

Hypertension, Hypokalemia and Hypoaldosteronism with Suppressed Renin: A Clinical Study of a Patient with Liddle's Syndrome

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Abstract

A 24-yr-old woman with hypertension, hypokalemic alkalosis, low plasma renin and hypoaldosteronism was studied. Plasma aldosterone, renin and potassium returned to normal and blood pressure fell after sodium restriction or the administration of triamterene. Thiazide therapy also normalized her blood pressure while dexamethasone, spironolactone and furosemide did not improve her symptoms. Plasma aldosterone levels were low and responded poorly to a short term ACTH injection, but responded well to the maximal adrenal stimulation by ACTH-Z. Plasma levels of cortisol, corticosterone and deoxycorticosterone were within the normal range. Adrenal scintigram with ¹³¹I-iodocholesterol and abdominal computed axial tomography did not reveal the presence of a sizeable adrenal tumor. In addition, the urinary kallikrein excretion was low after sodium restriction and showed no response to saline infusion. These findings suggest that the excessive secretion of unusual mineralocorticoids may not exist in this case. From these observations and the results of the therapeutic responses to the diuretic agents, we conclude that the primary cause of the disorder of this patient seems to be a renal defect in the distal tubule in handling sodium and potassium which is similar to that in Liddle's syndrome.

In 1963, Liddle *et al.* (1963) described a familial renal disorder simulating primary aldosteronism but with negligible aldosterone secretion. Similar cases have subsequently been reported (Aarskog *et al.*, 1967; Milora *et al.*, 1967). Liddle originally assumed the features of this condition to be due to a defect of the kidney to conserve sodium and excrete potassium in distal tubule. However, there are many problems about the pathophysiology remaining unsolved because of few cases reported. We here report a patient whose characteristic symptoms suggested a case similar to that described by Liddle *et al.*

Case Report

A 23-yr-old Japanese woman was referred to our clinic on July 1, 1980, in order to examine the cause of her hypertension. She had been diagnosed as hypertensive for 10 years. In 1974, she had been admitted to another hospital with a presumptive diagnosis of primary aldosteronism because of marked hypokalemia with hypertension. However, biochemical results for endocrine studies had revealed no positive findings for hyperaldosteronism. Since then, the hypertension was controlled by treatment with thiazide diuretic with potassium supplement and mild restriction of salt intake. There was nothing in her family history to

suggest hypertension. On admission, the patient appeared pale but was well. The height was 157 cm, the weight 50.6 kg and the pulse 64/min regular. Blood pressure was 180/130 when off drugs for 2 weeks. Electrocardiography showed changes consistent with hypokalemia. A grade 1 hypertensive retinopathy (Keith-Wagener's classification) was noted. Chest X-ray revealed moderate cardiomegaly. Laboratory data were: hemoglobin, 9.2 g/dl; hematocrit, 28.1%; plasma sodium, 142 mEq/L; potassium, 2.7 mEq/L; chloride, 102 mEq/L; bicarbonate, 28.7 mEq/L; creatinine, 0.8 mg/dl; creatinine clearance, 98.8 ml/min; BUN, 12 mg/dl; and arterial blood pH, 7.47. The maximum urine concentration after fluid deprivation for 12 hrs was 639 mOsm/L. The following tests were normal: urine microscopy and culture, skull X-ray, intravenous urogram and abdominal computerized axial tomography. Thyroid function test results were normal. Urinary catecholamines were also within the normal range. Urinary 17-OHCS and 17-KS on three occasions were 3.2–4.6 mg/day and 3.5–6.8 mg/day, respectively. Adrenal scintigram with ¹³¹I-adosterol (6 β -iodomethyl-19-norcholest-5(10)-en-3 β -ol, Daiichi Radioisotopes Laboratories Ltd., Tokyo) revealed diffuse concentration of ¹³¹I on bilateral adrenals whereas the uptake of ¹³¹I disappeared after the administration of dexamethasone.

