TWO CASES OF LOW-RENNIN HYPERTENSION THOUGHT TO BE DUE TO
EXCESSIVE SECRETION OF UNKNOWN MINERALOCORTICOID

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Two patients with low renin hypertension showing an increased urinary excretion with 17-KS, with normal level of plasma deoxycorticosterone and no signs of virilization were reported. Dexamethasone induced reduction in blood pressure and elevation of serum K, in spite of acceleration of the renin-angiotensin-aldosterone system. Thus, it has been inferred that the hypertension was not associated with adrenogenital syndrome but was due to excessive production of an unknown mineralocorticoid.

It has been clarified that low level renin activity is noted in an appreciable percentage of patients with essential hypertension. Recently, we encountered 2 patients with hypertension who showed an increased urinary excretion of 17-ketosteroids and low renin activity, which did not respond to various renin stimulating tests. These patients disclosed normal plasma deoxycorticosterone levels and no abnormal findings on both adrenal glands by using pneumo-retroperitoneum and adrenal scintigram. Upon administration of dexamethasone, blood pressure was reduced and serum K level was elevated. Therefore, it has been inferred that the low renin hypertension was not associated with adrenogenital syndrome but was due to excessive secretion of an unknown steroid exerting abnormalities on water and electrolyte metabolism by an ACTH-dependent action.

CASE REPORT

Case 1

A 28 year-old man was admitted to our hospital on March 31, 1977 because of headache and hypertension for the past 8 years. His family history showed no hypertension, and his past medical history was not significant. He married at 20 and had 2 children. At the age of 20, hypertension appeared for the first time, but he was not medicated with an antihypertensive agent because he had had no complaints. At the age of 28, he complained of headaches and high blood pressure. One month of antihypertensive therapy was not enough to improve his hypertension.

On examination, his height was 161.0 cm and weight 53.0 kg. His blood pressure was 190/116 mmHg, and his pulse rate was 74/min and regular. No pigmentation was found on either the skin or mucous membrane. There were no pathological findings in the neck or chest. The liver, kidney and spleen were not enlarged, and there were no mass or bruit in the abdomen. There were no sexual abnormality and abnormal neurological findings. Chvostek's and Trousseau's phenomena

Key Words:
Low-renin hypertension
17-ketosteroids
Mineralocorticoid
ACTH-dependent
Dexamethasone

(Received March 12, 1981; accepted September 1, 1981)
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Japanese Circulation Journal Vol. 46, February 1982
were both negative. No edema was found.

Laboratory studies disclosed the following: the erythrocyte sedimentation rate was 7 mm (1 hour), serum Na 142 mEq/L, serum K 3.9 mEq/L, serum Cl 109 mEq/L, serum Ca 4.6 mEq/L and serum P 3.0 mEq/L. The arterial acid base balance was within normal limits. The creatinine clearance was 93.0 ml/min, PSP excretion rate (30 min) 58.9% and Fishberg's concentration test 1.027 in maximal specific gravity of urine. 100g-OGTT was normal. The basal metabolic rate (BMR) was +11%, protein binding iodine (PBI) 5.3 μg/dl, and triosorb test 32.7%. The urinary vanilmandelic acid (VMA) excretion was normal, and phentolamine test was negative. Excretion of urinary adrenaline was 3.9 μg/day and noradrenaline 3.6 μg/day. Urinary 17-hydroxycorticosteroids (17-OHCS) was 9.5 mg/day (normal: 3.6–10.5 mg/day), however urinary 17-ketosteroids (17-KS) was remarkably high at 29.8 mg/day (normal: 3.7–16.0 mg/day). Potassium clearance on injecting sodium thiosulfate (K-clearance) was relatively high at 29.4 ml/min. Plasma renin activity (PRA) and plasma aldosterone level (PAC) were both suppressed to 0 ng/ml/h and 3.1 ng/dl, respectively. Plasma corticosterone level (B) was 0.33 μg/dl, plasma dehydroepiandrosterone level (DHEA) 0.14 μg/dl and plasma 18-hydroxy-11-deoxycorticosterone level (18-OH-DOC) 4.1 ng/dl, and these steroids were found within low normal limits. Plasma deoxycorticosterone level (DOC) was 11.6 ng/dl, plasma cortisol level (F) 7.3 μg/dl and plasma ACTH level (ACTH) 66 pg/ml, and these levels were within normal limits.

The roentgenogram of the chest and abdomen showed no abnormalities. Electrocardiographic findings were normal. Grade IIa on the Keith-Wagener hypertensive changes were noted in the optic fundi. The urine contained no protein and glucose. Intravenous pyelogram (IVP) and angiogram showed no abnormalities. Pneumoretroperitoneum (PRP) and adrenal scintigram showed no abnormal findings on both adrenal glands.

