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Case Report

A 56-Year-Old Male Patient With 21-Hydroxylase Deficiency Presenting With Fatigue: A Case Report

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Abstract

Aims/Background: Congenital adrenal hyperplasia (CAH) results from 21-hydroxylase deficiency (21-OHD), which is the most frequent form of CAH and often presents with atypical symptoms. Patients with non-classic 21-OHD (NC-21-OHD) are particularly susceptible to diagnostic challenges, including misdiagnosis and underdiagnosis. This study reports a case of NC-21-OHD and underscores the associated challenges in its diagnosis, treatment, and clinical management. **Case Presentation**: This study reports a 56-year-old male patient who presented with fatigue lasting over a year. Initial ultrasound revealed a hypoechoic mass above the left kidney, and further evaluation, including renal tumor evaluation and computed tomography angiography, indicated thickening of the adrenal glands and multiple lesions. Endocrinological assessment revealed reduced luteinizing and follicle-stimulating hormone levels, along with elevated dehydroepiandrosterone sulfate and abnormal corticotropin, ultimately diagnosing the patient with primary adrenal insufficiency. Furthermore, genetic screening identified heterozygous mutations in the *CYP21A2* (cytochrome P450, family 21, sub-family A, polypeptide 2) gene, confirming CAH due to NC-21-OHD. The patient was treated with hydrocortisone at a dosage of 20 mg twice a day. **Results**: Hydrocortisone therapy resulted in a significant alleviation of fatigue symptoms and a substantial reduction in 17α-hydroxyprogesterone (17-OHP) levels, thereby enhancing the patient's confidence in disease management. **Conclusion**: This case emphasizes the significance of early recognition of nonspecific symptoms, prompt diagnosis, and timely treatment in managing CAH to enhance the overall quality of life and reproductive health in affected individuals.

Keywords: congenital adrenal hyperplasia; 21-hydroxylase deficiency; 17α-hydroxyprogesterone; fatigue; case report

1. Introduction

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders resulting from enzyme deficiencies in the adrenal steroidogenesis pathway. Among these, 21-hydroxylase deficiency (21-OHD) is the most common type, accounting for approximately 95% of cases [1]. The clinical spectrum of CAH varies widely; in particular, non-classic CAH (NCCAH) poses significant diagnostic challenges attributed to its subtle endocrine manifestations and subclinical impairments in spermatogenesis; therefore, early diagnosis and management are crucial to prevent long-term complications, such as infertility and metabolic disorders [1,2]. Diagnosis of NCCAH depends on a combination of biochemical and genetic evaluations, including elevated 17α-hydroxyprogesterone (17-OHP) levels, low cortisol, high adrenocorticotropic hormone (ACTH) levels, and confirmatory gene testing, alongside imaging studies to assess adrenal morphology. Individualized glucocorticoid replacement therapy remains the standard option of NCCAH treatment. Despite this, there is a paucity of systematic studies on CAH in adult males, particularly those with NCCAH. A European multicenter study revealed that only approximately 20% of male CAH patients are over 50 years of age [3]. Significant evidence gaps persist regarding adult male CAH, with limited large-scale studies and a lack of standardized monitoring protocols for NCCAH in this population [4].

In this case report, we present a 56-year-old male patient diagnosed with CAH secondary to non-classic 21-OHD (NC-21-OHD), prepared following the case report (CARE) framework (**Supplementary Material**). This case is particularly noteworthy due to the patient's atypical presentation, including infertility and fatigue, accompanied by significant endocrine abnormalities. Identifying such cases is essential, as they highlight the need for clinicians to consider CAH in adults presenting with unexplained symptoms such as fatigue, skin pigmentation changes, and reproductive issues, or adrenal masses [5,6]. The significance of this case lies in its potential to enhance awareness of CAH as a differential diagnosis in adult patients, particularly those with a history of infertility and endocrine dysfunction. Furthermore, it underscores the significance of genetic screening and detailed family history in understanding the hereditary nature of this disorder, which can inform tailored treatment strategies and ultimately improve patient outcomes [7].

2. Case Report

One year ago, a 56-year-old Chinese male from Zhejiang province first experienced fatigue, which he did not consider crucial and did not seek any medical attention. Over the past month, his fatigue symptoms progressively aggravated and he visited Xiaoshan Mercy Hospital, where an ultrasound examination revealed a hypoechoic mass above the left kidney. He was advised to consult the department of urology and undergo an adrenalectomy if necessary.

