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An Unusual Case of Non-classical 21-Hydroxylase Deficiency Presenting with Hypercortisolemia and Hyperandrogenemia: A Case Report

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Case Report

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Abstract

Background

Non-classical 21-hydroxylase deficiency (NC-21OHD) typically presents with hyperandrogenemia and low-to-normal cortisol levels. However, elevated cortisol levels are exceedingly rare and may lead to diagnostic confusion with Cushing's syndrome.

Case Presentation:

We report a 25-year-old woman who presented with a three-month history of menstrual irregularities. Physical examination revealed a full-moon face, hirsutism, male-pattern pubic hair distribution, and clitoral hypertrophy. Laboratory investigations demonstrated hypercortisolemia (serum cortisol: 27.98 μg/dL at 8 AM; urinary free cortisol: 264.38 μg/24h) and hyperandrogenemia (testosterone: 1.25 ng/mL; DHEA-S: 1025 μg/dL). Enhanced computed tomography revealed bilateral adrenal thickening. Although these findings initially suggested Cushing's syndrome, low-dose dexamethasone suppression testing markedly suppressed both cortisol (15.88 → 0.63 μg/dL) and testosterone (1.25 → 0.63 ng/mL), effectively excluding Cushing's syndrome and indicating an adrenal source of hyperandrogenemia. Notably, basal 17-hydroxyprogesterone (17-OHP) was within the normal range (0.77 ng/mL), but cosyntropin stimulation elevated 17-OHP to 11.54 ng/mL. Subsequent genetic testing confirmed CYP21A2 mutations, establishing the diagnosis of NC-21OHD. Glucocorticoid therapy with prednisone (2.5 mg nightly) normalized menstrual cycles and androgen levels within one month, with follow-up imaging showing significant adrenal size reduction at six months.

Conclusions

This case highlights that hypercortisolemia can occur in NC-21OHD and may coexist with features mimicking Cushing's syndrome. The combination of low-dose dexamethasone suppression testing—to simultaneously exclude Cushing's syndrome and confirm adrenal-derived hyperandrogenemia—followed by ACTH stimulation testing and genetic confirmation, represents a critical diagnostic pathway. Clinicians should maintain heightened awareness of this atypical presentation to avoid misdiagnosis.

Background

Congenital adrenal hyperplasia (CAH) comprises a group of autosomal recessive disorders arising from defects in steroidogenic enzymes involved in cortisol synthesis from cholesterol. Among these, 21-hydroxylase deficiency (21-OHD), caused by mutations in the CYP21A2 gene, is the most common form of CAH [1]. Based on residual enzyme activity, 21-OHD is classified into classical (C-21OHD) and non-classical (NC-21OHD) forms. In NC-21OHD, ACTH production is usually normal, cortisol response to ACTH may be normal or slightly impaired, and adrenal androgen secretion is increased. However,

hypercortisolemia represents an uncommon biochemical profile that may confound the diagnostic process [2].

The differential diagnosis of hypercortisolemia in reproductive-aged women is broad, encompassing Cushing's syndrome, polycystic ovary syndrome (PCOS), and pseudo-Cushing's states induced by psychological stress, obesity, or chronic illness [3, 4]. Accurate distinction between these entities is paramount, as management strategies differ substantially. We herein report a case of NC-21OHD presenting with the unusual constellation of hypercortisolemia and hyperandrogenemia, initially misdiagnosed as Cushing's syndrome, and discuss the diagnostic reasoning that led to the correct identification.

Case presentation

A 25-year-old graduate student presented with a three-month history of menstrual irregularities. Menarche occurred at age 12, with previously regular 28–30 day cycles lasting 5–7 days. Over the preceding three months, her cycle length extended to > 50 days, with menstrual duration shortening to 1–2 days and markedly reduced flow. She was unmarried and nulliparous.

Physical examination revealed normal vital signs and a body mass index of 21.02 kg/m². Notable findings included a full-moon face without centripetal obesity or purple striae. Hirsutism was evident, with excessive fine hair and prominent whiskers on the upper lip and jaw. Breast development corresponded to Tanner stage B5. Pubic hair was at stage PH5 with a male-like distribution pattern, and clitoral hypertrophy was present.