Methods

Investigations carried out during 3 months' hospitalization. All medications were discontinued 2 weeks before admission and the diet was prepared to contain 15 g, less than 2 g and 5 g of salt as shown in Fig. 1. Furosemide test was performed by a 1 hr upright posture following 40 mg of intravenous (iv) injection of furosemide. A rapid ACTH test was carried out by an iv injection of 250 μ g of α^{1-24} ACTH (Cortrosyn; Daiichi Co., Tokyo). These tests were done on two occasions during sodium replete and restricted states. One thousand and five hundred milliliters of physiologic saline solution were

infused iv during 2 hrs in a supine position after sodium restriction for 6 days. This maneuver was also applied to 4 patients with benign essential hypertension. Plasma renin activity (PRA) was determined by radioimmunoassay of angiotensin I using a commercially available kit (Dainabot Radioisotopes Laboratories Ltd.). Plasma aldosterone, corticosterone and deoxycorticosterone were measured by radioimmunoassay after purification by a Sephadex LH-20 column (Sakamoto *et al.*, 1975). Urinary aldosterone was also determined by radioimmunoassay as the acid-labile conjugate of aldosterone (aldosterone 18-glucuronide) (Langan *et al.*, 1974). Plasma cortisol was measured by direct radioimmunoassay (Sakamoto *et al.*, 1977). Urinary kallikrein was measured by the method based on the colorimetric determination of α -naphthol released by the enzyme reaction (Hitomi *et al.*, 1980). Urinary 17-OHCS (Silber and Porter, 1954) and 17-KS (Direkter *et al.*, 1952) were measured by conventional methods. Urinary catecholamine was determined by fluorometry following high performance liquid chromatography (Ohgitali *et al.*, 1979). Plasma and urinary electrolytes were analyzed with an autoanalyzer.

Results

Basal levels of PRA and plasma aldosterone were low and they did not change appreciably during the furosemide test (Table 1). However, increase in PRA and plasma aldosterone were observed following strict restriction of sodium intake or after the administration of triamterene and thiazide (Fig. 1). Plasma aldosterone showed no response to rapid ACTH test whereas plasma deoxycorticosterone, corticosterone and cortisol increased normally (Table 1). However, maximal stimulation by ACTH-Z caused the increases in plasma and urine aldosterone (Fig. 1, 2). Urinary kallikrein excretion was low and responded poorly to physiologic saline load in comparison with that in 4 patients with essential hypertension (Fig. 3). During the period of treatment, her blood pressure, PRA, plasma aldosterone, serum potassium, urinary sodium and potassium were monitored and the results are given in Fig. 1. Salt restriction, administration of triamterene and thiazide diuretic gave rise to a marked im-

Table 1. Measurement of plasma steroid concentration and plasma renin activity (PRA) in various conditions.

| <i>On sodium replete diet (NaCl; 15 g/day)</i> | | | | |
|--|---------------|-------|--------|--------|
| | Normal range* | 0 min | 30 min | 60 min |
| Rapid ACTH test | | | | |
| Aldosterone (ng/dl) | 9.1±4.2 | 1.8 | 2.8 | 3.1 |
| Deoxycorticosterone (ng/dl) | 8.8±5.4 | 10.8 | 17.7 | 13.9 |
| Corticosterone (µg/dl) | 0.3-0.9 | 0.5 | 1.6 | 1.9 |
| Cortisol (µg/dl) | 10.4±2.9 | 6.2 | 9.8 | 12.3 |
| Furosemide plus upright posture | | | | |
| PRA (ng/ml/hr) | 1.1±0.4 | 0.1 | 0.1 | 0.1 |
| Aldosterone (ng/dl) | | 2.9 | 3.6 | 3.6 |
| <i>On sodium restricted diet (NaCl; less than 2 g/day)</i> | | | | |
| Rapid ACTH test | | | | |
| Aldosterone (ng/dl) | | 4.4 | 6.7 | 7.2 |
| Furosemide plus upright posture | | | | |
| PRA (ng/ml/hr) | | 0.4 | 0.6 | 0.6 |
| Aldosterone (ng/dl) | | 5.0 | 6.2 | 6.2 |

* Values for normal range are expressed as mean±S.E. of 20 normal subjects in supine position at 0800 hr.