Subsequently, the patient independently sought medical attention at the First Affiliated Hospital, Zhejiang University School of Medicine. Renal tumor evaluation and computed tomography angiography (CTA) showed thickening of the right adrenal gland and multiple lesions in the left adrenal gland, meeting the criteria for adrenalectomy (Fig. 1). During consultation, the patient incidentally mentioned the recent development of cutaneous hyperpigmentation, prompting targeted endocrine evaluation. Therefore, the patient was admitted to the geriatric department for further assessment and management.

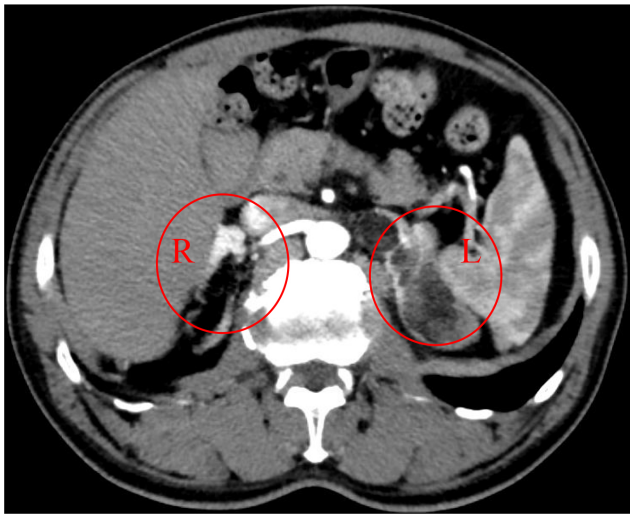

Fig. 1. Renal tumor evaluation and computed tomography angiography (CTA). Thickening of the right adrenal gland and multiple lesions in the left adrenal gland (circles) were observed.

Both parents of the patient were deceased, preventing assessment of any family history of endocrine disorders. He has two married sisters with no living children.

On admission, we recorded the patient's height (154 cm), body weight (53.6 kg), and body mass index (BMI, 22.6 kg/m^2), with his height remaining unchanged since age 12. He has experienced a weight loss of 5 kg over the past year. Vital signs showed a heart rate of 66 beats/minute, a body temperature of 36.3 °C, and a blood pressure of 100/46 mmHg. Physical examination revealed cutaneous hyperpigmentation and genital atrophy, although pubic hair was observed. Furthermore, the patient also reported reduced sexual desire. However, cardiovascular, respiratory, and abdominal assessment showed no observable abnormalities. Laboratory examinations and clinical assessments revealed impaired renal function, with a serum creatinine (Cr) of 112 µmol/L and estimated glomerular filtration rate (eGFR) of 62.5 mL/min (Table 1).

The patient's electrolyte levels were within normal range. Gonadotropins were substantially suppressed, with luteinizing hormone (LH) at 0.04 mIU/mL and follicle-stimulating hormone (FSH) at 0.6 mIU/mL. In contrast, adrenal androgen levels were significantly increased, including dehydroepiandrosterone sulfate (DHEAS) at 559.2 µg/dL and androstenedione >10 ng/mL. This hormonal profile effectively ruled out the possibility of central hypogonadism.

Subsequently, the diurnal fluctuations in cortisol and ACTH levels were examined. Cortisol levels were 5.85 µg/dL at 8 AM and 3.32 µg/dL at 4 PM, whereas ACTH was elevated in the morning (61.00 pg/mL at 8 AM) and normalized in the afternoon (30.90 pg/mL at 4 PM) (Table 1), suggesting that both cortisol and ACTH maintained their diurnal rhythm. Following this, an exercise experiment trial was performed to assess the levels of cortisol and ACTH after 30 min of physical activity, serving as an adjunctive method to simulate physiological stress and evaluate adrenal stress response capacity [8,9]. Post-exercise results revealed a modest increase in ACTH to 79.80 pg/mL at 8 AM, whereas the cortisol levels did not increase, remaining lower than the baseline level at 8 AM without exercise (5.07 µg/dL). Furthermore, 24-h urinary free cortisol levels were reduced (<24 µg/24 h; normal reference range: 4.3–176 µg/24 h) (Table 1). These outcomes indicate that the patient's adrenal physiological responses are impaired, with a poor cortisol response to ACTH stimulation.

