NOTE

Plasma Aldosterone Level in a Female Case of Pseudohyperaldosteronism (Liddle's Syndrome)

KAZUHISA TAKEUCHI, KEISHI ABE*, MAKITO SATO, MINORU YASUJIMA, KEN OMATA, OSAMU MURAKAMI AND KAORU YOSHINAGA

Second Department of Internal Medicine, and *Department of Clinical Biology and Hormonal Regulation, Tohoku University, School of Medicine, 1-1 Seiryo-cho, Sendai 980, Japan

Abstract

A 22-yr-old female suffering from hypertension, hypokalemic alkalosis and suppressed plasma renin activity was studied. The plasma aldosterone concentration (PAC) ranged between subnormal and normal levels while the other adrenal mineralocorticoids were normal. Examinations through computed tomography and ultrasonography showed no abnormal findings. For differential diagnosis, dexamethasone, spironolactone and triamterene were administered. Triamterene alone corrected the abnormalities in this case, and the therapeutic effect was further enhanced by sodium restriction. Therefore, the present case is strongly suggested to be one of Liddle's syndrome, which is characterized by a primary defect in renal tubular sodium handling and can be corrected with triamterene. However, the patient in our study is different from the first reported case in which aldosterone secretion was estimated to be low. Analysis of the changes in PAC has shown that PAC is parallel with the level of plasma progesterone in accordance with the rhythm of the menstrual cycle and, in the follicular phase, PAC is rather low. It is concluded that the patient was suffering from Liddle's syndrome, and it is assumed that PAC is not always subnormal and, as same as in normal females, PAC may change in accordance with the rhythm of the menstrual cycle in a female case of Liddle's syndrome.

Pseudohyperaldosteronism is characterized by hypertension, hypokalemia and hyporeninemia, suggesting a diagnosis of primary aldosteronism. However, pseudohyperaldosteronism is not associated with either aldosterone or other endogenous mineralocorticoid excess (Biglieri, 1981; Sebastian et al., 1982). This state is brought about by several factors, including the administration of synthetic mineralocorticoids, and the ingestion of substances causing mineralocorticoid-like activity, as well as Liddle's syndrome. Liddle's syndrome is markedly different from the other conditions, because its symptoms are not
due to the renal action of mineralocorticoid but to a primary defect in renal sodium-potassium handling in renal distal tubules. The present case was considered to be a case of Liddle's syndrome, although the plasma aldosterone concentration (PAC) was not consistently subnormal. We evaluated the change in PAC in relation to the menstrual cycle and demonstrated a close relationship between them.

Case Report

A 22-yr-old female suffering from hypertension and hypokalemia was admitted to our department. She had been complaining of recurrent headaches and general muscular weakness for several years. An aunt (on her mother's side of the family) had died suddenly of an unknown etiology at the age of 35, and an uncle, on the same side, had died of kidney disease with edema at age 5.

Eight years before admission to our department, a school examination had disclosed that the patient was suffering from high blood pressure (180/110 mmHg). At that time, she was referred to the department of pediatrics of a general hospital. Tests showed that she had hypertension (blood pressure ranged between 190/130 and 170/100 mmHg), hypokalemia (serum potassium 2.8 mEq/L). Plasma renin activity (PRA) was low and the plasma aldosterone concentration (PAC) was in the high-normal range. A tentative diagnosis of primary aldosteronism was made, and 75 mg/day of spironolactone was administered. However, her headaches persisted and the other abnormal findings remained. After a few months, she refused to take the medication and terminated her hospital visits. A few months before admission to our department, she visited a physician due to a common cold. At that time, her blood pressure was found to be 180/100 mmHg and hypokalemia was again confirmed. In spite of the administration of a calcium antagonist, nifedipine 60 mg/day, and a potassium supplement of K⁺ 24 mEq/day, the abnormalities persisted and she was referred to our department for a thorough examination. It was determined that she had no history of excessive licorice ingestion, steroid hormone abuse or use of contraceptives.

