CASE REPORT

A RARE CASE OF NON-CLASSICAL TYPE OF CONGENITAL ADRENAL HYPERPLASIA IN A 27-YEAR-OLD FEMALE

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This case report presents the case of a 27-year-old female patient with a complex clinical presentation, diagnosed with nonclassical congenital adrenal hyperplasia (NCCAH). The patient presented with a constellation of symptoms including hirsutism, acne, hyperpigmentation, amenorrhea, frontal baldness, and renal stones, posing diagnostic challenges. Comprehensive evaluation revealed NCCAH, emphasizing the importance of considering this condition in cases of hyperandrogenism. Treatment with oral dexamethasone and oral contraceptive pills resulted in gradual symptom improvement. This case underscores the necessity for thorough clinical assessment and awareness of NCCAH as a differential diagnosis in patients with hyperandrogenic symptoms.

Keywords: Nonclassical congenital adrenal hyperplasia; Hirsutism; Hyperpigmentation

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INTRODUCTION

Non-classic congenital adrenal hyperplasia is a common autosomal recessive disorder that can present in adolescence or adulthood.[1] The typical symptoms of hirsutism, amenorrhea, clitoromegaly, acne, and premature pubarche lead to an ascertainment bias in favour of identifying the affected women. The clinical consequences of NCCAH[2] extend from infancy, that is, accelerated growth, to adolescence and adulthood, that is, premature pubarche, cutaneous symptoms, and oligo-ovulation in a polycystic ovary syndrome (PCOS)-like clinical picture. The basal 17-hydroxyprogesterone (17-OHP) concentration should be used for screening. Compared to classical CAH[3], patients with non-classic CAH have more residual enzymatic activity and do not generally suffer from clinically relevant glucocorticoid deficiency. However, these patients may develop symptoms owing to elevated adrenal androgen levels.

Genetic testing should not be considered as a first-line diagnostic test for females suspected of having NCCAH. We obtained morning 17-OHP concentrations in the follicular phase of reproductive-aged females, and if they were positive[1], a follow-up ACTH stimulation test was performed for the patient. This remains an essential clinical tool for the diagnosis of NCCAH.

CASE PRESENTATION

A 27-year-old female with 21 BMI presented with a myriad of symptoms, including hirsutism, acne, hyperpigmentation of the skin, clitoromegaly, secondary amenorrhea, and frontal baldness. The patient had menarche at the age of 8 years and has been experiencing secondary amenorrhea for the past 2 years. She also had a history of renal stones. Physical examination revealed signs of hyperandrogenism, and initial investigations aimed at identifying the cause of the hyperandrogenism were inconclusive.

The patient's complex clinical presentation prompted a comprehensive diagnostic work-up. The initial differential diagnoses included congenital adrenal hyperplasia, polycystic ovarian syndrome and androgen-secreting tumours. Brain MRI revealed a micro-pituitary adenoma and incidental white matter hyperintense foci. CT abdomen and pelvis findings indicated moderate hepatosplenomegaly, bilaterally enlarged kidneys (see figure-1). These symptoms of hyperandrogenism and oligo-anovulation signifies that the patient has polycystic ovary syndrome (PCOS).[4] The bilateral adrenal glands were normal in size without definite nodules, and the remaining structural findings were normal

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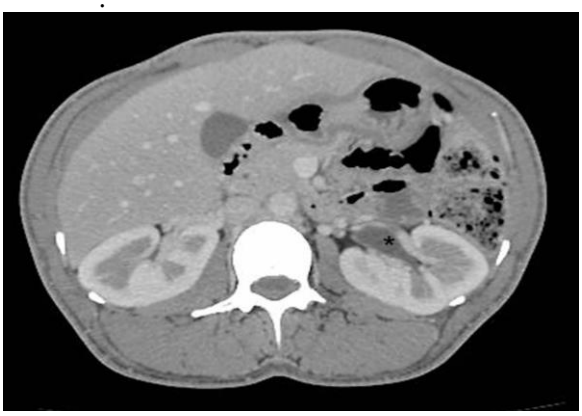

Figure-1: CT with contrast of abdomen and pelvis shows bilaterally enlarged kidneys
(asterisk* indicates the mild degree of hydronephrosis on the left side)

The patient's serum levels of 17-hydroxyprogesterone (during the follicular phase), intact parathyroid hormone, testosterone, and progesterone were elevated. Insulin-like growth factor 1 (IGF-1) and random blood sugar levels were within normal ranges. Serum growth hormone (GH) and fasting GH levels decreased, while serum thyroid-stimulating hormone (TSH) levels were normal. Dehydroepiandrosterone (DHEA) levels were low, and morning cortisol levels were normal. These results indicate that the patient had a non-functioning pituitary adenoma (NFA). This information is presented in table *1*. Previous (6 months ago) high levels of blood calcium explained the cause of renal stones in this patient (Table-2).

Our diagnosis of NCCAH was confirmed by the ACTH stimulation test, which showed an increase of 17-OHP from 2.16 ng/ml basal level to 30.6 ng/ml after ACTH injection (Table 3).

The patient was administered oral dexamethasone. OCPs with anti-androgen therapy were initiated for hirsutism and hormonal control. Treatment resulted in a gradual improvement of the patient's condition. She recovered from symptoms associated with hyperandrogenism, such as hirsutism and acne. Her levels of androgens, such as testosterone and 17-hydroxyprogesterone, also decreased. Hence, it was concluded that the hyper-adrogenism was attributed to NCCAH.