In 56-year-old males, normal testicular dimensions are generally in the range of 32–50 × 23–30 × 16–25 mm (volume 12–20 mL). Ultrasound examination of the patient showed bilateral testicular atrophy, with the left testis measuring 12 × 10 × 8 mm and the right measuring 13 × 10 × 7 mm (Fig. 2).

Additionally, enhanced magnetic resonance imaging (MRI) of the adrenal gland revealed multiple medullary lipomas in both the inner and outer limbs of the left adrenal gland, an adenoma in the outer limb of the left adrenal gland, and thickening of the right adrenal gland, consistent with adrenal hyperplasia (Fig. 3). No significant retroperitoneal lymphadenopathy was observed, and pituitary MRI did not reveal any apparent abnormalities. Based on these comprehensive clinical and imaging findings, a provisional diagnosis of CAH was established.

The intermediate metabolites involved in steroidogenesis were also examined. As shown in Table 1, the level of 17-OHP, a substrate of 21-hydroxylase, was significantly elevated at 356.19 nmol/L. Chromosomal karyotyping confirmed a 46XY karyotype. Furthermore, comprehensive

Table 1. Clinical parameters of 56-year-old patient upon admission.

Peripheral Blood					
Parameter	Value	Reference range	Parameter	Value	Reference range
Red blood cells	4.55×10^{12}/L	4.09–5.74	Lymphocytes	38%	20.0–40.0
Hemoglobin	147 g/L	131–172	Monocytes	5.8%	3.0–10.0
White blood cells	4.28×10^{9}/L	4.0–10.0	Eosinophils	1.9%	0.5–5.0
Neutrophils	53.8%	50.0–70.0	Platelets	175×10^{9}/L	83–303
Blood Biochemistry					
Parameter	Value	Reference range	Parameter	Value	Reference range
Total protein	66.5 g/L	65.0–85.0	HDL-C	0.81 mmol/L	0.78–1.81
Albumin	43.3 g/L	40.0–55.0	BUN	4.26 mmol/L	3.10–8.00
Total bilirubin	23.3 µmol/L	20.0–40.0	UA	378 µmol/L	208–428
AST	8 U/L	9–50	Cr	112 µmol/L	57–97
ALT	12 U/L	15–40	eGFR	62.5 mL/min	
γ-GTP	12 U/L	10–60		Electrolytes	
ALP	74 U/L	45–125	Potassium	3.65 mmol/L	3.50–5.30
LDH	172 U/L	120–250	Sodium	146 mmol/L	137–147
Plasma glucose	4.06 mmol/L	3.90–6.10	Chloride	107 mmol/L	99–110
Triglyceride	2.09 mmol/L	0.30–1.70	Calcium	2.29 mmol/L	2.11–2.52
Cholesterol	3.31 mmol/L	3.14–5.86	Phosphorus	1.23 mmol/L	0.85–1.51
LDL-C	1.45 mmol/L	1.31–3.29			
Endocrine Markers					
Parameter	Value	Reference range	Parameter	Value	Reference range
TSH	1.131 mIU/L	0.35–4.94	Estradiol	26.42 pg/mL	11.0–44.0
FT3	4.66 pmol/L	2.43–6.01	FSH	0.60 mIU/mL	0.95–11.95
FT4	13.15 pmol/L	9.01–19.05	LH	0.04 mIU/mL	0.57–12.07
GH	0.07 ng/mL	0.0–3.0	Prolactin	12.07 ng/mL	3.46–19.40
IGF-1	156 ng/mL	45.0–210.0	Pregnanediol	6.45 ng/mL	0.0–0.2
Adrenaline	50.67 pg/mL	14–90	Testosterone	864.31 ng/dL	142.39–923.14
Noradrenaline	110.81 pg/mL	19–121	DHEAS	559.2 µg/dL	48.6–361.8
Androstenedione	$>$10.0 ng/mL	0.6–3.1	SHBG	55.50 nmol/L	17.1–77.6
17-OHP	356.19 nmol/L	$\leq$6.11	FTI	54%	2.40–81.20%
Cortisol			ACTH		
8 AM	5.85 µg/dL	5–25	8 AM	61.00 pg/mL	0–46
4 PM	3.32 µg/dL		4 PM	30.90 pg/mL	
30 min after	5.07 µg/dL		30 min after	79.80 pg/mL	
Urine Collection Test					
Parameter	Value	Reference range	Parameter	Value	Reference range
Cortisol	$<$24 µg/24 h	4.3–176.0	Aldosterone	39.4 µg/24 h	1.2–28.0
Potassium	23.19 mmol/d	25.00–100.00	Calcium	2.16 mmol/d	2.50–7.50
Sodium	114 mmol/d	130.00–260.00	Magnesium	2.25 mmol/d	2.50–8.50
Chloride	88.8 mmol/d	170.00–250.00	Phosphorus	14.7 mmol/d	12.9–42.0

AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, γ-glutamyl transpeptidase; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol; BUN, blood urea nitrogen; UA, uric acid; Cr, creatinine; TSH, thyroid-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; GH, growth hormone; IGF-1, insulin-like growth factor 1; 17-OHP, 17α-hydroxyprogesterone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; DHEAS, dehydroepiandrosterone sulfate; SHBG, sex hormone-binding globulin; FTI, free testosterone index; ACTH, adrenocorticotropic hormone; eGFR, estimated glomerular filtration rate.

whole-exome sequencing (WES) unveiled compound heterozygous mutations in the *CYP21A2* (cytochrome P450, family 21, sub-family A, polypeptide 2) gene, including a severe loss-of-function allele (*c.293-13C>G*, I2G) causing near-complete enzymatic inactivity, and a moderately impaired allele (*c.518T>A*, p.Ile173Asn) retaining partial

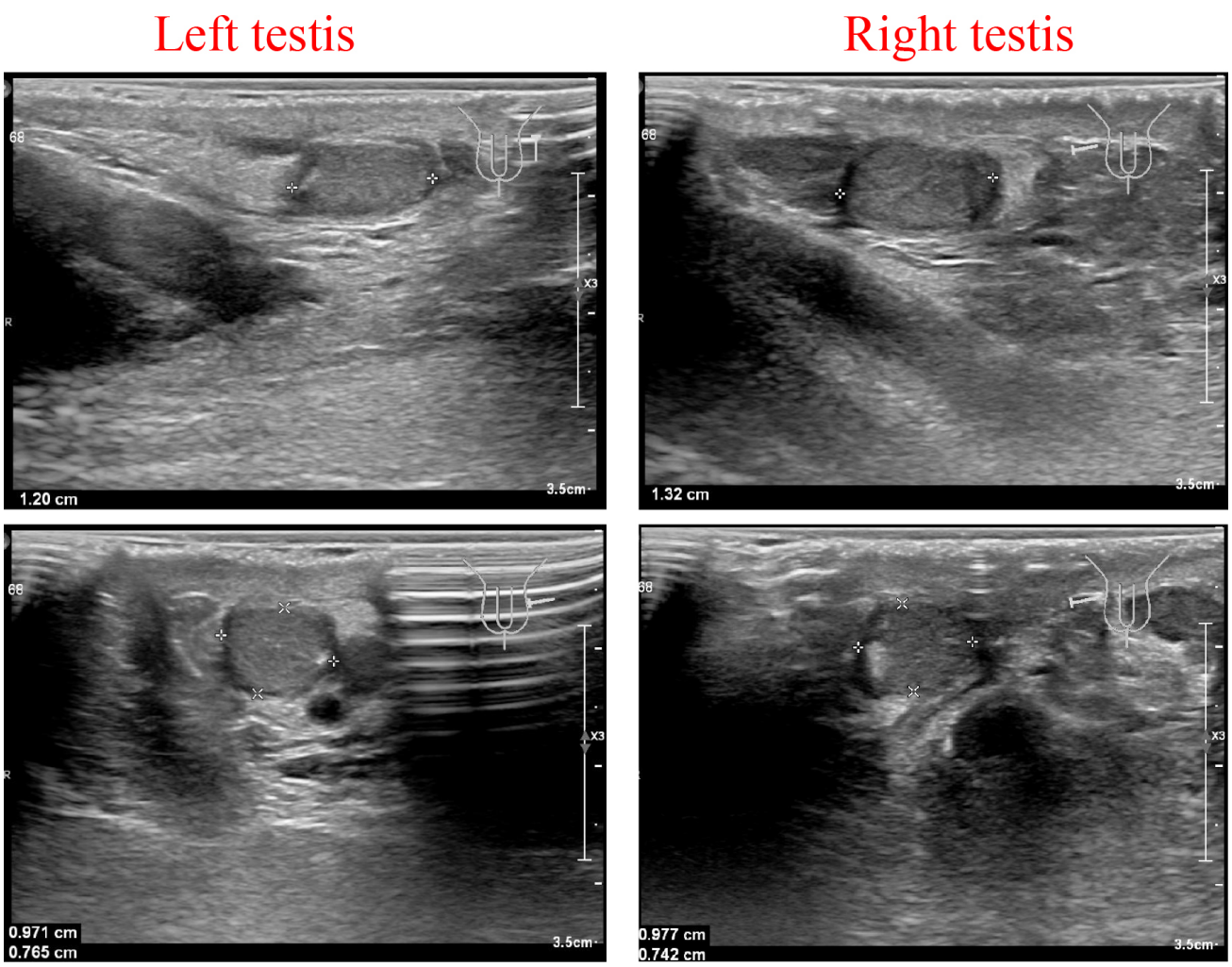

Fig. 2. Testicular ultrasound report of the patient. Ultrasound examination showed bilateral testicular atrophy.

function (Fig. 4). Notably, both sisters of the patient were identified as heterozygous carriers. This specific combination of severe and moderate mutation results in the NCCAH phenotype. After a multidisciplinary team evaluation, the patient was diagnosed with CAH due to NC-21-OHD deficiency.

After the diagnosis, the patient started receiving hydrocortisone 20 mg twice daily [10]. At a one-month follow-up, a significant improvement in fatigue was observed compared to baseline. Biochemically, the level of 17-OHP significantly reduced to 136.22 nmol/L, whereas cortisol and ACTH levels at 8 AM were 3.37 µg/dL and 33.10 pg/mL, respectively. The patient was advised to continue oral hydrocortisone therapy and to adhere to regular follow-up examinations.

