

A Case of 17 $\alpha$ -Hydroxylase Deficiency in  
Genetic Female with Normal Plasma  
Aldosterone Level and Rudimentary Uterus

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Abstract

Background: 17 $\alpha$ -hydroxylase deficiency is a rare cause of congenital adrenal hyperplasia and endocrine hypertension. Only around 124 cases were reported in literature.

Case: A 35-year-old Taiwanese female presented with severe hypertension (220/130 mmHg), absence of secondary sexual characteristics and primary amenorrhea.

Chromosome study revealed 46XX karyotype. The laboratory data revealed hypokalemia, suppressed plasma renin activity, low level of sex steroids with high gonadotropin, morning cortisol level: 1.8 $\mu$ g/dl and ACTH: 235 pg/ml. Her plasma level of aldosterone (sitting position) was at high level of normal (23.6 ng/dl). We made the diagnosis of 17 $\alpha$ -hydroxylase deficiency. Plasma aldosterone level was suppressed in most of the reported cases while normal or elevated levels were also described in a considerable number. Her uterus was found to be rudimentary, which was reported in only one genetic female case before.

Conclusion : We report a case of 17  $\alpha$  -hydroxylase deficiency in genetic female with normal level of plasma aldosterone and rudimentary uterus. ( J Intern Med Taiwan 2002;13: 141-146 )

Key Words : 17  $\alpha$  -hydroxylase deficiency, Aldosterone, Rudimentary uterus, Secondary hypertension, Hypogonadism

Introduction

Among syndromes of congenital adrenal hyperplasia, 11 $\beta$ -hydroxylase deficiency and 17 $\alpha$ -hydroxylase deficiency can cause hypertension secondary to mineralocorticoid excess other than aldosterone, and are rare. In addition, abnormalities of sexual differentiation are the features. Here we report a case of 17 $\alpha$ -hydroxylase deficiency in a genetic female Taiwanese.

## Case Report

A 35-year-old female visited our clinic of Cardiology in Aug. 2000. She complained of spasm of fingers and numbness of tongue after a long journey in hot weather. Severe hypertension was noted. In fact, she found herself to have hypertension as early as 19 years old. The measured blood pressure was always severely high. But she did not care because of minimal symptom. In addition, she never had menstruation. She was told that the uterus was absent by sonogram at other hospital.

The patient had a female appearance and voice. She was 159 cm in height and 62 kg in weight. Physical examinations showed: blood pressure 220/130 mmHg, regular heart beat, no murmur, no abdominal bruit, normal face appearance without abnormal hair. The skin appeared mildly hyperpigmented. In particular, there was no axillary and pubic hair, and the breast did not develop. The external genitalia was female type. Results of initial laboratory investigation demonstrated : FSH (follicle stimulating hormone): 102 mIU/ml, LH (luteinizing hormone): 39.1 mIU/ml, E2 (estradiol): 16.4 pg/ml (normal level: early follicular: 20-100, preovulatory: 100-350, luteal: 100-350, postmenopausal: 10-30 pg/ml), progesterone: 14.8 ng/ml (normal level: follicular phase: 0.3-0.8 ng/ml, luteal phase: 4-20 ng/ml), creatinine: 0.9 mg/dl, potassium: 2.2 meq/L. Chromosome study revealed 46XX karyotype. Subsequently, we found that plasma aldosterone concentration (in a sitting position) was at high level of normal (23.6 ng/dl, normal values: supine: 2.9-15.9, standing: 3.8-30.7) and PRA (plasma renin activity) in sitting position was low (0.2 ng/ml/hr, normal value: 1.31-3.95). Plasma levels of some steroids are shown in Figure 1, which also illustrates the steroidogenic pathway. The plasma level of ACTH (adrenocorticotrophic hormone) was high (235 pg/ml). These results revealed decreased level of down-stream hormones of P450c17 (cortisol, DHEA-S, testosterone, estradiol). The level of progesterone, which is one of the substrate for P450c17, was high. Although DOC (deoxycorticosterone) and other mineralocorticoid precursors could not be measured at our laboratory, we could make the diagnosis of "17 $\alpha$ -hydroxylase deficiency in a genetic female" based on the available steroid levels and clinical manifestations.

