Hiroshima J. Med. Sci.
Vol.39, No.4, 145~147, December, 1990
HIJM 39-24

A Case of Cogenital Adrenal Hyperplasia with Concomitant Abnormalities of Steroid 21- and 11β-hydroxylase Activities

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ABSTRACT

Abnormalities in the steroid 21-hydroxylase and 11β-hydroxylase activities were suspeted in a 25-year-old female with congenital adrenal hyperplasia (CAH). The patient showed signs of masculinization such as hirsutism, amenorrhea, and enlarged clitoris, but the blood pressure was normal. Adrenocorticotropic was increased to 200 pg/ml. Plasma levels of deoxycorticosterone and 11-deoxyortisol as well as progesterone and 17-hydroxyprogesterone were elevated. Plasma cortisol level was normal at 5.8 μg/dl. CT scan revealed enlargement of the bilataral adrenal glands.

This case suggests that enzyme abnormalities in CAH are more diverse than have been generally considered.

Key words: *Congenital adrenal hyperplasia, 21-hydroxylase, 11β-hydroxylase*

Congenital adrenal hyperplasia (CAH), is a rare disease. Only 488 cases in Japan have been reported during the 10 years since 1968[1]. The disease is often detected during the neonatal period by measurement of urinary steroid metabolites. Recently, more accurate diagnosis has become possible with the development of radioimmunoassay of circulating adrenocortical hormones. We report a rare case of adult CAH with concomitant abnormalities of both steroid 21-hydroxylase (21-OH-lase) and 11β-hydroxylase (11β-OH-lase) activities.

CASE REPORT

Patient

A 25-year-old female (height 155cm, body weight 52 kg) was admitted to the Second Department of Internal Medicine, Hiroshima University Hospital with primary complaints of amenorrhea and hirsutism. She was noted to have enlarged clitoris already at birth but had not since been treated. She become aware of hairiness of her legs, and denseness of pubic and axillary hair at about 14 years of age. Since she had not had menarche even at the age 25 years, she consulted the daepartment of gynecology of our hospital, where enlarged clitoris and male escutcheon were noted.

Physical examination disclosed a blood pressure of 100/60 mmHg, a masculine body build, pigmentation of the skin, and poor development of breasts. Her intelligence was normal.

Laboratory examinations

No anemia was observed with red blood cell count $439 \times 10^6/mm^3$, hemoglobin 13.6 g/dl, and hematocrit 41.8%. White blood cell count was $5,400/mm^3$ with no abnormalities in their subpopulations. Pulmonary and renal functions were normal. The electrolyte levels were normal with Na 142 mEq/liter, K 4.4 mEq/liter, C1 107 mEq/liter, and P 3.2 mg/dl.

Electrocardiograms and chest X-rays were also normal. The chromosome pattern was 44XX. Computed tomography revealed enlargement of the bilateral adrenal glands, and ^{131}I-adosterol scintigrams showed marked accumulation of the radionuclide in both adrenal glands.

Endocrine studies

Plasma steroid hormones and ACTH were measured by radioimmunoassay. As shown in Fig. 1, the plasma cortisol (F) level was in the low normal range, and ACTH was elevated. In the mineralcorticoid series, progesterone (P) was 4 times, and 11-deoxycorticosterone (DOC) about 36 times the normal levels. The aldosterone (Ald) concentration had increased to 280 pg/ml. The plasma renin activity (PRA) was also elevated at 4.3 (0.1—2.0 ng/ml/h).

In the glucocorticoid series, not only 17-OH-P but 11-deoxycortisol (S) had also increased to about 7 times the normal level. The blood levels of all the male steroid hormones were elevated.

