

## Liddle's Syndrome: A Report in a Middle-Aged Woman

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### Abstract

A 54-year-old woman with diabetes mellitus was hospitalized with generalized edema and weakness. She was also found to have hypertension, hypokalemia and metabolic alkalosis. Detailed examination showed subnormal plasma renin activity and plasma aldosterone concentration. Adrenal CT scanning revealed no adrenal tumor. A successful treatment with amiloride established the diagnosis of Liddle's syndrome for the patient. Liddle's syndrome, a rare hereditary disease usually found in young patients, should be considered in the differential diagnosis of hypertension even in elderly individuals.

**Key Words:** Liddle's syndrome, hypertension, hypokalemia, amiloride

### INTRODUCTION

Liddle's syndrome was first reported by Liddle et al in 1963.<sup>1</sup> It is a rare disease inherited as an autosomal dominant trait.<sup>2-5</sup> Patients with Liddle's syndrome are characterized by expanded plasma volume caused by excessive salt and water reabsorption in the distal nephron, resulting in low levels of plasma renin activity (PRA), plasma aldosterone concentration (PAC) and serum potassium, and metabolic alkalosis. Correction can be accomplished by salt restriction and administration of antagonists of the cortical collecting duct epithelial sodium channel (ENaC), e.g. amiloride and triamterene.<sup>6,7</sup> Mutations in the cytoplasmic C-terminal of either the  $\beta$  or  $\gamma$  subunits of the amiloride-sensitive ENaC have been implicated with increasing the channel activity with higher current causing excessive salt resorption.<sup>8</sup> The disease is usually detected at an early age in most cases, however, it can also be detected in patients aged 50 years or more.<sup>9-12</sup> There have been about 30 case reports of Liddle's syndrome worldwide, but none in Korean. Now we report a 54-year-old Korean woman with Liddle's syndrome who was

treated effectively with amiloride and potassium supplement.

### CASE REPORT

A 54-year-old woman had been treated for diabetes mellitus (DM) at a local clinic for 1 year by oral hypoglycemic agents. In January 1999, she was admitted to the Department of Internal Medicine, CHA General Hospital in Korea for 2 months with generalized edema and weakness. Her past history was unremarkable except for DM and the family history was negative. Physical examination on admission showed body weight and height of 64.5 kg and 154 cm, respectively and body temperature of 36.6°C. Blood pressure was 210/130 mmHg and pulse rate was regular at 72 beats/min. There were no signs of anemia or jaundice, but generalized edema was noted. Heart and respiratory sounds were normal. There were no significant findings on abdominal examination and the patient had normal genital organs. A chest X-ray examination showed clear lung fields with a normal-sized heart. Laboratory findings on admission indicated the presence of anemia (Hgb 11.1 g/dL, Hct 32.7%). Biochemical analysis showed hypokalemia (2.5 mEq/L) with normal sodium level (135 mEq/L). The 24-hour urinary K<sup>+</sup> excretion was 38.7 mEq/day and calculated transtubular K<sup>+</sup> gradient (TTKG) was 9.19. Arterial blood gas analysis showed metabolic alkalosis. Since an endocrine abnormality can be found in a patient who is not on agents

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Table 1. Endocrinological Data

Item	Concentration (ng/ml)	Item	Level
Plasma renin		Plasma cortisol	
resting	0.23 (0.15–2.33)	8 a.m.	16.46 $\mu$ g/dl (5–18)
standing	0.74 (1.3–3.95)	4 p.m.	13.38 $\mu$ g/dl (2–13)
Plasma aldosterone		Plasma ACTH	33.4 pg/ml (6–56.7)
resting	<1.0 (1.0–16.0)	Urine free cortisol	17.2 $\mu$ g/day (20–90)
standing	<1.0 (4.0–31.0)	Urine 17-OHCS	4.2 mg/day (3–15)

Values in parenthesis indicate normal range.

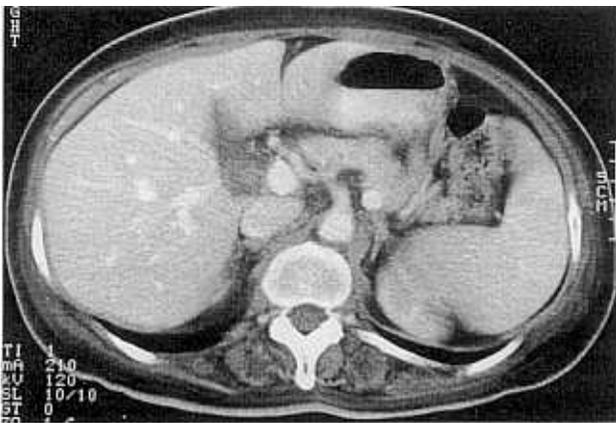


Fig. 1. Photograph of abdominal computed tomography (CT) of a patient with Liddle's syndrome. There were no signs of swelling of the adrenal gland or of tumorous lesions.

