A Case of 17α-Hydroxylase Deficiency with Retained Menstruation

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Abstract. A patient with 17α-hydroxylase deficiency (17OHD) who continued to menstruate is reported. A 24-year-old woman who presented with hypertension, hypokalemia and irregular menses had increased plasma ACTH and mineralocorticoids without any increase in glucocorticoids or sex steroids, and a bilateral adrenal enlargement on abdominal X-ray CT. ACTH stimulation test revealed hyperresponse of the metabolites of the mineralocorticoid pathway and blunted or absent response of those of the glucocorticoid and androgen pathway. Almost all of the abnormalities disappeared after dexamethasone administration. While 17OHD is usually known to accompany hypergonadotropic hypogonadism, the patient continued to menstruate, though irregularly. Although human chorionic gonadotropin administration failed to induce response, basal plasma levels of ovarian steroid (estradiol) and gonadotropins as well as response to LHRH stimulation test were all normal. Thus, the clinical and biochemical features of this case is compatible with the partial deficiency of both adrenals and ovaries, being less severe in the latter. A further analysis especially at molecular level is needed to elucidate the basis for the heterogeneity of this disorder.

Key words: Congenital adrenal hyperplasia, 17α-Hydroxylase deficiency, Irregular menstruation, Renin-angiotensin-aldosterone system.

SINCE THE first description by Biglieri et al. [1], 17α-hydroxylase deficiency (17OHD) has been understood as a disease causing hypertension, hypokalemic alkalosis and deficient secondary sexual characteristics in both genders with primary amenorrhea in the female and pseudohermaphroditism in the male as typical clinical features [2]. It is now clear that 17OHD is caused by a complete or partial defect of a single polypeptide, P450 17α, which catalyses both 17α-hydroxylation and 17, 20-lyase reaction in the synthetic pathway of steroids. Several genetic defects, such as a point mutation or a deletion of the coding DNA [3, 4], have been demonstrated.

Despite the biochemical evidence related to 17OHD, some genetically female patients are reported to have normal or irregular menstruation [5-9], suggesting a possible discrepancy in the enzyme activity and/or the gene expression between the adrenal and ovary in these cases. We report here another such rare case of 17OHD with typical features of adrenal 17OHD who continued to menstruate, although irregularly. Although the response of estrogen to human chorionic gonadotropin (hCG) was absent, normal plasma levels of estradiol, LH, FSH, as well as normal response of LH and FSH to LHRH, suggest that the ovarian enzyme activity was relatively preserved.

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Case Report

A 24-year-old female was referred to our hospital for examination of irregular menstruation, hypertension and increased plasma ACTH. The menstruation had been irregular since her menarche at 15 years of age; the cycle was about 2 or 3 months and the menstruation periods were sometimes over 10 days, and hypertension had been pointed out since the age of 20. She had not been examined further nor medicated.

Physical examination showed a well proportioned female appearance with a height of 161 cm and a weight of 46 kg. Blood pressure was 176/120 mmHg and a mild arteriosclerotic change was observed on her fundus. No pigmentation was observed in her skin or mucosa. Her breasts were poorly developed (Tanner 3), and there was no axillary or pubic hair. The external genitalia were feminine and a uterus was palpable. Laboratory examinations on admission are demonstrated in Table 1. Serum potassium was decreased to 2.8 meq/l and urinary excretion of potassium was increased (49.4 meq/day on regular diet), and blood gas analysis revealed mild metabolic alkalosis. Chromosomal analysis showed 46 XX. A marked bilateral adrenal enlargement was demonstrated on abdominal X-ray CT. Gynecological sonogram showed a small uterus and normal sized ovaries with a left ovarian cyst (3.7X5.1 cm).

