CASE REPORTS

Hypertension, hypokalemia, and left adrenal tumor mimicking primary aldosteronism in a patient with 17α-hydroxylase deficiency

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ABSTRACT

17α-hydroxylase deficiency (17OHD) is a rare disorder of secondary hypertension caused by congenital adrenal hyperplasia. In addition, co-occurrence of an adrenal tumor with 17OHD is extremely rare and easily misdiagnosed. A 33-year-old female with sicca syndrome, persistent hypertension, hypokalemia, and a left adrenal tumor was referred for confirmation of primary aldosteronism. However, the absence of secondary sexual characteristics, persistent growth beyond puberty, and laboratory data of low plasma renin activity, high aldosterone, low cortisol, low sex hormones, elevated adrenocorticotropic hormone, elevated luteinizing hormone, elevated follicle-stimulating hormone, and most importantly, decreased 17-hydroxypregnenolone, supported a diagnosis of 17OHD. We sequenced the CYP17A1 gene of the patient and her parents, which demonstrated genetic defects (D487-S,488-F489 deletion and Y329K418X). 17OHD was diagnosed. The left adrenal tumor was assessed, and a non-functional adrenal incidentaloma was confirmed; NP-59 adrenal cortical scintigraphy and adrenal venous sampling showed no functional activity and non-lateralization. Hormone replacements with estrogen, spironolactone, and prednisolone were given. The patient became more feminized and confident, and her hypertension was controlled. Early diagnosis and treatment of 17OHD not only can prevent delay development of secondary sexual characteristics but also help the patient maintain mental health and improve their quality of life. In addition, the concomitant presence of a left adrenal tumor makes misdiagnosis of a functional adenoma more likely, possibly causing unnecessary surgery and delay inappropriate treatment.

Key Words: 17α-Hydroxylase Deficiency, Primary aldosteronism, Adrenal incidentaloma

1. INTRODUCTION

17α-hydroxylase deficiency (17OHD) is a rare form (< 1%) of congenital adrenal hyperplasia (CAH), usually presenting as amenorrhea, lack of pubertal development, hypertension, hypokalemia, and hypogonadism in a female.[1] 17OHD results from overproduction of aldosterone and a decrease in sex hormones and cortisol production caused by a genetic defect in 17α-hydroxylase.[2] The clinical manifestations of hypertension and hypokalemia may be easily confused with hyperaldosteronism, especially with the presence of a

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concomitant adrenal tumor. We previously reported a case of 17OHD in which there was a long process to reach the final diagnosis.[3] Here, we report another patient with hypertension, hypokalemia, and a left adrenal tumor referred for confirmation of primary aldosteronism (PA). However, through a series of hormonal and genetic examinations, the patient was eventually confirmed to have instead of PA caused by a left adrenal tumor.

2. CASE PRESENTATION

A 33-year-old Taiwanese female with a history of Sicca syndrome received prednisolone and hydroxychloroquine for 5 years. She noted blood pressures as high as 140–150/90 mmHg since she was a teenager in high school. She experienced no weakness, no excess sweating, or episodes of headache previously. However, her hypertension was persistent, even with three anti-hypertension drugs (atenolol 50 mg, amlodipine 5 mg, and valsartan 160 mg). Because of the presence of hypokalemia with the initial impression of primary aldosteronism, she received an abdominal computed tomography examination, and a 1.5 cm tumor over her left adrenal gland was identified, and suspected to be a functional adrenal adenoma. She was then transferred to Kaohsiung Medical University Hospital for further care. The initial impression was PA caused by an adrenal tumor, but this was soon excluded after the patient reported a history of amenorrhea, delay development of secondary sexual characters, and persistent growth even after the end of puberty (height: 176 cm, in the top 3%). Her parents were within the normal percentiles of height (father: 168 cm; mother: 163 cm), and no one of her family had history of delayed or absent puberty. Physical examination revealed a blood pressure of 140/100 mmHg, no breast buds, no axillary hair, no pubic hair, no striae, no plethora, and no pigmentation. Laboratory tests showed hypokalemia (3.3 mmol/L), metabolic alkalosis (HCO_3- of 28.9 mmol/L), transtubular potassium gradient of 10.79 (serum/urine potassium: 3.4/91 mmol/L; serum/urine osmolality: 294/729 mOsm/kg), hyperaldosteronism (aldosterone of 30.87 ng/dl), and low plasma renin activity (0.36 pg/ml/hr). Hormonal studies demonstrated low levels of sex hormones(estradiol: < 20 pg/ml, progesterone: 6.3 ng/dl) and cortisol(< 0.1 μg/dl), high follicle-stimulating hormone (FSH) (98 mIU/ml), high leutinizing hormone (LH) (30.8 mIU/ml), and high adrenocorticotropic hormone (ACTH) (190.83 pg/ml). Brain magnetic resonance imaging revealed a normal pituitary gland (1 cm $\times$ 0.9 cm $\times$ 0.8 cm). X-rays of the bilateral hands and wrists showed significantly retarded bone age equivalent to 13 years old. Gynecologic sonography also showed retardation of development of the uterus (10 years old) and bilateral ovaries (right side: 11–12 years old; left side: 13 years old). The insulin tolerance test and clonidine test revealed normal growth hormone levels (9.46 ng/ml), but low cortisol (< 0.1 μg/dl). These results were compatible with primary hypogonadism and adrenal insufficiency. The clinical and laboratory results strongly suggested the possibility of 17OHD, and 17-OHP and dehydroepiandrosterone (DHEA) were below normal limits (0.3 ng/ml and 28.42 μg/dl) (see Table 1). Thus, 17OHD of CAH was diagnosed. For genetic diagnosis, we sequenced the CYP17A1 gene,[4,5] which showed two mutations. The first mutation was maternal segregation, at 1459_1467 delGACTCTTTC, deletion of amino acid 487-489 (Asp-Ser-Phe) in exon 8. The second mutation was paternal segregation, at c.985_987delTACinsAA, p. Y329Kfs (termination at aa 418) in exon 6. Then, she received with estrogen, cortisone acetate for hormone replacement and spironolactone for hypertension control. After 3 years treatment, she became more feminized, and experienced no further growth in height (176.5 cm). Hypertension was also controlled. To survey the previous left adrenal tumor, adrenal venous sampling (see Figure 1) and NP-59 adrenal cortical scintigraphy (see Figure 2) were performed, and the results showed a non-functional adrenal incidentaloma.