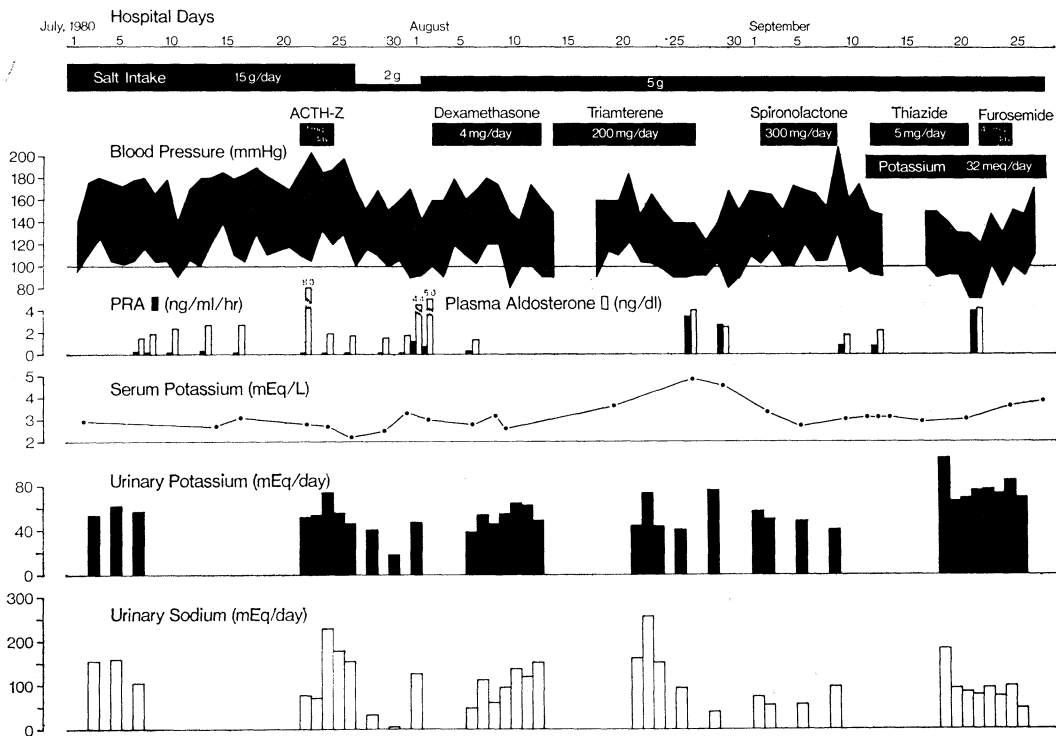


Fig. 1. Metabolic balances of sodium and potassium correlated with various periods of therapy, hormonal measurements and blood pressure.

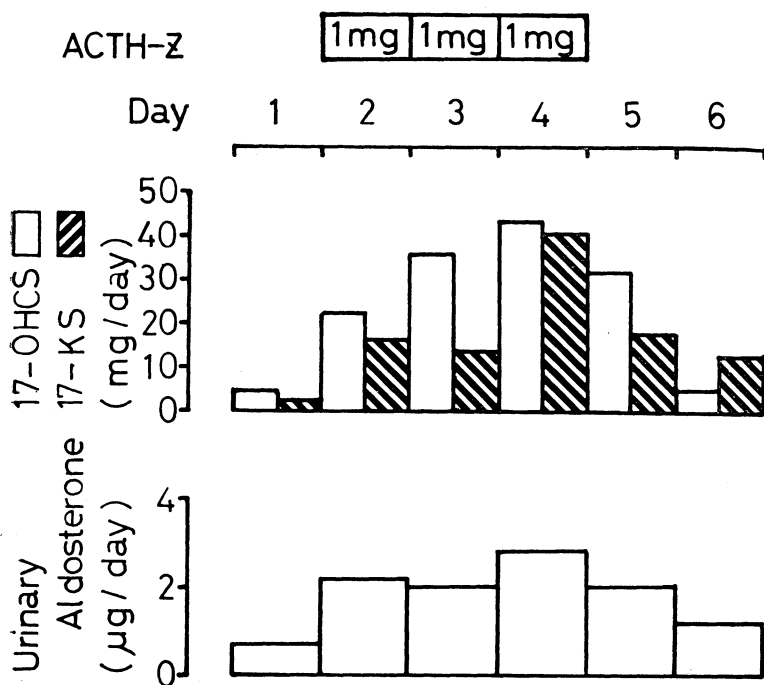


Fig. 2. Effect of ACTH-Z injections for 3 days on urinary 17-OHCS, 17-KS and acid-labile aldosterone excretion.

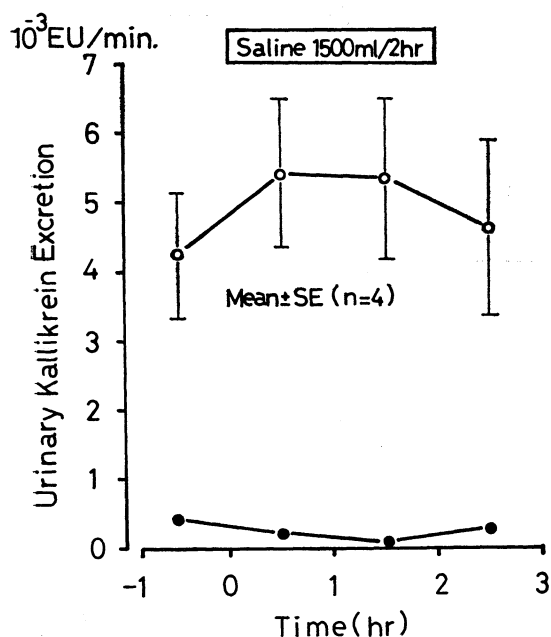


Fig. 3. Effect of physiologic saline infusion on urinary kallikrein excretion in the present patient (closed circle) and patients with essential hypertension (open circle).

