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CASE REPORT

NONCLASSICAL 21-HYDROXYLASE DEFICIENCY PRESENTED AS ADDISON'S DISEASE AND BILATERAL ADRENAL INCIDENTALOMAS

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Abstract

Background. 21-hydroxylase deficiency (21 OHD) is the most common form of congenital adrenal hyperplasia (CAH) and it has been widely described in the literature. Adrenocortical incidentalomas are unfrequently the presenting manifestations of CAH, especially in nonclassical form of 21 OHD (NC 21 OHD). Myelolipoma has previously been reported more frequently than other adrenal adenomas associated with CAH.

Case. We report a 40-year old male case of NC 21 OHD with hypoadrenocorticism after unilateral adrenalectomy of the right side because of a large solid incidentaloma (5×4×4cm^3) at the age of 31. This patient began to suffer from obvious symptoms of adrenal insufficiency after 9 years from the surgery. He was reviewed and a very low-density adrenal mass (4.1×3.9cm) was found on computed tomography of the abdomen. After he was admitted to our hospital, this patient was confirmed with NC 21 OHD and presented low level cortisol, striking elevated ACTH, aldosterone insufficiency, increased 17-hydroxyprogesterone, progesterone, decreasing androgens and azoospermatism.

Conclusion. Patients with 21 OHD could be on risk not only for adrenal hyperplasia, but also to develop adrenal adenomas, particularly if the disease was poorly controlled.

Key words: Nonclassical 21-hydroxylase deficiency, congenital adrenal hyperplasia (CAH), Addison's disease, adrenal incidentaloma, myelolipoma, hypoadrenocorticism.

INTRODUCTION

The widespread use of abdominal ultrasonography and computed tomography (CT) has lead to increasing recognition of adrenal incidentalomas (1-3). It is gradually realized that some untreated congenital adrenal hyperplasia (CAH) patients including 21-Hydroxylase deficiency (21OHD) patients may present adrenal incidentaloma, especially in the later-onset nonclassical form (4-7). The etiology of most adrenal tumors caused by CAH is unknown, but they may appear in patients with chronic increases in adrenocorticotrophic hormone (ACTH), such as those with untreated CAH and Cushing's disease (8). The risk of primary adrenal insufficiency will increase significantly for patients with undiagnosed CAH who were treated with adrenalectomy because of a large adrenal mass (9). Here we report a case of 21-OHD that presented with multiple episodes of bilateral adrenal incidentalomas and Addison's disease after unilateral adrenalectomy.

CASE REPORT

A 40-year-old Chinese male patient was admitted to the endocrine department of Western China Hospital because of generalized hyperpigmentation for 9 years and fatigue, anorexia and dizziness for 3 weeks. 9 years ago the patient underwent abdomen ultrasound examination for routine health checkup, which revealed an adrenal mass on the right side. Further evaluation by computed tomography (CT) scan confirmed a well circumscribed, heterogeneous mass of 5×4cm in the right adrenal area. The left adrenal was normal. His medical history, physical examination results and routine laboratory values are unremarkable. Right adrenalectomy was performed in a local hospital since the potential malignancy could not be completely ruled out. The histopathologic diagnosis was adenoma of the adrenal cortex and Ki67 or MIB1 labeling index of the tumor cells was less than 1%. After surgery, his weight dropped by 6 kg and presented with generalized hyperpigmentation. Besides, the symptoms such as progressive lethargy, anorexia or dizziness have no longer affected him.

Three weeks before admission, the patient developed dizziness, fatigue and weakness. He was examined in a local hospital for evaluation of his symptoms. On examination, diffuse hyperpigmentation was noticed, the blood pressure was 128/76 mm Hg, laboratory-test results showed blood potassium 7.6 mmol/L, sodium 119.0 mmol/L, creatinine 129.4

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mmol/L, morning cortisol 132.2 nmol/L,ACTH1136 pg/mL, aldosterone>1000pg/mL, a renin activity 31.07 ng/ml/h and catecholamines level normal. The abdomen CT scan detected a large lipid-dense mass in the left adrenal gland. The patient was diagnosed with primary adrenal insufficiency and treated with prednisone 5mg per day. His symptoms improved and then he was referred to our hospital for further evaluation.