Table 1. Laboratory data of before and after treatment

Item	Before	After	Reference range
Potassium (mmol/L)	3.3	4.0	3.5-5.1
HCO_3^- (mmol/L)	28.9	24.6	22-26
Cortisol 8:00 a.m (μg/dl)	< 0.1	7.75	5-25
ACTH (pg/ml)	190.83	13.06	10-50
Aldosterone (ng/dl)	30.87	6.35	4-31
PRA (ng/mL/hr)	0.36	1.62	0.84-2.5
Estradiol (pg/ml)	< 20	132.88	60-200
Progesterone (ng/ml)	6.3	2.02	0.15-1.4
Testosterone (ng/dl)	< 24	8.3	ND-81
FSH (mIU/ml)	98.0	68.40	3.3-8.8
LH (mIU/ml)	30.8	36.08	0.6-6.2
TSH (μIU/ml)	1.08	1.36	0.25-4.0
Prolactin (ng/ml)	11.4	-	1-27
DHEA (μg/dl)	28.42	-	35-430
17-OH-progesterone (ng/ml)	0.3	0.2	0.5-2.4

Note. ACTH, adrenocorticotropic hormone ; DHEA, dehydroepiandrosterone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; PRA, renin plasma activity; TSH, Thyroid-stimulating hormone