In addition, MRI of abdomen showed that the uterus was rudimentary ( Fig. 2 ). This is an unusual condition and will be discussed later. The adrenal glands did not show significant hyperplasia.

X-ray of hand showed unclosed growth plate and osteoporosis. Dual energy X-ray absorptiometry of the lumbar spine revealed osteoporosis ( T-score: -3.45 ).

We started treatment with dexamethasone 0.5 mg per day and ACTH level was suppressed to less than 10 pg/ml. But the blood pressure was still high and large doses

of antihypertensive agents were needed. At the end of 3rd month after treatment, daily use of spironolactone 150 mg, labetalol 800 mg and amlodipine 5 mg with dexamethasone 0.5 mg could only control blood pressure at 170/124 mmHg, with PRA: 5.3 ng/ml/hr and serum potassium 3.8 meq/L. The dose of amlodipine was increased to 10 mg per day and blood pressure was 140/90 mmHg at the end of 4th month. Thereafter, the blood pressure was controlled better. We noted that ACTH level was 65.5 pg/ml at the end of 6th month with dexamethasone 0.5 mg per day, so this dosage was maintained. The doses of antihypertensive agents could be tapered gradually 9 months later and could keep normal blood pressure. The dose of dexamethasone was decreased to 0.25 mg at bedtime and ACTH level could be suppressed to 27.1 pg/ml.

### Discussion

Congenital adrenal hyperplasia (CAH) refers to a group of syndromes caused by defects in any one of five enzymes involved in cortisol synthesis. These include four distinct forms of cytochrome P450: P450<sub>sc</sub>, P450<sub>C21</sub>, P450<sub>11 $\beta$</sub>  and P450<sub>17 $\alpha$</sub> , as well as 3 $\beta$ -hydroxysteroid dehydrogenase 1. The most common form of CAH, 21-hydroxylase deficiency, accounts for 90-95% of CAH. 11 $\beta$ -hydroxylase deficiency and 17 $\alpha$ -hydroxylase deficiency are rare causes of CAH and the only forms leading to hypertension. Since the first description by Biglieri et al. 3, at least 124 cases of 17 $\alpha$ -hydroxylase deficiency have been reported 1,4,5. Furthermore, 14 cases of 17,20-lyase deficiency with normal 17 $\alpha$ -hydroxylase activity have been reported 1. However, it has been proven that P450<sub>17 $\alpha$</sub>  can catalyze both the 17 $\alpha$ -hydroxylase and 17,20-lyase reactions 1. So, it is now considered that a defect on a single polypeptide, P450<sub>17 $\alpha$</sub> , is responsible for either or both 17 $\alpha$ -hydroxylase and 17,20-lyase deficiencies.

Most cases of 17 $\alpha$ -hydroxylase deficiency are diagnosed around the period from puberty into twenties, at which time sexual abnormalities are manifest 1.

Overproduction of mineralocorticoids (such as corticosterone, DOC, 18-hydroxy-DOC, 18-hydroxycorticosterone and 19-norDOC) results in hypertension with hypokalemia and low renin activity 6,7. The degree of hypertension seems to vary from mild to severe 1. Hypokalemia often leads to generalized muscle weakness. Level of aldosterone was suppressed in most cases in spite of the increased levels of corticosterone and DOC 1. The favored explanation is that significantly increased DOC and corticosterone causes expansion of blood volume, which in turn suppresses plasma renin and aldosterone secretion 8,9. On the other hand, a considerable number of cases of 17 $\alpha$ -hydroxylase deficiency have normal (16 cases) or elevated (18 cases) aldosterone levels 1,4. Most of them were reported from Japan 1. In this case, plasma aldosterone level was at high level of normal. The exact mechanism of such

differences in aldosterone level remains unclear.