His family history and past medical history were not contributory. He appeared peak height velocity from 7 to 9 years old and stopped growing in height at age 11. His height was lower than of his parents. He did not feel any problem concerning the progression of secondary sexual characteristics compared with his peers. He married at age 27 and subsequently maintained an active sex life, but acknowledged no semen production. He complained of diminished libido in the last 2 years.

On admission, he stood 149 cm and weighed 56 kg, body mass index 25.2 kg/m^2. His blood pressure 110/80 mmHg and pulse 78 beats/min. Examinations revealed mild frontal balding, and sparse axillary and pubic hair. There were diffused brown hyperpigmentation, most conspicuous in folds of the skin, palmar creases, axillae and nipples. The penis was half-normal in size of 6 cm and size of the bilateral testicles were about 3cm×2cm. The rest of the examination findings were normal.

The most pertinent laboratory tests results are listed in Table 1 and included a very high plasma ACTH concentration, partially defective cortisol secretion, normal blood catecholamine level. An extraordinary high level of serum 17-hydroxyprogesterone and progesterone were noted. Routine blood and urine tests, hepatic and renal functions were normal. Chromosomal analysis revealed a 46,XY karyotype. Semen quality analysis showed that sperm concentration was less than (0-1)×10^3/HP. The thin-slice abdomen CT (Figs 1 and 2) revealed a very low density (Hu -61) 4.1 × 3.9 cm homogeneous mass in the left adrenal, consistent with adrenal myelolipomas. The residual right adrenal and a size of 0.7 cm nodule of low density were seen.

DISCUSSION

This patient referred to our hospital for further evaluation, the causes of Addison's disease and recurrent bilateral adrenal incidentalomas. He had clinical features of chronic primary adrenal insufficiency and electrolyte abnormalities (hyponatremia and hyperkalemia), associated with striking elevated ACTH concentration and lower morning cortisol level. So the diagnosis of Addison's disease can be established, but the cause was obscure. Given the strong compensatory adrenal functions, it was unlikely this patient had hypoadrenalism after unilateral adrenalectomy. In view of the clinical signs of precocious puberty, azoospermia, low testosterone levels and elevated progesterone, non-classical 21OHD was suspected. Thus, serum 17-hydroxyprogesterone was tested which was extraordinary high. Accordingly, the clinical diagnosis of CAH, non-classical 21OHD can appear.

Table 1. Laboratory data of the patient

Variable	The patient values	Reference Range, Adults
Na	116.1-130.9mmol/L	[138.0-145.0]
K	6.38mmol/L	[3.5-5.3]
Cl	97.0mmol/L	[99.0-110.0]
ACTH(8:00)	>2000 ng/L	[5.0-78]
cortisol(8:00)	157.8nmol/L	[147.3-609.3]
FPG	3.82mmol/L	[3.9-5.9]
17 OHP	21.13ng/mL	[0.31-2.01]
DHEA-S	1.99umol/L	[2.41-11.6]
LH	5.8mIU/mL	[1.7-8.6]
FSH	8.0mIU/L	[1.5-12.4]
P	5.25ng/mL	[0.2-1.4]
T	1.81ng/mL	[2.49-8.36]
E_2	17.94pg/mL	[25.8 -60.7]
aldosterone	14.83ng/dL	[4.5-17.5]
PRA	>12.0ng/mL·h	[0.05-0.79]

Note: FPG, fasting plasma glucose; 17 OHP, 17-hydroxyprogesterone; DHEA-S, dehydroepiandrosterone sulfate; LH, luteinizing hormone; FSH, Follicle-stimulating hormone; P, progesterone; T,testosterone; E2, estradiol; PRA, plasma renin activity. Na represented range of sodium values of three times measurement in the first 2 days on admission.

