

Nonclassical Congenital Adrenal Hyperplasia

Maya Rani¹, Miss Jeny², Dalliya Roy³¹PG Trainee, Department of Obstetrics & Gynaecology, Mata Gujri Memorial Medical College & LSK Hospital, Kishanganj, Bihar, India.²Assistant Professor, Department of Obstetrics & Gynaecology, Mata Gujri Memorial Medical College & LSK Hospital, Kishanganj, Bihar, India.³PG Trainee, Department of Obstetrics & Gynaecology, Mata Gujri Memorial Medical College & LSK Hospital, Kishanganj, Bihar, India.

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Corresponding Author: Dr. Maya Rani

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Abstract:

Background: Nonclassical congenital adrenal hyperplasia (NCAH) is a milder variant of congenital adrenal hyperplasia characterized by partial enzyme deficiency, leading to hyperandrogenism. It often presents later in life with symptoms such as amenorrhea, hirsutism, and virilization, posing diagnostic and management challenges. This case report aims to illustrate the complexity of diagnosing and managing NCAH in adulthood, emphasizing the importance of individualized treatment and a multidisciplinary approach.

Case Report: A 23-year-old female presented with a five-year history of amenorrhea, increased facial and body hair growth, deepening of the voice, underdeveloped breasts, and clitoral enlargement. Menarche occurred at 15-16 years, followed by irregular menstruation and complete cessation at age 18. Physical examination revealed male-pattern hair growth, Tanner stage 1-2 breast development, male-pattern pubic hair distribution, and clitoromegaly. Laboratory findings included elevated serum total testosterone, free testosterone, and 17- α -OH progesterone levels. Ultrasound showed a small uterus with normal ovaries, and karyotyping confirmed a 46XX genotype. Initial treatment with dienogest and ethinylestradiol regulated menstruation, while dexamethasone was discontinued due to side effects. Spironolactone was introduced to manage hyperandrogenism. The patient underwent successful reduction clitoroplasty to address clitoromegaly.

Result: Six months post-treatment, the patient showed significant clinical improvement, including Tanner stage 3 breast development, regularized menstrual cycles, and reduced hirsutism. The surgical intervention achieved a normal clitoral appearance.

Conclusion: This case underscores the importance of a comprehensive, individualized approach in managing NCAH. Hormonal therapy and surgical intervention can significantly improve clinical outcomes and quality of life. Regular monitoring and a multidisciplinary approach are crucial for optimal long-term management.

Keywords: Nonclassical Congenital Adrenal Hyperplasia, Hyperandrogenism, Amenorrhea, Clitoromegaly, Individualized Treatment.

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Introduction

Nonclassical congenital adrenal hyperplasia (NCAH) is a milder and more common form of congenital adrenal hyperplasia (CAH), a group of inherited disorders affecting adrenal steroidogenesis. Unlike the classical form, NCAH typically presents later in life, often during childhood or adolescence, with symptoms that can be subtle and vary widely. The most common enzyme deficiency in NCAH is 21-hydroxylase deficiency, resulting from mutations in the CYP21A2 gene [1]. This deficiency impairs the adrenal glands' ability to produce cortisol and aldosterone, leading to an overproduction of androgen precursors.

NCAH prevalence is estimated to be 1 in 1000 in the general population, but it is significantly higher

in specific ethnic groups, such as Ashkenazi Jews [2]. The phenotypic presentation of NCAH can range from mild virilization in females, such as hirsutism and menstrual irregularities, to advanced bone age and short stature in both sexes. Due to the variability in clinical presentation, NCAH is often underdiagnosed or misdiagnosed, particularly in patients with milder symptoms.

Recent advances in genetic testing have enhanced our understanding of NCAH. Next-generation sequencing and other molecular diagnostic tools have facilitated more accurate and rapid identification of CYP21A2 mutations, leading to improved diagnosis and management of the disorder [3]. Genetic screening for NCAH is particularly important for individuals with a family

history of CAH or related symptoms, as early diagnosis can significantly improve clinical outcomes through appropriate treatment and management strategies [4].

