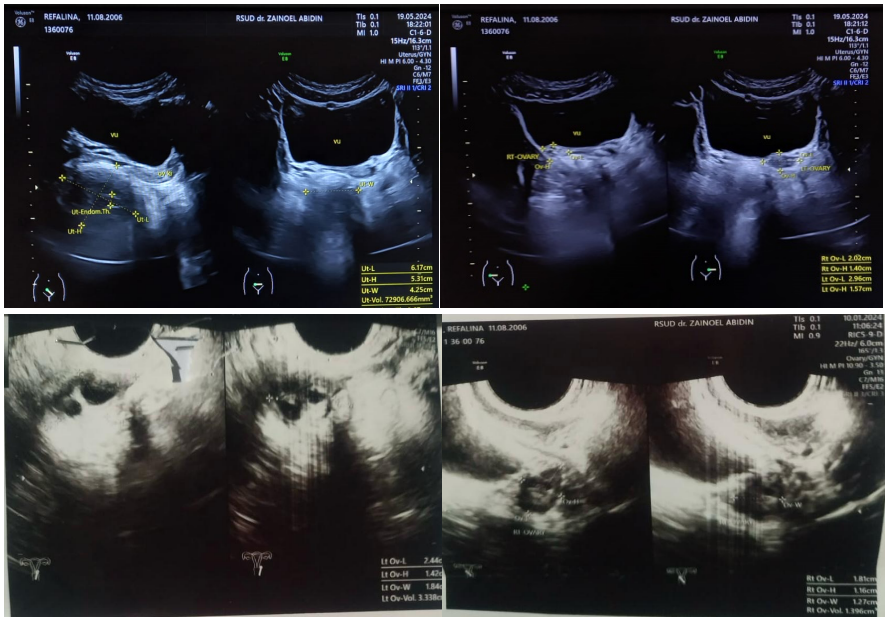


Figure 2. Ultrasound examination

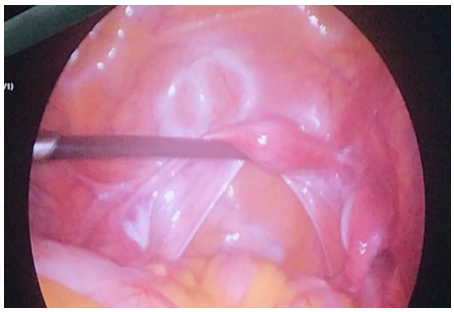


Figure 3. Diagnostic laparoscopy procedure

Gynecological examination revealed no abnormalities on inspection, with a vulva within normal limits and no signs of inflammation. Rectal examination showed a tight anal sphincter, smooth mucosa, no palpable masses extraluminally, and a non-collapsed rectal ampulla. Tanner staging indicated pubic hair and breast underdevelopment corresponding to Tanner Stage 2.

Imaging studies, including transrectal and transabdominal ultrasonography, demonstrated an anteflexed uterus and normal-sized ovaries with no free fluid. Laboratory investigations revealed elevated serum testosterone levels at 3.01 mg/mL, with all other hematological and biochemical parameters within normal limits. Magnetic resonance imaging (MRI) confirmed normal internal genitalia. Diagnostic laparoscopy showed a normal uterus, ovaries, and fallopian tubes, with the

presence of a megaclitoris. The 17-hydroxyprogesterone examination revealed an increased level at 221.53 ng/mL.

The patient was diagnosed with primary amenorrhea due to non-classical CAH. The patient was educated about the condition, its implications, and the available therapeutic options. The patient's family received counseling on CAH management, including the importance of multidisciplinary care. The patient was referred to the fertility, endocrinology, and reproductive division of the RSUDZA Obstetrics and Gynecology Clinic for comprehensive management.

DISCUSSION

The diagnosis of congenital adrenal hyperplasia (CAH) can be established through a combination of anamnesis, physical examination, and supporting tests, including the measurement of 17-hydroxyprogesterone levels in term infants between 48–96 hours post-birth or before hospital discharge. CAH is confirmed when serum 17-hydroxyprogesterone levels are ≥300 nmol/L (10,000 ng/dL). While molecular genetic testing of the CYP21A2 gene is not routinely required for CAH diagnosis, it may be employed in atypical cases or for genetic counseling purposes (Momodu et al., 2023; Yau et al., 2019; New et al., 2022).

CAH is a notable endocrine disorder that accounts for approximately 1% of cases of primary amenorrhea. CAH is classified into three phenotypes: classical salt-wasting, classical simple virilizing, and non-classical CAH. The classical forms are apparent at birth, while non-classical CAH typically presents with late-onset symptoms and is often undetected prenatally. The non-classical variant is an autosomal recessive disorder caused by a deficiency of the enzyme P450C21 (21-hydroxylase) due to mutations in the CYP21A2 gene. Non-classical CAH has a prevalence of 0.6% to 9% among women presenting with symptoms of hyperandrogenism (Ikatan Dokter Anak Indonesia, 2018; Bajpai & Menon, 2014).

In this case, the 17-year-old patient exhibited primary amenorrhea, which is defined as the absence of menarche by age 16 despite the presence of secondary sexual characteristics. The patient's delayed sexual maturation was assessed using the Tanner Staging system. Secondary sexual characteristics, such as pubic hair development consistent with Tanner Stage 2, were present; however, breast development was absent. This lack of breast development is attributable to elevated testosterone levels competing with estrogen at the receptor sites, inhibiting proper breast tissue growth.

Further diagnostic evaluations, including laparoscopy, revealed normal uterine morphology and follicular presence in both ovaries, without organ adhesions. Laboratory results showed elevated testosterone levels, and imaging studies (ultrasound and MRI) confirmed typical uterine and adnexal structures. Although limited resources prevented 17-hydroxyprogesterone testing, the clinical and laboratory findings were consistent with a diagnosis of non-classical CAH.

Non-classical CAH can manifest across a spectrum of ages and clinical presentations, often characterized by hyperandrogenic features such as acne, hirsutism, infertility, menstrual irregularities, and ambiguous genitalia in females. Its differentiation from classical CAH involves careful clinical, laboratory, and radiological evaluations. Unlike classical CAH, non-classical CAH typically entails milder enzyme deficiencies and distinct management strategies.

Effective treatment includes glucocorticoid therapy to restore hormonal balance and mitigate excessive androgen production. For this patient, options include hydrocortisone (15–25 mg/day, divided into 2–3 doses), prednisone (5–7.5 mg/day, divided into two doses), prednisolone (4–6 mg/day, divided into two doses), or dexamethasone (0.25–0.5 mg/day as a single dose). Additional management emphasizes genetic counseling, fertility support, psychological

counseling, and adequate therapeutic monitoring to optimize outcomes (Cheng & Speiser, 2012; Dauber et al., 2010; Falhammar & Thorén, 2012). Subsequently, the patient was treated with glucocorticoid therapy, specifically prednisone at a dosage of 5–7.5 mg/day divided into two doses. The treatment was proven effective for this patient, as it resulted in the initiation of regular menstruation.

CONCLUSION

In conclusion, diagnosing and managing non-classical CAH in a resource-limited setting is found to be complex. Effective management requires a multidisciplinary approach, including medication such as glucocorticoids, hormonal therapy, genetic counseling, and psychosocial support. Addressing barriers to diagnostic and therapeutic access is essential to improve outcomes for patients with CAH. This case underscores the importance of early recognition and intervention to enhance physical development, reproductive health, and psychological well-being in affected individuals.

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