INTERNAL MEDICINE

□ CASE REPORT □

Hyponatremia in an Elderly Patient due to Isolated Hypoaldosteronism Occurring after Licorice Withdrawal

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Abstract

Hyponatremia is one of the most common electrolyte disorders encountered in the elderly. We present the case of an 81-year-old man who developed hyponatremia due to isolated hypoaldosteronism occurring after licorice withdrawal. He had severe hypokalemia with hypertension and was diagnosed with pseudoaldosteronism. He had been taking a very small dose of licorice as a mouth refresher since his early adulthood. Five months after licorice withdrawal, he developed hypovolemic hyponatremia, which was resolved with administration of fludrocortisone acetate. Our experience with this case suggests that isolated hypoaldosteronism occurring after licorice withdrawal should be considered as a potential cause of hyponatremia in elderly patients.

Key words: hyponatremia, isolated hypoaldosteronism, elderly, licorice and pseudoaldosteronism, Jintan®

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Introduction

Hyponatremia is one of the most common electrolyte disorders in the elderly population and is associated with adverse clinical outcomes (1). Acute severe hyponatremia is a medical emergency characterized by severe neurological symptoms (2). Furthermore, chronic hyponatremia is associated with cognitive impairment, susceptibility to falls, osteoporosis, and bone fractures and often requires hospital admission as well as long-term care (3-8). The elderly are particularly susceptible to developing hyponatremia, due to multiple consequences of aging: changes in body composition, alterations in the renal function, and changes in the hypothalamic-pituitary regulation of thirst and AVP secretion (1). The underlying cause of hyponatremia is often multi-factorial, and it is often extremely difficult to make a differential diagnosis (9).

Pseudoaldosteronism, which is caused by licorice-induced inhibition of 11 beta-hydroxysteroid dehydrogenase type 2 (11β-HSD2) activity, results in hypertension, hypokalemia, and metabolic alkalosis. Although the clinical signs and symptoms of pseudoaldosteronism generally improve within several weeks of licorice withdrawal, the duration for which subclinical renin-angiotensin-aldosterone system (RAAS) suppression is likely to persist is not well understood. The continued suppression of the RAAS may lead to a hyponatremic state. However, to our knowledge, no case of hyponatremia due to hypoaldosteronism following the cessation of licorice administration has been described in the literature.

In this report, we present a case of hyponatremia due to isolated hypoaldosteronism occurring after licorice withdrawal. Our experience with this case suggests that isolated hypoaldosteronism following cessation of long-term licorice administration should be considered during an evaluation of hyponatremia in elderly patients.

Case Report

An 81-year-old man presented to the emergency department of our institution complaining of muscular weakness in his lower and upper extremities. The patient's blood investigations revealed hypokalemia, at which point he was emergently admitted to our hospital. The patient had a history of gradual-onset of anorexia and loss of body weight over the last 5 months. He had a history of hypertension for more

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Table 1. Laboratory Data at the Time of the First Admission.

		Normal range			Normal range
WBC	10,000 /μL	(3,500-8,500)	*Arterial Gas Analysis*		
RBC	411×10⁴ /μL	(430-560)	pH	7.633	(7.35-7.45)
Hb	13.1 g/dL	(13.0-17.0)	PCO_2	35.5 mmHg	(35-45)
Plt	16.5×10⁴ /μL	(13-35)	PO_2	86.5 mmHg	(69-116)
TP	8.4 g/dL	(7.2-8.3)	HCO^{3-}	36.8 mmol/L	(22-26)
Alb	4.5 g/dL	(3.9-4.9)	BE	14.8 mmol/L	(-2.3-+2.3)
AST	81 U/L	(0-35)	*Urinalysis*		
ALT	35 U/L	(0-30)	U-Cre	14.3 mg/dL	
CPK	2,632 U/L	(0-200)	U-Na	60 mEq/L	
BUN	14.6 mg/dL	(8-21)	U-K	8.6 mEq/L	
Cre	0.76 mg/dL	(0.3-1.1)	FEK	20.8 %	
UA	2.4 mg/dL	(2.6-5.7)	*Hormone Analysis*		
Na	142 mEq/L	(135-147)	ACTH	22.7 pg/mL	(7.2-63)
K	2.2 mEq/L	(3.3-4.8)	Cortisol	13.4 μg/dL	(4.0-19.3)
Cl	87 mEq/L	(98-109)	PRA	0.7 ng/mL/h	(0.2-2.7)
Ca	9.5 mg/dL	(8.2-10.2)	PAC	5.7 ng/dL	(3.0-16.0)
Mg	1.6 mg/dL	(1.9-2.5)	TSH	0.403 μIU/mL	(0.35-4.94)
BS	104 mg/dL	(70-110)	FT3	2.33 pg/mL	(1.71-3.71)
HbA1c	5.3 %	(4.6-6.2)	FT4	1.51 ng/dL	(0.70-1.48)