which may cause electrolyte imbalance such as diuretics or glycyrrhiza, various tests were performed. Laboratory data for the patient showed suppressed PRA and PAC. Plasma levels of cortisol, ACTH and 24-hour urinary levels of cortisol and 17-hydroxycorticoid (OHCS) were all within normal limits (Table 1). Abdominal computed tomography (CT) showed neither swelling of the adrenal gland nor any tumorous lesions (Fig. 1). Based on the presence of hypertension, hypokalemia, metabolic alkalosis, hyporeninemia and hypoaldosteronemia with no abnormal endocrine findings, the patient was diagnosed as Liddle's syndrome. Accordingly, a potassium-sparing diuretic, amiloride (5 mg/day) was administered for the period indicated (Fig. 2) with an oral potassium preparation (12 mEq/day as  $K^+$ ). The amiloride therapy resulted in a marked improvement of hyper-

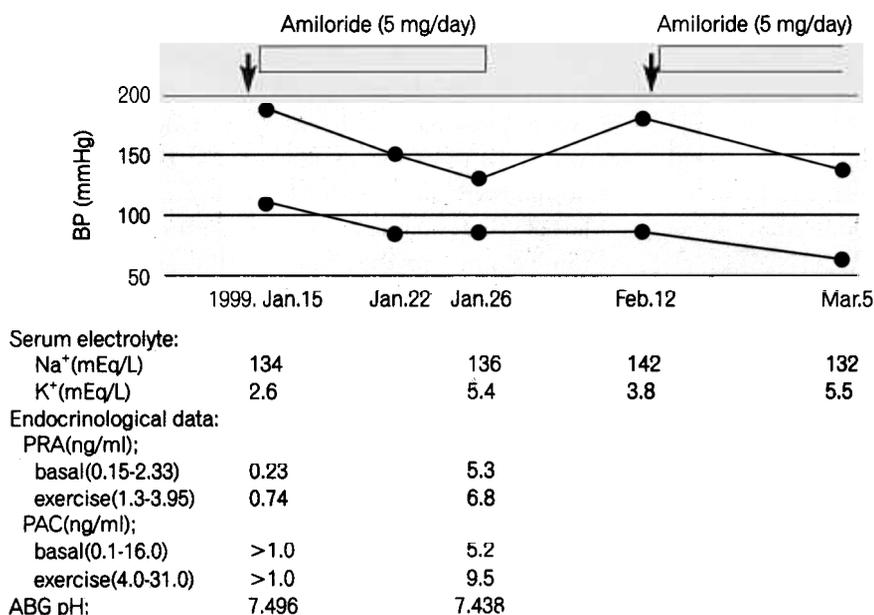


Fig. 2. Clinical change of a patient with Liddle's syndrome treated with amiloride. Amiloride (5 mg/day) was administered orally at the date indicated ( $\downarrow$ ). Amiloride therapy resulted in a marked improvement of hypertension, hypokalemia, PRA, PAC and metabolic alkalosis. PRA, plasma renin activity; PAC, plasma aldosterone concentration; ABG pH, arterial blood gas pH. Values in parenthesis indicate normal range.

tension and hypokalemia. Both PRA and PAC were normalized and alkalosis was corrected and the TTKG improved from 9.19 to 3.54. For hyperkalemia, the amiloride was stopped after 16 days but it was resumed when hypertension recurred and serum  $K^+$  level decreased. The typical symptoms, laboratory findings, response to amiloride therapy and laboratory data after the amiloride load test confirmed the correct diagnosis of Liddle's syndrome for this patient. Interestingly, hypertension, hypokalemia and hypernatremia was not improved by the administration of a mineralocorticoid antagonist, spironolactone, earlier in the patient's admission. In addition, other anti-hypertensive drugs, angiotensin converting enzyme (ACE) inhibitor, loop diuretic,  $Ca^{++}$ -channel blocker were also ineffective although the general edema was initially treated successfully with lasix therapy. The patient also underwent a work-up for the causes of secondary hypertension. The result of thyroid function test was normal and renal scan without captopril loading test showed normal findings.

## DISCUSSION

In 1963, Liddle et al.<sup>1</sup> described a familial disorder in which the clinical manifestations closely resembled those of primary hyperaldosteronism, but in which the measured rate of aldosterone secretion and excretion was subnormal. Most physicians believe that this syndrome is a rare case of hypertension. The clinical features of this syndrome are severe hypertension, hypokalemia, and chloride-unresponsive metabolic alkalosis. The primary abnormality appears to be a cortical collecting duct ENaC defect resulting in hyperabsorption of sodium, and causing volume expansion, hypertension, hypokalemia, metabolic alkalosis, and suppression of renin and aldosterone secretion.<sup>13</sup>

The differential diagnosis of secondary hypertension for the present case included renal artery stenosis, Cushing's syndrome, Conn's syndrome (aldosterone-secreting adenoma or bilateral adrenal hyperplasia) and hyperthyroidism. The reporting patient had not ingested carbenoxolone sodium, licorice or any oral contraceptives. The diagnosis of primary hyperaldosteronism was excluded by the low serum and/or urinary aldosterone levels. CT scans of the adrenal glands were normal. And the dramatic improvement

of hypertension and hypokalemia in response to amiloride provided additional evidence that the patient had Liddle's syndrome. Furthermore, a trial of high-dose spironolactone failed to control the hypertension and hypokalemia.

