

A rare case of 17 α -hydroxylase/17, 20-lyase deficiency: Clinical and genetic findings and follow-up outcomes

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Abstract

Here, we reported a case of a 16-year-old Chinese female patient (46, XX) diagnosed as 17 α -hydroxylase/17, 20-lyase deficiency (17-OHD) in June 2018 and over 3 years follow-up outcomes; 17-OHD is a rare form of congenital adrenal hyperplasia. The patient presented with primary amenorrhea, underdeveloped secondary sexual characteristics, hypertension and hypokalemia. Hormonal findings revealed decreased estrogen and androgen, increased progesterone, low cortisol concentration and compensatory high adrenocorticotropic hormone level. Mutation analysis of the *CYP17A1* gene identified the c.1459_1467del GACTCTTTC homozygous deletion in exon 8, namely, D487_F489del mutation, resulting in the deletion of Aspartate–Serine–Phenylalanine amino acids. The patient's father and mother were all heterozygous carriers of this mutation. The diagnosis and follow-up outcomes provided useful insights to support clinical decision-making and appropriate treatment.

Keywords

17 α -hydroxylase/17, 20-lyase deficiency, congenital adrenal hyperplasia, *CYP17A1* gene mutation, follow-up, primary amenorrhea

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Introduction

Congenital adrenal hyperplasia (CAH) is the consequence of autosomal recessive disorder caused by defects in enzymes necessary for adrenal steroidogenesis. 17 α -hydroxylase/17, 20-lyase deficiency (17-OHD), caused by mutations in the cytochrome P450 family 17 subfamily A member 1 gene (*CYP17A1*), is a rare cause of CAH.¹ The cytochrome P450 17 α -hydroxylase/17, 20-lyase (P450c17) is a multi-functional enzyme with the activities of 17 α -hydroxylase and 17, 20-lyase, which is necessary for the synthesis of adrenal steroidogenesis.^{2,3} Because of this enzymatic defect, levels of cortisol, estrogen and androgen decrease while upstream products of the enzyme accumulate. On one hand, as the result of negative feedback, low cortisol level leads to excess adrenocorticotropic hormone (ACTH) production and adrenal hyperplasia; on the other hand, increased substrates of this enzyme lead to overproduction of the precursors of aldosterone such as

deoxycorticosterone (DOC), and DOC has a mineralocorticoid action which could induce hypertension and hypokalemia. Apart from these, the synthesis of sex hormones is blocked, which affects gender differentiation. Female patients with 46, XX are characterized by primary amenorrhea; while males with 46, XY present with disorders/differences of sex development (DSD).⁴ Here, we reported a case of a 16-year-old girl with rare homozygous mutation in *CYP17A1* gene causes 17-OHD.^{5,6}

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Case report

A 16-year-old Chinese girl with primary amenorrhea was referred to the Department of Endocrinology of Zhongshan Hospital Xiamen University in June 2018. On physical examination, the patient's admission blood pressure was 135/92 mmHg, the body weight was 48.9 kg, and her height was 165 cm. Her breasts were in Tanner stage I, pubic hair and armpit hair were absent, and the external genitalia were infantile.

Chromosomal analysis showed a 46, XX karyotype. Laboratory tests revealed that the patient had hypokalemia and normal plasma sodium level. Further hormonal tests revealed that estradiol (E2) and testosterone (T) decreased, progesterone (P) elevated, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) increased subsequently; cortisol reduced and ACTH secretion increased; aldosterone levels in standing and supine positions were normal along with slightly decreased renin activity, and the ratio of aldosterone/renin activities was not increased; prolactin (PRL) and growth hormone (GH) were within the normal range (Table 1).

In other examinations, pelvic ultrasound showed a primordial uterus and faintly visible bilateral ovaries. The size of the uterus was about 1.87 cm × 0.17 cm. Renal artery ultrasound was normal. Computed tomography (CT) scanning (unenhanced and contrast material-enhanced scanning) suggested the hyperplasia in bilateral adrenal gland (Figure 1). Enhanced magnetic resonance

imaging (MRI) of the pituitary demonstrated that the pituitary gland was normal.