3. Discussion

Atypical 21-hydroxylase deficiency (21-OHD) is a milder form of CAH characterized by hyperandrogenism. In this case report, we present a 56-year-old Chinese male patient with non-classic 21-OHD (NC-21-OHD). The patient reported atypical manifestations, including growth arrest from age 12 (final height 154 cm, –3.2 Standard Deviation Score (SDS)) and persistent fatigue, accompanied by a left adrenal mass identified on imaging. Despite these outcomes, assessment for 21-OHD was not initially conducted until biochemical testing confirmed elevated 17-OHP and ACTH [11]. Integrating the hormonal profile (cortisol and ACTH 17-OHP levels), imaging findings, and genetic analysis, a diagnosis of NC-21-OHD was confirmed.

Clinical manifestations, endocrine profiles, and hormonal replacement therapy regimens vary significantly among male patients with NC-21-OHD. Gonadal function can be substantially compromised in men with CAH. A cross-sectional clinical study revealed that 14 out of 69 male patients demonstrated serum testosterone levels below the reference range [3]. For example, a 31-year-old male diagnosed with 21-OHD presented with infertility [12]. Unlike the case presented in this study, he did not show skin hyperpigmentation or genital atrophy. His ACTH level was high, cortisol was 6.9 µg/dL, and LH and FSH levels were both low, while free testosterone, estradiol, and 17-OHP levels were significantly elevated, which was consistent with the