$17\alpha$ -OH is expressed in both the adrenal glands and gonads. So, this type of CAH has diminished production of sex hormone, which results in failure of sexual differentiation with increased levels of both FSH and LH. Genetic females (46XX) with complete deficiency of  $17\alpha$ -hydroxylase have primary amenorrhea and no pubertal development leading to hypoplastic breasts and lack of axillary and pubic hair [1]. Patients of genetic male (46XY) have absence of masculinization. Normal Mullerian duct regression occurs because of normal production of Mullerian Inhibitory Factor from the testis [10]. Thus, such patients have a blind vagina, absence of Mullerian structure (Fallopian tubes and uterus, upper third of vagina), and female external genitalia. Sexual hair is absent in male patients, too [1]. It is an extraordinary finding that uterus was hypoplastic in this case. In previous literature, only one similar case was reported by De Gennes [11]. That genetic female was found to have bilateral streak gonads in addition to the rudimentary uterus and Fallopian tubes by laparoscopy. The cause is unknown.

$17\alpha$ -hydroxylase deficiency, unlike  $21$ -hydroxylase deficiency, is not linked to HLA. It also follows an autosomal recessive pattern [1].

The treatment of  $17\alpha$ -hydroxylase/ $17,20$ -lyase deficiency is similar to that of other types of congenital adrenal hyperplasia. Treatment with dexamethasone not only replaces the deficient glucocorticoid but also suppresses ACTH overproduction, resulting in remission of hypertension and potassium depletion by suppressing the overproduction of mineralocorticoid. A rise in plasma renin activity and aldosterone level during glucocorticoid therapy indicates that the therapeutic goal of eliminating ACTH-dependent mineralocorticoid excess has been achieved [6]. Care must be taken to prevent the complications of glucocorticoid excess. Small doses of mineralocorticoid antagonists can be added, allowing modest glucocorticoid doses [12]. In a few patients, residual hypertension may persist for months or years after glucocorticoid therapy is administered [13]. The addition of a calcium channel blocker is usually sufficient [12,13]. But in this patient, daily doses of up to 150 mg of spironolactone and 0.5 mg of dexamethasone resulted in rise of PRA to 5.3 ng/ml/hr, which was higher than normal and may indicate over-diuresis. But the blood pressure was still high and large doses of antihypertensive agents were needed. This could be explained by an increase in peripheral vascular resistance, which is typically present in long-standing mineralocorticoid excess [14]. And we learned that the dosage of spironolactone given was more than needed.

Affected 46XY patients require removal of intra-abdominal testis to prevent malignancy. Male pseudohermaphrodites with ambiguous genitalia needs sex assignment. Decision should be made with more consideration on the physiological

and anatomical character of the genitalia than genetic sex 1. Genetic female patients need combined estrogen / progestin cyclic therapy. Combined estrogen and glucocorticoid therapy rather than estrogen alone improves the development of breast in genetically female patients 15. Sexual hair growth can be stimulated by testosterone therapy 9.

Here, we report a rare case of  $17\alpha$ -hydroxylase deficiency in genetic female. The plasma level of aldosterone was normal rather than suppressed. It is unusual that the uterus was rudimentary. Only one similar case was reported before.  $17\alpha$ -hydroxylase deficiency should be considered if male pseudohermaphroditism or sexual infantilism in females is present with hypertension.

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一例  $17\alpha$ -羥化酉每缺乏的女性其血漿醛酮濃度  
正常且子宮發育不全

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## 摘 要

$17\alpha$ -羥化酉每缺乏是先天性腎上腺增生及內分泌高血壓中少見的原因，文獻中只有約 124 例。一位 35 歲臺灣人女性有嚴重高血壓 (220/130 mmHg)、缺乏第二性徵及原發性無月經。染色體分析顯示 46XX，實驗室數據：低血鉀、血漿腎素活性抑制、性類固醇低而性促素高、早晨血中皮質醇濃度：1.8  $\mu$ g/dl 而腎上腺皮促素濃度：235 pg/ml。其血漿中醛酮濃度正常但偏高。我們診斷為  $17\alpha$ -羥化酉每缺乏。之前大部分的病例血漿中醛酮濃度都受抑制，然而亦有為數不少者為正常或高。我們發現她的子宮發育不全，在這之前的女性(46XX)病患僅有一例類似的報告。