Special Endocrinological Examination

(1) Under the condition of 155 mEq/day sodium intake, fasting PRA was 0 ng/ml/h at 8 a.m. after recumbent state for 11 hours, and was suppressed to 0.1 ng/ml/h after quiet ambulation for 2 hours together with having administered 1 mg/kg furosemide. PRA rose to 4.5 ng/ml/h after administration of 150 mg/day of spironol-
actone and 75 mg/day of hydrochlorothiazide on 30 mEq/day of sodium intake for 3 days. PRA were suppressed to 0 ng/ml/h 6 hours after 0.5 mg ACTH-Z or after 3.0 g/day metopirone for 3 days, but it was slightly elevated from 0 ng/ml/h to 0.7 ng/ml/h after administration of 2 mg dexamethasone for 2 days. PAC were within low normal limits from 3.0 ng/dl to 4.2 ng/dl in the recumbent state at 8 a.m., and was slightly increased from 1.8 ng/dl to 4.6 ng/dl after quiet ambulation for 2 hours together with administered 1 mg/kg furosemide, and showed no significant change after an administration of ACTH-Z or metopirone, but elevated to 6.2 ng/dl after dexamethasone.

(2) ACTH Test: Figure 1 illustrates the change in blood pressure, serum electrolytes, 17-OHCS, 17-KS and urinary volume after an administration of 1 mg/day of ACTH-Z for 3 days. Systolic blood pressure elevated to 220 mmHg and diastolic to 130 mmHg. Serum K decreased from 3.5 mEq/L to 2.9 mEq/L. 17-OHCS increased remarkably from 10.0 mg/day to 58.2 mg/day and 17-KS from 28.1 mg/day to 42.9 mg/day, respectively. Urinary volume decreased from 2050 ml/day to 850 ml/day. B, DHEA and PAC showed a significant elevation, respectively.

(3) Metopirone Test (Fig. 2): Systolic and diastolic blood pressure elevated to 220 mmHg and 130 mmHg after 3-day administration of 3.0 g/day of metopirone. Serum K decreased from 3.6 mEq/L to 3.1 mEq/L. 17-OHCS increased from 14.0 mg/day to 55.1 mg/day and 17-KS from 27.0 mg/day to 45.8 mg/day, respectively. Urinary volume decreased from 1900 ml/day to 1100 ml/day. PAC, B and F were all decreased. On the contrary, DOC was remarkably elevated from 4.2 ng/dl to 67.8 ng/dl. DHEA was unchanged.

(4) Dexamethasone Test (Fig. 3): Dexamethasone was administered first 2 mg/day for 2 days, next 8 mg/day for 2 days, then 16 mg/day for 2 days, and finally 2 mg/day for 24 days. Systolic blood pressure decreased from 218 mmHg to 142 mmHg and diastolic from 126 mmHg to 96 mmHg after one month's administration of dexamethasone. Serum K increased from 3.7 mEq/L to 4.3 mEq/L after 20 days of this maneuver. 17-OHCS decreased from 10.7
mg/day to 7.1 mg/day and 17-KS 27.9 mg/day to 11.3 mg/day with 16 mg/day of dexamethasone. Moreover, 17-OHCS decreased to 5.0 mg/day and 17-KS to 7.1 mg/day after one month of dexamethasone, and urinary volume increased from 880 – 1950 ml/day to 2200 – 2550 ml/day, PRA rose from 0 ng/ml/h to 5.6 ng/ml/h and PAC from 3.1 ng/dl to 14.1 ng/dl, respectively. On the other hand, both F and DHEA decreased. Circulating plasma volume decreased from 52.3 ml/kg to 47.6 ml/kg. After one month’s administration of 150 mg/day spironolactone, systolic and diastolic blood pressures did not decreased and serum K was slightly elevated from 3.6 mEq/L to 4.0 mEq/L. PRA, PAC, F, DHEA, DOC, 17-OHCS, 17-KS and urinary volume were unchanged by this medication.

Case 2
A 31-year-old unmarried woman was admitted to our hospital on May 8, 1977, because of headache and hypertension. Her parents had hypertension from the fifth decade, but her 6 brothers were healthy and had normal blood pressure. Appendectomy and tonsillectomy were done at the age of 20, and at that time, hypertension (200/120 mmHg) was pointed out for the first time. Antihypertensive therapy did not improved her high blood pressure. One year later, she received anti-hypertensive medication for 3 months, but it did not improve her hypertension. Moreover, at the age of 31, she again had high blood pressure and suffered from persistent headache.