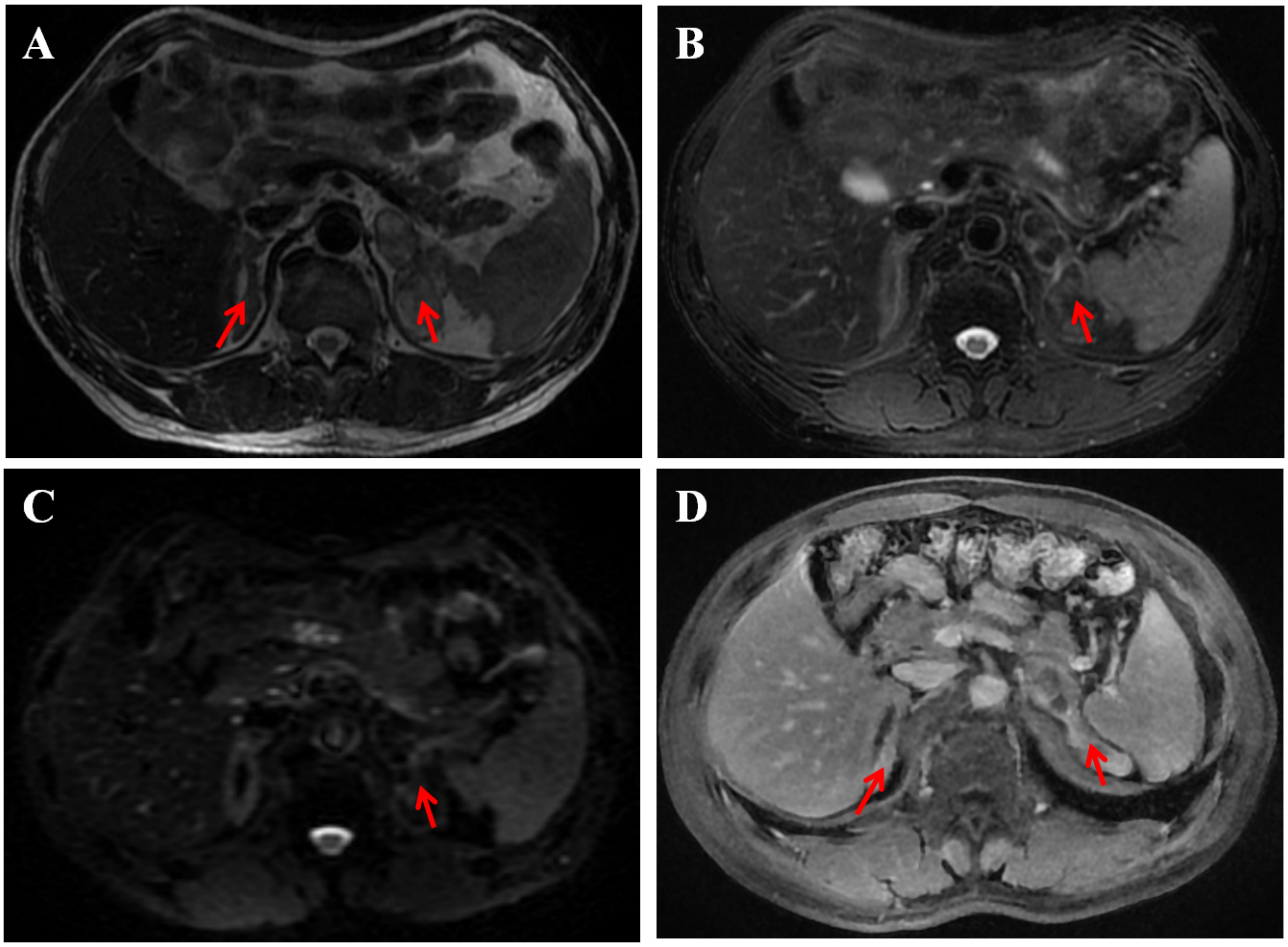

Fig. 3. Enhanced magnetic resonance imaging of the adrenal gland. The report of the patient indicated multiple medullary lipomas within the inner and outer limbs of the left adrenal gland, an adenoma in the outer limb of the same gland, and thickening of the right adrenal gland, which is suggestive of adrenal hyperplasia. (A) On T2-weighted imaging (T2WI), the right adrenal gland is thickened and multiple abnormal masses in the left adrenal gland showed high signal intensity (the red arrows). (B) On the T2WI fat-saturated sequence, the left adrenal masses presented low signal intensity (the red arrow). (C) The diffusion-weighted imaging (DWI) signal was not high (the red arrow). (D) After contrast enhancement, the right adrenal gland showed obvious enhancement, and the left adrenal gland showed marginal enhancement (the red arrows).

hormonal profile observed in our study. Despite administering 0.5 mg of long-acting dexamethasone, his infertility persisted, although sexual desire was moderately enhanced. Conversely, our patient received hydrocortisone 20 mg twice daily [10], leading to reduced fatigue and lowered 17-OHP levels. These findings highlight the significance of a comprehensive assessment and the development of tailored treatment plans for each male patient with NC-21-OHD.

A comprehensive preoperative endocrine evaluation should be considered standard practice for all adrenal lesions before surgical intervention, regardless of whether they are incidentally identified. This is essential to assess functional hyperplasia or tumors and to guide perioperative management. In our study, the patient was fortunate to receive a diagnosis of NC-21-OHD after a comprehensive evaluation, and hormonal therapy proved effective. This case underscores the critical importance of systematic endocrine evaluation for adrenal masses, including assessment of the cortisol axis, catecholamine secretion, and mineralocorticoid function, as these parameters directly impact surgical planning and postoperative care [6,13]. Atypical symptoms are often misdiagnosed as metabolic diseases, such as hypothyroidism.