Endocrinological examinations

In Fig. 1, the plasma and urine levels of steroid hormones and their metabolites are shown along the pathway of steroid hormone synthesis and metabolism. Plasma corticosterone, 11-deoxycorticosterone (DOC) and 11-deoxycortisol were measured by radioimmunoassay after purification through a Sephadex LH 20 column. In the mineralocorticoid pathway, the levels of plasma DOC and corticosterone were greatly increased but plasma aldosterone (measured with an SPAC-S Aldosterone RIA kit) was normal. The plasma levels of steroids in the glucocorticoid pathway were generally normal but urinary excretion of 17OHC was decreased in contrast to greatly increased excretion of pregnandiol, which is a metabolite of pregnenolone and progesterone. Plasma levels of adrenal androgens were clearly depressed, but the ovarian steroid, estradiol, was within the normal range. Plasma renin activity (PRA) was suppressed to 0.2 ng/ml/h (normal 0.3–2.9) and plasma ACTH was greatly increased to 270 pg/ml. Basal plasma levels of LH and FSH were 8.1 mIU/ml and 14.8 mIU/ml, respectively, and their responses to LHRH were also within the normal ranges (LH and FSH (mIU/ml) at 30 min: 21.1, 16.9; at 60 min: 20.0, 17.6; and at 90 min: 15.7, 14.6, respectively).

Under the diagnosis of 17OHD, the patient was treated with 1.0 mg/day of dexamethasone, and her blood pressure, serum potassium, plasma ACTH and DOC returned to the normal ranges (Fig. 2). Plasma aldosterone was suppressed transiently at 2 weeks after the therapy with a decrease in plasma ACTH, and increased gradually to low normal with a concomitant increase of PRA. Subsequently, the dose of dexamethasone was reduced to 0.5 mg/day. An ACTH stimulation test under

<table>
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<tr>
<th>Table 1. Laboratory data on admission</th>
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<tr>
<td><strong>Peripheral blood</strong></td>
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<tr>
<td>WBC 5400/µl</td>
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<tr>
<td>RBC 502×10⁶/µl</td>
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<tr>
<td>Hb 16.0g/dl</td>
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<tr>
<td>Ht 44.5%</td>
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<td>Plat 23.6×10⁹/µl</td>
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<td>Blood gas analysis</td>
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<td>pH 7.437</td>
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<td>PaO₂ 103.4 mmHg</td>
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<td>PaCO₂ 42.1 mmHg</td>
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<tr>
<td>HCO₃⁻ 28.1 mmol/L</td>
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<td>base excess 3.6 mmol/L</td>
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Fig. 1. The plasma and urine levels of steroid hormones and their metabolites. The data are shown along the pathway of steroid hormone metabolism. Black bars indicate the loci of defect presumed to be present in the adrenal of this patient. The normal values are shown in parentheses.

Fig. 2. Clinical course after administration of dexamethasone. Blood pressure, serum potassium, plasma ACTH and DOC were recovered to normal ranges after dexamethasone administration. Plasma aldosterone was suppressed transiently along with the decrease in ACTH and increased gradually subsequent to the increase in PRA. SBP, systolic blood pressure; DBP, diastolic blood pressure; ALD, aldosterone.
these conditions induced hyperresponse of DOC and corticosterone, as well as clear response of aldosterone, although 17\textit{O}H-progesterone and cortisol did not respond (Fig. 3). The marked bilateral adrenal enlargement disclosed by X-ray CT on admission was reduced in size at 4 months after the initiation of dexamethasone administration (Fig. 4). Plasma estrogen, LH and FSH levels remained within the normal ranges during the clinical course and LHRH stimulation test under dexamethasone administration revealed a normal response (data not shown). An hCG stimulation test (5000 U/day for 3 days) failed to increase estradiol (estradiol (pg/ml) before: 26.6; 3 days after: 15.2) under dexamethasone administration at 0.5 mg/day.