Laboratory investigations revealed elevated serum androgen levels: testosterone 1.25 ng/mL (reference: 0.11–0.57) and DHEA-S 1025 μg/dL (reference: 95.80–511.70). Serum cortisol was elevated at 27.98 μg/dL at 8 AM (reference: 8.7–22.4), and 24-hour urinary free cortisol was 264.38 μg/24h (reference: 28.50–213.70). Comprehensive testing—including complete blood count, electrolytes, glucose, insulin, thyroid function, ACTH (22.4 ng/L; reference: 7.2–66.3), basal 17-OHP (0.77 ng/mL; reference: 0.1–0.8), hCG, estradiol, progesterone, prolactin, LH, and FSH—demonstrated all other parameters within normal limits (Table 1). Pelvic ultrasound showed normal uterine and adnexal anatomy. Enhanced adrenal CT revealed bilateral adrenal thickening (Fig. 1).

Table 1
Blood test results on admission

Serum Dehydroepiandrosterone Sulfate (μg/dL)	**Results**	**Reference range**
	1025	**95.80-511.70**
Serum Testosterone(ng/mL)	1.25	0.11–0.57
Serum Estradiol(pg/ml)	34.5	follicular phase: 21.0-251.0
Serum Progesterone(ng/ml)	0.35	follicular phase: <0.10–0.30
Serum Prolactin(ng/ml)	33.14	5.18–29.93
Serum Luteinizing Hormone(mIU/mL)	8.64	follicular phase: 1.80-11.78
Serum Follicle-stimulating Hormone(mIU/mL)	2.85	follicular phase: 3.06–8.08
Serum 17-hydroxyprogesterone(ng/ml)	0.77	follicular phase: 0.1–0.8
Serum Cortisol(μg/dL)	27.98	8am:8.7–22.4
Serum Adrenocorticotropic Hormone(ng/L)	22.4	8am:7.2–66.3
Urine Free Cortisol (ug/24h)	264.38	28.50-213.70
Thyroid Stimulating Hormone (μIU/mL)	2.99	0.350–4.940
Fasting Blood Glucose (mmol/L)	5.37	3.90–6.10
Fasting Insulin (μIU/mL)	10.11	2.60–24.90

Given the combination of hypercortisolemia, hypercortisoluria, bilateral adrenal hyperplasia, hirsutism, and full-moon face, Cushing's syndrome was initially suspected. Low-dose dexamethasone suppression testing (0.5 mg every 6 hours for 48 hours) was performed. Serum cortisol decreased from 15.88 to 0.63 μg/dL, and 24-hour urinary free cortisol decreased from 333.31 to 9.75 μg/24h, effectively excluding Cushing's syndrome (Table 2). Notably, serum testosterone also decreased from 1.25 to 0.63 ng/mL, representing a ~ 50% suppression (40% threshold for adrenal source identification) [5,6.

Table 2
Results of low-dose dexamethasone suppression test

	Results		**Reference range**
	Before	**After**	
Serum Cortisol (μg/dL)	15.88	0.63	8am:8.7–22.4
Urine Free Cortisol (μg/24h)	333.31	9.75	28.5-213.7
Serum Testosterone (ng/ml)	1.25	0.63	0.11–0.57

The significant suppression of both cortisol and androgens by low-dose dexamethasone, combined with the absence of adrenal tumors on imaging, strongly suggested NC-21OHD as the underlying diagnosis. Although basal 17-OHP was normal, cosyntropin stimulation testing (250 μg intravenous) elevated 17-OHP to 11.54 ng/mL, exceeding the diagnostic threshold of > 10.0 ng/mL [7]. Subsequent genetic testing confirmed pathogenic mutations in the CYP21A2 gene, cementing the diagnosis of NC-21OHD.

Treatment was initiated with prednisone 2.5 mg nightly. Within one month, menstrual cycles normalized and androgen levels decreased to within the normal range. A follow-up enhanced CT at six months demonstrated a significant reduction in bilateral adrenal gland size. The patient reported good adherence to prednisone therapy and tolerated the treatment well, with no treatment-related adverse events observed during follow-up.