21-OHD results from mutations in the *CYP21A2* gene, located on chromosome 6p21.3, which encodes the 21-hydroxylase (P450c21) enzyme [14]. The clinical manifestations and severity of 21-OHD correlate with the degree of residual CYP21 (cytochrome P450, family 21) enzymatic activity determined by specific allelic variant [15]. In this patient, the presence of compound heterozygous mutations, which are a known hotspot in the Chinese population with CAH due to 21-OHD, explains the mild biochemical phenotype, consistent with heterozygote effects

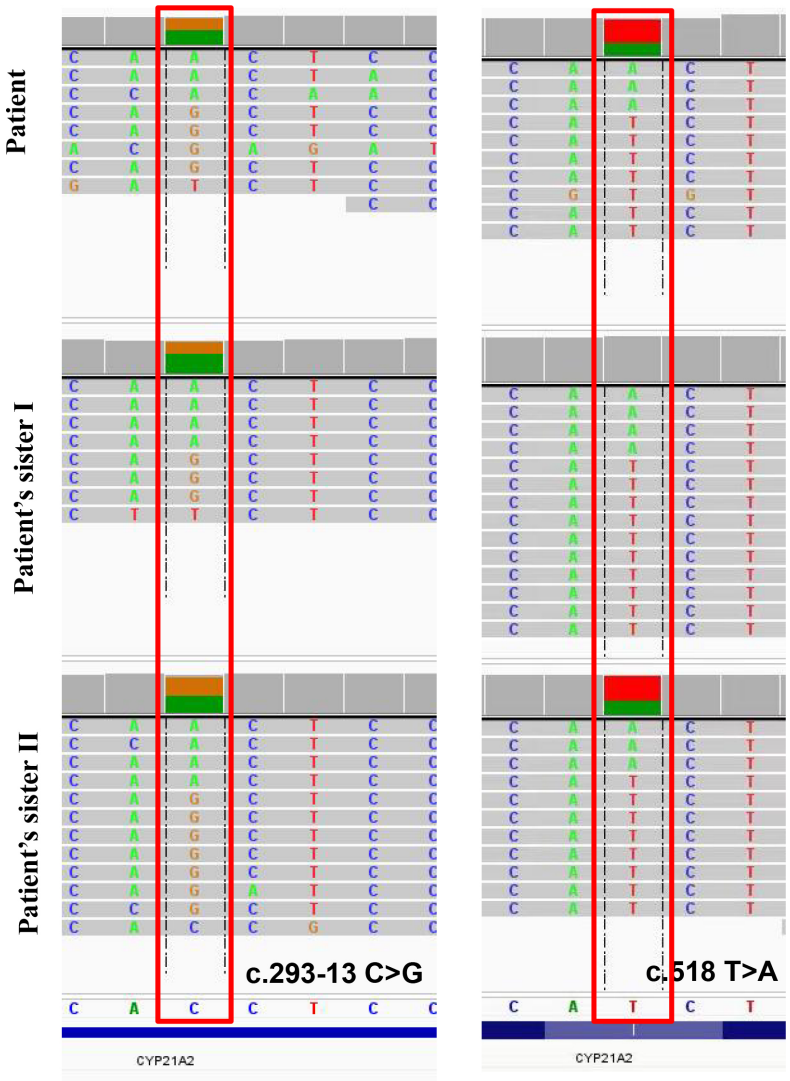

Fig. 4. A comprehensive whole-exome sequencing of *CYP21A2* (cytochrome P450, family 21, sub-family A, polypeptide 2) gene. The following heterozygous mutations were observed: *c.518T>A* (p.Ile173Asn) and *c.293-13C>G* (I2G). Both sisters were identified as heterozygous carriers.

[16]. Notably, the *c.518T>A* (p.Ile173Asn) mutation reduces 21-hydroxylase activity to ~25%, while the *c.293-13C>G* (I2G) mutation allows 10–20% normal splicing, both of which are typically associated with non-classic phenotypes [17]. Furthermore, the identification of heterozygous mutations in the patient's sisters supports a familial pattern, which aligns with the autosomal recessive inheritance of CAH, and emphasizes the significance of family screening to identify asymptomatic carriers [7]. Collectively, these results highlight the significance of genetic testing in accurately diagnosing and assessing familial risk of CAH.

In this patient, the elevated 17-OHP levels (356.19 nmol/L), accompanied by low cortisol and high ACTH, are consistent with the pathophysiology of CAH, in which steroidogenesis is disrupted due to 21-hydroxylase deficiency. These biomarkers serve as critical indicators in diagnosing CAH and distinguishing it from other adrenal pathologies. The significant increase in 17-OHP supports its diagnostic potential in clinical practice [18].