A physical examination showed the patient to be a phenotypically normal female, 160 cm in height, weighing 50 kg, and having no abnormal skin pigmentation. She had normal secondary sexual characteristics and a regular menstrual cycle. Her menarche had occurred at age 12. Blood pressure ranged between 200/120 and 150/100 mmHg. Her chest X-ray was normal. However, electrocardiography revealed left ventricular hypertrophy, and fundoscopic examination revealed mild arteriolar thickening. Her serum sodium level was found to be 144 mEq/L and serum potassium 2.6 mEq/L (normal value; 3.4-4.2 mEq/L). Arterial blood gas analysis showed the following: PH, 7.47; standard bicarbonate, 30.8 mmol/L; pCO₂, 44.1 mmHg; pO₂, 88.0 mmHg; and base excess, +7.2 mEq/L. Blood urea nitrogen was found to be 12 and creatinine 1.1 mg/dl. A complete blood count, urinalysis, and measurements of serum concentrations of calcium, phosphorus, magnesium, albumin, globulin, glucose, uric acid, lactic dehydrogenase, glutamic-oxaloacetic transaminase and cholesterol were done. All were found to be within normal limits. Creatinine clearance was 73 ml/min and para-amino hippuric acid clearance 468 ml/min. The findings of venous pyelography were normal. Urinary catecholamines, 17-ketosteroids (17-KS) and 17-hydroxycorticosteroids (17-OHCS) were normal. PRA was undetectable (<2.5 ng/ml/6 hr; normal value: 5–30 ng/ml/6 hr), PAC was low within normal limits (2.4 ng/dl; normal value: 2–12 ng/dl). Adrenal scintigram with ¹³¹I-adosterol (6β-
iodomethyl-19-nor-cholest-5(10)-en-3β-ol, Daiichi Radioisotopes Laboratories Ltd., Tokyo) showed diffuse accumulation of $^{131}$I on bilateral adrenals and the uptake of $^{131}$I almost disappeared with the administration of dexamethasone. Examinations through echosonography and computed tomography showed normal findings in the abdomen.

These data were not consistent with the usual findings in primary aldosteronism. Therefore, further diagnostic examinations, including administration of dexamethasone, spironolactone and triamterene were carried out.

Methods

All examinations were carried out during 4 months' hospitalization. The patient received a salt restricted diet containing less than 5g NaCl (Na+ 85mEq)/day for a full month; for the remainder of her stay, she received a regular diet containing 12g NaCl (Na+ 200mEq)/day and K+ 80mEq/day. During hospitalization, 60 mg nifidipine and 50 mg/day atenolol had to be administered to prevent a hypertensive crisis, because high blood pressure and complaints of headache persisted following admission. In a furosemide test, blood samples were collected to measure PRA and PAC after the patient had stood upright for one and two hours, respectively, following the intravenous injection of furosemide 60mg. A rapid ACTH test was performed by intravenous injection of 250 μg of α1-24 ACTH (Cortrosyn: Daiichi Co., Tokyo), as well as a dexamethasone suppression test by means of the oral administration of either 1 or 8mg of dexamethasone. Four studies on metabolic balance were carried out to examine changes in blood pressure and renal electrolyte excretion in response to: 1) inhibition of adrenal biosynthesis by dexamethasone 2mg/day for 2 weeks; 2) administration of triamterene 100 and 200mg/day for 3 weeks; 3) administration of triamterene 200mg/day and salt restriction (Na+ 85mEq/day) and, 4) blockade of mineralocorticoid hormone receptors using 150 and 300mg/day spironolactone for 2 weeks. During these periods dietary potassium was kept at around 80mEq/day.

Blood pressure was measured with a standard sphygmomanometer at 0600 h in recumbency every day. Plasma ACTH, aldosterone, cortisol, progesterone, corticosterone, deoxycorticosterone (DOC) and 18-hydroxy-deoxycorticosterone (18-OH-DOC) were measured by radioimmunoassay using commercially available kits (Dinabot Co., Tokyo). PRA was measured by radioimmunoassay of angiotensin I as previously reported (Abe et al., 1973). 19-hydroxypregnenolone was measured by Dr. Sekihara of Tokyo University.