Considering the patient's hormone changes and adrenal hyperplasia above-mentioned, along with hypertension and hypokalemia, CAH should be suspected, and 17-OHD was the most possible reason. Then, the peripheral blood samples of the patient and her parents were sent to analyze the *CYP17A1* genetic sequence.

The genetic mutation analysis results confirmed our presumption of the diagnosis. The bases deletion at nucleotide positions 1459–1467 in exon 8, namely, the GACTCTTTC homozygous mutation was identified in the patient. The genetic mutation resulted in deletion of Asp-Ser-Phe (aspartate-serine-phenylalanine) amino acids at nucleotide positions 487–489, which made the function of 17 α -hydroxylase/17, 20-lyase damaged and caused typical clinical presentations of CAH consequently. The patient's father and mother were all heterozygous carriers of this mutation (Figure 2).

After being diagnosed as 17-OHD, the patient was prescribed dexamethasone starting at 0.75 mg/day to suppress ACTH secretion, and the dose was gradually reduced to 0.25 mg/day after 2 years according to the patient's condition and continuously maintained until now. In addition, estrogen and progestin supplements were provided to induce an artificial menstrual cycle and promote the development of secondary sexual characteristics with oral femoston (a combination of 2 mg estradiol brick-red tablet and 1 mg estradiol with 10 mg dydrogesterone yellow tablet).

Table 1. Biochemical parameters and relevant hormones results of the patient before the treatment.

Items	Results	Reference range
E2 (pmol/L)	<18.35 ↓	45.4–854 (follicular phase)
T (nmol/L)	<0.087 ↓	0.29–1.67 (female)
P (nmol/L)	27.77 ↑	0.181–2.84 (follicular phase)
LH (IU/L)	49.64 ↑	2.4–12.6 (follicular phase)
FSH (IU/L)	95.03 ↑	3.5–12.5 (follicular phase)
PRL (mIU/L)	440.5	102–496
GH (ng/mL)	5.3	0.123–8.05
Cortisol (μ g/L)		
8:00 a.m.	8.0 ↓	48.2–195
4:00 p.m.	4.35 ↓	24.7–119
0:00 a.m.	3.15 ↓	24.7–119
ACTH (pg/mL) 8:00 a.m.	74.7 ↑	7.2–63.3
Aldosterone (pg/mL) (standing)	108.5	70–300
Renin activity (ng/mL/h) (standing)	0.06 ↓	0.10–6.56
Δ ARR (standing)	1.81	0–12
Aldosterone (pg/mL) (supine)	109.8	30–160
Renin activity (ng/mL/h) (supine)	0.06 ↓	0.15–2.33
Δ ARR (supine)	1.83	0–12
Potassium (mmol/L)	3.29 ↓	3.5–5.3
Sodium (mmol/L)	141	137–147

E2: estradiol; T: testosterone; P: progesterone; LH: luteinizing hormone; FSH: follicle-stimulating hormone; PRL: prolactin; GH: growth hormone; ACTH: adrenocorticotropic hormone; ARR: aldosterone-to-renin activity ratio; Δ ARR: aldosterone (pg/mL)/renin activity (ng/mL/h).