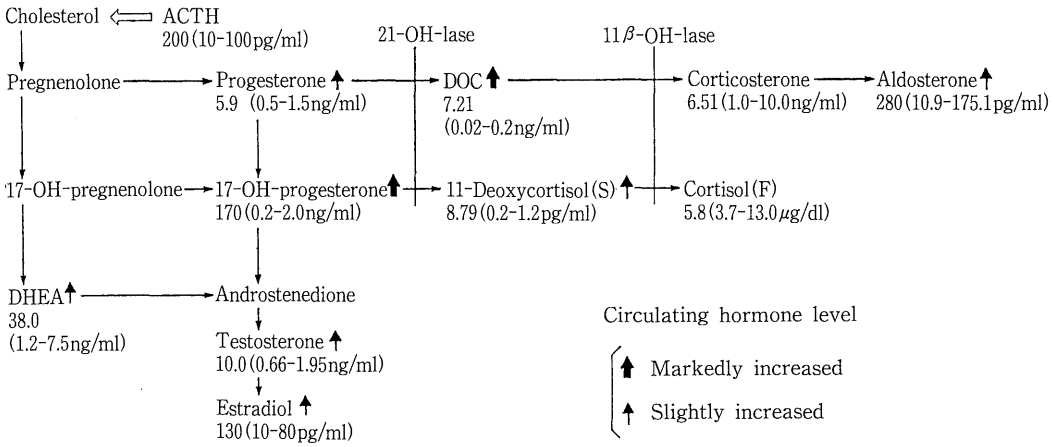

Fig.1. Plasma concentrations of corticosteroid and ACTH

Table 1. Urinary steroid analysis

17-OHCS	6.9 (1.5-4 mg/day)
17-KS	25.7 (4-8 mg/day)
Subfractions of 17KS	
Androsterone	6.73 (0.4-3.0 mg/day)
Etiocholanolone	4.75 (0.3-2.50)
Dehydroepidrosterone	3.37 (0.04-2.60)
11-keto-androsterone	0.38 (<0.07)
11-keto-eticholanolone	1.55 (0.03-0.50)
11-OH-androsterone	7.88 (0.22-1.60)
11-OH-etiocholanolone	3.44 (0.22-0.65)
Subfractions of 17-KGS	
11-deoxy-17-KGS	73.1 (0.3-2.7 mg/day)
11-oxy-17-KGS	19.4 (2.7-8.5)
Pregnanediol	1.98 (0.28-1.42 mg/day)
Pregnanetriol	20.68 (0.13-1.30)

Urinary steroid analysis (Table 1)

The urinary 17-ketosteroid (17-KS) concentration was markedly elevated in terms of the mean value in pooled urine on 3 consecuitive days, but the 17-hydroxycorticosteroid (17-OHS) level was only slightly increased. In the subfractions of 17-KS, not only 11-deoxy-17-KS, a metabolite of gonadal steroids, but also 11-oxy-17-KS, a product through action of 11β-OH-lase increased.

Of the subfractions of 17-ketogenic steroid (17-KGS), 11-deoxy-17-KGS had increased remarkably. Likewise, 11-oxy-17-KGS also showed an increase to twice the normal level, with 11-deoxy-17-KGS/11-oxy-17-KGS reaching a high of 3.76. Pregnanediol, a urinary metabolite of P, and pregnanetriol, a metabolite of 17-hydroxyprogesterone (17-OH-P) were both elevated, but the extent of the increase was greater in the latter.

Dexamethasone suppression test (Table 2)

After administration of dexamethasone at 2 mg/day, ACTH was normalized with reduction of F to less than the normal value. When 8 mg dexamethasone was administered, DOC, S, dehydroepiandrosterone, urinary 17-KS, and 17-OHCS were all reduced to the normal range or less.

DISSCUSSION

In this patient, the high levels of DOC and S suggested abnormal 11β-OH-lase activity, but the 17-OH-P level had also increased to 85 times the normal value, suggesting a concomitant abnormality of the 21-OH-lase activity. From the extent of the increase in each hormone (Fig. 1), abnormality of the 11β-OH-lase activity is considered to be more notable in the mineralcorticoid series in the zona glomerulosa and that of the 21-OH-lase activity in the glucocorticoid series in the zone fasciculata[5]. Although not shown in the results, the oral administration of 1,500 mg Metopirone induced an elevation of S from 8.79 to 19.7 pg/ml with an increase in ACTH (from 160 to 180 pg/ml), suggestig that the abnormality of the 21-OH-lase activity in the zona fasciculate was not complete.