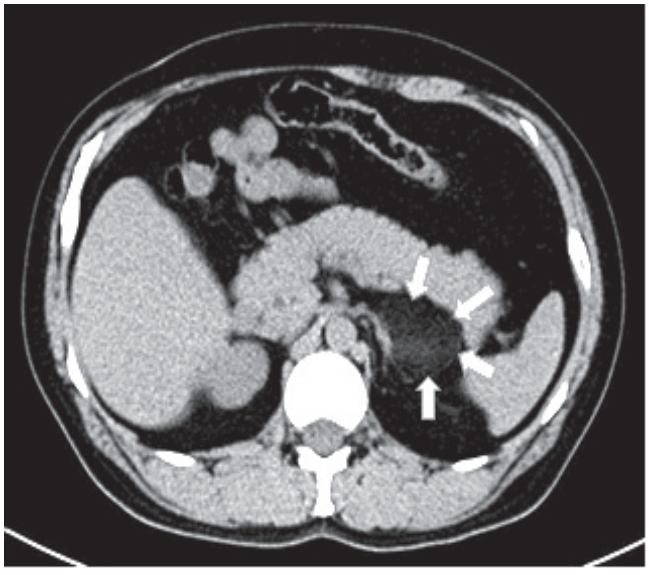

Figure 1. CT image of the adrenal glands.

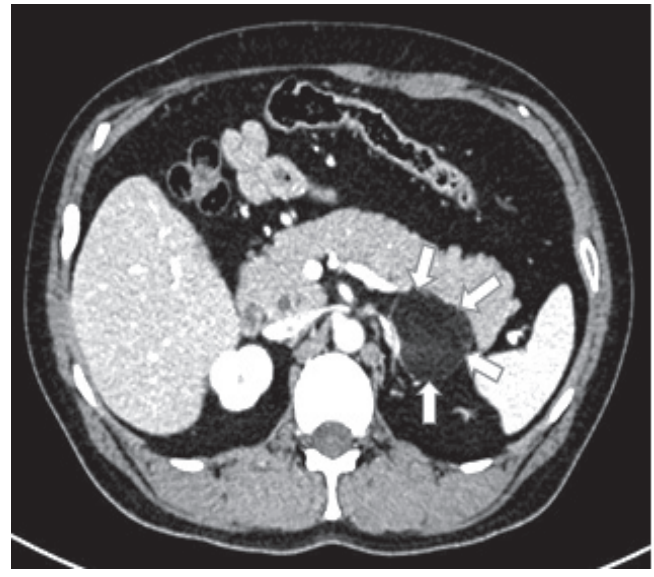

Figure 2. Enhanced CT scan of the adrenal glands.

The defective conversion of 17-hydroxyprogesterone to 11-deoxycortisol in patients with CYP21A2 deficiency results in decreased cortisol synthesis and therefore increased ACTH secretion, the latter stimulating adrenal hyperplasia in order to maintain normal secretion of adrenal cortical hormone. The adrenalectomy performed in the case of this patient disturbed the balance and he started to develop symptoms of primary adrenal insufficiency, such as hyperpigmentation and weight loss after surgery. The patient can barely maintain nearly normal life at the expense of significantly increased ACTH, manifested as marked hyperpigmentation, until 9 years later after surgery.