Discussion

We report an unusual case of NC-21OHD presenting with hypercortisolemia—a biochemical profile that deviates from the typical low-to-normal cortisol levels described in this condition. The pathophysiology of this atypical presentation may involve several mechanisms. In 21-OHD, impaired cortisol synthesis reduces negative feedback on the hypothalamic-pituitary-adrenal (HPA) axis, resulting in ACTH-driven adrenal hyperplasia. While classical teaching emphasizes cortisol deficiency in CAH, compensatory adrenal enlargement may occasionally produce cortisol levels that exceed the normal range, particularly when superimposed on stress-induced HPA activation [8].

In 2012, Kim et al. reported a 41-year-old man with CAH and adrenal tumorous lesions who exhibited normal serum cortisol (7.4 μg/dL) but elevated 24-hour urinary free cortisol (226.4 μg/24h), which was markedly suppressed by low-dose dexamethasone [8]. Our case extends this observation by demonstrating that serum cortisol itself may be frankly elevated in NC-21OHD, creating an even more convincing mimic of Cushing's syndrome.

The diagnostic complexity was further compounded by the presence of pseudo-Cushing's features. The patient reported significant anxiety related to thesis preparation over the preceding six months. Psychological stress is a well-recognized cause of pseudo-Cushing's syndrome (PCS), characterized by reversible HPA axis activation with clinical and biochemical features of hypercortisolism [3, 4]. In our case, the combination of underlying NC-21OHD with stress-induced PCS likely contributed to the pronounced hypercortisolemia, illustrating the importance of evaluating psychosocial factors in the differential diagnosis of hypercortisolism.

A critical diagnostic turning point was the observation that low-dose dexamethasone suppression testing not only excluded Cushing's syndrome (through cortisol suppression) but also simultaneously indicated an adrenal source of hyperandrogenemia (through androgen suppression > 40%) [5, 6] This "dual utility" of a single diagnostic test is particularly valuable in resource-limited settings or when rapid clinical decision-making is required. The androgen suppression pattern effectively distinguished adrenal

from ovarian hyperandrogenism, narrowing the differential diagnosis to adrenal-origin disorders including CAH, androgen-secreting adrenal tumors, or Cushing's syndrome [9].

The normal basal 17-OHP level (0.77 ng/mL) in our patient highlights a well-known pitfall in NC-21OHD diagnosis. Up to 12.6% of women with suspected PCOS or overlapping features may harbor undiagnosed NC-21OHD [10], and basal 17-OHP screening (threshold ~ 2 ng/mL) may miss subtle cases [11, 12]. ACTH stimulation testing remains the gold standard for biochemical confirmation, with post-stimulation 17-OHP > 10 ng/mL considered diagnostic [7]. The marked elevation to 11.54 ng/mL following cosyntropin administration, despite normal baseline levels, underscores the necessity of dynamic testing in patients with high clinical suspicion.

Genetic testing for CYP21A2 mutations provided definitive confirmation. The 2018 Endocrine Society Clinical Practice Guideline emphasizes that genetic analysis is valuable for confirming the diagnosis, predicting phenotype severity, and providing genetic counseling [11]. In our case, genetic confirmation was particularly important given the atypical biochemical presentation.

The therapeutic response to low-dose glucocorticoid replacement (prednisone 2.5 mg nightly) was rapid and sustained, with normalization of menstrual cycles and androgen levels within one month and radiographic evidence of adrenal regression at six months. This favorable response further validated the diagnosis and highlights the importance of accurate identification, as inappropriate management of misdiagnosed Cushing's syndrome could have led to unnecessary interventions. A strength of this case is the comprehensive diagnostic evaluation, including dynamic endocrine testing, genetic confirmation, and longitudinal clinical and radiological follow-up. Nevertheless, as a single case, the extent to which NC-21OHD itself contributed to the observed hypercortisolemia remains uncertain. Psychological stress may also have played a role through HPA axis activation, although its relative contribution could not be determined.

Conclusion

This case illustrates that NC-21OHD can present with hypercortisolemia, creating a diagnostic challenge that mimics Cushing's syndrome. The key diagnostic approach involves: (1) recognition that hypercortisolemia does not automatically indicate Cushing's syndrome; (2) utilization of low-dose dexamethasone suppression testing for dual purposes—excluding Cushing's syndrome and identifying adrenal-derived hyperandrogenemia; (3) awareness that normal basal 17-OHP does not exclude NC-21OHD, necessitating ACTH stimulation testing; and (4) genetic confirmation via CYP21A2 analysis. Heightened awareness of this atypical presentation among endocrinologists, gynecologists, and general practitioners can prevent diagnostic delay and ensure appropriate management.