On examination, her height was 155.0 cm, and weight 70.0 kg. Her blood pressure was 230/130 mmHg, pulse rate 76/min and regular. Neither moonface nor central obesity were found. There were no pigmentation, hypertrichosis and striae cutis on her skin and no pathological findings in the neck or chest. The liver, kidney and spleen were not enlarged, and there were no mass or bruist in the abdomen. The neurological findings were normal, and there were no sexual abnormalities. Menstruation was irregular. Chvostek’s and Trousseau’s phenomena were both negative. No edema was found.

Laboratory studies disclosed the following: the erythrocyte sedimentation rate was 7 mm (1 hour), serum Na 136 mEq/L, serum K 4.3 mEq/L, serum Cl 103 mEq/L, serum Ca 4.6 mEq
### Table 1 Fractions of Urinary 17-KS in Case 2

<table>
<thead>
<tr>
<th>Fraction of 17-KS</th>
<th>mg/day</th>
<th>Normal limit (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>androsterone</td>
<td>5.76</td>
<td>0.08 – 2.6</td>
</tr>
<tr>
<td>etiocholanolone</td>
<td>3.78</td>
<td>0.04 – 1.1</td>
</tr>
<tr>
<td>DHEA</td>
<td>0.18</td>
<td>0.02 – 1.0</td>
</tr>
<tr>
<td>11-OH-androsterone</td>
<td>0.36</td>
<td>0.05</td>
</tr>
<tr>
<td>11-OH-etiocholanolone</td>
<td>(−)</td>
<td>0.04</td>
</tr>
<tr>
<td>11-oxo-androsterone</td>
<td>(±)</td>
<td>0.01 – 1.0</td>
</tr>
<tr>
<td>11-oxo-etiocholanolone</td>
<td>0.72</td>
<td>0.2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>10.80</strong></td>
<td><strong>0.40 – 5.7</strong></td>
</tr>
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/L and serum P 3.7 mEq/L. The arterial acid base balance was within normal limits. The creatinine clearance was 92.3 ml/min. PSP excretion rate (30 min) 61.5%, and Fishberg’s concentration test 1.037 in maximal specific gravity of urine. 100g-OGTT was normal. BMR was +11%, PBI 5.3 µg/dl, and Tiosorb test 24.2%. The VMA excretion was normal and phenolamine test was negative. The urinary adrenaline was 5.0 µg/day and noradrenaline 3.4 µg/day. 17-OHCS was 7.1 mg/day (normal: 2.4 – 8.4 mg/day), however, 17-KS was remarkably high at 26.1 mg/day (normal: 3.4 – 9.0 mg/day). K clearance was relatively high at 27.9 ml/min. PRA and PAC were both low at 0.2 ng/ml/h and 1.6 ng/dl. DOC and DHEA were normal at 9.6 ng/dl and 0.21 µg/dl, respectively. F and B were both low at 4.6 µg/dl and 0.31 µg/dl. ACTH was 66 pg/ml. The roentgenogram of the chest and abdomen showed no abnormalities. The electrocardiographic finding was normal. Grade IIa on the Keith-Wagener hypertensive changes were noted in the optic fundi. The urine contained no protein and glucose. IVP and angiogram showed no abnormalities. PRP and adrenal scintigram showed no abnormal findings on both adrenal glands.

**Special Endocrinological Examination**

(1) Under the condition of 155 mEq/day sodium intake, fasting PRA was 0.2 ng/ml/h at 8 a.m. after recumbent state for 11 hours, and slightly rose to 1.4 ng/ml/h after quiet ambulation for 2 hours along with the administration of 1 mg/kg of furosemide. PAC increased from 1.8 ng/dl to 4.6 ng/dl. PRA and PAC rose to 1.7 ng/ml/h and 9.6 ng/dl after administration of 150 mg/day of spironolactone and 75 mg/day of hydrochlorothiazide on 30 mEq/day of sodium intake for 3 days.

(2) ACTH-Z Test (Fig. 4): Systolic blood pressure elevated from 182 mmHg to 222 mmHg and diastolic blood pressure from 128 mmHg to 136 mmHg. Serum K decreased from 4.3 mEq/L to 3.9 mEq/L, but serum Na unchanged. 17-OHCS increased significantly from 4.2 mg/day to 54.1 mg/day and 17-KS from 23.1 mg/day to 74.4 mg/day, respectively. PAC, F, B and DHEA showed a significant elevation, but PRA was unchanged. Urinary volume decreased from 1300 ml/day to 750 ml/day.