Management of NCAH typically involves glucocorticoid therapy to suppress adrenal androgen production, thereby alleviating symptoms. The choice and dosage of glucocorticoids are tailored to each patient's clinical presentation and biochemical markers [5]. In addition to pharmacotherapy, lifestyle modifications and psychological support are crucial components of comprehensive care for individuals with NCAH.

Recent research has also highlighted the importance of monitoring metabolic health in patients with NCAH, as they may have an increased risk of metabolic syndrome, obesity, and cardiovascular disease. Long-term follow-up studies are necessary to better understand these associations and to develop targeted interventions to mitigate these risks.

Despite advancements in diagnosis and treatment, there remain challenges in the management of NCAH. Variability in clinical presentation, potential side effects of long-term glucocorticoid use, and the psychological impact of the disorder necessitate a multidisciplinary approach to care. Ongoing research and clinical trials are essential to further elucidate the pathophysiology of NCAH and to develop novel therapeutic strategies.

This case report aims to illustrate the complexity of diagnosing and managing NCAH in adulthood, emphasizing the importance of individualized treatment and a multidisciplinary approach.

Case Presentation: A 23-year-old female presented to the outpatient department (OPD) at Mata Gujri Memorial Medical College Kishanganj, Bihar, with complaints of amenorrhea for five years, increased growth of facial and body

hair, deepening of the voice, underdeveloped breasts, and clitoral enlargement.

Medical History: The patient reported menarche at the age of 15-16 years. Her menstrual cycles were initially irregular and scanty, followed by complete cessation at the age of 18.

Physical Examination: On physical examination, the patient appeared of average stature with a height of 153 cm and weight of 53 kg. She exhibited male-pattern facial and body hair growth. Inspection revealed underdeveloped breasts, classified as Tanner stage 1-2, male pattern of pubic hair distribution, and clitoromegaly. There were no palpable lumps or masses in the abdomen.

Laboratory Investigations

- Serum total testosterone: 161.00 ng/dL (normal range: 6 - 82 ng/dL).
- Serum free testosterone: 3.64 pg/mL (normal range: 0.49 – 2.87 pg/mL).
- 17- α -OH progesterone: 42.93 ng/mL (a level >10 ng/mL is highly suggestive of congenital adrenal hyperplasia (CAH)).
- DHEA-S: 357 mcg/dL (normal range: 134-407 mcg/dL)
- Ultrasound (USG): Small uterus, normal appearing ovaries.
- Karyotyping: Revealed 46XX.

Management: The patient was initially advised a combination of dienogest (2 mg) and ethinylestradiol (30 mcg) for menstrual regulation. Additionally, dexamethasone (4 mg) was prescribed but later discontinued due to the development of moon facies, a side effect indicative of Cushingoid features. Subsequently, spironolactone (initially 50 mg, later increased to 100 mg) was started to manage hyperandrogenism.

The patient underwent a reduction clitoroplasty in Mumbai, a procedure designed to preserve the neurovascular bundle supplying the glans clitoris and sever the corpora cavernosa.



Figure 1: Before treatment

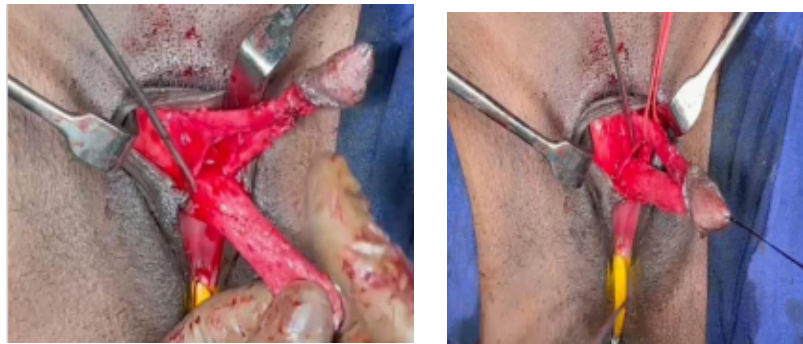


Figure 2: Intra-operative



Figure 3: After treatment

Follow-Up

Six months after the initiation of medical treatment and surgical intervention, the patient exhibited significant improvements:

- Breast development advanced to Tanner stage 3.
- Menstrual cycles regularized.
- Progressive reduction in the growth of facial and body hair.
- Normal clitoral appearance was achieved post-surgery.