Table-1: Hormonal Panel

Test	Current Results	Units	Range
Serum 17-OH Progesterone	2.136	ng/ML	0.15-0.70 (follicular phase)
Serum Total Testosterone	97.65	ng/dL	15-70
Serum IGF-1	194.50	ng/ML	107.8-246.7
Serum T3	1.90	nmol/L	1.08-3.14
Serum T4	7.40	ug/dL	5.5-11
Serum TSH	2.69	uIU/ml	0.4-4.2
Random Blood Sugar	96	mg/dL	80-160
Serum GH	0.39	ng/ml	2.0-5.0
Progesterone	1.86	ng/ml	0.31-1.52
Estrogen (ESTRADIOL)	27	ng/ml	24-114
Serum Prolactin	23.6	ng/ml	5.2-27.0
DHEA/SO4	45.64	ug/dL	98.80-340.00
Serum Cortisol (Morning)	12.9	ug/dL	3.7-19.4

Table-2: Electrolyte Panel

Test	Current Result	Previous Result (6 months ago)	Unit	Range
Serum Sodium	139	136	mmol/L	136-145
Serum Potassium	4.0	4.0	mmol/L	3.5-5.1
Serum Calcium	10.0	11.1	mg/dl	8.6-10.2
Serum Phosphorus	5.0	4.3	mg/dl	2.5-4.5

Table-3: ACTH Stimulation Test

Test	Current Result	Unit	Range
17-OHP (Basal)	2.162	ng/ml	See below
17-OHP (after 60 mins of ACTH Injection)	30.6	ng/ml	See below

Interpretation: 1. If basal level is <2 ng /ml it is normal and CAH is excluded. **2.** If level is >10 ng/ml after ACTH Stimulation it indicates the presence of non-classical variety of CAH. **3.** If level is >2.6 ng/ml above the Basal Level it is suggestive of Classical variety of CAH

DISCUSSION

This case report highlights the diagnostic journey of a 27-year-old female with a complex clinical presentation ultimately attributed to non-classical congenital adrenal hyperplasia. The patient's diverse array of symptoms, ranging from hyperandrogenism[5] to amenorrhea and renal stones, highlight the intricacies of NCCAH diagnosis. There is no known familial history of NCCAH in this patient.

The pathophysiology of NCCAH is intricately linked to adrenal steroid synthesis.[6] In this case, it is caused by a deficiency in 21-hydroxylase. 21-hydroxylase is responsible for the conversion of 17-hydroxyprogesterone (17-OHP) to 11-deoxycortisol in the adrenal cortex.[7] This deficiency disrupts the synthesis of cortisol and aldosterone, two critical hormones involved in the regulation of various physiological processes. Understanding pathophysiology is important because of its significant impact on a patient's clinical presentation and long-term health. Reduced enzymatic activity results in the accumulation of precursors, particularly 17-OHP, which can have varying effects depending on the individual's genetic makeup and other hormonal factors.[8] Elevated 17-OHP levels can lead to excessive androgen production.[8]

By navigating through a maze of clinical features and investigative assessments, a definitive diagnosis was reached through an ACTH stimulation test that demonstrated elevated 17-OHP levels. Our case

aligns with the existing literature that highlights the wide-ranging clinical manifestations of NCCAH, which can extend from infancy to adulthood, resembling polycystic ovary syndrome (PCOS.[9] Genetic counselling is strongly advised for women with NCCAH who wish to conceive, as is the genotyping of the father.[10] Children with classic CAH are known to have increased fat mass compared to controls.[10] Limited data is available on obesity, hypertension, and insulin resistance in patients with NCCAH.[11] At present, even with limited data, healthy lifestyle counselling should begin early to prevent an increase in body fat and metabolic dysregulation.[11]

The use of OCP is important for the treatment of dermatological symptoms caused by high testosterone [3]. Different mechanisms contribute to the anti-androgenic effects of oral contraceptives. Oestrogen has negative feedback on the pituitary gland, thereby lowering the levels of luteinizing hormone and resulting in lower ovarian androgen production in females.[3] An individualized approach with topical or hormonal treatment is necessary for treating the signs of hyperandrogenism, and consultation with a dermatologist can be of added value for these patients. Daily glucocorticoid therapy is not recommended[3] anymore because of its adverse side effects. It has a direct effect on bone metabolism and increases bone resorption by upregulating osteoclasts, which leads to hypercalcemia. The long-term usage of steroid therapy might be the reason behind nephrolithiasis[12] in this case.

CONCLUSION

In conclusion, grasping the pathophysiology of non-classical congenital adrenal hyperplasia is crucial for accurate diagnosis and effective management. This case underscores the complexity of diagnosing NCCAH, particularly when the clinical features overlap with those of other conditions. The presence of hyperandrogenic features, hormonal abnormalities, and an affirmative ACTH stimulation test eventually led to the diagnosis. It should be considered in the differential diagnosis of hyperandrogenism and secondary amenorrhea. A thorough clinical evaluation, complemented by hormonal and imaging assessments, is crucial for accurate diagnosis and optimal management. In most cases, the only treatment modality is symptomatic, and managing the medication of patients can be difficult for the medical team. Early detection and intervention can improve patient outcomes.

Competing interests:

The authors have no competing interests to declare.

Consent Statement:

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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