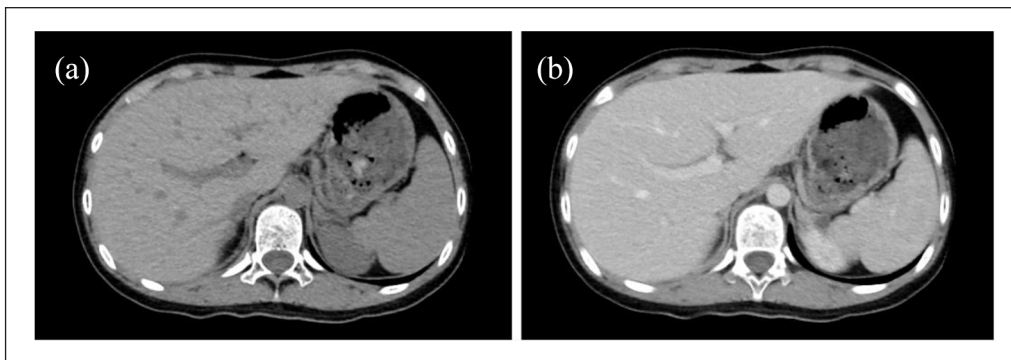


Figure 1. CT scanning revealed that bilateral adrenal hyperplasia before the treatment. (a) Unenhanced CT scanning and (b) contrast material-enhanced CT scanning.