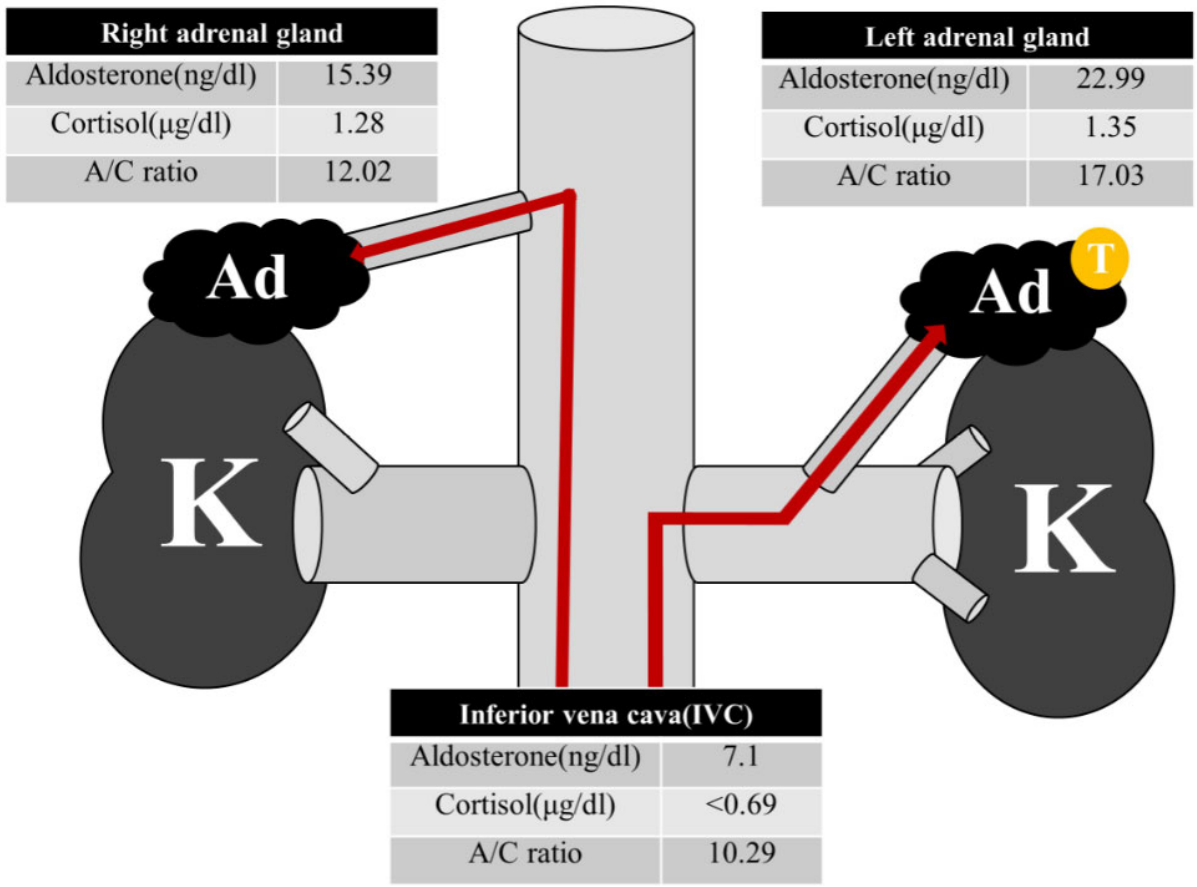

Figure 1. Adrenal venous sampling (K: Kidney; Ad: Adrenal gland; T:Adrenal tumor) Successful adrenal venous sampling (adrenal gland/IVC cortisol ratio > 2) showed low cortisol levels with similar aldosterone/cortisol levels of the bilateral adrenal gland and inferior vena cava; there was no lateralization, and the findings did not favor a unilateral aldosterone-producing adenoma.

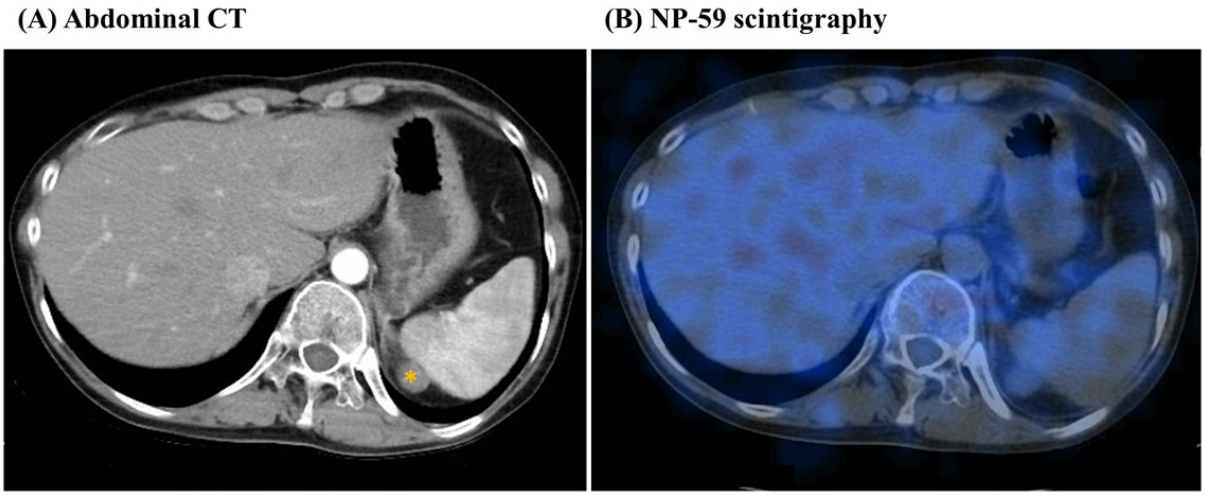

Figure 2. Abdominal computed tomography and NP-59 scintigraphy. The result showed no obvious NP59 avidity of the left adrenal tumor. A non-functional adrenal tumor was diagnosed and was compatible with the patient's conditions.