結論：我們報告了一例  $17\alpha$ -羥化酉每缺乏的女性，其血漿醛酮濃度正常且子宮發育不全。

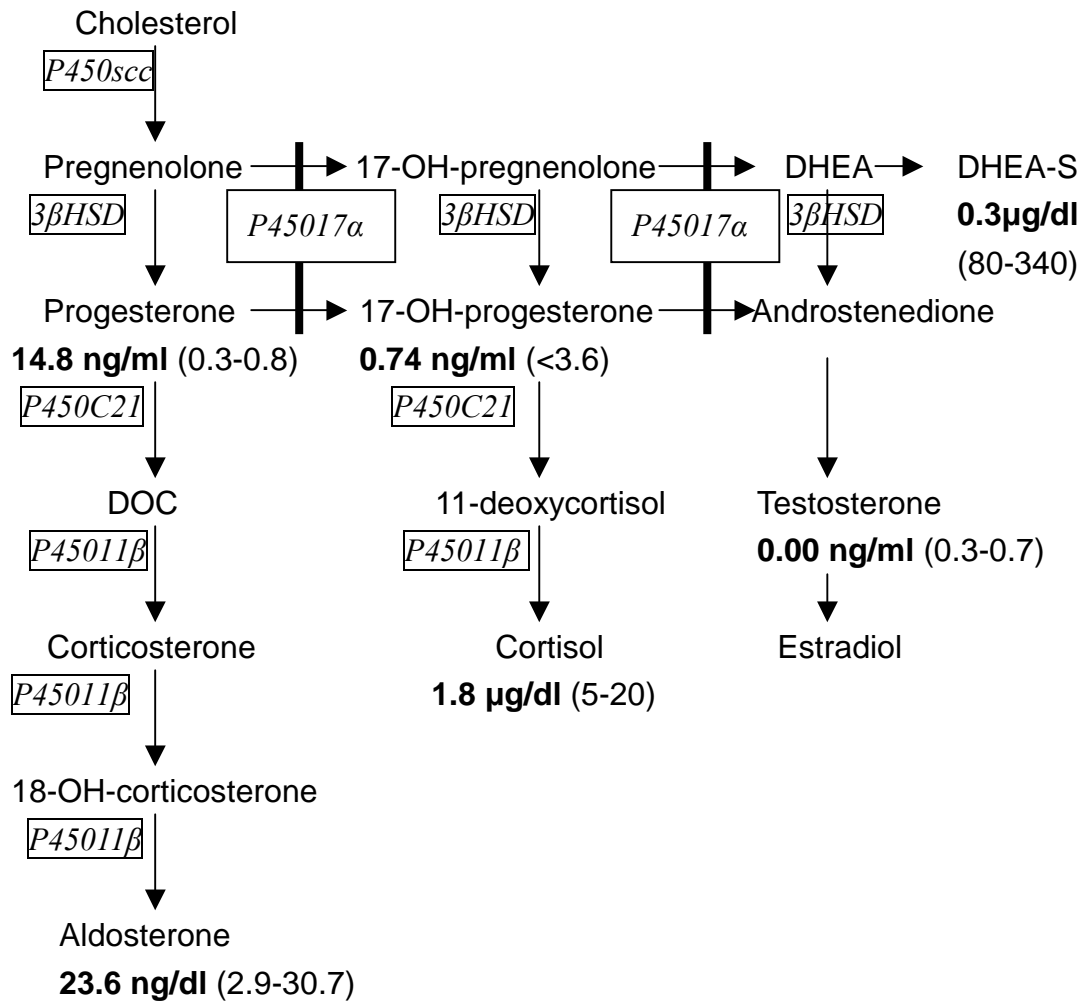


Fig.1. Steroidogenic pathways in the adrenal cortex and gonads. Plasma levels of some steroids and normal values (in parentheses) are shown. P450scc, cholesterol side chain cleavage cytochrome P450; P45017 $\alpha$ , 17 $\alpha$ -hydroxylase cytochrome P450; P450C21, 21-hydroxylase cytochrome P450; P45011 $\beta$ , 11 $\beta$ -hydroxylase cytochrome P450; 3 $\beta$ -HSD, 3 $\beta$ -hydroxysteroid dehydrogenase; DOC, deoxycorticosterone; DHEA, dehydroepiandrosterone; DHEA-S, DHEA-sulfate.



(A)



(B)

Fig.2. Sagittal view of magnetic resonance image of abdomen. A: vagina.  
B: rudimentary uterus (arrows).