Recent multi-center studies have highlighted persistent controversies regarding the optimal basal 17-OHP cutoff for screening NC-21-OHD. Proposed thresholds range from 1.7 to 3.19 ng/mL across different populations, each demonstrating optimal sensitivity and specificity profiles (85–93%/92–97%) [19]. In this context, the cutoff of 2.02 ng/mL has been implemented. A growing number of research findings indicate that cutoff values can differ among distinct populations and geographic regions, which highlights an urgent need for region-specific validation attributable to ethnic differences in the CYP21A2 mutation spectrum and baseline hormonal levels [19,20]. A threshold of 2.02 ng/mL reduces false positives compared with 1.7 ng/mL, while enhancing sensitivity to 3.19 ng/mL. For

neonatal mass screening of 21-OHD, the primary concern remains the high false-positive rate (low positive predictive value) [21]. However, using liquid chromatography- tandem mass spectrometry (LC-MS) has effectively enhanced diagnostic performance [22]. Furthermore, a strong correlation between 17-OHP and progesterone levels has been observed in NC-21-OHD patients, particularly during the early follicular phase, when luteal phase progesterone interference is minimal [23]. Preliminary studies reveal that an early follicular progesterone level $>$0.6 ng/mL (1.9 nmol/L) may serve as a pragmatic screening threshold (sensitivity 78%, specificity 92%); however, its utility in males remains unvalidated, due to fundamental difference in sex-steroid metabolism and testicular contribution to progesterone clearance.

Despite certain promising outcomes, our study has some limitations. Due to the lack of long-term follow-up, the sustained efficacy of hormonal therapy in this case could not be comprehensively assessed. In our future investigations, we will strive to extend the follow-up duration and systematically monitor the dynamic changes of various biochemical indicators and clinical symptoms, thereby offering a more comprehensive understanding of the long-term efficacy and prognosis of hormonal therapy in male patients with NC-21-OHD.

4. Conclusion

This case demonstrates that endocrine disorders can manifest with nonspecific symptoms such as fatigue. Clinically, vigilance for hormonal abnormalities and a comprehensive endocrine evaluation are imperative, providing a basis for routine endocrine assessment in cases with similar presentations to facilitate early diagnosis and optimal management of conditions like CAH. The diagnosis and management of NC-21-OHD remain challenging; however, multidisciplinary collaboration, standardized neonatal screening, and long-term monitoring of hormonal replacement therapy can help reduce complications, including adrenal crisis and infertility, thereby improving long-term patient prognosis.

Learning Points

• Routine endocrine assessment is pivotal for early diagnosis of CAH and related disorders.

• NC-21-OHD poses substantial diagnostic and management challenges, demanding heightened clinical vigilance.

•Multidisciplinary collaboration and long-term monitoring of hormonal replacement therapy can minimize long-term complications.

Abbreviations

CAH, congenital adrenal hyperplasia; 21-OHD, 21-hydroxylase deficiency; NC-21-OHD, non-classic 21-OHD; 17-OHP, 17α-hydroxyprogesterone; ACTH, adrenocorticotropic hormone; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, γ-glutamyl transpeptidase; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol; BUN, blood urea nitrogen; UA, uric acid; Cr, Creatinine; TSH, thyroid stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; LH, luteinizing hormone; FSH, follicle stimulating hormone; GH, growth hormone; IGF-1, insulin-like growth factor 1; DHEAS, dehydroepiandrosterone sulfate; FTI, free testosterone index; CT, computed tomography; CTA, computed tomography angiography; MRI, magnetic resonance imaging; PETCT, positron emission tomography-computed tomography; DWI, diffusion-weighted imaging; T2WI, T2-weighted imaging; eGFR, estimated glomerular filtration rate.

Availability of Data and Materials

The datasets used or analyzed in the current study are available from the corresponding author upon reasonable request.

Author Contributions

SMH, WZW, YW, and JQW collected and analyzed data and wrote the manuscript. SMH, LJZ, YMY, and QZ made substantial contributions to the conception and design of the study, data acquisition, data analysis and interpretation, and contributed to the discussion. All authors contributed to revising the manuscript critically for important intellectual content. All authors have read and agreed to the published version of the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine (approval number: 2025B.No.0947). All methods were carried out in accordance with relevant guidelines and regulations. Written informed consent was obtained from the patient for the publication of this case report.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/BJHM53026.

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