3. DISCUSSION

Congenital adrenal hyperplasia caused by defects in enzymes involved in cortisol synthesis.[6] The most common form is 21-hydroxylase deficiency, which accounts for 90% of CAH. 17OHD is inherited as an autosomal recessive trait and is a rare cause of CAH, which causes hypertension. 17OHD was first reported by Biglieri et al.,[1] and most cases were diagnosed around puberty into the 20s, at which time sexual abnormalities manifested.[1, 7, 8]The defects of enzymatic reactions include 17α-hydroxylation of progesterone, pregnenolone, and conversion of 17-OHP to DHEA, which leads to decrease sex hormones with elevated FSH and LH. Clinically, the patient has amenorrhea and failure to develop secondary sexual characteristics, including no pubic hair or breast buds; however, the uterus is usually intact. Only a few cases of hypoplastic uteri have been reported.[9] Furthermore, overproduction of mineralocorticoids like corticosterone, deoxycorticosterone (DOC), and normal-to-high levels of plasma aldosterone induces hypertension, hypokalemia, suppressed renin activity, and uncommon adrenal insufficiency compared with other forms of CAH. The empiric diagnosis of 17OHD is established by clinical manifestations, and laboratory data demonstrate elevated DOC, corticosterone, and progesterone, but low cortisol, suppressed renin activity, and low sex hormones. However, genetic diagnosis is gradually becoming more important with the advancement of genetic analysis, and approximately 100 mutations in the CYP17A1 gene have been identified.[10] Our patient has a compound heterozygous mutation in the CYP17A1 gene (D487-S488-F489 deletion and Y329K418X), which was first identified in a 14-year-old Thai girl in 1993 and a 32-year-old Korean female in 2003. According to current statistics, these changes were possibly the main genetic mutations of 17OHD in Chinese people.[11] The first goal of 17OHD treatment is to recover secondary sexual characteristics and correct cortisol deficiency by glucocorticoid replacement and sex hormone supply.[12] Glucocorticoids must be supplied not only for cortisol replacement, but also for ACTH suppression to diminish mineralocorticoid production. Mineralocorticoid antagonists can also be prescribed to minimize the dose of glucocorticoids, and to avoid the side effects of long term use. The second goal of treatment is to evaluate plasma renin activity, aldosterone levels, and status of hypertension. However, hypertension and renin suppression may persist for months or years, even after successful treatment by mineralocorticoid antagonists. Adjustments of medications and adding other anti-hypertension drugs can help reach the blood pressure target. Our patient received daily spironolactone 50 mg, prednisolone 5 mg, amlodipine 5 mg, and estradiol 1 mg. We used prednisolone to replace cortisone acetate for a glucocorticoid supply, because the patient also had sicca syndrome. The more feminized sexual characteristics increased self-confidence and social activity in our patient. Hypertension was also gradually controlled, and no further increase in body height was noted. Many cases of CAH with adrenal incidentaloma have been reported, but mainly in cases of 21-hydroxylase deficiency.[13, 14] Only a few case reports of 17OHD combined with adrenal incidentalomas have been described in the literature. The possible cause of adrenal incidentalomas is currently thought to be related to the high concentration of 17OHP and ACTH hypersecretion for the stimulation of adrenal tissue. Some research has even suggested that elevated 17-OHP level might accompany a large adrenal adenoma or an adrenocortical carcinoma.[15] However, several questions persist. First, most cases of adrenal incidentalomas are unilateral rather than bilateral. Second, low 17OHP concentration in our case conflicted with previous reports. These findings highlight that the pathogenesis is still unknown, and more cases need to be accumulated for future analysis. Despite that 17OHD is a very rare type of CAH, early diagnosis helps to prevent delay development of secondary sexual characteristics and improve the patient's quality of life and confidence. The concomitant presence of a left adrenal tumor in this hypokalemic and hypertensive case made the diagnosis prompt to be adrenal adenoma induced primary aldosteronism as in previous report.[16] In the previous study, the patient received a left adrenalectomy, but still experienced uncontrolled hypertension. Thus, the value of this case report is that we had alertness from our previous experiences, and through careful physical examination, multiple confirmation studies, including genetic analysis, we made the correct dialysis of 17OHD and avoided unnecessary surgical intervention. During the follow up period, we finally performed adrenal venous sampling and NP-59 adrenal cortical scintigraphy to confirm that the left adrenal tumor was a non-functional incidentaloma because of no NP59 avidity and non-lateralization.

4. CONCLUSION

We present the clinical experience in the prompt and correct diagnosis of a rare disease of 17OHD in a patient with concurrent adrenal incidentaloma through careful history taking, physical examination and complete hormonal and genetic studies.

CONFLICTS OF INTEREST DISCLOSURE

The authors have declared no conflicts of interest.

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