BE: base excess, FEK: fractional excretion of potassium, PRA: plasma renin activity, PAC: plasma aldosterone concentration

than 15 years, for which he had received 40 mg of telmisartan and 5 mg of amlodipine. Cilostazol had been prescribed for an old cerebral infarction, and mecobalamin had been given for the peripheral nerve disorder. There was no family history of hypokalemia. A physical examination showed that the patient's height was 157 cm, and his weight was 37.6 kg; his body mass index was 15.3 kg/m^2. His blood pressure and pulse rate at admission were 141/80 mmHg and 68 beats/min, respectively. There were no remarkable findings on chest and abdominal examinations. The findings of the neurological examination were unremarkable, except for muscle weakness.

The laboratory data are shown in Table 1. Blood examinations revealed severe hypokalemia (serum K, 2.2 mEq/L) and mild hypomagnesemia. Arterial blood gas analysis in room air revealed severe alkalemia due to metabolic alkalosis. The creatine phosphokinase (CPK) level was extremely high, and the transaminase levels were mildly elevated, which was likely attributable to rhabdomyolysis. The plasma renin activity (PRA) and plasma aldosterone concentration (PAC) were lower-normal levels (PRA, 0.7 ng/mL/h; reference range 0.2-2.7 ng/mL/h, and PAC, 5.7 ng/dL; reference range 3.0-16.0 ng/dL). A urinary electrolyte analysis showed renal wasting of potassium [fractional excretion of potassium (FEK), 20.8%]. Computed tomography revealed normal adrenal glands. Owing to the presence of hypertension and laboratory abnormalities, the patient's hypokalemia was presumed to be caused by pseudoaldosteronism.

Repeated detailed history taking revealed that the patient had been taking about 20 granules of Jintan® (Morishita Jintan Co., Osaka, Japan) per day since his early adulthood. Jintan®, a mouth refresher popular among the Japanese, contains licorice. His clinical parameters, including blood pressure, laboratory data, and medication records, are shown in Figure. The patient stopped taking Jintan® and was treated with an oral potassium chloride supplement. His blood pressure and FEK gradually decreased, and normal serum potassium levels without potassium chloride supplementation were achieved two months later.

Approximately five months later, the patient presented with general malaise and anorexia. Blood investigations revealed severe hyponatremia (serum Na, 119 mEq/L), for which he was readmitted to our hospital. His blood pressure was 92/59 mmHg, and his pulse rate was 79 beats/min. His weight was 36.6 kg, which reflected weight loss since his first admission. His oral cavity was dry, and there was no sign of edema of the extremities. These findings were consistent with a state of hypovolemic hyponatremia.

The second admission laboratory data are shown in Table 2. The patient had elevated PRA (20.5 ng/mL/h; reference range 0.2-2.7 ng/mL/h) and normal PAC (7.8 ng/dL; reference range 3.0-16.0 ng/dL). The FEK was decreased in the presence of an upper-normal potassium level. The antihypertensive drugs were discontinued, and oral sodium chloride and 0.05 mg/day fludrocortisone acetate were started. Immediately after starting treatment, the hyponatremia was resolved, and the serum potassium levels decreased. However, owing to an abnormal rise in his blood pressure, treatment with fludrocortisone acetate had to be discontinued while the antihypertensive drugs were reintroduced. Subsequently, he experienced sustained mild hyponatremia despite consuming a high-salt diet. At 11 months after discontinuation of Jintan®, an ACTH stimulation test was performed (Table 3). Although the plasma cortisol increased somewhat, the PAC did not increase in response to provocative stimuli. About 19 months after discontinuing Jintan®, his serum Na and FEK levels had increased gradually, and a repeated ACTH stimulation test revealed a mild recovery of the increase in PAC (Table 3).