provement in blood pressure and led to a decrease in urinary potassium and a rise in serum potassium except during the period of potassium supplement therapy. Intramuscular injection of ACTH-Z (1 mg, daily) for 3 days caused a gradual rise in blood pressure. Oral administrations of dexamethasone, spironolactone and furosemide did not improve her blood pressure.

Discussion

Characteristic symptoms and laboratory findings including hypertension, hypokalemic alkalosis and decreased aldosterone values with suppressed renin in the present patient suggested strongly the possibility of Liddle's syndrome. Furthermore, the lack of therapeutic responses to spironolactone or dexamethasone accompanied with a good response to triamterene confirmed this diagnosis. Familial occurrence has usually been observed in Liddle's syndrome (Liddle *et*

al., 1963; Gardner *et al.*, 1971; Ohno *et al.*, 1973; Matsui *et al.*, 1976), while we were not able to find a patient with hypertension in her pedigree. Sporadic cases have also been reported (Aarskog *et al.*, 1967; Takahashi *et al.*, 1979).

Hyporeninemic hypoaldosteronism was shown in our patient. However, PRA and aldosterone were increased by sodium restriction and the administration of triamterene and thiazide. Aldosterone also increased in the maximal stimulation by ACTH-Z. From these results, a primary defect of renin production in juxtaglomerular cells and of aldosterone synthesis in the adrenal cortex could be excluded.

Increased activity of mineralocorticoids except aldosterone may also induce similar clinical manifestation of this syndrome. In the present study, hypersecretion of deoxycorticosterone, corticosterone and cortisol were not demonstrated. However, the overproduction of unusual mineralocorticoids is not negligible. Her hypertension and hypokalemia were not improved by spironolactone which is the specific antagonist of mineralocorticoid receptor. In addition, we could not demonstrate a sizeable tumor or enlarged glands in adrenal scintigram and computed axial tomography. These observations do not favor the presence of adrenal tumor at least more than 1 cm in diameter and unresponsiveness to spironolactone indicates that her hypertension and hypokalemia might not be the result of overactivity of mineralocorticoids. Margolius *et al.* (1974) have reported that urinary kallikrein excretion increases in normal subjects during a low sodium diet and in response to mineralocorticoid. Holland *et al.* (1980) also described that urinary kallikrein had to be elevated in some patients with primary aldosteronism and mineralocorticoid excess syndrome. These findings may lead to the use of the urinary kallikrein excretion rate as an index of mineralocorticoid activity. Levy *et al.*

(1978) reported that an intravenous infusion of 5% glucose after sodium restriction increased urinary kallikrein activity in normal subjects. The basal level of urinary kallikrein after sodium restriction was low in our patient who did not show an increase following saline infusion, in comparison with patients with essential hypertension. Although the mechanism regulating kallikrein excretion is still obscure, this may suggest that the overproduction of unusual mineralocorticoid do not exist in this patient.

A primary cause of Liddle's syndrome has been postulated to be a renal tubular abnormality with excess sodium conservation even in the virtual absence of mineralocorticoid. On the other hand, the presence of abnormal sodium transport in circulating erythrocytes in this syndrome has been shown by Helbock and Reynolds (1970) and Gardner *et al.* (1971). Similar evidence has subsequently been reported by Hyman *et al.* (1979). They suggested generalized membrane abnormality in sodium transport. However, there are few reports with regard to the site of a defect in renal tubules. In our patient, triamterene and thiazide alleviated her symptoms whereas furosemide did not. It is well known that triamterene acts on the distal renal tubular cells leading to a depression of the exchange of sodium for hydrogen and potassium ions and these actions are independent of mineralocorticoid. Thiazide diuretic also acts on distal convoluted tubules to inhibit the reabsorption of sodium and its attendant anion. However, furosemide acts primarily to inhibit chloride and sodium reabsorption in the ascending limb of the loop of Henle with a minor effect on the distal tubule. From the facts described above, we concluded that the affected portion in the renal tubules in our patient is limited to the distal tubular cells dominating the state of sodium retention or the kaliuresis without mineralocorticoid action.

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