**Discussion**

From the typical complex of hypertension, hypokalemia and elevated ACTH and mineralocorticoid intermediates without any increase in glucocorticoids or sex steroids, the patient was diagnosed to have congenital adrenal hyperplasia due to 17\textit{O}HD. 17\textit{O}HD is caused by a defect in P450 17\textit{a} catalysing both 17\textit{a} hydroxylase and 17, 20 lyase reaction. Human P450 17\textit{a} gene was identified as a single copy mapped to chromosome 10 [10–12], and mutations of structural gene such as deletion [13], duplication [14–16], nonsense [17] and missense [18] mutation responsible to 17\textit{O}HD have been clarified. The DNA analysis of this case is in progress and the preliminary data have also
indicated the abnormality in the coding region of P450 17α gene (S. Kado, in preparation).

In this case, low levels of serum DHEA and androstenedione in the presence of normal levels of serum cortisol, 17OH-progesterone and 17OH-corticosterone may indicate dominant impairment in 17, 20 lyase. Although a few cases of isolated 17, 20 lyase deficiency have been reported [2], this case with a serum cortisol level inappropriately low as compared to marked increase in plasma ACTH is classified as a partial combined deficiency of 17α hydroxylase/17, 20 lyase. The results of the ACTH stimulation test were compatible with the diagnosis: hyperresponse of the metabolites of the mineralocorticoid pathway and blunted or absent response of the metabolites of the glucocorticoid pathway. Greatly enlarged bilateral adrenal glands were reduced to almost the normal size at 4 months after the initiation of dexamethasone administration, indicating the reversibility of morphological change in this disorder. Since the inheritance is generally recognized as autosomal recessive [2], we made a familial investigation, including blood pressure, serum electrolites, plasma ACTH and cortisol, and no abnormalities were observed in her parents or two brothers.

Although 17OHD is usually accompanied by hypergonadotropic hypogonadism, some genetically male patients have been reported to possess normal external genitalia with an almost normal level of testosterone [2]. Likewise, some genetically female patients have been proven to possess normal or irregular menstruation and almost normal levels of serum estradiol, LH and FSH [5-9], and blunted response of estradiol to hCG test [5], as demonstrated in the present case. In these cases, it is suggested that the deficiency of the ovarian enzyme was such an extent as to fail to cause estrogen response with the stimulus of 5000 U of hCG for 3 days. Estrogen level as low as 30-45 pg/ml has been reported to stimulate the endometrial proliferation [19] and fluctuation of progesterone level might lead to withdrawal bleeding observed in these cases.

In typical cases of this disorder, the aldosterone level has been shown to be suppressed in association with the increase in corticosterone and DOC, and to normalize along with the decrease in these steroids after dexamethasone therapy. These changes are presumed to occur as sodium retention due to the mineralocorticoid action of greatly increased DOC and corticosterone increases the circulating volume of and suppresses the renin-angiotensin-aldosterone system. However, a considerable number of cases with 17OHD have been reported to have normal or increased aldosterone with suppressed PRA, as was observed in the present case. Although Yanase et al. indicated that the normal or increased aldosterone levels might be derived from cross-reaction in the aldosterone radioimmunoassay with other increased steroids such as DOC or corticosterone [2], such cross-reactions are generally considered to be minimal in the assay employed [20]. It has been suggested that continuously increased ACTH might stimulate aldosterone synthesis through the enhancement of P450 corticosterone methylloxidase activity which has been observed especially in cases of a marked decrease in serum cortisol and an associated increase in plasma ACTH [21]. It is noteworthy that the plasma aldosterone level in the present case decreased transiently below normal after dexamethasone administration along with the decrease in the plasma ACTH level and returned to normal subsequent to the increase in PRA.

Although most cases of 17OHD would have typical features as indicated by Biglieri in the first reported case of the disease, the clinical features of the present case and others would imply heterogeneity in this disorder. Further study is needed to elucidate the mechanism regulating expression and enzyme activity as well as a detailed analysis of each patient correlating clinical profile and biochemical study of P450 17α gene.

References

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