(3) Metopirone Test (Fig. 5): Systolic blood pressure elevated from 184 mmHg to 210 mmHg and diastolic blood pressure from 116 mmHg to 144 mmHg. Serum K decreased from 4.3 mEq/L to 3.7 mEq/L, but serum Na unchanged. 17-OHCS increased significantly from 8.4 mg/day to 48.6 mg/day and 17-KS from 19.6 mg/day to 52.7 mg/day. PAC, F, B and DHEA were all decreased. DOC was remarkably elevated from 8.1 ng/dl to 58.4 ng/dl. PRA decreased from 0.3 ng/ml/h to 0 ng/ml/h. Urinary volume decreased from 1840 ml/day to 680 ml/day.

(4) Dexamethasone Test (Fig. 6): Dexamethasone was administered first 2 mg/day for 2 days, next 8 mg/day for 2 days, 2 mg/day for 2 weeks, then 1 mg/day for 1 week and finally 0.5 mg for 1 week. Systolic blood pressure decreased from 232 mmHg to 164 mmHg and diastolic blood pressure from 140 mmHg to 92 mmHg after 20 days. At this time, serum K rose from 4.0 – 4.1 mEq/L to 5.0 mEq/L, but serum Na decreased from 140 – 141 mEq/L to 135 – 138 mEq/L. 17-OHCS decreased from 9.3 mg/day to 2.0 mg/day and 17-KS from 20.1 mg/day to 3.1 mg/day after 8 mg/day with dexamethasone, respectively. Both PRA and PAC rose from 0.4 ng/ml/h to 1.6 ng/ml/h and from 3.1 ng/dl to 7.4 ng/dl after 20 days with dexamethasone, and urinary volume increased.
from 770 – 1150 ml/day to 980 – 2850 ml/day. Circulating plasma volume decreased from 53.1 ml/kg to 46.5 ml/kg after one month of this medication.

After one and half month’s administration with 150 mg/day with spironolactone, systolic and diastolic blood pressure did not change and serum K was slightly elevated from 3.8 mEq/L to 4.4 mEq/L. PRA, PAC, F, DHEA, DOC, 17-OHCS, 17-KS and urinary volume were unchanged.

(5) Fractions of Urinary 17-KS in Case 2 (Table I): Excretion of androsterone, etiocholanolone, 11-OH-androsterone and 11-oxo-etiocholanolone were remarkably high and 11-OH-etiocholanolone and 11-oxo-androsterone were relatively low. Excretion of DHEA was normal.

DISCUSSION

In these 2 cases of hypertension with low renin activity, plasma aldosterone level was low in spite of relatively increased K-clearance. Consequently, the etiology was thought to be an excessive secretion of mineralocorticoid other than aldosterone. However, plasma DOC, B, F and DHEA levels were normal in both cases and moreover plasma 18-OH-DOC level was also normal in Case 1. Therefore, it seems that the other unknown mineralocorticoid was secreted to an excessive degree. On the other hand, urinary excretion of 17-KS increased remarkably in both cases. Administration of ACTH and metopiron caused an elevation in blood pressure, a decrease of serum K level and a decrease in urine volume. Furthermore, administration of dexamethasone brought about a reduction in blood pressure, together with an elevation in serum K and an increase in urine volume. These facts suggest that the hypertension was not caused by adrenal tumor but by adrenal hyperplasia with excessive production of steroid included in the 17-KS fraction, the ACTH-dependent steroid exerting abnormalities of water and electrolyte metabolism. Nevertheless, it was presumed from the normal ACTH level that some stimulation mechanism other than ACTH was accelerated.

Typical hypertension showing an increase in urinary excretion of 17-KS is an adenogenital syndrome due to 11β-hydroxylase deficiency, of which hypertension results from excessive secretion of DOC. In our cases, however, plasma DOC, B, F and DHEA levels were all within normal limits and urinary 17-OHCS excretion was also normal. Furthermore, neither sexual prematurity of the male patient nor virilization of the woman was noted. These facts enable us to deny the presence of deficiency in 11β-hydroxylase.

Among the steroids included in the 17-KS fraction, 16β-hydroxy-dehydroepiandrosterone (16β-OH-DHEA) is known to act on water and electrolyte metabolism. It is said that the secretion of this steroid is stimulated by ACTH and suppressed by dexamethasone. The plasma level of 16β-OH-DHEA in patients with toxemia of pregnancy is relatively higher than that of normal pregnancy. Recently, Sennett has reported that when urine sample were analyzed by chromatography an unknown mineralocorticoid existed in the same position as 16β-OH-DHEA. The plasma level of 16β-OH-DHEA was not determined in our cases, but the ACTH-dependent steroid exerts abnormal mechanism of water and electrolyte metabolism except for serum K in our 2 patients. Further investigation is required to determine what kind of unknown mineralocorticoid is excessively secreted in these cases.

REFERENCES


Japanese Circulation Journal Vol. 46, February 1982