21OHD is the most common form of CAH, and can be categorized into salt wasting (SW), simple virilizing (SV) forms and later-onset non-classical form according to clinical severity and the time of manifestation. The clinical signs and symptoms of SW form were clinically manifested as aldosterone deficiency that includes poor feeding, vomiting, failure to thrive, lethargy, and sepsis-like symptoms with the determination of surgical wound infections or some forms of acne refractory to conventional dermatological treatment (10, 11). These features may alert the clinician to the diagnosis in a male baby. In the SV form, loss of cortisol negative feedback on the hypothalamus and pituitary increases ACTH secretion, which leads to adrenocortical hyperplasia and stimulates the adrenal gland to move cholesterol into the steroidogenic and virilization of an affected female fetus. While males are phenotypically normal at birth, there is a high risk of misdiagnosing. Some of them may present signs of precocious pseudopuberty in early childhood, such as sexual precocity, pubic hair development, or growth acceleration due to premature androgen excess (12, 13). These symptoms can be varied because of the different period of diagnosis. In NC 21OHD, a partial enzymatic block is not severe enough to cause cortisol insufficiency at most condition, as there is 5%-20% residue activity of the adrenal function (14). This patient did not have crises spontaneously, but he suffered adrenal insufficiency and symptoms appeared after he accepted surgery, and he benefited from replacement therapy. Besides cortisol and aldosterone deficiency, 21 OHD may suffer from severe androgen excess. The mild to moderate defect in 21OHD causes characteristic accumulation of 17OHP and elevated progesterone, these precursors above the block diverted to androgens. Hence other marked clinical features of the patient were the much earlier puberty among his peers, normal sexual function after he entered adulthood yet azoospermatism was diagnosed later. Research on the pathophysiology of 21 OHD has shown endocrinopathies beyond the characteristic abnormalities of the adrenal cortex, including insulin resistance. This patient had a BMI of 25.2 kg/m^2, without insulin resistance or hyperglycemia, but fasting hypoglycemia on admission instead, the hypoglycemia may be associated with serious hypoadrenalism. At day 6 of the hydrocortisone treatment, we reviewed the FPG of 4.61mmol/L. The clinical course of NC 21OHD may be insidious. Hyponatremia, and hyperkalemia with raised plasma renin activity, hypotension, and hypoglycemia may not be obvious or absent of an adult man patient. However, the major feature of

impaired fertility, adrenal androgen excess (DHEAS, androstenedione) with sexual precocity, and relatively low height in men with 21OHD can be detected by reviewing past regimens and potentia generali (15). We would presume, if the patient went to clinic for infertility and run tests for azoospermatism, he might be correctly diagnosed and began hormone replacement and would not suffer from adrenal insufficiency and incidentaloma the second time after the adrenalectomy.

The development of an adrenocortical tumor due to chronic adrenal cortical stimulation by excessive ACTH production in adult patients with untreated CAH may be not a rare occurrence. Jaresch *et al.* reported a high prevalence of silent adrenal adenomas in patients with CAH, nearly 82% of patients with homozygous gene mutations and 45% of patients with a heterozygous gene mutation (5). The unilateral incidentalomas in CAH are far more frequently than bilateral ones. There were very few research which reported bilateral tumors in CAH patients (3, 5, 16, 17). The etiology of adrenal incidentalomas varies, but the frequency of the different tumor types in CAH is unknown. The adrenal hyperplasia of 21OHD is also associated with tumors of the adrenal cortex, and myelolipomas are commonly found and can be enormous, requiring removal for mass effect (6, 16, 18). Some researches indicate that chronically elevated levels of ACTH may play a role in the pathogenesis of incidentalomas (4, 5, 7, 19-22). Clinically, researchers showed that patients who were untreated for a long time and older ones had the most hyperplastic adrenals, but with no significant difference between patients with and without tumor formation in terms of age or age at onset of replacement therapy (4). This patient developed another incidentaloma after nine years interval of uncontrolled 21 OHD, which maybe associated with the sustained elevated ACTH. The 2016 guideline of adrenal incidentalomas recommended that all patients should undergo detailed history and physical examination, particularly of growth parameters and sexual function, no matter with bilateral or unilateral adrenal incidentalomas (23). If necessary, clinical and hormonal assessment should be performed, this may be more important in asymptomatic patients with bilateral tumors (4). It also demonstrated rapidly developing hirsutism, precocious puberty, impaired fertility, which are clinical indicators for 21 OHD, and should be addressed by measuring testosterone and androgen precursors (23).

When patient had the clinical features above, hormonal assessment should include sexual hormones. If there is unexplained elevated progesterone, a note of caution for diagnosis of CAH should be added and unconventional examination of 17 OHP need to be detected. It is important not to neglect the 21 OHD with adrenal incidentalomas, especially non-classical ones, in case of misdiagnosing with non-classical CAH, screening of the potential adrenal insufficiency, elevated of precursors and abnormal product-hormones if suspected on clinical grounds.

Conflict of interest

The authors declare that they have no conflict of interest concerning this article.

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