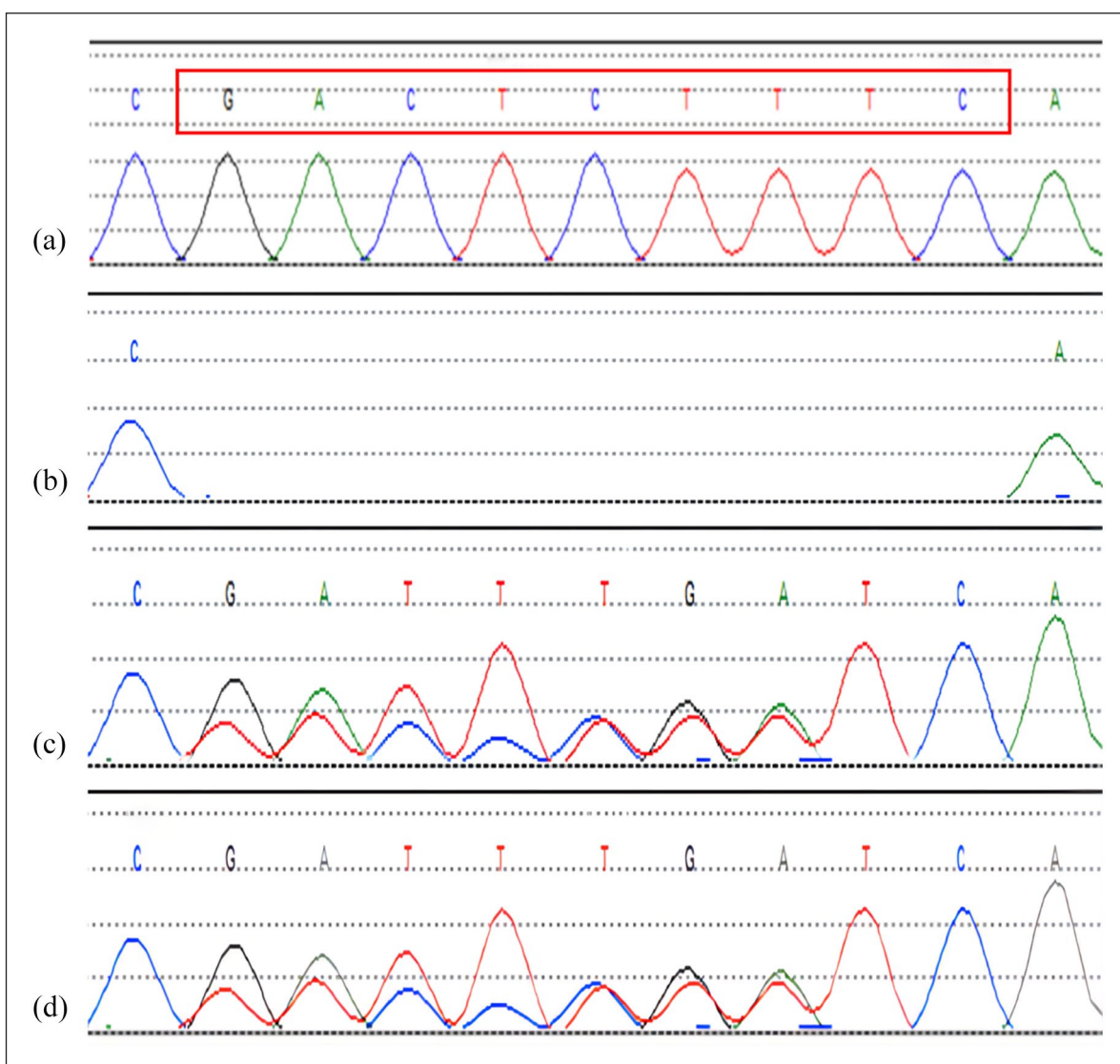


Figure 2. The *CYP17A1* genetic mutation sequence of the patient and her parents. (a) Normal reference sequence of *CYP17A1* gene. (b) The *CYP17A1* genetic sequence of the patient showed GACTCTTTC bases deletion at nucleotide position 1459–1467 in exon 8. (c) The *CYP17A1* genetic sequence of the patient's father showed GACTCTTTC heterozygous mutation. (d) The *CYP17A1* genetic sequence of the patient's mother showed GACTCTTTC heterozygous mutation.



Figure 3. The re-examined adrenal unenhanced CT scanning of the patient showed that the adrenal hyperplasia did not aggravate over 3 years after treatment.

Three months later, the patient began to menstruate, but the menstruation cycle was not regular. And her bilateral breasts were slightly developed. After 6 months, regular menstrual bleeding occurred. Her breast development progressed to Tanner stage II. Pelvic ultrasound was repeated, and it showed an infantile uterus with the size of 2.80 cm × 1.40 cm × 2.30 cm indicating that the uterus was a little more developed than before, but still with faintly visible bilateral ovaries. One and half years later, the measurement of the patient's uterus was 2.80 cm × 1.70 cm × 2.40 cm, with slightly enlarged ovaries bilaterally. Three years later, the size of her uterus was 2.80 cm × 2.00 cm × 2.70 cm, and bilateral ovaries were visible. And the re-examined adrenal unenhanced CT scanning of the patient showed that the adrenal hyperplasia did not aggravate (Figure 3). During the follow-up period, the blood pressure fluctuated between 120–130/78–85 mm Hg, the plasma potassium and ACTH levels returned to the normal range. No drug-related side effects were found. The levels of hormone and electrolyte were detailed in Table 2.

Discussion

The clinical manifestations of 17-OHD are characterized by hypogonadism, hypokalemia and hypertension. For understanding the mechanism of this disease, the classic biosynthesis pathway of adrenocortical and gonadal steroids is detailed in Figure 4.

The adrenal cortex produces three major classes of steroids: glucocorticoids, mineralocorticoids and sex steroids with substrate of cholesterol catalyzed by kinds of enzymes. The 17 α -hydroxylase/17, 20-lyase plays an essential role in the biosynthesis of both glucocorticoids and sex steroids, which is a multi-functional enzyme that mediates both 17 α -hydroxylase and 17, 20-lyase activities expressed in the adrenal glands and gonads.⁷ The 17 α -hydroxylase enzyme activity is required for the synthesis of cortisol, and 17, 20-lyase enzyme activity is essential for the production of sex steroids.⁸ Blockage of the

pathway catalyzed by 17 α -hydroxylase/17, 20-lyase leads to decreased cortisol, estradiol and testosterone productions, and results in overproductions of progesterone, 11-deoxycorticosterone (11-DOC) and corticosterone.

The hormonal investigations of the patient showed low estradiol and testosterone levels and high progesterone levels which accorded with the decrease in 17-OHD. The impairment of sex steroids production is associated with sexual immaturity. Low level of estradiol causes elevated levels of FSH and LH, indicating hypergonadotropic hypogonadism which leads to the presentations of amenorrhea and external genital dysplasia.