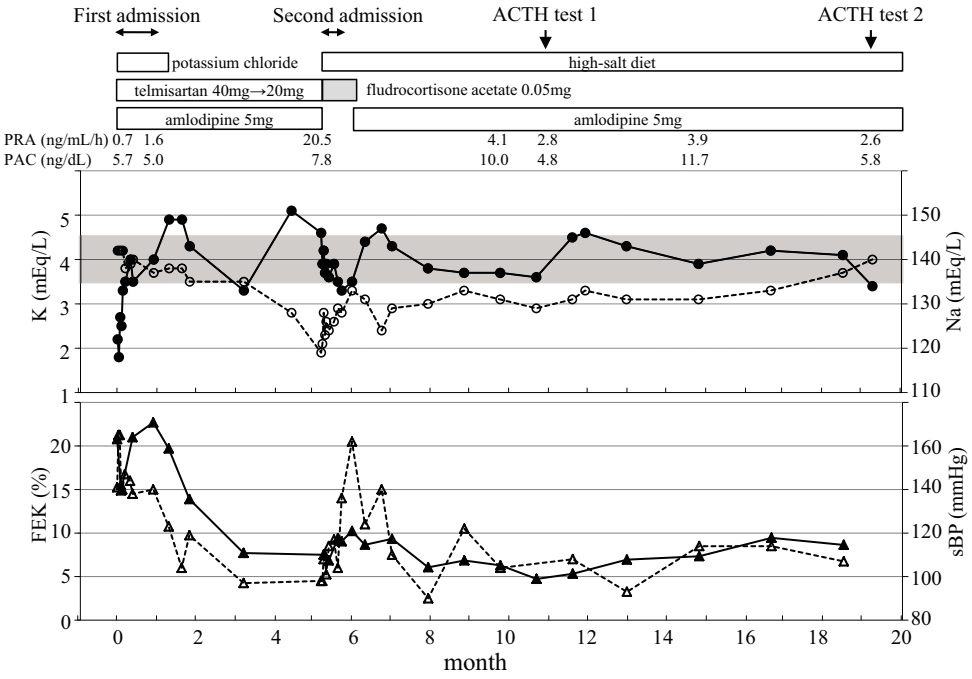

Figure. **Representation of the clinical course of the reported case. Changes in serum K (●) and Na (○) concentrations over time are indicated in the upper panel. FEK (▲) and sBP (△) are indicated in the lower panel. PRA: plasma renin activity, PAC: plasma aldosterone concentration, FEK: fractional excretion of potassium, sBP: systolic blood pressure**

Table 2. **Laboratory Data at the Time of the Second Admission.**

		Normal range			Normal range
BUN	21.2 mg/dL	(8-21)	*Hormone Analysis*		
Cre	0.94 mg/dL	(0.3-1.1)	ACTH	68.0 pg/mL	(7.2-63)
UA	4.3 mg/dL	(2.6-5.7)	Cortisol	19.7 μg/dL	(4.0-19.3)
Na	119 mEq/L	(135-147)	PRA	20.5 ng/mL/h	(0.2-2.7)
K	4.6 mEq/L	(3.3-4.8)	PAC	7.8 ng/dL	(3.0-16.0)
Cl	86 mEq/L	(98-109)	DHEAS	50 μg/dl	(13-264)
Urinalysis			TSH	0.587 μIU/mL	(0.35-4.94)
U-Cre	60.8 mg/dL		FT3	1.79 pg/mL	(1.71-3.71)
U-Na	104 mEq/L		FT4	1.37 ng/dL	(0.70-1.48)
U-K	20.4 mEq/L				
FEK	6.9 %				

FEK: fractional excretion of potassium, PRA: plasma renin activity, PAC: plasma aldosterone concentration, DHEAS: dehydroepiandrosterone sulfate

Table 3. **Results of the ACTH Stimulation Test.**

	0	30	60	90	120
Test 1 (11 months after initial presentation)					
Cortisol (μg/dL)	15.9	23.7	25.8	28.5	31.6
Aldosterone (ng/dL)	4.8	7.3	6.6	6.5	6.7
Test 2 (19 months after initial presentation)					
Cortisol (μg/dL)	9.7	16.2	17.9	18.4	22.5
Aldosterone (ng/dL)	5.8	9.7	9.2	10.5	9.7

Discussion

In this case, pseudoaldosteronism was caused by a very small dose of licorice regularly taken over a period of about 60 years as an ingredient of a mouth refresher. Two months after licorice withdrawal, the serum potassium levels had normalized, and the blood pressure had decreased. However, five months later, the patient developed hypovolemic hyponatremia, and these abnormalities were resolved with administration of fludrocortisone acetate. The clinical course of our patient suggested that hyponatremia was caused by isolated hypoaldosteronism following cessation of long-term licorice administration. Since the hyponatremia was resolved 19 months later, it is assumed that the suppression of the RAAS persisted for at least 19 months. The present case had the following interesting characteristics: 1) pseudoaldosteronism was caused by a very small dose of licorice taken for a long period, and 2) hyponatremia was caused by isolated hypoaldosteronism after licorice withdrawal.