Discussion

This case report highlights the clinical presentation, diagnostic challenges, and management of nonclassical congenital adrenal hyperplasia (NCAH) in a young adult female. NCAH can present with symptoms that overlap with other hyperandrogenic disorders, such as polycystic ovary syndrome (PCOS), making accurate diagnosis crucial for effective management.

The patient's elevated 17- α -OH progesterone levels were a key diagnostic indicator of NCAH, supported by elevated serum testosterone levels. The initial treatment with dexamethasone aimed to suppress adrenal androgen production but had to be discontinued due to side effects, illustrating the need for individualized treatment plans. Spironolactone effectively managed hyperandrogenism, reducing hirsutism and normalizing menstrual cycles.

Surgical intervention for clitoromegaly was necessary to address the significant virilization. The successful reduction clitoroplasty highlights the importance of surgical options in comprehensive NCAH management, especially for patients with pronounced physical symptoms.

The patient's positive response to medical and surgical treatment underscores the importance of a multidisciplinary approach in managing NCAH. Regular follow-up is essential to monitor treatment efficacy, manage side effects, and address any psychological or quality-of-life issues.

Overall, this case emphasizes the need for heightened awareness and accurate diagnostic strategies for NCAH, enabling timely and effective treatment to improve patient outcomes.

A study provided insights into the fertility aspects of patients with nonclassical congenital adrenal hyperplasia (NC-CAH). The study highlighted that NC-CAH is often misdiagnosed as polycystic ovary syndrome (PCOS), and early detection can improve management of hyperandrogenic symptoms and assist in ovulation induction. The nuanced understanding of NC-CAH helps in detecting pregnancies at risk for severe genetic steroid disorders [6].

A study on the clinical features of 57 patients with lipid congenital adrenal hyperplasia (LCAH) was conducted, revisiting the criteria for the nonclassical form. The study found that patients with NC-LCAH had a median diagnosis age of 4.0 years

compared to 0.0 years for classical LCAH (CLCAH). The presence of STAR mutations (p.Arg272Cys or p.Met225Thr) was more frequent in NC-LCAH patients [7].

A study reported on the pubertal development and pregnancy outcomes in 46,XX patients with NC-LCAH. The study documented normal pubertal development with spontaneous thelarche and menarche. Two patients successfully conceived, with one using clomiphene citrate for ovulation induction. This suggests that patients with NC-LCAH can maintain ovarian function and achieve successful pregnancies without progesterone replacement therapy [8].

Moreover, a study analyzed growth trajectory and adult height in children with NC-CAH. The study found that chronological age, bone age/chronological age ratio, and height at diagnosis were significant factors affecting adult height and growth trajectory. Pubertal growth was higher in males, and factors such as BMI and bone age/chronological age ratio negatively influenced growth outcomes [9].

A study established a new screening cut-off value for 17 hydroxyprogesterone and evaluated the reliability of the long intramuscular ACTH stimulation test in diagnosing NC-CAH. The study suggested a cut-off value of 3.19 ng/ml for screening and highlighted the increased sensitivity of the intramuscular ACTH stimulation test at 180 minutes [10].

Conclusion

This case highlights the complexity of managing nonclassical congenital adrenal hyperplasia (NCAH) presenting in adulthood. Nonclassical CAH is considered a milder form of CAH due to the retention of some enzymatic activity. Most patients seek medical advice at any stage of life due to hyperandrogenism. The combination of hormonal therapy and surgical intervention in this case resulted in significant clinical improvement and enhanced the patient's quality of life. Treatment decisions should be based on an assessment of individual factors and should follow an individualized approach. Ongoing monitoring

and a multidisciplinary approach are essential for optimal long-term management.

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