Cushing's syndrome was ruled out by the absence of signs and symptoms of this syndrome and the normal serum cortisol levels. The diagnosis of Liddle's syndrome cannot be made with certainty until enzymatic deficiencies in the aldosterone synthetic and cortisol degradation pathways are excluded. The syndrome of "apparent mineralocorticoid excess" is associated with  $11\beta$ -hydroxylase and  $5\beta$ -reductase deficiencies, enzymes that convert cortisol into its inactive metabolite cortisone.<sup>13-16</sup> Renal tubular mineralocorticoid receptors sensitive to  $11$  hydroxycortisol metabolites and to the renally-cleared cortisol induce sodium retention and potassium wasting, resulting in hypokalemic hypertension. This form of hypertension responds to spironolactone since it occurs via an aldosterone receptor-dependent mechanism. Interestingly, glycyrrhizic acid, the active component in licorice, produces manifestations similar to the apparent mineralocorticoid excess syndrome via suppression of  $11\beta$ -hydroxysteroid dehydrogenase.<sup>17</sup> In this study, the normal serum cortisol levels, the absence of virilization or hypogonadism, the absence of a response to spironolactone and a dramatic response to amiloride could exclude the possible diagnosis of  $11\beta$ - or  $17\alpha$ -hydroxylase deficiencies and the apparent mineralocorticoid excess syndrome in the patient.

References to Liddle's syndrome have indicated that it is probably underdiagnosed and underreported. Botero-Velez et al.<sup>4</sup> studied 43 members of the family of the original patient described by Liddle et al., out of which 18 (43%) were affected and the transmission of it followed an autosomal dominant pattern. But none of these patients was diagnosed as Liddle's syndrome prior to the study. In the original report, Liddle et al. speculated that the etiology of this syndrome was an abnormal  $Na^+$  pump affecting the distal nephrons, since administration of triamterene, which inhibits the cortical collecting duct  $Na^+$  channel was effective in these patients. The authors speculated that retention of sodium caused the increase in body fluid volume, hypertension and inhibition of the renin-aldosterone system with excessive secretion of  $K^+$  and  $H^+$  ions, followed by hypokalemia and metabolic alkalosis. Recent studies have described

mutations in the cytoplasmic C-terminal of either the  $\beta$  or  $\gamma$  subunits of the amiloride-sensitive ENaC.<sup>8</sup> All of the mutations observed to date in unrelated Liddle families have resulted in COOH-terminus deletions or in missense mutations affecting the PY motif of either the  $\beta$ ENaC or  $\gamma$ ENaC subunit.<sup>18</sup> Thus, abnormalities of ENaC in the principal cells present at the apical membrane of the cortical collecting duct which can increase  $\text{Na}^+$  resorption followed by the generation of lumen-negative transepithelial potential difference (TEPE), may result in the increase of  $\text{K}^+$  secretion in Liddle's syndrome. In the present case, genetic abnormalities of the  $\text{Na}^+$  channel were not investigated and the molecular changes associated with Liddle's syndrome in this patient are uncertain.

Liddle's syndrome may occur in members of a certain family with high probability and is therefore considered to be inherited as an autosomal dominant disorder.<sup>8</sup> However, the patient reported here has no family history of hypertension and her two sons who were also subjected to the investigation proved to be non-hypertensive.

In the diagnosis of Liddle's syndrome, muscle weakness as well as hypertension should be considered in the suspicion of the disease in elderly patients. Matsushita et al. suggested that young patients are suspected to be afflicted with Liddle's syndrome based on the presence of hypertension alone, whereas diagnosis of the disease in the majority of elderly patients was based on muscle weakness rather than hypertension in the clinical observation.<sup>19</sup> To date, no studies have yet examined the differences in the etiological mechanisms of Liddle's syndrome in young versus elderly patients. Thus, further studies are warranted to clarify the pathogenesis of this disease.

Physicians may consider hypertension as an essential complication of DM or other vascular diseases without routine clinical and laboratory investigation to determine the underlying mechanisms of hypertension in elderly population. Therefore, physicians should be aware of the existence of Liddle's syndrome in elderly hypertensive patients with muscle weakness. Diagnosis of Liddle's syndrome in this age group is also important since treatment with amiloride or triamterene is simple and effective.

In conclusion, we described a 54-year-old patient with Liddle's syndrome. The disorder was effectively treated with amiloride which is tolerated in elderly

patients. Physicians should suspect Liddle's syndrome in an elderly patients in the differential diagnosis of hypertension.

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