S decreased below the normal range with a concomitant decrease in F when ACTH secretion was suppressed by the administration of dexamethasone. These changes indicate the presence of feedback mechanism, which barely maintained the F concetration at normal level by excessive secretion of ACTH, and the incompleteness of the abnormalities of 21-OH-lase and 11β-OH-lase activities.

In urinary steroid analysis, the mild increase in 17-OHCS and the marked increase in pregnanetriol likely reflected increases in the blood levels of S and 17-OH-P, respectively. However, of paticular interest were the increases in both 11-deoxy-17-KS and 11-oxy-17-KS such as 11-OH-androsterone and 11-OH-etiocholanolone among the subfractions of urinary 17-KS. These results suggest that the 11-oxy-17-KS fraction, except for F, is a product of metabolism of Δ^4-androstenedione by 11β-OH-lase, and that the increase in this fraction is evidence of the absence or mild abnormalities in the 11β-OH-lase activity in the zona reticularis.

Based upon the above results, the 11β-OH-lase

Table 2. Dexamethasone suppression test

	ACTH (10-100 pg/ml)	Cortisol (3.7-13.0 μg/ml)	DOC (0.02-0.2 ng/ml)	11-Deoxy-cortisol (0.2-1.2 pg/ml)	DHEA (1.2-7.5 ng/ml)	17-KS (4-8 mg/day)	17-OHCS (1.5-4 mg/day)
0 mg	200	5.8	7.21	8.8	38.0	18.7	5.2
0.5	150	8.5	—	—	—	—	—
1	130	5.7	—	—	—	—	—
2	19	3.6	—	—	—	12.2	2.9
4	29	1.1	—	—	—	—	—
8	25	1.0	0.07	0.2	0.6	3.4	2.7

and 21-OH-lase activities were considered to be abnormal in this patient, and the degree of abnormality varied between the zone glomerulasa and zona fasciculata for 21-OH-lase and among the zona glomerulosa, zona fasciculata, and zona reticularis for 11β-OH-lase.

There are several reports of complex enzyme abnormalities related to both 21-OH-lase and 11β-OH-lase[1,2,7]. However, these reports have been frequently based on urinary steroid analysis and rarely on direct measurement of circulating steroid levels.

There are several mechaisms to induce these hormonal conditions. The first possibility is incomplete deficiency of 21-OH-lase activity. Androgen that accumulates in the circulation in incomplete 21-OH-lase deficiency is reported to have an inhibitory effect on the 11β-OH-lase activity[8], leading to secondary development of the abnormal 11β-OH-lase activity. If this was the case, 21-OH-lase deficiency is considered to be always accompanied by abnormalities of the 11β-OH-lase activity. With regard to this point, Kolanowski et al demonstrated varying degrees of abnormal 11β-OH-lase activity in all 7 patients with CAH based on incomplete 21-OH-lase deficiency[4].

The second possibility is that the condition is based in the presence of genetically inherited abnormal 11β-OH-lase as reported by Maschler et al[6]. The abnormal mutaion of 11β-OH-lase induces change in the affinity for its normal substrate and shows a greater affinity to 17-OH-P than to S. As a result, S increases in the blood, because of a deficiency in its 11β-hydroxylation. On the other hand, 21-deoxy cortisol is produced from 17-OH-P by 11β-hydroxylation and accumulates in the circulation. Since 21-deoxy cortisol increases also in 21-OH-lase deficiency, it may produce a hormonal state resembling that induced by concurrent abnormalities of both 11β- and 21-OH-lase activities. Hurwitz et al supported this view through a study of 3 families with both 21- and 11β-OH-lases abnormality[3]. However, precise explanation of the mosaic enzyme abnormalities in this case is difficult, and clearly further studies are needed.

Blood pressure was normal in this patient despite the high DOC and Ald levels. The high level may have been a result of renin secretion due to greater anti-mineralcorticoid effect of P or 17-OH-P than the mineralcorticoid effect of DOC. The reason for absence of hypertension is unknown, but abnormal resposes of mineralcorticoid receptors may have been involved.

(Received July 6, 1990)
(Accepted October 22, 1990)

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