Results

Baseline Condition (Fig. 1)

High blood pressure persisted during this period. Serum potassium was 2.6 mEq/L. Urinary excretion of potassium was above 50mEq/day, suggesting the kidney's inability to conserve potassium. PRA was undetectable during the furosemide test. PAC was normal (5.8 ng/dl) and constant during the furosemide test. Corticosterone, DOC and 18-OH-DOC were all within normal limits. Urinary 17-OHCS and 17-KS excretions were normal. The basal plasma cortisol level (8.0 μg/dl) was normal (normal value: 5-16 μg/dl) and showed a normal response to the rapid ACTH test, because the basal plasma cortisol level was increased to 17.3, 17.4 and 24.5 μg/dl at 30, 60 or 90 min after the injection of ACTH, respectively. In the dexamethasone (Dx.) suppression test, the basal plasma cortisol (5.4 μg/dl) was decreased to an undetectable level either by Dx. 1 mg or Dx. 8 mg, indicating a normal response, whereas PAC showed a very weak response to both a stimulatory and an inhibitory procedure. In the rapid ACTH test, the basal PAC (8.0 ng/dl) was not changed significantly at 30 min (8.5 ng/dl), 60 min (9.3 ng/dl) or 90 min (10.1 ng/dl) after the injection of ACTH, and in the Dx. suppression test, the basal PAC (9.6 ng/dl)
was not suppressed significantly by either Dx. 1 mg (4.7 ng/dl) or Dx. 8 mg (4.3 ng/dl). The plasma 19 hydroxyandrostenedione level was normal (36 pg/ml).

**Effect of Dexamethasone (Fig. 1)**

As shown in Fig. 1, the dexamethasone administration (Dx. 2 mg/day) for 2 weeks had no effect on blood pressure or serum potassium. There was no change in urinary electrolytes or the urinary sodium/potassium excretion ratio. Plasma ACTH and plasma cortisol were under the lower limit for the assay. PRA was undetectable except at one point during hospitalization. PAC was not suppressed during this period.

**Effect of Triamterene (Fig. 1)**

Triamterene was administered at 100 mg/day for 2 weeks, followed by 200 mg/day for another 2 weeks on a diet containing 12 g NaCl (Na⁺ 200 mEq)/day. In response to triamterene, blood pressure decreased significantly. Urinary potassium

![Fig. 1. Changes in blood pressure, serum potassium, urine volume (UV), urinary sodium excretion (U_{Na}V), urinary potassium excretion (U_{K}V), urinary sodium/potassium ratio (Na/K), plasma aldosterone concentration (PAC) and plasma renin activity (PRA) during hospitalization. PAC, normal value: 2-12 ng/dl. PRA, normal value: 5-30 ng/ml/6hr. n.d.: not detectable.](image)
excretion decreased with a concomitant increase in the urinary sodium/potassium ratio, and serum potassium progressively increased within the normal level. PRA was not detectable. PAC was within normal limits. Subsequently, in addition to triamterene 200 mg/day, salt intake was restricted to 5 g/day (Na⁺ 85 mEq/day). Blood pressure further decreased and the serum potassium level increased to 4.4 mEq/L with a concomitant decrease in the urinary sodium/potassium ratio. PRA was undetectable and PAC ranged between the normal and subnormal levels.

After discontinuing the treatment with triamterene and salt restriction, serum potassium progressively decreased to the subnormal level with increases in blood pressure and the urinary sodium/potassium ratio.

**Effect of Spironolactone (Fig. 1)**

Spironolactone was administered at 150 mg/day for 7 days, followed by 300 mg/day for 3 weeks. The urinary sodium/potassium ratio and serum plasma level did not increase. Blood pressure increased significantly compared to the level during triamterene administration. PRA was undetectable and PAC was normal.