Low level of cortisol increases ACTH secretion as the result of negative feedback regulation by pituitary which can induce adrenal hyperplasia. Decreased cortisol level, elevated ACTH level and bilateral adrenal hyperplasia manifestation in CT scanning of this patient were consistent with the characteristics of 17-OHD. Although cortisol decreased, the patient had no manifestation of adrenocortical hypofunction such as fatigue, vomiting, diarrhea and pigmentation. Reviewing the literature, patients with 17-OHD rarely have manifestation of adrenocortical hypofunction or adrenal crisis due to the elevated corticosterone which has mild glucocorticoid activity which compensates for cortisol.⁹

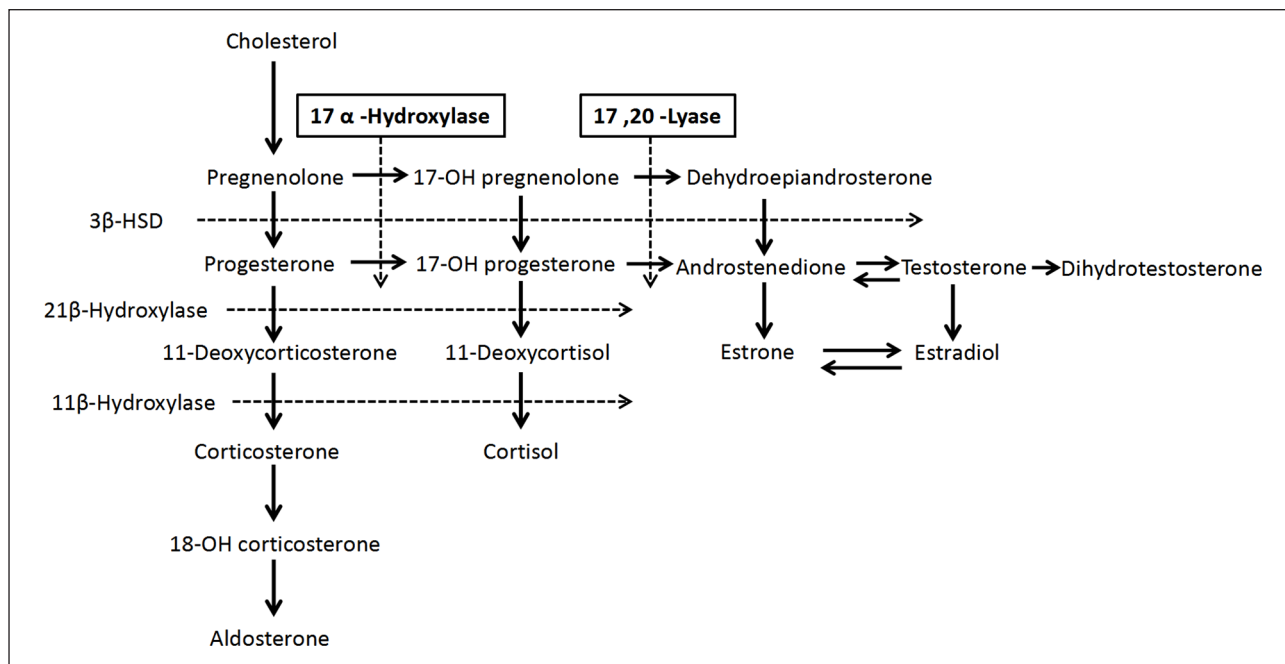
Other laboratory tests of this young female patient exhibited decreased renin activity, normal aldosterone level, with low plasma potassium level. In patients with 17-OHD, high levels of aldosterone precursors such as 11-DOC and corticosterone can suppress the Renin–Angiotensin–Aldosterone System (RAAS), consequently the renin activity and aldosterone level decrease; on the other hand, the excess aldosterone precursors can also stimulate the production of aldosterone. So, the actual aldosterone level may vary in different patients. In addition, high levels of aldosterone precursors have potent mineralocorticoid effects which induce sodium and fluid retention with loss of potassium, resulting in hypertension and hypokalemia.¹⁰ However, reviewing the literature, the incidence and severity of hypertension can be variable, even in cases with the same mutation. The environmental and other genetic factors may also influence the severity of hypertension.¹¹

Furthermore, estradiol plays an important role in bone metabolism. It can not only accelerate bone closure but also increase calcium deposition.¹² In 17-OHD patients with low estradiol levels, they can eventually manifest as tall and slender figures and have increased risk of osteoporosis. In this case, the lanky physique of patient was in accordance with the disease.