Abbreviations

ACTH
Adrenocorticotropic hormone

CAH
Congenital adrenal hyperplasia
C-21OHD
Classical 21-hydroxylase deficiency
CT
Computed tomography
CYP21A2
Cytochrome P450 family 21 subfamily A member 2
DHEA-S
Dehydroepiandrosterone sulfate
FSH
Follicle-stimulating hormone
hCG
Human chorionic gonadotropin
HPA axis
Hypothalamic-pituitary-adrenal axis
LH
Luteinizing hormone
NC-21OHD
Non-classical 21-hydroxylase deficiency
PCOS
Polycystic ovary syndrome
PCS
Pseudo-Cushing's syndrome
UFC
Urinary free cortisol
17-OHP
17-hydroxyprogesterone
21-OHD
21-hydroxylase deficiency

Declarations

Ethics approval and consent to participate: This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Huzhou Central Hospital. Clinical trial number: Not applicable. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Consent for publication: Written informed consent for publication of this case report and accompanying images was obtained from the patient.

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Authors' contributions: YJQ contributed to conceptualization, data curation, formal analysis, and writing—original draft preparation. LQZ contributed to data collection and methodology. YFP and JPY contributed to supervision, project administration, and writing—review and editing. YFP and JPY are the corresponding authors. All authors read and approved the final manuscript.

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Figures

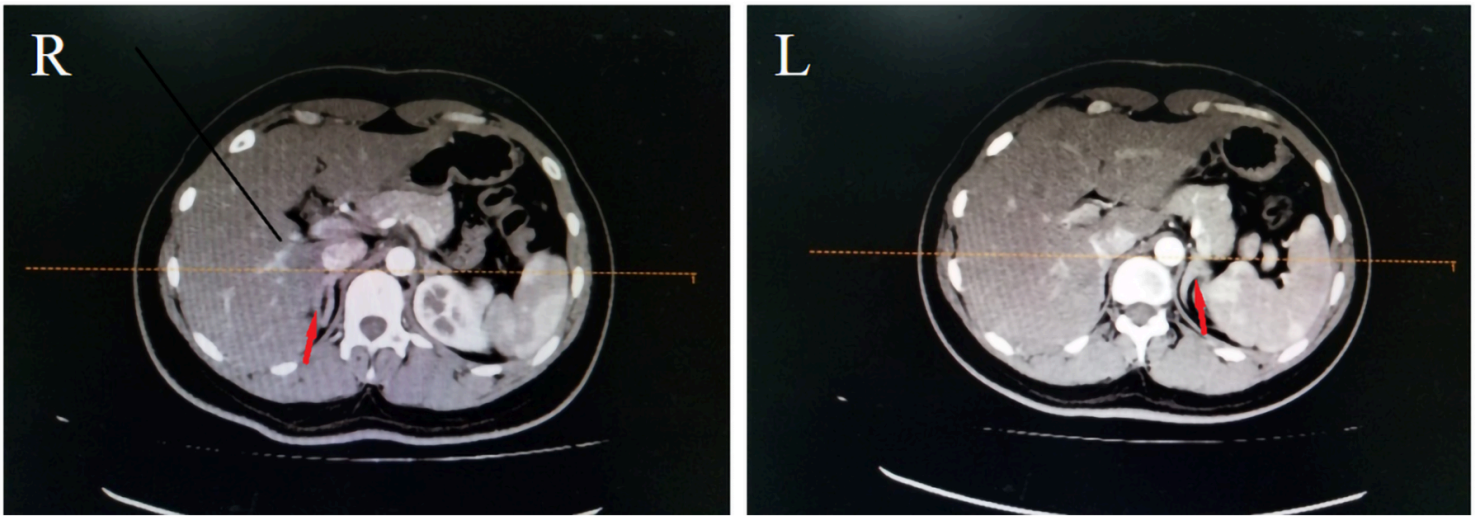


Figure 1

Computed tomography of her adrenal glands before treatment