**Relationship between PAC and Menstrual Cycle (Fig. 2)**

After the patient was discharged, we analyzed the change in PAC and found that there had been a peak every month in accordance with the menstrual cycle. As illustrated in Fig. 2, menses occurred regularly every 4 weeks, accompanied by the normal biphasic pattern of basal body temperature, and the plasma progesterone level showed a peak in the mid-luteal phase, thus indicating that the patient's gonadal function was normal. The change in PAC was parallel with that in the plasma progesterone level. In the follicular phase, PAC was shown to be subnormal.

**Discussion**

The findings of hypertension, hypoka-
lemic alkalosis, renal potassium wasting and a low suppressed level of PRA, strongly suggest a state of hyperaldosteronism in the patient. However, such a diagnosis was excluded for the following reasons: first, the level of PAC was not high, nor were the levels of the other steroid hormones causing mineralocorticoid activity such as DOC, 18-OH-DOC and corticosterone; second, there was no evidence of adrenal adenoma or hyperplasia; third, the patient had never used any drugs causing mineralocorticoid activity and fourth, the mineralocorticoid antagonist spironoractone had failed to correct the abnormalities. Finally, since dexamethasone administration did not correct the abnormalities, dexamethasone suppressive hyperaldosteronism and ACTH-dependent mineralcorticoidism were excluded (Biglieri, 1981). Nevertheless, a state of salt retention was confirmed by the failure of PRA to respond to a furosemide test.

In the present study, triamterene increased serum potassium with a concomitant decrease in urinary potassium excretion and an increase in the urinary sodium/potassium ratio. Since triamterene is a diuretic directly affecting sodium resorption in the renal distal tubules (Baba et al., 1964), the abnormalities described in the present case would be attributed to a defect in renal resorption of sodium as described by Liddle (1966) and this case is considered to be a case of Liddle's syndrome. Liddle et al. (1963) reported two siblings with this renal disorder characterized by hypertension, hypokalemic alkalosis, suppressed plasma renin levels and negligible aldosterone secretion. In the original cases, the renin-angiotensin-aldosterone system was thought to be secondarily suppressed by the sodium retention which is caused by primary renal abnormality in sodium resorption in renal distal tubules.

Since the time of Liddle's original report, similar cases have been described (Aaskog et al., 1967; Milora et al., 1967; Bravo et al., 1970; Helbock and Reynolds, 1970; Ohno et al., 1975; Hyman et al., 1979; Wang et al., 1981; Sakamoto et al., 1981; Rodriguez et al., 1981). Although no inheritability of the syndrome has been confirmed in this case, several cases of sporadic occurrence of Liddle's syndrome have been reported (Aaskog et al., 1967; Helbock and Reynolds, 1970; Hyman et al., 1979; Wang et al., 1981; Sakamoto et al., 1981; Rodriguez et al., 1981). However, all but one of the cases showed subnormal plasma aldosterone levels (Ohno et al., 1975). In the present female patient, PAC was not always low, and ranged between normal limits. Analysis of changes in PAC showed that PAC was parallel with plasma progesterone levels in close accordance with the menstrual cycle. In normal female subjects, PAC has been reported to reach a peak in the mid- or late-luteal phase (Katz and Romfh, 1972), and there are some studies proposing that the changes in PAC may be due to stimulation of the renin-angiotensin system, possibly caused by progesterone-induced natriuresis (Katz and Romfh, 1972; Sasaki et al., 1972; Laidlaw et al., 1962). However, in the present case, since PRA was suppressed throughout the patient's period of hospitalization, changes in PAC could not have been caused by changes in renin activity. It is possible that changes in PAC were due to plasma progesterone, which may reach the adrenal and serve as a precursor to aldosterone, as hypothesized by Laidlaw et al. (1962) in pregnant subjects. Stein (1985) has suggested the possibility that the severity of the syndrome may lessen during pregnancy because sodium retention would be lessened by an increase in natriuretic progesterone; actually a patient with Liddle's syndrome, who gave birth to a girl, was reported by Wang et al. (1981). In spite of these suggestions, the relationship between PAC and plasma progesterone has
not yet been determined. In future, more attention should be paid to the relationship in order to clarify the pathophysiology of the syndrome.

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References