The diagnosis of isolated hypoaldosteronism is not straightforward. In patients with suspected hypoaldosteron-

ism, measurement of PRA and PAC is recommended after administration of a loop diuretic or in an upright position (10). However, as in this case, it is difficult to conduct the test under these conditions in elderly patients. The PAC of our patient was lower-normal level despite his hypovolemic state, indicating the existence of hypoaldosteronism. ACTH has a slight stimulatory effect on aldosterone, and synthetic ACTH 1-24 has been used to evaluate aldosterone secretion (11). However, whether or not the magnitude of the response is normal is uncertain. In our patient, although the plasma cortisol level increased, PAC did not increase adequately after ACTH stimulation. Given these laboratory findings, we believe that the diagnosis of isolated hypoaldosteronism is plausible in our patient.

The occurrence of transient hypoaldosteronism requiring mineralcorticoid replacement after adrenalectomy has been reported in some aldosterone-producing adenoma (APA) patients (12). A recent study reported the occurrence of prolonged "zona glomerulosa insufficiency" after adrenalectomy in up to 5% of APA patients (13). These patients required continuous mineralocorticoid replacement therapy for a period of 11-46 months. A multivariate analysis showed that a higher age and a pre-existing impaired renal function was associated with a higher risk of developing transient hypoaldosteronism. Corticosteroid replacement therapy is known to be necessary after adrenalectomy for cortisol-producing adrenal tumor and after exogenous glucocorticoid withdrawal. Although mineralocorticoid replacement therapy may also be necessary after licorice withdrawal in pseudoaldosteronism patients, there have been few reports of isolated hypoaldosteronism in these patients. One reason may be that isolated hypoaldosteronism occurring after licorice withdrawal is not diagnosed adequately. Based on our experience and other reports, we recommend that the possibility of isolated hypoaldosteronism be considered after licorice withdrawal in pseudoaldosteronism patients, especially in elderly patients and patients with an impaired renal function.

The most common form of hypoaldosteronism is type IV renal tubular acidosis (RTA), which manifests as hyperkalemia and mild hyperchloremic metabolic acidosis with decreased urinary ammonium excretion. The causes of type IV RTA are based on the primary mechanism: reduced aldosterone production or aldosterone resistance (14). Reduced aldosterone production is often observed in a primary adrenal disorder or secondary to hyporeninemia in patients with chronic nephropathies due to diabetes, systemic lupus erythematosus, and AIDS, while aldosterone resistance is often observed in a number of tubulointerstitial renal diseases (14). Although aldosterone promotes sodium retention, hyponatremia is uncommon in patients with hypoaldosteronism. The reason for this observation is likely due to the compensatory mechanisms that include the up-regulation of other sodium-retaining mechanisms, such as angiotensin II and norepinephrine (10). Furthermore, since type IV RTA is associated with volume expansion, hypovolemia-induced stimulation of ADH release does not occur in these patients (9). However, elderly patients may easily develop volume deprivation and insufficient sodium intake (1). Therefore, both hypovolemia-induced stimulation of ADH release and insufficient sodium intake may lead to hyponatremia in elderly hypoaldosteronism patients.

Pseudoaldosteronism is a well-known adverse reaction in patients receiving licorice and its more purified product, glycyrrhizic acid (GA) (15). A daily intake of 10 mg/day or 0.2 mg/kg/day of GA is considered safe for most healthy adults, using a safety factor of 10 (16, 17). Jintan®, a mouth refresher popular among the Japanese, consists of licorice, cinnamon, ginger, and other spices. Since one granule of Jintan® contains 5.1 mg of licorice, which corresponds to 0.2 mg of GA, the average daily intake of GA in our patient was estimated to be approximately 4 mg/day (18). To date, only four cases of Jintan®-induced pseudoaldosteronism have been reported (18-21). While the intake of GA exceeded 10 mg/day in 3 of these 4 cases (270-540, 150-220, and 20-26 mg/day), a 69-year-old woman had a history of consistent daily intake of 6-10 mg/day of GA over a period of 40 years. It is likely that the development of pseudoaldosteronism is associated with the dosage and duration of the intake of licorice. There is apparently considerable inter-individual variation in susceptibility to the effect of GA. GA is hydrolyzed to its pharmacologically active compound, glycyrrhetic acid, by the intestinal microflora. As such, one possible reason for the wide inter-individual variation may be the differences in the intestinal microflora profiles (22). The case described in this report suggests that even very small doses of licorice may cause pseudoaldosteronism, and therefore, careful history taking is important in such patients.

In summary, we herein reported a case of hyponatremia in an elderly patient due to isolated hypoaldosteronism occurring after licorice withdrawal. This case suggests that, in elderly patients, RAAS suppression may persist for a long time after licorice withdrawal and may cause hyponatremia if dietary sodium intake is insufficient. Herbal medicines are popular among elderly people in Japan, with a vast majority of these drugs containing licorice (23). The possibility of isolated hypoaldosteronism following cessation of long-term licorice administration should be considered a potential cause of hyponatremia in elderly patients.

The authors state that they have no Conflict of Interest (COI).

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