17-OHD is a congenital disease that cannot be cured and its therapy generally consists of glucocorticoid and sex steroids replacements. In patients with 17-OHD, appropriate glucocorticoid administration is the cornerstone of therapy in order to decrease ACTH and 11-DOC levels, which can suppress adrenal hyperplasia and normalize the blood pressure as well as plasma potassium level.¹³ Dexamethasone, a long-acting glucocorticoid agent is

Table 2. Comparison of hormone and plasma potassium levels before and after treatment.

Items	Baseline	2 months	3 months	6 months	18 months	36 months	Reference range
ACTH (pg/mL) 8:00 a.m.	74.4 ↑	67.4 ↑	19.97	21.45	17.78	18.31	7.2–63.3
Cortisol (μg/L) 8:00 a.m.	8.0 ↓	8.74 ↓	2.5 ↓	6.56 ↓	2.98 ↓	3.27 ↓	48.2–195
Potassium (mmol/L)	3.29 ↓	4.41	4.47	4.48	4.74	4.56	3.50–5.30

**Figure 4.** Simplified flow chart of adrenocortical and gonadal steroid hormone synthesis pathways.

generally used in therapy of 17-OHD. The initial dose of dexamethasone is 0.75–2 mg/day and the maintenance dose is 0.1–0.375 mg/day.¹⁴ Management is supposed to be individualized, and the dose should be adjusted according to the patient's blood pressure, plasma potassium and hormone levels. Some patients remained with hypertension even after using glucocorticoid, which may be related to complications such as atherosclerosis. Then, the mineralocorticoid receptor antagonist, spironolactone is preferred to be an effective optional agent in the treatment of refractory hypertension.

Sex steroids hormone supplementation therapy is recommended to be started early in adolescent female patients to allow the development of genitals and secondary sexual characteristics, and estrogen can also stimulate normal bone metabolism.¹⁵ The young female patients usually require cyclical estrogen and progestin therapy for menstruation;¹⁰ infertility is common and assisted reproduction can be performed if necessary.¹⁶

In this case, after the diagnosis of 17-OHD, the patient was administered with dexamethasone and the dosage was adjusted according to the patient's condition. Sequential therapy of estrogen and progesterone with femoston (complex packing estradiol tables/estradiol and dydrogesterone

tables) was also prescribed to the patient. Follow-up over 3 years, the girl's menstruation cycle gradually became regular with secondary sexual characteristics developed. Blood pressure, plasma potassium and ACTH levels also recovered to normal.

In summary, 17-OHD is a rare and challenging endocrine disease to diagnose. Although it is a congenital disease that cannot be cured, the patient state of illness can be improved by reasonable treatment.

Limitations

In view of the definite diagnosis by genetic examination, we did not perform bone age and bone densitometry determination for the girl.

Conclusion

For female patients with a 46, XX karyotype manifesting primary amenorrhea, hypogonadism with hypertension and hypokalemia, 17-OHD should be considered and *CYP17A1* genetic mutation testing is supposed to be performed to clarify the diagnosis and provide appropriate treatment in time.

Declarations

Ethics approval and consent to participate

The written informed consent to publish the case and images was obtained from patients' legal representatives. The exemption from ethics approval for this report was given by the Medical Ethics Council for Researchers in Zhongshan Hospital Xiamen University. The acceptance number of this statement was 2022-170.

Consent for publication

Not applicable.

Author contribution(s)

Li-Zhen Dai: Conceptualization; Formal analysis; Writing – original draft; Writing – review & editing.

Hong Ma: Conceptualization; Formal analysis; Methodology; Writing – review & editing.

Jian-Fang Ke: Conceptualization; Writing – original draft.

Chen-Shi Lin: Investigation.

Yanling Huang: Methodology.

Yuan Tian: Investigation.

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Competing interests

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Availability of data and materials

All data included in this manuscript can be accessed from the corresponding author upon request through the email address.

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